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Novel amphiphilic fluoroalkylated derivatives of xylitol, D-glucose and D-galactose for medical applications: hemocompatibility and co-emulsifying properties☆

Oldřich Paleta,[a,*] Ivona Dlouhá,[a] Robert Kaplánek,[a] Karel Kefurt,[b] Milan Kodíček[c]

[a]*Department of Organic Chemistry, Prague Institute of Chemical Technology, Technická 5, 16628 Prague 6, Czech Republic*
[b]*Department of Natural Compounds Chemistry, Prague Institute of Chemical Technology, Technická 5, 16628 Prague 6, Czech Republic*
[c]*Department of Biochemistry and Microbiology, Prague Institute of Chemical Technology, Technická 5, 16628 Prague 6, Czech Republic*

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Abstract

1-*O*-(4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluorononyl)xylitol **6** was synthesized as a novel standard compound for the assessment of hemocompatibility and co-emulsifying properties in microemulsions for biomedical uses. 3-*O*-(1,1,2,4,4,5,7,7,8,8,9,9,9-Tridecafluoro-5-trifluoro-methyl-3,6-dioxanonyl)-D-glucose **9** and 6-*O*-(1,1,2,4,4,5,7,7,8,8,9,9,9-tridecafluoro-5-trifluoromethyl-3,6-dioxanonyl)-D-galactose **12** were synthesized by nucleophilic addition of protected carbohydrates to perfluorinated vinyl oligoether. Biological tests revealed very good hemocompatibility and co-emulsifying properties for the amphiphiles **6**, **9** and **12**.

Keywords: Radical addition; Reduction of C-I bond; Perfluoroalkyl iodides; Perfluoro(alkyl vinyl oligoether); *O*-(Fluoroalkyl)xylitol; *O*-Fluoroalkyl-D-glucose; *O*-Fluoroalkyl-D-galactose; Hemocompatibility; Microemulsion stability

1. Introduction

Amphiphilic compounds possessing a hydrophilic sugar moiety and perfluorinated hydrophobic moiety have been proposed as biocompatible surfactants for a series of medicinal applications. They display unique properties for the formulation of multi-phase and multi-component colloidal systems including perfluorocarbon emulsions for oxygen carriers, oxygen transporting gels and drug delivery systems.[1–4] A series of perfluoroalkylated sugar amphiphiles have displayed stabilisation effects on perfluorocarbon emulsions.[1–4] For this purpose, perfluoroalkylated derivatives of xylitol,[5] D-glucose[6,7] and D-galactose[6] were prepared and tested.[5–7] The aim of this paper has been, first, synthesis of a chemically stable standard compound on the basis of xylitol for testing hemocompatibility and co-emulsifying properties; second, to prepare new fluoroalkylated derivatives of D-glucose and D-galactose using the perfluorinated vinyl ether **1** as a building block.

Recently, perfluoroalkylated derivatives of xylitol possessing an unsaturated spacer between the hydrophilic saccharide and hydrophobic perfluoroalkyls have been reported.[5] However, unsaturation could cause chemical and biochemical instability of such molecules in potential medical applications. To avoid the instability, we have developed here the synthesis of an analogous *O*-alkylated xylitol derivative **6** having a saturated spacer with three carbon atoms. Amphiphilic sugar derivatives of perfluorinated ethers have not yet been reported. As perfluorinated vinyl oligoethers have become industrially available, we applied perfluorinated vinyl diether in a two-step synthesis of the new sugar derived surfactants **9** and **12**. For an assessment of the hemocompatibility of the new amphiphiles we have developed methodology similar to that previously reported.[5] Co-emulsifying properties have been assessed using our methodology.[8]

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* Corresponding author. Fax: +4202-2431-1082
E-mail address: oldrich.paleta@vscht.cz (O. Paleta).

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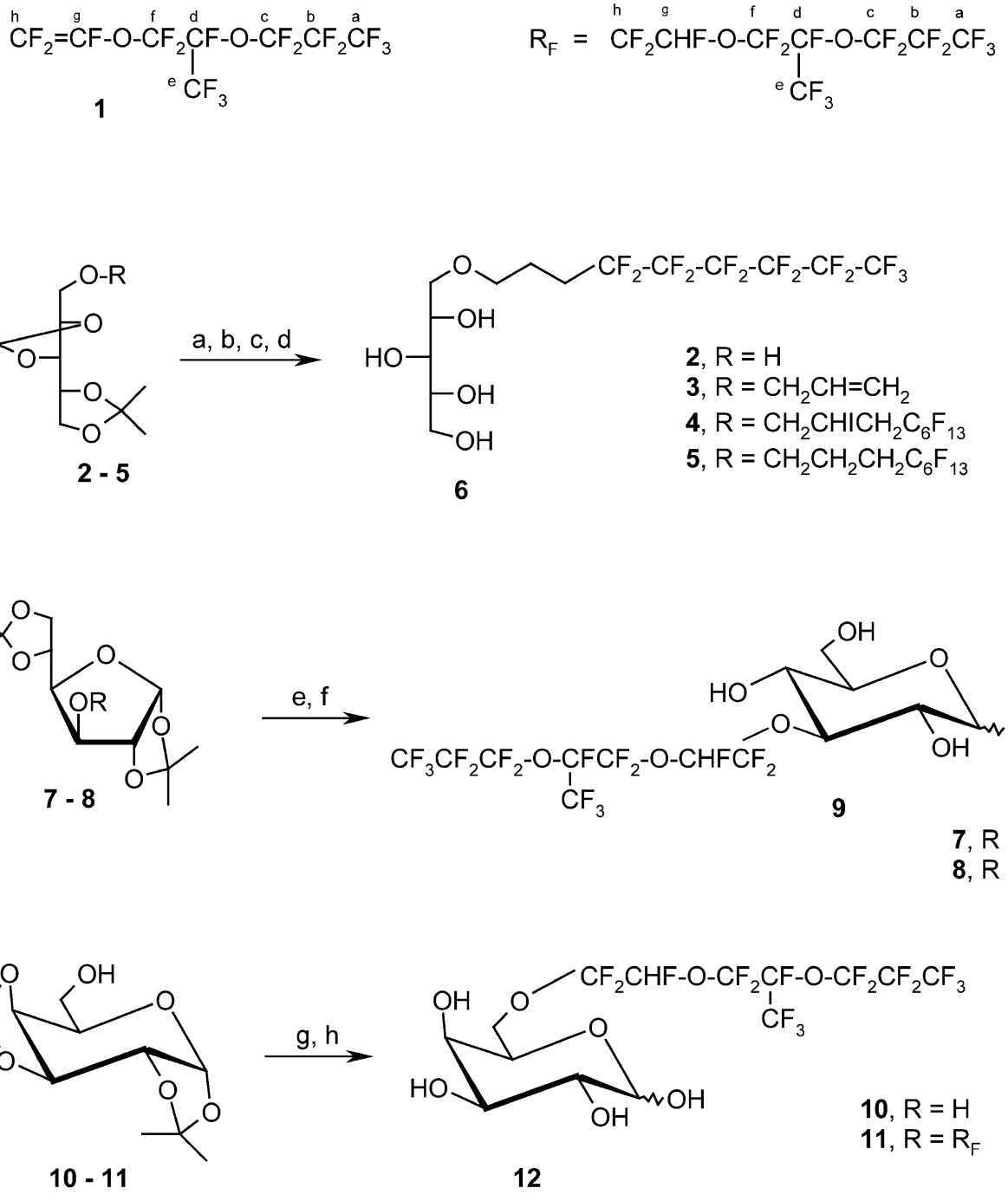
2. Results and discussion

For the synthesis of *O*-fluoroalkylated xylitol **6** (Scheme 1), we applied a modified previously reported strategy in the initial two steps, namely the peparation of protected *O*-allyl ether of xylitol[5] **3** and the radical addition of perfluorohexyl iodide[5,6] to the allyl part of **3**. The addition, which had been originally performed on alkyl allyl ether,[9] can also be initiated with sodium dithionite.[10,11] Azo-bis(isobutyronitrile) was applied as an intiator, which afforded the adduct **4** in a higher yield than reported.[5] For the reduction of a C–I bond in perfluoroalkylated compounds, several methods heve been reported, viz. catalytic reduction with hydrogen,[9,11] reduction with zinc in the presence of hydrochloric[12] or acetic acids,[13] reduction with sodium



Scheme 1. (a) 1. NaH, toluene, 100 °C, 3 h; 2. $CH_2=CH\text{-}CH_2Br$, toluene, reflux, 18 h; (b) $C_6F_{13}I$, AIBN, 100 °C, 3 h; (c) $Zn–NiCl_2{\cdot}6H_2O$, THF–H_2O, r.t., 24 h; (d) $HCl_{conc.}$, methanol, r.t., 1 h; (e) 1.BuLi, THF, −78 °C; 2. **1**, THF, −78 °C 2 h + r.t. 96 h; (f) $CF_3COOH–H_2O$ (9:1), 30 min; (g) = (e); (h) = (f).

Table 1
Hemocompatibility of new amphiphilic compounds

	Emulsifier	Substitution of Pluronic F-68 by tested emulsifiers (% w/v PF-68)				
		20%	40%	60%	80%	100%
		Range of hemolysis (%)				
6	[Xylitol-1-*O*-yl]-CH_2-CH_2-CH_2-$CF_2CF_2CF_2CF_2CF_2CF_3$	0[a]	0	0	0	0
9	[D-Glucose-3-*O*-yl]-CF_2CHF-O-$CF_2CF(CF_3)$-O-$(CF_2)_2CF_3$	0	0	0	nt[b]	nt
12	[D-Galactose-6-*O*-yl]-CF_2CHF-O-$CF_2CF(CF_3)$-O-$(CF_2)_5CF_3$	0	0	nt	nt	nt

[a] Zero value means hemolysis below 0.5%.
[b] nt, not tested.

borohydride[14], tributyltin hydride[15] or using zinc-nickel chloride[16] mixture. In the present paper, the reduction with zinc-nickel chloride[16] was applied giving complete conversion of the iodo compound **4** and afforded the reduced product **5** in a moderate isolated yield.

The *O*-fluoroalkylated D-glucopyranose **9** and D-galactopyranose **12** were prepared by nucleophilic additions of the protected glucofuranose **7** and galactopyranose **10** to the perfluorinated vinyl diether **1** (Scheme 1). Nucleophilic additions of aliphatic or alicyclic hydroxy compounds to perfluorinated vinyl alkyl ethers and vinyl oligoethers have rarely been reported in the literature, e.g. Refs 17–19. Our addition procedure[20–22] was applied in this work to afford the corresponding adducts **8** or **11** in moderate isolated yields. The additions of sugar alkoxides were completely regioselective, no regioisomeric products were observed in ^{1}H, ^{19}F and ^{13}C NMR spectra. The sodium alkoxide of the protected glucofuranose **7** afforded the adduct **8** in a three times lower yield than the corresponding lithium salt (yield 33%). Therefore, the lithium salt of **10** was also used in the fluoroalkylation with the perfluorinated vinyl oligoether **1** to afford the product **11** in a 52% yield. Deprotection of the fluoroalkylated intermediate **8** using a classical hydrolysis with sulfuric acid was completely unsuccessful, while the deprotection with trifluoroacetic acid afforded the final amphiphilic sugar derivatives **9** and **12** in ca. 50% isolated yields.

The structures of the sugar parts in the products **6**, **9** and **12** were elucidated on the basis of reported NMR data.[5,6,23–25] The NMR spectra are consistent with the pyranose structure for **9**; it forms a mixture of anomers[23,24] in the approximate ratio $\alpha:\beta = 60:40$ (^{13}C NMR). For **12**, the approximate anomer ratio $\alpha:\beta = 35:65$ (^{13}C NMR) was found.[23,24] The polyether fluorinated chains in structures **8**–**9** and **11**–**12** possess two stereogenic carbon atoms thus giving the possibility of the formation of four stereoisomers. However, no defined stereoisomers could be recognized by the analysis of multiplet signals in ^{13}C NMR and ^{19}F NMR spectra.

The sugar amphiphiles **6**, **9**, **12** were tested as co-surfactants for potential oxygen carriers. Their hemolytic activity on human erythrocytes was tested using a reference microemulsion of Pluronic F-68 with perfluorodecalin mixed with erythrocytes. In this heterogeneous mixture, Pluronic was gradually substituted with the amphiphile tested and the amount of extracellular hemoglobin was determined spectrophotometrically as per cent degree of hemolysis. This is a modified method to that previously reported.[5] Compound **6** was synthesized as a reference amphiphile compared to the reported[5] xylitol derivative having unsaturation at the spacer part that could cause biochemical instability. Co-emulsifiers for microemulsions are usually used[1–5] in amounts up to10% relatively to the main emulsifier, e.g. Pluronic F-68. The xylitol amphiphile **6** appeared to be completely non-hemolytic in the whole concentration range up to 100% substitution of the Pluronic and it can be used as a non-hemolytic standard. Similarly, amphiphiles **9** and **12** with 2*H*-perfluorinated polyether chain showed no apparent hemolysis up to 60% (**9**) and 40% (**12**) substitution of the emulsifier Pluronic. Thus, their hemocompatibility has appeared to be very good (Table 1).

Preliminary testing of co-emulsifying properties was based on visual evaluation of the state of an emulsion (the methods are described in Section 3). The first test was 6 h standing of the emulsion with co-emulsifier (Table 2). The xylitol amphiphile **6** caused no apparent (visual) colaps of the emulsion even at 100% substitution of the Pluronic. Glucose derivative **9** caused colaps of the emulsion at 60% substitution of the Pluronic, while at 40% content of **9** was the emulsion stable. Similarly, substitution of Pluronic with 40% of the galactose amphiphile **12** did not affect the emulsion stability.

Centrifugation is a very efficient test of the emulsion stability that was first used in this study. The results of

testing for amphiphiles **6**, **9** and **12** are summarised in Table 3. The xylitol derivative **6** caused unstability of the emulsion when more than 60% of Pluronic was substituted with **6**. Co-emulsifiers **9** and **12** did not affect the emulsion stability when their portion of Pluronic substitution was not higher than 40%. It can be summarised that all three new amphiphiles **6**, **9** and **12** let the Pluronic emulsion stable in much higher concentrations than that usually applied[1–5] (up to 10%) for co-emulsifiers.

3. Experimental

General.—The temperature data were not corrected. Distillations of high boiling compounds were carried out on a Vacuubrand RC5 high vacuum oil pump. Column chromatography: silica gel, aluminum oxide; weight ratio compound/sorbent 1/30. GC analyses were performed on a Micromat HRGC 412 (GCa, Nordion Analytical; 25 m glass capilary column, SE-30) and Chrom 5 (GCb, Laboratorní prístroje, Prague; FID, 380 × 0.3 cm packed column, silicone elastomer E-301 on Chromaton N-AW-DMCS (Lachema, Brno), nitrogen) instruments. NMR spectra were recorded on a Varian Gemini 300 HC (^{1}H at 300 MHz, ^{13}C at 75.46 MHz) and a Bruker WP 80 SY (^{19}F at 75.4 MHz) instruments: TMS and $CFCl_3$ as the internal standards, chemical shifts in ppm (s singlet, d doublet, t triplet, qua quadruplet, qui quintet, sex sextet, m multiplet, bs broad singlet, q quasi), coupling constants *J* in Hz, solvent $CDCl_3$ and DMSO-d_6. For the assignment of signals in NMR spectra of compounds **9**, **11** and **12**, ^{1}H and ^{13}C HETCOR technique was applied. MS spectra were scanned on a Hewlett-Packard MSD 5971A instrument (1989, EI 70 eV). UV-VIS spectra were measured on a UV-160A apparatus (Shimadzu). Infrared spectra were scanned on a NICOLET 740 USA apparatus.

Chemicals used were as follows: Silica gel (60–100 μm, Merck), hexafluoropropene-1,2-oxide (Aldrich), perfluorohexyl iodide (gift of Elf Atochem S.A.); xylitol, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose and D-galactose (all Aldrich) were dried before use; allyl bromide (Lachema), trifluoroacetic acid (Reachim). Zinc chloride (anhydrous, Lachema), nickel chloride hydrate (Lachema), sodium hydride (60% suspension in oil, Aldrich), butyllithium (2.5 M in hexane, Aldrich), azo-

Table 2
Stability after mixing at 37°C for 6 hrs

	Emulsifier	Substitution of Pluronic F-68 by tested emulsifiers (% w/v PF-68)				
		20%	40%	60%	80%	100%
		Emulsion stability				
6	[Xylitol-1-*O*-yl]-CH_2-CH_2-CH_2-$CF_2CF_2CF_2CF_2CF_2CF_3$	+[a]	+	+	+	+
9	[D-Glucose-3-*O*-yl]-CF_2CHF-O-$CF_2CF(CF_3)$-O-$(CF_2)_2CF_3$	+	+	−	−	nt[b]
12	[D-Galactose-6-*O*-yl]-CF_2CHF-O-$CF_2CF(CF_3)$-O-$(CF_2)_5CF_3$	+	+	nt	nt	nt

[a] Plus value means no apparent change of emulsion; minus value means colapse of the emulsion.
[b] nt, not tested.

Table 3
Stability after centrifugation

	Emulsifier	Substitution of Pluronic F-68 by tested emulsifiers (% w/v PF-68)				
		20%	40%	60%	80%	100%
		Emulsion stability				
6	[Xylitol-1-*O*-yl]-CH_2-CH_2-CH_2-$CF_2CF_2CF_2CF_2CF_2CF_3$	+[a]	+	+	−	−
9	[D-Glucose-3-*O*-yl]-CF_2CHF-O-$CF_2CF(CF_3)$-O-$(CF_2)_2CF_3$	+	+	−	−	nt[b]
12	[D-Galactose-6-*O*-yl]-CF_2CHF-O-$CF_2CF(CF_3)$-O-$(CF_2)_5CF_3$	+	+	nt	nt	nt

[a] Plus value means no apparent change of emulsion; minus value means colaps of the emulsion.
[b] nt, not tested.

bis(isobutyronitril) (AIBN, crystallised before use, Fluka). Diethyl ether (distilled over Na), dichloromethane (distilled, b.p. 42 °C), methanol (distilled over Na, stored over molecular sieves); other solvents used were purified and dried according to standard procedures.

Preparation of chemicals.—Perfluoro-[2,5-dimethyl-(3,6-dioxa)nonanoyl] fluoride was prepared according to our previously reported procedure.[26,27] 1,2:3,4-Di-*O*-isopropylidenexylitol was prepared according to Refs 5,28.

Preparation of emulsions.—Perfluorodecalin (0.125 mL) was mixed with isotonic Tris–HCl buffer of pH 7.4 and Pluronic F-68 (block co-polymer of polyoxypropylene and polyoxyethylene, 5% w/v) as a standard emulsifier and the mixture was sonicated for 15 s to afford 0.5 mL of an emulsion. (For a more detailed description of the testing procedures see Ref. 29).

Hemocompatibility testing[5,29].—Human erythrocytes (from a healthy donor, stored in a refrigerator not longer than 1 week) were washed by isotonic Tris-HCl buffer. Packed erythrocytes (0.5 mL) were added to the emulsion of perfluorodecalin (see above), the mixture was then gently stirred at 37 °C for 6 h and after that shortly centrifuged. The amount of the extracellular hemoglobin in the water phase was determined spectrophotometrically and used as a measure of hemolytic activity of the co-emulsifier tested. (For a more detailed description of the procedure see Ref. 29).

Testing of co-emulsifying properties: in the preparation of an emulsion (see above), Pluronic F-68 was partly or completely substituted by the tested co-emulsifier; if any apparent phase separation of water and perfluorodecalin phases did not appear immediately after finishing the test, the emulsion was considered to be stable (indicated as '+' in Tables 2 and 3). Unstable emulsion is marked by the sign '−' in Tables 2 and 3. Stabilities of the mixtures were tested under two different conditions: (1) Stability at 37 °C: the emulsion was gently stirred (magnetic spibar) at 37 °C for 6 h (see hemolytic test above). (2) Stability during centrifugation: the emulsion was centrifuged for 5 min. at 400 × *g*.

1,1,2,4,4,5,7,7,8,8,9,9,9 - Tridecafluoro - 5 - trifluoromethyl-(3,6-dioxa)non-1-ene[27,30] ***1***.—A mixture of perfluoro-(2,5-dimethyl-3,6-dioxanonanoyl) fluoride (20.75 g, 41.7 mmol), distilled water (20 mL) and ethanolic solution of phenolphthaleine (6 drops) in a flask equipped with a dropping funnel was titrated with a water solution of NaOH (10%) while stirring (magnetic spinbar). The mixture was evaporated to dryness and then dried on an oil pump (0.3 mmHg, 150 °C, 6 h).

Dry sodium perfluoro-(2,5-dimethyl-3,6-dioxanonanoate) was then heated to 260–340 °C in a distillation apparatus to afford raw product **1** (fraction 95-140 °C). This distillate was dried ($MgSO_4$) and after filtration fractionally distilled (Vigreux column, 15 cm heated jacket) to afford pure **1**, b.p. 101–102 °C, yield 10.9 g (62%), purity 98% (check by ^{19}F NMR and GC). When the sodium salt was not completely dry, 1,1,1,2,4,4,5,7,7,8,8,9,9,9 - tetradecafluoro - 5 - trifluoromethyl-3,6-dioxanonane was formed up to 25% rel.

^{19}F NMR ($CDCl_3$): δ −80.4 (qs, 3F, F-e), −81.9 (qs, 3F, F-a), −82.2 (qs, 2F, F-c), −85.2 (qs, 2F, F-f), −113.5 (dd, 1F, $J_{F,F}$ 83.0 Hz, $J_{F,Fcis}$ 65.9 Hz, F-h_{cis}), −122.0 (tdd, 1F, $J_{F,Ftrans}$ 112.0 Hz, $J_{F,F}$ 5.5 Hz, F-h_{trans}), −130.1 (qs, 2F, F-b), −136.0 (tdd, 1F, $J_{F,F}$ 5.8 Hz, F-g), −145.4 (m, 1F, F-d).

1-O-Allyl-2,3:4,5-di-O-isopropylidenexylitol[5] ***3***.—To a suspension of NaH (0.36 g, 15 mmol) in toluene (15 mL) a solution of diacetonexylitol **2** (2.32 g, 10 mmol) in toluene (3 mL) was added dropwise. The mixture was stirred at 100 °C for 3 h, then cooled to r.t. and allyl bromide (2.42 g, 20 mmol) in toluene (3 mL) was added portionwise. The mixture was refluxed for 18 h while stirring, then cooled to r.t. and water was added dropwise under reflux condenser. The resulting mixture was extracted with diethyl ether (2 × 15 mL), the ethereal extract was washed with $NaHCO_3$ water solution to neutral pH, dried over $MgSO_4$ and the solvent was removed on rotary evaporator at 40 °C. Distillation of the residue—a raw product **3** on a Hickmann-type short-way distillation apparatus in vacuum of the oil pump afforded product **3** as a colourless liquid, yield 1.78 g (69%), b.p. 95 °C/0.4 mmHg (lit.:[5] b.p. 90–100 °C/0.3 mm Hg).

^1H NMR ($CDCl_3$): δ 1.33 and 1.38 (2x s (1:3), 12H, 4x CH_3), 3.52 (m, 2H, H-$1'_a$, H-$1'_b$), 3.70-4.24 (m, 7H, xylitol protons), 5.06 (dd, 1H, *J* 1.65 Hz, *J* 10.4 Hz, H-$3'_{trans}$), 5.30 (dd, 1H, *J* 1.65 Hz, *J* 17.6 Hz, H-$3'_{cis}$), 5.80 (ddt, 1H, *J* 5.5 Hz, *J* 10.4 Hz, *J* 17.5 Hz, H-2′).

^{13}C NMR ($CDCl_3$): δ 25.3 and 26.1 and 26.9 (3x s, 4C, 4x CH_3), 65.5, 70.5, 72.3 (3x s, 3C, C-1, C-1′, C-5), 75.5, 76.3, 78.3 (3x s, 3C, C-2, C-3, C-4), 109.4 (s, 1C, kvart. C), 109.5 (s, 1C, kvart. C), 107.1 (s, 1C, C-3′), 134.2 (s, 1C, C-2′).

IR ($CHCl_3$); *ν* 1060 (s), 1080 (s), 1157 (m), 1372 (s), 2897 (m), 2937 (m), 2991 (s), 3017 (s).

Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 61.72; H, 9.02.

1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose[31] ***10***.—Anhydrous $ZnCl_2$ (21.6 g, 158.5 mmol) was dissolved in acetone (225 mL) by stirring under inert atmosphere. Small amount of $Zn(OH)_2$ present was dissolved by dropwise addition of H_2SO_4 through septum. Finely ground anhydrous galactose (18 g, 0.1 mol) was added to the solution and stirred (magnetic spinbar) for 4 h at r.t. A suspension of Na_2CO_3 (36 g) in water (63 mL) was then added portionwise to the mixture, which was stirred until the liquid layer contained zinc ions, and filtrated. The solid was washed on

the filter with acetone (3 × 15 mL) and combined filtrates were evaporated under reduced pressure (30 °C, 200 mmHg, rotary evaporator). The residue was extracted with diethyl ether (3 × 50 mL) and the ethereal extract was dried over $MgSO_4$. After distilling off the solvent, the residue was dried in vacuum (0.05 mmHg, 100 °C) to afford a sirup-like raw product (23.4 g). Its distillation on a Hickmann-type short-way distillation apparatus in vacuum of the oil pump afforded product **10** as a colourless viscous liquid, yield 21.9 g (84.1%) b.p. 131–135 °C/0.3 mmHg.

4. Products 4-12

*Radical addition of perfluorohexyl iodide to protected 1-*O*-allylxylitol (**3**). 2,3:4,5-Di-*O*-isopropylidene-1-O-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-2-iodononyl)-xylitol (**4**).*—The reaction was carried out in a double-neck round-bottomed flask equipped with a Dimroth condenser that was connected with atmosphere by a hydraulic seal. Nitrogen was slowly introduced in the mixture of 1-*O*-allyl-2,3:4,5-di-*O*-isopropylidenexylitol (**3**, 0.5 g, 1.94 mmol), perfluorohexyl iodide (1.34 g, 3 mmol) and AIBN (20 mg) for 20 min while stirring (magnetic spinbar) and the mixture was then heated on a oil bath at 100–110 °C for 3 h.

Volatile components were then removed on a rotary evaporator (45 °C, 30 mm Hg) and lastly by oil pump (45 °C, 30 mm Hg) to get the raw product **4**. Pure product **4** was obtained as a slightly pinky liquid by purification on column chromatography (silica gel, 40 g, dichloromethane), yield 1.19 g (88%).

^{1}H NMR ($CDCl_3$): δ 1.30 and 1.35 (2x s (1:3), 12H, 4x CH_3), 2.44-2.80 and 2.83-3.16 (2x m, 2H, H-3′), 3.46-4.44 (m, 10H, 7x xylitol protons and H-2′ and H-1′).

^{13}C NMR ($CDCl_3$): δ 13.9 and 14.0 (2x s, 1C, C-2′), 25.2 (s, 1C, CH_3), 26.0 (s, 1C, CH_3), 26.7 (s, 1C, CH_3), 26.8 (s, 1C, CH_3), 37.5 and 37.6 (2x t, 1C, $J_{C,F}$ 20 Hz, C-3′), 65.5, 70.5, 71,1, 71.2, 76.3 (4x s, 3C, C-1, C-1′, C-5), 75.1, 75.2, 76.2, 77.7, 77.8 (5x s, 3C, C-2, C-3, C-4), 109.6 (s, 1C, kvart. C), 109.7 (s, 1C, kvart. C), 103.8-123.6 (m, 6C, 5x CF_2 and CF_3).

^{19}F NMR ($CDCl_3$): δ −81.4 (t, 3F, $J_{F,F}$ 10.2 Hz, CF_3), −113.9 (m, 2F, CF_2-CH_2), -122.2 (qs, 2F, CF_2), −123.3 (qs, 2F, CF_2), −124.0 (qs, 2F, CF_2), −126.6 (m, 2F, CF_2).

Anal. Calcd for $C_{20}H_{24}F_{13}IO_5$: C, 33.44; H, 3.37. Found: C, 33.69; H, 3.73.

*Reduction of C–I bond in adduct **4**. 2,3:4,5-Di-*O*-isopropylidene-1-O-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)xylitol (**5**).*—Reducing agent was prepared by stirring (magnetic spinbar) a mixture of powdered zinc (0.34 g, 4.80 mmol), nickel(II) chloride hexahydrate (0.10 g, 0.42 mmol), THF (3 mL) and a droplet of water in a flask under inert atmosphere for 30 min at r.t. 1-*O*-(4,4,5,5,6,6,7,7,-8,8,9,9,9-Tridecafluoro-2-iodononyl)-2,3:4,5-di-*O*-isopropylidenexylitol (**4**) (0.25 g, 0.36 mmol) was then added to the agent and the mixture was stirred for 24 h at r.t. Volatile components were then removed on a rotary evaporator (40 °C, 60 mmHg) and the residue was chromatographed (silica gel, 20 g, diethyl ether) to afford product **5** as slightly yellowish viscous liquid, yield 95 mg (46%).

^{1}H NMR ($CDCl_3$): δ 1.38 and 1.43 (2x s, 12 H, 4x CH_3), 1.80-1.98 (m, 2H, H-2′), 2.05-2.44 (m, 2H, H-3′), 3.40–4.30 (m, 9H, H-1′and 7x xylitol protons).

^{13}C NMR ($CDCl_3$): δ 20.7 (s, 1C, C-2′), 28.9 (s, 1C, C-3′), 65.6, 70.0, 71.4 (3x s, 3C, C-1, C-5, C-1′), 75.4, 76.4, 78.0 (3x s, 3C, C-2, C-3, C-4), 109.6 (s, 1C, kvart. C), 109.7 (s, 1C, kvart. C), 105.0-125.0 (m, 6C, 5x CF_2 and CF_3).

^{19}F NMR ($CDCl_3$): δ −81.3 (t, 3F, $J_{F,F}$ 9.8 Hz, CF_3), −114.8 (m, 2F, CF_2–CH_2), −122.4 (m, 2F, CF_2), −123.4 (qs, 2F, CF_2), −124.0 (m, 2F, CF_2), −126.6 (m, 2F, CF_2).

Anal. Calcd for $C_{20}H_{25}F_{13}O_5$: C, 40.05; H, 4.25. Found: C, 39,74; H, 4.73.

*1-O-(4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluorononyl)-xylitol (**6**).*—To a solution of 2,3:4,5-di-*O*-isopropylidene-1-*O*-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)-xylitol (**5**) (0.50 g, 0.9 mmol) in methanol (25 mL) concentrated HCl (36%, 5 mL) was added dropwise by a syringe and the mixture was stirred (magnetic spinbar) at r.t. After 24 h reaction, no starting compound was detected in the mixture (TLC, $CHCl_3$/CH_3OH 5:1). Volatile components were then removed on a rotary evaporator (40 °C, 35 mmHg) and the residue was chromatographed (silica gel, 50 g, $CHCl_3$/CH_3OH 5:1) to afford product **6** as a slightly yellow waxy compound, yield 240 mg (55%).

^{1}H NMR ($CDCl_3$): δ 1.78–2.00 (m, 2H, H-2′), 2.14–2.50 (m, 2H, H-3′), 3.40–4.00 (m, 9H, H-1′ and 7x xylitol protons), 4.86 (s, 4H, 4x OH).

^{13}C NMR ($CDCl_3$): δ 21.9 (s, 1C, C-2′), 29.3 (s, 1C, C-3′), 64.3, 70.8, 73.4 (3x s, 3C, C-1, C-5, C-1′), 72.2, 72.3, 73.9 (3x s, 3C, C-2, C-3, C-4), 106.0–126.0 (m, 6C, 5x CF_2 and CF_3).

^{19}F NMR (CD_3OD) δ −81.0 (t, 3F, $J_{F,F}$ 9.8 Hz, CF_3), −112.4 (m, 2F, CF_2–CH_2), -121.5 (qs, 2F, CF_2), −122.6 (qs, 2F, CF_2), −123.3 (qs, 2F, CF_2), −126.0 (m, 2F, CF_2).

*Addition of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7**) to perfluorovinyl ether (**1**); 1,2:5,6-di-*O*-isopropylidene-3-O-(1,1,2,4,4,5,7,7,8,8,9,9,9-tridecafluoro-5-trifluoromethyl-3,6-dioxanonyl)-α-D-glucofuranose (**8**).*—Procedure A (reaction of lithium salt): To a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7**, 112 mg, 0.43 mmol) in dry THF (2 mL) under nitrogen atmosphere in a flask with septum, which was immersed in dry-ice bath (ethanol), a solution of butyl-

lithium (0.1 mL, 0.12 mmol, 2.47 mol/L in hexane) was added dropwise. The solution of lithium salt of **7** was transferred under nitrogen in 5 min by syringe to a mixture of perfluoro-5-methyl-3,6-dioxanon-1-ene (**1**, 193 mg, 0.45 mmol) immersed to a dry-ice bath (ethanol). The reaction mixture, which formed two layers, was stirred at −70 °C for 2 h and then 40 h at r.t., but the mixture still contained unreacted perfluoro vinyl ether **1**. The reaction was stopped by the addition of trifluoroacetic acid (pH ≅ 5.5), volatile components were removed on a rotary evaporator (40 °C, 30 mmHg) and the residue was chromatographed (aluminum oxide, 30 g, heptane:acetone 4:1) to afford syrup-like pure product **8** (TLC check, heptane:ethyl acetate 10:1) yield 101 mg (33%).

Procedure B (reaction of sodium salt): Using the methodology as above, sodium salt of **7** was prepared by its reaction with NaH in DMF at r.t. and reacted with perfluorinated vinyl ether 1 at r.t. After 2 d reaction at r.t., the mixture did not contained any product and 93% of the starting **7** was recovered.

^{1}H NMR[23] ($CDCl_3$): δ 1.33 and 1.39 (2x s, 6H, 2x CH_3), 1.51 (s, 6H, 2x CH_3), 3.99 (m, 1H, H-6a), 4.06 (m, 1H, *J* 7.7 Hz, H-6b), 4.17 (m, 2H, H-4 and H-5), 4.62 (m, 1H, H-2), 4.82 (m, 1H, H-3), 5.88 (d, 1H, $J_{1,2}$ 3.3 Hz, H-1), 6.10 (d, 1H, $J_{H,F}$ 53.3 Hz, H-g).

^{13}C NMR[23] ($CDCl_3$): δ 25.6 and 26.8 and 27.3 and 27.5 (4x s, 4C, 4x CH_3), 67.9 (s, 1C, C-6), 72.6 (s, 1C, C- 5), 77.9 (s, 1C, C-4), 80.5 (s, 1C, C-2), 84.0 (s, 1C, C-3), 105.6 (s, 1C, C-1), 98.5 (ttd,, $J_{C,F}$ 244.9 Hz, $J_{C,F}$ 41.8 Hz, $J_{C,F}$ 4.5 Hz, C-g), 103.0 (sex d, 1C, $J_{C,F}$ 268.4 Hz, $J_{C,F}$ 37.2 Hz, C-d), 107.7 (sex t, 1C, $J_{C,F}$ 268.4 Hz, $J_{C,F}$ 36.1 Hz, C-b), 110.1 and 113.3 (2x s, 2C, kvart. C), 115.8 (dt, 1C, $J_{C,F}$ 287.3 Hz, $J_{C,F}$ 32.8 Hz, C-c), 117.0 (dt, 1C, $J_{C,F}$ 282.1 Hz, $J_{C,F}$ 29.2 Hz, C-f), 117.7 (tq, 1C, $J_{C,F}$ 287.7 Hz, $J_{C,F}$ 32.9 Hz, C-a), 118.2 (dt, 1C, $J_{C,F}$ 268.9 Hz, $J_{C,F}$ 29.2 Hz, C-h), 118.3 (dq, 1C, $J_{C,F}$ 288.1 Hz, $J_{C,F}$ 31.2 Hz, C-e).

^{19}F NMR ($CDCl_3$): δ −80.5 (m, 3F, F-e), −81.8 (q, 3F, F-a), −81.9 and −82.3 (m, 2F, $J_{F,F}$ 147.4 Hz, F-c), −85.7 and −87.0 (d, 2F, $J_{F,F}$ 146.1 Hz, F-h), −84.1 and −86.1 and −83.9 and −85.7 (2x d, 2F, $J_{F,F}$ 5.6 Hz, $J_{F,F}$ 141.5, $J_{F,F}$ 144.2 Hz, F-f), −130.1 (s, 2F, F-b), −143.9 and −144.7 and −144.1 and −144.8 (2x d, 1F, $J_{F,F}$ 8.3 Hz, F-g), −145.4 (t, 1F, $J_{Fd,Ff}$ 21.0 Hz, F-d).

Anal. Calcd for $C_{20}H_{20}O_8F_{16}$: C, 34.70; H, 2.91; F, 43.90. Found: C, 34.45; H, 2.85; F, 44.34.

*Deprotection of **8**. 3-*O*-(1,1,2,4,4,5,7,7,8,8,9,9,9-Tridecafluoro-5-trifluoromethyl-3,6-dioxanon-1-yl)-*D*-glucopyranose (**9**).*—Procedure A: A mixture of fluoroalkylated glucofuranose **8** (141 mg, 0.20 mmol), methanol (1 mL), water (1 mL) and H_2SO_4 (0.1 mL) was refluxed for 1 h and then neutralized with a warm solution of $BaCO_3$. No deprotected product **9** was identified in the reaction mixture (TLC check, heptane:ethyl acetate 10:1).

Procedure B[6]: A mixture of fluoroalkylated derivative **8** (363 mg, 0.10 mmol), water solution of trifluoroacetic acid (1.5 mL, 1:9) was stirred (magnetic spinbar) for 30 min at r.t. when the conversion was complete (TLC as in Procedure A.). Reaction mixture was evaporated to dryness (rotary evaporator), then, petroleum ether (2.5 mL) was added to the wet residue, evaporated and the operation was twice repeated. The crude product **9** was chromatographed (aluminum oxide, 50 g, methanol) to afford pure waxy product **9,** yield 158 mg (49%). For analytical purposes, the product **9** was dried for 42 h (35 °C, 0.02 mm Hg).

^{1}H NMR[24] ($CDCl_3$ and MeOD): δ 3.7 and 3.8 (m, H-6), 4.57 (d, $J_{1,2}$ 7.6 Hz, H-1-β) and 5.21 (bs, H-1-α), 6.22 (d, $J_{H,F}$ 53.1 Hz, H-g).

^{13}C NMR[24] ($CDCl_3$ and MeOD): anomer ratio α:β ca. 60:40: δ 61.0 and 61.2 (2x s, 1C, α- and β-C-6), 70.0 and 70.1 (2x s, 1C, α- and β-C-4), 72.6 and 75.6 (2x s, 1C, α- and β-C-5), 92.2 and 96.2 (2x s, 1C, α,β-C-1), 98.3 (td, 1C, $J_{C,F}$ 241.7 Hz, $J_{C,F}$ 39.9 Hz, C-g), 102.5 (sex d, 1C, $J_{C,F}$ 259.4 Hz, $J_{C,F}$ 35.4 Hz, C-d), 106.2 (sex t, 1C, $J_{C,F}$ 268.0 Hz, $J_{C,F}$ 37.5 Hz, C-b), 115.1 (tt, 1C, $J_{C,F}$ 290.1 Hz, $J_{C,F}$ 27.9 Hz, C-c), 115.2 (dt, 1C, $J_{C,F}$ 288.1 Hz, $J_{C,F}$ 28.9 Hz, C-f), 117.2 (tq, 1C, $J_{C,F}$ 279.4 Hz, $J_{C,F}$ 39.0 Hz, C-a), 116.8 (dt, 1C, $J_{C,F}$ 286.9 Hz, $J_{C,F}$ 28.6 Hz, C-h), 117.5 (dq, 1C, $J_{C,F}$ 280.8 Hz, $J_{C,F}$ 29.0 Hz, C-e).

^{19}F NMR ($CDCl_3$ and MeOD): δ −80.5 (m, 3F, F-e), −81.8 (q, 3F, F-a), −82.0 (m, 2F, F-c), −84 to −88 (m, 4F, F-h and F-f), −130.1 (s, 2F, F-b), −145.3 (m, 1F, F-d), −144.6 to −145.8 (m, 1F, F-g).

Anal. Calcd for $C_{14}H_{12}O_8F_{16}$: C, 27.46; H, 2.01. Found: C, 26,83; H, 2.55.

*Addition of 1,2:3,4-di-*O*-isopropylidene-α-*D*-galactopyranose (**10**) to perfluorovinyl ether **1**. 1,2:3,4-di-*O*-isopropylidene-6-O-(1,1,2,4,4,5,7,7,8,8,9,9,9-tridecafluoro-5-trifluoromethyl-3,6-dioxanonyl)-α-*D*-galactopyranose (**11**).*—To a solution of 1,2:3,4-di-*O*-isopropylidene-α-*D*-galactopyranose (**10**, 390 mg, 1.50 mmol) in dry THF (3 mL) under nitrogen atmosphere in a flask with septum, which was immersed in dry-ice bath (ethanol), a solution of butyllithium (0.6 mL, 0.48 mmol, 2.47 mol/L in hexane) was added dropwise. The solution lithium salt of **10** was transferred under nitrogen in 5 min by syringe to a mixture of perfluoro-5-methyl-3,6-dioxanon-1-ene (**1**, 647 mg, 1.50 mmol) immersed to a dry-ice bath (ethanol). The reaction mixture was stirred at −70 °C for 2 h and then 40 h at r.t. The reaction was stopped by the addition of trifluoroacetic acid (pH ≅ 5.5), volatile components were removed on a rotary evaporator (40 °C, 30 mm Hg) and the residue was chromatographed (aluminum oxide, 50 g, heptane:acetone 4:1) to afford waxy pure product **11** (TLC check, heptane:ethyl acetate 10:1) yield 537 mg (52%).

^{1}H NMR[24,25] ($CDCl_3$): δ 1.33 (s, 6H, 2x CH_3), 1.45 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 3.99 (m, 1H, H-6a), 4.06 (m, 1H, $J_{a,b}$ 7.7 Hz, H-6b), 4.17 (m, 2H, H-4 and H-5), 4.62 (m, 1H, H-2), 4.82 (m, 1H, H-3), 5.88 (d, 1H, $J_{1,2}$ 3.3 Hz, H-1), 5.89 (d, 1H, $J_{H,F}$ 53.4 Hz, H-g).

^{19}F NMR ($CDCl_3$): δ −80.3 (m, 3F, F-e), −81.6 (q, 3F, F-a), −81.6 and −82.0 (d q, 2F, $J_{F,F}$ 150.5 Hz, F-c), −89.5 and −90.7 (d q, 2F, $J_{F,F}$ 140.0 Hz, F-h), −83.5 (−86.1) (m, 2F, F-f), −129.8 (s, 2F, F-b), −145.1 (t, 1F, $J_{F,F}$ 21.0 Hz, F-d), −144.5 (−145.1) (m, 1F, F-g).

Anal. Calcd for $C_{20}H_{20}O_8F_{16}$: C, 34.70; H, 2.91. Found C, 34.47 ; H, 2.85.

Deprotection of ***11****. 6-*O*-(1,1,2,4,4,5,7,7,8,8,9,9,9-Tridecafluoro-5-trifluoromethyl-3,6-dioxanon-1-yl)-*D*-galactopyranose* ***12****.*—A mixture of fluoroalkylated α-D-galactopyranose (**11**, 216 mg, 0.31 mmol), water solution of trifluoroacetic acid (3 mL, 1:9) was stirred (magnetic spinbar) for 30 min at r.t. when the conversion was complete (TLC as for **9**). Reaction mixture was evaporated to dryness (rotary evaporator). Petroleum ether (2.5 mL) was then added to the wet residue, evaporated and the operation was twice repeated. The crude product **12** crystallised (THF/chloroform 1:3) to afford pure product **12,** yield 103 mg (51%). For analytical purposes, product **12** was dried for 42 h (35 °C, 0.02 mmHg).

^{1}H NMR[24,25] (DMSO): δ 3.5 and 3.6 (m, H-6), 4.2 (m, H-1-β) and 4.9 (s, H-1-α), 6.8 (d, $J_{H,F}$ 52.6 Hz, H-g).

^{13}C NMR[24,25] (DMSO): anomer ratio α:β ca. 35:65: δ 60.5 (s, 1C, C-6); 68.2, 68.8, 70.3, 72.1, 73.5, 75.0 (6x s, C-2, C-3, C-4, C-5) 92.5 and 97.5 (2x s, 1C, α and β-C-1).

^{19}F NMR ($CDCl_3$ and MeOD): δ −80.0 (m, 3F, F-e), −81.2 (m, 3F, F-a), −81.3 (m, 2F, F-c), −83 to −93 (m, 2F, F-h), −83.8 (m, 1F, F-f), −129.4 (s, 2F, F-b), −144.7 (m, 1F, F-d), −144.3 to −145.5 (m, 1F, F-g).

Anal. Calcd for $C_{14}H_{12}O_8F_{16}$: C, 27.46; H, 2.01. Found: C, 26,91; H, 2.60.

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