Organofluorine Compounds and Fluorinating Agents; 20:[1] The Nucleophilic Perfluoroalkylation of Sugar Aldehydes Using a Sonochemical Barbier-Type Reaction

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Abstract: A convenient synthesis of *C*-perfluoroalkylated carbohydrates **2a–c** and **3a–c** based on a sonochemical Zn-mediated reaction of the sugar aldehyde **1** with perfluoroalkyl iodides (C_4F_9I, $C_6F_{13}I$, $C_8F_{17}I$) has been developed. Stirring or reflux at 120°C gives no detectable products and hence the application of ultrasound is crucial. The obtained carbohydrate derivatives were stepwise deprotected (intermediates **6a–c**) to the amphiphilic mesogenic compounds **7a–c** consisting of a sugar moiety with free hydroxyl groups and a perfluoroalkyl tail directly attached to a sugar carbon. Moreover, the amphiphiles **7a–c** were peracetylated to the furanose **8** and the pyranose **9**, respectively.

Key words: carbohydrates, amphiphiles, mesogens, perfluoroalkylation, ultrasound

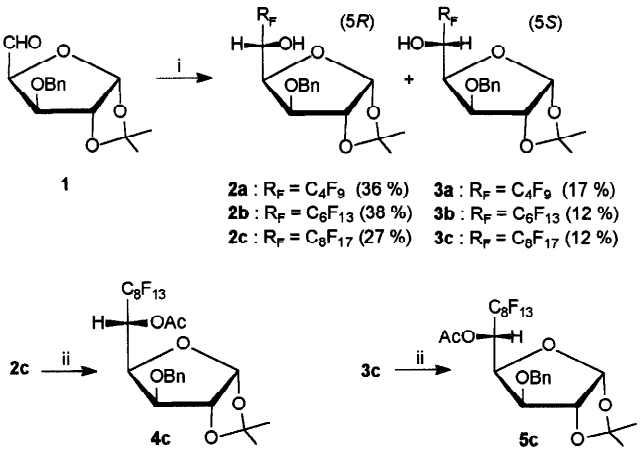
Perfluoroalkylated monosaccharides which contain the strongly hydrophobic perfluoroalkyl chain and a biocompatible polar head group should be useful surfactants and emulsifiers for biomedical applications.[2] The sugar moiety may allow specific *in vivo* recognition and hence such substances may be capable of drug targeting.[3] On the other hand, such amphiphilic compounds may have interesting liquid-crystalline properties; however, mesogenic properties of perfluoroalkylated carbohydrate amphiphiles have not been described so far.

Perfluoroalkyl halides are readily available and reactive reagents for the nucleophilic introduction of perfluoroalkyl chains into organic molecules.[4] Recently, we reported on two methods of introducing perfluoroalkyl chains into carbohydrates, namely the dithionite-catalyzed addition of perfluoroalkyl iodides to unsaturated carbohydrates[1] and the non-conventional acetalation of pyranosides with perfluoroalkanals.[5,6] A further method presented in this paper is aimed at the synthesis of amphiphilic perfluoroalkyl substituted carbohydrates with a stable C–C bond between the sugar moiety and the perfluoroalkyl tail.

Numerous publications describe fluorinated organometallics as synthetic intermediates for the perfluoroalkylation of organic molecules (References 4, 7 and literature cited therein). Thus, perfluoroalkyltrimethylsilanes[8,9] and perfluoroalkylmagnesium reagents[10] have been used for that purpose. Because the latter are rather unstable, it is favourable to generate these reagents in situ by a metal-halogen-exchange reaction.[4,11] Portella at al.[12] have used these reagents in carbohydrate chemistry.

The in situ generation of an organometallic reagent in the presence of the substrate (Barbier-type reactions) has been applied for perfluoroalkylations with fluoro-substituted organozinc reagents.[13,14] Kitazume and Ishikawa[13] found that ultrasonic agitation is suitable to shorten the reaction time and to increase the yield in such perfluoroalkylations. Cavitational effects result in cleaning of surfaces and the erosion of solids.[15] Moreover, ultrasound promotes reactions on metal surfaces owing to cavitation.

We report here the perfluoroalkylation of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylopentodialdo-1,4-furanose (**1**)[16,17] with perfluorobutyl, perfluorohexyl or perfluorooctyl iodide in the presence of zinc (solvent: DMF). In the course of each reaction two diastereomeric products were formed, i.e. the epimers **2a**/**3a**, **2b**/**3b** and **2c**/**3c**. The crystalline (5*R*)-diastereomers **2a**, **2b**, and **2c** could be chromatographically separated from the corresponding syrupy (5*S*)-diastereomers **3a**, **3b**, and **3c** (Scheme 1, Table 2). The ratios of the corresponding (5*R*)- to (5*S*)-epimers were after the chromatographic separation 2.1 : 1 (**2a**/**3a**), 3.2 : 1 (**2b**/**3b**), and 2.3 : 1 (**2c**/**3c**), respectively.



i) R_FI/Zn/DMF, sonication, r.t., 1.5–8 h; ii) Ac_2O/pyridine, r.t., 12 h

Scheme 1

The influence of ultrasonic agitation on the outcome of the reaction was tested under several reaction conditions (Table 1). Hardly any product could be detected by stirring at room temperature or at 120°C, even after using prolonged reaction times. The overall yields were higher with the shorter chain perfluoroalkyl iodides and increased with the sound intensity in the investigated range. Thus, in a 35 kHz ultrasonic cleaning bath the yield was much better than under stirring; with a 850 kHz focused

high-frequency bath it increased somewhat. However, the experimental data are not sufficient to give a general statement on the frequency effect. The best yields could be obtained with a 20 kHz probe system, where the ultrasonic transducer can be directly immersed into the reaction mixture and which is much more intensive than a cleaning bath system. It is not possible to increase the power input beyond a certain value because decoupling occurs and the sonochemical effect decreases sharply.[18] For the reaction a reactor system was used which allowed the immersion of the transducer under argon and intensive cooling at the same time.[18]

Table 1. Overall Yields in the Nucleophilic Perfluoroalkylations of **1** with Perfluoroalkyl Iodides Depending on the Reaction Conditions

Conditions	Yield (%)		
	2a and **3a**[a]	**2b** and **3b**[b]	**2c** and **3c**[c]
stirring; r.t.	7	–	<1
stirring; 120°C	–	<1	<1
ultrasonic bath; 35 kHz	35	22	20
ultrasonic probe; 20 kHz, 120 W	53	50	39
ultrasonic probe; 20 kHz, 60 W	–	35	–
ultrasonic bath; 850 kHz	43	–	–

[a] Reaction time 1.5 h.
[b] Reaction time 3 h.
[c] Reaction time 8 h.

The structures of the products **2a–c** and **3a–c** are supported by their ^{1}H, ^{13}C, and ^{19}F NMR spectra, respectively. Thus, the perfluoroalkyl chain is represented by ^{19}F signals for the CF_2-groups in the range of $\delta = -127$ to -105 and the signal for the CF_3-group at about – 80. In the ^{13}C NMR spectra of the compounds the signals for the C-5 carbon atoms appear as double doublets with coupling constants of about 22 and 29 Hz, because of their coupling with the neighbouring F-atoms. Because the $J_{4,5}$ coupling constants of **2a–c** and **3a–c** were not exactly observable in the ^{1}H NMR spectra owing to overlapping signals, the epimers **2c** and **3c** were acetylated to **4c** and **5c**, respectively (Scheme 1). The relatively small $J_{4,5}$ couplings of **4c** (3.1 Hz**)** indicate a (5*R*) configuration, the large $J_{4,5}$ couplings of **5c** (12.2 Hz) correlate with a (5*S*) configuration. In addition, the NOESY-spectrum of the derivative **3a** recorded in DMSO-d_6 did show weak cross peaks between the OH-proton in position 5 and the H-3 as well as between the H-1 and H-5 protons expected for a (5*R*) configuration. Consequently, the minor products **3a–c** are D-*gluco* configurated and the major diastereomers **2a–c** are L-*ido* configurated. To support this stereochemical assignment additionally, NMR data of 5-C-substituted (non-fluorinated) 3-*O*-methyl- and 3-*O*-benzyl-1,2-*O*-isopropylidene-L-ido- and D-glucofuranoses reported in the literature were used.[19,20]

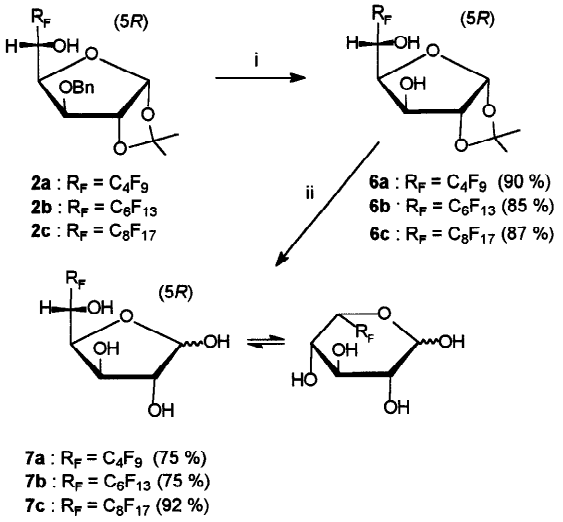
The debenzylation of **2a–c** to **6a–c** by hydrogenation in the presence of palladium on charcoal required fairly long reaction times, i.e. the neighbouring perfluoralkyl group reduces significantly the reactivity of the benzylic ether function. In comparison the isopropylidene moiety could be removed without difficulties yielding the fully deprotected 5-*C*-(perfluoroalkyl)-D-xyloses **7a–c** (Scheme 2, Table 2). It is noticeable that these amphiphilic products are liquid crystals forming *smectic* A phases. The thermal behaviour was investigated by polarising microscopy and DSC measurements (for more details see Ref. 21).

The NMR data of the three amphiphilic L-idoses **7a–c** correspond as expected in various details with the published ^{1}H[22,23] and ^{13}C NMR data[23,24] of D-idose. However, because of the overlapping of numerous α/β-pyranose and

Table 2. Compounds **2a–c**, **3a–c**, **4c**, **5c**, **6a–c**, **7a–c**, **8**, and **9** Prepared

Substrate	Product[a]	Yield g (%)	mp (°C) (solvent)	$[\alpha]_D^{22}$ (c)[b]	R_f[c]
1	**2a**	1.79 (36)	56–58 (hexane)	–31.9 (1.24)	0.66
	3a	0.85 (17)	syrup	–29.8 (1.12)	0.74
1	**2b**	2.27 (38)	59–60 (hexane)	–26.5 (1.17)	0.57
	3b	0.72 (12)	syrup	–24.9 (1.19)	0.66
1	**2c**	1.85 (26.5)	84–85 (heptane)	–23.2 (1.01)	0.55
	3c	0.87 (12.5)	syrup	–21.7 (1.07)	0.64
2c	**4c**	0.44 (95)	65–67 (heptane)	–9.4 (1.10)	0.55[d]
3c	**5c**	0.37 (88)	70–71 (heptane)	–18.2 (1.12)	0.69[d]
2a	**6a**	0.61 (90)	120–124 (hexane/EtOAc)	–5.1 (1.12)	0.41
2b	**6b**	1.2 (85)	130–131 (hexane/EtOAc)	–6.2 (1.09)	0.30
2c	**6c**	0.59 (87)	143–145 (hexane/EtOAc)	–10.1 (1.03)[e]	0.22
6a	**7a**	0.24 (75)	145–148[f] (heptane/acetone)	–	0.41[g]
6b	**7b**	0.92 (88)	163–166[f] (heptane/acetone)	–	0.36[g]
6c	**7c**	0.21 (92)	174–176[f] (heptane/acetone)	–	0.30[g]
7b	**8**	0.05 (22)	syrup	–26.8 (1.14)	0.59[h]
	9	0.09 (37)	syrup	+49.0 (0.50)	0.51[h]

[a] Satisfactory microanalyses obtained: C ± 0.33, H ± 0.21 (Exception: **3c**, C –0.57).
[b] $CHCl_3$.
[c] Toluene/EtOAc (3:1).
[d] Heptane/EtOAc (5:1).
[e] Acetone.
[f] Clearing points: **7a**, 126–137°C (S_A-phase, monotropic), **7b**, 159–168°C (S_A-phase, enantiotropic), **7c**, 188–192°C (S_A-phase, enantiotropic).
[g] Toluene/EtOAc (1:2).
[h] Heptane/EtOAc (1:1).



i) H_2/Pd-C/EtOH/MeOH, r.t. 70–96 h; ii) 90% TFA, r.t., 6–20 h

Scheme 2

α/β-furanose signals the ^{1}H and ^{13}C NMR spectra of the amphiphiles **7a–c** could not be evaluated in detail. The ^{1}H NMR spectra of **7a–c** recorded in acetone-d_6/D_2O show the existence of the anomeric pyranose and furanose forms by displaying four different H-1 signals (Table 3). To assign these signals, first of all the corresponding C-1 signals were evaluated by comparison of the ^{13}C NMR spectra of **7a–c** with the C-1 data of the four anomeric D-idoses (furanoses α/β:δ = 103.1/96.8; pyranoses α/β:δ = 94.4/93.7).[23] The chemical shifts and splittings of the anomeric protons of **7a–c** assigned by a ^{1}H,^{13}C-COSY experiment using the C-1 data correspond to those of the D-idofuranoses (α:δ = 5.19, $J_{1,2}$ = 1.3 Hz; β:δ = 5.41, $J_{1,2}$ = 4.3 Hz) and D-idopyranoses (α:δ = 4.97, $J_{1,2}$ = 6.0 Hz; β:δ = 5.05, $J_{1,2}$ = 1.6 Hz) as well.[22,23] Integration of the H-1 signals shows that in acetone-d_6/D_2O the amount of furanoses is unusually high (Table 3). However, this result is not surprising for *ido*-configurated sugars since Angyal [25,26] has observed high concentration of furanoses (25–32%) in the equilibrium of unprotected D-idose as well. Both the pyranose forms have such unfavourable interactions that the furanoses, although also disfavoured, become important contributors to the equilibrium.[25] In the case of **7a–c**, the perfluoroalkyl chains seem to favour additionally the furanose form (see also Ref. 21).

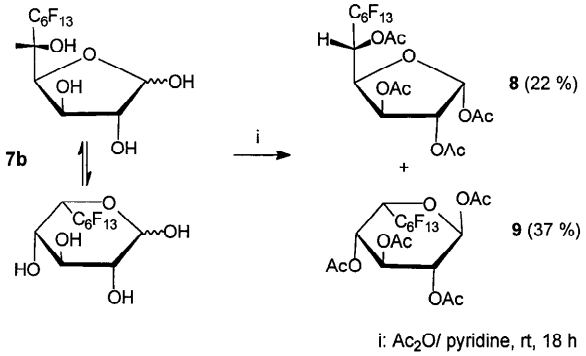
To support the L-*ido* configuration of the diastereomers **2a–c**, **6a–c**, and **7a–c**, the unprotected sugar **7b** was subjected to acetylation (Scheme 3). Two main products, **8** and **9**, were separated and characterized by NMR-spectroscopic investigations. For the furanose **8** no coupling was observable between H-1 and H-2, the coupling constant between H-2 and H-3 was likewise very small (1.6 Hz) indicating the β-furanose configuration.

As expected, the H-4,H-5-coupling constant of the pyranose **9** ($J_{4,5}$ ≈ 2.9 Hz) does not correspond to a D-*gluco*-derivative which should adopt a $^4C_1$-conformation and give a significantly larger $J_{4,5}$ value. The ^{1}H NMR data of

Table 3. Composition of the Pyranose/Furanose Mixtures of the Amphiphiles **7a–c** in Acetone-d_6

Product	Anomeric form	Concentration (%)	δ (H-1)[a]	$J_{1,2}$ (Hz)	δ (C-1)[b]
7a	α-pyranose	12.0	5.12	≈1	96.0
	β-pyranose	29.2	5.01	≈1	93.6
	α-furanose	24.0	5.36	4.3	96.1
	β-furanose	34.8	5.15	1.8	102.6
7b	α-pyranose	12.1	5.15	1.2	96.0
	β-pyranose	29.5	5.04	<1	93.6
	α-furanose	22.0	5.38	4.3	96.1
	β-furanose	36.3	5.18	1.4	102.6
7c	α-pyranose	20.7	5.14	1.2	95.7
	β-pyranose	26.7	5.03	<1	93.2
	α-furanose	20.3	5.37	4.3	95.7
	β-furanose	32.3	5.17	1.6	102.1

[a] ^{1}H NMR (250 MHz).
[b] ^{13}C NMR (62 MHz).



Scheme 3

9 correspond to an α-L-*ido*-diastereomer which adopts a distorted boat conformation ($b_{0,3}$). In such a conformation, the relatively stiff perfluoroalkyl chain as well as the acetyl groups in 1-, 2-, and 3-position are quasi-equatorially arranged. Therefore, the H-2, H-3 and H-4 ring protons are approximately *trans*-diaxial oriented to each other which is indicated by relatively large coupling constants ($J_{2,3}$ ≈ 7.6 Hz, $J_{3,4}$ ≈ 7.5 Hz). The coupling constants $J_{1,2}$ ≈ 4.5 Hz and $J_{4,5}$ ≈ 2.9 Hz are also in good agreement with the assumed conformation of **9**. Additionally, the chemical shift of δ = 6.45 indicates an equatorial position for the H-1, corresponding to an α-L-*ido* configuration.

In summary the generation of the L-*ido*-products **2a–c** is significantly favoured over the corresponding D-*gluco*-epimers **3a–c** in sonochemical Zn-mediated nucleophilic additions of 1-iodoperfluoroalkanes to the sugar aldehyde **1**. Furthermore, it is noticeable that the equilibrium mixtures of the amphiphilic 5-*C*-perfluoroalkylated sugars **7a–c** contain unusually high parts of the anomeric furanoses and that the corresponding pyranoses prefer a conformation between $^4C_1$ and $^1C_4$ with a quasi-equatorial arrangement of the perfluoroalkyl chain (see also Ref. 21).

Solvent systems are given in v/v. ^{1}H and ^{13}C {^{1}H} NMR: Bruker AC 250; internal standard TMS, *J* values in Hz. ^{19}F {^{1}H} NMR: external standard $CFCl_3$. To acetone-d_6 as NMR solvent three drops of D_2O were added. TLC: silica gel foils 60 F_{254} (Merck). Column chromatography: silica gel 60 (63–200 μm) (Merck). Melting points: Polarising microscope Leitz Laborlux 12 Pol equipped with a hot stage Mettler FP 90. Sonications were performed with a) ultrasonic bath, Bandelin Sonorex 102 H, 35 kHz; 2 × 120 W electrical power input; b) immersion probe, Vibracell VX 400, 20 kHz, probe ∅ 13 mm, 120 W (setting 30%) or 60 W (setting 15%) electrical power input; c) ultrasonic bath, UST Meinhardt, K 80/5, 850 kHz, focus transducer, 100 W (power setting 4) electrical power input.

Perfluoroalkylation of 1; General Procedure A:
To a solution of **1**[17] (2.78 g, 10 mmol) in anhyd DMF (15 mL) was added zinc dust (1.34 g, 20 mmol) under an argon atmosphere. Then the mixture was sonicated (immersion probe, electrical power input 120 W/setting 30%) and the corresponding perfluoroalkyl iodide (20 mmol) was added. After a short induction period the reaction became strongly exothermic and decoupling may occur. In this case the sonication had to be switched off for some minutes. When the starting material had disappeared (TLC control, eluent: toluene/EtOAc, 3:1), the reaction mixture was poured into 2% aq HCl (50 mL). After extraction with Et_2O (100 mL) the separated organic phase was successively washed with satd aq solution of NH_4Cl (50 mL), a 10% aq solution of $Na_2S_2O_3$ (50 mL), and brine (50 mL). The Et_2O phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Subsequently, the syrupy residue was purified by column chromatography (eluent: toluene/EtOAc, 15:1).

Acetylation of 2a–c; General Procedure B (cf. Ref. 27):
To an ice cooled solution of the sugar **2** (1.0 mmol) in Ac_2O (1.5 mL) was added pyridine (1.5 mL) and the mixture was allowed to warm up to r.t. and allowed to stand overnight. After addition of Et_2O (10 mL), the organic phase was separated and washed with satd aq citric acid solution (2 × 5 mL), satd aq NH_4Cl solution (5 mL), and brine (5 mL). Then, the organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Traces of pyridine were removed by co-distillation with $CHCl_3$/toluene (7:3). The residue was purified by column chromatography (eluent: heptane/EtOAc, 5:1).

Debenzylation of 2a–c; General Procedure C (cf. Ref. 28):
3-*O*-Benzyl derivative **2a**, **2b**, or **2c** (1.0 mmol) was dissolved in EtOH/MeOH 1:1 (5 mL), 10% Pd/C (0.03 g) was added and the mixture stirred under H_2 at r.t. until the starting material had disappeared. After filtration and evaporation of the solvents under reduced pressure, the obtained white solid was purified by column chromatography and/or recrystallization.

Deisopropylidenation of 6a–c; General Procedure D (cf. Ref. 29):
The 1,2-*O*-isopropylidene derivative **6a**, **6b**, or **6c** (0.5 mmol) was dissolved in 90% TFA (5 mL) and the mixture was stirred at r.t. until the starting material had disappeared (approx. 6–20 h; monitored by TLC). Then the mixture was codistilled under reduced pressure in a rotary evaporator with toluene (3 or 4 × 10 mL) in order to remove TFA and H_2O. The residue was purified by chromatography and/or recrystallization.

(5R)-3-O-Benzyl-1,2-O-isopropylidene-5-C-perfluorobutyl-α-D-xylofuranose (**2a**) and *(5S)-3-O-Benzyl-1,2-O-isopropylidene-5-C-perfluorobutyl-α-D-xylofuranose* (**3a**): Compound **1**[17] (2.78 g, 10 mmol) was reacted with perfluorobutyl iodide (6.92 g, 3.4 mL, 20 mmol) according to the general procedure A (reaction time: 1.5 h). After column chromatographic separation, the crystalline 5*R*-product **2a** and the syrupy 5*S*-product **3a** were isolated (Table 2).

2a:
^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25, 1.41 (s, 3 H, CH_3), ≈ 3.13 (br, 1 H, OH), 4.00 (m, 1 H, H-3), 4.40 (m, 1 H, H-4), 4.43 (d, 1 H, *J* = 11.5 Hz, CH_2Ph), 4.47 (m, 1 H, H-5), 4.55 (d, 1 H, $J_{1,2}$ = 4.0 Hz, H-2), 4.61 (d, 1 H, CH_2Ph), 5.91(d, 1 H, $J_{1,2}$ = 4.0 Hz, H-1), 7.19–7.31 (m, 5 H, C_6H_5).
^{13}C NMR (62 MHz, $CDCl_3$) : δ = 26.3, 26.8 (CH_3), 67.6 (dd, $J_{C\text{-}5,F}$ = 21.5 Hz, $J_{C\text{-}5,F'}$ = 29.3 Hz, C-5), 72.4 (*C*H_2Ph), 75.7 (C-4), 82.0 (C-2), 83.2 (C-3), 105.0 (C-1), 112.6 [$C(CH_3)_2$], 105–120 (m, 3 CF_2, CF_3), 127.9, 128.4, 128.7, 136.4 (C_6H_5).
^{19}F NMR (235 MHz, $CDCl_3$): δ = –127.6 to –124.2 (m, 3 F, CF_2), –122.7 to –122.6 (m, 2 F, CF_2), –120.3 to –119.0 (m, 1 F, CF_2CH_2), –80.7 (CF_3).
MS (70 eV): *m*/*z* = 499 (M^+ + H).
3a:
^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.26, 1.42 (s, 3 H, CH_3), 4.22 (m, 3 H, H-3, H-5, OH), 4.30 (m, 1 H, H-4), 4.48 (d, 1 H, *J* = 11.0 Hz, CH_2Ph), 4.56 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-2), 4.60 (d, 1 H, *J* = 11.0 Hz, CH_2Ph), 5.94 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1), 7.18–7.34 (m, 5 H, C_6H_5).
^{13}C NMR (62 MHz, $CDCl_3$) : δ = 26.1, 26.6 (CH_3), 69.9 (dd, $J_{C\text{-}5,F}$ = 21.9 Hz, $J_{C\text{-}5,F'}$ = 25.8 Hz, C-5), 72.8 (*C*H_2Ph), 74.8 (C-4), 81.8 (C-2), 84.7 (C-3), 104.6 (C-1), 112.2 [$C(CH_3)_2$], 105 –120 (m, 3 CF_2, CF_3), 128.2, 128.7, 128.8, 135.8 (C_6H_5).
^{19}F NMR (235 MHz, $CDCl_3$): δ = –127.6 to – 123.9 (m, 3 F, CF_2), –122.7 to –122.4 (m, 2 F, CF_2), –120.0 to –118.7 (m, 1 F, CF_2CH_2), –80.7 (CF_3).
MS (70 eV): *m*/*z* = 499 (M^+ + H).

(5R)-3-O-Benzyl-1,2-O-isopropylidene-5-C-perfluorohexyl-α-D-xylofuranose (**2b**) and *(5S)-3-O-Benzyl-1,2-O-isopropylidene-5-C-perfluorohexyl-α-D-xylofuranose* (**3b**): Compound **1**[17] (2.78 g, 10 mmol) was reacted with perfluorohexyl iodide (8.92 g, 4.3 mL, 20 mmol) according to the general procedure A (reaction time: 3 h). After column chromatographic separation the crystalline 5*R*-product **2b** and the syrupy 5*S*-product **3b** were isolated (Table 2).
2b:
^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25, 1.41 (s, 3 H, CH_3), ≈ 3.14 (br, 1 H, OH), 4.00 (m, 1 H, H-3), 4.40 (m, 1 H, H-4), 4.43 (d, 1 H, *J* = 11.3 Hz, CH_2Ph), 4.47 (m, 1 H, H-5), 4.56 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-2), 4.61 (d, 1 H, *J* = 11.3 Hz, CH_2Ph), 5.91(d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1), 7.20–7.30 (m, 5 H, C_6H_5).
^{13}C NMR (62 MHz, $CDCl_3$) : δ = 26.3, 26.8 (CH_3), 67.6 (dd, $J_{C\text{-}5,F}$ = 21.0 Hz, $J_{C\text{-}5,F'}$ = 29.7 Hz, C-5), 72.4 (*C*H_2Ph), 75.7 (C-4), 82.0 (C-2), 83.1 (C-3), 104.9 (C-1), 112.6 [$C(CH_3)_2$], 105 –120 (m, 5 CF_2, CF_3), 128.4, 128.6, 128.9, 136.4 (C_6H_5).
^{19}F NMR (235 MHz, $CDCl_3$): δ = –127.2 to –124.4 (m, 3 F, CF_2), –122.6 to –121.7 (m, 6 F, CF_2), –120.1 to – 118.9 (m, 1 F, CF_2CH_2), –80.6 (CF_3).
MS (CI-isobutane): *m*/*z* = 599 (M^+ + H).
3b:
^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.26, 1.42 (s, 3 H, CH_3), 4.29 (m, 3 H, H-3, H-5, OH) 4.38 (m, 1 H, H-4), 4.56 (d, 1 H, *J* = 11.0 Hz, CH_2Ph), 4.64 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-2), 4.68 (d, 1 H, *J* = 11.0 Hz, CH_2Ph), 5.94 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1), 7.20–7.30 (m, 5 H, C_6H_5).
^{13}C NMR (62 MHz, $CDCl_3$) : δ = 26.1, 26.6 (CH_3), 70.0 (dd, $J_{C\text{-}5,F}$ = 22.0 Hz, $J_{C\text{-}5,F'}$ = 26.7 Hz, C-5), 72.8 (*C*H_2Ph), 74.8 (C-4), 81.8 (C-2), 84.7 (C-3), 104.6 (C-1), 112.2 [*C*$(CH_3)_2$], 105–120 (m, 5 CF_2, CF_3), 128.2, 128.7, 128.9, 135.8 (C_6H_5).
^{19}F NMR (235 MHz, $CDCl_3$): δ = –126.1 to –125.0 (m, 3 F, CF_2), –122.4 to –121.5 (m, 6 F, CF_2), –119.8 to –118.6 (m, 1 F, CF_2CH_2), –80.5 (CF_3).
MS (CI-isobutane): *m*/*z* = 599 (M^++H).

(5R)-3-O-Benzyl-1,2-O-isopropylidene-5-C-perfluorooctyl-α-D-xylofuranose (**2c**) and *(5S)-3-O-Benzyl-1,2-O-isopropylidene-5-C-perfluorooctyl-α-D-xylofuranose* (**3c**): Compound **1**[17] (2.78 g, 10 mmol) was reacted with perfluorooctyl iodide (10.92 g, 20 mmol), dissolved

in anhyd DMF (2 mL) according to the general procedure A (reaction time: 8 h). After column chromatographic separation, the crystalline 5*R*-product **2c** and the syrupy 5*S*-product **3c** were isolated (Table 2).

2c:

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25, 1.41 (s, 3 H, CH_3), ≈ 3.16 (br, 1 H, OH), 4.00 (m, 1 H, H-3), 4.40 (m, 1 H, H-4), 4.42 (d, 1 H, J = 11.6 Hz, CH_2Ph), 4.47 (m, 1 H, H-5), 4.56 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-2), 4.61 (d, 1 H, J = 11.6 Hz, CH_2Ph), 5.91 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1), 7.18–7.30 (m, 5 H, C_6H_5).

^{13}C NMR (62 MHz, $CDCl_3$) : δ = 26.3, 26.8 (CH_3), 67.6 (dd, $J_{C\text{-}5,F}$ = 21.5 Hz, $J_{C\text{-}5,F'}$ = 28.7 Hz, C-5), 72.4 (CH_2Ph), 75.8 (C-4), 82.1 (C-2), 83.2 (C-3), 104.9 (C-1), 112.6 [C(CH_3)$_2$], 105 –120 (m, 7 CF_2, CF_3), 128.2, 128.7, 129.0, 136.5 (C_6H_5).

^{19}F NMR (235 MHz, $CDCl_3$): δ = –126.2 to –125.0 (m, 3 F, CF_2), –122.5 to –121.7 (m, 10 F, CF_2), –120.1 to – 118.9 (m, 1 F, CF_2CH_2), –80.7 (CF_3).

MS (CI-isobutane): m/z = 699 (M^+ + H).

3c:

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.26, 1.42 (s, 3 H, CH_3), 4.20 (m, 3 H, H-3, H-5, OH), 4.31 (m, 1 H, H-4), 4.49 (d, 1 H, J = 11.0 Hz, CH_2Ph), 4.56 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-2), 4.60 (d, 1 H, J = 11.0 Hz, CH_2Ph), 5.95 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1), 7.20–7.31 (m, 5 H, C_6H_5).

^{13}C NMR (62 MHz, $CDCl_3$) : δ = 26.1, 26.6 (CH_3), 69.9 (dd, $J_{C\text{-}5,F}$ = 22.5 Hz, $J_{C\text{-}5,F'}$ = 25.8 Hz, C-5), 72.8 (CH_2Ph), 74.8 (C-4), 81.8 (C-2), 84.7 (C-3), 104.6 (C-1), 112.1 [C(CH_3)$_2$], 105 –120 (m, 7 CF_2, CF_3), 128.2, 128.7, 128.8, 135.8 (C_6H_5).

^{19}F NMR (235 MHz, $CDCl_3$): δ = –127.8 to –124.8 (m, 3 F, CF_2), –123.6 to –121.6 (m, 10 F, CF_2), –117.9 to –116.7 (m, 1 F, CF_2CH_2), –81.3 (CF_3).

(5R)-5-O-Acetyl-3-O-benzyl-1,2-O-isopropylidene-5-C-perfluorooctyl-α-D-xylofuranose (**4c**): Compound **2c** (0.43 g, 0.62 mmol) was acetylated with Ac_2O/pyridine as described in the general procedure B. After column chromatographic separation (R_f = 0.55, eluent: heptane/EtOAc, 5 : 1), the crystalline product **4c** was isolated (Table 2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.31, 1.50 (s, 3 H, CH_3), 2.04 (s, 3 H, $COCH_3$), 4.03 (dd, 1 H, $J_{3,4}$ = 3.7 Hz, $J_{4,5}$ = 3.1 Hz, H-4), 4.48 (d, 1 H, J = 11.3 Hz, CH_2Ph), 4.51 (dd, 1 H, $J_{2,3}$ = 8.5 Hz, H-3), 4.62 (d, 1 H, J = 11.3 Hz, CH_2Ph), 4.62 (dd, 1 H, $J_{1,2}$ = 4.0 Hz, H-2), 5.90 (d, 1 H, $J_{1,2}$ = 4.0 Hz, H-1), 6.15 (ddd, 1 H, $J_{5,F}$ = 20.0 Hz, $J_{5,F'}$ = 8.4 Hz, H-5), 7.26–7.39 (m, 5 H, C_6H_5).

^{13}C NMR (62 MHz, $CDCl_3$) : δ = 20.6 (COCH_3), 26.6, 27.1 [C(CH_3)$_2$], 66.0 (dd, $J_{C\text{-}5,F}$ = 20.9 Hz, $J_{C\text{-}5,F'}$ = 30.3 Hz, C-5), 72.6 (CH_2Ph), 76.1 (C-3), 82.6 (C-4), 82.7 (C-2), 104.8 (C-1), 112.5 [C(CH_3)$_2$], 105–120 (m, 7 CF_2, CF_3), 128.3, 128.4, 128.8, 137.0 (C_6H_5), 168.7 (COCH_3).

^{19}F NMR (235 MHz, $CDCl_3$): δ = –125.8 (s, 2 F, CF_2CF_3), –123.6 to –119.9 (m, 11 F, CF_2), –118.6 to –117.0 (m, 1 F, CF_2CH_2), –80.6 (CF_3).

(5S)-5-O-Acetyl-3-O-benzyl-1,2-O-isopropylidene-5-C-perfluorooctyl-α-D-xylofuranose (**5c**): Compound **3c** (0.40 g, 0.57 mmol) was acetylated with Ac_2O/pyridine as described in the general procedure B. After column chromatographic separation (R_f = 0.69, eluent: heptane/EtOAc, 5 : 1), the crystalline product **5c** was isolated (Table 2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.31, 1.49 (s, 3 H, CH_3), 1.95 (s, 3 H, $COCH_3$), 3.98 (d, 1 H, $J_{3,4}$ = 3.0 Hz, H-3), 4.46 (d, 1 H, J = 11.3 Hz, CH_2Ph), 4.53 (dd, 1 H, $J_{4,5}$ = 12.2 Hz, H-4), 4.54 (d, 1 H, J = 11.3 Hz, CH_2Ph), 4.54 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-2), 5.87 (m, 1 H, H-5), 5.94 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1), 7.26 –7.39 (m, 5 H, C_6H_5).

^{13}C NMR (62 MHz, $CDCl_3$) : δ = 20.1 (COCH_3), 26.3, 26.8 [C(CH_3)$_2$], 66.7 (dd, $J_{C\text{-}5,F}$ = 23.7 Hz, $J_{C\text{-}5,F'}$ = 27.3 Hz, C-5), 72.1 (CH_2Ph), 75.9 (C-4), 80.5 (C-3), 81.6 (C-2), 105.8 (C-1), 112.3 [C(CH_3)$_2$], 105–120 (m, 7 CF_2, CF_3), 128.2, 128.6, 128.7, 136.6 (C_6H_5), 167.3 (COCH_3).

^{19}F NMR (235 MHz, $CDCl_3$): δ = –125.9 (s, 2 F, CF_2CF_3), –122.5 (s, 2 F, CF_2), –121.4 (m, 10 F, CF_2), –120.2 to –116.3 (m, 2 F, CF_2CH_2), –80.6 (CF_3).

(5R)-1,2-O-Isopropylidene-5-C-perfluorobutyl-α-D-xylofuranose (**6a**): Compound **2a** (0.83 g, 1.66 mmol) was debenzylated according to the general procedure C (reaction time: 96 h). The residue was crystallized from hexane/EtOAc (colourless needles) (Table 2).

^{1}H NMR (250 MHz, acetone-d_6): δ = 1.29, 1.43 (s, 3 H, CH_3), 4.32 (m, 1 H, H-3), 4.39 (m, 1 H, H-4), 4.57 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-2), 4.70 (dddd, 1 H, $J_{5,F}$ = 22.7 Hz, $J_{5,F'}$ = 3.5 Hz, $J_{5,OH}$ = 1.8 Hz, H-5), ≈ 4.9 (br, 2 H, OH), 5.95 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1).

^{13}C NMR (62 MHz, acetone-d_6): δ = 26.6, 27.3 (CH_3), 68.5 (dd, $J_{C\text{-}5,F}$ = 20.8 Hz, $J_{C\text{-}5,F'}$ = 28.6 Hz, C-5), 76.5 (d, $J_{C\text{-}3,F}$ = 3.7 Hz, C-3), 77.5 (C-4), 86.6 (C-2), 105.6 (C-1), 112.5 [C(CH_3)$_2$], 110–122 (m, 3 CF_2, CF_3).

^{19}F NMR (235 MHz, acetone-d_6): δ = –128.2 to –124.4 (m, 3 F, CF_2), –123.1, –122.7 (s, 1 F, CF_2), –119.7 to –118.5 (m, 1 F, CF_2CH_2), –81.6 (CF_3).

(5R)-1,2-O-Isopropylidene-5-C-perfluorohexyl-α-D-xylofuranose (**6b**): Compound **2b** (1.64 g, 2.74 mmol) was debenzylated according to the general procedure C (reaction time: 70 h). The residue was crystallized from hexane/EtOAc (Table 2).

^{1}H NMR (250 MHz, acetone-d_6): δ = 1.29, 1.43 (s, 3 H, CH_3), 4.32 (m, 1 H, H-3), 4.39 (m, 1 H, H-4), 4.57 (d, 1 H, $J_{1,2}$ = 3.8 Hz, H-2), 4.63–4.79 (m, 1 H, H-5), ≈ 4.86 (br, 1 H, OH), ≈ 4.98 (br, 1 H, OH), 5.95 (d, 1 H, $J_{1,2}$ = 3.8 Hz, H-1).

^{13}C NMR (62 MHz, acetone-d_6): δ = 26.6, 27.3 (CH_3), 68.6 (dd, $J_{C\text{-}5,F}$ = 21.6 Hz, $J_{C\text{-}5,F'}$ = 28.1 Hz, C-5), 76.6 (d, $J_{C\text{-}3,F}$ = 4.0 Hz, C-3), 77.6 (C-4), 86.6 (C-2), 105.7 (C-1), 112.5 [C(CH_3)$_2$], 105–122 (m, 5 CF_2, CF_3).

^{19}F NMR (235 MHz, acetone-d_6): δ = –127.9 to –125.1 (m, 3 F, CF_2), –123.1, –122.8, –122.5 (s, 1 F, CF_2), –122.0 (s, 3 F, CF_2), –119.6 to –118.4 (m, 1 F, CF_2CH_2), –81.4 (CF_3).

(5R)-1,2-O-Isopropylidene-5-C-perfluorooctyl-α-D-xylofuranose (**6c**): Compound **2c** (0.78 g, 1.11 mmol) was debenzylated according to the general procedure C (reaction time: 84 h). The residue was crystallized from hexane/EtOAc (Table 2).

^{1}H NMR (250 MHz, acetone-d_6): δ = 1.29, 1.43 (s, 3 H, CH_3), 4.33 (m, 1 H, H-3), 4.39 (m, 1 H, H-4), 4.57 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-2), 4.62–4.78 (m, 1 H, H-5), ≈ 4.84 (br, 1 H, OH), ≈ 4.97 (br, 1 H, OH), 5.95 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1).

^{13}C NMR (62 MHz, acetone-d_6): δ = 26.6, 27.3 (CH_3), 68.6 (dd, $J_{C\text{-}5,F}$ = 21.7 Hz, $J_{C\text{-}5,F'}$ = 28.1 Hz, C-5), 76.6 (d, $J_{C\text{-}3,F}$ = 4.0 Hz, C-3), 77.6 (C-4), 86.6 (C-2), 105.7 (C-1), 112.5 [C(CH_3)$_2$], 105–122 (m, 7 CF_2, CF_3).

^{19}F NMR (235 MHz, acetone-d_6): δ = –126.4 to –125.0 (m, 3 F, CF_2), –122.9 (s, 1 F, CF_2), –122.1 to –121.9 (m, 9 F, CF_2), –119.5 to –118.4 (m, 1 F, CF_2CH_2), –81.4 (CF_3).

(5R)-5-C-Perfluorobutyl-D-xylose (**7a**): Compound **6a** (0.36 g, 0.89 mmol) was deacetylated according to the general procedure D (reaction time: 6 h). The residue was recrystallized from heptane/acetone (Table 2).

^{19}F NMR (235 MHz, $CDCl_3$): δ = –127.1 to –118.0 (m, 3 CF_2), –81.6 (CF_3) (see also Table 3).

(5R)-5-C-Perfluorohexyl-D-xylose (**7b**): Compound **6b** (1.14 g, 2.24 mmol) was deacetylated according to the general procedure D (reaction time: 20 h). The residue was recrystallized from heptane/acetone (Table 2).

^{19}F NMR (235 MHz, $CDCl_3$, $CFCl_3$): δ = –126.6 to –118.0 (m, 5 CF_2), –81.4 (CF_3) (see also Table 3).

(5R)-5-C-Perfluorooctyl-D-xylose (**7c**): Compound **6c** (0.25 g, 0.4 mmol) was deacetylated according to the general procedure D (reaction time: 20 h). The residue was recrystallized from heptane/acetone (Table 2).

^{19}F NMR (235 MHz, $CDCl_3$, $CFCl_3$): δ = –126.7 to –116.6 (m, 7 CF_2), –81.4 (CF_3) (see also Table 3).

(5R)-1,2,3,5-Tetra-O-acetyl-5-C-perfluorohexyl-β-D-xylofuranose (**8**) and *(5R)-1,2,3,4-Tetra-O-acetyl-5-C-perfluorohexyl-α-D-xylopyranose* (**9**)*:* To an ice cooled solution of **7b** (0.19 g, 0.4 mmol) in Ac_2O (0.7 mL) was added pyridine (0.7 mL) and the mixture was allowed to warm up to r.t. and allowed to stand overnight. After addition of Et_2O (10 mL) the organic phase was separated and washed with satd aq citric acid solution (5 mL), satd aq NH_4Cl solution (5 mL), and brine (5 mL). Then, the organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Traces of pyridine could be removed by codistillation with $CHCl_3$/toluene (7:3). The residue was purified by column chromatography (eluent: heptane/EtOAc, 5:1) yielding the syrupy β-furanose **8**, and the syrupy α-pyranose **9** (Table 2).

8*:*

^{1}H NMR (250 MHz, acetone-d_6): δ = 2.09, 2.10, 2.10, 2.12 (s, 3 H, CH_3), 4.76 (dd, $J_{3,4}$ = 5.7 Hz, $J_{4,5}$ = 8.3 Hz, 1 H, H-4), 5.17 (d, 1 H, $J_{2,3}$ = 1.6 Hz, H-2), 5.35 (ddd, 1 H, $J_{3,5}$ = 2.8 Hz, H-3), 5.97–6.10 (m, 1 H, H-5), 6.03 (s, 1 H, H-1),

^{13}C NMR (62 MHz, acetone-d_6): δ = 20.2, 20.3, 20.6, 20.9 (CH_3), 65.4 (dd, $J_{C\text{-}5,F}$ = 20.0 Hz, $J_{C\text{-}5,F'}$ = 30.9 Hz, C-5), 74.1 (d, $J_{C\text{-}3,F}$ = 2.7 Hz, C-3), 77.0 (C-4), 79.6 (C-2), 97.6 (C-1), 105–122 (m, 5 CF_2, CF_3), 168.3, 169.0, 169.0, 169.2 (C=O).

^{19}F NMR (235 MHz, acetone-d_6): δ = –125.9 (s, 2 F, CF_2), –123.0 to –121.3 (m, 7 F, CF_2), –119.1 to –117.6 (m, 1 F, CF_2CH_2), –80.6 (s, 3 F, CF_3).

9:

^{1}H NMR (250 MHz, acetone-d_6): δ = 2.06, 2.07, 2.08, 2.20 (s, 3 H, CH_3), 4.91 (ddd, 1 H, $J_{3,4}$ = 7.5 Hz, $J_{4,5}$ = 2.9 Hz, $J_{4,F}$ = 1.5 Hz, H-4), 5.32 (dd, 1 H, $J_{1,2}$ = 4.5 Hz, $J_{2,3}$ = 7.6 Hz, H-2), 5.54 (dd, 1 H, $J_{2,3}$ = 7.6 Hz, $J_{3,4}$ = 7.5 Hz, H-3), 5.51–5.61 (m, 1 H, H-5), 6.45 (d, 1 H, $J_{1,2}$ = 4.5 Hz, H-1),

^{13}C NMR (62 MHz, acetone-d_6) : δ = 20.3, 20.4, 20.5, 20.8 (CH_3), 65.1 (dd, $J_{C\text{-}5,F}$ = 21.2 Hz, $J_{C\text{-}5,F'}$ = 26.8 Hz, C-5), 73.4 (C-3, C-4), 74.2 (C-2), 92.4 (C-1), 105–120 (m, 5 CF_2, CF_3), 168.2, 168.9, 169.6, 170.3 (C=O).

^{19}F NMR (235 MHz, acetone-d_6): δ = –126.1 to –116.3 (m, 10 F, CF_2), –80.6 (CF_3).

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