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Carbohydrate Research 318 (1999) 171–179

CARBOHYDRATE RESEARCH

Note

A convenient synthesis of fluoroalkyl and fluoroaryl glycosides using Mitsunobu conditions

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Received 8 February 1999; accepted 10 April 1999

Abstract

A new procedure for the synthesis of fluoroalkyl and fluoroaryl glycosides from primary, secondary, and tertiary fluoroalkyl alcohols and pentafluorophenol using Mitsunobu conditions is reported. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Glycosylation; Fluoroalkyl and fluoroaryl glycosides; Mitsunobu reaction

To date, fluoroalkyl glycosides have received moderate attention in carbohydrate chemistry. 1,1-Difluoroalkyl glucosides have been investigated as a new class of irreversible inhibitors of yeast α-glucosidase [1]; fluoroalkyl derivatives of *N*-acetylmuramyl-L-alanyl-D-isoglutamine were reported as immunogenic agents [2]. Perfluoroalkylated monosaccharides which contain the strongly hydrophobic perfluoroalkyl chain and a biocompatible polar head group were shown to be surfactants and emulsifiers for biomedical applications [3]. The sugar may allow specific in vivo recognition and hence such substances may be capable of drug targeting [4]. In other respects, such amphiphiles also display interesting thermotropic liquid-crystalline properties [5a,b]. In most cases, however, the fluorinated segment was separated from the sugar moiety by a two- or three-methylene spacer arm.

In contrast, fluoroalkyl glycosides with only one carbon between the fluoroalkyl moiety and O-1 are not common. For instance, trifluoroethyl glycosides have been isolated in low yields in solvolytic reactions of D-glucopyranosyl derivatives in trifluoroethanol [6]. Some years ago, Vasella and co-workers described the formation of fluoroalkyl glucosides through the insertion of a glycosylidene carbene—generated from an anomeric diazirine under thermal and/or photolytic conditions—into fluoroalkyl alcohols and pentafluorophenol [7,8]. However, the synthesis of the per(*O*-benzylated)-D-*gluco*-diazirine precursor requires five steps

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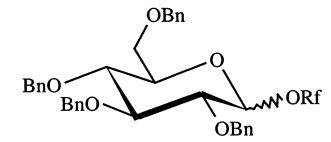
PII: S0008-6215(99)00089-0

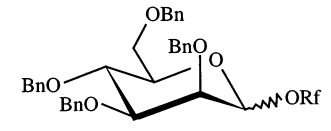
from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose and moreover this thermally unstable diazirine has to be stored at −25°C. This approach is therefore not really convenient from a synthetic point of view. More recently, the electrochemical condensation of fluorinated alcohols initiated by anodic oxidation of triphenylphosphine [9] or the radical addition of perfluoroalkyl iodides to double bonds using sodium dithionite as initiator [5b] were also shown to result in fluoroglycosides. Expectedly, the standard Koenigs–Knorr glycosidation approach gave poor results, thus reflecting the low nucleophilicity of highly fluorinated alcohols [10].

With a view to studying antimalarials with prolonged plasma half-life, we have recently investigated the preparation of fluoroalkyl acetals from dihydroartemisinin, a semisynthetic derivative of the natural diterpenic endoperoxide artemisinin [11]. We have thus observed that the best general method to prepare fluoroalkyl derivatives of this type of complex lactol was the Mitsunobu reaction whatever the class (primary, secondary or tertiary) of the fluorinated alcohol involved.

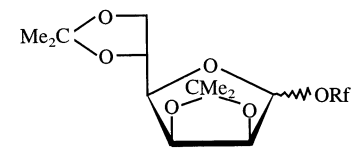
The efficiency of the Mitsunobu procedure in the case of fluoroalkoxylation has been previously reported by Falck et al. [12] for the synthesis of non-symmetric polyfluoroethers. The reaction was effective even with sterically hindered 1,1,1,3,3,3-hexafluoro-2-phenylisopropyl alcohol [13] and perfluoro-*tert*-butyl alcohol [14]. The low pK_a of fluorinated alco-



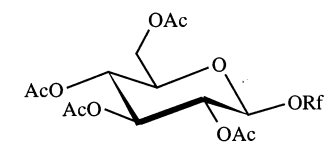
1a,b Rf = CH_2CF_3
2a,b Rf = $CH(CF_3)_2$
3 Rf = $C(Ph)(CF_3)_2$
4a,b Rf = C_6F_5



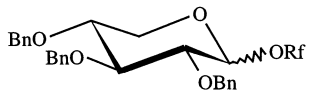
8a,b Rf = CH_2CF_3
9 Rf = $CH(CF_3)_2$



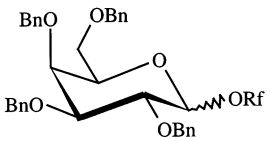
11 Rf = CH_2CF_3
12 Rf = $CH(CF_3)_2$
13 Rf = $C(Ph)(CF_3)_2$
14 Rf = C_6F_5
15a,b Rf = $C(Me)(CF_3)_2$



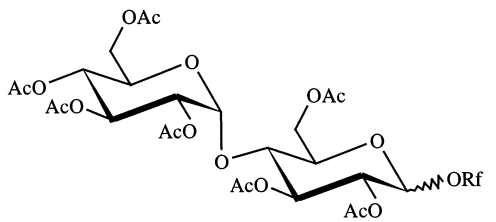
18 Rf = C_6F_5



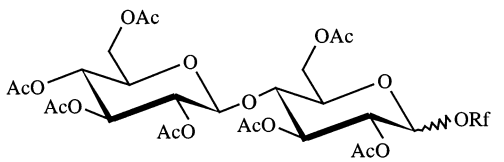
5a,b Rf = CH_2CF_3
6a,b Rf = $CH(CF_3)_2$
7 Rf = C_6F_5



10a,b Rf = CH_2CF_3



16a,b Rf = $CH(CF_3)_2$



17a,b Rf = $CH(CF_3)_2$

Scheme 1.

Table 1
Yields and physicochemical data for fluoralkyl and fluoralkyl glycosides **1–18**

Fluorinated glycosides	Formula	Eluent (petroleum ether–ethyl acetate)	Isolated yield (%)	M+H	α:β	$[\alpha]_D$ (*c* 1, $CHCl_3$) (°)	Mp (°C)	Elemental analyses	
								Calcd	Found
1a,b	$C_{36}H_{37}F_3O_6$	9:1	91	645 (M+Na)	20:80		[a]	C, 69.44; H, 5.99	C, 69.15; H, 5.65
2a,b	$C_{37}H_{36}F_6O_6$	19:1	97	691	15:85		[a]	C, 64.34; H, 5.25	C, 64.19; H, 5.18
3	$C_{43}H_{40}F_6O_6$	19:1	56	789 (M+Na)	100:0	+56	136	C, 67.35; H, 5.26	C, 67.73; H, 5.58
4a,b	$C_{40}H_{35}F_5O_6$	19:1	80 [b]	707	65:35		[a]	C, 67.98; H, 4.99	n.d. [c]
5a,b	$C_{28}H_{29}F_3O_5$	19:1	73	525 (M+Na)	80:20		[a]	C, 66.92; H, 5.82	C, 66.74; H, 5.71
6a,b	$C_{29}H_{28}F_6O_5$	9:1	79	571	15:85		[a]	C, 61.05; H, 4.95	n.d.
7	$C_{32}H_{27}F_5O_5$	19:1	29 [d]	587	100:0	+69	[a]	C, 65.52; H, 4.64	C, 65.68; H, 4.78
8a,b	$C_{36}H_{37}F_3O_6$	9:1	66	623	85:15		[a]	C, 69.44; H, 5.99	C, 69.24; H, 5.87
9	$C_{37}H_{36}F_6O_6$	19:1	50	691	0:100	+40	[a]	C, 64.34; H, 5.25	C, 64.62; H, 5.37
10a,b	$C_{36}H_{37}F_3O_6$	9:1	67	623	65:35		[a]	C, 69.44; H, 5.99	C, 69.59; H, 6.14
11	$C_{14}H_{21}F_3O_6$	19:1	85	365 (M+Na)	0:100	+47	51	C, 49.12; H, 6.18	C, 49.35; H, 6.31
12	$C_{15}H_{20}F_6O_6$	19:1	83	411	0:100	+50	[a]	C, 43.91; H, 4.91	C, 44.07; H, 5.04
13	$C_{21}H_{24}F_6O_6$	9:1	26	487	0:100	+11	[a]	C, 51.85; H, 4.97	C, 51.63; H, 4.79
14	$C_{18}H_{19}F_5O_6$	17:3	64	427	0:100	+10	[a]	C, 50.71; H, 4.49	C, 50.53; H, 4.34
15a,b	$C_{16}H_{22}F_6O_6$	19:1	31	425	15:85		[a]	C, 45.29; H, 5.23	C, 45.56; H, 5.42
16a,b	$C_{29}H_{36}F_6O_{18}$	3:2	97 [d]	787	25:75		[a]	C, 44.28; H, 4.61	n.d.
17a,b	$C_{29}H_{36}F_6O_{18}$	3:2	57 [d]	787	5:95		[a]	C, 44.28; H, 4.61	n.d.
18	$C_{20}H_{19}F_5O_{10}$	4:1	79	515	0:100	−10	145	C, 46.70; H, 3.72	C, 46.94; H, 3.83

[a] With the exception of **3**, **11** and **18**, which spontaneously crystallized, all compounds were obtained as syrups.
[b] Because of persistent C_6F_5OH contamination, the yield was estimated by ^1H NMR.
[c] n.d., not determined.
[d] Because of persistent $DEADH_2$ contamination, the yield was estimated by ^1H NMR.

Table 2
^{1}H NMR chemical shifts (δ in ppm) and coupling constants (J in Hz) for fluorinated glycosides of benzylated sugars

Fluorinated glycosides	H-1	H-2	H-3	H-4	H-5	H-6	R_f
1a	4.84, $J_{1,2}$ 3.9	3.63, $J_{2,3}$ 11.8	4.03, n.d. [a]	3.72, n.d.	3.80, n.d.	3.72, n.d.	3.93, $J_{H,F}$ 8.7
1b	4.53, $J_{1,2}$ 7.8	3.50, $J_{2,3}$ 8.6	3.70	3.75, $J_{4,5}$ 9.4	3.50, $J_{5,6a}$ 2.3	3.70, $J_{5,6b}$ 4.4	4.01, 4.28, $J_{H,H}$ 12.4, $J_{H,F}$ 8.7, $J_{H,F}$ 8.5
2a	4.99, $J_{1,2}$ 3.8	3.50	3.95	n.d.	n.d.	n.d.	n.d.
2b	4.50, $J_{1,2}$ 7.2	3.40, $J_{2,3}$ 8.0	3.50, n.d.	3.50, $J_{4,5}$ 9.3	3.30, $J_{5,6a}$ 2.3	3.50, $J_{5,6b}$ 4.5	n.d.
3	5.39, $J_{1,2}$ 3.5	3.69, $J_{2,3}$ 10.0	4.27, $J_{3,4}$10.0	3.92, $J_{4,5}$ 10.0	4.18, $J_{5,6a}$ 2.2	3.72, 3.94, $J_{6a,6b}$ 10.8	n.d.
4a	5.55, $J_{1,2}$ 3.4	3.81, $J_{2,3}$ 10.0	4.22, n.d.	3.82, $J_{4,5}$ 10.0	4.26, $J_{5,6a}$ 2.7	3.67, n.d.	
4b	5.00, $J_{1,2}$ 7.6	3.80, n.d.	3.80, n.d.	3.80, $J_{4,5}$ 9.2	3.46, n.d.	3.67, $J_{5,6b}$ 3.2	
5a	4.77, $J_{1,2}$ 3.7	3.57, $J_{2,3}$ 9.6	3.9, n.d.	n.d.	n.d.	n.d.	3.80, n.d.
5b	4.49, $J_{1,2}$ 7.4	3.45, $J_{2,3}$ 8.9	3.65, n.d.	3.30, n.d.	3.30, n.d.	n.d.	4.00, 4.02, n.d.
6a	4.84, $J_{1,2}$ 3.9	3.63, $J_{2,3}$ 11.8	n.d.	n.d.	n.d.	n.d.	4.58, $J_{H,F}$ 6.0
6b	4.75, $J_{1,2}$ 6.8	3.53, $J_{2,3}$ 9.0	3.65, $J_{3,4}$ 8.0	3.68, $J_{4,5b}$ 7.8	3.38, 4.01, $J_{4,5a}$ 4.5, $J_{5a,5b}$ 11.9	n.d.	n.d.
7	5.42, $J_{1,2}$ 3.5	3.64, $J_{2,3}$ 9.8	4.11, $J_{3,4}$ 9.4	3.64, $J_{4,5b}$ 11.1	3.75, 3.95, $J_{4,5a}$ 5.6, $J_{5a,5b}$ 11.2	n.d.	
8a	4.81, $J_{1,2}$ 2.0	3.75, $J_{2,3}$ 3.0	3.85, $J_{3,4}$ 9.3	3.99, $J_{4,5}$ 9.3	3.70, n.d.	3.60, 3.70, n.d.	3.75, n.d.
8b	4.19, $J_{1,2}$ 0.0	n.d.	n.d.	n.d.	n.d.	3.65, 3.75, n.d.	3.62, 3.80, n.d.
9	5.14, $J_{1,2}$ 0.0	3.90, $J_{2,3}$ 3.1	3.91, $J_{3,4}$ 7.0	4.12, $J_{4,5}$ 9.0	3.90, $J_{5,6a}$ 1.8	3.72, 3.83, $J_{5,6b}$ 4.4, $J_{6a,6b}$ 10.9	5.9, n.d.
10a	4.76, $J_{1,2}$ 3.7	3.8, n.d.	n.d.	n.d.	n.d.	n.d.	3.7, n.d.
10b	4.3, $J_{1,2}$ 6.7	n.d.	n.d.	n.d.	n.d.	n.d.	3.7, 4.0, n.d.

[a] n.d., not determined.

Table 3
^{1}H NMR chemical shifts (δ in ppm) and coupling constants (J in Hz) for fluorinated glycosides of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose

Fluorinated glycosides	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	R_f	CMe_2
11	5.03, $J_{1,2}$ 0.0	4.64, $J_{2,3}$ 5.9	4.77, $J_{3,4}$ 3.6	3.95, $J_{4,5}$7.4	4.37, $J_{5,6a}$ 6.4	3.97, $J_{6a,6b}$ 8.8	4.07, $J_{5,6b}$ 4.5	3.81–3.87, $J_{H,H}$ 12.2, $J_{H,F}$ 8.6, $J_{H,F}$ 8.5	1.29, 1.34, 1.40, 1.43
12	5.20, $J_{1,2}$ 0.0	4.74, $J_{2,3}$ 5.8	4.83, $J_{3,4}$ 3.5	4.02, $J_{4,5}$ 7.6	4.38, $J_{5,6a}$ 6.4	3.93, $J_{6a,6b}$ 8.7	4.08, $J_{5,6b}$ 4.6	4.40, $J_{H,F}$ 6.0	1.31, 1.35, 1.40, 1.43
13	5.26, $J_{1,2}$ 0.0	4.89, $J_{2,3}$ 5.8	4.93, $J_{3,4}$ 3.4	4.19, $J_{4,5}$ 7.9	4.36, $J_{5,6a}$ 6.3	4.00, $J_{6a,6b}$ 8.8	4.09, $J_{5,6b}$ 4.5	7.5–7.6, n.d. [a]	1.34, 1.39, 1.39, 1.48
14	5.35, $J_{1,2}$ 3.2	4.87, n.d.	4.87, n.d.	3.93, $J_{4,5}$ 8.3	4.55, $J_{5,6a}$ 4.3	3.99, $J_{6a,6b}$ 9.0	4.04, $J_{5,6b}$ 4.2		1.36, 1.40, 1.40, 1.59
15a	5.42, $J_{1,2}$ 0.0	4.73, $J_{2,3}$ 5.9	4.90, $J_{3,4}$ 3.6	n.d.	n.d.	3.65, $J_{6a,6b}$ 11.4, $J_{5,6a}$ 6.0	3.82, $J_{5,6b}$ 3.1	2.10, n.d.	n.d.
15b	5.38, $J_{1,2}$ 0.0	4.72, $J_{2,3}$ 5.9	4.84, $J_{3,4}$ 3.6	4.04, $J_{4,5}$ 7.7	4.36, $J_{5,6a}$ 6.5	3.94, $J_{6a,6b}$ 8.7	4.08, $J_{5,6b}$ 4.8	1.70, n.d.	1.32, 1.37, 1.42, 1.46

[a] n.d., not determined.

Table 4
^{1}H NMR chemical shifts (δ in ppm) and coupling constants (J in Hz) for fluorinated glycosides of disaccharides

Fluorinated glycosides	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	H-1′	H-2′	H-3′	H-4′	H-5′	H-6a′	H-6b′	R_f
16a	5.71, $J_{1,2}$ 5.3	n.d. [a]	n.d.	n.d.	n.d.	n.d.	n.d.	5.46, $J_{1',2'}$ 4.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
16b	4.80, $J_{1,2}$ 7.6	4.90, $J_{2,3}$ 8.9	5.24, $J_{3,4}$ 8.9	4.03, $J_{4,5}$ 9.6	3.74, $J_{5,6a}$ 3.1	4.54, $J_{6a,6b}$ 12.2	4.30, $J_{5,6b}$ 4.3	5.40, $J_{1',2'}$ 4.1	4.83, $J_{2',3'}$ 10.6	5.33, $J_{3',4'}$ 9.6	5.03, $J_{4',5'}$ 9.9	3.95, $J_{5',6a'}$ 6.5	4.05, $J_{6a',6b'}$ 12.4	4.25, $J_{5,6b'}$ 2.4	4.47, $J_{H,F}$ 5.9
17a	4.74, $J_{1,2}$ 7.6	4.97, $J_{2,3}$ 9.3	5.70, $J_{3,4}$ 9.2	3.82, $J_{4,5}$ 9.8	3.65, $J_{5,6a}$ 6.0	4.07, $J_{6a,6b}$ 12.1	4.56, $J_{5,6b}$ 3.4	4.52, $J_{1',2'}$ 7.9	4.90, $J_{2',3'}$ 9.4	5.13, $J_{3',4'}$ 9.4	5.04, $J_{4',5'}$ 9.5	3.65, $J_{5',6a'}$ 4.5	4.03, $J_{6a',6b'}$ 12.5	4.33, $J_{5,6b'}$ 2.4	4.44, $J_{H,F}$ 6.0

[a] n.d., not determined.

Table 5
^{13}C NMR chemical shifts (δ in ppm) and coupling constants (J in Hz) for fluorinated glycosides of benzylated sugars

Fluorinated glycosides	C-1	C-2	C-3	C-4	C-5	C-6	R_f
1a	97.9	79.7	81.6	77.3	71.0	68.2	64.7, 123.8, $^2J_{C,F}$ 35.0, $^1J_{C,F}$ 282.0
1b	103.7	81.7	84.4	77.5	75.1	68.7	66.0, 123.8
2a	99.5	81.1	n.d. [a]	n.d.	n.d.	n.d.	n.d.
2b	103.5	81.3	84.0	77.1	75.3	68.5	72.3, 120.9, 121.8, $^2J_{C,F}$ 30.0, $^1J_{C,F}$ 280.0, $^1J_{C,F}$ 283.0
3	95.1	81.5	80.3	77.5	72.1	67.9	83.0, 122.1, 123.0, $^2J_{C,F}$ 29.2, $^1J_{C,F}$ 287.1, $^1J_{C,F}$ 289.2
4a	101.2	79.3	81.3	74.4	72.5	68.3	n.d.
4b	105.0	82.0	84.3	77.3	75. 6	67.9	n.d.
5a	97.8	79.4	80.9	77.6	60.5		64.5, 123.8, $^2J_{C,F}$ 34.8, $^1J_{C,F}$ 279.0
5b	104.1	81.3	83.3	77.6	64		65.9, $^2J_{C,F}$ 34.8
6a	99.3	80.7	n.d.	n.d.	n.d.		n.d.
6b	104.0	80.7	82.7	77.6	64.0		71.1, 120.8, 121.8, $^2J_{C,F}$ 34.8, $^1J_{C,F}$ 282.5, $^1J_{C,F}$ 287.7
7	101.0	79.2	80.8	77.3	61.9		n.d.
8a	98.6	74.4	79.7	74.5	73.0	69.0	64.1, 123.7, $^2J_{C,F}$ 34.7, $^1J_{C,F}$ 278.3
8b	101.3	n.d.	n.d.	n.d.	n.d.	n.d.	63.8, n.d.
9	100.6	74.4	79.1	74.2	73.4	68.8	72.0, 121.0, 122.0$^2J_{C,F}$ 32.5, $^1J_{C,F}$ 281.0, $^1J_{C,F}$ 283.0
10a	98.2	n.d.	n.d.	n.d.	n.d.	n.d.	64.5, 123.9, $^2J_{C,F}$ 34.6, $^1J_{C,F}$ 279.9
10b	103.9	n.d.	n.d.	n.d.	n.d.	n.d.	65.7, 123.8, $^2J_{C,F}$ 34.6, $^1J_{C,F}$ 279.4

[a] n.d., not determined.

hols [15] allowing better deprotonation under the Mitsunobu reaction conditions, the resulting alkoxide would displace the oxyphosphonium leaving group under milder conditions as compared with non-fluorinated alcohols. Since the pioneering work of Grynkiewicz on the formation of phenyl glycosides [16], O-glycosylation using a Mitsunobu reaction has been performed only with phenolic nucleophiles [17].

The synthesis of fluoroalkyl glycosides was therefore investigated under Mitsunobu conditions with regard to diverse parameters (type of fluorinated alcohol, sugar series, nature of the protective group, etc.). The reaction proceeded under comparatively mild conditions representing a special variant of the Mitsunobu protocol in which the fluoroalcohol, due to its acidity (pK_a 9–12), acts as the proton donor/nucleophile. The fluoroalkyl and fluoroaryl glycosides prepared from diversely protected mono- and disaccharides are shown in Scheme 1 and characterized in Table 1.

The influence of the pK_a of the glycosyl acceptor in Mitsunobu glycosylations has previously been pointed out [18]: for each sugar series, we are presently investigating the correlation between the α/β ratios observed and the structure and pK_a of the fluorinated reactants.

Experimental

General methods.—Evaporation was conducted in vacuo with a Buchi rotary evaporator. Optical rotations were determined at 20 °C with a Perkin–Elmer model 141 polarimeter. Melting points were measured on a Buchi apparatus and are uncorrected. TLC was performed on precoated Silica Gel 60F-254 plates (E. Merck), with detection by UV light (254 nm) and spraying with a 10% solution of concd H_2SO_4 in MeOH followed by heating. Low-resolution mass spectra (MS) were measured on a Perkin–Elmer SCIEX API 300 (ion spray or heated nebulizer). NMR spectra were performed on a Bruker ARX 400 using two probes: a broad band inverse probe, equipped with field gradients (^1H at 400.13 MHz and ^{13}C at 100.62 MHz) and an inverse dual $^{19}F/^1H$ probe (^{19}F at 386.6 MHz). All compounds were dissolved in $CDCl_3$ unless when dissolution in C_6D_6 was required for spectrum interpretation. Total assignment of the carbon and proton signals was made

Table 6
^{13}C NMR chemical shifts (δ in ppm) and coupling constants (J in Hz) for fluorinated glycosides of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose

Fluorinated glycosides	C-1	C-2	C-3	C-4	C-5	C-6	R_f	CMe_2
11	106.5	84.7	79.2	81.0	72.9	66.6	63.9, 124.0, $^2J_{C,F}$ 34.9, $^1J_{C,F}$ 278.1	24.4, 25.1, 25.7, 26.7, 109.2, 112.8
12	107.5	84.6	79.2	81.9	72.6	66.6	71.7, 121.0, 121.5, $^2J_{C,F}$ 33.0, $^1J_{C,F}$ 285.3, $^1J_{C,F}$ 286.4	24.3, 25.1, 25.7, 26.6, 109.3, 113.1
13	103.9	86.2	79.2	81.6	72.8	66.8	122.7, 123.2, 127.6, 128.5, 128.9, 130.5, $^1J_{C,F}$ 287.4, $^1J_{C,F}$ 289.3	24.4, 25.2, 25.7, 26.8, 110.0, 113.0
14	103.5	80.6	78.7	79.4	73.2	66.5	n.d. [a]	25.2, 25.2, 25.4, 26.9, 109.5, 115.3
15a	103.0	85.3	79.7	80.0	70.1	64.2	12.1, n.d.	24.3, 24.3, 25.7, 26.7, 109.5, 113.0
15b	103.2	85.5	79.3	81.3	72.7	66.7	12.1, 122.1, $^1J_{C,F}$ 287.3	24.3, 24.3, 25.7, 26.7, 109.5, 113.0

[a] n.d., not determined.

Table 7
^{13}C NMR chemical shifts (δ in ppm) and coupling constants (J in Hz) for fluorinated glycosides of disaccharides

Fluorinated glycosides	C-1	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	R_f
16a	95.2	n.d. [a]	n.d.	n.d.	n.d.	n.d.	95.6	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
16b	100.5	71.5	74.7	72.3	72.6	62.2	95.6	70.0	69.7	68.1	68.6	62.2	73.4, 122.0, n.d.
17a	100.7	71.0	71.9	67.7	73.0	61.1	100.8	71.5	72.0	75.9	72.8	61.5	73.5, 121.0, $^1J_{C,F}$ 289.0

[a] n.d., not determined.

Table 8
^{19}F NMR chemical shifts (δ in ppm) and coupling constants (J in Hz) for fluoroalkyl glycosides

Fluoroalkyl glycosides	**1a**	**1b**	**2a**	**2b**	**3**	**5a**	**5b**	**6b**	**8a**	**8b**	**9**	**10a**	**10b**	**11**	**12**	**13**	**16a**	**16b**	**17a**	**17b**
CF_3	−74.4, $J_{H,F}$ 8.7	−75.1, $J_{H,F}$ 8.6	−73.0, n.d. [a]	−73.6, −73.5, n.d.	−68.1, $J_{F,F}$ 10.8, −75.1	−73.7, $J_{H,F}$ 8.7	−74.4, $J_{H,F}$ 8.6	−73.5, $J_{H,F}$ 6.3, $J_{F,F}$ 8.8, −73.9, $J_{F,F}$ 9.2	−75.2, $J_{H,F}$ 8.6	−75.3, $J_{H,F}$ 8.6	−73.5, −73.8, $J_{F,F}$ 9.0, $J_{H,F}$ 6.0	−73.7, $J_{H,F}$ 8.6	−74.2, $J_{H,F}$ 8.6	-74.5, $J_{H,F}$ 8.6	—74.1, n.d.	−69.4, −73.5, $J_{F,F}$ 10.6	−73.6, −73.1, $J_{F,F}$ 9.5, $J_{H,F}$ 5.9, $J_{H,F}$ 6.0	−74.1, −73.9, $J_{H,F}$ 7.0	−74.1, −73.9, $J_{H,F}$ 6.0	−73.2, −73.5

[a] n.d., not determined.

Table 9
^{19}F NMR chemical shifts (δ in ppm) and coupling constants (J in Hz) for fluoroaryl glycosides

Fluoroaryl glycosides	**4a**	**4b**	**7**	**14**
F ortho	−155.0, *J* 19.1	−154.6, *J* 19.4	−154.9, *J* 20.0	−156.0, *J* 18.0
F meta	−162.9, *J* 1.9	−163.2, *J* 2.0	−163.0, n.d. [a]	−164.2, *J* 2.1
F para	−161.3, *J* 21.8	−161.2, *J* 22.0	−161.5, *J* 22.0	−162.9, *J* 21.9

[a] n.d., not determined.

through COSY, HMQC and HMBC experiments (Tables 2–9). For most compounds, the determination of the anomeric carbon and proton chemicals shifts, together with the coupling constant $J_{1,2}$, allowed the determination of the α ($J_{1,2}$ 4 Hz) or β ($J_{1,2}$ 7 Hz) structure. In the case of furanosidic compounds, the $J_{1,2}$ value was not informative: homonuclear-NOESY and heteronuclear NOE-difference experiments allowed the attribution of the β anomeric configuration to compounds **15b** and **14**, respectively. When neither homo- or hetero-NOE experiments gave structural information (compounds **11**, **12** and **13**), only the comparison of the chemical shift values of some specific carbons (C-5 and C-6) with those of unambiguously determined compounds (**15b** and **14**) allowed their anomeric configuration to be determined as β(D).

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose [4132-28-9] was purchased from Sigma and 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose [14131-84-1] from Aldrich.

Non-commercially available benzyl protected hemiacetalic substrates were prepared through standard acid-catalysed glycoside hydrolysis [19]. Disaccharide precursors to compounds **16** and **17** were obtained from maltose and cellobiose octaacetates, respectively, through hydrazine acetate-catalyzed selective transesterification [20].

General procedure for the synthesis of fluoroalkyl and fluoroaryl glycosides.—To a stirred solution of the hemiacetalic sugar (1 mmol) in dry toluene (10 mL) were added triphenylphosphine (2 equiv), the fluorinated alcohol (2–8 equiv) and diethyl azodicarboxylate (2 equiv). The mixture was stirred under argon atmosphere at room temperature and monitored by TLC (reaction time: 1.5–48 h). After evaporation under reduced pressure, the residue was chromatographed (see Table 1) on silica gel.

*Pentafluorophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside* (**18**).—^1H NMR ($CDCl_3$): 5.31–5.24 (m, 2H, H-2 and H-3), 5.19 (t, 1H, $J_{4,3} = J_{4,5}$ 9.1 Hz, H-4), 5.00 (d, 1H, $J_{1,2}$ 7.2 Hz, H-1), 4.26 (dd, 1H, $J_{6a,6b}$ 12.4 Hz, $J_{6a,5}$ 5.0 Hz, H-6a), 4.11 (dd, 1H, $J_{6b,5}$ 2.6 Hz, H-6b), 3.73 (m, 1H, H-5), 2.08, 2.04 and 2.01 (3s, 12H, $4CH_3CO$); ^{13}C NMR ($CDCl_3$): 170.9–169.6 (4CO), 144.2–130.8 (CF), 102.7 (C-1), 72.7 (C-5 and C-3), 71.5 (C-2), 68.4 (C-4), 61.8 (C-6), 20.9 ($4CH_3CO$).

Acknowledgements

We thank the MENRT and the CNRS for financial support. The authors also thank Dr J. Greiner and Dr H. Driguez for valuable discussions and Dr B. Perly for NMR expertise.

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