Hydrogen Bonding of Fluorinated Saccharides in Solution: F Acting as H-Bond Acceptor in a Bifurcated H-Bond of 4-Fluorinated Levoglucosans[1])

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4-Fluorinated levoglucosans were synthesised to test if OH···F H-bonds are feasible even when the O···F distance is increased. The fluorinated 1,6-anhydro-β-D-glucopyranoses were synthesised from 1,6:3,4-dianhydro-β-D-galactopyranose (**8**). Treatment of **8** with KHF_2 and KF gave 43% of 4-deoxy-4-fluorolevoglucosan (**9**), which was transformed into the 3-*O*-protected derivatives **13** by silylation and **15** by silylation, acetylation, and desilylation. 4-Deoxy-4-methyllevoglucosan (**19**) and 4-deoxylevoglucosan (**21**) were prepared as reference compounds that can only form a bivalent H-bond from HO–C(2) to O–C(5). They were synthesised from the $^{i}Pr_3Si$-protected derivative of **8**. Intramolecular bifurcated H-bonds from HO–C(2) to F–C(4) and O–C(5) of the 4-fluorinated levoglucosans in $CDCl_3$ solution are evidenced by the ^{1}H-NMR scalar couplings ^{h1}J(F,OH) and ^3J(H,OH). The OH···F H-bond over an O···F distance of *ca.* 3.0 Å is thus formed in apolar solvents, at least when favoured by the simultaneous formation of an OH···O H-bond.

Introduction. – We have investigated intra- and intermolecular H-bonds of partially protected mono- and disaccharides, and closely related compounds in solution in $CDCl_3$ and in (D_6)DMSO, and characterized them by NMR-spectroscopy [1–4]. A defined orientation of an OH group and, thus, its involvement in an intramolecular H-bond is evidenced by large or small ^3J(H,OH) (> 5.5 and ≤ 3 Hz), while freely rotating OH groups show typical intermediate values [5]. The persistence of the H-bonds decreases with increasing polarity of the solvent. Complete persistence – even for H-bonds between diequatorial OH groups – is observed for solutions in $CDCl_3$, whereas, in (D_6)DMSO, weak intramolecular H-bonds are mostly or completely replaced by intermolecular H-bonds, and only strong intramolecular H-bonds survive partially or completely[2]). The typical dependence of ^3J(H,OH) on the orientation of the OH group should also contribute to analyzing the H-bonds of hydroxylated organofluoro compounds in solution.

Dunitz and *Taylor* concluded from a detailed analysis of crystal structures and from molecular-orbital calculations that organofluoro compounds hardly ever accept H-

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[1]) Part of this work has been presented as a poster at the 'International Symposium: Fluorine in the Life Sciences', held at Bürgenstock in 2003 (p. 92 of the Conference papers).

[2]) Our concept of H-bond analysis was adopted by a Spanish group [6]. However, we concluded from ^{1}H-NMR data that there is a flip-flop intramolecular H-bond between HO–C(2) and HO–C(4) of levoglucosans (see [1]) and not a directed intramolecular H-bond from HO–C(2) to HO–C(4) as postulated by this group.

bonds [7]. However, even weak intramolecular H-bonds are favoured in an aprotic environment (such as in $CDCl_3$ and C_6D_6 solution), and one expects that fluoro alcohols form a (weak) intramolecular F···H–O H-bond in such solvents as long as the geometry is favourable, and there is no competition by better H-bond acceptors. Intramolecular H-bonds are usually detected by IR and ^{1}H-NMR parameters, such as the shift of OH bands to lower frequency ($\Delta\nu$(OH)), the chemical shift of the OH group and its coupling with geminal H-atoms (δ(OH) and ^3J(H,OH)), the temperature dependence of δ(OH) ($\Delta\delta$(OH)/ΔT), and the splitting of the OH signals upon partial deuteriation (SIMPLE ^{1}H-NMR; $\Delta\delta$(OH)). F···H–X (X = O, N, or S). The H-bonds of fluoroorganic compounds are further evidenced by scalar couplings between F and XH[3]). ^{h1}J(F,XH)[4]) decreases with decreasing stability of the F···H H-bond, as illustrated by values ranging from 530 Hz (gaseous HF [13]) to 440–430 Hz (Ir···F–H···N [14]), 68–49 Hz (Ir–F···H–N [14][15], Os–F···H–O [16]), $\leq$10 Hz (C–F···H–O [17–21] and C–F···H–N [22–24]), and $\leq$5 Hz (close contact between C–F and H–C [24–29]).

Intramolecular H-bonds of fluoro alcohols were observed in compounds with a short distance between the OH and F groups. The strongest intramolecular O–H···F H-bonds were detected in 1,3-diaxial fluoro alcohols (^{h1}J(F,OH) = 7.5–10 Hz; see below and **1**–**4** in *Fig. 1*). We intend to show that F in organofluoro compounds is a better H-bond acceptor than expected, by analyzing the ^{1}H-NMR spectra of fluoro alcohols with an O···F distance that is longer than the one in the known fluoroalcohols. 4-Fluorinated levoglucosans appeared suitable model compounds. On account of the short bridge between C(4) and C(1), these 1,6-anhydro-β-D-glucopyranose derivatives are characterised by a C(2)OH···F distance that is distinctly longer than the one of **2** (*anti*-reflex effect; see [30] and refs. cit. therein), so that the O–H···F H-bond should be disfavoured. The distance between O–C(2) and O–C(5) of *ca.* 2.73 Å favours a C(2)OH···OC(5) H-bond that either competes with the H-bond to F–C(4), or favours it by a cooperative effect, thus *a priori* complicating the interpretation. A combined analysis of ^{h1}J(F,OH) and ^3J(2,OH) should ideally allow an unambiguous assignment of the H-bonds from HO–C(2). For a better differentiation between a bifurcated H-bond to O–C(5) and F–C(4), and a H-bond exclusively to O–C(5), we planned to also analyze the H-bonds of 4-deoxy-4-methyl- and 4-deoxylevoglucosans which can only form an intramolecular H-bond of HO–C(2) to O–C(5).

Discussion. – 1. *Known Intramolecular H-Bonds of Fluoro Alcohols in Solution*. A restricted number of NMR data of fluoro alcohols and some analyses of their H-bonds have been published. We determined the solvent dependence of the intramolecular O–H···F H-bond of the fluorinated *myo*-inositols **1** [17] and **2** [18] (*Fig. 1*). The intramolecular O–H···F H-bond of **1** and **2** in $CDCl_3$ is evidenced by ^{h1}J(F,OH) of

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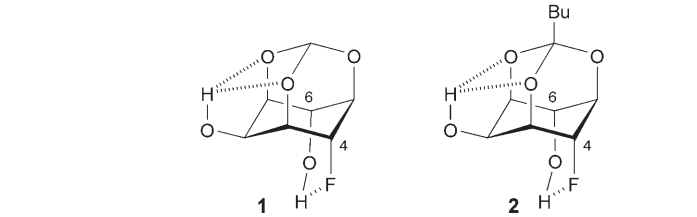
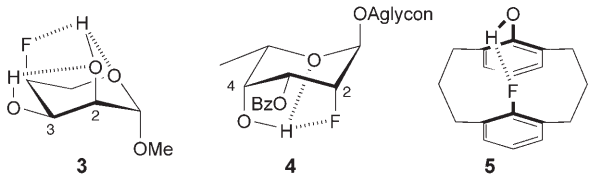
[3]) Scalar couplings *via* H-bonds of alcohols, amines, and amides are well documented. However, their detection requires special NMR techniques (small couplings of $<$0.5 Hz in 1,3-diols [8]) or ^{15}N labeling (couplings with ^{15}N in peptides and nucleosides [9–11]).

[4]) The $^{h\#}J$(Y,XH) (# = digit) notation was introduced by *Wüthrich* and co-workers [12] to emphasise that one bond between the coupling partners Y and XH is a H-bond although couplings *via* H-bonds follow the same polarization mechanism as couplings *via* covalent bonds [9].



	^{h1}J(F,OH)	^{3}J(6,OH)	^{h1}J(F,OH)	^{3}J(6,OH)	
$CDCl_3$:	8.8	7.8	8.3	8.3	Hz
CD_2Cl_2:			7.3	7.0	Hz
(D_8)dioxane:	0	5.0	0	5.0	Hz
(D_6)DMSO:	0	3.8			Hz



	^{h1}J(F,OH)	^{3}J(2,OH)	^{h1}J(F,OH)	^{3}J(4,OH)	^{h1}J(F,OH)	
$CDCl_3$:	7.5	11.5	*ca.* 10	10.5	6.0	Hz
(D_6)DMSO:					0	Hz

Fig. 1. *Intramolecular H-bonds* (dashed lines) *of* **1**–**5** *in chlorinated solvents and their* ^{h1}J*(F,OH) and* ^{3}J*(H,OH) values in several solvents*

8.3–8.8 Hz and by the large ^{3}J(6,OH) (7.8–8.3 Hz), agreeing well [31] with the calculated torsion angle H–C(6)–O–H of 150°. In CD_2Cl_2, the intramolecular O–H ··· F H-bond of **2** is already partially broken (^{3}J(6,OH) ≈ ^{h1}J(F,OH) ≈ 7.3 Hz). The same H-bond of **1** and **2** in (D_8)dioxane is largely broken (^{3}J(6,OH) = 5.0, ^{h1}J(F,OH) = 0 Hz). In (D_6)DMSO, the O–H ··· F H-bond of **1** is completely replaced by a H-bond to the solvent, as evidenced by the disappearance of ^{h1}J(F,OH) coupling and by ^{3}J(6,OH) = 3.8 Hz, a typical value for completely solvated axial OH groups [1]. Scalar ^{h1}J(F,OH) couplings have been published by *Takagi* and co-workers for the α-D-ribopyranoside **3** (^{h1}J(F,OH) = 7.5 Hz [19]) and the α-L-talopyranoside **4** (^{h1}J(F,OH) ≈ 10 Hz [20]) without, however, identifying H-bonds. The ^{3}J(H,OH) values of 10.5–11.5 Hz evidence torsion angles H–C(2)–O–H of **3** and H–C(4)–O–H of **4** of *ca.* 180°, and thus bifurcated H-bonds to the ring O- and the F-atom. The intramolecular O–H ··· F H-bond of the fluorinated phenol **5** in $CDCl_3$ (^{h1}J(F,OH) = 6.0 Hz) is completely broken in (D_6)DMSO (^{h1}J(F,OH) = 0 Hz) [21][5]). Solvent-dependent ^{h1}J(F,OH) and ^{h1}J(F,NH) ≤ 4.8 Hz were observed in 2-fluorophenols [25], 2-(trifluoromethyl)phenols [33], 2-fluoroanilines [22], and 2-fluorobenzamides [24], and a solvent-independent J(F,CH_3) value of 2.0 Hz was observed in 2-fluorotoluene [25]. The solvent dependence allows to discriminate between intramolecular H-bonds (solvent-dependent) and close contacts (solvent-independent), although, in the 2-

[5]) This is the only example of an intramolecular OH ··· F H-bond quoted in a recent review [32].

fluorotoluene, transmittance of the coupling *via* an intramolecular C–H···F H-bond cannot be excluded.

2. *4-Fluorinated Levoglucosans as Model Compounds for H-Bond Investigations.* To estimate the structural properties of 4-fluorinated levoglucosans that may qualify them as model compounds, as discussed in the *Introduction*, we compared the solid-state-structure of the *myo*-inositols **1** [17] and **6** [30] with that of levoglucosan (**7**) [34], and modeled the structure of the 4-fluorinated levoglucosan **9** and its defluoro analogue **21** (*Fig. 2*). In the crystalline state, the O···O distance between HO–C(4) and HO–C(6) of *myo*-inositol (**6**) is 2.768 Å. The F···O distance between F–C(4) and HO–C(6) of the fluorinated analogue **1** is slightly larger (2.834 Å, $\Delta l = 0.066$ Å). This difference is due to an intramolecular H-bond in **6** that is absent in **1**, rather than to the different bond lengths of C–F (as in **1**: 1.402 Å) and C–O (as in **6**: 1.429 Å). As the *anti*-reflex effect suggested, the O···O distance between HO–C(2) and HO–C(4) of levoglucosan (**7**; 3.299 Å), and the F···F distance of the corresponding 2,4-difluorinated derivative [35] (3.305 Å) are much larger than the O···O distance between HO–C(4) and HO–C(6) of **6** ($\Delta l \approx 0.53$ Å). All OH groups of crystalline **7** are engaged in intermolecular H-bonds, but a weak intramolecular H-bond between HO–C(2) and HO–C(4) of **7** appears feasible, since the O···O distance is distinctly smaller than the

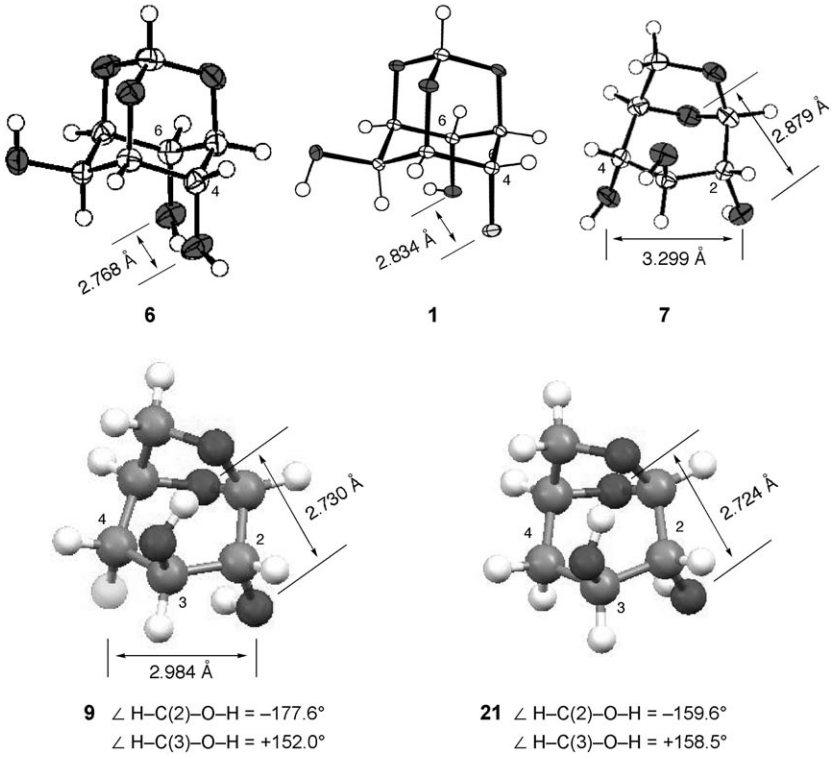


Fig. 2. *Crystal structure* of **1**, **6**, *and* **7**, *and MM3* calculated structures of* **9** *and* **21**: *Selected O···O and O···F distances, and calculated H–C–O–H torsion angles*

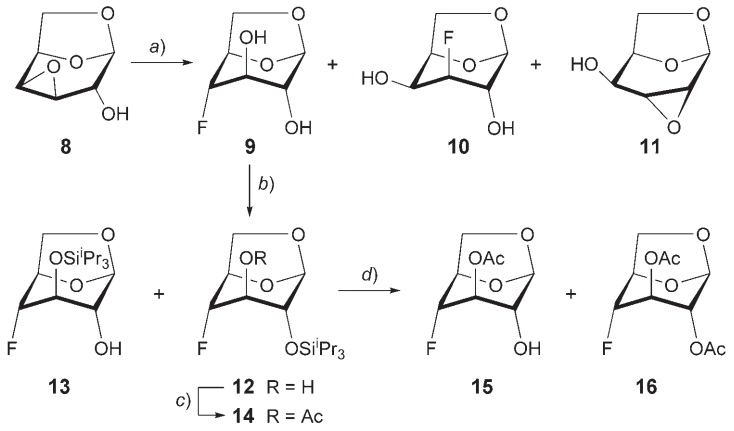
sum of the corresponding *van der Waals* radii (3.8 Å). To obtain information about the desired O–H···F H-bond, we modeled the structure of 4-deoxy-4-fluorolevoglucosan (**9**) and 4-deoxylevoglucosan (**21**) using a force-field programme (MM3* in Macromodel V. 6.0 [36]). Gas-phase modeling of **9** suggests a bifurcated H-bond from HO–C(2) to O–C(5) and to F–C(4), and a H-bond from HO–C(3) to O–C(6). The calculated F···O distance between F–C(4) and HO–C(2) of **9** (2.984 Å) is by 0.315 Å smaller than the corresponding experimental O···O distance in **7**, as the consequence of the intramolecular H-bond in **9** that increases the puckering of the pyranose ring. This F···O distance is, however, larger by 0.216 Å than the O···O distance between HO–C(4) and HO–C(6) of **6**, suggesting a weaker O–H···F H-bond in **9** than in **1**. The bifurcated H-bond of **9** and the C(2)OH···OC(5) of **21** have a similar influence upon the pyranose ring conformation, as evidenced by C(2)O···OC(5) distances of 2.730 and 2.724 Å, respectively.

Modeling of the fluoro diol **9** predicts a torsion angle H–C(2)–O–H of −177.6° evidencing a bifurcated H-bond characterized by OH···F and OH···OC(5) distances of 2.347 and 2.334 Å, respectively. According to *Fraser et al.* [31], this torsion angle corresponds to a ^3J(2,OH) value of 12.1 Hz. Indeed, ^3J(2,OH) and ^3J(4,OH) values of 10.0 to 12.0 Hz, respectively, evidence bifurcated H-bonds of HO–C(2 or 4) to O–C(5) and the substituent at C(4 or 2) of partially protected levoglucosans [37], and of 4-ethynylated [38] and 2-azidylated [39] derivatives in $CDCl_3$. The 4-deoxy diol **21** forms an intramolecular H-bond from HO–C(2) to O–C(5), evidenced by the H–C(2)–O–H torsion angle of −159.6° corresponding to a ^3J(2,OH) value of 10.7 Hz. Thus, the experimental ^3J(2,OH) value of **9** should allow to discriminate between a bifurcated H-bond and one exclusively to O–C(5), although the difference of the coupling constants is expected to be rather small. The different H-bond of HO–C(2) of **9** and **21** has an influence upon the H-bond of HO–C(3). The boat conformation of the six-membered ring formed by the HO–C(3) H-bond is more puckered in **9** than in **21** as evidenced by H–C(3)–O–H torsion angles of 152.0 and 158.5°, respectively, suggesting a smaller ^3J(3,OH) value for **9** (9.6 Hz) than for **21** (10.6 Hz).

These results suggest that 4-fluorinated levoglucosans are appropriate models for the investigation of weak O–H···F H-bonds.

3. *Synthesis and Characterization of 4-Fluorinated and 4-Deoxygenated Levoglucosans.* We planned to use the known fluorination of the D-*galacto* epoxide **8** [40][41] with 4.6 equiv. of KHF_2. It was reported that this fluorination in ethylene glycol for 1 h at 200° yielded 65% of the fluorohydrin **9** [42][43] (*Scheme 1*). We were, however, not able to reproduce this yield, obtaining only 18% of **9** besides large amounts of 4-*O*-(2-hydroxyethyl)levoglucosan. Ethylene glycol could not be completely replaced by another solvent, but treating **8** with 6 equiv. of KHF_2 and KF [44] in ethylene glycol/diethylene glycol diethyl ether 1:1 for 1 h at 200°, followed by flash chromotography, yielded 43% of the desired fluoro diol **9**, 12% of its regioisomer **10**, and 3% of the D-*gulo* epoxide **11** [40][45]. The side products are the result of the known rearrangement of **8** to the isomeric epoxide **11** [40], and the transformation of **11** into the D-*galacto*-configured fluoro diol **10**. Silylation of **9** with 2.4 equiv. of $^iPr_3SiCl$ (TIPSCl) and flash chromatography gave the silyl ether **12** (62% of pure **12** and *ca.* 11% of slightly contaminated **12**), a 9:1 mixture of TIPSCl and **13** (*ca.* 7% of **13**), and a fraction

Scheme 1



a) 6 equiv. of KHF_2, 6 equiv. of KF, ethylene glycol/diethylene glycol diethyl ether 1:1, 200°; 43% of **9**, 12% of **10**, 3% of **11**. *b*) 2.4 equiv. of $^{i}Pr_3SiCl$ (TIPSCl), pyridine/CH_2Cl_2 1:1, 0°; 73% of **12**, 7% of **13**, 15% of the disilyl ether derived from **9**. *c*) Ac_2O, 4-(dimethylamino)pyridine (DMAP), pyridine; 83%. *d*) With **14**, $Bu_4NF \cdot 3\ H_2O$, 15-crown-5, $KHCO_3$, THF; 47% of **15**, 3% of **16**.

containing *ca.* 15% of the disilyl ether derived from **9**. The monosilyl ether **12** was acetylated to **14** (83%). Desilylation of **14** and flash chromatography gave 47% of the hydroxy acetate **15** [43] and a 9:2 mixture of $^{i}Pr_3SiF$ and the diacetate **16** [42] (*ca.* 3% of **16**). Desilylation in the presence of solid $NaHCO_3$ prevented migration of the Ac group of **15** to the 2-position (*via* a $B_{3,O}$ conformer).

To obtain the reference compounds in which only O–C(5) can act as H-bond acceptor for HO–C(2), we prepared the 4-deoxy-4-methyl- and the 4-deoxylevoglucosans **19**, **21**, and **23** (*Scheme 2*). Treatment of the epoxy silyl ether **17** [38] with MeMgBr and CuI in THF [41] gave the alcohol **18**[6]) (32%), which was desilylated to the diol **19** (68%). The rapid reductive ring opening of **17** with $LiEt_3BH$ [47] to form **20** was superior to the slow reduction with $LiAlH_4$ (1 h *vs.* 3 d; 82 *vs.* 43% yield). The alcohol **20** was either desilylated (91%) to the diol **21** [48][49], or acetylated to **22** (59%). Desilylation of **22** with $Bu_4NF \cdot 3\ H_2O$ and solid $NaHCO_3$ in THF afforded 91% of the hydroxy acetate **23**.

In $CDCl_3$, the 4-fluorolevoglucosans **9** and **12**–**16** show characteristic couplings of F with H–C(4) ($^2J(4,F) = 44.3–46.3$ Hz), H–C(3) ($^3J(3,F) = 13.3–16.8$ Hz), H–C(5) ($^3J(5,F) = 10.3–12.8$ Hz), H_{exo}–C(6) ($^4J(6_{exo},F) = 4.4–5.3$ Hz), and H_{endo}–C(6) ($^4J(6_{endo},F) \leq 1.3$ Hz). These F/H–C couplings of **9** and **15** do not change much upon changing the solvent to (D_6)DMSO, with the exception of an increase of $^3J(3,F)$ to 18.0–20.6 Hz. The J(H,F) couplings of **9** and **15** in $CDCl_3$ and (D_6)DMSO were unambiguously assigned by recording both F-coupled and F-decoupled ^{1}H-NMR spectra. These spectra evidence also that both HO–C(2) and HO–C(3) of **9** show a F-coupling in $CDCl_3$, although for different reasons (see *Fig. 3* and discussion below),

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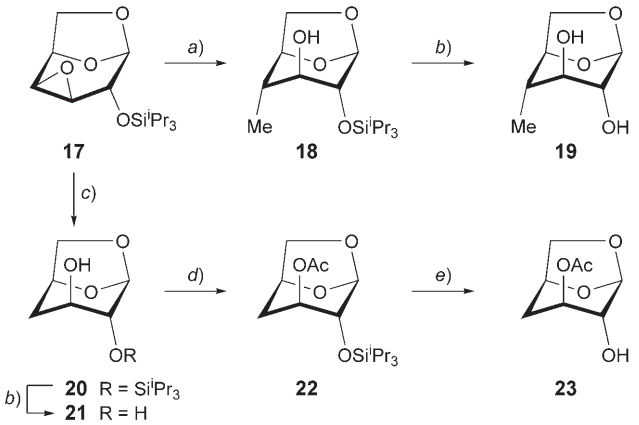
6) For a synthesis of the enantiomer, see [46].

Scheme 2



a) MeMgBr, CuI, THF; 32%. *b*) $Bu_4NF \cdot 3\ H_2O$, THF; 68% of **19**; 91% of **21**. *c*) $LiEt_3BH$, THF; 82%. *d*) Ac_2O, DMAP, pyridine; 59%. *e*) $Bu_4NF \cdot 3\ H_2O$, $NaHCO_3$, THF; 91%.

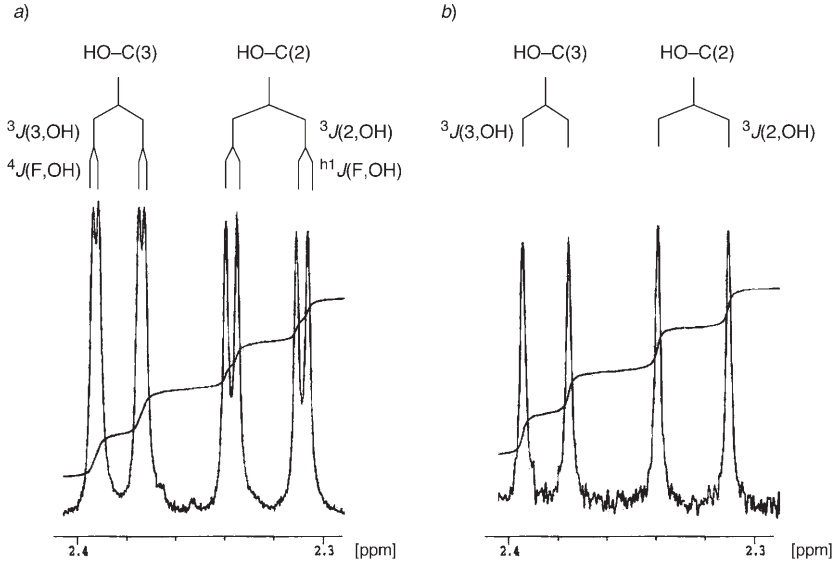


Fig. 3. *^{1}H-NMR OH Signals of the fluoro diol* **9** *in $CDCl_3$. a*) F-Coupled and *b*) F-decoupled spectrum.

whereas only the F-coupling of HO–C(3) persists in (D_6)DMSO. The unambiguous assignment of HO–C(2) and HO–C(3) of **9** is based on a DQF-COSY spectrum ($CDCl_3$) or on selective homodecoupling experiments ((D_6)DMSO). The ^{13}C-NMR spectra of **9** in (D_6)DMSO, and of **15** in $CDCl_3$ and (D_6)DMSO show characteristic F-couplings for C(2) to C(6) (*Table 1* in the *Exper. Part*).

The F-couplings of the 3-fluorinated diol **10** in $CDCl_3$ and (D_6)DMSO were unambiguously assigned by recording F-coupled and F-decoupled spectra. A typical

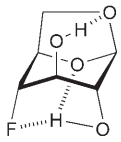
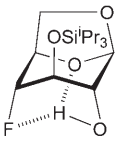
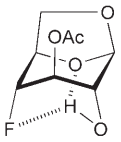
large ^2J(3,F) value of 48.7–48.9 Hz evidences fluorination at C(3). A distinctly larger ^3J(4,F) value (26.1–29.5 Hz) than ^3J(2,F) (11.2–14.1 Hz) evidences an antiperiplanar H–C(4) and a *gauche*-oriented H–C(2). The *galacto*-configuration is corroborated by small J(1,2) and J(2,3) ($\leq$1.6 Hz), and by medium J(3,4) and J(4,5) (4.3 Hz) values. The assignment of the HO–C(2) and HO–C(4) signals of **10** in $CDCl_3$ is based on selective homodecoupling experiments. The corresponding signals of **10** in (D_6)DMSO were not assigned, as they are almost isochronous (5.38 and 5.40 ppm), and as both show a ^3J(H,OH) value of 6.8 Hz. Only HO–C(4) in $CDCl_3$ shows a coupling with the F-atom (see below). Characteristic F-couplings of C(2) to C(6) are observed in the ^{13}C-NMR spectra of **10** in $CDCl_3$ and (D_6)DMSO (*Table 1* in the *Exper. Part*).

The D-*gluco*-configuration of **18** and **19** is evidenced by small J(1,2), J(2,3), J(3,4), and J(4,5) values ($\leq$2.2 Hz). Similarly, the 4-deoxylevoglucosans **20**–**23** show small J(1,2), J(2,3), $J(3,4_{eq})$, and $J(4_{eq},5)$ values (<2 Hz), whereas the larger $J(3,4_{ax}) = 5.1$–5.6 Hz and $J(4_{ax},5) = 4.0$–4.3 Hz evidence the *cis*-orientation of H–C(3), H_{ax}–C(4), and H–C(5). The HO–C(3) *d* of **18**–**21** in $CDCl_3$ resonates downfield to the *d* of HO–C(2) of **19**, **21**, and **23** (2.33–2.52 *vs.* 1.98–2.22 ppm). As expected, deoxygenation leads to an upfield shift for C(4) of **19** (39.1 ppm) and of **20**–**23** (30.6–32.9 ppm; *Table 2* in the *Exper. Part*). The Me group of **19** resonates at 18.1 ppm.

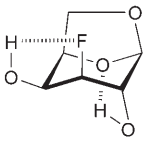
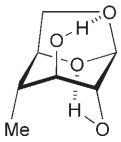
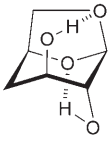
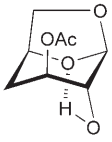
4. *Intramolecular OH···F H-Bonds in $CDCl_3$.* The ^{1}H-NMR spectra were obtained of 5–35 mM solutions in $CDCl_3$ of **9**, **10**, **13**, **15**, **19**, **21**, and **23** ($\leq$10 mg/ml) and of 43–87 mM solutions in (D_6)DMSO of **9**, **10**, and **15** (*Fig. 4*). Intermolecular H-bonds in $CDCl_3$ can be excluded, since the IR spectra of **10**, **15**, **19**, **21**, and **23** show only weak associated OH bands for 89–141 mM solutions in $CHCl_3$. Unfortunately, IR spectroscopy does not appear a useful tool to assign intramolecular OH···F H-bonds of **9**, **10**, **13**, and **15**, considering that the OH···F H-bond of **2** led only to a weak shift of the OH band ($\Delta\tilde{\nu} \approx 7$ for a CCl_4 and < 2 cm^{-1} for a CH_2Cl_2 solution [18]).

In $CDCl_3$, HO–C(2) of the 4-deoxylevoglucosans **19**, **21**, and **23**, and HO–C(3) of **9**, **19**, and **21** form intramolecular H-bonds to O–C(5) and O–C(6), respectively (*Fig. 4*). The experimental ^3J(2,OH) of **19**, **21**, and **22** (8.6–10.2 Hz), and ^3J(3,OH) of **9**, **19**, and **21** (6.9–7.8 Hz) are smaller than the values calculated for **21** (^3J(2,OH) = 10.7, ^3J(3,OH) = 10.6 Hz). This is due to the presence of polar substituents decreasing the vicinal couplings (not included in the *Karplus* equation) and, in the case of ^3J(3,OH), to a stronger puckering of the boat conformation of the six-membered ring formed by the C(3)OH···OC(6) H-bond.

The $CDCl_3$ ^{1}H-NMR spectra of the 4-fluorinated levoglucosans show a ^{h1}J(F,HO–C(2)) value of 1.8–1.2 Hz for **9**, **13**, and **15** (*Fig. 4*), evidencing that F acts as intramolecular H-bond acceptor for HO–C(2). In (D_6)DMSO, HO–C(2) of **9** and **15** is more or less completely engaged in H-bonding to the solvent, as evidenced by the disappearance of the ^{h1}J(F,HO–C(2)) coupling and by ^3J(2,OH) values of 5.0–4.5 Hz (compare with 3.5–4.5 Hz that is typical for a completely solvated axial OH group [1]). In contradistinction, the diol **9** shows ^4J(F,HO–C(3)) values of 0.8–0.7 Hz both in $CDCl_3$ and (D_6)DMSO, evidencing that it is a *w* coupling and not one transmitted by a H-bond. As expected, ^{h1}J(F,HO–C(2)) of the 1,6-anhydro-β-D-glucopyranoses **9**, **13**, and **15** is distinctly smaller than ^{h1}J(F,HO–C(6)) of the *myo*-inositols **1** and **2** (8.3–8.8 Hz; *Fig. 1*). The value of this coupling constant decreases from 1.8 Hz for the diol **9** *via* 1.6 Hz for the silyl ether **13** to 1.2 Hz of the acetate **15**. The large ^3J(2,OH) =

	9		**13**	**15**		
Solvent:	$CDCl_3$	(D_6)DMSO	$CDCl_3$	$CDCl_3$	(D_6)DMSO	
Concentration:	13	87	5	35	70	mM
δ(HO–C(2)):	2.33	5.17	2.23	2.57	5.52	ppm
^3J(2,OH):	11.5	5.0	12.1	10.3	4.5	Hz
^{h1}J(F,OH):	1.8	0	1.6	1.2	0	Hz
δ(HO–C(3)):	2.39	5.56				ppm
^3J(3,OH):	7.4	4.4				Hz
^4J(F,OH):	0.8	0.7				Hz

	10		**19**	**21**	**23**	
Solvent:	$CDCl_3$	(D_6)DMSO	$CDCl_3$	$CDCl_3$	$CDCl_3$	
Concentration:	26	43	18	19	19	mM
δ(HO–C(2)):	1.95	5.40[a])	1.98	2.10	2.22	ppm
^3J(2,OH):	9.7	6.8	8.6	10.2	9.0	Hz
δ(HO–C(3 or 4)):	2.35	5.38[a])	2.33	2.52		ppm
^3J(3 or 4,OH):	9.5	6.8	6.9	7.8		Hz
^{h1}J(F,OH):	4.6	0				Hz

[a]) Assignment may be interchanged.

Fig. 4. *Intramolecular H-bonds* (dashed lines) *of the 4-deoxy-4-fluorolevoglucosans* **9**, **13**, *and* **15**, *the 3-deoxy-3-fluoro regioisomer* **10**, *and the 4-deoxylevoglucosans* **19**, **21**, *and* **23** *in* $CHCl_3$, *and their OH* ^{1}*H-NMR parameters* (δ(OH), ^3J(H,OH), and J(F,OH)) *in* $CHCl_3$ *and* (D_6)*DMSO*

12.1 Hz of **13** corresponds to a H–C(2)–O–H torsion angle of 180° [31], evidencing a symmetric bifurcated H-bond. The smaller ^3J(2,OH) values of 11.5 and 10.3 Hz for **9** and **15** correspond to torsion angles of ±167 and ±158°, respectively. The ^3J(2,OH) values of the 4-fluorinated levoglucosans **9**, **13**, and **15** are larger than those of 4-deoxy analogues **19**, **21**, and **23** (8.6–10.2 Hz). Together with the ^{h1}J(F,HO–C(2)) values, they reveal bifurcated H-bonds. The decrease of the ^{h1}J(F,HO–C(2)) values for **9** to **13** and to **15** evidence a different sign of the H–C(2)–O–H torsion angle of **9** (+167°) and **15** (−158°; see formulae in *Fig. 4*). Thus, the H-accepting properties of F–C(4) are electronically influenced by the substituent at C(3): the electron-rich H-bonded (= partially deprotonated) OH group of **9** enhances the H-accepting properties of F, whereas the electron-withdrawing AcO group of **15** reduces it.

The *galacto*-configured fluoro diol **10** in $CDCl_3$ is expected to form intramolecular H-bonds from HO–C(4) to F–C(3) and from HO–C(2) to O–C(5). Such H-bonds

are indeed evidenced by $^{h1}J(F,HO-C(4)) = 4.6$, $^{3}J(4,HO-C(4)) = 9.5$, and $^{3}J(2,HO-C(2)) = 9.7$ Hz. The value of $^{h1}J(F,HO-C(4))$ agrees well with an intermediate stability of the O–H···F H-bond of **10** as compared to that of **1**/**2** and **9**/**13**/**15**. In (D_6)DMSO, both intramolecular H-bonds of **10** are only partially replaced by intermolecular H-bonds ($^{3}J(H,OH) = 6.8$ *vs.* 4.0–5.0 Hz for fully solvated equatorial OH groups [1]), but no $^{h1}J(F,HO-C(4))$ could be detected.

Conclusions. – In apolar solvents, F–C(4) of 4-deoxy-4-fluorolevoglucosans acts together with O–C(5) as H-bond acceptor of HO–C(2). It cannot be excluded that the formation of the weak OH···F H-bond (O···F distance *ca.* 3.0 Å) is favoured by the presence of the OH···O H-bond. Independently of whether the OH···F H-bond is considered as the result of a cooperativity between the two H-bond acceptors, or as the result of a competition between them, these observations strongly suggest that the validity of the contention of *Dunitz* and *Taylor* [7] is restricted to the solid state, and evidence that organofluoro compounds may act as H-bond acceptor in an apolar environment, *e.g.*, in the active site of an enzyme. We are not aware of any publication investigating the H-accepting properties of organofluoro compounds in the active site by analysing scalar $^{h1}J(F,XH)$ (X = O, N, or S) couplings.

We thank the undergraduate students *F. Post*, *A. Neumann*, and *D. Baumann* for their synthetic contribution, and the *Swiss National Science Foundation* for generous support.

Experimental Part

General. ^{1}H-NMR Spectra were obtained of ≤ 35 mM solns. of the alcohols and diols in $CDCl_3$ (filtered through basic Al_2O_5 immediately before use) and of 40–90 mM solutions in (D_6)DMSO.

Fluorination of **8**. A suspension of **8** [40][41] (1.595 g, 11.1 mmol), KHF_2 (5.202 g, 66.6 mmol) and KF (3.901 g, 67.1 mmol) in ethylene glycol/diethylene glycol diethyl ether 1:1 (100 ml) was stirred for 60 min at 200°. After cooling to r.t., the solid was filtered off and exhaustively extracted with AcOEt. After evaporation of the combined filtrate, and extractions at 40°/220 Torr and then at 70°/0.5 Torr, bulb-to-bulb distillation at 90°/0.2 Torr left a residue which was separated by FC (CH_2Cl_2/AcOEt 1:2) affording **11** [40][45] (45 mg, 3%) and **9**/**10** 4:1 (0.995 g). Crystallisation from acetone/Et_2O gave pure **9** (563 mg, 31%) and a residue of **9**/**10** *ca.* 1:1 (430 mg, 24%).

*Data of 1,6-Anhydro-4-deoxy-4-fluoro-β-*D*-glucopyranose* (**9**) [42]. M.p. 121–122° ([42]: 118–122°). $[\alpha]_D^{25} = -51.2$ ($c = 0.55$, MeOH) ([42]: $[\alpha]_D = -53$ ($c = 2$, H_2O)). ^{1}H-NMR (400 MHz, 13 mM in $CDCl_3$; F-coupled and F-decoupled spectrum): 5.53 (*t*, $J = 1.9$, H–C(1)); 4.72 (*ddt*, $^{3}J(F,H) = 10.3$, $J = 5.5$, 1.9, H–C(5)); 4.50 (*dq*, $^{2}J(F,H) = 44.4$, $J = 1.9$, H–C(4)); 4.15 (*dt*, $J = 7.9$, 0.9, $^{4}J(F,H) = 0.9$, H_{endo}–C(6)); 3.96 (*ddquint.*, $^{3}J(F,H) = 13.3$, $J = 7.4$, 1.8, H–C(3)); 3.82 (*dt*, $J = 7.9$, 5.8, $^{4}J(F,H) \approx 4.6$, H_{exo}–C(6)); 3.56 (*dq*, $J = 11.5$, 1.8, H–C(2)); 2.39 (*dd*, $J = 7.4$, $^{4}J(F,OH) = 0.8$, HO–C(3)); 2.33 (*dd*, $J = 11.5$, $^{h1}J(F,OH) = 1.8$, HO–C(2)). ^{1}H-NMR (400 MHz, 87 mM in (D_6)DMSO; F-coupled and F-decoupled spectrum): 5.36 (*dd*, $J = 4.4$, $^{4}J(F,OH) = 0.7$, HO–C(3)); 5.20 (br. *s*, H–C(1)); 5.17 (*d*, $J = 5.0$, HO–C(2)); 4.62 (*ddq*, $^{3}J(F,H) = 14.0$, $J = 6.1$, 1.4, H–C(5)); 4.33 (br. *dt*, $^{2}J(F,H) = 47.0$, $J = 1.4$, H–C(4)); 3.85 (*dt*, $J = 7.4$, 1.1, $^{4}J(F,H) = 1.1$, H_{endo}–C(6)); 3.54 (*ddd*, $J = 7.3$, 6.0, $^{4}J(F,H) = 4.1$, H_{exo}–C(6)); 3.53 (*ddquint.*, $^{3}J(F,H) = 20.6$, $J = 4.2$, 1.4, H–C(3)); 3.22 (br. *dt*, $J = 5.0$, 1.4, H–C(2)). ^{13}C-NMR (100 MHz, 87 mM in (D_6)DMSO): see *Table 1*. ^{19}F-NMR (37.6 MHz, 13 mM in $CDCl_3$): −184.53 (br. *dddd*, $J = 44.4$, 13.3, 10.3, 5.0). ^{19}F-NMR (37.6 MHz, 87 mM in (D_6)DMSO): −199.63 (br. *ddd*, $J = 48.9$, 29.6, 14.1).

*Data of 1,6-Anhydro-3-deoxy-3-fluoro-β-*D*-galactopyranose* (**10**). Data obtained of a pure fraction of another batch. R_f (CH_2Cl_2/AcOEt 1:2) 0.19. M.p. 193–195°. $[\alpha]_D^{25} = -32.8$ ($c = 0.45$, MeOH). IR (104 mM in $CHCl_3$): 3615*w*, 3570*m*, 3490*w* (sh), 2962*m*, 2929*w*, 2903*w*, 1478*w*, 1428*w*, 1394*w*, 1349*w*, 1326*w*, 1309*w*, 1261*w*, 1220*w*, 1182*m*, 1128*m*, 1090*m*, 1084*m*, 1057*s*, 1009*m*, 994*m*, 965*m*. ^{1}H-NMR (400 MHz,

Table 1. *^{13}C-NMR Chemical-Shift Values* [ppm] *of the Fluorinated 1,6-Anhydro-β-*D*-hexopyranoses* **9**, **10**, *and* **15** (J(F,C) [Hz] in parenthesis)

C-Atom	**9** (D_6)DMSO	**10** $CDCl_3$	**10** (D_6)DMSO	**15** $CDCl_3$	**15** (D_6)DMSO
C(1)	102.26	100.46	100.34	101.45	101.35
C(2)	70.94 (5.3)	64.69 (17.9)	63.87 (16.8)	68.18 (1.4)	67.98 (3.3)
C(3)	71.24 (26.5)	90.12 (180.5)	90.95 (182.2)	71.73 (30.9)	71.73 (30.5)
C(4)	91.95 (177.8)	69.65 (24.6)	69.26 (23.8)	88.76 (180.7)	88.10 (179.0)
C(5)	73.38 (22.3)	74.36 (1.0)	73.63	73.88 (21.2)	73.88 (21.4)
C(6)	63.66 (10.6)	63.63 (3.4)	62.93 (3.9)	64.26 (8.9)	63.41 (10.0)
AcO	–	–	–	169.59, 20.88	169.19, 20.70

26 mM in $CDCl_3$; F-coupled and F-decoupled spectrum): 5.39 (t, J = 1.5, H–C(1)); 4.75 (ddq, ^2J(F,H) = 48.7, J = 4.4, 1.6, H–C(3)); 4.48 (br. t, $J \approx$ 4.8, H–C(5)); 4.16 (br. d, J = 7.9, H_{endo}–C(6)); 4.08 (br. ddt, ^3J(F,H) = 26.1, $J \approx$ 9.2, 4.3, H–C(4)); 3.95 (br. ddt, ^3J(F,H) = 11.2, $J \approx$ 9.6, 1.6, H–C(2)); 3.73 (ddt, $J \approx$ 7.8, 5.2, 1.2, H_{exo}–C(6)); 2.35 (dd, J = 9.5, ^{h1}J(F,H) = 4.6, HO–C(4)); 1.95 (d, J = 9.7, HO–C(2)). ^{1}H-NMR (400 MHz, 43 mM in (D_6)DMSO; F-coupled and F-decoupled spectrum): 5.40 (d, J = 6.8), 5.38 (d, J = 6.8) (HO–C(2), HO–C(4)); 5.19 (t, J = 1.5, H–C(1)); 4.45 (ddq, ^2J(F,H) = 48.9, J = 4.3, 1.6, H–C(3)); 4.29 (br. dd, $J \approx$ 5.0, 4.3, H–C(5)); 4.05 (br. d, J = 7.1, H_{endo}–C(6)); 3.84 (br. ddt, ^3J(F,H) = 29.5, $J \approx$ 9.7, 4.3, H–C(4)); 3.61 (br. ddt, ^3J(F,H) = 14.1, $J \approx$ 5.6, 1.5, H–C(2)); 3.46 (br. ddt, $J \approx$ 6.9, 5.6, 0.5, H_{exo}–C(6)). ^{13}C-NMR (100 MHz, 26 mM in $CDCl_3$): see *Table 1*. ^{13}C-NMR (100 MHz, 43 mM in (D_6)DMSO): see *Table 1*. ^{19}F-NMR (37.6 MHz, 26 mM in $CDCl_3$): –204.44 ($dddd$, J = 48.7, 26.2, 11.2, 4.5). ^{19}F-NMR (37.6 MHz, 43 mM in (D_6)DMSO): –199.63 (ddd, J = 48.9, 29.7, 14.2). HR-ESI-MS: 186.9953 ($[M+Na]^+$, $C_6H_9FNaO_4^+$; calc. 187.0383). HR-EI-MS: 144.0419 (1, $[M-HF]^+$, $C_6H_8O_4^+$; calc. 144.0423), 73.0273 (100), 72.0264 (43), 71.0132 (16), 62.0162 (17), 57.0337 (61), 56.0266 (54), 55.0189 (31), 47.0166 (26), 45.0338 (19), 44.0296 (28), 43.0226 (31). Anal. calc. for $C_6H_9FO_4$ (164.13): C 43.91, H 5.53, F 11.58; found: C 44.07, H 5.54, F 11.57.

Silylation of **9**. A soln. of **9** (563 mg, 3.4 mmol) in pyridine/CH_2Cl_2 1:1 (8 ml) at 0° was treated with ^{i}Pr$_3$SiCl (TIPSCl) (2.2 ml, 8.2 mmol) and stirred for 60 min. Dilution with H_2O, extraction with Et_2O, washing with 1M HCl and sat. $NaHCO_3$ soln. (2×), drying ($MgSO_4$), evaporation, and FC (cyclohexane/AcOEt 4:1) gave a mixture containing the disilyl ether derived from **9** (256 mg, *ca.* 15%; R_f (cyclohexane/AcOEt 2:1) 0.72), a 9:1 mixture of TIPSCl and **13** (455 mg, *ca.* 7% of **13**), *ca.* 95% pure **12** (128 mg, *ca.* 11%), and pure **12** (686 mg, 62%).

*Data of 1,6-Anhydro-4-deoxy-4-fluoro-2-*O*-(triisopropylsilyl)-β-*D*-glucopyranose* (**12**). R_f (cyclohexane/AcOEt 2:1) 0.34. ^{1}H-NMR (300 MHz, 28 mM in $CDCl_3$): 5.43 (br. s, H–C(1)); 4.71 (ddt, ^3J(F,H) = 12.8, J = 5.2, 1.5, H–C(5)); 4.41 ($dquint.$, ^2J(F,H) = 46.3, J = 1.4, H–C(4)); 3.99 (dt, J = 7.8, 0.9, ^4J(F,H) = 0.9, H_{endo}–C(6)); 3.86 ($ddtt$, ^3J(F,H) = 16.5, J = 6.9, 2.8, 1.4, H–C(3)); 3.74 (ddd, J = 7.8, 5.3, ^4J(F,H) = 4.4, H_{exo}–C(6)); 3.64 (br. t, J = 1.3, H–C(2)); 2.24 (d, J = 6.9, HO–C(3)); 1.11–1.04 (m, $(Me_2CH)_3Si$). HR-EI-MS: 259.1364 (15, $[M-H_2O-MeCHMe]^+$, $C_{12}H_{20}FO_3Si^+$; calc. 259.1166), 213.1303 (20), 173.0993 (49, ^{i}Pr$_3$SiO$^+$), 159.0839 (17), 131.0888 (40), 103.0570 (41), 87.0449 (33), 83.0485 (100), 75.0260 (60), 73.0456 (16), 69.0322 (20), 61.0117 (40), 59.0322 (43), 55.0559 (18), 45.0218 (15), 43.0192 (23), 41.0452 (22).

*Data of 1,6-Anhydro-4-deoxy-4-fluoro-3-*O*-(triisopropylsilyl)-β-*D*-glucopyranose* (**13**). R_f (cyclohexane/AcOEt 2:1) 0.46. ^{1}H-NMR (300 MHz, 5 mM in $CDCl_3$; TIPSCl/**13** 9:1): 5.46 (br. t, $J \approx$ 1.6, H–C(1)); 4.71–4.66 (m, H–C(5)); 4.41 (dq, ^2J(F,H) = 44.5, J = 1.6, H–C(4)); 4.18 (dt, J = 7.2, 1.3, ^4J(F,H) = 1.3, H_{endo}–C(6)); 4.03 ($dquint.$, ^3J(F,H) = 14.3, J = 1.7, H–C(3)); 3.79 (ddd, J = 7.2, 5.9, ^4J(F,H) = 5.3, H_{exo}–C(6)); 3.49 (dq, J = 12.1, 1.6, H–C(2)); 2.23 (dd, J = 12.1, ^{h1}J(F,H) = 1.6, HO–C(2)); 1.10–0.99 (m, $(Me_2CH)_3Si$ and TIPSCl).

*3-*O*-Acetyl-1,6-anhydro-4-deoxy-4-fluoro-2-*O*-(triisopropylsilyl)-β-*D*-glucopyranose* (**14**). A soln. of **12** (813.5 mg, 2.5 mmol) and DMAP (132 mg, 1.0 mmol) in pyridine (3 ml) was treated with Ac_2O

(0.6 ml) and stirred for 15 min, it turned yellow. The mixture was poured into a sat. $NaHCO_3$ soln. (cooling and stirring) and treated portionwise with solid $NaHCO_3$, until gas evolution ceased. After extraction with AcOEt and washing of the org. layer with brine (1×), 2N $CuSO_4$ (several times, until the absence of a colour change), brine (2×), and H_2O (1×), drying ($MgSO_4$), and evaporation, FC (cyclohexane/AcOEt 4:1) gave **14** (760 mg, 83%). Colourless oil. R_f (cyclohexane/AcOEt 2:1) 0.40. ^{1}H-NMR (300 MHz, 21 mM in $CDCl_3$): 5.41 (br. *s*, H–C(1)); 4.97 (*dquint.*, ^3J(F,H) = 16.5, J = 1.9, H–C(3)); 4.75–4.68 (*m*, H–C(5)); 4.31 (br. *d*, ^2J(F,H) = 44.5, H–C(4)); 3.95 (br. *d*, J = 7.8, H_{endo}–C(6)); 3.77 (*ddd*, J = 7.8, 5.7, ^4J(F,H) = 5.1, H_{exo}–C(6)); 3.64 (br. *s*, H–C(2)); 2.11 (*s*, AcO); 1.14–1.00 (*m*, $(Me_2CH)_3Si$).

Desilylation of **14**. A soln. of $Bu_4NF \cdot 3\,H_2O$ (1.848 g, 5.9 mmol) and 15-crown-5 (220 mg, 1.0 mmol) in THF (10 ml) was treated with $KHCO_3$ (3.460 g, 34.56 mmol) and then with a soln. of **14** (688 mg, 1.9 mmol) in THF (5 ml; pH ≈ 7), and stirred for 10 min at 0°. Immediate filtration through silica gel and FC (cyclohexane/AcOEt 2:1) gave a 2:9 mixture of **16** and ^{i}Pr$_3$SiF (49 mg, *ca.* 3% of **16**), and **15** (184 mg, 47%).

*Data of 3-*O*-Acetyl-1,6-anhydro-4-deoxy-4-fluoro-β-*D*-glucopyranose* (**15**) [43]. R_f (cyclohexane/AcOEt 2:1) 0.14. M.p. 101–103° ([43]: 102–104°). IR (141 mM in $CHCl_3$): 3571*w*, 3490*w* (br.), 2969*w*, 2907*w*, 1750*s*, 1479*w*, 1398*w*, 1373*m*, 1350*w*, 1293*w*, 1230*s*, 1149*m*, 1115*m*, 1082*w*, 1067*s*, 1052*s*, 1024*m*, 1008*m*, 986*m*, 963*w*. ^{1}H-NMR (400 MHz, 35 mM in $CDCl_3$; F-coupled and F-decoupled spectrum): 5.47 (br. *t*, J = 1.5, H–C(1)); 4.95 (*dquint.*, ^3J(F,H) = 16.3, J = 1.7, H–C(3)); 4.73 (br. *dddt*, ^3J(F,H) = 10.7, J = 5.9, 1.2, 0.6, H–C(5)); 4.42 (*dtdd*, ^2J(F,H) = 44.2, J = 1.8, 1.2, 0.6, H–C(4)); 4.01 (*dtd*, J = 7.8, 1.1, 0.3, ^4J(F,H) = 1.1, H_{endo}–C(6)); 3.83 (*dt*, J ≈ 7.8, 5.2, ^4J(F,H) ≈ 5.2, H_{exo}–C(6)); 3.50 (*dq*, J = 10.1, 1.4, H–C(2)); 2.58 (br. *dd*, J = 10.3, ^{h1}J(F,H) = 1.2, HO–C(2)); 2.12 (*s*, AcO). ^{1}H-NMR (400 MHz, 70 mM in (D_6)DMSO; F-coupled and F-decoupled spectrum): 5.52 (*d*, J = 4.5, HO–C(2)); 5.28 (br. *s*, H–C(1)); 4.72 (*dquint.*, ^3J(F,H) = 18.0, J = 1.7, H–C(3)); 4.705 (br. *ddq*, ^3J(F,H) = 12.5, J = 6.0, 1.5, H–C(5)); 4.47 (br. *dt*, ^2J(F,H) = 45.1, J = 1.5, H–C(4)); 3.87 (*dt*, J = 7.8, 1.2, ^4J(F,H) = 1.2, H_{endo}–C(6)); 3.61 (*ddd*, J = 7.8, 5.8, ^4J(F,H) = 4.8, H_{exo}–C(6)); 3.30–3.26 (br. *s*, H–C(2)); 2.05 (*s*, AcO). ^{13}C-NMR (100 MHz, 35 mM in $CDCl_3$): see *Table 1*. ^{13}C-NMR (100 MHz, 70 mM in (D_6)DMSO): see *Table 1*. ^{19}F-NMR (37.6 MHz, 35 mM in $CDCl_3$): −182.94 (br. *dddd*, J = 44.4, 16.3, 10.8, 4.8). ^{19}F-NMR (37.6 MHz, 60 mM in (D_6)DMSO): −181.10 (*ddddd*, J = 45.3, 17.9, 12.6, 4.6, 1.0).

*Data of 2,3-Di-*O*-acetyl-1,6-anhydro-4-deoxy-4-fluoro-β-*D*-glucopyranose* (**16**) [42]. R_f (cyclohexane/AcOEt 2:1) 0.30. ^{1}H-NMR (300 MHz, 8 mM in $CDCl_3$; **16**/^{i}Pr$_3$SiF 2:9): 5.48 (br. *t*, J = 1.2, H–C(1)); 4.99 (*dquint.*, ^3J(F,H) = 16.8, J = 1.6, H–C(3)); 4.79–4.74 (*m*, H–C(5)); 4.60 (br. *d*, J = 1.2, H–C(2)); 4.38 (br. *dquint.*, ^2J(F,H) = 44.5, J = 1.2, H–C(4)); 4.00 (br. *d*, J = 7.8, H_{endo}–C(6)); 3.82 (*dt*, J = 7.5, 5.1, ^4J(F,H) = 5.1, H_{exo}–C(6)); 2.15, 2.13 (2*s*, 2 AcO); 1.10–0.98 (*m*, ^{i}Pr$_3$SiF).

*1,6-Anhydro-4-deoxy-4-*C*-methyl-2-*O*-(triisopropylsilyl)-β-*D*-glucopyranose* (**18**). According to [41], a soln. of CuI (64.5 mg, 0.34 mmol) in freshly distilled THF (16 ml) was cooled to −45°, treated with a soln. of MeMgCl in THF (10.93 ml, 25.88 mmol) and then portionwise with **17** [38] (1.009 g, 3.36 mmol). The mixture was allowed to warm to r.t. and stirred for 17.5 h. The resulting dark yellow soln. was cooled to 0° and diluted with Et_2O (40 ml; evolution of gas and formation of a grey precipitate). The mixture was poured portionwise into a 5M aq. NH_4Cl soln. (40 ml; evolution of gas). The colour of the org. layer changed to yellow and that of the aq. layer to dark blue. The mixture was diluted with Et_2O and washed with 5M NH_4Cl soln. The combined org. layers were dried ($MgSO_4$) and evaporated. FC (AcOEt/hexane 1:3) and drying *i.v.* gave **18** (337 mg, 32%). Colourless oil. R_f (AcOEt/hexane 2:1) 0.10. $[\alpha]_D^{25} = -23.6$ (c = 1.07, $CHCl_3$). IR (94 mM in $CHCl_3$): 3570*w*, 3440*w* (br.), 3008*w*, 2982*s*, 2896*m*, 2868*s*, 1464*m*, 1384*w*, 1367*w*, 1115*s*, 1075*m*, 1048*w*, 1018*s*, 957*w*, 903*w*, 882*s*, 861*m*. ^{1}H-NMR (200 MHz, 23 mM in $CDCl_3$): 5.40 (br. *s*, H–C(1)); 4.29 (br. *d*, J = 5.1, H–C(5)); 4.11 (*d*, J = 7.0, H_{endo}–C(6)); 3.71 (*dd*, J = 7.0, 4.9, H_{exo}–C(6)); 3.64 (*q*, J = 1.8, H–C(2)); 3.53 (*dquint.*, J = 7.8, 1.6, H–C(3)); 2.33 (*d*, J = 7.8, HO–C(3)); 1.84 (br. *q*, J ≈ 7.3, H–C(4)); 1.29 (*d*, J = 7.4, Me); 1.10–1.01 (*m*, $(Me_2CH)_3Si$).

*1,6-Anhydro-4-deoxy-4-*C*-methyl-β-*D*-glucopyranose* (**19**). A soln. of **18** (152 mg, 0.48 mmol) in THF (3 ml) was treated with 1M $Bu_4NF \cdot 3\,H_2O$ in THF (1.4 ml), stirred for 15 min, treated with AcOH (32.1 mg, 0.54 mmol), and stirred for 5 min. FC (AcOEt/hexane 1:1) of this soln. and drying *i.v.* gave **19** (52 mg, 68%). Colourless crystals. R_f (AcOEt/hexane 2:1) 0.08. M.p. 69.4–70.0°. $[\alpha]_D^{25} = -83.0$ (c = 0.51, $CHCl_3$). IR (119 mM in $CHCl_3$): 3583*m*, 3426*w* (br.), 2969*m*, 2902*m*, 1456*w*, 1396*w*, 1329*w*, 1147*m*, 1116*w*,

1061*s*, 1018*s*, 980*w*, 954*m*, 923*m*, 872*m*, 846*w*. ^{1}H-NMR (600 MHz, 18 mM in $CDCl_3$): 5.45 (*td*, $J \approx 1.7$, 0.4, H–C(1)); 4.32 (br. *d*, $J = 5.1$, H–C(5)); 4.13 (*ddd*, $J = 7.1$, 0.7, 0.3, H_{endo}–C(6)); 3.78 (*ddd*, $J = 7.1$, 5.1, 0.4, H_{exo}–C(6)); 3.57 (*dquint.*, $J = 6.9$, 1.5, H–C(3)); 3.56 (br. *d*, $J = 8.9$, H–C(2)); 2.33 (*d*, $J = 6.9$, HO–C(3)); 1.98 (*d*, $J = 8.6$, HO–C(2)); 1.87 (*qdt*, $J = 7.6$, 2.2, 1.5, H–C(4)); 1.28 (*d*, $J = 7.6$, Me). ^{13}C-NMR (150.9 MHz, 18 mM in $CDCl_3$): see *Table 2*. HR-EI-MS: 142.0630 (1, $[M - H_2O]^+$, $C_7H_{10}O_3^+$; calc. 142.0630), 72.0572 (20), 71.0494 (34), 60.0208 (100), 57.0356 (22), 55.0567 (69), 43.0249 (24), 41.0465 (21).

Table 2. *^{13}C-NMR Chemical-Shift Values* [ppm] *of the 4-Deoxylevoglucosans* **19**–**23** *in $CDCl_3$*

C-Atom	**19**	**20**	**21**	**22**	**23**
C(1)	102.4	102.33	101.68	101.72	101.29
C(2)	71.89	71.27[a])	70.27[a])	70.79[a])	70.08[a])
C(3)	74.09	69.63	68.57	69.18	68.34
C(4)	39.13	32.86	32.59	30.67	30.61
C(5)	77.31	71.94[a])	72.27[a])	71.08[a])	71.55[a])
C(6)	68.39	67.30	67.62	67.05	67.46
Me–C(4)	18.08	–	–	–	–
AcO	–	–	–	169.84, 21.40	170.52, 21.45
^{i}Pr$_3$SiO	–	18.01, 12.26	–	18.02, 12.29	–

[a]) Assignments may be interchanged.

*1,6-Anhydro-4-deoxy-2-*O*-(triisopropylsilyl)-β-*D*-*xylo*-hexopyranose* (**20**). A soln. of **17** (2.020 g, 6.72 mmol) and 1M $LiEt_3BH$ in THF (40 ml, 40 mmol) in THF (18 ml) was stirred for 95 min at r.t., diluted with AcOEt, washed with brine (3×), dried ($MgSO_4$), and evaporated. A suspension of the residue in AcOEt was treated with charcoal and filtered through *Celite*. FC (cyclohexane/AcOEt 2:1) gave an impure fraction of **20** (0.388 g, *ca.* 10%) and pure **20** (1.463 g, 72%). R_f (cyclohexane/AcOEt 2:1) 0.25, R_f (cyclohexane/AcOEt 1:1) 0.48. $[\alpha]_D^{25} = -11.2$ ($c = 0.55$, $CHCl_3$). IR (99 mM in $CHCl_3$): 3566*w*, 2960*s*, 2946*s*, 2896*s*, 2868*s*, 1464*m*, 1423*w*, 1384*w*, 1368*w*, 1349*w*, 1325*w*, 1254*w*, 1244*w*, 1188*m*, 1124*s*, 1083*s*, 1055*m*, 1014*m*, 994*m*, 968*w*. ^{1}H-NMR (300 MHz, 31 mM in $CDCl_3$): 5.42 (br. *s*, H–C(1)); 4.52 (br. *t*, $J \approx 4.2$, H–C(5)); 4.14 (*d*, $J = 7.2$, H_{endo}–C(6)); 3.77 (br. *tquint.*, $J \approx 6.9$, 1.4, H–C(3)); 3.71–3.66 (*m*, H–C(2), H_{exo}–C(6)); 2.49 (*d*, $J = 8.4$, HO–C(3)); 2.34 (*dddd*, $J \approx 15.9$, 5.1, 4.1, 1.4, H_{ax}–C(4)); 1.72 (br. *d*, $J \approx 14.6$, H_{eq}–C(4)); 1.16–1.01 (*m*, $(Me_2CH)_3Si$). ^{13}C-NMR (75 MHz, 95 mM in $CDCl_3$): see *Table 2*.

*1,6-Anhydro-4-deoxy-β-*D*-xylo-hexopyranose* (**21**) [48][49]. A soln. of **20** (1.353 g, 4.5 mmol) and 1M $Bu_4NF \cdot 3\ H_2O$ in THF (13.4 mmol) in THF (15 ml) was stirred for 0.5 h at r.t. FC, evaporation, and crystallisation from AcOEt/hexane gave **21** (592 mg, 91%). White, hygroscopic crystalline product. R_f (AcOEt) 0.11. M.p. 138–143° ([48]: 158–160°, [49]: 158°). IR (89 mM in $CHCl_3$): 3615*w*, 3570*m*, 3475*w* (sh), 2962*m*, 2904*w*, 1478*w*, 1428*w*, 1394*w*, 1364*w*, 1349*w*, 1326*w*, 1309*w*, 1261*m*, 1220*w*, 1183*m*, 1128*m*, 1092*m*, 1084*m*, 1057*s*, 1009*s*, 994*m*, 965*m*. ^{1}H-NMR (300 MHz, 19 mM in $CDCl_3$): 5.48 (br. *s*, H–C(1)); 4.55 (br. *t*, $J = 4.5$, H–C(5)); 4.20 (*d*, $J = 7.2$, H_{endo}–C(6)); 3.84 (*ddquint.*, $J = 8.1$, 5.1, 1.5, addition of $D_2O \rightarrow$ br. *d*, $J \approx 5.1$, H–C(3)); 3.76 (*ddd*, $J = 7.2$, 5.1, 1.5, H_{exo}–C(6)); 3.59 (br. *dq*, $J = 10.2$, 1.5, addition of $D_2O \rightarrow$ br. *s*, H–C(2)); 2.52 (*d*, $J = 7.8$, exchange with D_2O, HO–C(3)); 2.31 (*dddd*, $J = 15.3$, 5.1, 4.2, 1.5, H_{ax}–C(4)); 2.20 (*d*, $J \approx 10.2$, exchange with D_2O, HO–C(2)); 1.78 (*dquint.*, $J = 15.3$, 1.5, H_{eq}–C(4)). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 2*.

*3-*O*-Acetyl-1,6-anhydro-4-deoxy-2-*O*-(triisopropylsilyl)-β-*D*-xylo-hexopyranose* (**22**). A suspension of **20** (2.116 g, 7 mmol) and DMAP (0.428 g, 4 mmol) in Ac_2O (37 ml) and pyridine (50 ml) was stirred for 10 min. The resulting yellow soln. was poured into a cold sat. $NaHCO_3$ soln. and treated portionwise with solid $NaHCO_3$, until gas evolution ceased. Dilution with AcOEt, washing with brine (1×) and 2N $CuSO_4$ (several times, until absence of the colour change), drying ($MgSO_4$), and FC (cyclohexane/

AcOEt 4:1) gave **22** (1.367 g, 59%). R_f (cyclohexane/AcOEt 2:1) 0.39. $[\alpha]_D^{25} = -24.2$ ($c = 0.6$, $CHCl_3$). IR (57 mM in $CHCl_3$): 2962*s*, 2946*s*, 2897*m*, 2868*s*, 1728*s*, 1464*m*, 1423*w*, 1385*w*, 1372*m*, 1350*w*, 1336*w*, 1246*s*, 1198*m*, 1118*s*, 1076*m*, 1047*s*, 1008*s*, 967*w*, 948*w*. ^{1}H-NMR (300 MHz, 34 mM in $CDCl_3$): 5.36 (br. *s*, H–C(1)); 4.82 (br. *dquint.*, $J = 5.6$, 1.2, H–C(3)); 4.50 (br. *t*, $J \approx 5.4$, H–C(5)); 4.06 (*d*, $J = 6.8$, H_{endo}–C(6)); 3.72 (*ddd*, $J = 6.8$, 5.4, 1.2, H_{exo}–C(6)); 3.66 (br. *q*, $J = 1.2$, H–C(2)); 2.44 (br. *dddd*, $J =$ 15.2, 5.6, 4.0, 1.6, H_{ax}–C(4)); 2.08 (*s*, AcO); 1.62 (br. *d*, $J = 15.2$, H_{eq}–C(4)); 1.10–1.02 (*m*, $(Me_2CH)_3Si$). ^{13}C-NMR (75 MHz, 68 mM in $CDCl_3$): see *Table 2*. HR-EI-MS: 301.1467 (22, $[M - MeCHMe]^+$, $C_{14}H_{25}O_5Si^+$; calc. 301.1471), 241.1253 (13), 175.0982 (14), 174.1021 (45), 173.0949 (100, $^iPr_3SiO^+$), 159.0844 (10), 131.0893 (15), 103.0578 (17), 83.0488 (39), 75.0261 (29), 73.0465 (14), 61.0126 (21), 59.0324 (34), 43.0231 (65).

3-O-*Acetyl-1,6-anhydro-4-deoxy-β*-D-xylo-*hexopyranose* (**23**). A soln. of $Bu_4NF \cdot 3\ H_2O$ (1.284 g, 4.07 mmol) in THF (10 ml) was treated with $NaHCO_3$ (1.124 g, 13.37 mmol) and then with a soln. of **22** (905 mg, 2.63 mmol) in THF (2 ml), and stirred for 10 min at r.t. Two FCs (cyclohexane/AcOEt 1:1) gave **23** (448 mg, 91%). R_f (AcOEt) 0.36. IR (117 mM in $CHCl_3$): 3609*w*, 3571*w*, 3463*w* (br.), 2964*w*, 2934*w*, 2902*w*, 1732*s*, 1478*w*, 1428*w*, 1372*m*, 1246*s*, 1196*m*, 1139*m*, 1110*m*, 1060*m*, 1050*s*, 1014*m*, 966*w*, 953*m*. ^{1}H-NMR (300 MHz, 19 mM in $CDCl_3$): 5.41 (br. *s*, H–C(1)); 4.84 (*dquint.*, $J = 5.6$, 1.3, H–C(3)); 4.52 (br. *t*, $J \approx 4.5$, H–C(5)); 4.10 (*d*, $J = 6.9$, H_{endo}–C(6)); 3.78 (*ddd*, $J = 6.8$, 5.3, 1.6, H_{exo}–C(6)); 3.57 (*dq*, $J = 9.2$, 1.6, H–C(2)); 2.42 (*dddd*, $J = 15.6$, 5.6, 4.3, 1.6, H_{ax}–C(4)); 2.22 (*d*, $J = 9.0$, HO–C(2)); 2.09 (*s*, AcO); 1.70 (*dquint.*, $J = 15.8$, 1.3, H_{eq}–C(4)). ^{13}C-NMR (75 MHz, 125 mM in $CDCl_3$): see *Table 2*.

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