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PHOTOHALOGENATION OF GLYCOPYRANOSYL HALIDES: AN EXPEDIENT ROUTE TO C-1 GEM DIHALOGENATED SUGARS

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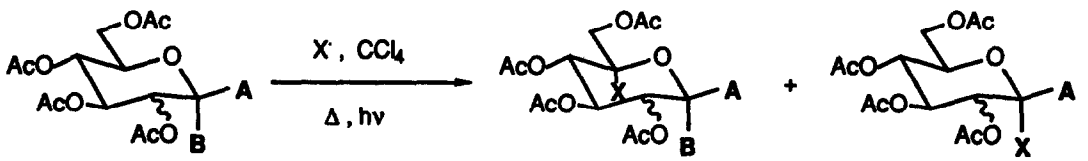
Abstract: Free-radical halogenation of peracetylated α and β-glycopyranosyl halides of $^4C_1$-D chair conformation takes place at C-1 or C-5 with an α-stereoselectivity. However the less reactive α-chloride and bromide moieties at first undergo a dehydrohalogenation reaction. β-Chlorides when treated with N-bromosuccinimide give new C-1 gem chlorobromo sugars in 65-70 % yield while new C-5 halogenated compounds are obtained predominantly with β-fluorides or when chlorination is carried out with sulfuryl chloride SO_2Cl_2. The peracetylated C-1 gem chlorobromo derivative of gluco configuration can be cleanly dehydrobrominated to yield a C-1 chlorinated glucal. It also reacts chemio and stereoselectively in the presence of silver fluoride to give the corresponding new C-1 gem chlorofluoro or difluoro derivatives, either in 70 % yield, depending on the stoechiometry. All these new compounds exhibit a good to excellent stability. ^{19}F- n.m.r. of three peracetylated 1-halogeno- β-D-glucopyranosyl fluorides shows that the J_{F,C_1} coupling constants increase with the increasing electronegativity of the geminal axial halogen while $^3J_{F,H}$ decreases.

The growing popularity [1,2,3,4] of free-radical processes has spurred recent developments in carbohydrate chemistry [5] and both domains benefit each other. In effect, these generally mild and chemioselective methods are compatible with highly functionalized substrates such as protected sugars [6]. In turn, the chirality contained in carbohydrates has been exploited to achieve highly stereoselective transformations [7,8,9], highlighting the specificities and the potential of free-radical approaches for the synthetic chemist [10]. Moreover, properly designed sugar derivatives are ideally suited for structural analysis of carbon radicals by E. S. R. techniques in view of a better understanding of their basic properties [11,12] and, consequently, a satisfactory rationale of the related chemical transformations. In connection with our interest in both free-radical chemistry[8] and stereoelectronic effects at the anomeric carbon [13], we focused our attention on photohalogenation reactions of sugar halides [14].

Although the photobromination reaction has been applied to O- [15], S- [16] and C-glycopyranosides[17,18] as well as furanosides [19] and uronic acid [20] derivatives, the reactivity of protected glycopyranosyl halides is not documented. However, a fortuitous synthesis of the first C-1 gem dibromo sugar [21] as well as the accessibility to C-1 nitrobromo [22] and nitrosobromo [23] sugars supported the hope of a possible access to a new class of C-1 gem dihalogenated sugars from readily available glycosyl halides.

To this end, photobromination of compounds 1 - 5, 8 and 9 has been carried out in a refluxing perhalomethane solution containing N-bromosuccinimide in excess, over a 250.W tungsten lamp[21]. A close examination of the resulting product distribution achieved with carbon tetrachloride as the solvent showed that it was sometimes more advantageous (see below) to use it in admixture with bromotrichloromethane (80-20 v/v, respectively). The use of solvents such as dichloromethane or chloroform did not offer preparative advantages [24]. Though the use of N-chlorosuccinimide results in a slower [18] and less selective transformation of compounds 1 and 8, their photochlorination has been successfully achieved by means of sulfuryl chloride and azo-bisisobutyronitrile (AIBN) in refluxing carbon tetrachloride. The outcome of these photohalogenations is shown in Scheme 1 as well as two closely related literature data [18,21].



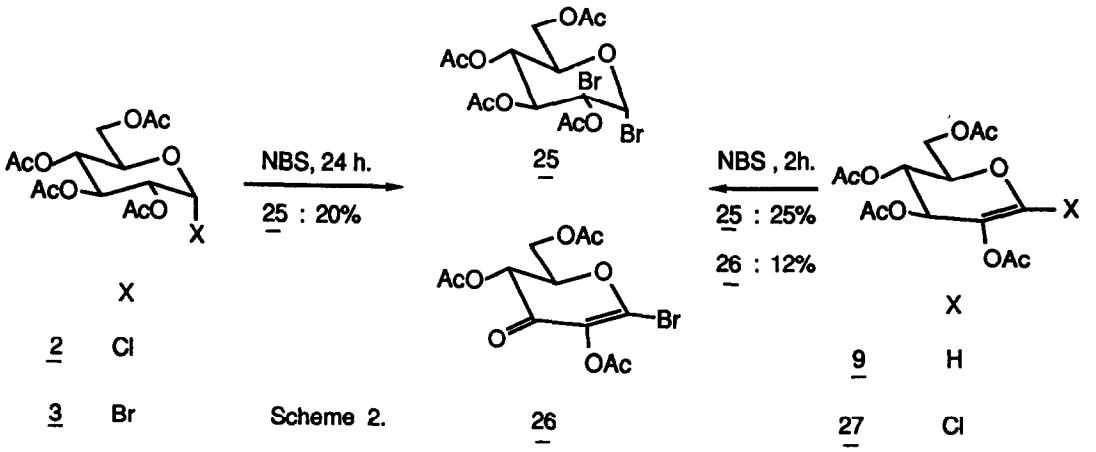
1 - 8 10 - 17 18 - 24

	A	B	Reaction time (h.)[a]	X		Products (yield %)
	Gluco configuration					
1	Cl	H	0.75	Br	10 : 14	18 : 65
1	Cl	H	18.5*	Cl	11 : 17	19 : 34
1	Cl	H	8.0**	Cl	11 : 52	19 : 16
2	H	Cl	25.0[b]	-	-	-
3	H	Br	24.0	-	-	-
4	F	H	2.5	Br	12 : 56	20 : 4
5	H	F	23[c]	Br	13 : 57	-
8[21]	OAc	H	2.0	Br	14 : 82	21 : 0
7[18]	CN	H	0.5	Br	15 : 0	22 : 83
	Manno configuration					
8	Cl	H	0.7	Br	16 : 12	23 : 72
8	Cl	H	8.0**	Cl	17 : 39	24 : 25

Scheme 1: a- The photohalogenations were carried out in the presence of N-bromosuccinimide unless otherwise indicated. The other halogenating agents are N-chlorosuccinimide (*) and sulfurylchloride (**). b- 25 % of the starting material was recovered. c- 15 % of the starting material was recovered.

From a synthetic point of view, it is interesting to note that the peracetylated β-chlorides 1 and 8 undergo a regio and stereoselective photobromination at the anomeric carbon. These transformations constitute an efficient route to the up- to - now unknown protected C-1 chlorobromo sugars, since yields as high as 65-70 % can be obtained for the syntheses of 18 and 23. Moreover, comparable yields are observed when the crude syrupy β-chloride 1, which results quantitatively from the treatment of β-D-glucopyranose pentaecetate (up to 12 g.) by aluminium trichloride in dry chloroform [25], is submitted to the photobromination reaction. In contrast to the preceeding results, the other sets of conditions used for the transformation of the β -halides 1, 4 and 8 favour the regio and stereoselective halogenation of C-5 to the detriment of the C-1 gem dihalogenated sugars 19, 20 and 24 which remain difficult to prepare in large amounts.

On the other hand, the peracetylated α-chloride and bromine 2 and 3 which are not completely transformed after 24 hours in the presence of N-bromosuccinimide, lead to compound 25 in a 20 % yield. After 2 hours of heating in the same conditions the unsaturated sugar 9 also yields compound 25 (25 % yield) together with the bromoenone 26 (12 % yield) (Scheme 2). Therefore, 9 is probably a common intermediate obtained from 2 and 3 via a dehydrohalogenation reaction. The reaction is supposed to proceed by subsequent addition of the in situ generated bromine on the carbon-carbon double bond. The stereoselective addition of bromine on the benzoylated analog of 9 also yields a trans diaxial dibromide of α -anomeric configuration [24]. Such an elimination is prevented in the case of the more stable α-fluoride 5 which mainly yields the C-5 brominated derivative 13 along with minor unidentified products.

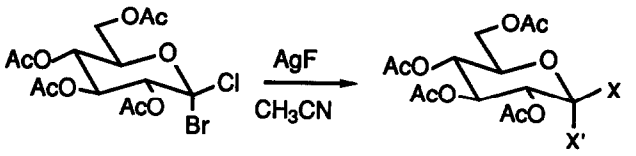


Scheme 2.

^{13}C-n.m.r. spectroscopy and to a lesser extent infra-red studies show that crude crystalline 18 is contaminated by the dichloride 19 (up to 20 %), unless careful purification is achieved by repeated crystallizations. Moreover, stirring an acetonitrile solution of crystalline 18 in the presence of 1.4-diazabicyclo [2.2.2]-octane (DABCO; 3 equivalents) resulted in the quantitative dehydrobromination of 18 [26]. The remaining unchanged starting material turned out to be the

dichloride **19** (10-20 %) which can be easily separated from the more polar chlorinated glucal **27**. Similarly, the syrupy manno derivative **23** is spoiled by comparable amounts of **24** which cannot be removed since crystallization and column chromatography are ineffective. The lower reactivity of the dichloride **19**, which is apparent from synthetic results, makes its presence troublesome for chemical transformations. Hence, the use of a solvent preventing chlorine abstraction to take place during the photobromination step is advisable in view of upgrading the purity of **18** and **23**. To this end, mixtures of carbon tetrachloride and bromotrichloromethane [27] were used as solvent. With an 80-20 mixture, ^{13}C-n.m.r. shows **19** and **24** to be present as trace components [28] in the outcoming **18** or **23**.

Two other C-1 gem dihalogenated compounds have been obtained from **18** by nucleophilic displacement of the halogen atoms (Scheme 3). In effect, treatment of this compound by silver fluoride (1.25 equivalent) in acetonitrile for ca. 24 h. allows a chemio and stereoselective substitution of the bromine atom. The crystalline monofluoride **28** is then obtained in 70 % yield [29]. Use of a larger amount of silver fluoride (3.3 equivalents) lead to the crystalline anomeric gem difluoride **29** in the same yield. The high stereoselectivity of the monofluorination reaction can be rationalized on the basis of an SN_2 process or by the participating effect of the 2-acetoxy group, both pathways favouring the attack of the incoming fluoride anion from the β -side of the glucopyranosyl ring.



18

	X	X'	%
28	F	Cl	70
29	F	F	70
30	Cl	F	-

Scheme 3.

All the prepared dihalogenated sugars exhibit a good to excellent stability: pure crystalline **18** has been kept for months at room temperature, whereas the syrupy **23** decomposes within a few weeks in the same conditions. Nevertheless, it can be kept, as well as the C-5 brominated compounds, for a prolonged time in a freezer. As a result, these readily available compounds should be useful intermediates in carbohydrate chemistry due to the opportunity they offer to vary the synthetic transformations at the anomeric centre of carbohydrates [31].

The regioselectivity of the photohalogenation reaction appears to depend mainly on three factors: the anomeric configuration, the anomeric substituent and the halogenating agent. The

poor reactivity of α-halides [32] towards photohalogenation is shown by their persistance after prolonged treatments and by the structure of the outcoming products. Compound **25** is obtained through synthetic pathways which apparently do not involve hydrogen abstraction by a halogen atom. In glycopyranosyl halides which prefer the $^4C_1$-D chair conformation, abstraction of an equatorial hydrogen atom is therefore a disfavoured process. There are examples of homolytic cleavage of equatorial carbon-hydrogen or carbon-halogen bonds in some high-yielding reactions which involve reactive radicals (e.g. alkoxy radicals [33]) or electrophilic radicals (e.g. trialkyltin radicals [8]). However, the higher reactivity of β-glycopyranosides in processes involving the homolytic cleavage of an axial C-H bond at the anomeric centre [7] has been observed several times. In particular, abstraction of axially oriented hydrogen [34-36] atoms by excited benzophenone, in anchored acetalic systems to yield acetalic radicals, takes place about 8 times [37] faster than for equatorial hydrogen atoms. The lower reactivity of both α-glycosides and their heterocyclic analogs bearing an axial alkoxy group has been ascribed to the fact that they are thermodynamically more stable than the β-anomers and that they cannot directly yield the thermodynamically more stable radical [38]. Both α and β-fluorides **5** and **4** yield predominantly C-5 brominated derivatives which are isolated in comparable amounts. However, the slower reaction observed for **5** can be the consequence of a strong anomeric effect which involves a stabilizing interaction between an oxygen lone pair and the antiparallel carbon-fluorine bond [39]. Such a strong interaction is not expected to stabilize radicals at C-5 [36]. Its absence in **4**, owing to the β anomeric configuration should result in a higher reactivity of the axial C-5-H bond, in agreement with the shorter reaction time and the complete consumption of the starting material.

Considering the regioselectivities which are observed for the β-anomers when exposed to N-bromosuccinimide, the nature of the equatorial substituent at C-1 appears to play a major role. Hydrogen abstraction by bromine atom or possibly succinimidyl radicals [40] is a selective process which involves predominantly weakened bonds [40] to yield stabilized radicals. The captodative substitution [41] of carbon atoms affords such a stabilization which is exemplified by the highly regioselective bromination at C-1 observed for the β-nitrile **7** [18] and its analogs [17,42]. However, the preferred chlorination at C-5 for the β-chlorides **1** and **8** probably reflects the polar effect due to the electron-withdrawing halogen at C-1 in conjunction with the electrophilic character of the chlorine atom [40]. It is well-known that chlorination involves electron-rich centres while bromination is directed towards weakened carbon-hydrogen bonds [40]. This and the reactivity difference between α- and β-halides show that the stereoelectronic effects [40b] should be considered to explain the efficiency for β-substituents in allowing the homolytic substitution at the anomeric centre with the sequence: CN > Cl >> F > OAc.

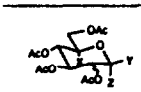
These free-radical halogenations show a high stereoselectivity which favours α-attack at C-1 or C-5 as observed for similar photohalogenation [17,18,21] or related C-O [33], C-C [9, 44], C-H [8] bond forming processes. At first, this generally observed α-stereoselectivity has been explained taking into account the anomeric effect in α-oxygenated radicals or the radical shielding by vicinal substituent, particularly for sugars of manno configuration [45]. However, intramolecular

carbon-carbon bond formation from the β-side of the sugar ring has been observed [46]. This raises the question of the structural features of the intermediate free radicals. In effect, while the initial radical obtained from the α-bromide **3** at 77 K retains the $^4C_1$-D chair conformation of its precursor [47], higher temperatures allow a shift towards a slightly twisted $B_{2,5}$-D boat conformation [11]. However, the corresponding mannopyranosyl radical, which is comparatively more easily formed [11], favours the $^4C_1$-D chair conformation. These conformations allow a stabilizing coplanar arrangement between the p-orbital of the unpaired electron and the σ^* orbital (LUMO) of the adjacent β-C-OR bond [11]. This favourable interaction is presumed to overcompensate the steric destabilization due to the boat conformation of the intermediate glucopyranos-1-yl radical which may undergo a quasi-equatorial attack at the anomeric centre [9]. The E. S. R. study of the carbon-centered radicals generated from **18**, **23** and **28** presently in progress should provide a better insight of the transients which govern the stereoselectivity of these photohalogenations.

For most of these new compounds, structure determination is readily carried out by n.m.r. spectroscopy. In particular, C-5 substitution is evident on the basis of the H-5 signal disappearance with simultaneous observation of an AB spin system for the H-6 and H-6' protons. This substitution pattern by bromine or chlorine also results in a downfield shift of the C-5 carbon by 23 and 25 ppm, respectively. Furthermore, the axial orientation of the newly created carbon-halogen bond can be established from the downfield shift of the 1,3-syn axially oriented protons H-3 and H-1, or H-5 for C-1 gem dihalides [21]. These latter compounds are best recognized from the absence of an anomeric proton signal or by the observation of a quaternary carbon between 101-124 ppm for β-fluorinated moieties and 104-112 ppm for the β-chlorides **18**, **19**, **23** and **24**. In each group, the C-1 gem dichloro derivative gives the lowest field resonance. However, C-1 configuration assignment by nuclear magnetic resonance turned out to be poorly reliable because of the similar influence of the chlorine and bromine atoms on the 1,3-syn axially oriented protons, as indicated by the close resemblance of the ^{1}H-n.m.r. spectra of α-halides **2** and **3**. An X-ray structure determination carried out on crystalline **18** proved its anomeric configuration to be R (Scheme 4). The same conclusion was reached for the manno dihalide **23** on the basis of optical rotation comparison. In effect, replacement of the axial chlorine in **19** by bromine to give **18** increases the corresponding optical rotations from + 103° to + 136°. The difference between the optical rotations recorded for the manno derivatives **24** and **23** (+ 63.8° and + 96.7°) also amounts to 33°, thereby indicating an R anomeric configuration for **23** as well. This approach appears valid for compounds **20** and **28** which both differ from **18** and **19** by the presence of a β-fluorine atom instead of a chlorine atom. The difference between their optical rotation (+ 29°) also supports an R anomeric configuration in **20**, in agreement with reliable ^{13}C and ^{19}F n.m.r. data.

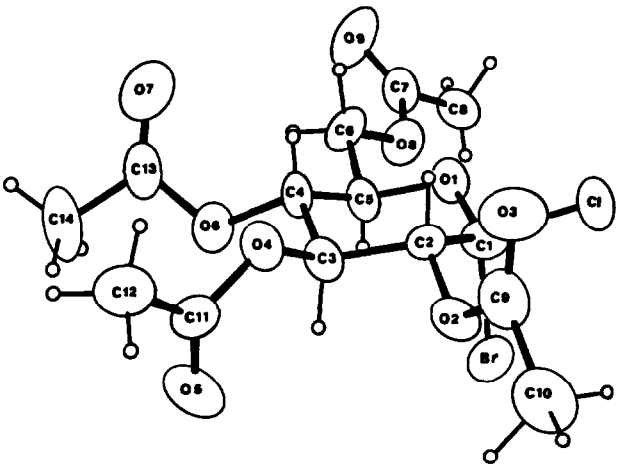
Structure determination turned out to be straightforward for fluorine containing samples due to the large number of angular dependent parameters available by ^{1}H, ^{13}C and ^{19}F-n.m.r.[48]. Besides the ^{19}F chemical shifts, more reliable information was extracted from the coupling constants: $^3J_{F,H}$, $^1J_{F,C}$ and $^3J_{F,C}$. However, $^2J_{F,H}$ is not very informative on the anomeric configuration. The data collected in this series lead to the following conclusions: (a) the unusually

Table I ^{1}H and ^{13}C-n.m.r. data [a]

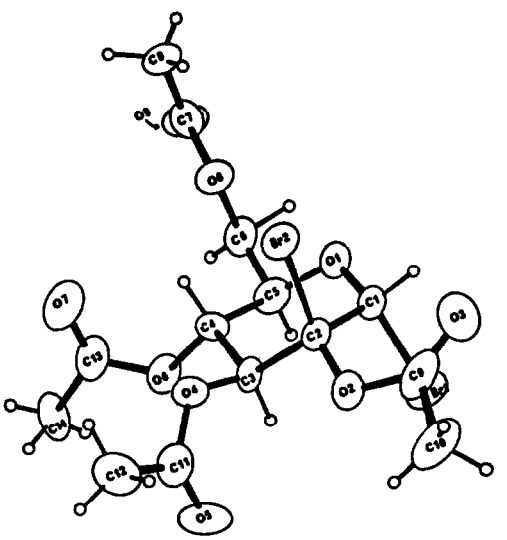


	X	Y	Z	H-1	H-2	H-3	H-4	H-5	H-6	H-6'	CH_3	C-1	C-2	C-3	C-4	C-5	C-6	C=O	CH_3
				$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$		$^{1}J_{F,C}$	$^{2}J_{F,C}$	$^{3}J_{F,C}$		$^{3}J_{F,C}$			
10	Br	Cl	H	5.73 9.3	5.30 9.4	5.50 9.4	5.29 -	- -	4.59 -	4 37 12.4	2.14 2.11 2.08 2.02	86.5	72.4	71.0	68.0	97.8	65.5	169.2 169.1 168.6 168.5	20.5 20.3
11	Cl	Cl	H	5 77 9.0	5.29 *	5.48 *	5.48 -	- -	4.24 -	4.48 12.0	2.14 2.11 2.08 2 02	84.9	72.8	70.2	68.1	100.2	64.9	169.8 169.8 169.0	20.8 20.5 20.5 20.4
12	Br	F	H	5.68 7.25 52.1[b]	5.27 9.5 14.0[c]	5.53 10.0	5.29 -	- -	4.56 -	4 41 12 6	2.13 2.12 2.09 2 02	106.6 -222.8	70.4 24.6	70.4 10.6	67.9	84.7 7.2	65.5	169.4 169.3 168.8 168.6	20.4
13	Br	H	F	5.93 3.5 52.9[b]	5.07 10.3 23.6[c]	5.65 10.3	5.22 -	- -	4.43 -	4.36 12 5	2.14 2.11 2.11 2.08	103.7 -239.6	69.3 22.7	67.7[**]	66.7[**]	91.9	66.0	169.5 169.1 168.9 168.7	20.4 20.3
16	Br	Cl	H	5.95 1.3	5.59 2.6	5.38 10.3	5.43 -	- -	4.57 -	4.41 12.5	2.25 2.14 2.11 2.00	85.0	69.6[**]	69.5[**]	65.3	99.8	66.1	169.7 169.5 169.2	20.6 20.6 20.4
17	Cl	Cl	H	6.02 1.2	5.60 3.1	5.40 10.5	5.63 -	- -	4.28 -	4.47 12.2	2.24 2.14 2.11 2.00	83.4	69.9[**]	68.4[**]	65.4	101.6	65.5	169.7 169.5 169.3	20.5 20.4 20.4
18	H	Cl	Br	- -	5.19 9.5	5.37 9 5	5.27 9.8	4.29 4.3	4.38 1.7	4.20 12.5	2.18 2.13 2.05 2.01	104.2	76.2[**]	71.6	66.3	76.1[**]	60.5	170.1 169.3 168.8 168.5	20.6 20.5 20.4
19	H	Cl	Cl	- -	5.44 9.5	5.38 9.2	5 28 9.7	4.35 *	4.35 *	4.19 11.0	2.18 2.13 2.04	111.9	75.8[**]	71.0	66.6	74.8[**]	60.7	170.5 169.7 169.2 168.9	20.7 20.5 20.5
23	H	Cl	Br	- -	5.73 3.3	5 79 10.0	5 35 10.1	4.22 5.5	4.34 *	4.22 13 2	2.23 2.13 2.08 2.00	101 5	74 8[**]	68.7	64.0	76.8[**]	61.04	170.3 169.3 169.3 168.9	20.5 20.3
24	H	Cl	Cl	- -	5.68 3.2	5.66 9.7	5.34 9.7	4.18 — 4.42 : m.[d] *			2.23 2.13 2.07 2.00	110 4	74.2[**]	68.7	64.2	75.4[**]	61.4	170.5 169.5 169.5 169.1	20.7 20.6 20.5 20.4
25				7.39 -	- -	5.61 9 6	5.47 9.5	4.18 — 4.32 : m.[d] *			2.15 2.12 2.11 2.07	88.4	69.7	71.2	67.1	73.2	61.1	169.9 169.9 168.7 168.6	21.5 20.4 20.3
26				- -	- -	- -	5.70 12.9	4 89 3.9	4.47 2.1	4.39 12.9	2.28 2.18 2.14	151.3	129.6	129.7	61.9	87.2	60.8	170.2 168.8 167.3	20.6 20.3 20.0
27				- -	- -	5.60 4.3	5 26 5.6	4.56 6.7	4.49 3.2	4.26 12.0	2.15 2.11 2.11 2.07	139.9	121.6	67.2[**]	67.4[**]	77.7	60.3	169.9 169.8 169.0 167.8	20.5 20.1
20	H	F	Br	- -	5.11 10.0 8.3[c]	5.38 9.5	5.25 12.2	4.15 — 4.45 : m.[d] *			2.14 2.12 2.06 2.02	120.3 -281.3	72.5 23.7	71.2 8.6	66.4	74.9 2.5	60.3	170.4 169.6 169.2 168.7	20.6 20.5 20.4
28	H	F	Cl	- -	5.23 — 5.45: m.[d] *			4.18 — 4.42 : m [d] *			2.14 2.10 2.04 2.01	123.7 -268.3	71.9 25.9	71.0 8.9	66.6	74.1 3.0	60.6	170.3 169.6 169.2 168.6	20.5 20.4 20.3
29	H	F	F	- -	5.37 *	5.37 9 2	5.26 9.2	4.19 *	4.19 4 3	4.32 13.3	2.14 2.12 2 05 2.03	120.3 -256.0 -271.7	68.7 30.6 30.6	70.7 9.4	66.6	72.6 2.8 4.0	60.63	170.1 169.4 168.9 168.7	20.5 20.3 20.2

a- The spectra have been obtained from deuteriochloroform solutions with tetramethylsilane as the internal reference. Chemical shifts (δ) and coupling constants (J) are expressed in p.p.m. and hertz, respectively. Coupling constants are not indicated for badly resolved spin systems (*). Some assignments may be reversed (**). b- $^{2}J_{F,H}$. c- $^{3}J_{F,H}$. d- m.= multiplet



Scheme 4: ORTEP drawing of compound **18**. Selected bond lengths (A) are: C5 - O1: 1.461 (8), O1 - C1: 1.353 (9), C1 - Cl: 1.771 (7), C1 - Br: 1.994 (8). Selected bond angles (degrees) are: Br - C1 - Cl: 107.3 (4), Br - C1 - O1: 112.3 (5), Br - C1 - C2: 109.0 (5), Cl - C1 - O1: 107.4 (5), Cl - C1 - C2: 108.9 (5).



Scheme 5: ORTEP drawing of compound **25**. Selected bond lengths (A) are: C5 - O1: 1.445 (11), O1 - C1: 1.369 (10), C1 - Br: 1.994 (9), C2 - Br: 1.968 (8). Selected bond angles (degrees) are: Br - C1 - O1: 111.3 (6), Br - C1 - C2: 108.8 (6), Br - C1 - H1: 104.9 (6).

low field resonance [49] of the axial fluorine atom in **13** result from a deshielding effect of the 1,3-syn diaxial bromine at C-5; (b) as a consequence of its negative sign, the $^{1}J_{F,C}$ coupling constant which involves the anomeric carbon is confirmed to be larger for equatorial fluorine atoms compared to axial nuclei [50], hence, the anomeric configuration induces comparable changes for the $^{1}J_{H,C}$ and $^{1}J_{F,C}$ coupling constants; (c) the $^{1}J_{F,C}$, $^{2}J_{F,C}$ and $^{3}J_{F,C}$ coupling constants (see Table 1 and experimental) increase [51] with the increasing electronegativity of the axial halogen at the anomeric carbon as seen in **20**, **26** and **29**, while $^{3}J_{F,H}$ decreases.

Compound **26** exhibits ^{1}H-n.m.r. and I.R. spectra which are very similar to those reported for the corresponding non-halogenated enone [52] (δ H-4: 5.67 ppm; $J_{4,5}$ = 12.8 Hz). Structure determination of **25** was achieved through X-ray analysis (Scheme 5) due to the difficulty of reaching a reliable conclusion from the literature data [53,54]. For both compounds **18** and **25**, the C-1-Br bond length is 1.994 A while the C-1-Cl bond in **18** is 1.771 A. These values show lower deviations from the standard carbon-halogen bond lengths observed for halomethanes (respectively 1.94 and 1.784 A [55]) compared to those recorded for α and β-glycopyranosyl halides: 2.002 and 1.754 A for **3** and 2,3,4-tri-O-acetyl- β-D-xylopyranosyl chloride which crystallizes in a $^{4}C_{1}$-D chair conformation.

In conclusion, free-radical halogenation of peracetylated-D-glycopyranosyl halides allows the stereoselective preparation of a variety of new and stable dihalogenated sugar derivatives under mild conditions. While substitution occurs either at C-1 or C-5, the newly created carbon-halogen bond always displays an axial orientation in the studied sugars of $^{4}C_{1}$-D chair conformation. Using N-bromosuccinimide, β-chlorides can be converted in high yield into the corresponding C-1 gem bromochloro derivative of R anomeric absolute configuration. The C-1 gem chlorobromo derivative of gluco configuration undergoes a facile dehydrobromination reaction to yield the corresponding C-1 chlorinated glucal. Furthermore, stereo and chemioselective substitution of the bromine atom or both halogens can be achieved in the presence of silver fluoride in suitable amounts to give new C-1 gem fluorochloro or difluoro derivatives. The availability of these new C-1 gem dihalogenated sugar derivatives together with the different strengths of the carbon-halogen bonds should allow unprecedented synthetic transformations at the anomeric carbon of sugars.

Experimental

General methods: Thin-layer chromatography and column chromatography were performed with silica gel (Kieselgel 60 F 254 and Kieselgel 60 Merck). Melting points are uncorrected. Optical rotations were measured with a PERKIN ELMER 241 polarimeter. I.R. spectra were recorded with a PERKIN ELMER 681 spectrophotometer. N.m.r. spectra were recorded with the following spectrometers: BRUKER AC 200 or BRUKER AM 300 (^{1}H and ^{13}C) and BRUKER WP 80 FT (^{19}F). In the latter case, samples were dissolved in deuteriochloroform containing fluorotrichloromethane as the internal reference for chemical shifts (Φ) which were expressed in p.p.m. X-ray analyses were carried out using an ENRAF-NONIUS automatic diffractometer (λ (Mok α) = 0.71073 A, scan w/2 θ = 1, t_{max} = 60 s). Elemental analyses were performed by the Service Central de Microanalyse du Centre National de la Recherche Scientifique (Vernaison-France).

Photohalogenations: in the presence of N-bromosuccinimide (method I). The substrate (0.2 g), N-bromosuccinimide (0.4 g) and carbon tetrachloride (20 ml) or a 80-20 v/v mixture of carbon tetrachloride and bromotrichloromethane in a flask equipped with a condenser was refluxed over a 250. W tungsten lamp. For larger scale preparations, a flat-bottomed Erlenmeyer flask was used, the flask and the lamp being maintained at a constant distance equal to 1 cm. After disappearance

of the starting material (t.l.c.), the insoluble materials were removed from the cold mixture by filtration. After concentration under reduced pressure, the residue was directly subjected to column chromatography with the following solvent systems: A: diethylether-petroleum ether 1-1 v/v; B: chloroform-acetone 100-5 v/v. For larger scale experiments or when the desired compound was a major isomer of low solubility such as **18**, the residue was extracted with diethylether and washed with cold water before chromatographic separation or crystallization [14].

in the presence of sulfuryl chloride (method II): The substrate (0.2g), sulfuryl chloride (0.15 ml) and azobisisobutyronitrile (0.025 g) in carbon tetrachloride (20 ml) were refluxed over a 250. W tungsten lamp. After completion of the reaction (t.l.c.) and addition of a saturated aqueous $NaHCO_3$ solution, the reaction mixture was taken up in diethylether. Finally, the mixture was worked up and resolved by column chromatography.

2,3,4,6-Tetra-O-acetyl-5-bromo- β -D-glucopyranosyl chloride **10**: *prepared using method I, eluent* A: syrup; $[\alpha]^{23}$ - 120° c 2.3 chloroform: Anal. Calcd. for $C_{14}H_{18}O_9BrCl$: C, 37.73, H, 4.07, O, 32.31, Br, 17.93, Cl, 7.95. Found: C, 37.03, H, 4.09, Br, 18.89, Cl, 7.31.

2,3,4,6-Tetra-O-acetyl-5-chloro- β -D-glucopyranosyl chloride **11**: prepared using method II, eluent A: crystals, m.p. 73° (diethyl ether); $[\alpha]^{21}$ -92° c 0.6 acetone: Anal. Calcd for $C_{14}H_{18}O_9Cl_2$: C, 41.91, H, 4.52, O, 35.89, Cl, 17.67. Found: C, 42.20, H, 4.44, O, 34.52, Cl, 18.86.

2,3,4,6-Tetra-O-acetyl-5-bromo- β and α -D-glucopyranosyl fluorides **12** and **13**: prepared using method I, eluent A or B, respectively: **12** syrup; $[\alpha]^{23}$ -109 c 0.75 acetone; ^{19}F-n.m.r.: -150.2, $^2J_{F,H-1}$: 51, $^3J_{F,H-2}$: 14. **13**: syrup; $[\alpha]^{23}$ - 36.8° c 0.65 acetone; 19 F-n.m.r.: - 146.6, $^2J_{F,H-1}$: 54, $^3J_{F,H-2}$: 24: Anal. Calcd for $C_{14}H_{18}O_9BrF$: C,39.17, H, 4.22, O, 33.55, Br, 18.62, F, 4.43. Found: C,39.50, H, 4.17, Br, 17.55, F, 4.01 (**12**): C, 37.29, H, 4.10, Br, 17.77, F, 4.05 (**13**).

2,3,4,6-Tetra-O-acetyl-5-bromo-β -D-mannopyranosyl chloride **16**: prepared using method I, eluent A: crystals, m.p. 129° (diethyl ether); $[\alpha]^{19}$ - 160 c 0.6 acetone: Anal. Calcd. for $C_{14}H_{18}O_9BrCl$: C, 37.73, H, 4.07, O, 32.31, Br, 17.93, Cl, 7.95. Found: C, 39.05, H, 4.31, O, 31.22, Br, 17.36, Cl, 8.65.

2,3,4,6-Tetra-O-acetyl-5-chloro- β -D-mannopyranosyl chloride **17**: prepared using method II, eluent A: crystals, m.p. 126-127° (diethyl ether); $[\alpha]^{23}$ - 123.5 c 0.6 acetone: Anal. Calcd. for $C_{14}H_{18}O_9Cl_2$: C, 41.91, H, 4.52, O, 35.89, Cl, 17.67. Found: C, 42.44, H, 4.58, O, 34.24, Cl, 19.09.

2,3,4,6-Tetra-O-acetyl-1-bromo-β -D-glucopyranosyl chloride **18**: prepared using method I, eluent A: crystals, m.p. 109° (diethylether-petroleum ether); $[\alpha]^{20}$ + 136 c 1.4 acetone: I.R. (KCl): characteristic bands: 623, 640 cm^{-1}; Anal. Calcd. for $C_{14}H_{18}O_9BrCl$: C, 37.73, H, 4.07, O, 32.31, Br, 17.93, Cl, 7.95. Found: C, 38.26, H, 4.15, Br, 17.18, Cl, 8.06. X-ray analysis of compound **18**: $BrClO_9C_{14}H_{18}$: Orthorhombic P $2_12_12_1$, a = 10.509 (5), b = 11.475 (5), c = 15.589 (6) A, V = 1879 (3) A^3, Mr = 445.4, μ= 19.5 cm^{-1}; Z = 4, Dx = 1.57 $Mg.m^{-3}$, F (000) = 904, T = 293K. The sample (prism 0.15 x 0.15 x 0.20 mm) gave 1914 reflections (1305 with $I > \sigma$ (I). The structure was solved with Direct methods. After anisotropic refinement (R =0.065), the hydrogen atoms were located in one Fourier Difference (between 0.54 and 0.30 $e.A^{-3}$). The best full-matrix refinement of the structure gave R =0.057 and R_ω = 0.059.

2,3,4,6-Tetra-O-acetyl-1-chloro- β -D-glucopyranosyl chloride **19**: prepared using method II, eluent A: crystals; m.p. 87° (diethyl ether); $[\alpha]^{21}$ + 103° c 0.7 acetone: I.R. (KCl): characteristic bands: 612, 633, 645 cm^{1}; Anal. Calcd. for $C_{14}H_{18}O_9Cl_2$: Cl, 17.67. Found: Cl, 18.42.

2,3,4,6-Tetra-O-acetyl-1-bromo- β -D-glucopyranosyl fluoride **20**: prepared using method I, eluent A: crystals; m.p. 38° (diethyl ether-petroleum ether); $[\alpha]^{22}$ + 129.5° c 0.8 acetone; ^{19}F-n.m.r.: -68.87, $^3J_{F,H-2}$ 8; m.s. (c.i. NH_3): 448 (100), 447 (16), 446 (98), 411 (32), 410 (5), 409 (30),350 (16), 349 (98).

2,3,4,6-Tetra-O-acetyl-1-bromo- β -D-mannopyranosyl chloride **23**: prepared using method I, eluent A: syrup; $[\alpha]^{19}$ + 96.7 c 0.5 acetone: Anal. Calcd. for $C_{14}H_{18}O_9BrCl$: Br, 17.93, Cl, 7.95. Found: Br, 17.07, Cl, 10.66.

2,3,4,6-Tetra-O-acetyl-1-chloro- β-D-mannopyranosyl chloride **24**: prepared using method II, eluent

A: crystals: m.p. 87° (diisopropylether): $[\alpha]^{24}$ + 64° c 0.5 acetone: Anal. Calcd. for $C_{14}H_{18}O_9Cl_2$: Cl, 17.67. Found: Cl, 18.25.

2,3,4,6-Tetra-O-acetyl-2-bromo - α -D-glucopyranosyl bromide **25**: prepared from **2**, **3** or **9** using method I, eluent B: crystals, m.p. 131° (diethylether): $[\alpha]^{29}$ + 20.5 c 0.8 acetone: Anal. Calcd. for $C_{14}H_{18}O_9Br_2$: C, 34.31, H, 3.70, O, 29.38, Br, 32.61. Found: C, 34.24, H, 3.73, O, 28.88, Br, 32.64. X-ray analysis of compound **25**: $Br_2O_9C_{14}H_{18}$: Orthorhombic P $2_12_12_1$, a = 7.509 (1), b = 11.374 (4), c = 22.053 (3) A, V = 1919 (2) A^3, Mr = 490.1, μ = 47.2 cm^{-1}, Z = 4, Dx = 1.70 $Mg.m^3$, F(000) = 922, T = 293 K. The sample (0.30 x 0.25 x 0.25 mm) gave 2981 reflections (1284 with I> σ(I)). The two Br atoms were located with a Patterson Map. The remaining non-hydrogen atoms were found by successive factor refinements and Fourier Difference. After anisotropic refinement (R = 0.08) the hydrogen atoms were located with two Fourier Differences and their coordinates fixed. The best refinement of the structure gave:R = 0.058, R_w = 0.055.

2,4,6-Tri-O-acetyl-1-deoxy-1-bromo-D-erythro-hex-1-enopyran-3-ulose **26**: prepared from **9** using method I, eluent B, syrup: $[\alpha]^{23}$ + 162° c 0.02 acetone: I.R. (neat), ν cm^{-1}: 1605 (C = C), 1705 (α, β insaturated C = O), 1740 to 1780 (C = O acetyl); m.s. (F.a.b.$^+$): 367 (90), 365 (100), 265 (79), 263 (83): Anal. Calcd. for $C_{12}H_{13}O_8Br$: C, 39.47, H, 3.59, O, 35.05, Br, 21.88. Found: C, 39.86, H, 3.86, O, 33.20, Br, 20.35.

2,3,4,6-Tetra-O-acetyl-1-deoxy-1-chloro-2-hydroxy-D-arabino-hex-1-enopyranose **27**: Stirring for 3 hours at room temperature an acetonitrile solution (5 ml) containing crude **18** (0.446 g, 1 mmole) and 1,4- diazabicyclo [2.2.2]-octane (0.336 g, 3 mmoles) followed by aqueous work up and column chromatography (eluent A) yielded 0.021 g of unchanged C-1 gem dichloro derivative **19** and 0.260 g (75 % yield) of the C-1 chlorinated glucal **27**; syrup: $[\alpha]^{22}$ - 55° c 0.9 acetone: Anal. Calcd.for $C_{14}H_{17}O_9Cl$: C, 46.10, H, 4.66, O, 39.5, Cl, 9.73. Found: C, 45.99, H, 4.79, O, 38.12, Cl, 9.34.

2,3,4,6-Tetra-O-acetyl-1-chloro- β -D-glucopyranosyl fluoride **28**: Stirring an acetonitrile solution (16 ml) of pure **18** (1.78 g, 4 mmoles) in the presence of powdered silver fluoride (0.61 g, 5 mmoles) for one day at 30° followed by addition of 1,4-diazabicyclo [2.2.2]-octane (0.112g, 1 mmole) and additional stirring for 3 hours, yielded after addition of a brine solution, work up and column chromatography (eluent A), 1.09 g of the crystalline C-1 fluorochloro derivative **28**: m.p. 57° (absolute ethanol): $[\alpha]^{29}$ + 101.5 c 0.5 acetone: ^{19}F-n.m.r.: - 68.25, $^3J_{F-H-2}$: 8.2: Anal. Calcd. for $C_{14}H_{18}O_9Cl$ F: Cl, 9.21, F, 4.94. Found: Cl, 9.69, F, 4.63.

2,3,4,6-Tetra-O-acetyl-1-fluoro- β -D-glucopyranosyl fluoride **29**: Stirring an acetonitrile solution (4 ml) of **18** (0.446 g, 1 mmole) at 30° for 4 days in the presence of powdered silver fluoride (0.474g, 3.9 mmoles) followed by addition of a brine solution, work up and column chromatography (eluent A) yielded crystalline C-1 gem difluoro derivative **29** (0.260 g: 71 %): crystals, m.p. 97° (diethylether petroleum ether): $[\alpha]^{23}$ +42° c 0.5 acetone: ^{19}F-n.m.r.:α -F: -86.37, $^3J_{\alpha-F,\ H-2}$: 17.5, β -F: -82.76, $^3J_{\beta-F-H-2}$: 3.4, $^2J_{F,F}$: 148.8: Anal. Calcd. for $C_{14}H_{18}O_9F_2$: F, 10.32. Found: F, 10.28.

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29. For this substitution reaction, pure 18 is advisable since the more stable dichloride 19 which is unaltered in these conditions proved very difficult to separate from the monofluoride 28 either by chromatography or by recrystallization.
30. The ^{19}F-n.m.r. spectrum of the crude product formed in the attempted fluorination reaction showed a major signal at -68.2 ppm corresponding to 28 and a minor one at -78.8 ppm which amounts to about 2 %. From its higher field ^{19}F-resonance and its coupling constant value ($^3J_{F,H-2}$= 21 Hz), this signal is tentatively attributed to the anomer 30.
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