Reactions with and in anhydrous hydrogen fluoride systems. Part 8*. Triethylamine trishydrofluoride – a convenient reagent for the stereoselective synthesis of glycosyl fluorides

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(Received December 6, 1991)

Abstract

Stereoselective fluorinations are effected by bromine–fluorine exchange at glycosyl bromides of the D- and L-series using triethylamine trishydrofluoride. Pyranosyl fluorides of D-xylose, L-arabinose, D-glucose, D-mannose and L-rhamnose derivatives, as well as of D-galacturonic acid esters, have been prepared. The influence of neighbouring groups in the 2-position is considered.

Introduction

Glycosyl fluorides may be of interest for glycosylations [2–4]. Anomerically pure glycosyl fluorides are of greatest importance, but many fluorination methods lead to anomeric mixtures [2]. Good selectivities are obtained by bromine–fluorine exchange at protected glycosyl bromides with the help of various fluorinating reagents [2, 5]. Recently, we found that the two-phase system $Et_3N \cdot 3HF/CCl_4$ is a convenient reagent for selective bromine–fluorine exchange with inversion at the anomeric centre of sugar derivatives [6a]. The advantages of the reagent result from a smaller expenditure of time and/or cost compared with other reported methods. Some additional investigations have now been carried out with this reagent to demonstrate the influence of neighbouring groups in the 2-position of a sugar molecule on the selectivity of fluorination.

*For part 7, see ref. 1.

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0022-1139/93/$6.00

Results and discussion

2,3,4-Tri-*O*-acetyl-α-D-xylopyranosyl- (**1**) [7a], 2,3,4-tri-*O*-acetyl-β-L-arabinopyranosyl- (**3**) [7b], 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl- (**5**) [7c], 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl- (**7**) [7d] and 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl bromide (**9**) [7e] as well as methyl- (**11**) [7f] and benzyl-(2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl bromide)uronate (**13**) [7g] were fluorinated under the same conditions as described in ref. 6a. Heating (reflux) of the pentosyl bromides **1, 3** (0–5 h) and hexosyl bromides **5, 7, 9, 11, 13** (2 h) in the $Et_3N \cdot 3HF/CCl_4$ system (1:5–6 v/v) gave the corresponding glycosyl fluorides (Table 1, Schemes 1 and 2). No anomerisation of the product glycosyl fluorides was observed with $Et_3N \cdot 3HF/CCl_4$. On the other hand, the same conditions were unable to effect the conversion of 3-*O*-(n-alkyl)-2,4,6-tri-*O*-acetyl-α-D-glucopyranosyl bromides with long chains (dodecyl or hexadecyl) into the corresponding β-fluorine derivatives [6c]. The high lipophilicity of such compounds and the shielding of the reaction centre by the alkyl chain hinder reagent attack.

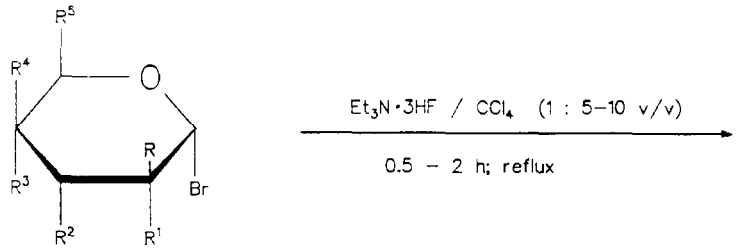
With the exception of compounds **4** and **14**, the glycosyl fluorides have been previously described in the literature, but their NMR data (Table 2) have only been partially published except for 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl fluoride (**2**) [12, 13]. The glycosyl bromides **11** and **13** are very unstable and were not isolated before fluorination (see example 2 in the Experimental section); the ester groups are also easily cleaved in **13** and **14**. All the noted yields are related to the work-up of the CCl_4 phases and the pure products (crude products in parentheses, Table 1); the other phase contained by-products (partially deprotected sugars).

The NMR data for D-xylopyranosyl fluoride (**2**) are identical with the literature values [12, 13]. The ^1H spectrum of 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl fluoride (**4**) was the same as that of the 2,3,4-tri-*O*-acetyl-α-D-arabinopyranosyl fluoride ($^4C_1$ conformation) described in ref. 12. Because

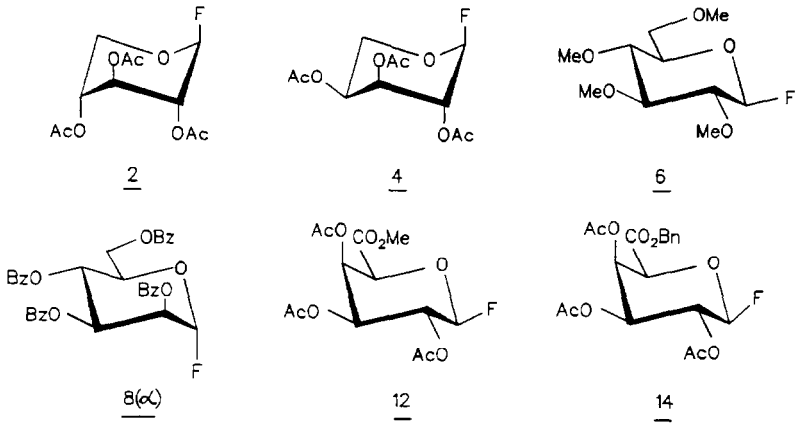
TABLE 1

Reactant	Product[a] (α:β)	Yield (%) (solvent)[b]	Melting point (°C)	
			Observed	Literature value
1 [7a]	**2**	39(83)	55–57[a]	56–57 [8]
3 [7b]	**4**	50(71)	50–51[a]	51–53[c]
5 [7c]	**6**	(73)	syrup	syrup [9]
7 [7d]	**8**(α)/**8**(β) (6:1)	(62)	syrup	129–131 (α) [5b, 10]
9 [7e]	**10**(α)/**10**(β) (3:2)	41	syrup	syrup (α) [5a, 11]
11 [7f]	**12**	56	152–154[a]	156 [5c]
13 [7g]	**14**	40	167–169[a]	

[a]See Schemes 1 and 2.
[b]Ether/pentane.
[c]2,3,4-Tri-*O*-acetyl-α-D-arabinopyranosyl fluoride (cf. **4**) [8, 12].



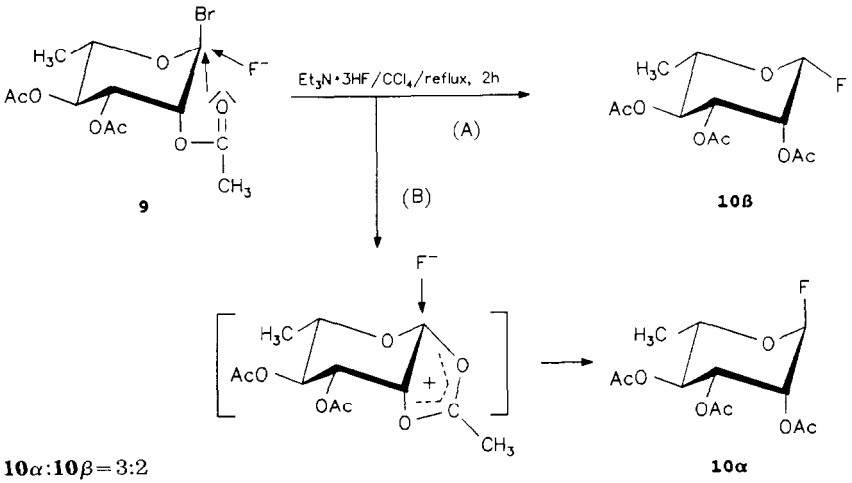
1 $R^1 = R^2 = R^3 = OAc$; $R = R^4 = R^5 = H$
3 $R^1 = R^2 = R^4 = OAc$; $R = R^3 = R^5 = H$
5 $R^1 = R^2 = R^3 = OMe$; $R = R^4 = H$; $R^5 = CH_2OMe$
7 $R = R^2 = R^3 = OBz$; $R^1 = R^4 = H$; $R^5 = CH_2OBz$
11 $R^1 = R^2 = R^4 = OAc$; $R = R^3 = H$; $R^5 = COOMe$
13 $R^1 = R^2 = R^4 = OAc$; $R = R^3 = H$; $R^5 = COOBn$



Scheme 1.

the coupling constants $J_{H\text{-}4,\ H\text{-}5a}$ and $J_{H\text{-}4,\ H\text{-}5e}$ are also the same as in ref. 12, the acetyl group in the 4-position cannot be axial but must be equatorial in agreement with a $^1C_4$ conformation for **4**. The relatively large coupling constants between the C-2 atom and fluorine in **2** and **4** ($J_{C\text{-}2,\ F} = 36$ and 34.8 Hz) provide a further reason for believing that the fluorine has an axial configuration. The ^{13}C NMR spectra of compounds **12** and **14** confirm the β-structure of these fluorides through chemical shifts of 106.8 ppm for C-1 and by the coupling constants $J_{C\text{-}1,\ F} = 221$ Hz and $J_{C\text{-}3,\ F} = 10.7\text{–}10.8$ Hz (Table 2). The literature value [5c] quoted for $\delta_{H\text{-}1}$ for compound **12** is not correct; we found that for both **12** and **14**, $\delta_{H\text{-}1} = 5.28$ (dd, $J_{H\text{-}1,\ H\text{-}2} = 7.0\text{–}7.2$ Hz) ppm.

The experimental results, including those of ref. 6, lead to the following conclusions:



10α:10β = 3:2

Competing attacks:

(A) *trans* attack of a fluoride ion on **9** producing **10β**

(B) *trans* attack of the 2-O-acetyl group, following an attack of a fluoride ion producing **10α**

Scheme 2.

1. Bromine–fluorine exchange takes place selectively with inversion and formation of only one anomer if the leaving group and the group in the 2-position are *cis*-orientated; the attack of the fluoride ion can take place from the *trans*-direction corresponding to a real S_N2-type reaction.
2. When a *trans* configuration exists for both groups, one obtains anomeric mixtures (**8, 10**) because the fluoride ion competes in an S_N2-type reaction with the lone pairs of the oxygen at the neighbouring group, which can form a cyclic oxonium ion (Scheme 2). The nucleophilicity of the fluoride ion in the corresponding fluorination system is decisive for the selectivity. Conformation effects support the formation of an α-anomer in the case of manno-configurated sugars ($\Delta 2$ effect [14]).

Experimental

All the glycosyl bromides were prepared using the HBr/acetic acid procedure described in ref. 7g. The properties of the several bromides are described in refs. 7a–g; see marked reactants in Table 1. Fluorination was controlled by the use of TLC methods using Alufolie Kieselgel 60 F 254 (Merck) and the solvent system toluene/ethyl acetate = 3:1. Triethylamine trishydrofluoride was also a commercial product, but the procedure described below was used to prepare the complete reagent system *in situ*.

NMR spectra using $CDCl_3$ solutions were obtained on a Bruker WM 250 MHz instrument; see Table 2.

Triethylamine trishydrofluoride/carbon tetrachloride system

Dried triethylamine (13.8 ml, 0.1 mol) in CCl_4 (100 ml) was placed in a 250 ml glass bottle and cooled down to < 0 °C. Anhydrous HF (6 ml, 0.3

TABLE 2

^1H NMR and ^{13}C NMR data ($CDCl_3$; TMS; δ in ppm; J in Hz)

10 (α):	5.43 (dd, 1H, $J_{H\text{-}1,\,H\text{-}2}=1.8$, $J_{H\text{-}1,\,F}=49.0$, H-1); 5.32 (m, 1H, H-2); 5.23 (ddd, 1H, $J_{H\text{-}3,\,H\text{-}4}=10.0$, $J_{H\text{-}3,\,F}=3.5$, H-3); 5.06 (t, 1H, $J_{H\text{-}4,\,H\text{-}5}=10.0$, H-4); 3.98 (dq, 1H, $J_{H\text{-}5,\,H\text{-}6}=6.3$, H-5); 1.21 (d, 3H, CH_3); 2.10 (s, 3H, OAc); 2.00 (s, 3H, OAc); 1.93 (s, 3H, OAc).
10 (β):	5.39 (dd, 1H, $J_{H\text{-}1,\,H\text{-}2}=1.2$, $J_{H\text{-}1,\,F}=50.0$, H-1); 5.45 (ddd, 1H, $J_{H\text{-}2,\,H\text{-}3}=3.0$, $J_{H-2,\,F}=6.0$, H-2); 5.01 (m, 2H, H-3/H-4); 3.62 (m, 1H, $J_{H\text{-}5,\,H\text{-}6}=6.5$, H-5); 1.30 (d, 3H, CH_3); 2.11 (s, 3H, OAc); 2.00 (s, 3H, OAc); 1.96 (s, 3H, OAc).
12:	5.28 (dd, 1H, $J_{H\text{-}1,\,H\text{-}2}=7.2$, $J_{H\text{-}1,\,F}=51.0$, H-1); 5.35 (m, 1H, $J_{H\text{-}2,\,H\text{-}3}=10.2$, H-2); 5.07 (dd, 1H, $J_{H\text{-}3,\,H\text{-}4}=3.4$, H-3); 5.75 (m, 1H, $J_{H\text{-}4,\,H\text{-}5}=1.6$, H-4); 4.44 (m, 1H, H-5); 2.13 (s, 3H, OAc); 2.10 (s, 3H, OAc); 2.03 (s, 3H, OAc); 3.80 (s, 3H, OCH_3).
14:	5.28 (dd, 1H, $J_{H\text{-}1,\,H\text{-}2}=7.0$, $J_{H\text{-}1,\,F}=52.0$, H-1); 5.33 (m, 1H, $J_{H\text{-}2,\,H\text{-}3}=10.0$, H-2); 5.10 (dd, 1H, $J_{H\text{-}3,\,H\text{-}4}=3.5$, H-3); 5.73 (m, 1H, H-4); 4.45 (m, 1H, H-5); 2.09 (s, 3H, OAc); 1.98 (s, 3H, OAc); 1.85 (s, 3H, OAc); 7.37 (m, 5H, arom.); 5.28 (d, 1H, CH_2); 5.12 (d, 1H, CH_2).
4:	104.6 (d, $J_{C\text{-}1,\,F}=223.2$, C-1); 67.8 (d, $J_{C\text{-}2,\,F}=34.8$, C-2); 67.8 (C-3); 64.6 (C-4); 59.1 (d, $J_{C\text{-}5,\,F}=3.6$, C-5); 20.6; 20.5; 20.5 (CH_3/OAc); 169.7; 169.7; 169.0 (CO/OAc).
6:	109.4 (d, $J_{C\text{-}1,\,F}=215.9$, C-1); 83.0 (d, $J_{C\text{-}2,\,F}=22.1$, C-2); 85.0 (d, $J_{C\text{-}3,\,F}=11.4$, C-3); 78.4 (C-4); 74.3 (d, $J_{C\text{-}5,\,F}=4.8$, C-5); 70.8 (C-6); 60.5; 60.3; 59.9; 59.2 (OCH_3).
8(α):	105.0 (d, $J_{C\text{-}1,\,F}=223.9$, C-1); 68.6 (d, $J_{C\text{-}2,\,F}=39.7$, C-2); 69.2 (C-3); 65.7 (C-4); 71.2 (d, $J_{C\text{-}5,\,F}=2.3$, C-5); 62.1 (C-6); 166.1; 165.3; 165.3; 165.1 (CO/Bz).
10 (β):	104.1 (d, $J_{C\text{-}1,\,F}=217.6$, C-1); 67.5 (d, $J_{C\text{-}2,\,F}=19.5$, C-2); 69.0 (d, $J_{C\text{-}3,\,F}=8.3$, C-3); 70.1 (C-4); 70.7 (d, $J_{C\text{-}5,\,F}=4.7$, C-5); 17.6 (CH_3, C-6); 20.6 ($3CH_3$/OAc); 170.1; 169.9; 169.7 (CO/OAc).
12:	106.8 (d, $J_{C\text{-}1,\,F}=221.3$, C-1); 68.4 (d, $J_{C\text{-}2,\,F}=24.5$, C-2); 69.6 (d, $J_{C\text{-}3,\,F}=10.7$, C-3); 67.6 (C-4); 72.4 (d, $J_{C\text{-}5,\,F}=5.7$, C-5); 165.5 (C-6); 20.6; 20.5; 20.5 (CH_3/OAc); 169.9; 169.6; 169.1 (CO/OAc); 53.0 (OCH_3).
14:	106.8 (d, $J_{C\text{-}1,\,F}=221.0$, C-1); 68.3 (d, $J_{C\text{-}2,\,F}=24.5$, C-2); 69.6 (d, $J_{C\text{-}3,\,F}=10.8$, C-3); 67.4 (C-4); 72.3 (d, $J_{C\text{-}5,\,F}=5.3$, C-5); 165.5 (C-6); 20.6; 20.5; 20.2 (CH_3/OAc); 169.9; 169.6; 169.1 (CO/OAc); 134.6; 129.2; 129.2; 128.8; 128.7; 128.7 (arom.); 67.9 (CH_2/Bn).

mol) was then added dropwise directly to the solution using an HF-resistant dropping tube with stirring. The solution warmed up during the reaction and a second phase ($Et_3N \cdot 3HF$) formed. **(Care! Do not contact glass with anhydrous HF.)** The glycosyl bromides **1, 3, 5, 7, 9, 11** or **13** (0.5–1.0 mmol) were then added directly or in CCl_4 to this reagent.

Example 1: (fluorination procedure)

2,3,4-Tri-O-acetyl-α/β-L-rhamnopyranosyl fluorides ***10α/10β***

2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl bromide (**9**) [7e] (1.77 g, 5 mmol) was added to $Et_3N \cdot 3HF$ (16 g, 0.1 mol)/CCl_4 (100 ml). After 2 h reflux* with vigorous stirring, the phases were separated and extracted with 30 ml CCl_4. Finally, the combined CCl_4 phases were washed free from acid with water. After filtration and evaporation of the solvent the anomeric mixture of **10α/β** was obtained as a syrup. Yield after chromatographic purification, 0.6 g (41%); for analytical data see Tables 1 and 2.

Example 2: (combination of bromination [7g] and fluorination procedures)

Benzyl(2,3,4-tri-O-acetyl-α-D-galactopyranosyl bromide)uronate ***(14)***

Benzyl(1,2,3,4-tetra-*O*-acetyl-α/β-D-galactopyranose)uronate [15] (3.17 g, 7 mmol), dissolved in 10 ml CCl_4, was added to a 30% HBr solution in acetic acid (45 ml) at 0 °C. After 2 h standing at this temperature (TLC control), the reaction mixture was poured on ice (100 g) and extracted with CCl_4 (2–3 times). The combined CCl_4 phases were washed with ice water until neutral, dried and evaporated at 30–40 °C. The syrup obtained was dissolved in some CCl_4 and added directly as a crude product to the $Et_3N \cdot 3HF$ (0.1 mol)/CCl_4 (100 ml) system described above. With stirring and reflux, fluorination was complete after 2 h. Work-up was as described for **10** in the fluorination procedure (Example 1). The syrup obtained was dissolved in ether and pentane was added until precipitation of crystalline **14** occurred. Yield, 1.15 g (40%); m.p., 167–169 °C (recrystallisation from ethyl acetate/hexane); $[\alpha]_D^{22} = +28.8$ ($c = 0.9$, $CHCl_3$); further analytical data in Tables 1 and 2.

Acknowledgements

We thank the 'Deutsche Forschungsgemeinschaft', Hoechst AG and the 'Fonds der Chemischen Industrie' for support of this work, as well as Dr C. Vogel for the gift of peracetylated galacturonic acid esters.

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*Pentose derivatives required 0.5 h reflux.

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