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Formation and Anomerization of Glycopyranosyl Fluorides and their Facile Conversion into Glycopyranosyl Azides

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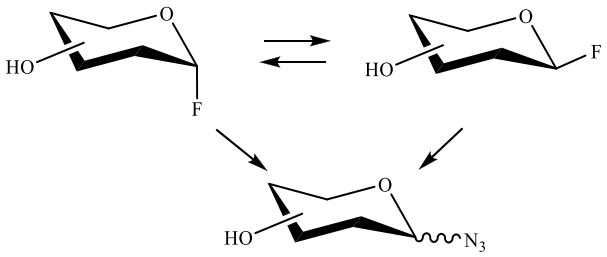
Graphical Abstract



Abstract

The straightforward formation of glycopyranosyl fluorides by transhalogenation as well as their conversion into the corresponding azides is reported.

Keywords: Glycopyranosyl fluorides; anomerization; glycopyranosyl azides.

1. Introduction

Early on in carbohydrate chemistry glycosylation, in essence the formation of complex acetals, was recognized as one of the central problems to be solved, in particular in a stereospecific manner. The first approach was the simple acid catalyzed method developed by Emil Fischer (Fischer glycosylation),[1] which has its merits for the formation of simple glycosides and could also be employed technically in large scale versions. Roughly, ten years later the silver salt catalyzed glycosylation of glycosyl halides reported by Koenigs and Knorr proved to be the most seminal approach.[2] In addition to the originally used silver carbonate, other silver salts such as silver silicate,[4] silver zeolite,[5] and silver triflate,[6] came in use, as well as catalysts like mercury cyanide.[7] The Koenigs-Knorr procedure has undergone a large number of modifications and impressive improvements within the recent century.[3,8]

In connection with studies on the formation and reactivity of glycosyl halides also fluorides were described early on,[9,10] however, their application as glycosyl donor structures and thus their use in glycosylation was reported not before the 80s of last century.[11-18] In the present contribution one focus is on more favorite developments for syntheses and anomerizations of glycosyl fluorides to establish further applications and improvements in their reactions. In addition, we will report on the facile transformation of glycosyl fluorides into glycosyl azides, a versatile group of functional units in carbohydrate chemistry.[19]

2.1 General Methods

All reactions were monitored by thin layer chromatography on silica gel foils GF_{254} (Merck). Detection was by UV or spraying with 20 % ethanolic sulfuric acid and subsequent heating. Column chromatography was done on silica gel 60 (230-400 mesh, Merck) by the flash mode with the solvent mixture recorded. ^{1}H-NMR (300 MHz) spectra were done on Bruker WM-300. Melting points are uncorrected and were taken with a Reichert heating table microscope. Optical rotations were measured with Perkin-Elmer polarimeter 241, cuvette length 10 cm, and temperature 20 °C.

2.2 Acetylation (General Procedure, GP).

The starting material dissolved in anhydrous pyridine

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was treated with acetic anhydride (3 eq) for 1 – 3h at 20 °C. The mixture was mixed with ice water and extracted with dichloromethane. The organic phase was washed with saturated sodium hydrogen carbonate and water, dried over $MgSO_4$, filtered, co-evaporated with toluene and purified by chromatography.

2.3 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl fluoride (4)

2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**2**,[20] 8.7 g, 21.2 mmol) dissolved in anhydrous acetonitrile (40 mL), was heated with potassium hydrogen difluoride (8.0 g, 102 mmol) under reflux for 6h. Following evaporation the residue was dissolved in dichloromethane, filtered via silica gel and evaporated to dryness. The material crystallized from ether to give 5.3 g (72 %) of **4** as colorless crystals; mp 100 °C, $[\alpha]_D^{20}$= + 17.5 (*c* = 1.03, $CHCl_3$); lit.[21]: mp 98-99 °C, $[\alpha]_D^{18}$= + 22 (MeOH).

2.4 2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl fluoride (6)

2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**2**,[20] 5.0 g, 12.2 mmol) dissolved in anhydrous acetonitrile (25 mL), was heated with potassium hydrogen difluoride (5.0 g, 64 mmol) and titanium tetrafluoride (250 mg, 2.0 mmol) under reflux for 10h. The cold solution was filtered via silica gel, evaporated to dryness and purified by chromatography (*n*-hexane/ethyl acetate 2 : 1). The syrup crystallized to give 1.35 g (32 %) of **6** as colorless crystals; mp 64 °C, $[\alpha]_D^{20}$= + 98.3 (*c* = 0.98, $CHCl_3$); lit.[21] : syrup, [α] = + 106.6 (*c* = 0.84, $CHCl_3$); lit.[22]: syrup, [α] = + 103 ($CHCl_3$);

2.5 2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl fluoride (8)

2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl bromide (**7**,[23] 10.0 g, 24.3 mmol) dissolved in anhydrous acetonitrile (50 mL), was heated with potassium hydrogen difluoride (10.0 g, 128 mmol) under reflux for 3h. The cold solution was filtered evaporated to dryness and the raw material crystallized from ether to give 6.56 g (77 %) of **8** as colorless crystals; mp 65-67 °C, $[\alpha]_D^{20}$= + 21.2 (*c* = 1.07, $CHCl_3$); lit.[24]: mp 68-69 °C, [α]= + 21.8 (*c* = 0.87, $CHCl_3$).

2.6 Methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate fluoride (11)

Methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate bromide (**9**,[25] 1.72 g, 4.3 mmol) dissolved in anhydrous acetonitrile (6 mL), was stirred with silver fluoride (1.65 g, 13.0 mmol) for 6h at 20 °C. The cold solution was filtered, evaporated to dryness, and the raw material crystallized from ethyl acetate/petroleum ether to give 1.14 g (78 %) of **11** as colorless crystals; mp 105.5 °C, $[\alpha]_D^{20}$= + 15.8 (*c* = 1.03, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.45 (dd, 1H, $J_{1,2}$ = 5.0, $J_{1,F}$ = 50.6 Hz, H-1), 5.11 (ddd, 1H, $J_{1,2}$ = 5.0, $J_{2,3}$ = 7.2, *C* Hz, H-2), 5.24 (m, 1H, H-3), 5.43 (m, 1H, H-4), 4.16 (d, 1H, $J_{4,5}$ = 8.8 Hz, H-5), 3.79 (s, 3H, OCH_3), 2.05, 2.06, 2.11 (3 x s, 9H, CH_3CO). Calcd. for $C_{13}H_{17}FO_9$ (336.09): C, 46.43; H, 5.10. Found: C, 46.70; H, 4.16.

2.7 2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl fluoride (16)

2,3,4,6-Tetra-*O*-benzyl-D-galactopyranose[26] (3.0 g, 5.6 mmol) dissolved in anhydrous dichloromethane (20 mL) was treated with oxalyl chloride (0.6 mL, 0.85 g, 6.7 mmol) and some drops of DMF at room temperature. After decay of the gas evolution, the mixture was filtered via silica gel and evaporated to dryness. The raw 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl chloride (**14,** 2.8 g, 93 %) was directly dissolved in anhydrous acetonitrile (20 mL) and stirred with silver fluoride (2.11 g, 16.6 mmol) for 1h at 20 °C. The raw material was purified by chromatography (toluene/ethyl acetate 50:1 to give 2.5 g (84 %) of **16** as colorless syrup; $[\alpha]_D^{20}$= + 15.8 (*c* = 0.93, $CHCl_3$). ^{1}H-NMR (300 MHz, C_6D_6): δ = 7.06-7.36 (m, 20H, Aryl-H), 5.09 (dd, 1H, $J_{1,2}$ = 7.0, $J_{1,F}$ = 53.5 Hz, H-1), 4.15 (ddd, 1H, $J_{1,2}$ = 7.0, $J_{2,3}$ = 9.8, $J_{2,F}$ = 13.1 Hz, H-2), 3.17 (dd, 1H, $J_{2,3}$ = 9.8, $J_{3,4}$ = 2.8 Hz, H-3), 3.76 (dd , 1H, $J_{3,4}$ = 2.8, $J_{4,5}$ = 1.0 Hz, H-4), 3.37 (ddd, 1H, $J_{4,5}$ = 1.0, $J_{5,6a}$ = 7.6, $J_{5,6b}$ = 5.6 Hz, H-5), 3.77 (dd, 1H, $J_{5,6a}$ = 7.6, $J_{6a,6b}$ = 9.0 Hz, H-6a), 3.62 (dd, 1H, $J_{5,6b}$ = 5.6, $J_{6a,6b}$ = 9.0 Hz, H-6b), 4.21, 4.27, 4.42, 4.52, 4.56, 4.60, 4.78, 4.97 (4 x AB, 8H, $OCH_2C_6H_5$). Calcd. for $C_{34}H_{35}FO_5$ (542.65): C, 75.26; H, 6.50. Found: C, 74.98; H, 6.32.

2.8 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl fluoride (17)

2.8.1 Method a: 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose[27] (5.0 g, 9.3 mmol) dissolved in anhydrous dichloromethane (30 mL) was treated with oxalyl chloride (0.96 mL, 1.41 g, 11.1 mmol) and some drops of DMF at room temperature. After decay of the gas evolution, the mixture was diluted with ethyl acetate (10 mL), filtered via silica gel and evaporated to dryness. The raw 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride (**13,**[29] 4.6 g, 90 %) was directly dissolved in anhydrous acetonitrile (30 mL) and heated with potassium hydrogen difluoride (4.6 g, 58.8 mmol) for 10h under reflux. The yellow-brown raw material was purified by chromatography (toluene/ethyl acetate 40:1 to give 2.0 g (40 %) of **17** as colorless crystals.

2.8.2 Method b: 2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl fluoride (**15,**[11] 150 mg, 0.28 mmol) dissolved in anhydrous acetonitrile (10 mL) was heated with potassium hydrogen difluoride (150 mg, 1.92 mmol) and a catalytic amount of titanium fluoride (10 mol %) for 8 h at 80°C. After workup a quantitative anomerization and transfer into compound **17** was observed; mp 70.5 °C $[\alpha]_D^{20}$= + 4.2 (*c* = 0.87, $CHCl_3$); lit.[29]: mp 64-64.5 °C, [α]= + 9.7 ($CHCl_3$); ^{1}H-NMR (300 MHz, C_6D_6): δ = 7.02-7.38 (m, 20H, Aryl-H), 5.61 (dd, 1H, $J_{1,2}$ = 2.6, $J_{1,F}$ = 53.6 Hz, H-1), 3.32 (ddd, 1H, $J_{1,2}$ = 2.6, $J_{2,3}$ = 9.8, $J_{2,F}$ = 25.8 Hz, H-2), 4.14 (dd, 1H, $J_{2,3}$= 9.8, $J_{3,4}$= 9.2 Hz, H-3), 3.90 (dd , 1H, $J_{3,4}$ = 9.2, $J_{4,5}$= 10.0 Hz, H-4), 4.08 (m, 1H, H-5), 3.88 (dd, 1H, $J_{5,6a}$ = 3.1, $J_{6a,6b}$ = 11.0 Hz, H-6a), 3.55 (dd, 1H, $J_{5,6b}$ = 1.8, $J_{6a,6b}$= 11.0 Hz, H-6b), 4.22, 4.42, 4.36(2), 4.63, 4.77, 4.92(2) (4 x AB, 8H, O$CH_2C_6H_5$).

2.9 Anomerization of β-D-Glucopyranosyl fluoride (19)

β-D-Glucopyranosyl fluoride (**19**,[30] 80 mg, 0.44 mmol) dissolved in anhydrous acetonitrile (10 mL), was heated with caesium fluoride (5.0 mg, 0.96 mmol) under reflux for 80h. Following evaporation the residue was peracetylated and worked up as in GP to give after crystallisation 50 mg (32 %) of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl fluoride (**5**), mp 105-106 °C, $[\alpha]_D^{20}$= + 86.0 (*c* = 1.20, $CHCl_3$); lit.[9]: mp 108 °C, [α]= + 90.1 ($CHCl_3$).

2.10 Formation of 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide (22), 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl azide (24), and Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (26)

2.10.1 Reaction conditions a (Scheme 3): α-D-Glucopyranosyl fluoride (**20**,[31] 200 mg, 1.1 mmol) dissolved in methanol/water (20 mL, 5:1) was heated with sodium azide (79 mg, 1.2 mmol) under reflux for 72h. The cold solution was filtered via silica gel, evaporated to dryness and peracetylated according to GP. The raw material was crystallized from ether to give 391 mg (95 %) of **22** as colorless crystals; mp 127-128°C, $[\alpha]_D^{20}$= - 26.0 (*c* = 0.9, $CHCl_3$); lit.[32]: mp 129°C, [α]= - 33 (*c* = 2.48, $CHCl_3$).

2.10.2 Reaction conditions c (Scheme 3): β-D-Glucopyranosyl fluoride (**19**,[30] 200 mg, 1.1 mmol) dissolved in acetonitrile (20 mL) and water (0.2 mL) was heated with sodium azide (79 mg, 1.2 mmol) under reflux for 72h. The cold solution was filtered via silica gel, evaporated to dryness and peracetylated according to GP. The raw material was crystallized from ether to give 190 mg (45 %) of **22** as colorless crystals.

2.10.3 Reaction conditions d (Scheme 3): β-D-Glucopyranosyl fluoride (**19**,[30] 200 mg, 1.1 mmol) dissolved in anhydrous acetonitrile (20 mL) was heated with sodium azide (79 mg, 1.2 mmol) under reflux for 72h. The cold solution was filtered via silica gel, evaporated to dryness and peracetylated according to GP. Ratio of anomers β (**22**) : α (**24**) = 27 : 73 by ^{1}H-NMR. Separation of anomers was by preparative layer chromatography on silica gel (petroleum ether/ ethyl acetate = 4 : 1, threefold development) to give 169 mg (41 %) of **22** as colorless crystals and 56 mg (14 %) of **24** as colorless syrup, $[\alpha]_D^{20}$= + 170.0 (*c* = 0.88, $CHCl_3$); lit.[33]: mp 103°C, [α]= + 173 ($CHCl_3$).

2.10.4 Reaction conditions a (Scheme 3): β-D-Glucopyranosyl fluoride (**19**,[30] 200 mg, 1.1 mmol) dissolved in methanol/water (20 mL, 5:1) was heated with sodium azide (79 mg, 1.2 mmol) under reflux for 72h. The cold solution was filtered via silica gel, evaporated to dryness and peracetylated according to GP. Following chromatographic separation (petroleum ether/ ethyl acetate 2 : 1) to give 290 mg (80 %) of **26** as colorless crystals; mp 100 °C, $[\alpha]_D^{20}$= + 124.0 (*c* = 1.08, $CHCl_3$); lit.[34]: mp 101-103°C, $[\alpha]_D^{25}$ = + 130 (*c* = 2.0, $CHCl_3$).

2.11 2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl azide (29)

(**Reaction conditions e** ; Scheme 3): α-D-Mannopyranosyl fluoride (**27**,[14] 120 mg, 0.66 mmol) dissolved in anhydrous acetonitrile (3 mL) was heated with sodium azide (47 mg, 0.73 mmol) under reflux for 80h. The cold solution was filtered via silica gel, evaporated to dryness and peracetylated according to GP to give after workup 177 mg (72 %) of **29** as colorless syrup, $[\alpha]_D^{20}$= + 95.7 (*c* = 0.91, $CHCl_3$); lit.[35]: syrup, [α]= + 91 (*c* = 1.0, dioxane). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.40 (d, 1H, $J_{1,2}$ = 1.9 Hz, H-1), 5.16 (dd, 1H, $J_{1,2}$ = 1.9, $J_{2,3}$ = 2.9 Hz, H-2), 5.25 (dd, 1H, $J_{2,3}$= 2.9, $J_{3,4}$= 9.2 Hz, H-3), 5.29 (dd , 1H, $J_{3,4}$ = 9.2, $J_{4,5}$= 10.3 Hz, H-4), 4.16 (m, 1H, H-5), 4.32 (dd, 1H, $J_{5,6a}$ = 5.7, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.17 (dd, 1H, $J_{5,6b}$ = 2.3, $J_{6a,6b}$= 12.5 Hz, H-6b), 2.00, 2.06, 2.12, 2.18 (4 x s, 12H, CH_3CO).

3. Results and Discussion

3.1 Synthesis of peracetylated glycopyranosyl fluorides

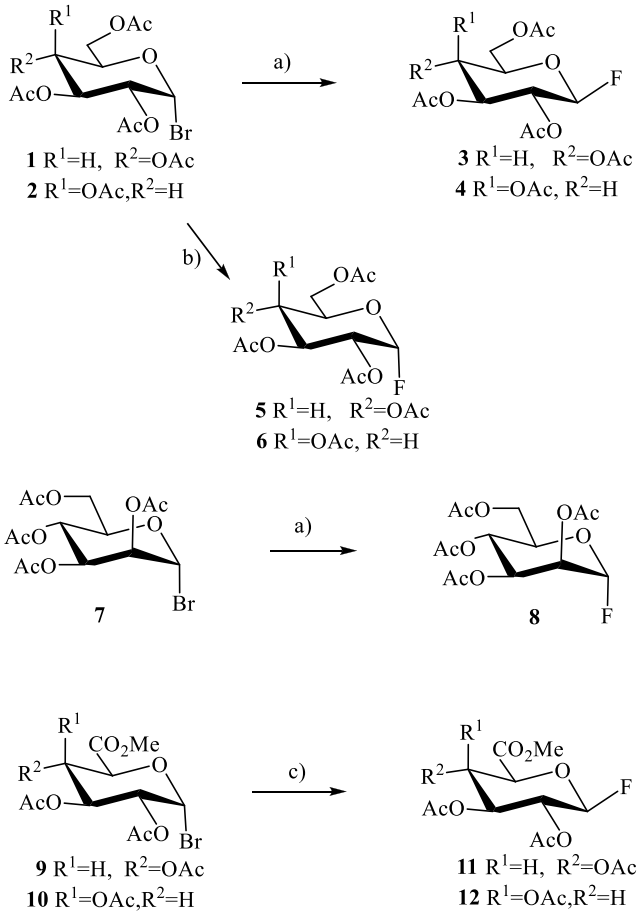
The first synthesis of a 2,3,4,6-tetra-*O*-actyl-α-D-glucopyranosyl fluoride (**5**) was by Brauns, who reacted glucose pentaacetate with liquid hydrogen fluoride.[8] In subsequent decades this became the general method to form glycosyl fluorides, until an essential improvement was by use of Olah´s reagent (50-70 % HF in anhydrous

pyridine).[36] This way a number of glycosyl fluorides could be prepared from peracetylated or unprotected sugar precursors.[29, 37-39] Formation of inverted glycopyranosyl fluorides was generally achieved by transhalogenation of their bromide or chloride precursors with silver fluoride in dipolar aprotic media.[40,41]

For synthesis of glycopyranosyl fluorides in larger scale at more favorite costs, we developed the reaction with potassium hydrogen difluoride in anhydrous acetonitrile under reflux. Thus, α-acetobromoglucose (**1**) was transformed into 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl fluoride (**3**) in 70 % yield.[16] The corresponding transformation of α-acetobromo-galactose (**2**) gave 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl fluoride (**4**)[21] in 72 % yield. Treatment of α-acetobromomannose (**7**) gave - as expected without inversion of configuration - 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl fluoride (**8**)[24] in 77 % yield. In all cases the primary formation of an 1,2-acetoxonium intermediate is assumed, the trans-diaxial opening of which leads to the glycosyl fluorides. Under these conditions direct inversions of the less stable β-fluorides **3** or **4** into the robust α-compounds **5** or **6**, respectively, were not observed.

However, under similar treatment of **1** with KHF_2 in acetonitrile in the presence of 10 mol% of titanium tetrafluoride only the α-glucopyranosyl fluoride **5** resulted. Correspondingly, in the galacto series **2** gave exclusively 2,3,4,6-tetra-*O*-acetyl-α-D-galacto-pyranosyl fluoride (**6**) in only 32 % yield. Apparently, after opening of the acetoxonium ion and formation of the β-fluoride **4**, this is again opened by the nucleophile in KHF_2 from the backside. Due to numerous side reactions under these conditions, only average yields were observed.

Finally, to obtain the uronic acid glycosyl fluorides the corresponding α-bromides **9**[25] and **10,**[28] respectively, could be treated in the classical way employing silver fluoride in anhydrous acetonitrile at room temperature. Obtained were methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate fluoride (**11**) in 78 % yield, and the corresponding galactopyranosyluronate fluoride (**12**)[16] in 82 % yield (**Scheme 1**).

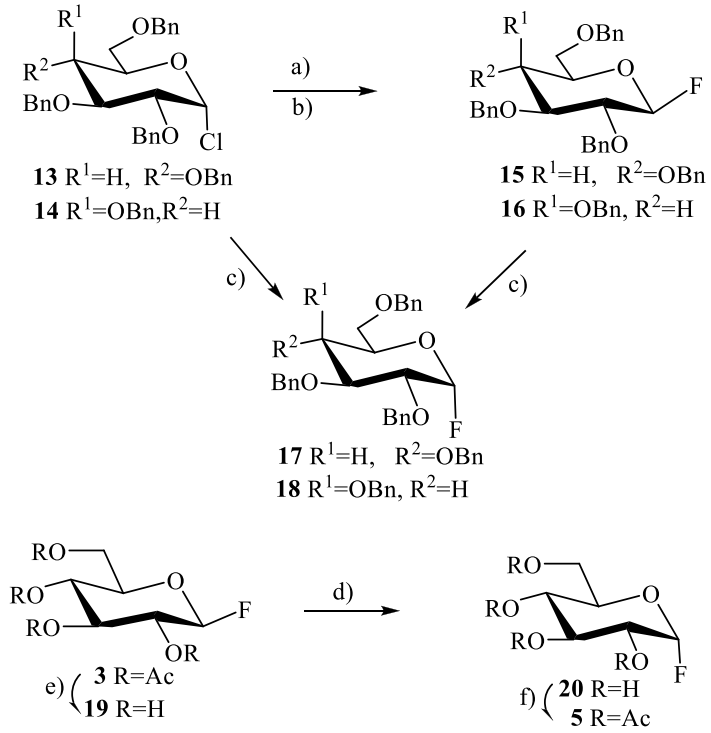


Scheme 1: Synthesis of glycopyranosyl fluorides.
Reaction conditions: a) KHF_2, MeCN; b) KHF_2/TiF_4, MeCN; c) AgF, MeCN.

3.2 Synthesis and anomerization of glycopyranosyl fluorides

Following the original method by use of silver fluoride for transhalogenation of other glycosyl halides,[40] Mukaiyama et al. reported on the reaction of compound **13**[22] to give the perbenzylated β-D-glucopyranosyl fluoride (**15**).[11] Treatment of 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose[26] with oxalyl chloride and some drops of DMF gave the perbenzylated α-D-galactopyranosyl chloride (**14**),[26] and with silver fluoride the β-fluoride **16** was obtained in 84 % yield. Previously, by deacetylation of **6** the unblocked α-D-galactopyranosyl fluoride was obtained,[37] which could be directly perbenzylated to give 2,3,4,6-tetra-*O*- benzyl-α-D-galactopyranosyl fluoride (**18**).[42] In contrast to this completely different approach, it was of interest to check, whether the corresponding *gluco* component could be obtained employing anomerization. Thus, tetra-*O*-benzyl-D-glucopyranose[27] was treated with oxalyl chloride/DMF to give the α-chloride **13**[28] *in situ*, which was dissolved in acetonitrile and refluxed with KHF_2 to give the crystalline 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl fluoride (**17**). An alternative way by treatment of the β-fluoride **15** with KHF_2 in anhydrous acetonitrile under reflux showed after 15 hours 40 % yield of a mixture β (**15**) : α (**17**) = 20 : 80. However, similar treatment in the presence of titanium tetrafluoride (10 mol %) gave after 8 hours a quantitative transfer to compound **17**. Apparently, the intermediate oxocarbenium ion is formed considerably less easily for fluorides compared to other glycosyl halides and subsequently attacked by the nucleophile fluoride from TiF_4.

Finally, it was of interest to check the anomerization of unblocked glycosyl fluorides. Thus, Zemplén transesterification[43] of compound **3**[16] with sodium methylate gave the free β-D-glucopyranosyl fluoride (**19**).[30] Its treatment in refluxing acetonitrile with a catalytic amount of sodium fluoride gave after 110 hours a mixture of β (**19**) : α (**20**) = 20 : 80. However, employing caesium fluoride led after 80 hours to a complete inversion to the α-component **20,**[31] which was characterized as peracetate **5**[31] (**Scheme 2**).

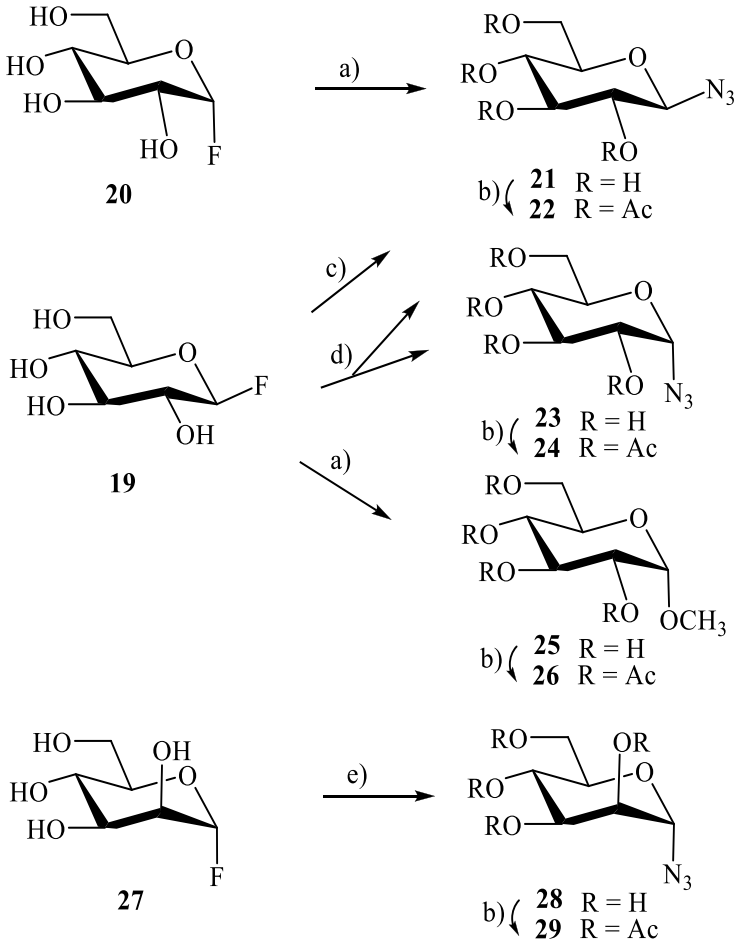


Scheme 2: Synthesis and anomerization of glycopyranosyl fluorides.
Reaction conditions: a) AgF, lit.[11]; b) AgF, MeCN;
c) KHF_2,TiF_4; d) CsF, MeCN; e) NaOMe/MeOH; f) Ac_2O, Py.

3.3 From glycopyranosyl fluorides to glycopyranosyl azides

Glycosyl azides represent versatile precursors for formation of glycoproteins, imines, hydrazines, and *N*-heterocyclic glycosides.[19] Their efficient syntheses from peracylated glycosyl chlorides or bromides with inorganic azides (sodium azide, silver azide) or better trimethyl silyl azides were broadly reported to give uniformly the 1,2-*trans* derivatives, likely via the 1,2-acetoxonium intermediates. Only two papers report on the formation of 1,2-*cis* derivatives under specific conditions.

In the course of reactions of unprotected glycosyl fluorides with sodium or calcium azide in polar, partially aqueous solvents under diverse conditions, glycosyl azides could be obtained directly.[34] By reaction of α-D-glucopyranosyl fluoride (**20**) with sodium azide in methanol/water = 5:1 the pure inversion product **21** resulted, which was proven after peracetylation to give the β-compound **22**. A neighboring group participation or the formation of an 1,2-epoxy intermediate is impossible, which renders the reaction clearly to proceed as S_N2 –type inversion. Starting with β-D-glucopyranosyl fluoride (**19**)[30] and sodium azide in acetonitrile/water 100 : 1 led exclusively and quantitatively to the pure β-azide **21**, again proven *via* peracetate **22**. With a non-neighboring OH-group at C-2



Scheme 3: Synthesis of glycopyranosyl azides.
Reaction conditions: a) NaN_3, $MeOH/H_2O$=5:1/quant.; b) Ac_2O, py/quant.;
c) NaN_3, $MeCN/H_2O$=100:1/quant.; d) NaN_3, anhydr. MeCN/ **21**:**23**=27:73;
e) NaN_3, anhydr. MeCN/quant.

the intermediate formation of an 1,2-epoxide is suggested, which in turn is *trans*-opened to give the β-azide product.

In anhydrous acetonitrile substitution of the same β-fluoride **19** gives a mixture of glucosyl azides β (**21**) : α (**23**) = 27: 73, again identified after peracetylation to **22** and **24** and determination of their ratio by ^{1}H-NMR. Apparently, enforced by an increased nucleophilicity of the azide due to the reduced solvation in anhydrous acetonitrile there is a preferred S_N2-type inversion competing well with the *trans*-opening of an intermediate 1,2-epoxide. Finally, treatment of the β-component **19** under the same conditions as its α-anomer **20** with sodium azide in methanol/water = 5:1 leads exclusively to the methyl α-D-glucopyranoside **25**, which gives **26** after peracetylation. At this stage, there is no meaningful interpretation, why under these conditions the nucleophile methylate competes favorably with the azide.

An outcome as expected was observed with α-D-mannopyranosyl fluoride (**27**)[18] in anhydrous acetonitrile with sodium azide leading to the 1,2-*trans* product **28**, again characterized as its peracetate **29**. As above, an intermediate 1,2-epoxide could be assumed to be opened exclusively in *trans*-manner (**Scheme 3**).

4. Conclusion

This contribution reported on facile and economic formations of both anomers of glycosyl fluorides. Further, their anomerizations were studied and realized and finally, their easy conversions into glycosyl azides of different anomerity could be performed.

Conflict of Interest: None.

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