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Synthesis of 2-fluoro-substituted and 2,6-modified purine 2′,3′-dideoxy-2′,3′-difluoro-D-arabinofuranosyl nucleosides from D-xylose

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Abstract

A series of novel purine-modified 2′,3′-dideoxy-2′,3′-difluro-D-arabinonucleosides, including fluorinated analogs of fludarabine and nelarabine, have been prepared via anion glycosylation reactions of salts of 2-fluoropurine derivatives with the glycosyl bromide. A short and efficient synthetic route to the carbohydrate precursor 5-*O*-benzoyl-2,3-difluoro-α-D-arabinofuranosyl bromide was developed in five steps from D-xylose. Improved synthesis of methyl 5-*O*-benzoyl-2,3-difluoro-α-D-arabinofuranoside based upon the study of diethylaminosulfur trifluoride (DAST)-reactions with 5-*O*-protected methyl D-xylosides was explored using mild reaction conditions on the key step. New peculiarities for selective fluorinations of 5-*O*-benzoylated α- and β-D-pentofuranosides with DAST leading to the formation of mono and difluoro-furanoside derivatives are reported.

Keywords

D-xylose; Regioselective benzoylation; Fluorination; Fluorodeoxy sugars; Glycosylation; Fluoronucleosides

1. Introduction

Modified nucleosides analogs are an important class of compounds possessing antiviral and anticancer activities. Fluorinated by the sugar moiety or in the heterocyclic base nucleosides have drawn a lot of attention because of their interesting biological properties and several of them are essential chemotherapeutics [1,2]. Introduction of fluorine atom(s) to synthetic nucleoside analog can influence conformational properties, metabolism, enhance

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.tet.2019.02.027. These data include MOL files and InChiKeys of the most important compounds described in this article.

Conflicts of interest

The authors declared no potential conflicts of interest in this work.

bioavailability, binding affinity and selectivity of fluorinated derivative, and plays a prominent role in the drug design due to improvement in the pharmacokinetic properties and a change in the bioactivity [3,4].

A number of purine-based nucleosides bearing a halogen atom at the 2-position in the nucleobase have been prepared and investigated as potential anticancer gents. Among these derivatives purine analogs with 2-fluorine or 2-chlorine atom have been shown to possess activity against human tumor cells. Fludarabine (**1a**) and its prodrug, fludarabine phosphate (9-β-D-arabinofuranosyl-2-fluroadenine 5′-*O*-phosphate, **1b**) (Fig. 1), [5–7] were explored as anticancer agents, and, after the clinical development, fludarabine phosphate is currently used for the treatment of chronic lymphocytic leukemia [8]. 2-Fluoro-2′-deoxyadenosine (**2**), a deoxyanalog of fludarabine (**1a**) with excellent substrate properties for *E. coli* purine nucleoside phorphorylase demonstrated better activity against tumors that express *E. coli* than fludarabine phosphate (**1b**) and is considered as a valuable asset in the suicide gene therapy strategy [9]. 2-Fluoro-3′-deoxyadenosine (**3**), the fluorinated analog of cordycepin was also synthesized using chemical or chemoenzymatic approaches [10,11] and identified as a selective and potent compound with trypanocidal activity *in vitro* and *in vivo*. Synthetic routes to 2′-deoxy-2′-fluoro-arabino and ribo 2-fluoroadenine nucleosides **4–5** (Fig. 1) were developed, and these compounds were evaluated for their cytotoxicity and *in vitro* anti-HIV activity [7,12,13].

2′-Fluoro-analog of fludarabine **4** showed cytotoxicities to a series of human tumor cell lines [7,12]. Besides, 2-fluorolodenosine (**6**) [7] as well as a number of other purine-modified 2′-fluoro-2′,3′-dideoxyarabinofuranosyl nucleosides were prepared and evaluated *in vitro* as anti-HIV agents [14,15]. 2′,3′-Dideoxy-2′,3′-difluoro D-arabino purine nucleosides were also prepared and the studies of *in vitro* antiviral activities led to the discovery of 2,6-diaminopurine (**7**) [16] and adenine (**8**) [17] 2′,3′-difluoro-β-D-arabinosides which display selective anti-HIV-1 activities. In order to extend this series of bioactive fluoronucleosides and evaluate their anticancer and antiviral potential, the further development of the synthetic methodology to 2′,3′-difluoroarabinofuranosyl nucleosides with structural modifications in the base was continued from the carbohydrate precursor and herein we report the synthesis of novel 2-fluorine and 2,6-disubstituted derivatives of purine 2′,3′-difluorinated nucleosides.

2. Results and discussions

2.1. Syntheses of 5-O-benzoylated mono and difluoro-d-pentofuranoside derivatives from d-xylose

Our synthetic strategy for designing purine-modified difluoro nucleosides starts from D-xylose and involves study of synthesis of the key intermediates, methyl 5-*O*-benzoyl-2,3-difluoro-α-D-arabinoside and the 1-α-bromosugar, for which several approaches were earlier investigated [16,17]. In order to improve the methods developed for the preparation of the difluoro sugar **15** [17] from methyl 5-*O*-benzoyl-α-D-xylofuranoside (**11a**), different synthetic routes to the latter were explored in detail on the first step (Scheme 1).

Direct and selective acylation of primary hydroxyl groups in methyl α/β-xylofuranosides (**9**), prepared quantitatively from readily available from D-xylose [18], using an excess of benzoyl chloride as the acylating agent was tested under various conditions (Table 1, entries 1–3). First, benzoylation of **9** in CH_2Cl_2/Py in the presence of Et_3N as a base catalyst gave 5-*O*-benzoates **11a**,**b** with a low yield (Table 1, entry 1). Second, the use of a mixture of Et_3N/$^{i}Pr_2NEt$ in the acylation reaction led to **11a**,**b** in 39–46% (entries 2–3), but the target α-xyloside **11a** was isolated in 39% yield after chromatography on silica gel (entry 3). Next, the Bu_2SnO method [19] widely used in carbohydrate chemistry for acylation and alkylation of D-hexopyranosides [20–22], and benzylation of 1,2-*O*-isopropylidene-D-xylofuranose [23] was investigated for selective 5-*O*-monobenzoylation of xylofuranosides **9** with benzoyl chloride (Table 1, entries 4,5).

Different reaction conditions have been reported [20–22] for regioselective and efficient acylations of sugars via activation of OH groups by Bu_2SnO followed by treatment of the cyclic tin intermediate with excess acyl chloride and triethylamine. The reaction of methyl α/β-xylofuranosides (**9**) with an equimolar amount of dibutyltin oxide in methanol under reflux produced intermediate 3,5-*O*-di-n-butylstannylene derivative **10** which was converted to 5-*O*-benzoates **11a** in 46% overall yield (Table 1, entry 4) by reaction with benzoyl chloride and $^{i}Pr_2NEt$ in toluene (Table 1, entry 4). The yield of the target products was improved to 97% via the dibutylstannylene derivatives in anhydrous 1,2-dimethoxyethane (entry 5). It should be noted that under the above reaction conditions (Table 1) benzoylation of a mixture of methyl α/β-xylosides **9** derived from D-xylose yielded the higher yields for 5-*O*-benzoyl derivative of β-xylofuranoside compared to that of the α-xyloside. Further, to improve yield of the target pentofuranoside, conversion of 5-*O*-benzoylated methyl β-xylofuranoside **11b** to isomeric α-xyloside **11a** was studied under mild acidic conditions (Table 2). Isomerization of **11b** to **11a** was tested in anhydrous MeOH in the presence of CH_3SO_2OH at room temperature (entry 1) and the yield of **11a** made up 32% after the methanolysis and treatment of the reaction mixture with aqueous $NaHCO_3$. Methanolysis of **11b** in MeOH/HCl generated by adding acetyl chloride to methanol at 0 °C afforded only a mixture of two anomers **11b** and **11b** with a ratio of 1:0.90 (from ^{1}H NMR data) and 47% yield of α-xyloside **11a** (entry 2). These findings indicate that acidic methanolysis resulted in the anomerization of **11b** with the formation of α-anomer **11a** and this simple procedure can be used for the increase of overall yield of the target 5-*O*-benzoylated α-xyloside (Scheme 1) after separation of the anomeric mixture with column chromatography on silica gel. Thus, novel synthetic approach to methyl 5-*O*-benzoyl-α,β-xylofuranoside (**11a**,**b**) via the 3,5-*O*-dibutylstannylene intermediates **10** was developed from D-xylose. This method gave 5-*O*-acylated xylosides in higher combined yields compared to the method reported earlier via 5-*O*-protected 1,2-*O*-isopropylidene-α-D-xylofuranose [24].

Fluorination of individual xylosides **11a** and **11b** with DAST, the widely used fluorinating agent [25,26] in carbohydrate chemistry [27,28], was reported for the synthesis of deoxyfluoro D-pentofuranosides [23]. In addition, fluorination of mixtures of methyl 5-*O*-benzyl or 5-*O*-*p*-toluoyl-α/β-D-xylofuranosides with DAST and Deoxo-Fluor was studied for preparation of 5-*O*-protected methyl 3-fluoro-3-deoxy-α/β-D-ribofuranosides [29,30].

Several pathways for the preparation of the 2,3-difluoride **15** were also explored from 2-*O*-sulfonates of methyl 3-fluoro-3-deoxy-α-D-ribofuranoside and selectively protected *α*-D-xylofuranoside **11a** [15]. As an extension of this work, new investigations on the DAST-reaction with **11a** were undertaken to develop a shorter and more efficient synthetic route to methyl 5-*O*-benzoyl-2,3-difluoroarabinoside (**15**) (Scheme 2). Treatment of **11a** with 5.6 eqiuv. of DAST in methylene chloride under 25–29 °C for 10 h resulted in the difluoride **15** (18%) and methyl 5-*O*-benzoyl-3-deoxy-3-fluoro-*α*-D-ribofuranoside (**14**) (51%) after workup of reaction mixture and chromatography on silica gel. In this case, decrease of the reaction time and an excess of the fluorinated agent compared to the previous data described for the double fluorination of the xyloside **11a** [15] gave rise to **15** with a lower yield and increased the formation of the α-riboside **14**. The results obtained when studying introduction of fluorine at C-2 of *O*-protected pyranoside and furanoside derivatives with DAST [24,31–34] indicate that the nature of the C1-substituent and its stereochemistry, the protecting groups in the pentofuranose ring, conformational peculiarities of the C-2-*O*-SF_2NEt_2 intermediates prepared by DAST-activation of hydroxyl groups, the temperature, and solvent should be considered as important factors affecting the S_N2-displacement reaction by fluoride in selectively protected pentofuranoside derivatives. From the above reasoning fluorination of the α-riboside **14** with an excess of DAST was carried out in a mixture of methylene chloride and pyridine under mild heating 35–37 °C for 18 h to give the difluoride **15** in 66% yield after chromatographic isolation (Scheme 2). A short and optimized synthesis of the key intermediate **15** was studied from D-xylose using mild reaction conditions for the fluorination reaction.

Next, synthesis of the 1-α-bromide **17** from **15** was explored taking into account the known two-step procedures [16,17]. Two methods were tested to directly prepare the bromide **17** from the α-arabinoside **15** without preparation of intermediate 1-*O*-acetates. Bromination of **15** with 34% HBr in CH_3COOH in the presence of TMSBr in CH_2Cl_2 for 18 h failed to prepare the target bromide and only the starting sugar was detected in the reaction mixture. Reaction of **15** with 34% HBr in CH_3COOH in a mixture of CH_3COOH/Ac_2O at room temperature did not also resulted in the bromide. ^1H NMR spectrum of the crude reaction mixture after removal of the reagents in vacuum under mild heating showed the absence of the signals corresponding to the bromo sugar. 5-*O*-Benzoyl-2,3-dideoxy-2,3-difluoro-α,β-D-arabinofuranose (**16**) derived likely from hydrolysis of the intermediate reaction products was isolated in 50% yield by chromatography on silica gel. Nevertheless, optimized reaction conditions for preparation of the 1-α-bromide **17** were found which include the acetolysis reaction of **15** in a mixture of $CH_3COOH/Ac_2O/H_2SO_4$ at 24–25 °C with a slight increase of sulfuric acid content and the reaction time followed by bromination of the intermediate 1-*O*-acetates with TMSBr in the presence of the catalyst (Scheme 2).

In continuation, fluorination of the β-xyloside **11b** with an excess of DAST in methylene chloride was carried out under 25–27 °C for 18 h (Scheme 3). Four products were prepared after the workup of the reaction mixture and the 3-fluoro-3-deoxy-β-D-riboside **21**, 2,3-difluoride **15**, 1,3-difluoride **22**, and methyl 5-*O*-benzoyl-2,3-anhydro-β-D-riboside (not presented in scheme) were isolated in 55%, 3%, 3% and 14% yields, respectively, after column chromatography on silica gel. A thorough analysis of prepared reaction products

made it possible to recognize new interesting peculiarities for the fluorination reaction of **11b**. In present study the formation of the 3-fluoro-β-riboside **21** was observed as the main product along with two difluoro derivatives of α-D-arabinofuranose **15** and **22** as side-products unlike a previous work [24].

The structures of fluorinated sugars were confirmed by ^{1}H, ^{13}C and ^{19}F NMR, mass and IR-spectroscopy. ^{1}H and ^{13}C NMR spectral data ($CDCl_3$) of isomeric difluorides **15** and **22** are distinguished essentially for H-1 and H-2 protones, C-1 and C-2 carbons (experimental part). Signals of the H-1 and H-2 protons of the 1,3-difluoride **22** displayed as a doublet at 5.90 ppm ($J_{1,F\text{-}1}$ = 60.4 and $J_{1,2}$ < 1.0 Hz) and a multiplet at 4.17 ppm in the ^{1}H NMR spectrum unlike those of isomeric 2,3-difluoride **15**. H-1 and H-2 resonances of the latter are revealed as a broad doublet at 5.19 ppm ($J_{1,F\text{-}2}$ = 10.0 and $J_{1,2}$ < 1.0 Hz) and a complex multiplet at 5.08 ppm, respectively. Small magnitudes of $^{3}J_{H\text{-}1,H\text{-}2}$ coupling constants are characteristic of the ^{1}H NMR data for the both difluorinated α-D-arabinofuranoside derivatives **15** and **22**. The large value of $^{3}J_{C\text{-}1,F\text{-}1}$ = 225.7 Hz inherent in the glycosyl fluorides [35] was displayed in the ^{13}C NMR spectrum of the 1,3-difluoride **22**. Very similar IR-spectroscopic data obtained in film were observed for isomeric difluorides **15** and **22** which differ from that of the 2,3-difluoride **16** with a hydroxy group at C-1. ^{19}F NMR data of 5-*O*-benzoylated fluorodeoxy monosaccharides **14–16**, **21–22** are indicative of the assigned structures of synthesized compounds. Fluorine resonance signals of 3-deoxy fluoro ribosides, 1,3 and 2,3-difluoro-containing arabinofuranose derivatives are revealed as double triplets or two complex multiplets, respectively, in their ^{19}F NMR spectra.

The proposed mechanism of the DAST-reaction with **11b** resulting to the fluoride **21**, difluorides **15** and **22** is outlined in Scheme 3. The results of fluorination of xyloside **11b** point to the interaction of DAST with hydroxyl groups of the β-xyloside as well as the α-xyloside **11a** gives rise to the predominant generation of classical C-3-*O*-SF_2NEt_2 derivative **18** on the first step. In addition, the formation of 5-*O*-benzoylated 2,3-anhydro-β-D-riboside via transient intermediate **18** took also place in this reaction. Conversions of the key intermediate **19** are likely to proceed with participation of β-methoxy group and production of the 2-*O*-activated intermediate **13** (via isomerization at C-1), and a methyloxiranium ion **20** (via 1,2-alkoxy migration) [32] followed by attacks with fluoride on C-2 or C-1 atoms, respectively, leading to difluorides **15** and **22** (path a). The formation of methyl 2,3-difluoro α-D-arabinofuranoside derivative **15**, but not the β-counterpart, from the β-xyloside **11b** is unexpected fact which may also be explained by another reaction pathway b via anomerization of the intermediate **18** forming on the first step to an isomeric intermediate **12** with a α-methoxy group under acidic reaction conditions (HF/CH_2Cl_2) followed by consecutive transformations of the latter with DAST into the C-2-*O*-SF_2NEt_2 derivative of the α-riboside **13** and the 2,3-difluoride **15** as in the case of the fluorination of the α-xyloside **11a** (Scheme 2).

Furthermore, the DAST-reaction of a mixture of isomeric xylosides **11a** and **11b** (a ratio - 3:2) was carried out in methylene chloride under 24–27 °C for 18 h to give to the 3-fluoro-α-D-riboside **14** (41%) and its β-anomer **21** (40%) in 40% overall yield as the main reaction products along with difluoro derivatives **15** (24%) and **22** (4%), and 5-*O*-benzoylated the

2,3-*ribo*-epoxide (14%). It should be noted that the fluorination reaction of a mixture of xylosides **11a**,**b** with predominant content of the α-anomer afforded 3-fluoro-3-deoxy-D-ribosides **13** and **20** in a similar yield, and the target 2,3-difluoro sugar **15** in moderate yield.

Based on the above findings, it may be concluded that the DAST-reactions with 5-*O*-protected α-**11a** and β-**11b** xylofuranosides resulted in fluorinations on several positions (C-3; C-3 and C-2; or C-3 and C-1) of the pentofuranose rings via the DAST-activation of free hydroxyl groups with formation of the C-3-*O*-SF_2NEt_2, and then C-2-*O*-SF_2NEt_2 derivatives, 1,2-alkoxy-migration or anomerization for the β-xyloside intermediate, and intermolecular attacks by fluoride-anion to afford mono-, difluorinated pentofuranoside derivatives.

2.2. Synthesis of novel purine-modified 2′,3′-difluoro-d-arabino nucleosides from the 1-α-bromide 17

As an extension of our previous studies, we prepared 2′,3′-dideoxy-2′,3′-difluoro-D-arabinofuranosyl nucleosides featuring fluorine substituted purine nucleobases from the universal carbohydrate precursor. A series of purine-modified 2′,3′-difluoro arabinonucleosides were synthesized via glycosylation reactions of 2-fluoroadenine and 6-chloro-2-fluoropurine with the bromide **17** prepared from D-xylose. Nucleobase anion glycosylation reaction of potassium salt of the 2-fluoroadenine, generated in the presence of potassium *t*-butoxide in anhydrous 1,2-dimethoxyethane, with the bromo sugar **17** in a mixture of anhydrous acetonitrile/methylene chloride in the presence of calcium hydride at room temperature afforded a mixture of protected N^9-β-D- and N^9-α-D nucleosides **23** and **24** which were separated by column chromatography on silica gel in 28% yield (Scheme 4). Debenzoylation of individual blocked nucleosides **23** and **24** with LiOH in aqueous acetonitrile [7] at room temperature gave pure β-2′,3′-difluoroarabino nucleoside **25** and its α-anomer **26** in 73% and 87% yield, respectively.

An alternative approach was investigated to prepare the target 2-fluorosubstituted nucleoside **25** through the coupling reaction of 6-chloro-2-fluoropurine instead of 2-fluoroadenine with the carbohydrate precursor **17** followed by transformations of intermediate protected N^9-β-D-arabinoside **27** (Scheme 5). Reaction of the potassium salt of 6-chloro-2-fluoropurine, prepared in the presence of potassium *t*-butoxide in anhydrous 1,2-dimethoxyethane, with the bromo sugar **17** at room temperature gave a mixture of N^9-β- and N^9-α-D-2′,3′-difluoroarabinonucleosides (a β/α-ratio = 8.5:1 according to ^{1}H NMR data) from which protected β-6-chloro-2-fluoropurine nucleoside **27** was isolated in 66% yield after column chromatography (Scheme 5). Standard deacylation of **27** with LiOH at room temperature gave β-6-chloro-2-hydroxypurine nucleoside **28** as the main product of the reaction in 61% yield after column chromatography on silica gel. The treatment of **27** with a saturated solution of ammonia in anhydrous 1,2-dimethoxyethane at room temperature for 18 h gave 5-*O*-benzoylated *β*-nucleosides of 6-chloro-2-aminopurine **29** and 2-fluoroadenine **23** which were successively isolated by chromatography on silica gel in 55% and 23% yield, respectively.

In this case, substitution reactions of halogen atoms in the purine base of β-D-nucleoside **27** with ammonia gave 5-*O*-protected 6-chloro-2-aminopurine β-nucleoside **29** as predominant product in contrast to the results prepared earlier under the same treatment of the protected N^9-β/α-D-2′,3′-difluoroarabinoside of 2,6-dicloropurine [17]. Deacylation of protected intermediate N^9-β-D-arabinonucleoside **27** with saturated at 0 °C methanolic ammonia in anhydrous tetrahydrofuran resulted in 6-chloro-2-aminopurine β-D-nucleoside **31** (54%) along with β-2-fluoroadenine derivative **25** (15%) which were separated by column chromatography on silica gel (Scheme 5). Deprotection of N^9-β-D-arabinonucleoside **27** with ammonia in a mixture of methanol/THF unexpectedly afforded also 2-amino-6-chloropurine derivative **31** as the main product after selective displacement of a fluorine atom at C-2 and the removal of benzoyl protecting group, and the target 2-fluorine-substituted nucleoside was prepared in low yield. The structures of nucleosides **29** and **31** were confirmed by comparison of their NMR data with those of the β-nucleosides synthesized via the glycosylation reaction of 6-chloro-2-aminopurine with the bromo sugar **17** followed by deacylation of intermediate nucleosides **28** and **29**, following a procedure we established earlier [16]. The above selective transformations in **27** demonstrate that this protected halogenated nucleoside as well as the 2,6-dichloropurine analog [16,17] is a valuable intermediate for the synthesis of different 2,6-substituted purine nucleoside derivatives of this class.

The treatment of β-anomer **31** with potassium carbonate in methanol at 80–82 °C gave 2-amino-6-methoxypurine β-arabinoside **33**, a close analog of the antileukemic nucleoside nelarabine (9-β-D-arabinofuranosyl-2-amino-6-methoxypurine) which is used for treatment of T-cell acute lymphatic leukemia [36]. 2′,3′-Difluoronelarabine **33** was isolated by chromatography on silica gel in 72% yield, while the α-isomer **35** was prepared from 2-amino-6-chloropurine derivative **32** in 75% yield through the nucleophilic displacement of the chlorine atom by the methoxide anion (Scheme 5). Thiation of 6-chloro-2-aminopurine β-arabinonucleoside **31** with thiourea in EtOH under refluxing gave 9-(2′,3′-difluoro-β-D-arabinofuranosyl)-6-thioguanine (**34**) (76%), a difluoro analog of 9-(β-D-arabinofuranosyl)-6-thioguanine [37] which displayed cytotoxicity against L1210 mouse leukemia.

The structures of fluorinated nucleosides were confirmed by ^1H, ^{13}C, ^{19}F NMR, and mass spectroscopy. The assignments of the configurations of synthesized purine nucleosides at the anomeric centres were based upon ^1H and ^{13}C NMR data. The diagnostic for the β-anomeric configuration of difluoronucleosides **23**,**25**, **27–31**, **33** and **34** is the five-bond couplings of 1.3–2.4 Hz between the H-8 protons of modified purine bases (doublets in their ^1H NMR spectra) and 2′-β-fluorine atoms [7,14–17,38]. The absence of the same long-range couplings is characteristic of the proton NMR spectra of α-anomers **24**, **26**, **35** and signals of the H-8 protons are displayed as singlets. The magnitudes of $^2J_{C\text{-}1',F\text{-}2'}$ coupling constants for β- and α-anomers of 2′,3′-difluoronucleosides **23** and **25** (16.9 and 17.1 Hz), **24** and **26** (30.9 and 35.9 Hz) in their ^{13}C NMR spectra also confirmed the stereochemistry of the purine analogs at the anomeric centres [16,17,39]. ^{19}F NMR data of nucleosides provided evidence in favor of the assigned structures of purine derivatives with 2′,3′-difluoro-D-arabinofuranosyl moiety. F-2′ and F-3′ resonance signals of the nucleosides are revealed as

complex multiplets for all series and F-2 resonances of 2-fluorine-substituted purine derivatives **23–26**, **27** appeared as singlets at a range of −49 to −53 ppm [40] in the ^{19}F NMR spectra.

3. Conclusions

In summary, synthetic routes to a series of new purine-modified 2′,3′-dideoxy-2′,3′-difluoro-D-arabino nucleosides were developed from readily available D-xylose using selective anion glycosylation reactions of 2-fluoropurine derivatives by the 1-α-bromide. A short and improved on key steps synthesis of 5-*O*-benzoyl 2,3-dideoxy-2,3-difluoro-α-D-arabinofuranosyl bromide was devised which includes a new and selective 5-*O*-monobenzoylation of methyl xylosides via their stannylene derivatives with benzoyl chloride, the efficient method for synthesis of 2,3-dideoxy-2,3-difluoro-α-D-arabinofuranoside derivative via fluorination reaction of 5-*O*-benzoylated methyl 3-fluoro-3-deoxy-α-D-ribofuranoside with DAST under mild heating, and bromination of the intermediate 1-*O*-acetates prepared under optimized conditions for the acetolysis reaction. New insights into the selective fluorination procedures of 5-*O*-benzoylated D-pentofuranosides with DAST have been obtained and these findings are of interest for the development of practical synthetic methods for different deoxyfluoro sugars. Novel 2-fluoro-substituted purine 2′,3′-difluoro D-arabino nucleosides have been prepared via selective coupling reactions of potassium salts of 2-fluoroadenine and 2-fluoro-6-chloropurine with the bromide. We showed that the protected 2-fluoro-6-chloropurine N^9-β-D-arabinoside can be used as a versatile and valuable intermediate to prepare various 2′,3′-difluoro-β-D-arabinofuranosyl 2,6-disubstituted purine nucleosides. Using the multi-step approach, we have successfully prepared 9-(2′,3′-difluoro-β-D-arabinofuranosyl)-2-fluoroadenine and 9-(2′,3′-difluoro-β-D-arabinofuranosyl)-2-amino-6-methoxypurine as sugar-difluorinated nucleoside analogs of fludrabine and nelarabine.

4. Experimental

4.1. General information

Column chromatography was performed on silica gel 60H (70–230 mesh; Merck, Darmstadt, Germany), and thin-layer chromatography (TLC) on Merck silica gel aluminum 60 F_{254} pre-coated plates. The anhydrous solvents were distilled over CaH_2, P_2O_5 or magnesium prior to the use. All commercially available reagents were used without further purification. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$, CD_3OD and DMSO-d_6 with a Bruker Avance-500-DRX spectrometer at 500.13, 126.76 and 470.59 MHz, respectively. ^{1}H and ^{13}C NMR chemical shifts (δ, ppm) are relative to internal chloroform peak (7.26 ppm for ^{1}H and 77.0 for ^{13}C NMR). Chemical shifts are also reported downfield from internal $SiMe_4$ (^{1}H) or external $CFCl_3$ (^{19}F). *J* values are reported in Hz. Melting points were determined on a Boetius apparatus and were uncorrected. IR spectra were measured on Perkin-Elmer Spectrum 100FT-IR spectrometer. High resolution mass spectra (HRMS) were recorded on an Agilent Q-TOF 6550 Instrument (USA) using ESI (electrospray ionization).

4.2. Syntheses of 5-O-benzoylated mono and di-fluorinated d-pentofuranoside derivatives from d-xylose

4.2.1. Selective 5-O-benzoylation of methyl α,β-d-xylofuranoside (9)

Method A.: To methyl α,β-D-xylofuranoside (**9**) (1.09 g, 6.64 mmol), prepared in quantitative yield after methanolysis of D-xylose [18] and purification on silica gel, in anhydrous CH_2Cl_2 (15 mL) was added triethylamine (1.57 mL, 11.26 mmol) and Pr_2NEt (1.0 mL, 5.6 mmol) and then to prepared solution was added slowly dropwise benzoyl chloride (1.0 mL, 8.62 mmol) in anhydrous CH_2Cl_2 (6 mL) at 0 °C (ice and sodium chloride). The reaction mixture was stirred for 15 min under cooling and then 18 h at room temperature. The solution was diluted with CH_2Cl_2 (60 mL), washed with water, the aqueous phase was extracted with CH_2Cl_2 (30 mL). The combined organic extracts were washed cooled 5% $NaHCO_3$, dried over anh. Na_2SO_4 and evaporated to dryness. The residue was chromatographed on silica gel using a mixtures of EtOAc-petroleum ether to give a mixture of 5-*O*-benzoates α/β-D-xylofuranosides of **11a**,**b** (819 mg, 46% overall yield). Chromatography of the prepared mixture, using a linear gradient of EtOAc (14 → 66%, v/v; 500 mL) in petroleum ether, afforded benzoate β-xyloside **11b** (428 mg, 45%). Mp.107–108 °C. ^{1}H NMR ($CDCl_3$): 7.42–8.07 (m, 5H, Ar-H), 4.89 (s, 1H, H-1), 4.67 (dd, 1H, $J_{5,4}$ = 4.5, $J_{5,5'}$ = 11.2, H-5), 4.64 (m, 1H, H-4), 4.50 (dd, 1H, $J_{5,4}$ = 6.6, H-5′), 4.25 (br.s, 1H, H-2), 4.16 (br.d, 1H, H-3), 3.40 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 166.7 (C=O, Bz), 133.2, 129.8, 129.4 (C_6H_5CO-), 108.7 (C-1), 80.8 (C-4), 79.6 (C-2), 76.4 (C-3), 64.4 (C-5), 55.4 (OCH_3). HRMS (ESI$^+$): *m*/*z* calcd for $[C_{13}H_{16}O_6+Na]^+$: 291.0840, found 291.0839.

And benzoate α-xyloside **11a** (324 mg, 39%) as a syrup. ^{1}H NMR ($CDCl_3$): 7.43–8.05 (m, 5H, Ar-H), 5.05 (d, 1H, $J_{1,2}$ = 4.4, H-1), 4.71 (dd, 1H, $J_{5,4}$ = 5.5, $J_{5,5'}$ =11.4, H-5), 4.43 (m, 1H, H-4), 4.38 (dd, 1H, $J_{5,4}$ = 5.0, H-5′), 4.26 (t, 1H, $J_{3,2}$ = 3.8, $J_{3,4}$ = 3.8, H-3), 4.18 (t, 1H, H-2), 3.51 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 166.9 (C=O, Bz), 133.3, 129.8, 129.7, 128.5 (C_6H_5CO-), 102.0 (C-1), 77.9 (C-4),76.9 (C-2), 76.6 (C-3), 62.6 (C-5), 56.2 (OCH_3). HRMS (ESI$^+$): *m*/*z* calcd for $[C_{13}H_{16}O_6+Na]^+$: 291.0840, found 291.0841.

Method B.: To methyl α,β-D-xylofuranoside **9** (256 mg, 1.56 mmol) in anhydrous MeOH (10 mL) was added Bu_2SnO (388 mg, 1.56 mmol) and then the reaction mixture was refluxed for 1 h and stirred for 15 min at rt. Prepared solution was evaporated dryness, to the residue was added anhydrous toluene (6 mL), then dropwise $^iPr_2NEt$ (0.53 mL, 2.96 mmol) and benzoyl chloride (0.36 mL, 3.10 mmol). The reaction mixture was stirred for 5 h at room temperature, and then evaporated. The residue was chromatographed on silica gel using a mixtures of EtOAc-petroleum ether to give a mixture of 5-*O*-benzoylated α/β-D-xylofuranosides **11a**,**b** (194 mg, 46% overall yield). Chromatography of the prepared mixture, using a linear gradient of EtOAc (14 → 66%, v/v; 500 mL) in petroleum ether, afforded β-xyloside **11b** (96 mg, 41%) and α-xyloside **11a** (65 mg, 35%).

Method C.: To methyl α,β-D-xylofuranoside **9** (256 mg, 1.56 mmol) in anhydrous MeOH (10 mL) was added Bu_2SnO (388 mg, 1.56 mmol) and then the reaction mixture was refluxed for 1 h and stirred for 15 min at rt. Prepared solution was evaporated dryness, to the residue was added 1,2-dimethoxyethane (4 mL) and then dropwise $^iPr_2NEt$ (0.65 mL, 3.63

mmol) and benzoyl chloride (0.54 mL, 4.65 mmol). The reaction mixture was stirred for 5 h at room temperature, and then evaporated. The residue was chromatographed on silica gel using a mixtures of EtOAc-petroleum ether to give a mixture of 5-*O*-benzoylated α/β-D-xylofuranosides **11 a**,**b** (404 mg, 97% overall yield). Chromatography of the prepared mixture using a linear gradient of EtOAc (14 → 66%, v/v; 500 mL) in petroleum ether afforded crystalline β-xyloside **10b** (206 mg, 89%) and α-xyloside **11a** (153 mg, 82%) as a syrup.

4.2.2. Isomerization of β-d-xylofuranoside 11b to α-d-xylofuranoside 11a

Method A.: To methyl β-D-xylofuranoside **11b** (108 mg, 0.64 mmol) in anhydrous MeOH (2.0 mL) was added CH_3SO_2OH (0.04 mL, 2.48 mmol) and then the reaction mixture was stirred for 18 h at rt. Prepared solution was treated by cooled 5%-aqueous $NaHCO_3$, the aqueous phase was extracted with CH_2Cl_2 (3 × 35 mL). The combined organic extracts were dried over anh. Na_2SO_4 and evaporated to dryness. A mixture of anomers was prepared as oil product (115 mg). Ratio of 5-*O*-benzoyl α/β-xylofuranosides **11b** and **11a** (1:0.66) was determined from the ^{1}H NMR spectrum of the mixture in $CDCl_3$.

Method B.: To methyl 5-*O*-benzoyl-β-D-xylofuranoside **11b** (155 mg, 0.58 mmol) was added MeOH/HCl (3.0 mL, 0.5 mmol HCl) from a solution prepared by adding 0.18 mL acetyl chloride to anhydrous 15 mL MeOH at 0 °C and then the reaction mixture was stirred for 3 h at rt. Prepared solution was evaporated under diminished pressure at 30–35 °C, coevaporated with anhydrous toluene. A mixture of anomers was prepared as oil product (155 mg). Ratio of 5-*O*-benzoyl α/β-xylofuranosides **11b** and **11a** (1:0.90) was determined from the ^{1}H NMR spectrum of the mixture in $CDCl_3$.

4.2.3. DAST-reaction with xyloside 11a—To a solution of methyl 5-*O*-benzoyl-α-xylofuranoside **11a** (272 mg, 1.01 mmol) in anhydrous CH_2Cl_2 (5.9 mL) was added dropwise 0.75 mL (5.66 mmol) DAST at room temperature. The reaction mixture was stirred for 30 min at rt and then for 10 h at 25–29 °C. The solution was diluted CH_2Cl_2 (10 mL), poured gradually into cooled 5%-aqueous $NaHCO_3$ with stirring, then after stirring for 30 min the aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts was washed with water (20 mL), and dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was chromatographed on a silica gel, using a mixture of 12:1, 9:1, and 1:1 hexane-EtOAc to afford the difluoride **15** (49 mg, 18%) as a syrup. IR (film, $CHCl_3$): *v* 2931, 2854, 1726, 1275, 1116, 1076, 712 cm^{-1}. ^{1}H NMR ($CDCl_3$): 7.44–8.06 (m, 5H, Ar-H), 5.19 (br.d, 1H, $J_{1,2}$ < 1.0, $J_{1,F\text{-}2}$ = 10.3, H-1), 5.10 (dm, 1H, H-3), 5.08 (ddd, 1H, H-2), 4.51–4.61 (m, 3H, H-4 an 2H-5), 3.44 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 166.1 (s, C=O, Bz), 133.3, 129.8, 129.4, 128.4 (4s, C_6H_5CO-), 105.9 (dd, $J_{C\text{-}1,F\text{-}3}$ = 4.0, $J_{C\text{-}1,F\text{-}2}$ = 35.2, C-1), 97.4 (dd, $J_{C\text{-}2,F\text{-}2}$ = 181.5, $J_{C\text{-}2,F\text{-}3}$ = 28.0, C-2), 94.9 (dd, $J_{C\text{-}3,F\text{-}2}$ = 30.5, $J_{C\text{-}3,F\text{-}3}$ = 186.5, C-3), 80.2 (d, $J_{C\text{-}4,\ F\text{-}3}$ = 28.9, C-4), 62.9 (d, $J_{C\text{-}5,F\text{-}3}$ = 5.4, C-5), 55.0 (OCH_3). ^{19}F NMR ($CDCl_3$): −195.35 (m, F-2), −192.93 (m, F-3). HRMS (ESI$^+$): *m/z* calcd for $[C_{13}H_{14}F_2O_4+Na]^+$: 295.0753, found 295.0751.

And methyl 5-*O*-benzoyl-3-deoxy-3-fluoro-α-D-ribofuranoside (**14**) (140 mg, 51%) as a syrup. IR (film, $CHCl_3$): *v* 3487, 2937, 1722, 1275, 1076, 712 cm^{-1}. ^{1}H NMR ($CDCl_3$):

7.44–7.99 (m, 5H, Ar-H), 4.98 (d, 1H, $J_{1,2}$ = 4.8, H-1), 4.91 (ddd, 1H, $J_{3,2}$ = 5.6, $J_{3,4}$ = 1.8, $J_{3,F}$ = 55.7, H-3), 4.59 (ddt, 1H, $J_{4,F}$ = 25.9, H-4), 4.51 (dd, 1H, $J_{5,4}$ = 3.7, $J_{5,5'}$ = 12.0, H-5), 4.45 (dd, 1H, $J_{5,4}$ = 3.5, H-5′), 4.21 (dt, 1H, $J_{2,F}$ = 22.1, H-2), 3.50 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 166.0 (C=O, Bz), 133.4, 129.5, 129.4, 129.3, 128.5 (4s, C_6H_5CO-), 102.2 (C-1), 90.4 (d, $J_{C-3,F-3}$ =186.5, C-3), 80.5 (d, $J_{C-4,\ F-3}$ = 25.2, C-4), 72.3 (d, $J_{C-2,F-3}$ = 16.6, C-2), 63.7 (d, $J_{C-5,F-3}$ = 10.3, C-5), 55.7 (OCH_3). ^{19}F NMR ($CDCl_3$): −195.3 (dt, F-3). HRMS (ESI^+): *m*/*z* calcd for $[C_{13}H_{15}O_5F+Na]^+$: 293.0796, found 293.0796.

4.2.4. Methyl 5-O-benzoyl-2,3-dideoxy-2,3-difluoro-α-d-arabinofuranoside (15)—

To a solution of methyl 5-*O*-benzoyl-3-deoxy-3-fluoro-α-ribofuranoside **14** (190 mg, 0.7 mmol) in anhydrous CH_2Cl_2 (6.6 mL) and pyridine (0.1 mL, 1.23 mmol) was added dropwise 0.34 mL (2.57 mmol) DAST at room temperature. The reaction mixture was stirred for 30 min and then for 18 h at 35–37 °C. The solution was diluted CH_2Cl_2 (10 mL), poured gradually into cooled 5%-aqueous $NaHCO_3$, the aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts was washed with water (10 mL), and dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was chromatographed on a silica gel, using a mixture of 12:1, 9:1 and 6:1 hexane-EtOAc to afford the difluoride **15** (127 mg, 66%) as a syrup.

4.2.5. Methyl 5-O-benzoyl-2,3-dideoxy-2,3-difluoro-α,β-d-arabinofuranose (16)—

To methyl arabinoside **15** (35 mg, 0.12 mmol) in CH_3COOH (0.27 mL), Ac_2O (0.064 mL) was added 34% HBr in acetic acid (0.3 mL). The resulting mixture was stirred for 18 h at room temperature, and then evaporated at 35–40 °C, coevaporated with anhydrous toluene. The residue was dissolved in CH_2Cl_2 (10 mL), and washed with water (3 mL), the organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The yellowish oil was chromatographed on a silica gel, using a mixture of 3:1, 1:1 hexane-EtOAc to afford 16 mg (50%) the difluoride **16** as a syrup. IR (film, $CHCl_3$): *v* 3451, 2957, 2927, 1726, 1278, 1073, 715 cm^{-1}. ^{1}H NMR ($CDCl_3$): 7.49–8.11 (3m, 7.08H, Bz), 5.68 (d, 1H, $J_{1,F-2}$ = 10.4, H-1α), 5.55 (m, 0.3H, H-1β), 5.34 (ddt, 0.3H, H-2β or H-3β), 5.12–5.27 (dm, 2H, H-2α and H-3α), 4.78 (dm, 1H, $J_{4,F}$ = 22.76, H-4α), 4.62 (dd, 1H, $J_{5,4}$ = 4.6, $J_{5,5'}$ = 12.0, H-5α), 4.56 (dd, 1H, $J_{5,4}$ = 4.9, H-5′α), 4.53–4.65 (m, H-5β and H-5″β), 4.5 (dm, 0.3H, $J_{4,F}$ = 23.08, H-4β). ^{13}C NMR ($CDCl_3$): 166.2 (s, C=O, Bz), 133.4, 129.8, 129.4, 128.5 (4s, C_6H_5CO-), 100.3 (dd, $J_{C-1,F-2}$ = 35.1, $J_{C-1,F-3}$ = 3.1, C-1), 97.4 (d, $J_{C-2,F-2}$ = 181.5, $J_{C-2,F-3}$ = 27.8, C-2), 94.8 (dd, $J_{C-3,F-3}$ = 182.5, $J_{C-3,F-2}$ = 30.7, C-3), 80.6 (d, $J_{C-4,\ F-3}$ = 38.0, C-4), 63.1 (d, $J_{C-5,F-3}$ = 6.9, C-5). ^{19}F NMR ($CDCl_3$): −192.5 (m, F-2 or F-3), −195.4 (m, F-3 or F-2). HRMS (ESI^+): *m*/*z* calcd for $[C_{12}H_{12}F_2O_4-OH]^+$: 241.0676, found 241.0675; calcd for $[C_{12}H_{12}F_2O_4+Na]^+$: 281.0596, found 281.0593; calcd for $[C_{12}H_{12}F_2O_4+MeOH+Na]^+$: 313.0858, found 313.0858.

4.2.6. 5-O-benzoyl-2,3-dideoxy-2,3-difluoro-α-d-arabinofuranosyl bromide (17)—

Concentrated H_2SO_4 (0.03 mL) was added to a solution of difluoride **15** (60 mg, 0.22 mmol) in acetic acid (0.38 mL) and acetic anhydride (0.12 mL) at 0 °C. The reaction mixture was stirred at this temperature for 20 min and then 3 h at 24–25 °C. To solution was added ice. After the ice melted, the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). Cooled aqueous $NaHCO_3$ was added to the aqueous layer and then it was extracted with

CH_2Cl_2 (20 mL), the combined organic extracts dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was used on the next step after coevaporation with anhydrous toluene (2 × 6 mL). To a suspension of intermediate 1-*O*-acetates and anhydrous $ZnBr_2$ (10 mg) in anhydrous CH_2Cl_2 (1.7 mL) was added TMSBr (0.06 mL, 0.46 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h, then 18 h at room temperature. The reaction mixture was poured into saturated cooled aqueous $NaHCO_3$, extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness, and coevaporated with anhydrous toluene to give 59 mg (combined yield 84%) of the bromide **17** as a yellowish oil which was used in the next step without an additional purification.

4.2.7. DAST-reaction with xyloside 11b—To a solution of β-D-xylofuranoside **11b** (86 mg, 0.32 mmol) in anhydrous CH_2Cl_2 (2.0 mL) was added dropwise 0.25 mL (1.92 mmol) DAST at room temperature. The reaction mixture was stirred for 18 h at 24–27 °C. The solution was diluted CH_2Cl_2 (10 mL), poured into cooled 5%-aqueous $NaHCO_3$, the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts was washed with water (15 mL), and dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was chromatographed on a silica gel, using a mixture of 12:1, 9:1, 4:1 and 1:1 hexane-EtOAc to afford the difluoride **15** (3 mg, 3%) as a syrup.

5-*O*-benzoyl-2-*O*-methyl-3-deoxy-3-fluoro-α-D-arabinofuranosyl fluoride (**22**) (3 mg, 3%) as a syrup. IR (film, $CHCl_3$): *v* 2943, 2851, 1725, 1276, 1112, 712 cm^{-1}. ^1H NMR ($CDCl_3$): 7.46–8.13 (m, 5H, Ar-H), 5.87 (d, 1H, $J_{1,F\text{-}1}$ = 60.4, $J_{1,2}$ < 1.0 Hz, H-1), 5.03 (dd, 1H, $J_{3,F\text{-}3}$ = 52.1, $J_{3,4}$ = 2.8, H-3), 4.83 (dm, 1H, $J_{4,F\text{-}3}$ = 25.64, H-4), 4.55 (dd, 1H, $J_{5,4}$ = 4.8, $J_{5,5'}$ =11.9, H-5), 4.49 (dd, 1H, $J_{5,4}$ = 5.1, H-5′), 3.51 (s, 3H, OMe), 4.17 (ddd, 1H, $J_{2,3}$ = 0.9 Hz, H-2). ^{13}C NMR ($CDCl_3$): 166.2 (s, C=O, Bz), 133.4,129.9, 129.5, 128.5 (4s, C_6H_5CO-),112.7 (dd, $J_{C\text{-}1,F\text{-}1}$ = 225.7, C-1), 94.1 (d, $J_{C\text{-}3,F\text{-}3}$ = 186.5, C-3), 87.7 (dd, *J* = 34.7, *J* = 25.1, C-2), 83.4 (d, $J_{C\text{-}4,\ F\text{-}3}$ = 28.3, C-4), 63.0 (d, $J_{C\text{-}5,F\text{-}3}$ = 7.1, C-5), 56.1 (OCH_3). ^{19}F NMR ($CDCl_3$): −123.59 (dt, F-1), −188.77 (m, F-3). HRMS (ESI^+): *m*/*z* calcd for $[C_{13}H_{14}F_2O_4+Na]^+$: 295.0753, found 295.0754.

Methyl 5-*O*-benzoyl-2,3-anhydro-β-D-ribofuranoside (11 mg, 14%) as a syrup. ^1H NMR ($CDCl_3$): 7.49–8.13 (m, 5H, Ar-H), 5.05 (s, 1H, H-1), 4.44–4.52 (m, 3H, H-4, H-5 and H-5′), 3.90 (d, 1H, H-2), 3.78 (d, 1H, H-3), 3.43 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 166.1 (s, C=O, Bz), 133.3, 129.8, 128.5 (C_6H_5CO-), 102.5 (C-1), 76.1 (C-4), 64.3 (C-5), 56.4, 55.5, 55.2 (C-2, C-3, OCH_3). HRMS (ESI^+): *m*/*z* calcd for $[C_{13}H_{14}O_5+Na]^+$: 273.0734, found 273.0737.

And methyl 5-*O*-benzoyl-3-deoxy-3-fluoro-β-D-ribofuranoside (**21**) (48 mg, 55%) as a syrup. IR (film, $CHCl_3$): *v* 3454, 2940, 2937, 1722, 1275, 1123, 712 cm^{-1}. ^1H NMR ($CDCl_3$): 7.44–8.07 (m, 5H, ArH), 5.2 (dt, 1H, $J_{3,2}$ = 4.7, $J_{3,4}$ = 4.7, $J_{3,F}$ =54.18, H-3), 4.91 (br.s, 1H, H-1), 4.52–4.59 (m, 1H, H-4 and H-5), 4.43 (dd, 1H, $J_{5,4}$ = 3.7, $J_{5,5'}$ = 12.0, H-5′), 4.25 (dt, 1H, $J_{2,F}$ = 22.1, H-2), 3.45 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 165.2 (s, C=O, Bz), 133.2, 129.7, 129.4 (3s, C_6H_5CO-), 107.9 (d, $J_{C\text{-}1,\ F\text{-}2}$ = 2.7, C-1), 92.9 (d, $J_{C\text{-}3,F\text{-}3}$ = 185.5, C-3), 78.4 (d, $J_{C\text{-}4,\ F\text{-}3}$ = 25.5, C-4), 74.4 (d, $J_{C\text{-}2,F\text{-}3}$ = 15.2, C-2), 64.1 (d, $J_{C\text{-}5,F\text{-}3}$ = 4.5,

C-5), 55.5 (OCH_3). ^{19}F NMR ($CDCl_3$): −195.3 (dt, F-3). HRMS (ESI^+):*m*/*z* calcd for $[C_{13}H_{15}O_5F+Na]^+$: 293.0796, found 293.0796

4.2.8. DAST-reaction with a mixture of xylosides 11a,b—To a solution of methyl 5-*O*-benzoyl-α/β-xylofuranoside **11a**,**b** (300 mg, 1.12 mmol, 3:2, ratio of **11a**/**11b**) in anhydrous CH_2Cl_2 (6.2 mL) was added dropwise 0.88 mL (6.75 mmol) DAST at 24–26 °C. The reaction mixture was stirred for 18 h and then diluted CH_2Cl_2, poured into cooled 5%-aqueous $NaHCO_3$, the aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts was washed with water (20 mL), and dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was chromatographed on a silica gel, using a mixture of 12:1, 9:1, 6:1 and 3:1 hexane-EtOAc to afford difluoride **15** (44 mg, 24%) as a syrup, 1,3-difluoride **22** (5 mg, 4%) as syrup, methyl 5-*O*-benzoyl-3-deoxy-3-fluoro-α-ribofuranoside (**14**) (74 mg, 41%) as a syrup, and methyl 5-*O*-benzoyl-3-deoxy-3-fluoro-β-ribofuranoside (**22**) (48 mg, 40%) as a syrup.

4.3. Synthesis of novel purine-modified 2′,3′-difluoro-d-arabino nucleosides from the 1-α-bromide

4.3.1. 2-Fluoro-9-(5-O-benzoyl-2,3-dideoxy-2,3-difluoro-β-d-arabinofuranosyl)adenine (23) and its α-anomer 24—Potassium *t*-butoxide (32 mg, 0.28 mmol) was added to 2-fluoroadenine (42 mg, 0.25 mmol) in anhydrous 1,2-dimethoxyethane (10 mL) at 0 °C and then the resulting solution was stirred for 9 min under cooling and then for 40 min at room temperature and evaporated to dryness coevaporated with anhydrous acetonitrile. Anhydrous acetonitrile (8 mL) was added to the residue and the suspension was stirred under argon at room temperature for 10 min, then a solution of the bromide **17** (80 mg, 0.25 mmol) in anhydrous methylene chloride (4 mL) and CaH_2 (12 mg, 0.28 mmol) were added sequentially to the suspension of prepared potassium salt of the purine. The reaction mixture was stirred under argon at room temperature for 20 h. Insoluble materials were removed by filtration and the solids were washed with MeCN (20 mL). The solvent was removed under reduced pressure and the residue was chromatographed on silica gel, eluting with EtOAc/petroleum ether 1:5, 3:2 and 2:1 to afford β-nucleoside **23** (28 mg, 28%). Mp.174–176 °C (EtOH). ^1H NMR ($CDCl_3$): 8.06 (d, 1H, $J_{H\text{-}8,\ F\text{-}2'}$ = 1.4, H-8), 7.46–8.07 (3m, 5H, Bz), 6.48 (dt, 1H, $J_{1',2'}$ = 2.7, $J_{1',F\text{-}3'}$ = 2.7, $J_{1',F\text{-}2'}$ = 21.79, H-1′), 5.43 (ddm, 1H, $J_{3',F\text{-}2'}$ = 12.18, $J_{3',F'}$ = 49.69, H-3′), 5.33 (ddm, 1H, $J_{2',1'}$ = 2.7, $J_{2',F\text{-}2'}$ = 49.38, $J_{2',F\text{-}3'}$ = 9.2, H-2′), 4.71 (dd, 1H, H-5′), 4.66 (dd, 1H-5″), 4.63 (dm, 1H, H-4′). ^{13}C NMR ($CDCl_3$): 166.3 (C=O, Bz), 159.3 (d, $J_{C\text{-}2,F\text{-}2}$ = 212.6, C-2), 158.4 (d, $J_{C6,F\text{-}2}$ = 21.9, C-6), 150.5 (d, $J_{C\text{-}6,F\text{-}2}$ = 20.3, C-4),139.6 (d, $J_{C\text{-}8,F\text{-}20'}$~ 4.0, C-8), 133.6, 129.6, 129.0, 129.0, 128.6 (C_6H_5CO-), 116.3 (s, C-5), 93.6 (dd, $J_{C\text{-}2',F\text{-}2'}$ = 192.5, $J_{C\text{-}2',F\text{-}3'}$ = 30.9, C-2′), 91.5 (dd, $J_{C\text{-}3',F\text{-}2'}$ = 29.9, $J_{C\text{-}3',F\text{-}3'}$ = 191.5, C-3′), 83.3 (d, $J_{C\text{-}1',\ F\text{-}2'}$ = 16.9, C-1′), 80.5 (d, $J_{C\text{-}4',F\text{-}3'}$ = 27.1, C-4′), 62.6 (d, $J_{C\text{-}5',F\text{-}3'}$ = 9.2, C-5′). ^{19}F NMR ($CDCl_3$): −49.86 (s, F-2), −188.71 (m, F-2′ or F-3′), −203.72 (m, F-3′ or F-2′). HRMS (ESI^+): *m*/*z* calcd for $[C_{17}H_{14}N_5F_3O_3 + H]^+$: 394.1122, found 394.1123.

And α-nucleoside **24** (28 mg, 28%). Mp. 238–240 °C (EtOH). ^1H NMR (DMSO-d_6): 8.32 (s, 1H, H-8), 7.56–8.05 (3m, 5H, Bz), 6.49 (dd, 1H, $J_{1',2'}$ = 2.3, $J_{1',F\text{-}2'}$ = 15.0, H-1′), 6.17 (ddm, 1H, H-2′), 5.75 (ddm, 1H, H-3′), 5.10 (dm, 1H, H-4′), 4.63 (dd, 1H, H-5′), 4.57 (dd,

1H, H-5″). ^{13}C NMR ($CDCl_3$): 165.9 (C=O, Bz),159.1 (d, $J_{C\text{-}2,F\text{-}2}$ = 206.5, C-2), 158.2 (d, $J_{C6,F\text{-}2}$ = 21.7, C-6), 150.7 (d, $J_{C\text{-}6,F\text{-}2}$ = 20.2, C-4), 139.8 (C-8), 134.1, 129.8, 129.7, 129.3 (C_6H_5CO-), 118.0 (d, $J_{C\text{-}5,F\text{-}2}$ = 3.4, C-5), 96.6 (dd, $J_{C\text{-}2',F\text{-}2'}$ = 186.5, $J_{C\text{-}2',F\text{-}3'}$ = 28.9, C-2′), 94.5 (dd, $J_{C\text{-}3',F\text{-}2'}$ = 28.9, $J_{C\text{-}3',F\text{-}3'}$ = 193.5, C-3′), 86.8 (dd, $J_{C\text{-}1',F\text{-}2'}$ = 30.9, $J_{C\text{-}1',F\text{-}3'}$ = 9.5, C-1′), 81.3 (d, $J_{C\text{-}4',F\text{-}3'}$ = 25.9, $J_{C\text{-}4',F\text{-}2'}$ = 4.1, C-4′), 63.7 (d, $J_{C\text{-}5',F\text{-}3'}$ = 5.2, C-50). ^{19}F NMR ($CDCl_3$+CD_3OD): −50.14 (s, F-2), −192.25 (m, F-2′ an F-3′). HRMS (ESI^+): *m*/*z* calcd for $[C_{17}H_{14}N_5F_3O_3+H]^+$: 394.1122, found 394.1121.

4.3.2. 2-Fluoro-9-(2,3-dideoxy-2,3-difluoro-β-d-arabinofuranosyl) adenine (25)—To solution of β-nucleoside **23** (13 mg, 0.03 mmol) in a mixture of acetonitrile (1.5 mL) and water (0.5 mL) was added lithium hydroxide monohydrate (4.7 mg, 0.11 mmol). The reaction mixture was stirred at room temperature for 6 h, then neutralized with acetic acid, evaporated, and coevaporated with toluene to dryness The residue was chromatographed on silica gel using for elution EtOAc, EtOAc:MeOH-9:1 and 6:1 to afford nucleoside **25** (7 mg, 73%). Mp. 221–224 °C (CH_2Cl_2/EtOH). ^{1}H NMR (CD_3OD): 8.25 (d, 1H, $J_{H\text{-}8,\ F\text{-}2'}$ = 2.3, H-8), 6.44 (ddd, 1H, $J_{1',2'}$ = 4.0, $J_{1',F\text{-}3'}$ = 1.74, $J_{1',F\text{-}2'}$ = 17.3, H-1′), 5.52 (dddd, 1H, $J_{2',1'}$ = 4.1, $J_{3',2'}$ = 2.37, $J_{2',F\text{-}2'}$ = 50.34, $J_{2',F\text{-}3'}$ = 15.06, H-2′), 5.50 (dm, 1H, $J_{3',F\text{-}3'}$ = 51.37, $J_{3',4'}$ = 3.9, $J_{3',F\text{-}2'}$ = 17.3, H-3′), 4.31 (dm, 1H, $J_{4',F\text{-}3'}$ = 20.77, H-4′), 3.90 (ddd, 1H, H-5′), 3.87 (dd, 1H, H-5″). ^{13}C NMR (CD_3OD): 159.4 (d, $J_{C\text{-}2,F\text{-}2}$ = 209.8, C-2), 157.8 (d, $J_{C6,F\text{-}2}$ = 20.1, C-6), 150.6 (d, $J_{C4,F\text{-}2}$ =18.8), 140.1 (br.s), 116.5 (d, $J_{C\text{-}5,F\text{-}2}$ = 3.0) (C-4, C-8, C-5), 93.4 (dd, $J_{C\text{-}2',F\text{-}2'}$ = 182.33, $J_{C\text{-}2',F\text{-}3'}$ = 28.5, C-2′), 92.6 (dd, $J_{C\text{-}3',F\text{-}2'}$ = 28.9, $J_{C\text{-}3',F\text{-}3'}$ = 191.8, C-3′), 83.7 (dd, $J_{C\text{-}1',F\text{-}2'}$ = 17.1, $J_{C\text{-}1',F\text{-}3'}$ = 3.1, C-1′), 80.7 (dd, $J_{C\text{-}4',\ F\text{-}3'}$ = 25.2, $J_{C\text{-}4',\ F\text{-}2'}$ = 2.2, C-4′), 60.1 (d, $J_{C\text{-}5',F\text{-}3'}$ = 6.2, C-5′). ^{19}F NMR (CD_3OD): −53.17 (s, F-2), −195.92 (m, F-2′ or F-3′), −204.4 (m, F-3′ or F-2′). HRMS (ESI^+): *m*/*z* calcd for $[C_{10}H_{10}N_5F_3O_2+H]^+$: 290.0860, found 290.0861.

4.3.3. 2-Fluoro-9-(2,3-dideoxy-2,3-difluoro-α-d-arabinofuranosyl) adenine (26)—To a solution of protected α-nucleoside **24** (14 mg, 0.03 mmol) in a mixture of acetonitrile (1.5 mL) and water (0.5 mL) was added lithium hydroxide monohydrate (4 mg, 0.09 mmol). The reaction mixture was stirred at room temperature for 7 h, then neutralized with acetic acid, evaporated, and coevaporated with toluene to dryness. The residue was chromatographed on silica gel using for elution EtOAc, EtOAc:MeOH - 9:1 and 6:1 to afford nucleoside **26** (9 mg, 87%). Mp. 187–191 °C (CH_2Cl_2/EtOH). ^{1}H NMR (CD_3OD): 8.17 (s, 1H, H-8), 6.36 (dd, 1H, $J_{1',F\text{-}2'}$ = 15.1, $J_{1',2'}$ = 2.56, H-1′), 6.01 (ddt, 1H, $J_{2',3'}$ = 2.81, $J_{2',F\text{-}2'}$ = 14.1, $J_{2',F'}$ = 50.3, H-2′), 5.31 (dddd, 1H, $J_{3',2'}$ = 2.9, $J_{3',F\text{-}3'}$ = 51.93, $J_{3',4'}$ = 4.1, $J_{3',F\text{-}2'}$ = 16.35, H-3′), 4.76 (dm, 1H, $J_{4',F\text{-}3'}$ = 20.77, H-4′), 3.79 (d, 2H, 2H-5′). ^{13}C NMR (CD_3OD): 155.6 (d, $J_{C\text{-}2,F\text{-}2}$ = 206.5, C-2), 154.1 (d, $J_{C6,F\text{-}2}$ = 20.83, C-6), 146.5 (C-4), 135.6 (C-8), 113.6 (C-5), 92.8 (dd, $J_{C\text{-}2',F\text{-}2'}$ = 187.0, $J_{C\text{-}2',F\text{-}3'}$ = 19.2, C-2′), 89.9 (dd, $J_{C\text{-}3',F\text{-}2'}$ = 27.7, $J_{C\text{-}3',F\text{-}3'}$ = 183.5, C-3′), 83.7 (dd, $J_{C\text{-}1',F\text{-}2'}$ = 35.9, $J_{C\text{-}1',F\text{-}3'}$ = 5.4, C-1′), 80.7 (dd, $J_{C\text{-}4',\ F\text{-}3'}$ = 24.8, $J_{C\text{-}4',F\text{-}2'}$ = 2.6, C-4′), 56.5 (d, $J_{C\text{-}5',F\text{-}3'}$ = 5.4, C-5′). ^{19}F NMR (CD_3OD): −52.78 (s, F-2), −196.13 (m, F-2′ or F-3′), −197.43 (m, F-3′ or F-2′). HRMS (ESI^+): *m*/*z* calcd for $[C_{10}H_{10}N_5F_3O_2+H]^+$: 290.0860, found 290.0861.

4.3.4. 2-Fluoro-6-chloro-9-(5-O-benzoyl-2,3-dideoxy-2,3-difluoro-β-d-arabinofuranosyl)-purine (27)—Potassium *t*-butoxide (19 mg, 0.17 mmol) was added to

2-fluoro-6-chloropurine (30 mg, 0.17 mmol) in anhydrous 1,2-dimethoxyethane (3.0 mL) at 0 °C and then the resulting solution was stirred for 7 min under cooling and 30 min at room temperature and then evaporated to dryness, coevaporated with anhydrous acetonitrile. Acetonitrile (1.5 mL) was added to residue and the suspension was stirred under argon at room temperature for 10 min, then a solution of bromide **17** (51 mg, 0.16 mmol) in an anhydrous acetonitrile (2.0 mL) was added to prepared potassium salt of the purine. The reaction mixture was stirred under argon at room temperature for 18 h. Insoluble materials were removed by filtration and the solids were washed with acetonitrile (20 mL). The solvent was removed under reduced pressure and the residue was chromatographed on silica gel, eluting with EtOAc/petroleum ether 1:5, 1:3 and 1:2.5 to afford β-nucleoside **27** (43 mg, 66%). Mp. 150–152 °C (EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$): 8.36 (d, 1H, $J_{H\text{-}8,\ F\text{-}2'}$ = 1.97, H-8), 7.52–8.36 (3m, 5H, Bz), 6.59 (dt, 1H, $J_{1',2'}$ = 2.7, $J_{1',F\text{-}3'}$ = 2.7, $J_{1',F\text{-}2'}$ = 21.79, H-1′), 5.52 (ddt, 1H, $J_{3',F\text{-}2'}$ = 12.21, $J_{3',F'}$ = 49.37, H-3′), 5.40 (dddd, 1H, $J_{1',2'}$ = 2.76, $J_{2',F\text{-}2'}$ = 49.37, $J_{2',F\text{-}3'}$ = 8.97, H-2′), 4.70–4.80 (m, 3H, H-4′, H-5′ and H-5″). ^{13}C NMR ($CDCl_3$): 166.1 (C=O, Bz), 157.4 (d, $J_{C\text{-}2,F\text{-}2}$ = 222.4, C-2), 153.3 (d, $J_{C\text{-}6,F\text{-}2}$ = 7.4, C-6), 144.7 (d, $J_{C\text{-}8,F\text{-}2'}$ = 2.99, C-8), 133.8, 129.8, 129.8, 129.0, 128.7 (C_6H_5CO- and C-5), 93.5 (dd, $J_{C\text{-}2',F\text{-}2'}$ = 184.5, $J_{C\text{-}2',F\text{-}3'}$ = 29.92, C-2′), 91.4 (dd, $J_{C\text{-}3',F\text{-}2'}$ = 30.9, $J_{C\text{-}3',F\text{-}3'}$ = 192.5, C-3′), 83.8 (d, $J_{C\text{-}1',\ F\text{-}2'}$ = 16.7, C-1′), 81.1 (d, $J_{C\text{-}4',F\text{-}3'}$ = 29.9, C-4′), 62.3 (d, $J_{C\text{-}5',F\text{-}3'}$ = 9.1, C-5′). ^{19}F NMR ($CDCl_3$): −48.68 (s, F-2), −188.60 (m, F-2′ or F-3′), −203.41 (m, F-3′ or F-2′). HRMS (ESI$^+$): *m*/*z* calcd for $[C_{17}H_{12}N_4F_3O_3Cl+H]^+$: 413.0623, found 413.0618.

4.3.5. 2-Hydroxy-6-chloro-9-(2,3-dideoxy-2,3-difluoro-β-d-arabinofuranosyl)purine (28)—

To solution of β-nucleoside **27** (11 mg, 0.02 mmol) in a mixture of acetonitrile (1.1 mL) and water (0.36 mL) was added lithium hydroxide monohydrate (4.7 mg, 0.11 mmol). The reaction mixture was stirred at room temperature for 280 min, then neutralized with acetic acid, evaporated, and coevaporated with toluene to dryness. The residue was chromatographed on silica gel using for elution EtOAc:hexane 2:1, EtOAc:MeOH-7:1 and 6:1 to afford nucleoside **28** (5 mg, 61%) as oil. ^{1}H NMR (CD_3OD): 8.41 (d, 1H, $J_{H\text{-}8,\ F\text{-}2'}$ = 1.3, H-8), 6.53 (ddd, 1H, $J_{1',2'}$ = 3.2, $J_{1',F\text{-}3'}$ = 1.2, $J_{1',F\text{-}2'}$ = 17.4, H-1′),5.45–5.62 (dm, H-2′ and H-3′), 4.32 (dm, 1H, $J_{4',F\text{-}3'}$ = 24.8, H-4′), 3.91 (ddd, 1H, H-5′), 3.88 (dd, 1H, H-5″). ^{13}C NMR (CD_3OD): 163.5, 163.4, 152.1, 111.5 (C-6, C-2, C-4, C-5), 144.4 (br.d, C-8), 94.8 (dd, $J_{C\text{-}2',F\text{-}2'}$ = 180.5, $J_{C\text{-}2',F\text{-}3'}$ = 28.6, C-2′), 93.9 (dd, $J_{C\text{-}3',F\text{-}2'}$ = 28.6, $J_{C\text{-}3',F\text{-}3'}$ = 192.5, C-3′), 84.2 (br.d, $J_{C\text{-}1',F\text{-}2'}$ = 20.9,C-1′), 83.5 (d, $J_{C\text{-}4',F\text{-}3'}$ = 23.9, C-4′), 61.5 (d, $J_{C\text{-}5',F\text{-}3'}$ = 6.2, C-5′). ^{19}F NMR (CD_3OD): −185.38 (m, F-2′ or F-3′), −193.35 (m, F-3′ or F-2′). HRMS (ESI$^+$): *m*/*z* calcd for $[C_{10}H_9N_4F_2O_3Cl+H]^+$: 307.0404, found 307.0400.

4.3.6. 2-Amino-6-chloro-9-(5-O-benzoyl-2,3-dideoxy-2,3-difluoro-β-d-arabinofuranosyl)purine (29)—

A solution of β-nucleoside **27** (20 mg, 0.05 mmol) in anhydrous 1,2-dimehoxyethane (10.0 mL) was saturated by dry ammonia for 1 h at 0 °C, and then the reaction mixture was left for 18 h at room temperature and evaporated. The residue was chromatographed on silica gel using for elution EtOAc:hexane 1:3, 1:1 and 2:1 to afford nucleoside **29** (11 mg, 55%) as an amorphous powder, and nucleoside **23** (4.4 mg, 23%). NMR spectroscopic data for nucleosides **29** and **23** were identical to those prepared

by glycosylation reactions of 6-chloro-2-aminopurine [16] and 2-fluoroadenine with the bromide **16**.

4.3.7. 2-Amino-6-chloro-9-(2,3-dideoxy-2,3-difluoro-β-d-arabinofuranosyl)purine (31)—

To solution of β-nucleoside **27** (25 mg, 0.06 mmol) in anhydrous THF (2.0 mL) was added in 4.8 mL methanol saturated at 0 °C with ammonia, the reaction mixture was stirring for 4 h under 0 °C, then for 18 h at room temperature and evaporated. The residue was chromatographed on silica gel using for elution EtOAc:hexane 2:1 and 3:1 and EtOAc:EtOH to afford nucleoside **31** (10 mg, 54%) as a syrup, and nucleoside **25** (2.6 mg, 15%).

4.3.8. 2-Amino-6-methoxy-9-(2,3-dideoxy-2,3-difluoro-β-d-arabinofuranosyl)purine (33)—

To solution of β-nucleoside **31** (7 mg, 0.02 mmol) in MeOH (1.0 mL) was added anhydrous potassium carbonate (12 mg, 0.087 mmol). The reaction mixture was stirred at 80–82 °C for 30 min, then cooled to room temperature and evaporated. The residue was chromatographed on silica gel using for elution $CHCl_3$, $CHCl_3$:MeOH-10:1 and 5:1 to afford nucleoside **33** (5 mg, 72%) as a syrup. ^{1}H NMR (CD_3OD): 8.03 (d, 1H, $J_{H\text{-}8,\ F\text{-}2'}$ = 2.4, H-8), 6.43 (ddd, 1H, $J_{1',2'}$ = 3.9, $J_{1',F\text{-}3'}$ = 1.92, $J_{1',F\text{-}2'}$ = 18.27, H-1′), 5.49 (dddd, 1H, $J_{2',1'}$ = 4.0, $J_{3',2'}$ = 2.2, $J_{2',F\text{-}2'}$ = 51.29, $J_{2',F\text{-}3'}$ = 14.42, H-2′), 5.48 (dm, 1H, $J_{3',F\text{-}3'}$ = 50.65, $J_{3',4'}$ = 3.8, $J_{3',F\text{-}2'}$ = 11.22, H-3′), 4.28 (dm, 1H, $J_{4',F\text{-}3'}$ = 24.68, H-4′), 4.09 (s, 3H, OCH_3), 3.88 (d, 2H, 2H-5). ^{13}C NMR (CD_3OD): 161.3 (C-6), 160.7, 153.3, 113.3 (C-2, C-4, C-5), 138.4 (d, $J_{C\text{-}8,F\text{-}2'}$ = 4.4, C-8), 93.6 (dd, $J_{C\text{-}2',F\text{-}2'}$ = 182.33, $J_{C\text{-}2',F\text{-}3'}$ = 28.5, C-2′), 92.5 (dd, $J_{C\text{-}3',F\text{-}2'}$ = 28.9, $J_{C\text{-}3',F\text{-}3'}$ = 191.85, C-3′), 82.6 (dd, $J_{C\text{-}1',\ F\text{-}2'}$ = 17.2, $J_{C\text{-}1',\ F\text{-}3'}$ = 2.5, C-1′), 81.9 (dd, $J_{C\text{-}4',F\text{-}3'}$ = 25.6, $J_{C\text{-}4',F\text{-}2'}$ = 1.7, C-4′), 60.2 (d, $J_{C\text{-}5',F\text{-}3'}$ = 6.7, C-5′), 52.9 (OCH_3). ^{19}F NMR (CD_3OD): −195.07 (m, F-2′ or F-3′), −204.61 (m, F-3′ or F-2′). HRMS (ESI$^+$):*m*/*z* calcd for $[C_{11}H_{13}N_5F_2O_3+H]^+$: 302.1060, found 302.1061, calcd for $[C_{11}H_{13}N_5F_2O_3+Na]^+$: 324.0879, found 324.0879.

4.3.9. 9-(2,3-Dideoxy-2,3-difluoro-β-d-arabinofuranosyl)-6-thioguanine (34)—

A mixture of nucleoside 31 (8 mg, 0.03 mmol), thiourea (14 mg, 0.18 mmol) in 5.0 mL ethanol was heated at reflux for 2 h. After cooling, the mixture was evaporated in vacuum. The residue was chromatographed on silica gel using for elution $CHCl_3$, $CHCl_3$:MeOH-10:1 to afford nucleoside **34** (6 mg, 76%) as an amorphous powder. ^{1}H NMR (CD_3OD): 8.04 (d, 1H, $J_{H\text{-}8,\ F\text{-}2'}$ = 2.46, H-8), 6.35 (ddd, 1H, $J_{1',2'}$ = 3.6, $J_{1',F\text{-}3'}$ = 1.7, $J_{1',F\text{-}2'}$ = 17.6, H-1′), 5.40–5.55 (dm, H-2′ and H-3′), 4.27 (dm, 1H, $J_{4',F\text{-}3'}$ = 25.0, H-4′), 3.87 (d, 2H, 2H-5′). ^{13}C NMR (CD_3OD): 177.5 (C-6), 176.1 (C-2), 155.1 (C-4), 140.6 (d, $J_{C\text{-}8,F\text{-}2'}$ = 4.4, C-8), 129.2 (C-5), 95.0 (dd, $J_{C\text{-}2',F\text{-}2'}$ = 181.5, $J_{C\text{-}2',F\text{-}3'}$ = 28.9, C-2′), 93.9 (dd, $J_{C\text{-}3',F\text{-}2'}$ = 28.9, $J_{C\text{-}3',F\text{-}3'}$ = 192.48, C-3′), 83.8 (dd, $J_{C\text{-}1',\ F\text{-}2'}$ = 17.9, $J_{C\text{-}1',\ F\text{-}3'}$ = 3.3, C-1′), 83.3 (br.d, $J_{C\text{-}4',F\text{-}3'}$ = 27.9, C-4′), 61.6 (d, $J_{C\text{-}5',F\text{-}3'}$ = 6.4, C-5′). ^{19}F NMR (CD_3OD): −195.27 (m, F-2′ or F-3′), −204.65 (m, F-3′ or F-2′). HRMS (ESI$^+$): *m*/*z* calcd for $[C_{10}H_{11}N_5O_2F_2S+H]^+$: 304.0680, found 304.0685.

4.3.10. 2-Amino-6-methoxy-9-(2,3-dideoxy-2,3-difluoro-α-d-arabinofuranosyl)purine (35)—

In a similar way, starting from (6 mg, 0.02 mmol) of α-

nucleoside **32** was prepared nucleoside **35** (4.4 mg, 75%) as an amorphous powder. ^{1}H NMR (CD_3OD): 7.97 (s,1H, H-8), 6.31 (dd,1H, $J_{1',2'}$ = 2.73, $J_{1',F\text{-}2'}$ = 15.3, H-1′), 6.07 (ddt, 1H, $J_{2',3'}$ = 2.83, $J_{2',F\text{-}2'}$ = 50.33, $J_{2',F\text{-}3'}$ = 14.43, H-2′), 5.42 (dddd, 1H, $J_{3',F\text{-}3'}$ = 52.5, $J_{3',4'}$ = 4.1, $J_{3',F\text{-}2'}$ = 16.67, H-3′), 4.76 (dm, 1H, $J_{4',F\text{-}3'}$ = 20.52, H-4′), 4.08 (s, 3H, OCH_3), 3.79 (d, 2H, 2H-5′). ^{13}C NMR (CD_3OD): 161.3 (C-6), 160.7, 153.2, 137.5, 115.6 (C-2, C-4, C-8, C-5), 96.4 (dd, $J_{C\text{-}2',F\text{-}2'}$ = 185.5, $J_{C\text{-}2',F\text{-}3'}$ = 28.9, C-2′), 93.8 (dd, $J_{C\text{-}3',F\text{-}2'}$ = 26.9, $J_{C\text{-}3',F\text{-}3'}$ = 184.5, C-3′), 87.2 (dd, $J_{C\text{-}1',F\text{-}2'}$ = 35.9, $J_{C\text{-}1',F\text{-}3'}$ = 5.3, C-1′), 84.2 (d, $J_{C\text{-}4',F\text{-}3'}$ = 25.2, C-4′), 60.2 (d, $J_{C\text{-}5',F\text{-}3'}$ = 6.7, C-5′), 52.8 (OCH_3). ^{19}F NMR (CD_3OD): −196.42 (m, F-2′ or F-3′), −197.79 (m, F-3′ or F-2′). HRMS (ESI$^+$): *m*/*z* calcd for $[C_{11}H_{13}N_5F_2O_3+H]^+$: 302.1060, found 302.1063.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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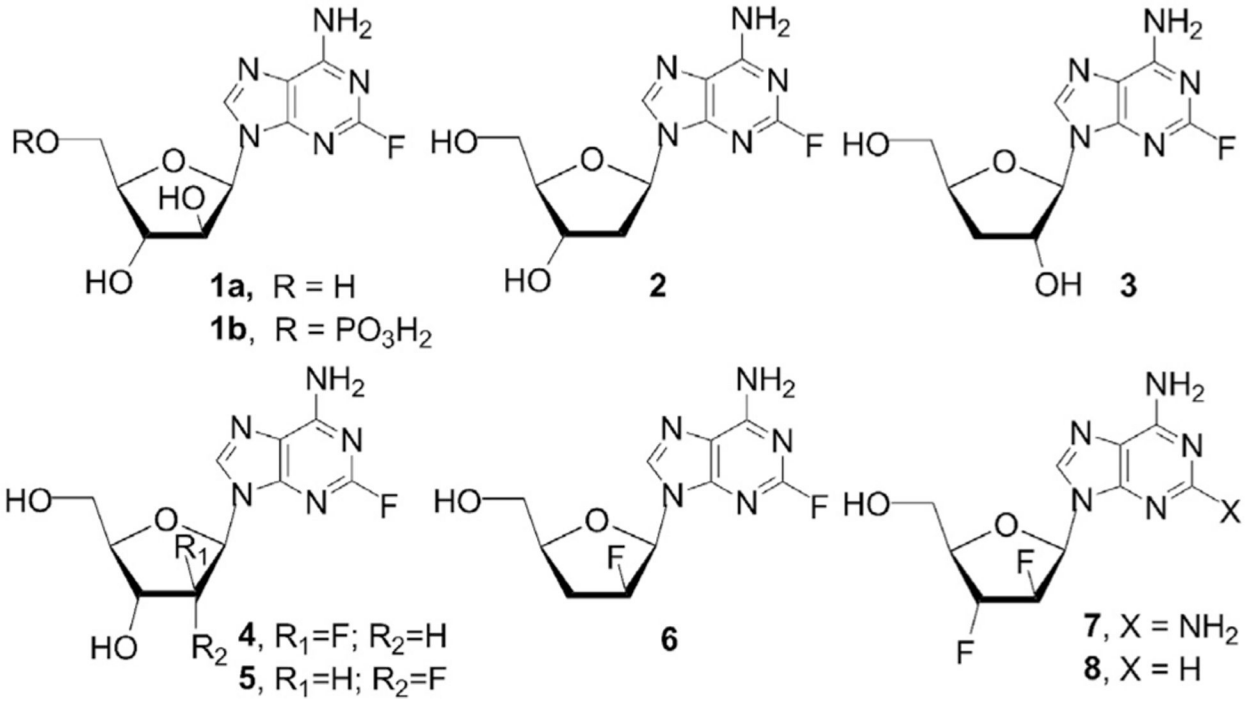
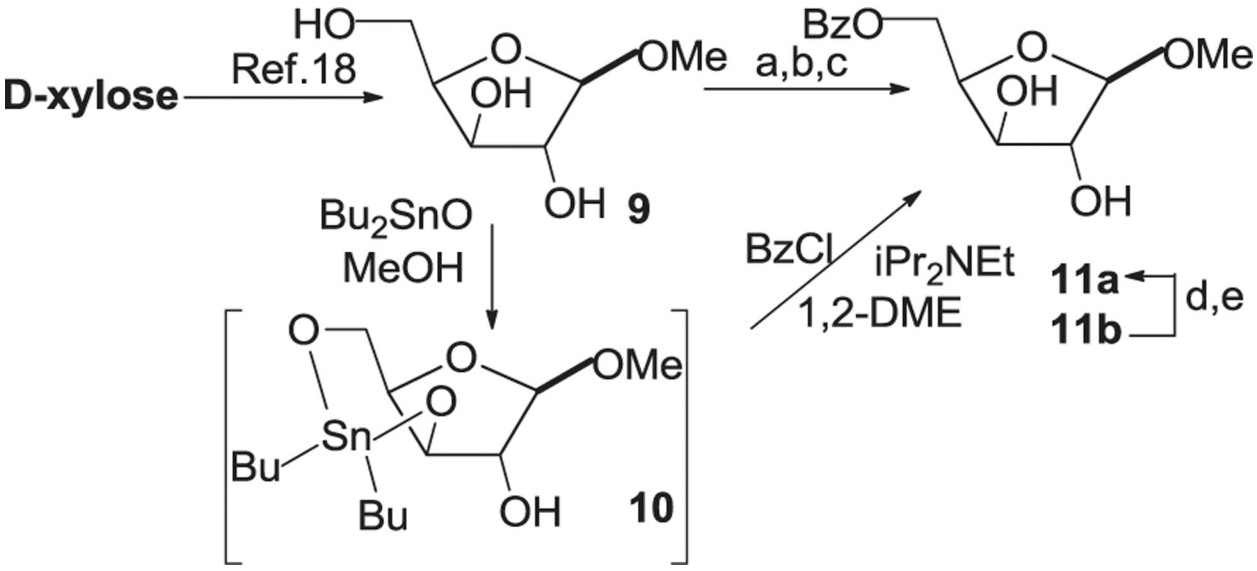
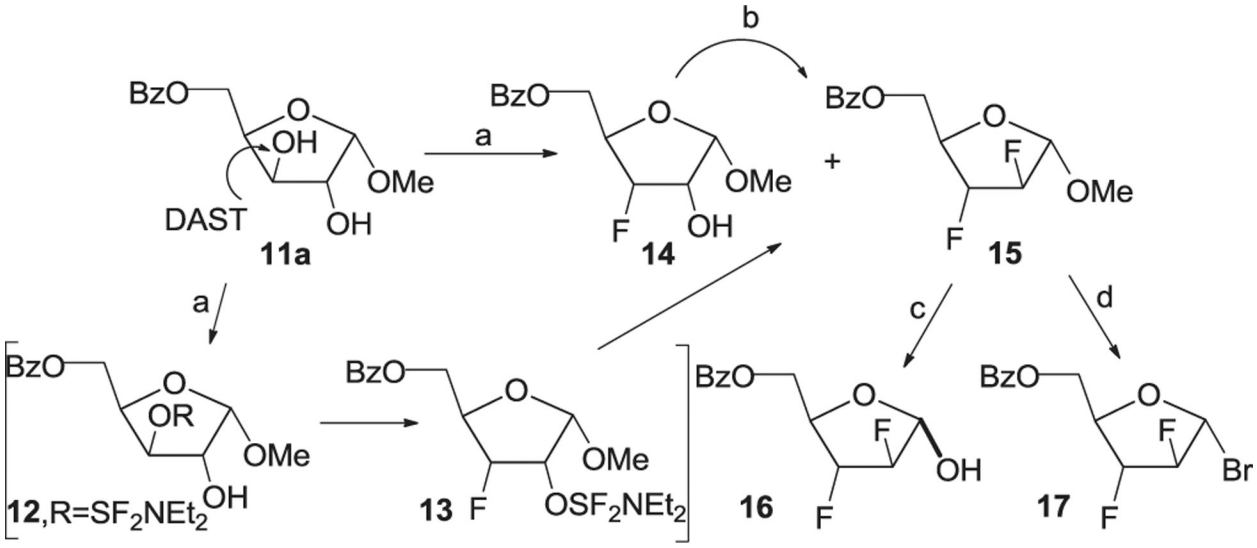


Fig. 1.
Fluorinated purine nucleosides with anticancer, antiviral and antibacterial activities.



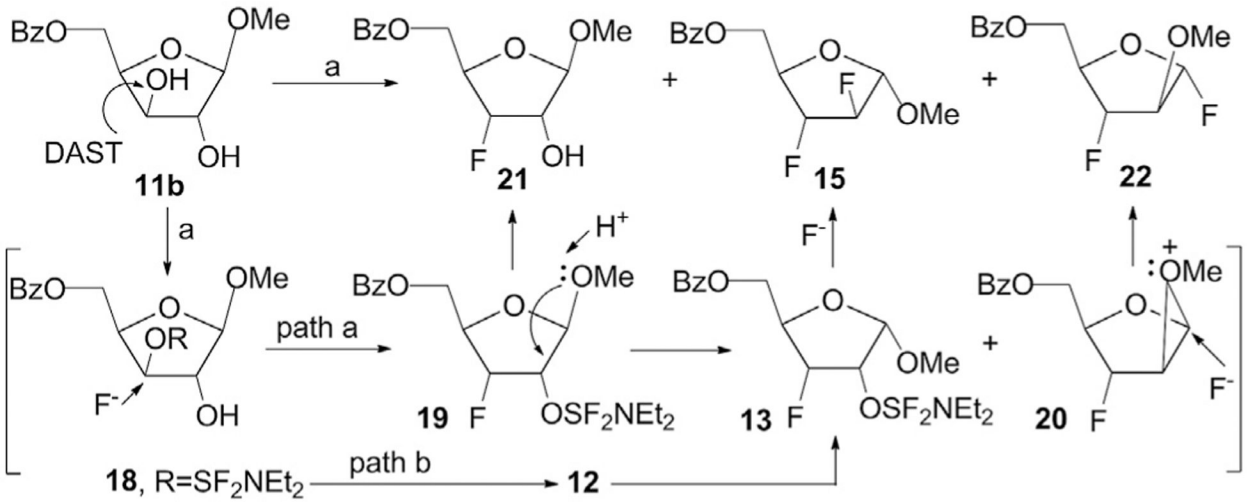
Scheme 1. Reagents and conditions.

a) **9**, $BzCl/CH_2Cl_2$, $Et_3N/^iPr_2NEt$, 0 °C→rt, 18 h, 46% overall to **11a,b**, 39% to **11a**; 45% to **11b**; b) i) **9**, Bu_2SnO/MeOH, reflux, 1 h; ii) $BzCl/^iPr_2NEt$, toluene, rt, 5 h, 46% overall to **11a,b**, 35% to **11a**; 41% to **11b**; c) i) **9**, Bu_2SnO/MeOH, reflux, 1 h; ii) $BzCl/^iPr_2NEt$,1,2-DME, rt, 5 h, 97% overall to **11a,b**, 82% to **11a**; 89% to **11b**; d) **11b**, $MeOH/CH_3SO_3H$, rt, 18 h, 32% to **11a**; e) **11b**, MeOH/HCl, rt, 3 h, 47% to **11a**.



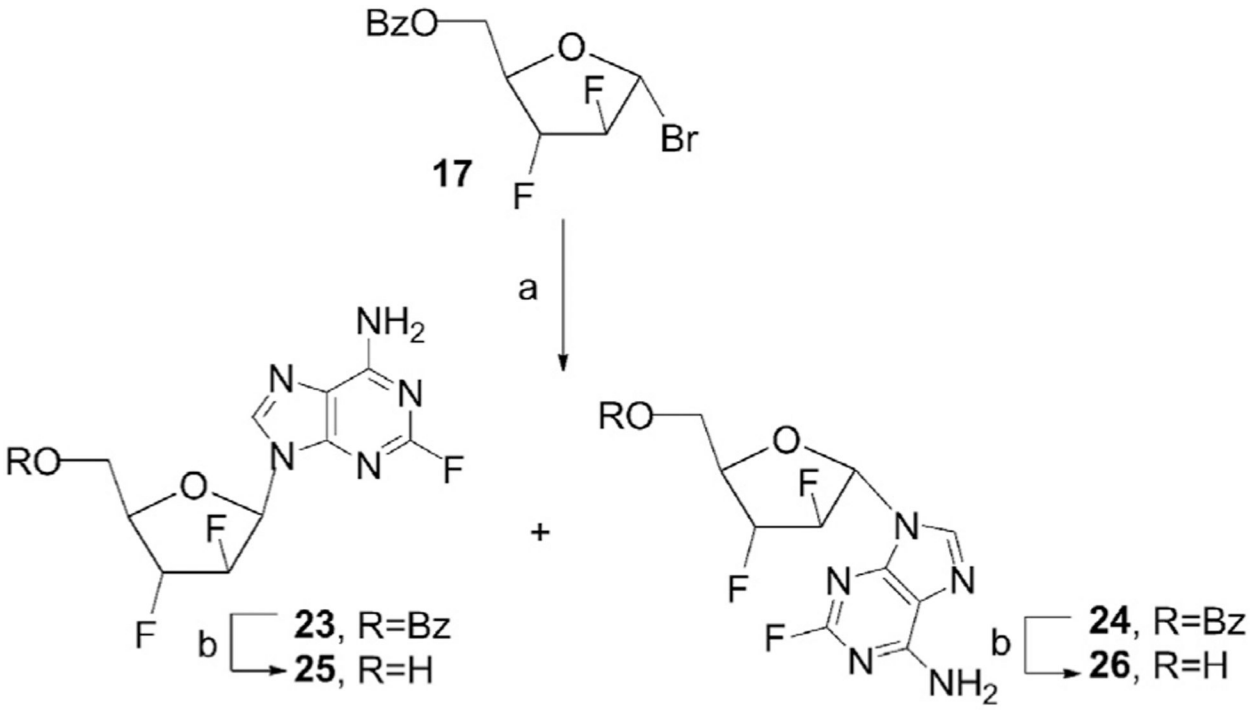
Scheme 2. Reagents and conditions.

a) **11a**, DAST/CH_2Cl_2, 25–29 °C, 10 h, 18% to **15**, 51% to **14;** b) **14**, DAST/CH_2Cl_2/Py, 35–37 °C, 18 h, 66% to **15**; c) CH_3COOH/Ac_2O, 34%-HBr in AcOH, 18 h, rt, **16**, 50%; d) i) **15**, $CH_3COOH/Ac_2O/H_2SO_4$, 0 °C→24–25 °C, 3 h; ii) TMSBr/CH_2Cl_2/$ZnBr_2$, 0 °C→rt, 16 h, 84%.



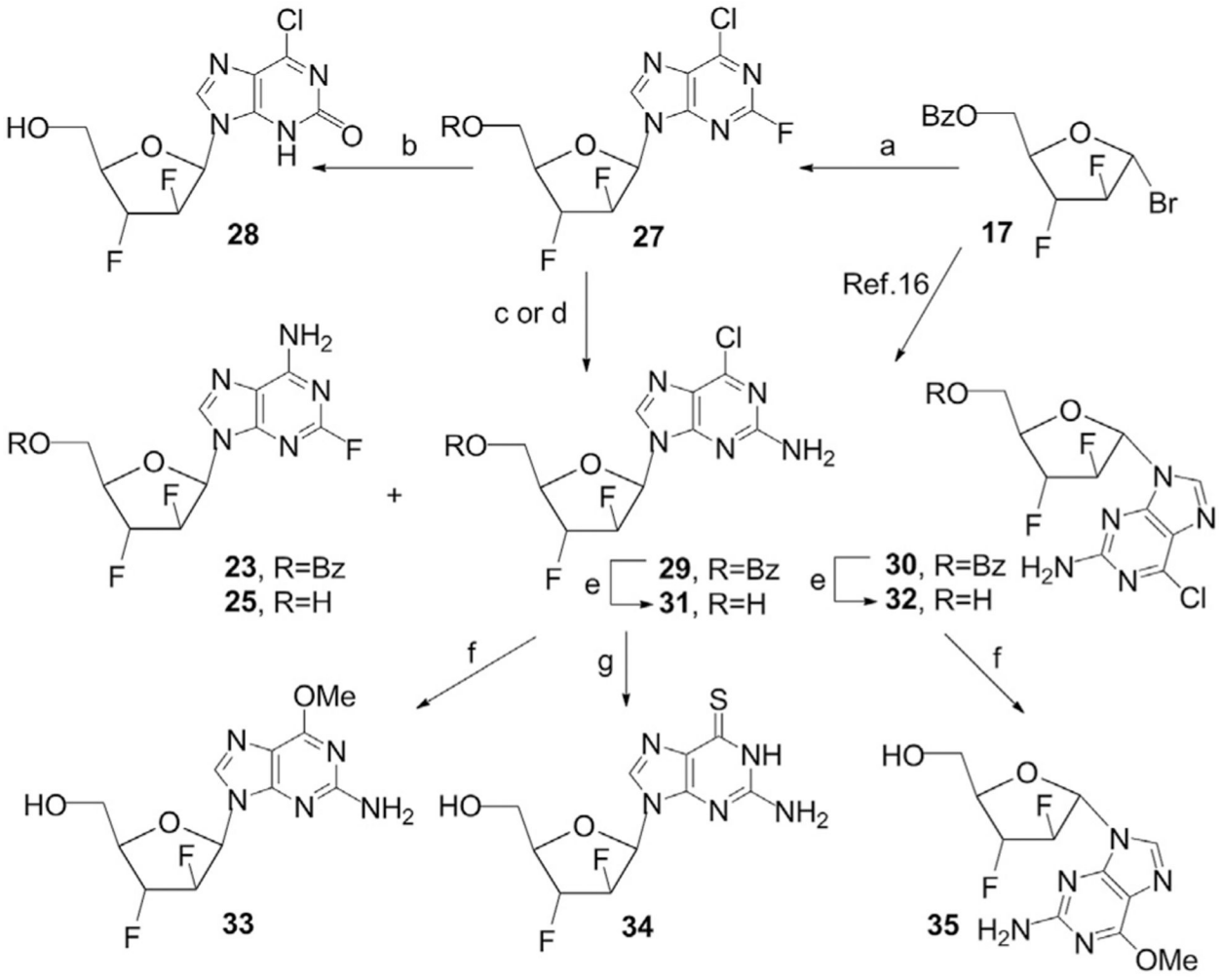
Scheme 3. Reagents and conditions.

a) **11b**, DAST/CH_2Cl_2, 25–27 °C, 18 h, **21**, 55%, **15**, 3%, **22**, 3%.



Scheme 4. Reagents and conditions.

a) **17**, K-salt of 2-fluoroadenine, CH_3CN/CH_2Cl_2, CaH_2, rt, **23**, 28%; **24**, 28%; b) **23**, $LiOH{\cdot}H_2O$, CH_3CN/H_2O, rt, **25**, 73%; **24**, $LiOH{\cdot}H_2O$, CH_3CN/H_2O, rt, **26**, 87%.



Scheme 5. Reagents and conditions.

a) **17**, K-salt of 2-fluoro-6-chloropurine, CH_3CN, rt, **27**, 66%; b) $LiOH{\cdot}H_2O$, CH_3CN/H_2O, rt, 87%; c) THF/NH_3 in MeOH, **31**, 54%; **25**, 15%; d) 1,2-DME/NH_3, 0 °C, 1 h, then 24 °C, 18 h, **29**, 55%, **23**, 23%; e) NH_3, MeOH, rt; f) **31**, MeOH, K_2CO_3, 80–82 °C, **33**, 72%; **32**, MeOH, K_2CO_3, 80–82 °C, **35**, 75%; g) **31**, EtOH, $CS(NH_2)_2$, reflux, 76%.

Table 1

Selective 5-*O*-benzoylation of methyl α/β-xylofuranosides (**9**) with PhCOCl

Entry	Regents and conditions	Base (equiv.)	BzCl (equiv.)	Time (h)	Ratios of 11b/11a[a]	Yields (%)[b]
1	$BzCl/CH_2Cl_2$/Py 0 °C→rt	Et_3N (1.0)	1.2	18	1.24:1	29
2	$BzCl/CH_2Cl_2$ 0 °C→rt	$Et_3N/{}^iPr_2NEt$(1.7/0.7)	1.3	18	1.29:1	39
3	$BzCl/CH_2Cl_2$ 0 °C→rt	$Et_3N/{}^iPr_2NEt$(1.7/0.8)	1.3	18	1.32:1	46 (39)
4	Bu_2SnO/MeOH reflux; BzCl/toluene, rt	$^iPr_2NEt$ (1.9)	2.0	5	1:0.72	46 (35)
5	Bu_2SnO/MeOH reflux; BzCl/1,2-DME, rt	$^iPr_2NEt$ (2.3)	3.0	5	1:0.80	97 (82)

[a]Ratio of 5-*O*-benzoyl α- and β-xylofuranosides determined from ^1H NMR spectrum of the anomeric mixture after chromatography.

[b]Combined isolated yields of 5-*O*-benzoates **11a,b** after chromatography on silica gel. Figures in parentheses refer to isolated yield of methyl 5-*O*-benzoyl α-xylofuranoside **11a** (calculated from α:β ratio of 1:1.25/1.14 in the starting methyl xyloside **9**).

Table 2

Study of isomerization of β-xylofuranoside **11b** to α-xylofuranoside **11a** under acidic conditions.

Entry	Regents and conditions	Acid (equiv.)	11b:11a[a]	Yields (%)[b]
1	MeOH/CH_3SO_2OH, rt, 18 h	5.5	1:0.66	32
2	MeOH/HCl, rt, 3 h	0.87	1:0.90	47

[a]Ratio of 5-*O*-benzoyl β/α -xylofuranosides **11b** and **11a** determined from the ^{1}H NMR spectrum of the anomeric mixture after treatment.

[b]Yields of methyl 5-*O*-benzoyl α-xylofuranoside **11a** refer to NMR yields.