A Novel Route for the Synthesis of Deoxy Fluoro Sugars and Nucleosides

by **Igor A. Mikhailopulo*** and **Grigorii G. Sivets**

Institute of Bioorganic Chemistry, National Academy of Sciences, 220141 Minsk, Acad. Kuprevicha 5, Belarus (phone/fax: +375/172/648324; e-mail: igormikh@ns.igs.ac.by)

Dedicated to Prof. Dr. *Frank Seela* on the occasion of his 60th birthday

The reaction of (diethylamino)sulfur trifluoride (DAST) with methyl 5-*O*-benzoyl-β-D-xylofuranoside (**1**) followed by column chromatography afforded the riboside **2** (62%) and the *ribo*-epoxide **3** (18%) (*Scheme 1*). Under similar reaction conditions, the α-D-anomer **4** gave the riboside **5** and the difluoride **6** in 60 and 9% yield, respectively. Treatment of the β-D-xyloside **10** with DAST gave, after chromatographic purification, the riboside **11** as the principal product (48%; *Scheme 2*). These results suggest that the C(3)–O–SF_2NEt_2 derivatives were initially formed in the case of the xylosides studied. The distinctive feature of the reaction of DAST with the β-D-arabinoside **12** consists in the formation of a 3- or 5-benzylideneoxoniumyl-substituted intermediate on one of the consecutive transformations, which finally give rise to the inversion of the configuration at C(3) affording the xylosides **17** (18%) and **18** (55%); the lyxoside **14** was also isolated from the reaction mixture in a yield of 25% (*Scheme 3*). In the presence of the non-participating 5-*O*-trityl group, *i.e.*, from the reaction products of **21** with DAST, the compounds **23** and **24** were isolated in 16 and 52% yield, respectively (*Scheme 4*). It may be thus reasonable to conclude that, in the case of the β-D-arabinosides **12** and **21**, the principal route of the reaction is the formation of the intermediate C(2)–O–SF_2NEt_2 derivative. Unlike **21**, the α-D-arabinoside **26** was converted to the *lyxo*-epoxide **25** (53%) and the lyxoside **27** (14%), which implies the intermediate formation of the C(3)–O–SF_2NEt_2 derivative (*Scheme 5*).

Introduction. – The synthesis of diverse deoxy fluoro pentofuranosides as key intermediates in a convergent approach to the corresponding nucleosides has been reported over the last decade from our laboratory [1]. In turn, a number of deoxyfluoro nucleosides displayed significant biological activity (for a review, see, *e.g.*, [2]) and, at the 5′-triphosphate level, are used as versatile probes for the DNA and RNA polymerases [1a][3]. Moreover, the incorporation of deoxyfluoro nucleosides into oligonucleotides imparts extraordinary biophysical and biochemical properties to fluorinated oligomers as compared to their unmodified counterparts [1h][4–8].

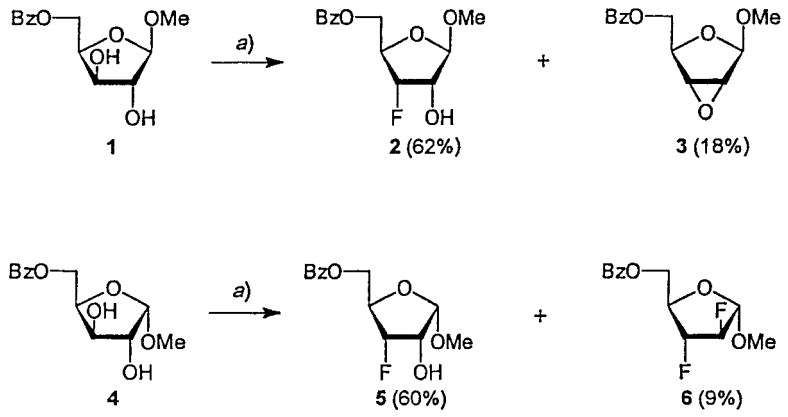
Despite the widespread interest in the chemistry of deoxyfluoro nucleosides, no generally applicable chemical methods have been available for the introduction of an F-atom [2][9]. The approaches to the synthesis of deoxyfluoro nucleosides may be divided into two main groups: *i*) glycosylation of heterocyclic bases with universal carbohydrate precursors, and *ii*) pentofuranose-ring fluorination of nucleosides. Utilizing the first approach (see, *e.g.*, [1b–d,g,i–l]), which has inherent advantages [10], we focused our attention on the development of practical methods for the preparation of deoxy fluoro sugars, which may be transformed in the universal glycosylating agents.

Recently, we have investigated the ring fluorination of methyl pentofuranosides with non-protected *trans*-arranged 2′- and 3′-OH groups under the action of (diethyl-

amino)sulfur trifluoride (DAST), which results in the formation of 2,3-*cis* arranged deoxy fluoro pentofuranosides [11]. Although the regioselectivity of this transformation was rather low and the yields of the desired deoxy fluoro derivatives were moderate, it became evident that this method is of practical utility due to its simplicity and the mildness of the reaction conditions. This study was continued and expanded, and was especially focused on the influence of the configuration at the anomeric center and the nature of the 5-*O*-blocking group on the course of the transformation.

Results and Discussion. – *Chemical Transformations.* Both starting methyl xylosides **1** and **4** were prepared in three steps from D-xylose, *viz.*, D-xylose was transformed to 1,2-*O*-isopropylidene-α-D-xylofuranose [12] in 80% yield, careful benzoylation of which in CH_2Cl_2 in the presence of Et_3N [13] gave the 5-*O*-benzoyl derivative (95%), which was finally treated with I_2 in MeOH [14] under reflux for 4 h to afford a mixture of the desired β-D- and α-D-xylosides in a ratio of *ca.* 1:1 in 69% yield (*Scheme 1*). Following chromatographic purification, the pure homogeneous **1** and **4** were isolated. Alternatively, the reaction of methyl 2,3-anhydro-5-*O*-benzoyl-β-D-lyxofuranoside with potassium benzoate in DMSO gave, after workup and subsequent chromatography as described previously [11], the xyloside **1** (23%) and the arabinoside **12** (22%). Treatment of methyl 5-*O*-benzoyl-β-D-xylofuranoside (**1**) with DAST in a molar ratio of 1:6 in anhydrous CH_2Cl_2 at room temperature for 19 h, followed by column chromatography (silica gel), afforded the β-D-riboside **2** and the *ribo*-epoxide **3** in 62 and 18% isolated yield, respectively. Under similar reaction conditions, the corresponding α-D-anomer **4** was completely transformed within 4 h at room temperature, and after column chromatography, the α-D-riboside **5** and the difluoride **6** were isolated in 60 and 9% yield, respectively [11]. These results tend to suggest that the C(3)–O–SF_2NEt_2 derivatives were initially formed in the case of both xylosides **1** and **4**. Interestingly, the C(3)–O–SF_2NEt_2 derivative of the β-D-anomer **1** mainly underwent intermolecular attack by an F-anion along with an intramolecular nucleophilic attack by the O-atom at C(2). On the contrary, we did not observe the

Scheme 1

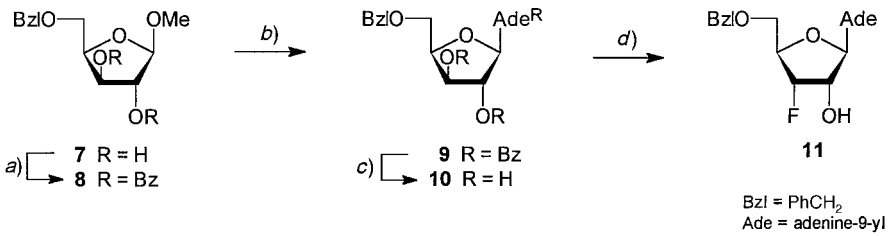


(*a*) DAST (**1** or **4**/DAST 1:6 (molar ratio)), anh. CH_2Cl_2, 20°, 19 (**1**) or 4 h (**4**).

formation of the corresponding epoxide in the case of the α-D-anomer **4**, but the fluoride **5** reacted with an excess of DAST to afford the difluoride **6** instead (*Scheme 1*). The most likely explanation of this observation may be the different conformations of the C(3)–O–SF_2NEt_2 derivatives of the β- and α-D-anomers **1** and **4**. It is noteworthy that the described preparation of 3-fluoro-3-deoxyribosides **2** and **5** from D-xylose offers a useful alternative to methods previously published [1b][11].

In extension of this work, we studied the reaction of DAST with 9-(5-*O*-benzyl-β-D-xylofuranosyl)adenine (**10**). The latter was prepared in three steps from methyl 5-*O*-benzyl-β-D-xylofuranoside (**7**) [11] (*Scheme 2*). Benzoylation of xyloside **7** quantitatively gave benzoate **8**, which was coupled with persilylated N^6-benzoyladenine under standard conditions [1b][15] to give the blocked nucleoside **9** in 63% isolated yield. Debenzoylation of the latter afforded the β-D-nucleoside **10**. The reaction of **10** with DAST in CH_2Cl_2 in the presence of pyridine (CH_2Cl_2/pyridine 13:1, (*v*/*v*)) at room temperature for 5 h gave a complex mixture from which the riboside **11** was isolated as the principal product (48% based on consumed **10**) besides the starting nucleoside **10** (24%). Once again, this result points to the interaction of DAST predominantly with the OH group at C(3′). Addition of pyridine was necessary to dissolve the starting nucleoside **10** before the addition of DAST (*Scheme 2*).

Scheme 2

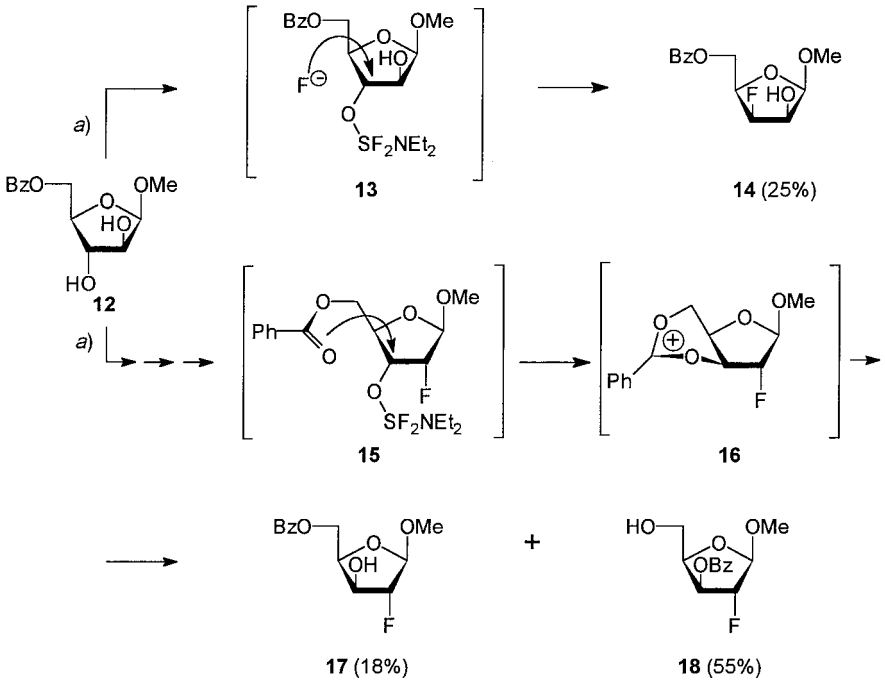


a) BzCl, pyridine, 20°, 18 h; 92%. *b*) **8**-persilylated N^6-benzoyladenine/$SnCl_4$ 1.0:1.5:2.94 (molar ratio), MeCN, reflux for 15 min, 20° for 30 min; 63%. *c*) Saturated (at 0°) NH_3/MeOH soln., 20°, 24 h; 70%. *d*) DAST (**10**/DAST 1:6 (molar ratio)), anh. CH_2Cl_2/pyridine 13:1 (*v*/*v*), 20°, 5 h; chromatography (SiO_2); 48% based on **10** consumed.

The course of the reaction was further studied on the example of methyl arabinosides. In this case, all reactions were performed under identical conditions (molar ratio sugar/DAST 1:6, CH_2Cl_2 as solvent, stirring at room temperature for 5 h, chromatographic isolation of the products as described previously [11]). At variance with the *xylo*-benzoates **1** and **4**, the stereochemical course of the reaction of *arabino*-benzoate **12** (for its preparation, *vide supra*) was dependent upon the participation of the 5-*O*-benzoyl function in one of the intermediate structures. The rather surprising predominant formation of the isomeric *xylo*-benzoates **17** (18%) and **18** (55%) most likely involved a 3- or 5-benzylideneoxoniumyl-substituted transient intermediate **16** (*Scheme 3*). One can speculate that the interaction of DAST with the arabinoside **12** results in the formation of the isomeric C(3)–O–SF_2NEt_2 derivative **13** and the C(2) counterpart (not shown) in a ratio of *ca.* 1:3. The former undergoes an intermolecular attack by an F-anion furnishing the lyxoside **14**, while the latter gives, in a similar manner, the methyl 5-*O*-benzoyl-2-deoxy-2-fluoro-β-D-ribofuranoside (not shown),

which reacts with an excess of DAST to afford **15**. Our data cannot exclude the reverse sequence of transformations, *viz.*, initial formation of a 3- or 5-benzylideneoxoniumyl-substituted intermediate, followed by activation of OH–C(2), followed by nucleophilic displacement of the C(2)–O–SF_2NEt_2 function by an F-anion leading to the common intermediate **16**. Conformational disposition of the 5-*O*-benzoyl group facilitates an intramolecular attack by the carbonyl O-atom at the C(3)-atom, giving rise to a 3- or 5-benzylideneoxoniumyl-substituted intermediate, which, upon workup, is transformed into **17** and **18** (*Scheme 3*).

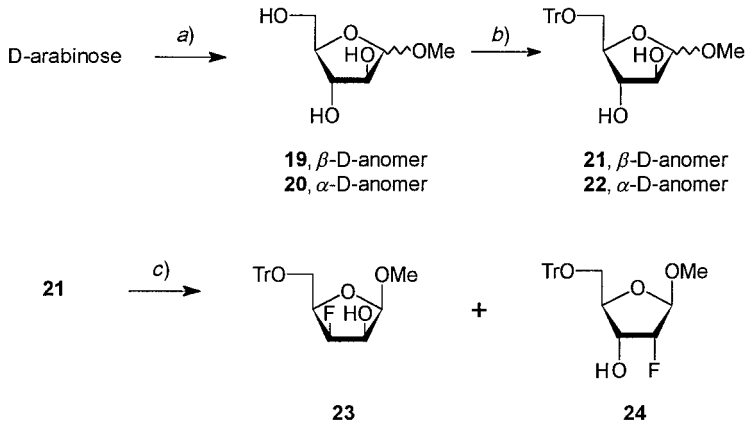
Scheme 3



a) DAST(**12**/DAST 1:6 (molar ratio)), anh. CH_2Cl_2, 20°, 5 h; chromatography (SiO_2 *Woelm* (20% water)).

Further support for the above considerations on the initial step of the DAST reaction with arabinoside **12** was given by the reaction with the 5-*O*-tritylated arabinoside **21**. Indeed, in the presence of a non-participating trityl group, the lyxoside **23** and the riboside **24** were formed in a ratio of *ca.* 1:3 (*Scheme 4*). Note that the reaction of methyl 5-*O*-benzyl-β-D-arabinofuranoside with DAST yielded the corresponding lyxoside and riboside in the ratio of *ca.* 1:2 [11]. The arabinoside **21** was prepared from D-arabinose by the modification of a literature procedure [16], in which D-arabinose was treated with *ca.* 0.3N HCl/MeOH at room temperature for 3–4 h leading to the predominant formation of methyl α-D-arabinofuranoside. In our experiments, treatment of D-arabinose with 0.18N HCl/MeOH at room temperature for 5.5 h furnished a mixture of the β-D- and α-D-anomeric methyl arabinosides **19** and **20**, respectively (β-D/α-D *ca.* 2:3 according to ^{13}C-NMR data; combined yield 79%).

Scheme 4



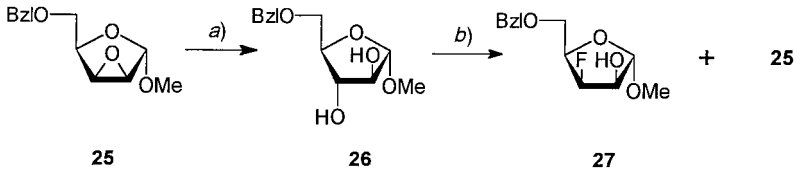
a) 0.18N HCl/MeOH, 20°, 5.5 h; **19**/**20** 79%; β-D/α-D *ca.* 2:3. *b*) TrCl, pyridine, 4-(dimethylamino)pyridine, 20°, 18 h; 60–70°, 4 h; 25% of **21**, 46% of **22**. *c*) DAST (**21**/DAST 1:6 (molar ratio)), anh. CH_2Cl_2, 20°, 18 h, chromatography (SiO_2), 16% of **23**, 52% of **24**.

Tritylation of this anomeric mixture followed by column chromatography afforded the 5-*O*-trityl derivatives **21** and **22** in 25 and 46% isolated yield, respectively.

In contrast to the β-D-arabinoside **21** and the methyl 5-*O*-benzyl-β-D-arabinofuranoside [11] as well, the reaction of methyl 5-*O*-benzyl-α-D-arabinoside **26** with DAST as described for its β-D-counterpart [11] furnished, after standard workup and subsequent chromatography, the *lyxo*-epoxide **25** as the main product, along with the lyxoside **27** in 53 and 14% isolated yield, respectively (*Scheme 5*). From this result, it may be reasonable to conclude that the principal route of the reaction is the formation of the $C(3)-O-SF_2NEt_2$ intermediate, which mainly undergoes an intramolecular nucleophilic attack at C(3) by the neighboring O-atom at C(2), to furnish the *lyxo*-epoxide **25**. It is noteworthy that the rate of conversion of **26** to the products was much slower than the analogous reaction with the β-D-anomer [11]. This reactivity displays a good resemblance with the reactivities of the pair of β-D- and α-D-xylosides **1** and **4**, respectively.

NMR Spectroscopic Studies. The assignment of the structures of the furanosides described here was based on NMR data (*Tables 1–3*). Confirmation of the F-atom position resulted from large one-bond coupling constants ^1J(C,F) of *ca.* 180–190 Hz,

Scheme 5



a) KOBz, DMSO, reflux, 1 h; sat. (at 0°) NH_3/MeOH, 20°, 18 h; 76%. *b*) DAST (**26**/DAST 1:6 (molar ratio)), anh. CH_2Cl_2/pyridine 18:1 (*v*/*v*), 20°, 5 h, chromatography (SiO_2); 14% of **27**; 53% (based on the consumed **26**) of 53%

Table 1. *^{1}H-NMR Chemical Shifts* ($CDCl_3$) *of* **1**–**5**, **10**–**12**, **14**, **17**, **18**, **21**, *and* **23**–**26**. δ(H) in ppm.

	H–C(1) (H–C(1′))	H–C(2) (H–C(2′))	H–C(3) (H–C(3′))	H–C(4) (H–C(4′))	H–C(5) (H–C(5′))	H′–C(5) (H′–C(5′))	Others[a])
1	4.90 (*s*)	4.26 (br. *d*)	4.16 (br. *dd*)		4.48–4.76 (*m*)		2.97 (*d*, OH–C(3)); 2.07 (*d*, OH–C(2))
2	4.93 (br. *s*)	4.27 (br. *s*)	5.20 (*dt*)		4.38–4.70 (*m*)		2.66 (br. *s*, OH–C(2))
3	5.02 (*s*)	3.86 (*d*)	3.75 (*d*)		4.38–4.54 (*m*)		
4	5.0 (*d*)	4.18 (*t*)	4.31 (*t*)		4.36–4.74 (*m*)		
5	4.98 (*d*)	4.22 (*m*)	4.91	4.60 (*dt*)	4.38–4.58 (*m*)		2.88 (*dd*, OH–C(2))
10[b])	5.90 (*d*)	4.37–4.28 (*m*)	4.06 (br. *t*)	4.37–4.28 (*m*)	3.83 (*dd*)	3.70 (*dd*)	8.23 (*s*, H–C(8)); 8.16 (*s*, H–C(2)); 6.04 (*d*, OH–C(3′)); 5.96 (*d*, OH–C(2′)); 7.34 (br. *s*, NH_2); 7.20 (br. *s*, Ph); 4.52 (*s*, PhCH_2)
11[c])	6.12 (*d*)	4.68 (*ddd*)	5.12 (*dd*)	4.52 (*dm*)	3.76 (*dm*)	3.69 (*dd*)	8.24 (*s*, H–C(8)); 8.10 (*s*, H–C(2)); 7.36 (br. *s*, NH_2, Ph); 4.55 (*s*, PhCH_2)
12	4.80 (*d*)	4.06–4.18 (*m*)	4.25 (*t*)	4.06–4.18 (*m*)	4.53 (*dd*)	4.37 (*dd*)	
14	*ca.* 4.90	4.20 (*m*)	5.04 (*dm*)		4.36–4.70 (*m*)		2.96 (*d*, OH–C(2))
17	5.08 (*d*)	4.93 (*d*)	4.39 (*m*)	4.62 (*m*)	4.72 (*dd*)	4.51 (*dd*)	2.98 (*d*, OH–C(3))
18	5.14 (*d*)	5.19 (*dd*)	5.63 (*ddd*)	4.68 (*dt*)	4.25 (br. *d*)		2.54 (br. *s*, OH–C(5))
21	4.82 (*d*)	4.02–4.16 (*m*)		3.95 (*dt*)	3.25 (*d*)		7.20–7.60 (*m*, Ph); 2.64 (br. *s*, OH–C(2), OH–C(3))
23	4.88 (*d*)	4.02–4.40 (*m*)	4.90 (*dt*)	4.02–4.40 (*m*)	3.32–3.48 (*m*)		7.20–7.60 (*m*, Ph); 2.80 (*d*, OH–C(2))
24	5.23 (*d*)	4.76 (*dd*)	4.35 (*dm*)	4.07 (*m*)	3.36 (*dd*)	3.23 (*dd*)	7.20–7.60 (*m*, Ph); 1.98 (*d*, OH–C(3))
25	4.94 (br. *s*)	3.74 (br. *d*)	3.62–3.66 (*m*)	4.18 (br. *t*)	3.62–3.66 (*m*)		7.26–7.40 (*m*, Ph); 4.54, 4.60 (2*d*, PhCH_2)
26	4.90 (*s*)	3.96 (*s*)	4.0 (br. *s*)	4.20 (br. *m*)	3.64 (*dd*)	3.72 (*dd*)	7.26–7.40 (*m*, Ph); 4.64, 4.54 (2*d*, PhCH_2)

[a]) δ(H) of MeO: 3.36–3.50 ppm; δ(H) of BzO: *ca.* 7.20–7.70 (*m*) and *ca.* 8.08 (*d*). [b]) In (D_6)DMSO. [c]) In $CDCl_3$/CD_3OD.

Table 2. *Coupling Constants* ^{3}J*(H,H) and* J*(H,F) of* **1**–**5**, **10**–**12**, **14**, **17**, **18**, **21**, *and* **23**–**26**[a]). *J* in Hz.

	J(1,2) (*J*(1′,2′))	*J*(2,3) (*J*(2′,3′))	*J*(3,4) (*J*(3′,4′))	*J*(4,5) (*J*(4′,5′))	*J*(4,5′) (*J*(4′,5″))	*J*(1,F) (*J*(1′,F))	*J*(2,F) (*J*(2′,F))	*J*(3,F) (*J*(3′,F))	*J*(4,F) (*J*(4′,F))	Others
1	< 1.0	< 1.0	3.0	n.d.	n.d.	–	–	–	–	*J*(3,OH) = 10.5, *J*(2,OH) = 4.35
2	1.5	4.5	4.5	n.d.	n.d.	1.5	n.d.	54.0	n.d.	
3	< 1.0	2.9	< 1.0	n.d.	n.d.	–	–	–	–	
4	3.75	3.75	3.75	n.d.	n.d.	–	–	–	–	
5	5.0	5.70	1.45	4.0	4.0	< 1.0	24.0	56.0	≈ 22	*J*(5,5′) = *J*(2, OH) = 12.0 *J*(F,OH) = 1.5
10	1.75	1.0	5.0	3.5	7.0	–	–	–	–	*J*(5′,5″) = 10.5, *J*(3,OH) = 5.25 *J*(2,OH) = 3.5
11	7.15	4.5	0.7	3.0	2.6	< 1.0	23.4	54.0	26.0	*J*(5′,5″) = 9.75, *J*(5′,F) = 1.3
12	4.3	7.4	7.4	3.2	5.2	–	–	–	–	*J*(5,5′) = 12.0
14	4.5	5.0	n.d.	n.d.	n.d.	< 1.0	25.0	50.0	n.d.	*J*(2,OH) = 11.5
17	< 1.0	0.9	4.0	4.5	6.0	10.0	48.5	11.5	< 1.0	*J*(5,5′) = 10.0, *J*(3,OH) = 10.0
18	< 1.0	2.5	6.2	4.5	4.5	14.0	50.5	20.5	< 1.0	
21	4.2	n.d.	6.3	4.5	4.5	–	–	–	–	
23	5.4	4.2	4.2	n.d.	n.d.	< 1.0	≈ 22	54.0	28.8	*J*(2,OH) = 10.8
24	< 1.0	3.9	8.0	3.5	7.5	10.5	53.5	25.0	< 1.0	*J*(5,5′) = 10.5, *J*(3,OH) = 9.0
25	< 1.0	2.5	n.d.	6.0	6.0	–	–	–	–	
26	< 1.0	< 1.0	< 1.0	2.5	2.5	–	–	–	–	*J*(5,5′) = 10.5

[a]) n.d.: not determined.

exhibited in the ^{13}C-NMR spectra by the F-substituted C-atoms. Large geminal constants ^2J(H,F) of *ca.* 48–55 Hz, displayed in the ^{1}H-NMR spectra were of the same diagnostic value. Thus, compounds **2**, **5**, **6**, **11**, **14**, **23**, and **27** clearly show fluorination at C(3), whereas **17**, **18**, and **24** are 2-deoxy-2-fluoro derivatives. The assignments of configuration for most of the compounds synthesized were based primarily on ^{13}C-NMR data (*Table 3*), taking into account previous empirical correlations of the effect of configuration of vicinal substituents in the furanose ring on the δ(C) values of the atoms bearing these groups [1i][18].

The conformational analysis of the furanose rings of the compounds described above was performed by the PSEUROT (Version 6.2) program, which calculates the best fits of three experimental ^3J(H,H) coupling constants (^3J(H–C(1),H–C(2)), ^3J(H–C(2),H–C(3)), and ^3J(H–C(3),H–C(4))) to the five conformational parameters (*P* and ψ_m for both N- and S-type conformers and corresponding mol fractions) [19]. In the PSEUROT program, a minimization of the differences between the experimental and calculated couplings is accomplished by a nonlinear *Newton-Raphson* minimization. This procedure is enhanced if the ratio of the number of data points *vs.* the number of optimized parameters increases. Three ^3J(H,H) values are of limited value for conformational analysis of a pentofuranose ring, especially if the equilibrium under consideration represents a mixture of conformations present in comparable proportions. Moreover, it is not axiomatic that a two-state $N \leftrightarrow S$ model

Table 3. *^{13}C-NMR Chemical Shifts* ($CDCl_3$) *and Coupling Constants* J*(C,H) and* J *(C,F) of* **1**–**6**, **12**, **14**, **17**, **18**, **21**, *and* **23**–**26**. δ(C) in ppm, *J* in Hz.

	C(1)	C(2)	C(3)	C(4)	C(5)	MeO	*J*(C(1),F)	*J*(C(2),F)	*J*(C(3),F)	*J*(C(4)F)	*J*(C(5)F)
1	108.6	79.6	76.4	80.9	64.3	55.3	–	–	–	–	–
	(*J* = 171.1)	(*J* ≈ 156)	(*J* ≈ 160)	(*J* ≈ 151.0)	(*J* ≈ 148.4)	(*J* ≈ 143.4)					
2	108.0	74.5	92.4	78.5	64.2[c])	55.6	4.0	14.9	187.4	25.3	4.5
	(*J* = 173.6)	(*J* = 155.5)	(*J* = 160.4)	(*J* = 151.0)	(*J* = 148.7)	(*J* = 141.5)					
3	102.5	56.4[d])	55.1[d])	76.1	64.2	55.4	–	–	–	–	–
	(*J* = 169.8)	(*J* = 194.4)	(*J* = 190.6)	(*J* = 150.9)	(*J* = 149.1)	(*J* = 142.8)					
4	101.9	76.7[d])	76.3[d])	78.0	63.3	55.9	–	–	–	–	–
	(*J* = 172.5)	(*J* = 151.0)	(*J* = 151.0)	(*J* = 147.2)	(*J* = 149.1)	(*J* = 142.7)					
5	102.4	72.5	90.5	80.5	63.8	55.8	< 2.0	16.5	185.5	25.3	10.3
	(*J* = 174.1)	(*J* = 147.6)	(*J* = 165.3)	(*J* = 149.8)	(*J* = 149.8)	(*J* = 143.2)					
6	106.1	96.0[d])	98.4[d])	80.2	63.6	55.0	1,F3 < 2.0	186.5[d])	180.0[d])	4,F2 < 2.0	< 2.0
	(*J* = 174.5)	(*J* = 162.5)	(*J* = 162.5)	(*J* = 150.4)	(*J* = 150.4)	(*J* = 142.4)	1,F2: 36.5	2,F3: 30.3	3,F2: 28.1	4,F3: 28.7	
12[e])	102.6	76.7	80.3	78.5	65.8	55.9	–	–	–	–	–
	(*J* = 174.9)	(*J* = 146.6)	(*J* = 147.8)	(*J* = 144.7)	(*J* = 149.4)	(*J* = 143.6)					
14	101.8	73.1	89.7	77.7	63.5	55.8	< 2.0	16.7	190.2	17.8	14.8
	(*J* = 171.7)	(*J* = 145.3)	(*J* = 166.1)	(*J* ≈ 150)	(*J* = 151.0)	(*J* = 143.4)					
17	106.0	96.8	73.6	80.9	63.7	55.5	32.6	183.0	25.6	< 2.0	< 2.0
	(*J* = 176.1)	(*J* = 163.6)	(*J* = 153.5)	(*J* = 151.0)	(*J* = 149.7)	(*J* = 144.3)					
18	106.6	98.3	75.7	81.4	61.4	55.9	35.3	182.7	29.1	< 2.0	< 2.0
	(*J* = 172.0)	(*J* = 160.5)	(*J* ≈ 152)	(*J* = 150.3)	(*J* = 144.7)	(*J* = 141.5)					
21	101.8	77.0[d])	78.0[d])	80.8	64.9	55.4	–	–	–	–	–
	(*J* = 173.6)	(*J* ≈ 150)	(*J* ≈ 150)	(*J* = 143.4)	(*J* = 142.5)	(*J* = 143.4)					
23	101.6	73.1	89.9	78.9	63.1	55.2	< 2.0	16.7	190.1	18.4	12.6
	(*J* = 174.2)	(*J* = 151.1)	(*J* = 164.3)	(*J* = 145.2)	(*J* = 142.7)	(*J* = 143.6)					
24	105.0	93.9	71.6	81.7	71.4	55.3	29.5	179.5	15.9	< 2.0	< 2.0
	(*J* = 173.0)	(*J* = 168.3)	(*J* = 147.8)	(*J* = 149.4)	(*J* = 141.5)	(*J* = 141.5)					
25	102.1	56.1[d])	54.2[d])	74.9	68.4	55.4	–	–	–	–	–
	(*J* = 172.0)	(*J* = 192.8)	(*J* = 191.8)	(*J* = 147.4)	(*J* = 142.5)	(*J* = 142.5)					
26[f])	109.5	78.8[d])	78.2[d])	86.2	69.4	54.8	–	–	–	–	–
	(*J* = 173.6)	(*J* = 154.7)	(*J* ≈ 152)	(*J* = 147.2)	(*J* = 143.4)	(*J* = 142.7)					

[a]) δ(C) of BzO: 165.8–167.3 (*s*, C=O); 128.4–129.0 (*dd*, ^1J(C,H) ≈ 158, ^3J(C,H) ≈ 7, C_m); 133.1–133.8 (*dt*, ^1J(C,H) ≈ 160, ^3J(C,H) ≈ 8, C_p); 129.3–130.4 (*dt*, ^1J(C,H) ≈ 162, ^3J(C,H) ≈ 6, C_o; *t*, ^3J(C,H) ≈ 8, C_{ipso}). [b]) The CH_3O signal in the ^{1}H-coupled ^{13}C-NMR shows an additional splitting into a *d* ($^3J(CH_3O, H-C(1)) = 2.8-4.7$ Hz; not observed (< 2.0 Hz) for **1** and **6**; the C(1) signal in the ^{1}H-coupled ^{13}C-NMR is a *d m:* $^3J(C(1), CH_3O) \approx 3.0$ and $^3J(C(1), H-C(4)) \approx 3.0$ for **2**, **3**, and **5**, $^3J(C(1), CH_3O) = 4.0$ and $^3J(C(1), H-C(4)) = 4.0$ Hz for **12**, **14**, **17**, **18**, and **22**. [c]) The C(5) signal displayed an additional *J*(C,H) of 4.5 (**2**), 2.2 (**5**), 4.0 (**12**), 6.0 (**14**), and 3.5 Hz (**17**) (tentatively assigned to $^3J(C(5), H-C(3))$). [d]) Data (δ and related *J*'s) may be interchanged. [e]) The C(3) and C(4) signals display additional couplings: $^3J(C(3), H-C(1)) = 3.0$ and $^3J(C(4), H-C(2)) = 2.2$ Hz), resp. [f]) The C(2) signal displays an additional coupling, tentatively assigned to $^3J(C(2), H-C(4))$ (3.7 Hz).

may accurately describe pentofuranose rings with other than β-D-*ribo*-configuration. Thus, two approaches are of interest to define more accurately the pseudorotational parameters P and ψ_m for two *N*- and *S*-conformers. *Serianni* and co-workers have shown that some of the J(C,H) coupling constants are equally valuable conformational probes for defining a rather narrow *N*- or *S*-domain of the pseudorotational wheel of the pentofuranose ring [20]. The main problem associated with this approach is that the J(C,H) coupling constants can be correctly measured only in ^{13}C-enriched molecules. With reference to deoxy fluoro nucleosides, *Chattopadhyaya* and co-workers have very recently developed a new *Karplus*-type relation between vicinal ^3J(H,F) coupling constants and the corresponding H–C–C–F torsion angles [21]. The use of temperature-dependent ^3J(H,F) coupling constants in combination with ^3J(H,H) greatly facilitates the conformational analysis of pentofuranose rings because of the overwhelming increase of the number of experimental data points over the puckering parameters P and ψ_m [21].

We have qualitatively examined the ^3J(C,F) spin-couplings as an additional conformational probe of furanose rings in solution. The conformational behavior was evaluated by the PSEUROT analysis of the ^3J(H,H) values only essentially as it was described previously [22]. The resulting optimized geometries of *N*- and *S*-pseudorotamers are presented in *Table 4*.

Table 4. *Pseudorotational Parameters of Some Selected Compounds*

	P_N	$\psi_{m(N)}$	P_S	$\psi_{m(S)}$	r.m.s.	$\lvert\Delta J_{max}\rvert$	%*S*
1	18.6	29.9	108[a])	34[a])	0.000	0.00	15
2	9.3	41[a])	220.0	38[a])	0.060	0.08	53
4	19.0	46[a])	121.1	46[a])	0.001	0.00	61
5	– 9[a])	44[a])	147.5	27.9	0.169	0.25	100
11	10[a])	39[a])	189.9	35.4	0.006	0.00	98
12	– 13.0	42[a])	137.4	38[a])	0.081	0.13	6
17	– 15.1	28.7	34[a])	108[a])	0.000	0.00	14
23	– 30.5	37.0	108[a])	46[a])	0.545	0.75	0
24	27.9	45.6	198[a])	44[a])	0.000	0.00	16
26	9[a])	30[a])	156.0	31.5	0.000	0.00	99

[a]) The values indicated were fixed during the final calculations.

The factors affecting the conformation of the pentofuranose rings of nucleosides in solution have been exensively investigated during last years by *Chattopadhyaya* and coworkers (see [21] and ref. cit. therein). The sugar moieties of nucleosides are involved in a two-state $N \leftrightarrow S$ pseudorotational equilibrium, which is driven by the relative strength of various *gauche* and anomeric stereoelectronic effects. It was shown that the stronger *gauche* effect of an F-substituent, due to its high electronegativity, governs the overall conformation of the pentofuranose rings [5][21][23]. Less is known regarding the contribution of a MeO group replacing a heterocyclic base to the conformational behavior of pentofuranose rings [24].

The dominating population of the *S*-conformer ($^2T_1 \leftrightarrow {}^2E$) of the α-D-riboside **5** is apparently caused by the *gauche* effects of the F–C(3)–C(4)–O(4), F–C(3)–C(2)–OH, and HO–C(2)–C(1)–OMe fragments. In such a conformation, the F–C(3)–

C(4)–C(5) and F–C(3)–C(2)–C(1) fragments are in a *anti*-periplanar (*ca.* 170°) and *gauche* (*ca.* 90°) arrangement, respectively, which is consistent with the corresponding ^3J(C,F) values of 10.3 and <2.0 Hz (*Table 3*). Changing the anomeric configuration from α-D to β-D gives rise to an equal population of the *N*- and *S*-type puckered conformers of the β-D-riboside **2**, which result mainly from the competing *gauche* interactions (F–C(3)–C(4)–O(4), F–C(3)–C(2)–OH, and HO–C(2)–C(1)–OMe fragments for *S*-type, and F–C(3)–C(2)–OH and HO–C(2)–C(1)–O(4) fragments for *N*-type). Note that, on the basis of the aforementioned *gauche* effects alone, the *N*- and *S*-conformers would not be equally populated in the β-D-riboside **2**. However, the coupling constants ^3J(C(1),F) (4.0 Hz) and J(F,C(5)) (4.5 Hz) of **2** take the intermediate values and are consistent with the presence of comparable proportions of the *N*- and *S*-conformers.

It is noteworthy that the conformational behavior of the β-D-riboside **2** substantially differs from that of 3′-deoxy-3′-fluoroadenosine (P_s 168, $\psi_{m(S)}$ 40.0; *S* 97%) [5] and of its 5′-*O*-benzyl derivative **11** as well. This may be due to the different anomeric effects of the MeO group and the adenine base. On the contrary, the conformational properties of the β-D-riboside **24** are closely related to those of 2′-deoxy-2′-fluoroadenosine [4]. In the case of the β-D-riboside **24**, the values of ^3J(H–C(1),F) (10.5 Hz) and ^3J(H–C(3),F) (25.0 Hz) are in good qualitative agreement with the predominant *N*-type ($^3E \leftrightarrow {}^3T_4$) conformation. Another interesting finding consists in that the population of the *S*-conformer increases by *ca.* 45% by going from the β-D-anomers **1** and **2** to the respective α-D-counterparts **4** and **5**. A more dramatic conformational change occurs on going from β-D-arabinoside **12** to its α-D-anomer **26**.

The ^3J(C(4),F) (<2.0 Hz) of xyloside **17** is in accord with predominant population of the *N*-conformer ($_2E$), for which the F–C(2)–C(3)–C(4) fragment is in the *gauche* orientation (*ca.* 90°). The migration of the benzoyl group from the 5-*O* to the 3-*O* position is accompanied by remarkable conformational changes, which are clearly reflected in the ^3J(H–C(1),F) and ^3J(H–C(3),F) values of **18** (*Table 2*). Unexpectedly, attempts to perform the PSEUROT analysis of the 3-benzoate **18** failed. Although we found a number of pseudorotational parameters with good (<0.2) root mean square (r.m.s.) deviations of the fit, the most populated conformations of **18** are not consistent with the ^3J(C(4),F) <2.0 Hz. In a similar way, the PSEUROT analysis of lyxosides **23** and **27** led to the pseudorotational parameters with rather large r.m.s. values (see, *e.g.*, the data for **23**; *Table 4*) which are, however, compatible with the ^3J(C(1),F) values of <2.0 Hz. These preliminary data tend to suggest that conformational behavior of lyxosides and, to some extent, xylosides cannot be adequately described by the two-state $N \leftrightarrow S$ pseudorotational equilibrium. More definitive conclusions can, however, be drawn after detailed conformational analysis with both ^3J(H,H) and ^3J(H,F) coupling constants [23].

In conclusion, the scope and limitations of ring fluorination of pentofuranosides containing free secondary OH groups under the action of DAST were established. We demonstrated that the synthesis of some fluorinated carbohydrates may be achieved in good overall yield starting from commercially available sugars. This approach does provide a useful alternative to the previously described methods.

I.A.M. is deeply grateful to the *Alexander von Humboldt Foundation*, Bonn/Bad-Godesberg, Germany, for partial financial support of this work. The authors are thankful to Dr. *Natalja B. Khripach*; Institute of Bioorganic Chemistry, Minsk, for the measurement of the NMR spectra.

Experimental Part

1. *General*. The solns. of compounds in org. solvents were dried (Na_2SO_4) for 4 h. Column chromatography (CC): silica gel *60* (70–230 mesh ASTM; *Merck*, Darmstadt, Germany), except where otherwise indicated. TLC: *Silufol UV$_{254}$* (Czech Republic); eluents: hexane/AcOEt 1:2 (*A*), hexane/AcOEt 4:1 (*B*), $CHCl_3$/MeOH 15:1 (*C*), and hexane/AcOEt 1:1 (*D*). M.p.: *Boetius* apparatus (Germany); not corrected. UV Spectra: *Specord M-400* spectrometer (*Carl Zeiss*, Germany). CD Spectra and $[\alpha]_D^{25}$: *J-20* spectropolarimeter (*JASCO*, Japan). ^{1}H- and ^{13}C-NMR Spectra: *AC-200* spectrometer equipped with an *Aspect 3000* data system (*Bruker*, Germany) at 23° and 200.13 (^{1}H) and 50.325 MHz (^{13}C); $CDCl_3$ soln., unless otherwise stated; δ values in ppm downfield from internal $SiMe_4$; assignments of δ(H), when possible, by selective homonuclear decoupling experiments.

2. *Methyl 5*-O-*Benzoyl-β*-D-*xylofuranoside* (**1**) *and Methyl 5*-O-*Benzoyl-α*-D-*xylofuranoside* (**4**). To a soln. of syrupy 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranose [12][13] (4.95 g, 16.82 mmol) in anh. MeOH (95 ml), crystalline I_2 (0.95 g) was added, and the mixture was heated under reflux for 4 h. After cooling, the mixture was poured into sat. aq. $Na_2S_2O_3$ soln. (150 ml) and extracted with $CHCl_3$ (3 × 200 ml), the combined org. extract washed with sat. aq. NaCl soln. (100 ml), dried, and evaporated, and the oily residue (4.92 g) submitted to CC (silica gel; 200 ml), linear gradient of hexane/AcOEt 1:2 (1.5 l) in hexane/AcOEt 7:1 (1.5 l): 1.6 g (35%) of **1**, and 1.52 g (34%) of **4**.

Data of **1**: M.p. 107–108° (from Et_2O/hexane). $[\alpha]_D^{25} = -46.0$ ($c = 1.0$, $CHCl_3$). TLC (*A*): R_f 0.49. Anal. calc. for $C_{13}H_{16}O_6$ (268.26): C 58.20, H 6.02; found: C 57.93, H 5.82.

Data of **4**: TLC (*A*): R_f 0.43.

3. *Reaction of DAST with* **1** *and* **4**. To a soln. of **1** (0.24 g, 0.89 mmol) in anh. CH_2Cl_2 (5 ml), DAST (0.71 ml, 5.36 mmol) was added and the mixture stirred at r.t. for 19 h. After cooling to 0°, the mixture was poured into sat. cold aq. $NaHCO_3$ soln. (60 ml), the aq. phase extracted with CH_2Cl_2 (3 × 80 ml), the combined org. extract dried and evaporated, and the residue chromatographed (silica gel *L* (*Chemapol*, Czech Republic, 40/100 μm; 80 ml), linear gradient of hexane/AcOEt 2:1 (350 ml) in hexane/AcOEt 6:1 (350 ml): 41 mg (18%) of **3** and 150 mg (62%) of **2**.

Methyl 5-O-*Benzoyl-3-deoxy-3-fluoro-β*-D-*ribofuranoside* (**2**). M.p. 68–70° (from Et_2O/hexane) $[\alpha]_D^{25} = -82.0$ ($c = 1.0$, $CHCl_3$). TLC (*B*): R_f 0.17. Anal. calc. for $C_{13}H_{15}FO_5$ (270.28): C 57.77, H 5.59; found: C 57.64, H 5.76.

Methyl 2,3-Anhydro-5-O-*benzoyl-β*-D-*ribofuranoside* (**3**). Syrup. TLC (*B*): R_f 0.40.

In a similar way, **4** (0.23 g, 0.86 mmol) was treated with DAST (0.68 ml, 5.14 mmol) in CH_2Cl_2 (5 ml) at r.t. for 4.5 h: 20 mg (9%) of **6** and 140 mg (60%) of **5**.

Methyl 5-O-*Benzoyl-2,3-dideoxy-2,3-difluoro-α*-D-*arabinofuranoside* (**6**): Syrup. TLC (*B*): R_f 0.62.

Methyl 5-O-*Benzoyl-3-deoxy-3-fluoro-α*-D-*ribofuranoside* (**5**): Syryp. TLC (*B*): R_f 0.29.

4. *5′*-O-*Benzyl-3′-deoxy-3′-fluoroadenosine* (**11**). To a soln. of methyl 5-*O*-benzyl-β-D-xylofuranoside [1b] (**7**; 0.3 g, 1.18 mmol) in anh. pyridine (3.5 ml), benzoyl chloride (0.33 ml, 2.84 mmol) was added, and the mixture was stirred at r.t. for 18 h. Standard workup followed by CC (silica gel (100 ml), linear gradient of hexane/AcOEt 10:1 (0.5 l) in hexane (0.5 l) gave 0.50 g (92%) of syrupy *2,3-di*-O-*benzoyl-5*-O-*benzyl-β*-D-*xylofuranoside* (**8**). TLC (*B*): R_f 0.67. ^{1}H-NMR ($CDCl_3$): 3.48 (*s*, MeO); 3.79 (*d*, $J = 6.0$, 2 H–C(5)); 4.46, 4.54 (2*d*, $J = 12$, PhCH_2); 4.82 (*dt*, $J = 6.0$, 5.5, H–C(4)); 5.10 (*s*, H–C(1)); 5.46 (*d*, $J = 1.8$, H–C(2)); 5.76 (*dd*, $J = 1.8$, 5.5, H–C(3)); 7.38–7.62, 8.0–8.08 (2*m*, 3 Ph).

A mixture of **8** (0.50 g, 1.08 mmol), $SnCl_4$ (0.37 ml, 3.17 mmol) and the bis(trimethylsilyl) derivative of N^6-benzoyladenine (obtained from 0.39 g (1.62 mmol) of N^6-benzoyladenine) in anh. MeCN (10 ml) was refluxed for 15 min and then allowed to cool to r.t. under stirring for an additional 30 min. After standard workup, the residue was purified by CC (silica gel; 100 ml), linear gradient of heptane/AcOEt 1:1 (0.5 l) in heptane (0.5 l), then heptane/AcOEt 1:2 (0.4 l): 0.46 g (63%) *of* N^6-*benzoyl-9-(2,3-di*-O-*benzoyl-5*-O-*benzyl-β*-D-*xylofuranosyl)adenine* (**9**). Foam. TLC (*C*): R_f 0.90. ^{1}H-NMR ($CDCl_3$): 3.84 (*dd*, $J = 5.1$, 11.0, H–C(5′)); 3.92 (*dd*, $J = 4.5$, 11.0, H′–C(5′)); 4.52, 4.60 (2*d*, $J = 12$, PhCH_2); 4.86 (*m*, $J = 4.2$, 4.5, 5.1, H–C(4′)); 5.92 (*dd*, $J = 4.2$, 2.5, H–C(3′)); 6.25 (*t*, $J = 2.5$, H–C(2′)); 6.50 (*d*, $J = 2.5$, H–C(1′)); 5.46 (*d*, $J = 1.8$, H–C(2)); 5.76 (*dd*, $J = 1.8$, 5.5, H–C(3)); 7.40–7.66, 7.88–8.12 (2*m*, 4 Ph); 8.46 (*s*, H–C(2)); 8.68 (*s*, H–C(8)).

Standard debenzoylation of **9** followed by CC (silica gel (130 ml), linear gradient of $CHCl_3$/EtOH 8:1 (0.6 l) in $CHCl_3$ (0.6 l)) afforded 0.16 g (70%) of *9-(5-*O*-benzyl-β-*D*-xylofuranosyl)adenine* (**10**). M.p. 83–85° (from CH_2Cl_2/MeOH). $[\alpha]_D^{25} = -41.0$ ($c = 0.54$, MeOH). TLC (*C*): R_f 0.17. UV (EtOH): 207 (23375), 260 (13880). CD (EtOH; $[\Theta]\cdot 10^{-3}$ (λ in nm)): −22.3 (220), −5.4 (250). Anal. calc. for $C_{17}H_{19}N_5O_4$ (357.40): C 57.13, H 5.36, N 19.60; found: C 57.00, H 5.52, N 19.41.

To a soln. of **10** (49 mg, 0.14 mmol) in CH_2Cl_2 (2 ml) and anh. pyridine (0.15 ml), a soln. of DAST (0.11 ml, 0.83 mmol) in the same solvent mixture (1.6 ml) was added, and the mixture was stirred at r.t. for 5 h. After dilution with CH_2Cl_2 (30 ml), the mixture was washed with sat. aq. $NaHCO_3$ soln. (30 ml), the aq. phase extracted with CH_2Cl_2 (5 × 35 ml), the combined org. extract dried and evaporated, and the residue submitted to CC (silica gel (50 ml), linear gradient of $CHCl_3$/MeOH 11:1 (0.35 l) in $CHCl_3$ (0.35 l)): 18 mg (48% based on the amount of consumed **10**) of **11** and 12 mg (24%) of recovered **10**.

Data of **11**: M.p. 180–181° (from EtOH). $[\alpha]_D^{25} = -71.0$ ($c = 0.65$, MeOH). TLC (*C*): R_f 0.24. UV(EtOH): 207 (28880), 260 (14600). CD (EtOH; $[\Theta]\cdot 10^{-3}$ (λ in nm)): −8.2 (217), −11.7 (260). Anal. calc. for $C_{17}H_{18}FN_5O_3$ (359.40): C 56.82, H 5.05, N 19.49; found: C 57.01, H 4.83, N 19.20.

5. *Reaction of DAST with Methyl 5-*O*-Benzoyl-β-*D*-arabinofuranoside* (**12**). The arabinoside **12** was prepared in two steps from methyl 2,3-anhydro-β-D-lyxofuranoside [17]. Standard benzoylation of the latter followed by the treatment of the syrupy 5-*O*-benzoate with KOBz in DMSO as described previously [11] gave, after CC separation, xyloside **1** (yield 23%; TLC (*A*): R_f 0.49) and syrupy arabinoside **12** (yield 22%; TLC (*A*): R_f 0.31). TLC of the mixture before CC showed the presence of two compounds with higher mobility than **1** and **12**, which were presumably the di-*O*-benzoyl derivatives of the latter and were not investigated.

To a soln. of **12** (0.32 g, 1.19 mmol) in CH_2Cl_2 (7 ml), DAST (0.95 ml, 7.18 mmol) was added and the mixture stirred at r.t. for 5 h and worked up as described for the reaction of **1**. CC (silica gel containing 20% of H_2O (*Woelm*, Germany, 80 ml), hexane/AcOEt 11:1 (400 ml), then hexane/AcOEt 1:2 (350 ml)) afforded the following syrupy-like compounds, in order of elution: *methyl 5-*O*-benzoyl-2-deoxy-2-fluoro-β-*D*-xylofuranoside* (**17**; 33 mg, 18%), *methyl 3-*O*-benzoyl-2-deoxy-2-fluoro-β-*D*-xylofuranoside* (**18**; 100 mg, 55%), *methyl 5-*O*-benzoyl-3-deoxy-3-fluoro-β-*D*-lyxofuranoside* (**14**, 45 mg, 25%), and the starting **12** (140 mg), TLC (*D*): R_f 0.69, 0.55, 0.46, and 0.19, resp.

6. *Reaction of DAST with Methyl 5-*O*-Trityl-β-*D*-arabinofuranoside* (**21**). Arabinoside **21** was prepared from D-arabinose in two steps by the following modification of a known procedure [16]: To a stirred suspension of D-arabinose (1.0 g, 6.66 mmol) in anh. MeOH (25 ml), a freshly prepared HCl soln. in MeOH (resulting from the addition of acetyl chloride (0.4 ml) to MeOH (6 ml) at 0°) was added, and stirring was continued at r.t. The mixture was homogeneous after *ca.* 5 h. After additional 0.5 h stirring, the mixture was neutralized by powdered $(NH_4)HCO_3$ to pH 7.0–7.5. Insoluble $(NH_4)HCO_3$ was filtered off and washed with MeOH (10 ml), silica gel (30 ml) was added to the combined MeOH solns., and the mixture was evaporated. The residue was put on top of a column packed with silica gel (50 ml) and submitted to CC ($CHCl_3$ (150 ml), then acetone (250 ml)): 0.86 g (79%) of oily *methyl β-*D*/α-*D*-arabinofuranoside* (**19**/**20**). ^{13}C-NMR ((D_6)DMSO): **19**/**20** 2:3; **19** 104.9 (C(1)); 78.2 (C(2)); 75.8 (C(3)); 83.9 (C(4)); 64.5 (C(5)); 55.0 (MeO); **20**: 109.6 (C(1)); 82.6 (C(2)); 77.6 (C(3)); 84.4 (C(4)); 62.0 (C(5)); 55.5 (MeO).

To a soln. of **19**/**20** (0.86 g, 5.24 mmol) in anh. pyridine (17 ml), 4-(dimethylamino)pyridine (0.71 g, 5.81 mmol) and trityl chloride (1.77 g, 6.35 mmol) were added, and the mixture was stirred first at r.t. for 18 h and then at 60–70° for 4 h. The mixture was allowed to cool to r.t. and poured into ice/water (80 ml), the org. phase separated after the ice was melted, the aq. phase washed with AcOEt (3 × 100 ml), the combined org. soln. washed with 5% aq. $NaHCO_3$ soln. (80 ml), dried, and evaporated, and the residue chromatographed (silica gel (150 ml), linear gradient (0 → 50%) of AcOEt (1.0 l) in hexane (1.0 l)): 0.97 g (46%) of **22** and 0.65 g (30%) of **21**.

*Methyl 5-*O*-Trityl-α-*D*-arabinofuranoside* (**22**): TLC (*D*): R_f 0.42. ^{1}H-NMR ($CDCl_3$): 3.42 (*dd*, $J = 2.0, 10.5$, H–C(5)); 3.66 (*s*, MeO); 3.89 (*dd*, $J = 2.5, 10.5$, H′–C(5)); 3.89 (br. *s*, H–C(3)); 3.98 (*s*, H–C(2)); 4.12 (*m*, H–C(4)); 5.00 (*s*, H–C(1)); 7.18–7.50 (*m*, 3 Ph).

β-D-Anomer **21**: M.p. 56–58° (from Et_2O/hexane). $[\alpha]_D^{25} = -52.0$ ($c = 1.0$, $CHCl_3$). TLC (*D*): R_f 0.27. Anal. calc. for $C_{25}H_{26}O_5$ (406.52): C 73.87, H 6.45; found: C 73.75, H 6.76.

As described for the reaction of **12**, **21** (0.25 g, 0.61 mmol) in CH_2Cl_2 (6 ml) was treated with DAST (0.52 ml, 3.93 mmol) at r.t. for 18 h. CC (silica gel (70 ml), linear gradient of hexane/AcOEt 3:1 (0.5 l) in hexane) gave 130 mg (52%) of **24** and 40 mg (16%) of **23**.

*Methyl 2-Deoxy-2-fluoro-5-*O*-trityl-β-*D*-ribofuranoside* (**24**): Syrup. TLC (*B*): R_f 0.41.

*Methyl 3-Deoxy-3-fluoro-5-*O*-trityl-β-*D*-lyxofuranoside* (**23**): TLC (*B*): R_f 0.27.

7. *Reaction of DAST with Methyl 5-*O*-Benzyl-α-*D*-arabinofuranoside* (**26**). Compound **26** was prepared by treatment of methyl 2,3-anhydro-5-*O*-benzyl-α-D-lyxofuranoside (**25**) [16][1b] (0.7 g, 2.96 mmol) with KOBz (1.4 g, 8.74 mmol) in DMSO (12 ml) under reflux for 1 h. Similarly to the synthesis of **12** (see above), TLC (*A*, R_f 0.31) of the residue after workup showed two main products, **26** (*D*; R_f 0.25) and a faster moving compound (*D*; R_f 0.51), probably the benzoyl derivative of **26**. The oily residue was dissolved in MeOH (40 ml), the soln. saturated at 0° with ammonia, stored at r.t. for 18 h, and evaporated, and the residue submitted to CC (silica gel (50 ml), linear gradient of hexane/AcOEt 1:1 (0.5 l) in hexane/AcOEt 1:8 (0.5 l)): syrupy **26** (0.57 g, 76%).

The reaction of **26** with DAST was performed as described previously for its β-D-anomer [11]. In contrast to the latter, **26** (0.14 g, 0.55 mmol) reacted very slowly and afforded, after stirring at r.t. for 5 h followed by standard workup and chromatography, *methyl 2,3-anhydro-5-*O*-benzyl-α-D-lyxofuranoside* (**25**; 37 mg, 53%; TLC (*D*): R_f 0.87) and *methyl 5-*O*-benzyl-3-deoxy-3-fluoro-α-D-lyxofuranoside* (**27**; 10 mg, 14% based on the amount of consumed **26**; TLC (*D*): R_f 0.64), and recovered **26** (65 mg). ^{1}H- and ^{13}C-NMR for **27**: in fair agreement with those previously reported for the same compound obtained by an alternative method [1i].

REFERENCES

[1] a) I. A. Mikhailopulo, T. I. Pricota, N. E. Poopeiko, G. G. Sivets, E. I. Kvasyuk, T. V. Sviryaeva, L. P. Savochkina, R. Sh. Beabealashvilli, *FEBS Lett*. **1989**, *250*, 139; b) I. A. Mikhailopulo, N. E. Poopeiko, T. I. Pricota, G. G. Sivets, E. I. Kvasyuk, J. Balzarini, E. De Clercq, *J. Med. Chem*. **1991**, *34*, 2195; c) I. A. Mikhailopulo, G. G. Sivets, T. I. Pricota, N. E. Poopeiko, J. Balzarini, E. De Clercq, *Nucleosides Nucleotides* **1991**, *10*, 1743; d) I. A. Mikhailopulo, T. I. Pricota, N. E. Poopeiko, T. V. Klenitskaya, N. B. Khripach, *Synthesis* **1993**, 700; e) I. A. Mikhailopulo, G. G. Sivets, N. E. Poopeiko, N. B. Khripach, *Nucleosides Nucleotides* **1995**, *14*, 383; f) I. A. Mikhailopulo, G. G. Sivets, N. E. Poopeiko, N. B. Khripach, *ibid*. **1995**, *14*, 381; g) N. E. Poopeiko, J. Poznanski, I. A. Mikhailopulo, D. Shugar, T. Kulikowski, *ibid*. **1995**, *14*, 435; h) E. N. Kalinichenko, T. L. Podkopaeva, N. E. Poopeiko, M. Kelve, M. Saarma, I. A. Mikhailopulo, J. E. van den Boogaart, C. Altona, *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 43; i) I. A. Mikhailopulo, G. G. Sivets, N. E. Poopeiko, N. B. Khripach, *Carbohydr. Res.* **1995**, *278*, 71; j) G. V. Zaitseva, G. G. Sivets, Z. Kazimierczuk, J. Vilpo, I. A. Mikhailopulo, *Bioorg. Med. Chem. Lett*. **1995**, *5*, 2999; k) N. E. Poopeiko, N. B. Khripach, Z. Kazimierczuk, J. Balzarini, E. De Clercq, I. A. Mikhailopulo, *Nucleosides Nucleotides* **1997**, *16*, 1083; (l) G. V. Zaitseva, A. I. Zinchenko, V. N. Barai, N. I. Pavlova, E. I. Boreko, I. A. Mikhailopulo, *ibid*. **1999**, *18*, 687; m) I. A. Mikhailopulo, G. G. Sivets, N. B. Khripach, *ibid*. **1999**, *18*, 689.

[2] F. Viani, in 'Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedical Targets', Ed. V. A. Soloshonok, John Wiley & Sons Ltd., 1999, Chapt. 13, pp. 419–449.

[3] Z. G. Chidgeavadze, A. V. Scamrov, R. Sh. Beabealashvilli, E. I. Kvasyuk, G. V. Zaitseva, I. A. Mikhailopulo, G. Kowollik, P. Langen, *FEBS Lett*. **1985**, *183*, 275; G. V. Zaitseva, E. I. Kvasyuk, N. E. Poopeiko, T. I. Kulak, V. E. Pashinnik, V. I. Tovstenko, L. N. Markovskii, I. A. Mikhailopulo, *Bioorg. Khim*. **1988**, *14*, 1275; E. I. Kvasyuk, G. V. Zaitseva, L. P. Savochkina, I. A. Mikhailopulo, Z. G. Chidgeavadze, R. Sh. Beabealashvilli, P. Langen, *ibid*. **1989**, *15*, 781; G. E. Wright, N. C. Brown, *Pharmacol. Ther.* **1990**, *47*, 447; A. A. Krayevsky, K. A. Watanabe, 'Modified Nucleosides as anti-AIDS Drugs: Current Status and Perspectives', Bioinform, Moscow, 1993, p. 211.

[4] R. H. Griffey, E. Lesnik, S. Freier, Y. S. Sanghvi, K. Teng, A. Kawasaki, C. J. Guinosso, P. D. Wheeler, V. Mohan, P. Dan Cook, in 'American Chemical Society Symposium Series 580. Carbohydrate Modifications in Antisense Research', Eds. Y. S. Sanghvi and P. Dan Cook, American Chemical Society, Washington, DC, 1994, Chapt. 14, p. 212.

[5] J. E. van den Boogaart, E. N. Kalinichenko, T. L. Podkopaeva, I. A. Mikhailopulo, C. Altona, *Eur. J. Biochem*. **1994**, *221*, 759.

[6] M. R. Player, P. F. Torrence, *Pharmacol. Ther.* **1998**, *78*, 55.

[7] H. Ikeda, R. Fernandez, A. Wilk, J. J. Barchi, Jr., X. Huang, V. E. Marquez, *Nucleic Acids Res.* **1998**, *26*, 2237.

[8] B. Reif, V. Wittmann, H. Schwalbe, C. Griesinger, K. Woerner, K. Jahn-Hofmann, J. W. Engels, *Helv. Chim. Acta* **1997**, *80*, 1952.

[9] P. Herdewijn, A. Van Aerschot, L. Kerremans, *Nucleosides Nucleotides* **1989**, *8*, 65.

[10] H. Vorbrueggen, in 'Nucleoside Analogues. Chemistry, Biology, and Medical Applications', Eds. R. T. Walker, E. De Clercq, and F. Eckstein, Plenum Press, New York, 1979, Vol. 26, Ser. A, NATO Advanced Study Institute, pp. 35–69.

[11] I. A. Mikhailopulo, G. G. Sivets, *Synlett* **1996**, 173.
[12] J. Moravcova, J. Capkova, J. Stanek, *Carbohydr. Res.* **1994**, *263*, 61.
[13] C. R. Johnson, D. R. Bhumralkar, *Nucleosides Nucleotides* **1995**, *14*, 185.
[14] W. A. Szarek, A. Zamojski, H. N. Tiwari, E. R. Ison, *Tetrahedron Lett*. **1986**, *27*, 3827.
[15] A. A. Akhrem, E. K. Adarich, L. N. Kulinkovich, I. A. Mikhailopulo, E. B. Poschastieva, V. A. Timoshchuk, *Dokl. Akad. Nauk SSSR* **1974**, *219*, 99; N. E. Poopeiko, E. I. Kvasyuk, I. A. Mikhailopulo, M. J. Lidaks, *Synthesis* **1985**, 605; J. A. Maurins, R. A. Paegle, M. J. Lidaks, E. I. Kvasyuk, I. A. Mikhailopulo, *Bioorg. Khim*. **1986**, *12*, 1514.
[16] R. K. Ness, H. G. Fletcher, Jr., *J. Am. Chem. Soc*. **1958**, *80*, 2007.
[17] B. R. Baker, R. E. Schaub, J. H. Williams, *J. Am. Chem. Soc*. **1955**, *77*, 7.
[18] A. A. Akhrem, I. A. Mikhailopulo, A. F. Abramov, *Org. Magn. Res.* **1979**, *12*, 247.
[19] J. van Wijk, C. Altona, 'PSEUROT 6.2. A Program for the Conformational Analysis of the Five-Membered Rings', University Leiden, July, 1993; C. A. G. Haasnot, F. A. A. M. de Leeuw, C. Altona, *Tetrahedron* **1980**, *86*, 2783, L. J. Rinkel, C. Altona, *J. Biomol. Struct. Dyns.* **1987**, *4*, 621.
[20] A. S. Serianni, in 'NMR of Biological Macromolecules', 'NATO ASI Series H, Cell Biology', Vol. 87, Ed. C. I. Stassinopoulou, Springer-Verlag, Berlin, 1994, p. 293; C. A. Podlasek, J. Wu, W. A. Stripe, P. B. Bondo, A. S. Serianni, *J. Am. Chem. Soc*. **1995**, *117*, 8635; C. A. Podlasek, W. A. Stripe, I. Carmichael, M. Shang, B. Basu, A. S. Serianni, *J. Am. Chem. Soc*. **1996**, *118*, 1413.
[21] C. Thibaudeau, J. Plavec, J. Chattopadhyaya, *J. Org. Chem*. **1998**, *63*, 4967.
[22] F. Seela, H. Debelak, H. Reuter, G. Kastner, I. A. Mikhailopulo, *Tetrahedron* **1999**, *55*, 1295.
[23] W. Guschlbauer, K. Jankowski, *Nucleic Acids Res.* **1980**, *8*, 1421; D. M. Cheng, L.-S. Kan, P. O. P. Ts'o, Y. Takatsuka, M. Ikehara, *Biopolymers* **1983**, *22*, 1427.
[24] J. Raap, J. H. van Boom, H. C. van Lieshout, C. A. G. Haasnot, *J. Am. Chem. Soc*. **1988**, *110*, 2736.

Received August 20, 1999