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# Oxidation–reduction sequence for the synthesis of peracylated fluorodeoxy pentofuranosides ☆

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**Abstract**

The oxidation of methyl 5-*O*-benzyl-3(2)-deoxy-3(2)-fluoro-α-D-pentofuranosides with dimethyl sulfoxide–acetic (trifluoroacetic) anhydride was accompanied by epimerization at the carbon atom bearing a fluoro function, resulting in the formation of the corresponding 2- or 3-keto derivatives as mixtures of two epimers in high combined yield. Reduction of a mixture of the *erythro/threo* epimeric 2-keto sugars (isolated as stable hydrates) with sodium borohydride in benzene–ethanol proceeded stereoselectively leading to the formation of 3-deoxy-3-fluoro ribo- and lyxo-furanosides, respectively. In the case of the *ribo* and *arabino* epimers of the 3-keto sugar (isolated as free ketones), reduction stereoselectivity of the former was > 95% for the 2-deoxy-2-fluoro *ribo* sugar, whereas a ca. 3:1 *lyxo/arabino* ratio of products was obtained for the latter. Treatment of a mixture of the 2-epimeric 3-keto sugars with triethylamine in carbon tetrachloride at room temperature for 3–5 h afforded the 2-deoxy-2-fluoro *ribo* ketone (ca. 90%). The synthesis of 1-*O*-acetyl-2,5-di-*O*-benzoyl-3-deoxy-3-fluoro-α,β-D-lyxofuranose (**8**) and 1-*O*-acetyl-3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-β-D-ribofuranose (**16**) and their use as glycosylating agents for bis-trimethylsilylated $N^6$-benzoyladenine is described.

*Keywords:* Fluorodeoxy pentofuranosides; Keto sugars; Epimerization

## 1. Introduction

Recently, we have shown that oxidation of methyl 5-*O*-benzyl-3-deoxy-3-fluoro-α-D-arabinofuranoside (**1a**) with dimethyl sulfoxide–acetic anhydride at room temperature

☆ For preliminary reports, see refs [1,2].

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results in the formation of a mixture of the epimeric ketones **2** and **3** as hydrates in the ratio of ca. 2:1 [3]. Reduction of this mixture with sodium borohydride, followed by benzoylation and chromatography, afforded the corresponding derivatives of 3-deoxy-3-fluoro-α-D-ribo- and -lyxo-furanosides, **5b** and **4b**, respectively, as the main products of the sequence in moderate combined yield. From the viewpoint of simplicity, this oxidation–reduction procedure to prepare **5b** appeared, however, to be more practical than the previously published route which involved inversion of configuration at C-2 of **1a** via tosylation followed by nucleophilic displacement of sulfonate ester by benzoate ion [4]. This prompted us to investigate the oxidation–reduction sequence in more detail, aiming at a convenient synthesis of riboside **5b**.

As a continuation of this study, the application of this methodology to methyl 2-deoxy-2-fluoro-α-D-arabinofuranoside (**10a**) was also investigated. The work presented here provides a convenient method for the synthesis on a preparative scale of crystalline 1-*O*-acetyl-3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-β-D-ribofuranose (**16**). The use of the latter as a glycosylating agent is illustrated by the reaction with bis-trimethylsilylated $N^6$-benzoyladenine to give 9-(2-deoxy-2-fluoro-β-D-ribofuranosyl)adenine (**17**) and its α-anomer (**18**) after deprotection and chromatographic separation.

## 2. Results and discussion

A careful study of oxidation of **1a** with dimethyl sulfoxide–acetic anhydride at room temperature showed that mixtures of epimeric *gem*-diols **2** and **3** are formed in ratios of 2:1 to 4:1 as judged by $^1$H and $^{13}$C NMR data (Tables 1–3). Reduction of the crude **2** and **3** with sodium borohydride in ethanol led to a mixture of alcohols that could not be cleanly separated by column chromatography. However, after benzoylation, chromatography on a preparative scale readily afforded pure riboside **5b**, and lyxoside **4b** together with minor products. Debenzoylation of the latter followed by column chromatography permitted isolation of pure lyxoside **4a**; in some experiments, the starting arabinoside **1a** and the 2-*O*-methylthiomethyl ether derivative **1c**, were also isolated at this stage of purification. The use of sodium borohydride, freshly recrystallized from methyl cellosolve, and 4:1 to 1:1 benzene–ethanol mixtures as solvent, gave better results in terms of both yield of the desired **5b** (43–52%) and chromatographic separation. In contrast, reduction in pyridine gave rise to a more complex mixture of products from which **5b**, **1a**, **4a**, and xyloside **6a** were isolated in yields of 21, 4, 3.6, and 0.6%, respectively (Scheme 1).

The use of sodium borodeuteride as reducing agent in the second step of the reaction sequence afforded the 2(*S*)- and 2(*R*)-deuterio derivatives of **5b** and **4b**, respectively. No deuterium was found according to $^1$H NMR data in compound **1a** isolated from the reaction mixture; xyloside **6a** was not isolated in this experiment. These data imply that the presence of **1b** in the reaction mixture was due either to a side reaction of glycoside **1a** upon oxidation, namely acylation, or to some starting **1a** that remained unchanged during the oxidation process. From these results, it may be reasonably concluded that reduction of ketone **2** proceeds stereoselectively via attack by the $BH_4^-$ anion at the less hindered β-face of the sugar ring, leading to exclusive formation of the riboside **5a** (isolated as benzoate **5b**). Surprisingly, the isomeric ketone **3** undergoes predominant

Table 1
$^1$H NMR spectral data of 3-deoxy-3-fluoro sugars and nucleoside **9** [a] ($\delta$)

| Compound | H-1 (H-1′) | H-2 (H-2′) | H-3 (H-3′) | H-4 (H-4′) | H-5 (H-5′) | H-5′ (H-5″) | Others |
|---|---|---|---|---|---|---|---|
| **1a** | 4.87 s | 4.04 d | 4.77 dd | 4.33 ddt | 3.66 dd | 3.61 dd | 7.26–7.35 (m, *Ph*$CH_2$), 4.59 (d, Ph*$CH_2$*), 4.50 (d, Ph$CH_2$), 3.36 (s, $OCH_3$) |
| **1b** | 5.09 s | 5.41 dd | 5.07 ddd | 4.47 ddt | 3.75 dd | 3.71 dd | 7.27–8.17 (m, arom.), 4.62 (s, Ph*$CH_2$*), 3.47 (s, $OCH_3$) |
| **1c** | 4.96 s | 4.39 dd | 4.86 ddd | 4.35 ddt | 3.65 d | | 7.28–7.35 (m, *Ph*$CH_2$), 4.67 (s, $CH_2S$) 4.61 (s, Ph*$CH_2$*), 3.41 (s, $OCH_3$), 2.16 (s, $CH_3S$) |
| **2** | 4.67 s | — | 4.49 dd | 4.40 dm | 3.69 d | | 7.32–7.38 (m, *Ph*$CH_2$), 4.64 (d, Ph*$CH_2$*), 4.57 (d, Ph*$CH_2$*), 3.46 (s, $OCH_3$), 5.17 (d, $J$ = 8.4 Hz, 2-OH), 5.02 (d, $J$ 8.4 Hz, 2-OH) |
| **3** | 4.86 d | — | ~ 4.70 dd | 4.48 dm | 3.74 dd | 3.68 ddd | 7.32–7.38 (m, *Ph*$CH_2$), 4.64 (d, Ph*$CH_2$*), 4.54 (d, Ph*$CH_2$*), 3.58 (s, $OCH_3$), 5.28 (d, $J$ = 6.5 Hz, 2-OH), 5.02 (d, $J$ 7.0 Hz, 2-OH) |
| **4a** | 4.86 t | 4.10 m | 5.26 ddd | 4.35 ddt | 3.75 ddd | 3.63 ddd | 7.27–7.38 (m, *Ph*$CH_2$), 4.61 (s, Ph*$CH_2$*), 3.48 (s, $OCH_3$) |
| **5a** | 4.95 d | 4.23 m | 4.82 ddd | 4.41 dm | 3.63 dd | 3.57 dd | 7.15–7.30 (m, *Ph*$CH_2$), 4.58 (d, Ph*$CH_2$*), 4.51 (d, Ph*$CH_2$*), 3.49 (s, $OCH_3$), |
| **6a** | 5.07 d | 4.36 m | 4.94 ddd | 4.38 dm | 3.71 dd | 3.64 ddd | 7.25–7.39 (m, *Ph*$CH_2$), 4.63 (d, Ph*$CH_2$*), 4.54 (d, Ph*$CH_2$*), 3.50 (s, $OCH_3$), |
| **7** | 5.37 s | 5.34 ddd | 5.49 ddd | 4.69 | ↔ | 4.56 | 7.42–8.10 (m, arom.), 3.48 (s, $OCH_3$) |
| **9** | 5.93 d | 5.23 dm | 5.10 dt | 4.60 ddt | 3.66 m | 3.56 m | 8.39 (s, H-8), 8.16 (s, H-2), 7.34 (s, $NH_2$), 4.91 (t, 5′-OH), 3.30 (d, 2′-OH) |

[a] The spectra of sugars and nucleoside were measured in $CDCl_3$ and $Me_2SO$-$d_6$ solutions, respectively.

Table 2
Coupling constants ($J$, Hz) for the $^1$H NMR data of 3-deoxy-3-fluoro sugars and nucleoside **9** [a]

| Compound | 1,2 (1′,2′) | 2,3 (2′,3′) | 3,4 (3′,4′) | 4,5 (4′,5′) | 4,5′ (4′,5″) | 2,F (2′,F) | 3,F (3′,F) | 4,F (4′,F) | Others |
|---|---|---|---|---|---|---|---|---|---|
| **1a** | < 1.0 | < 1.0 | 1.8 | 2.4 | 2.4 | 12.9 | 51.6 | 26.1 | 10.8 (*5,5′*) |
| **1b** | < 1.0 | 1.2 | 4.2 | 4.8 | 4.8 | 15.9 | 51.6 | 22.1 | 10.8 (*5,5′*) |
| **1c** | < 1.0 | 1.8 | 4.8 | 4.7 | 4.7 | 16.8 | 54.0 | 20.4 | |
| **2** | — | — | 1.8 | 3.6 | 3.6 | — | 54.0 | 26.4 | |
| **3** | — | — | 2.8 | 5.5 | 6.0 | — | ~ 54.0 | 27.2 | 10.0 (*5,5′*), 1.8 (*5′,F*) 1.2 (*1,F*) |
| **4a** | 1.8 | 5.1 | 5.7 | 4.2 | 3.6 | 7.2 | 53.7 | 15.9 | 10.8 (*5,5′*), 1.8 (*1,F*), 1.8 (*5,F*), 1.8 (*5′,F*) |
| **5a** | 4.8 | 5.1 | 1.2 | 3.3 | 3.3 | 22.8 | 56.4 | 26.4 | 10.5 (*5,5′*) |
| **6a** | 4.9 | 2.4 | 3.7 | 4.9 | 6.7 | 19.6 | 52.8 | 25.0 | 10.5 (*5,5′*), 1.2 (*5′,F*) |
| **7** | < 1.0 | 4.8 | 3.0 | n.d. | n.d. | 15.3 | 52.2 | n.d. | |
| **9** | 7.2 | 2.4 | 1.8 | 6.6 | 6.6 | 27.6 | 54.0 | 31.2 | 12.0 (*5′,5″*), 4.8 (*5′,OH*), 4.8 (*5″,OH*), 7.8 (*2′,OH*) |

[a] The $^1J_{H,H}$ of Ph$CH_2$ was found to be 12.0 Hz for all compounds but **1b**, **1c**, and **4a**. n.d.—not determined.

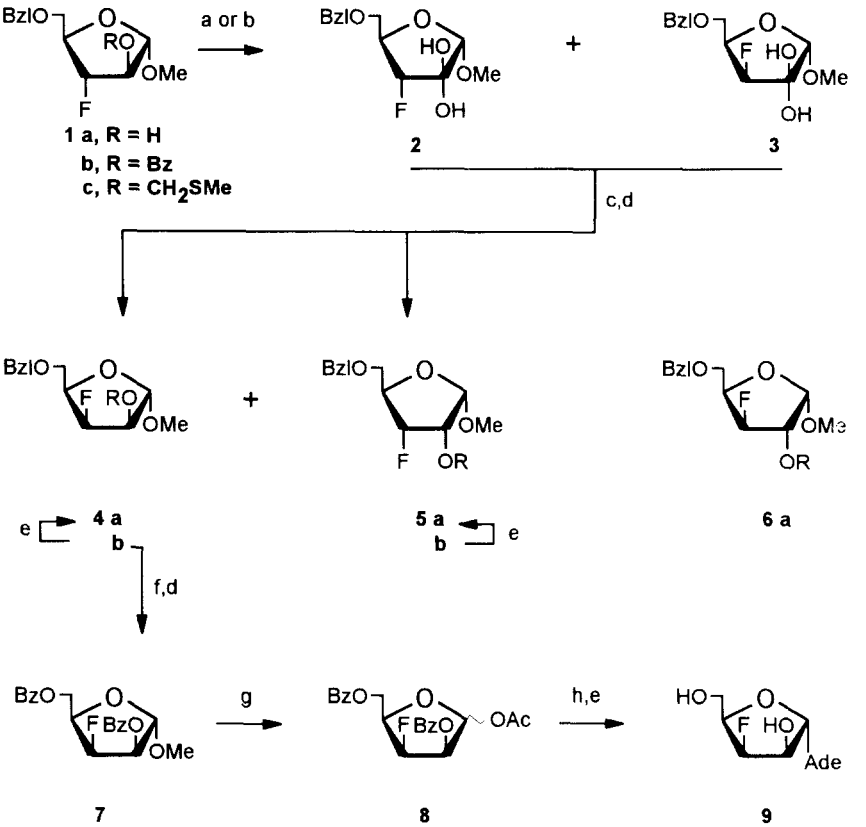
attack at the $\alpha$-face of the sugar ring, suggesting negligible steric and/or electronic hindrance from the methoxyl group on the one hand, and significant hindrance (probably electronic) from the fluorine atom on the other. In this context, it is interesting that Morizawa et al. [5] mentioned, without providing experimental details, that a similar oxidation–reduction procedure applied to methyl 5-*O*-benzyl-3-deoxy-3-fluoro-$\beta$-D-arabinofuranoside did not result in epimerization at C-2, implying predominant attack by the $BH_4^-$ anion at the $\alpha$-face.

Further support for the above considerations on the stereochemistry of sodium

Table 3
$^{13}$C NMR spectral data of some 3-deoxy-3-fluoro sugars in $CDCl_3$

| Compound | Chemical shifts [a] ($\delta$) ($^1J_{C,H}$ coupling constants, Hz) | | | | | | $J_{C,F}$ coupling constants (Hz) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | C-1 | C-2 | C-3 | C-4 | C-5 | OMe | C-1,F | C-2,F | C-3,F | C-4,F | C-5,F |
| **1a** | 110.1 (172.5) | 77.7 (150.0) | 97.3 (165.0) | 83.2 (150.0) | 69.3 (141.0) | 55.1 (142.5) | < 2.0 | 24.4 | 187.4 | 27.1 | 9.1 |
| **5a** | 102.5 (177.5) | 72.4 (150.0) | 91.1 (163.7) | 82.0 (150.0) | 69.1 (142.6) | 55.7 (140.8) | < 2.0 | 16.0 | 183.3 | 24.2 | 11.1 |
| **2** | 106.0 (176.3) | 99.2 | 93.7 (165.0) | 81.5 (150.0) | 69.3 (140.0) | 55.5 (142.5) | < 2.0 | 18.3 | 191.6 | 26.0 | 8.1 |
| **3** | 98.1 (176.3) | | 86.7 (157.5) | 76.4 (150.0) | 67.6 (140.0) | 56.0 (142.5) | < 2.0 | | 195.8 | 26.0 | < 2.0 |
| **4a** | 108.1 (173.6) | 74.8 [b] (153.5) | 91.2 (162.0) | 76.6 [b] (145.9) | 67.1 (143.4) | 55.6 (142.6) | < 2.0 | 15.8 [b] | 192.2 | 14.0 [b] | 9.2 |
| **6a** | 101.7 (173.6) | 76.5 [b] (151.0) | 97.1 (166.1) | 77.3 [b] (144.9) | 67.4 (139.6) | 56.1 (143.4) | 4.5 | 28.9 [b] | 181.2 | 20.4 [b] | 10.4 |

[a] The $^{13}$C resonances of benzyl groups were at ca. 73.5 (s, $CH_2$; $^1J_{C,H}$ = 142.5 Hz), 127.7–128.3 (*meta* and *para*), 128.5 (*ortho*), 136.6–137.6 (*ipso*) ppm.
[b] The data ($\delta$ and related $^2J_{C\text{-}2,F}$ and $^2J_{C\text{-}4,F}$) may be interconvertible.




Scheme 1. (a) $Ac_2O$, $Me_2SO$, 20°C, 20 h (**2**/**3**, 2:1 to 4:1; 85–95%); (b) $(CF_3CO)_2O$, $Me_2SO$, $CH_2Cl_2$, −78°C, 30 min, $Et_3N$ (**2**–**3**, 6:1 to 8:1; 90–97%); (c) $NaBH_4$, EtOH or EtOH–benzene, 1:4 to 1:1, ($NaBD_4$, $CD_3OD$), 20°C, 2–20 h; (d) BzCl, pyridine, 20°C, 24 h; (e) saturated at 0°C methanolic ammonia, 20°C, 24 h; (f) $H_2$, 10% Pd–C, EtOH, 20°C, 72 h (f+d, Σ 85%); (g) AcOH–$Ac_2O$–$H_2SO_4$ (14.3:1.70:1.0, v/v), 20°C, 20 h (88%); (h) **8**–persilylated $N^6$-benzoyladenine–$SnCl_4$, (1.0:1.0:2.1, mol), 1,2-dichloroethane, 20°C, 18 h [h+e, **9** (64%)].

borohydride reduction of **2** and **3** was found in an examination of this reaction with purified *gem*-diols. We have examined the chromatographic separation of a mixture of **2** and **3** under a number of different conditions (adsorbents and eluents) and found that, on a column of Silica Gel Woelm (20% water) eluted with a linear diethyl ether gradient in hexane, a partial separation occurred, giving two fractions. The faster migrating mixture contained roughly 80% of **3** ($^1$H NMR; see the Experimental section) as well as a new product having an $R_f$ greater than those of **2** and **3**; the more slowly migrating fraction consisted of a mixture of **2** (ca. 60%) together with a new product (ca. 40%) that also displayed higher TLC mobility than both **2** and **3**. Both unidentified products displayed the same TLC mobility in a variety of systems, whereas the *gem*-diols **2** and **3** are readily separated by TLC. Reduction of the faster fraction with sodium borohydride in ethanol gave the lyxoside **4a** in a yield of ca. 85% ($^1$H NMR). Unexpectedly, similar reduction of the slower fraction led, essentially quantitatively, to **5a**. These data tend to

suggest that each fraction consisted of the ketone and its *gem*-diol derivative. It also appears that chromatography on a column of Silica Gel Woelm does not lead to complete dehydration of the *gem*-diols, which would lead to inseparable mixtures of the corresponding ketones. The partial formation of the free ketones is likely to be a consequence of evaporation of pooled fractions.

These combined data led us to conclude that, in order to achieve a better yield of the desired **5a,b**, 3-epimerization should be inhibited. For this purpose, we have examined the conversion of **1a** to *gem*-diols using dimethyl sulfoxide–trifluoroacetic anhydride [6]. Indeed, oxidation of the arabinoside **1a** with this reagent in dichloromethane, followed by quenching with triethylamine at −78°C, afforded mixtures of *gem*-diols **2** and **3** in ratios of 6:1 to 8:1 according to $^1$H NMR data. Reduction of the crude mixture of **2** and **3** with sodium borohydride in 4:1 benzene–ethanol followed by benzoylation and column chromatography yielded 65–77% of **5b**. Once again, the lyxoside **4a** and, in some experiments, the aforementioned minor products were also isolated. No decrease in yield of **5b** in larger scale preparations (ca. 5 g of **1a**) was observed. This oxidation–reduction sequence therefore offers a useful alternative to the previously described [4] two-step route.

It should be emphasized that none of the corresponding $\beta$ anomers of **1–6** were detected ($^1$H and $^{13}$C NMR spectroscopy) in the mixtures of *gem*-diols or in either of the purified products under any of the oxidation–reduction conditions investigated.

A mixture of *gem*-diols **2** and **3** was also obtained upon oxidation of the lyxoside **4a**. Unlike **1a**, however, the lyxoside **4a** underwent no significant oxidation with dimethyl sulfoxide–trifluoroacetic anhydride at −78°C for 1 h. It was necessary to conduct the reaction at room temperature for 1 h in order to reach roughly 50% conversion to a mixture of **2** and **3**. As might be expected, under these vigorous conditions, the oxidation is accompanied by intense epimerization and the **2**/**3** ratio was found to be 3.5:1.

The assignments of configuration for all the compounds synthesized were based primarily upon $^{13}$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 $\delta(^{13}C)$ values of the atoms bearing these groups [7]. For example, in the riboside **5a**, as compared with the arabinoside **1a**, vicinal eclipsing interaction exists between the 1,2-*cis* and 2,3-*cis* substituents, which shifts the signals of C-1, C-2, and C-3 upfield by 7.6, 5.3, and 6.2 ppm, respectively. Similarly, when passing from the lyxoside **4a** to the xyloside **6a**, (*i*) the C-1 and C-3 resonances are shifted upfield (6.4 ppm) and downfield (5.9 ppm), respectively, and (*ii*) the C-2 resonance is shifted downfield (ca. 1.7 ppm), as a result of the introduction of 1,2-eclipsing and removal of 2,3-eclipsing. By analogy, the C-4 resonances of the epimeric pair **1a** and **5a** with the D-*erythro* configuration at C-3 and C-4 are shifted downfield by ca. 5.6 ppm compared with the other pair, **4a** and **6a** with the D-*threo* configuration. Note that the 3,4-*cis* relationship of the fluorine atom and $CH_2OBzl$ group leads to a ca. 2 ppm downfield shift for C-5 of **4a** and **6a** vs. **1a** and **5a** with *trans*-location of the same substituents. The $J_{CF}$ coupling constants recorded for **1a** and **5a** are in good agreement with those previously reported for closely related compounds [8].

The most striking findings are the variations observed in the chemical shifts of C-1 and C-3 of the *gem*-diols **2** and **3** on the one hand, and **2** and its D-*erythro* precursors **1a**

Table 4
$^1$H NMR spectral data of 2-deoxy-2-fluoro sugars and nucleosides [a] ($\delta$)

| Compound | H-1 (H-1′) | H-2 (H-2′) | H-3 (H-3′) | H-4 (H-4′) | H-5 (H-5′) | H-5′ (H-5″) | Others |
|---|---|---|---|---|---|---|---|
| **10a** | 5.06 d | 4.82 dd | 4.00 ↔ 4.20 m | | 3.62 d | | 7.28–7.38 (m, *Ph*CH$_2$), 4.58 (s, PhC*H*$_2$), 3.40 (s, OCH$_3$) |
| **10b** | 5.12 br d | 4.86 br d. | 5.12 br dd | 4.22 m | 3.77 dd | 3.70 dd | 7.25–7.38 (m, *Ph*CH$_2$), 4.64 (s, PhC*H*$_2$), 3.42 (s, OCH$_3$), 2.10 (s, CH$_3$CO) |
| **10c** | 5.06 br d | 4.92 br d | 4.34 dd | 4.16 dt | | 3.67 d | 7.26–7.40 (m, *Ph*CH$_2$), 4.74 (d, PhC*H*$_2$), 4.64 (d, PhC*H*$_2$), 4.62 (d, *J* 1.8 Hz, OC*H*$_2$SCH$_3$), 3.42 (s, OCH$_3$), 2.08 (SCH$_3$) |
| **11** | ~ 5.32 [b] | 4.58 dd | — | 4.30 br q | 3.84 dd | 3.78 dd | 7.20–7.40 (m, *Ph*CH$_2$), 4.62 (s, PhC*H*$_2$), 3.53 (s, OCH$_3$) |
| **12** | 5.30 br d | 5.16 ddd | — | 4.14 br t | | 3.75 d | 7.20–7.40 (m, *Ph*CH$_2$), 4.50 (d, PhC*H*$_2$), 4.57 (d, PhC*H*$_2$), 3.53 (s, OCH$_3$) |
| **13a** | 5.06 d | 4.91 ddd | 4.17 [b] | 4.26 [b] | | 3.62 d | 7.24–7.40 (m, *Ph*CH$_2$), 4.50 (d, PhC*H*$_2$), 4.60 (d, PhC*H*$_2$), 3.50 (s, OCH$_3$) |
| **14a** | 5.08 d | 4.77dd | c | 4.27 m | 3.84 dd | 3.75 dd | 7.28–7.38 (m, *Ph*CH$_2$), 4.68 (d, PhC*H*$_2$), 4.57 (d, PhC*H*$_2$), 3.38 (s, OCH$_3$) |
| **15** | 5.18 dd | 5.12 ddd | 5.46 dt | 4.62 m | 4.71 dd | 4.54 dd | 7.37–8.10 (m, 2Bz), 3.55 (s, OCH$_3$) |
| **16** | 6.39 d | 5.25 dd | 5.60 ddd | 4.71 ↔ 4.82 m | | 4.47 dd | 7.35–8.10 (m, 2Bz), 1.94 (s, OAc) |
| **17** | 6.24 dd | 5.44 ddd | 4.49 dm | 4.00 m | 3.76 ddd | 3.58 ddd | 8.37 (s, H-8), 8.16 (s, H-2), 7.39 (s, NH$_2$), 5.65 (d, 3′-OH), 5.33 (t, 5′-OH) |
| **18** | 6.47 dd | 5.20 dt | 4.39 dm | 4.22 m | 3.68 ddd | 3.50 ddd | 8.22 (d, H-8), 8.15 (s, H-2), 7.36 (s, NH$_2$), 5.92 (d, 3′-OH), 5.00 (t, 5′-OH) |

[a] The spectra of sugars and nucleosides were measured in $CDCl_3$ and $Me_2SO$-$d_6$ solutions, respectively.
[b] The poorly resolved multiplet.
[c] The value was not determined owing to overlap by an intense low-field doublet of the PhC*H*$_2$ methylene group.

and **5a** as well as **3** and its D-*threo* counterparts **4a** and **6a**, on the other. In the first case, the most probable explanation may be the different conformational disposition of the C-1 carbon atom and fluorine atom in the $\gamma$-position, i.e. the *anti*-periplanar or *gauche* (*syn*-clinal) arrangement [9]. Note that conformational mobility of both epimeric *gem*-diols may be restricted by the formation of intramolecular hydrogen bonds between methoxyl and 2-hydroxyl groups. As for the second point, the chemical shift values for C-1 and C-3 of the *gem*-diol **2** are the semi-sum of the $\delta(^{13}C)$ values for the corresponding carbon atoms of **1a** and **5a**, implying a mutual compensation of the effects of the *gem*-hydroxyl groups vs. the 2(*S*)- and 2(*R*)-hydroxyl groups of **1a** and **5a**, respectively. Contrary to this, the C-1 and C-3 nuclei of **3** resonate at higher field than the same nuclei of both **4a** and **6a**. Clearly, a detailed conformational analysis of these compounds is necessary for the interpretation of these data, even on semi-quantitative level.

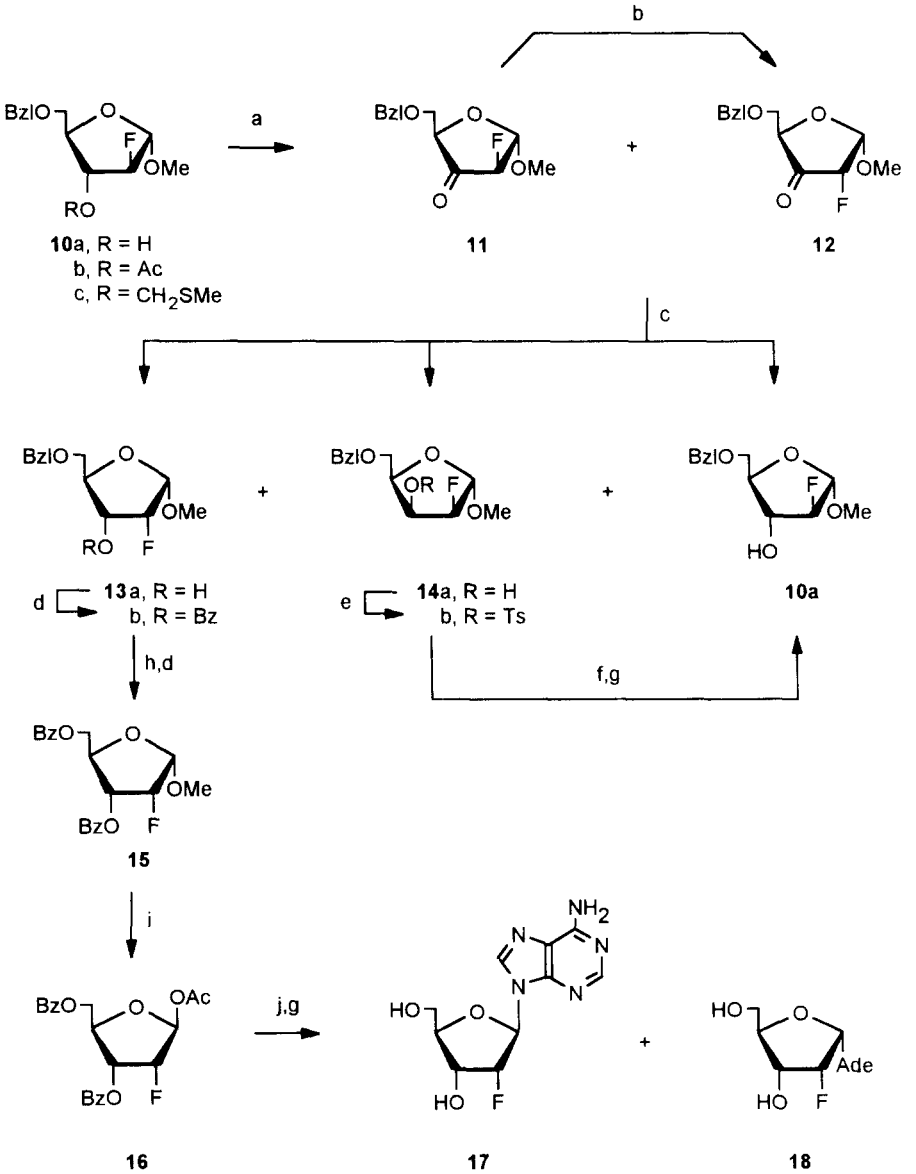
Starting from **4b**, 9-(3-deoxy-3-fluoro-$\alpha$-D-lyxofuranosyl)adenine (**9**) was prepared essentially as described earlier [4]. Catalytic hydrogenolysis of **4b** in the presence of 10% Pd/C in ethanol followed by standard benzoylation gave **7**, which was converted to the acetate **8** by acetolysis in a 72% combined yield. Condensation of the latter with persilylated $N^6$-benzoyladenine in the presence of excess tin(IV) chloride (1.0:1.0:2.1, mol) [10,11] in 1,2-dichloroethane at room temperature, followed by debenzoylation, afforded **9** in 64% yield (Scheme 1). The structure of **9** was proved by UV, CD, and $^1$H NMR data (see the Experimental section and Tables 1 and 2). As reported for 9-($\alpha$-D-lyxofuranosyl)adenine [12], the lyxoside **9** displays a positive $B_{2u}$ Cotton effect; in contrast, the envelope centred at 212 nm is negative.

In extension of this work, we have investigated the application of the oxidation–reduction procedure to methyl 5-*O*-benzyl-2-deoxy-2-fluoro-$\alpha$-D-arabinofuranoside (**10a**), aiming, inter alia, at the development of a practical synthesis of a universal glycosylat-

Table 5
Coupling constants ($J$, Hz) for the $^1$H NMR data of 2-deoxy-2-fluoro sugars and nucleosides

| Compound | 1,2 (1′,2′) | 2,3 (2′,3′) | 3,4 (3′,4′) | 4,5 (4′,5′) | 4,5′ (4′,5″) | 1,F (1′,F) | 2,F (2′,F) | 3,F (3′,F) | Others [a] |
|---|---|---|---|---|---|---|---|---|---|
| **10a** | < 1.0 | < 1.0 | b | 5.0 | 5.0 | 10.0 | 50.0 | b | |
| **10b** | < 1.0 | < 1.0 | ~ 4.0 | 3.8 | 5.5 | ~ 11.0 | 49.5 | ~ 24.0 | 10.0 (*5,5″*) |
| **10c** | < 1.0 | < 1.0 | 5.5 | 5.0 | 5.0 | ~ 13.0 | 52.0 | 24.0 | |
| **11** | 1.5 | — | — | 1.5 | 2.5 | ~ 9.0 | 50.5 | — | 3.5 (*4,F*), < 1.0 (*2,4*) 10.0 (*5,5″*) |
| **12** | 4.5 | — | — | 2.5 | 2.5 | < 1.0 | 49.5 | — | 1.0 (*2,4*), < 1.0 (*4,F*) |
| **13a** | 4.0 | 5.5 | n.d. | 3.0 | 3.0 | < 1.0 | ~ 50.0 | n.d. | |
| **14a** | < 1.0 | 4.5 | 6.5 | 3.5 | 4.0 | 10.0 | 52.5 | n.d. | 11.0 (*5,5′*) |
| **15** | 4.5 | 6.2 | 5.5 | 2.5 | 3.5 | 1.2 | 50.5 | 5.5 | 11.0 (*5,5′*) |
| **16** | < 1.0 | 4.0 | 7.5 | c | 5.0 | 10.0 | 52.0 | 23.0 | 13.0 (*5,5′*) |
| **17** | 3.0 | 4.0 | 6.0 | 2.5 | 3.9 | 16.5 | 53.0 | 17.5 | 12.0 (*5,5′*) |
| **18** | 4.0 | 4.0 | 4.0 | 2.2 | 3.8 | 17.0 | 55.5 | 19.5 | 12.0 (*5,5′*), 2.8 (*H-8,F*) |

[a] The $^1J_{H,H}$ of Ph$CH_2$ was found to be 12.0 Hz for all compounds but arabinoside **10** and ketone **11**.
[b] The values were not determined owing to overlap of the resonances of H-3 and H-4.
[c] The value was not determined owing to overlap of the resonances of H-4 and H-5.




Scheme 2. (a) $Ac_2O$, $Me_2SO$, 20°C, 20 h (**11**/**12**, ~3:1; 85–95%); (b) $Et_3N$, $CCl_4$, 20°C, 5 h (**11**/**12**, ~1:9); (c) $NaBH_4$, EtOH, 20°C, 20 h; (d) BzCl, pyridine, 20°C, 24 h; (e) TsCl, pyridine, 20°C, 18 h (96%); (f) BzOK, $Me_2SO$, reflux, 30 min (59%); (g) saturated at 0°C methanolic ammonia, 20°C, 24 h; (h) 20% $Pd(OH)_2$–C, EtOH, cyclohexene, reflux, 50 min (h+d, Σ 98%); (i) AcOH–$Ac_2O$–$H_2SO_4$ (14.7:1.75:1.0, v/v), 20°C, 20 h (83%); (j) **16**–persilylated $N^6$-benzoyladenine–$SnCl_4$, (1.0:1.5:2.9, mol), $CH_3CN$–1,2-dichloroethane (2.5:1, v/v), reflux, 3 h [j+g, **17** (48%) + **18** (13%)].

ing derivative of 2-deoxy-2-fluoro-D-ribofuranose for subsequent coupling with silylated bases in the presence of Friedel–Crafts catalysts.

Oxidation of arabinoside **10a** with dimethyl sulfoxide–acetic anhydride afforded a mixture of epimeric free ketones **11** and **12** in a ratio of ca. 3:1 ($^1$H NMR; Tables 4 and 5) in combined yields of 85–95%, contaminated with the acetate **10b** and the 3-*O*-methylthiomethyl ether derivative, **10c**. Both by-products could be easily removed by silica gel column chromatography, whereas **11** and **12** were inseparable. At the same time, we observed ($^1$H NMR) **11** → **12** isomerization during silica gel column chromatography, affording mixtures in reversed ratios of 1:1.5 to 1:2.5. Reduction of a purified ca. 1:2 mixture of **11** and **12** with sodium borohydride in ethanol followed by column chromatography gave lyxoside **14a** (22%), starting arabinoside **10a** (11%), and riboside **13a** (65%), which implied predominant attack by the $BH_4^-$ anion on the $\alpha$-face of the sugar ring of ketone **11** (ca. 2:1 *lyxo/arabino* ratio) and stereoselective reduction of ketone **12** quantitatively furnishing **13a** (Scheme 2). The latter suggestion was confirmed by quantitative reduction of **12** (purity > 90%) to **13a** when the former had been obtained by treatment of chromatographically purified **11/12** mixture with triethylamine in carbon tetrachloride (vide infra). These results, of the sodium borohydride reduction of ketones **11** and **12**, are to be contrasted with those obtained by Motawia and Pedersen [13] concerning the reduction of $\alpha$ and $\beta$ anomers of methyl 2,3-dideoxy-5-*O*-(4-phenylbenzoyl)-D-*glycero*-pentofuranosid-3-ulose: reduction of both anomers was stereospecific and led to the corresponding $\alpha$ and $\beta$ anomers of methyl 2-deoxy-5-*O*-(4-phenylbenzoyl)-D-*threo*-pentofuranoside. The stereochemical course of the reduction is likely to be dependent upon the nature of the substituent on the 5-hydroxyl group, namely ester or ether, on one hand, and, as in the case of **2** and **3** (see above), upon the configuration of the $\alpha$-fluorine atom, on the other.

In order to obtain a better yield of the desired riboside **13a**, it was of interest to attempt epimeric equilibration of the **11/12** mixture to *ribo*-isomer **12**. We found that treatment of a mixture of **11** and **12** with triethylamine in ethanol at room temperature for 3.5 h resulted in ca. 90% conversion of **11** to **12** ($^1$H NMR). However, the practical yields of **12** fluctuated and were lower in larger scale preparations. We have, therefore, examined the isomerization under a number of different conditions (solvent, concentration of triethylamine, temperature) and reproducible results were obtained by treatment of chromatographically purified mixtures of **11** and **12** with triethylamine in carbon tetrachloride at room temperature for 5 h, the conversion to **12** in this case being 85–90%. Direct addition of ethanol to this reaction mixture followed by treatment with sodium borohydride gave the riboside **13a** in 70% combined yield.

In contrast to oxidation of the lyxoside **4a** vs. the arabinoside **1a** (see above), oxidation of the isomeric lyxoside **14a** with dimethyl sulfoxide–acetic anhydride proceeded smoothly, giving almost exclusively a ca. 3:1 mixture of **11** and **12** ($^1$H NMR). Reduction followed by chromatographic separation afforded the lyxoside **14a** (43%), the arabinoside **10** (14%), and the riboside **13a** (18%). Once again, these data point to predominant attack by the $BH_4^-$ anion at the $\alpha$-face of the sugar ring of ketone **11** (ca. 3:1 *lyxo/arabino* ratio) and stereoselective reduction of ketone **12**.

The assignments of configuration to **13a** and **14a** were based upon the same $^{13}$C NMR arguments used for methyl 3-deoxy-3-fluoro-$\alpha$-D-pentofuranosides (vide supra). In

Table 6
$^{13}C$ NMR spectral data of 2-deoxy-2-fluoro sugars in $CDCl_3$

| Compound | Chemical shifts [a] ($\delta$) ($^1J_{C,H}$ coupling constants, Hz) | | | | | | $J_{C,F}$ coupling constants (Hz) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | C-1 | C-2 | C-3 | C-4 | C-5 | OMe [b] | C-1,F | C-2,F | C-3,F | C-4,F |
| **10a** | 106.1 | 99.3 | 76.3 | 83.9 | 70.0 | 54.9 | 34.4 | 181.8 | 17.3 | < 2.0 |
| | (177.4) | (162.3 [c]) | (149.5) | (149.1) | (141.5) | (144.7) | | | | |
| **11** | 103.2 | 88.4 | 205.9 | 78.1 | 69.0 | 55.6 | 28.9 | 189.2 | 13.4 | < 2.0 |
| | (176.1 [d]) | (163.5) | | (151.0) | (143.4 [e]) | (143.4) | | | | |
| **12** | 98.2 | 89.4 | 205.1 | 76.5 | 68.0 | 55.4 | 14.6 | 209.9 | 27.3 | 3.7 |
| | (179.9 [d]) | (156.5) | | (151.0) | (143.4 [e]) | (143.4) | | | | |
| **13a** | 101.5 | 88.5 | 70.1 | 84.3 | 69.7 | 55.4 | 16.5 | 201.0 | 15.9 | 2.1 |
| | (174.6 [f]) | (159.6) | (154.7) | (151.0) | (141.5) | (141.9) | | | | |
| **14a** | 104.7 | 93.5 | 71.3 | 77.8 | 69.0 | 55.1 | 30.0 | 185.1 | 16.0 | < 2.0 |
| | (174.5) | (163.0) | (152.0) | (145.4) | (143.2) | (142.5) | | | | |

[a] The $^{13}C$ resonances of benzyl groups were at ~ 73.5 (s, $CH_2$; $^1J_{C,H}$ ~ 150 Hz), 127.7 (*meta* and *para*), 128.4 (*ortho*), 137.8 (*ipso*) ppm.
[b] Resonances of $OCH_3$ displayed additional C,H couplings of 3.8 Hz (**10a**), 3.5 Hz (**11**), 4.7 Hz (**12**), ~ 2.0 Hz (**13a**), and 4.4 Hz (**14a**).
[c] Resonance of C-2 displayed an additional C,H coupling of 5.7 Hz.
[d] Resonance of C-1 displayed an additional splitting into a quadruplet ($^3J_{C1,OCH3}$) of ~ 5.0 Hz.
[e] Resonance of C-5 displayed an additional splitting into a triplet of 4.7 Hz.
[f] Resonance of C-1 displayed two additional C,H couplings of ~ 4.5 Hz.

particular, the chemical shift differences for C-1 and C-4 resonances of ketones **11** and **12** and their respective precursors **10** and **13** (Table 6) find close analogy with those reported for the pairs of related nucleoside derivatives [14].

The glycoside **13a** was converted to the crystalline $\beta$-acetate **16** (71%; overall) essentially as described previously [4]. It is interesting to note that acetolysis of **15** under conditions employed in the present work (see the Experimental section) was readily accomplished, giving crystalline **16** in 83% yield (cf. ref. [15]). The acetate **16** was allowed to react with persilylated $N^6$-benzoyladenine in the presence of excess tin(IV) chloride (1.0:1.5:2.9, mol) in refluxing 1:2.5 dichloroethane–acetonitrile for 3 h to afford, after deblocking and column chromatography, 9-(2-deoxy-2-fluoro-$\beta$-D-ribofuranosyl)adenine (**17**) and its $\alpha$ anomer (**18**) in 48 and 13% isolated yield, respectively (Scheme 2). The assignments of the anomeric configuration for **17** and **18** were based primarily upon $^1H$ NMR spectroscopy. Diagnostic of the $\alpha$-anomeric configuration of the latter is a long-range coupling of H-8 to fluorine exhibited in its $^1H$ NMR spectrum. This coupling is generally indicative of the physical proximity of the nuclei involved [16] and is not observed in the $\beta$ anomer. The CD spectrum of **17** displays, like that of adenosine [12], a negative long-wavelength envelope near 260 nm and, in contrast to adenosine, the transition centred at 217 nm is negative (see the Experimental section).

In conclusion, the isomerization investigated in the present paper bears a resemblance to the *erythro* → *threo* conversion at C-3′ of 3,5-di-*O*-benzoyl-$\beta$-D-xylofuranosides of uracil, thymine, and adenine upon oxidation with dimethyl sulfoxide–dicyclohexylcarbodiimide described by Gosselin et al. [17]. Reduction of intermediate 2′-keto derivatives with sodium borohydride led to the formation of the corresponding arabino-

sides. As was the case in the methyl 3-deoxy-3-fluoro-α-D-pentofuranoside series (vide supra), these authors, and others in a closely related study [14] did not observe isomerization at C-1′. It is interesting to note that, to the best of our knowledge, the use of electron-donating silyl protecting groups for the remaining hydroxyl function(s) of a substrate did not lead to the epimerization at the α-carbon [14,18]. Thus, it seems likely that the presence of the electronegative α-fluoro substituent has a strong activating effect for isomerization at the carbon atom bearing this function.

## 3. Experimental

*General methods.*—The UV and IR spectra were recorded on Specord M-400 and UR-20 instruments (Carl Zeiss, Germany), respectively. $^1$H and $^{13}$C NMR spectra were measured at 200.13 and 50.325 MHz, respectively, at 23°C on an AC-200 spectrometer equipped with an Aspect 3000 data system (Bruker, Germany) with $Me_4Si$ as an internal standard (s = singlet; d = doublet; t = triplet; m = multiplet; br s = broad signal); assignments of proton resonances were confirmed, when possible, by selective homonuclear decoupling experiments. The solvent employed for recording the spectra was $CDCl_3$, unless otherwise stated. FAB-mass spectra were obtained on a Kratos MS80 (UK) spectrometer from samples dissolved in $Me_2SO$ with glycerol as matrix under Xe-atom bombardment (6–8 keV). CD spectra and $[\alpha]_D^{18}$ values were obtained on a J-20 (JASCO, Japan) spectropolarimeter. Standard (1) Silufol $UV_{254}$ (Czechoslovakia) and (2) Kieselgel 60 $F_{254}$ (E. Merck, Germany) plates were used for thin layer chromatography (TLC); solvent systems used were (v/v): 1:2 hexane–diethyl ether (A), 4:1 hexane–EtOAc (B), 4:1 $CHCl_3$–MeOH (C). Column chromatography of sugars and nucleosides was performed on Silica Gel L (Chemapol, Czechoslovakia) 100/400 μm and 40/100 μm, respectively; in some cases, Silica Gel Woelm containing 20% water (Germany) was used for column chromatography. Freshly distilled anhydrous $Me_2SO$ was used throughout this work. Anhydrous solvents were obtained as described [4]. Reduction of ketones was performed with $NaBH_4$ freshly recrystallized from methyl cellosolve and dried at 40°C/0.1 mm for 24 h; $NaBD_4$ was purchased from Fluka (Switzerland). In all condensation reactions, freshly distilled $SnCl_4$ and trimethylsilyl trifluoromethanesulfonate (Fluka, Switzerland) were used. The solutions of compounds in organic solvents were dried with anhyd $Na_2SO_4$ for 4 h. Elemental analyses of new crystalline compounds were carried out in the Microanalytical Laboratorium at the Institute of Organic Chemistry, Ukrainian Academy of Sciences (Kiev, Ukraine). Except where otherwise indicated, the reactions were carried out at 20°C.

*Oxidation–reduction of methyl 5-O-benzyl-3-deoxy-3-fluoro-α-D-arabinofuranoside* (**1a**).—*Procedure A.* To a stirred solution of **1a** [19] [2.2 g, 8.58 mmol; $R_f$ 0.54 (1,A)] in $Me_2SO$ (29 mL), acetic anhydride (18.5 mL) was added, the mixture was stirred for 20 h and poured into ice–water (120 mL). The product was extracted with $CHCl_3$ (4 × 100 mL), the combined organic extracts were washed with saturated aq $NaHCO_3$ (100 mL), water (2 × 50 mL), dried, and evaporated to dryness under reduced pressure to afford 2.1 g (90%) of a mixture of epimeric *gem*-diols **2** and **3** as the main products of the reaction in a ratio of ca. 3:1 according to $^1$H NMR data, $R_f$ 0.23 and 0.33 (1,A),

respectively; $\nu_{max}$ (film): 3400 (OH) $cm^{-1}$; no carbonyl absorption in the 1700–1800 $cm^{-1}$ region.

The crude mixture of **2** and **3** (2.1 g) was dissolved in 1:1 benzene–EtOH (80 mL), $NaBH_4$ (1.1 g, 29.07 mmol) was added, the mixture was stirred for 20 h, and then evaporated to dryness. After addition of water (50 mL), the mixture was extracted with $CHCl_3$ (4 × 75 mL), and the combined extracts were dried and evaporated. The residue was dissolved in pyridine (40 mL) and treated with benzoyl chloride (1 mL, 1.2 g, 8.6 mmol). After stirring for 48 h, the mixture was poured into 0.4 L of aq $NaHCO_3$ and ice, and the product was extracted with $CHCl_3$ (3 × 100 mL). The combined extracts were dried and evaporated to dryness. The residue was chromatographed on a silica gel column (120 mL), using a linear EtOAc gradient (0 → 33%, v/v; 2 × 500 mL) in hexane to afford an unresolved mixture of **1b** and **4b** [0.73 g; 24%; $R_f$ 0.46 (1,B)] and syrupy riboside **5b** [1.55 g; 50%; $R_f$ 0.42 (1,B)]. Yields given are based on **1a**.

A solution of **5b** (0.1 g, 0.28 mmol) in MeOH (20 mL), saturated with ammonia at 0°C, was kept for 48 h and evaporated. The residue was purified by silica gel (50 mL) column chromatography, using a linear EtOAc gradient (0 → 50%, v/v; 2 × 500 mL) in hexane to afford 63 mg (90%) of methyl 5-*O*-benzyl-3-deoxy-3-fluoro-α-D-ribofuranoside (**5a**) as a syrup; $R_f$ 0.53 (1,A).

Debenzoylation of a mixture of **1b** and **4b** (0.73 g) as just described, followed by silica gel (100 mL) column chromatography, using a linear diethyl ether gradient (0 → 50%, v/v; 2 × 1.0 L) in hexane, gave 0.3 g (14%) of the starting arabinoside (**1a**) and 0.2 g (9%) of methyl 5-*O*-benzyl-3-deoxy-3-fluoro-α-D-lyxofuranoside (**4a**) as a syrup; $R_f$ 0.44 (1,A). Moreover, in some experiments, a small quantity of **1c** was also isolated as a syrup; $R_f$ 0.46 (1,B).

Benzoylation of **4a** (1.03 g, 4.02 mmol), followed by chromatography as just described, gave 1.22 g (84%) of **4b**: mp 77–78°C (from MeOH); $[\alpha]_D^{18}$ +65.6° (*c* 1.585, $CHCl_3$); $R_f$ 0.46 (1,B). $^1$H NMR: δ 8.08–7.27 (m, 10 H, arom.), 5.34 (m, 1 H, $J_{2,3}$ 4.2, $J_{3,4}$ 3.0, $J_{3,F}$ 53.0 Hz, H-3), 5.27 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 5.24 (m, 1 H, $J_{2,F}$ 15.3 Hz, H-2), 4.60 (m, 2 H, $CH_2$Ph), 4.45 (ddd, 1 H, $J_{4,5}$ 5.4, $J_{4,5'}$ 6.6, $J_{4,F}$ 26.4 Hz, H-4), 3.80 (ddd, 1H, $J_{5,5'}$ 10.0, $J_{5,F}$ 1.8 Hz, H-5), 3.74 (ddd, 1 H, $J_{5',F}$ 1.8 Hz, H-5'), 3.46 (s, 3 H, OMe). FABMS: *m/z* 361 $(M + H)^+$. Anal. Calcd for $C_{20}H_{21}FO_5 \cdot 0.25$ MeOH: C, 66.02; H, 6.02; F, 5.16. Found: C, 66.03; H, 5.99; F, 5.41.

The use of pyridine as a solvent instead of a benzene–EtOH mixture for the reduction step (24 h, room temperature) of a mixture of **2** and **3** afforded **5b** (21%), **1a** (4%), **4a** (3.6%), and methyl 5-*O*-benzyl-3-deoxy-3-fluoro-α-D-xylofuranoside (**6a**) as a syrup [0.6%; $R_f$ 0.47 (1,A)].

*Procedure B.* The crude mixture of **2** and **3** (2.4 g; ca. 3:1) was chromatographed on a Silica Gel Woelm (20% water; 200 mL) column eluted with a linear diethyl ether gradient (0 → 50%, v/v; 2 × 1 L) in hexane. Two fractions were collected and evaporated.

The faster migrating zone yielded 0.33 g of syrupy residue consisting mainly of **3**; TLC and $^1$H NMR showed the presence of another product with $R_f$ 0.48 (1,A) for which only the OMe resonance at δ 3.50 (< 20% compared to that of **3**) was detected; $\nu_{max}$ (diluted solution in $CCl_4$): 1740 and 1795 (C=O, ketone), 3525, and 3600 $cm^{-1}$ (OH, *gem*-diol). Reduction of this residue as in procedure A afforded 0.26 g (ca. 85%) of **4a**.

The more slowly migrating zone (0.98 g) was shown to contain **2** and another product with $R_f$ 0.48 (1,A) [$\nu_{max}$ (diluted solution in $CCl_4$): 1735 and 1790 (C=O, ketone), 3515, and 3600 $cm^{-1}$ (OH, *gem*-diol)] for which the following $^1H$ NMR signals were recorded: $\delta$ 4.91 (br s, H-1), ca. 4.40 (m, H-4), 3.91 (dd, H-5), 3.81 (dd, H-5′), 3.52 (s, OMe). The ratio of the two products was estimated to be ca. 3:2 based on the integral intensity of OMe resonances. Reduction of this mixture as in procedure A gave 0.90 g (95%) of **5a**.

*Procedure C.* To a stirred solution of $Me_2SO$ (2.8 mL, 3.12 g, 40 mmol) in anhyd $CH_2Cl_2$ (45 mL) at −78°C, a solution of $(CF_3CO)_2O$ (4.2 mL, 6.25 g, 29.6 mmol) in $CH_2Cl_2$ (12 mL) was slowly added and the mixture was stirred at −78°C for 10 min. A solution of **1a** (5.12 g, 19.98 mmol) in anhyd $CH_2Cl_2$ (40 mL) was then added dropwise (ca. 10 min) and the mixture was stirred for an additional 30 min. Then, $Et_3N$ (8.0 mL) was added dropwise, the mixture was allowed to warm to room temperature, diluted with $CH_2Cl_2$ (200 mL), and the resulting solution was washed with water (2 × 50 mL). The combined water phases were washed with $CH_2Cl_2$ (50 mL). The organic solutions were combined, dried, and evaporated to dryness under reduced pressure to give 5.3 g (97%) of a mixture of epimeric *gem*-diols **2** and **3** in a ratio of ca. 8:1 ($^1H$ NMR).

The crude mixture of **2** and **3** (5.3 g) was dissolved in 4:1 benzene–EtOH (200 mL) and $NaBH_4$ (1.5 g, 39.65 mmol) was added. After stirring for 2 h, the mixture was adjusted to pH 7.0 with 10% aq AcOH and evaporated to dryness. The residue was extracted with $CHCl_3$ (2 × 100 mL), and the combined extracts were dried and evaporated. The residue was dissolved in pyridine (100 mL) and treated with benzoyl chloride (2.6 mL, 3.15 g, 22.4 mmol). After stirring for 48 h, the mixture was poured into 1 L of an ice–saturated $NaHCO_3$ mixture, and after the ice had melted, the product was extracted into $CHCl_3$ (3 × 250 mL). The combined organic extracts were dried and evaporated to dryness. The residue was chromatographed on a silica gel column (300 mL), using a linear EtOAc gradient (0 → 50%, v/v; 2 × 1.0 L) in hexane to afford an unresolved mixture of **1b** and **4b** (0.34 g; 4.8%) along with the pure riboside **5b** (5.4 g; 77%).

Debenzoylation of a mixture of **1b** and **4b** (0.34 g) as described above, followed by silica gel (50 mL) column chromatography, using a linear diethyl ether gradient (0 → 50%, v/v; 2 × 1.0 L) in hexane, gave **1a** (120 mg) and **4a** (55 mg). Once again, in some experiments, a small quantity of **1c** was also isolated.

*Procedure D.* Five 10-mL portions of $CD_3OD$ were successively added to, and evaporated from, a mixture of **2** and **3** [prepared as in procedure C from 0.256 g (1 mmol) of **1a** without purification]. The material was then dissolved in $CD_3OD$ (20 mL), $NaBD_4$ (0.42 g, 10 mmol) was added, and the mixture was stirred for 2 h under Ar. The mixture was worked up, benzoylated and chromatographed as in procedure C to afford 0.14 g (39%; based on **1a**) of methyl 2-*O*-benzoyl-5-*O*-benzyl-2(*S*)-deuterio-3-deoxy-3-fluoro-α-D-ribofuranoside {**5b**[2(*S*)d]} and 0.14 g of a mixture of **1b** and methyl 2-*O*-benzoyl-5-*O*-benzyl-2(*R*)-deuterio-3-deoxy-3-fluoro-α-D-lyxofuranoside {**4b**[2(*R*)d]}. Debenzoylation of this mixture followed by chromatography as in procedure C yielded 50 mg (20%) of **1a** and 11 mg (4.3%) of **4a**[2(*R*)d]. The $^1H$ NMR spectra of the deuterated compounds readily confirmed the assigned structures.

*Oxidation of methyl 5-O-benzyl-3-deoxy-3-fluoro-α-D-lyxofuranoside* (**4a**).—To a

stirred solution of $Me_2SO$ (0.14 mL, 0.15 g, 2 mmol) in anhyd $CH_2Cl_2$ (2 mL) at −78°C, a solution of $(CF_3CO)_2O$ (0.21 mL, 0.32 g, 1.5 mmol) in $CH_2Cl_2$ (1 mL) was slowly added and the mixture was stirred at −78°C for 10 min. A solution of **4a** (0.256 g, 1.0 mmol) in anhyd $CH_2Cl_2$ (3 mL) was then added dropwise (ca. 10 min), the mixture was allowed to warm to room temperature, and stirred for an additional 1 h. Then, $Et_3N$ (0.4 mL) was added dropwise, and the solution was diluted with $CH_2Cl_2$ (25 mL) and washed with water (3 × 10 mL). The organic phase was dried, evaporated, and chromatographed on the Silica Gel Woelm (20% water; 25 mL), by elution with a linear diethyl ether gradient (0 → 50%, v/v; 2 × 250 mL) in hexane, to afford **4a** (0.12 g), *gem*-diol **3** (30 mg), and *gem*-diol **2** (106 mg). As in the case of the similar oxidation of **1a**, both of the latter fractions contained (TLC and $^1H$ NMR) the products with $R_f$ 0.48 (1,A). Reduction of these fractions as described above gave essentially quantitatively (TLC and $^1H$ NMR) the lyxoside **4a** and the riboside **5a**, respectively.

*Methyl 2,5-di-*O*-benzoyl-3-deoxy-3-fluoro-α-*D*-lyxofuranoside* (**7**).—A mixture of **4b** (1.48 g, 4.11 mmol) and 1.5 g of 10% Pd/C in EtOH (150 mL) was stirred under $H_2$ for 72 h. The catalyst was filtered off and washed with EtOH (2 × 50 mL). The filtrates were evaporated and coevaporated with toluene (2 × 50 mL). Standard benzoylation of the residue followed by silica gel (150 mL) column chromatography [a linear EtOAc gradient (1 → 50%; v/v; 2 × 500 mL) in hexane] afforded **7** (1.3 g, 85%); mp 79.5–80.5°C (from MeOH); $[\alpha]_D^{18}$ +214° (*c* 1.355, $CHCl_3$); $R_f$ 0.36 (1,B). FABMS: *m/z* 375 $[M + H]^+$, 343 $[M - MeO]^+$. Anal. Calcd for $C_{20}H_{19}FO_6$: C, 64.17; H, 5.12; F, 5.08. Found: C, 63.95; H, 5.31; F, 4.99.

*1-*O*-Acetyl-2,5-di-*O*-benzoyl-3-deoxy-3-fluoro-α,β-*D*-lyxofuranose* (**8**).—Concentrated $H_2SO_4$ (0.32 mL) was added to a solution of **7** (0.53 g, 1.42 mmol) in HOAc (4.7 mL) and $Ac_2O$ (0.56 mL), the mixture was stirred for 20 h and poured into ice–water (50 mL). It was then extracted with $CHCl_3$ (4 × 80 mL), the combined organic extracts were washed with saturated aq $NaHCO_3$ (100 mL), water (2 × 50 mL), dried, and evaporated in vacuo to dryness. The residue was purified by silica gel (100 mL) column chromatography, using a linear EtOAc gradient (0 → 50%, v/v; 2 × 500 mL) in hexane to afford the acetate **8** (0.5 g, 88%); mp 105–108°C (from MeOH); $[\alpha]_D^{18}$ +61.08° (*c* 1.02, $CHCl_3$); $R_f$ 0.19 (1,B). $^1H$ NMR: (an α,β ratio ca. 2.5:1): δ 7.41–8.11 (m, arom.), 6.60 (d, H-1β, $J_{1,2}$ 4.8 Hz), 6.54 (d, H-1α, $J_{1,2}$ 3.0 Hz), 5.48 (ddd, H-2α, $J_{2,3}$ 4.6, $J_{2,F}$ 16.2 Hz), 5.47 (m, H-3α + H-3β), 5.32 (dt, H-2β, $J_{2,3}$ 4.8, $J_{2,F}$ 25.2 Hz), 4.78–4.57 (m, H-4α,β, H-5α,β, and H-5′α,β), 2.15 (s, OAcβ), 2.13 (s, OAcα). FAB-MS: *m/z* 403 $[M + H]^+$. Anal. Calcd for $C_{21}H_{19}FO_7 \cdot MeOH$: C, 60.83; H, 5.34; F, 4.37. Found: C, 61.03; H, 5.00; F, 4.61.

*9-(3-Deoxy-3-fluoro-α-*D*-lyxofuranosyl)adenine* (**9**).—A solution of **8** (0.5 g, 1.24 mmol), $SnCl_4$ (0.3 mL, 0.67 g, 2.57 mmol), and the bis(trimethylsilyl) derivative of $N^6$-benzoyladenine [obtained from 0.30 g (1.25 mmol) of $N^6$-benzoyladenine] in anhyd 1,2-dichloroethane (15 mL) was stirred for 18 h. After standard work-up, the residue was purified by silica gel (60 mL) column chromatography, using a linear MeOH gradient (2 → 10%, v/v; 2 × 500 mL) in $CHCl_3$ to afford the benzoylated derivative of **9** as a foam (0.59 g, 82%).

Standard debenzoylation of the product followed by crystallization from EtOH afforded **9** (0.18 g, 78%); mp 260–261°C; $[\alpha]_D^{18}$ +75.4° (*c* 0.69, 1:1 $H_2O$–DMF); $R_f$

0.30 (2,C); $\lambda_{max}$ ($H_2O$) 260 nm ($\epsilon$ 14900); CD ($H_2O$), $\lambda$, nm ($[\Theta] \times 10^{-3}$): 212 (−9.35), 250 (+3.74), 247, 280 (0)]. FABMS: $m/z$ 270 $[M + H]^+$. Anal. Calcd for $C_{10}H_{12}FN_5O_3 \cdot 0.25$ EtOH: C, 44.92; H, 4.85; F, 6.77; N, 24.95. Found: C, 45.06; H, 4.72; F, 7.08; N, 25.20.

Methyl 5-*O*-benzyl-2-deoxy-2-fluoro-α-D-arabinofuranoside (**10a**) was obtained [16] along with methyl 5-*O*-benzyl-3-fluoro-3-deoxy-α-D-xylofuranoside in 38% and 12% yield, respectively.

*Oxidation–reduction of methyl 5-O-benzyl-2-deoxy-2-fluoro-α-D-arabinofuranoside* (**10a**).—*Procedure A*. To a solution of the fluoride **10a** [0.52 g, 2.03 mmol; $R_f$ 0.56 (1,A)] in anhyd $Me_2SO$ (4.4 mL) was added acetic anhydride (2.6 mL), the mixture was stirred for 20 h, poured under vigorous stirring into ice–water (50 mL), and, after the ice had melted, it was extracted with $CHCl_3$ (3 × 100 mL). The combined organic extracts were washed with water (3 × 50 mL), dried, and evaporated to give 0.52 g of a mixture of isomeric fluorodeoxy ketones **11** and **12** in a ratio of ca. 3:1 according to $^1H$ NMR data (resonances of H-4), $R_f$ 0.71 (1,A), contaminated with the acetate **10b** and the 3-*O*-methylthiomethyl derivative **10c**.

The above mixture was chromatographed on a silica gel L (60 mL) column by elution with a linear diethyl ether gradient (0 → 33%, v/v; 2 × 350 mL) in hexane to afford, in order of elution, syrupy **10c** [65 mg, 10%; $R_f$ 0.92 (1,A)], **10b** [40 mg, 7%; $R_f$ 0.83 (1,A); $\nu_{max}$ (film) 1748 $cm^{-1}$ (acetate CO)], and a mixture of **11** and **12** (0.42 g, 81%) in a ratio of ca. 1:2 according to $^1H$ NMR data; $\nu_{max}$ (film) 1792 (ketone CO; more intensive band), 1725 $cm^{-1}$ (ketone CO; less intensive band).

The mixture of **11** and **12** (0.42 g, 1.65 mmol) was dissolved in EtOH (11 mL) and treated with $NaBH_4$ (0.37 g, 9.78 mmol). After stirring for 20 h, the mixture was evaporated and coevaporated with $CHCl_3$ (100 mL). The residue was triturated with $CHCl_3$ (100 mL), the precipitate that formed was filtered off and washed with $CHCl_3$ (100 mL). The combined organic filtrates were dried and evaporated, and the residue was chromatographed on a silica gel (150 mL) column with a linear EtOAc gradient (0 → 33%, v/v; 2 × 500 mL) in hexane. The fractions containing individual products were collected and evaporated to afford, in order of elution, syrupy methyl 5-*O*-benzyl-2-deoxy-2-fluoro-α-D-lyxofuranoside (**14a**) [93 mg (22%); $R_f$ 0.59 (A)], the starting arabinoside **10a** [46 mg (11%)], and methyl 5-*O*-benzyl-2-deoxy-2-fluoro-α-D-ribofuranoside (**13a**) [275 mg (65%); $R_f$ 0.31 (1,A)].

To a solution of the fluoride **14a** (0.3 g, 1.17 mmol) in anhyd pyridine (10 mL) was added tosyl chloride (1.0 g, 5.24 mmol), the mixture was stirred for 18 h, poured under vigorous stirring into saturated aq $NaHCO_3$ (100 mL), and extracted with $CHCl_3$ (3 × 100 mL). The combined organic extracts were washed with water (3 × 20 mL), dried, and evaporated to dryness. The residue was purified by silica gel (80 mL) column chromatography using a linear EtOAc gradient (0 → 11%, v/v; 2 × 300 mL) in hexane, to afford syrupy **14b** (0.46 g, 96%); $^1H$ NMR: $\delta$ 7.78 and 7.29 (2 × d, 4 H, *p*-$MeC_6H_4$-$SO_2$), 7.32 (m, 5 H, *Ph*$CH_2$), 5.16 (ddd, 1 H, $J_{2,3}$ 4.5, $J_{3,4}$ 6.5, $J_{3,F}$ 16.0 Hz, H-3), 5.03 (d, 1 H, $J_{1,F}$ 9.5 Hz, H-1), 4.72 (dd, 1 H, $J_{2,F}$ 51.5 Hz, H-2), 4.52 (s, 2 H, $CH_2$Ph), 4.39 (m, 1 H, $J_{4,5} = J_{4,5'} = 6.5$ Hz, H-4), 3.63 (d, 2 H, H-5 and H-5′), 3.35 (s, 3 H, OMe), 2.42 (s, 3 H, *p*-*Me*$C_6H_4$-$SO_2$).

A solution of **14b** (0.46 g, 1.12 mmol) and KOBz (1.0 g, 6.24 mmol) in anhyd

$Me_2SO$ (5 mL) was refluxed for 30 min. After cooling to room temperature, a precipitate that formed was filtered off and washed with diethyl ether (2 × 100 mL). The combined organic phase was washed with water (50 mL), dried, and evaporated. The residue was treated with MeOH (50 mL), saturated with ammonia at 0°C, for 48 h, the mixture was evaporated, and the residue purified by silica gel (90 mL) column chromatography using a linear EtOAc gradient (0 → 30%, v/v; 2 × 500 mL) in hexane to afford the arabinoside **10a** (0.17 g, 59%) that was identical with an authentic sample (TLC and $^1$H NMR).

*Procedure B.* A mixture of **11** and **12** [ca. 1:1.5; 4.2 g (16.5 mmol); prepared as in procedure A after silica gel column chromatography] was dissolved in $CCl_4$ (56 mL), $Et_3N$ (0.92 mL, 6.64 mmol) was added, and the reaction mixture was stirred at room temperature. After 5 h, analysis by $^1$H NMR revealed the presence of a ca. 9:1 mixture of **11** and **12**. Following addition of EtOH (11 mL) and $NaBH_4$ (3.7 g, 97.8 mmol), the mixture was stirred for 20 h and worked up and chromatographed as in procedure A to yield 250 mg (6%) of the lyxoside **14a**, 120 mg (3%) of the arabinoside **10a**, and 3.68 g (87%) of the riboside **13a**.

Oxidation–reduction of methyl 5-*O*-benzyl-2-deoxy-2-fluoro-α-D-lyxofuranoside (**14a**) was performed as described above for **10a**. Starting from 0.25 g (0.975 mmol) of **14a**, 0.23 g of a ca. 3:1 mixture of **11** and **12** was produced, slightly contaminated with **10b** and **10c** according to $^1$H NMR.

Without purification, this mixture was dissolved in EtOH (5 mL) and treated with $NaBH_4$ (0.26 g, 6.87 mmol). After stirring for 20 h, the mixture was evaporated, water (30 mL) was added to the residue, and the mixture was extracted with $CHCl_3$ (3 × 50 mL). The extracts were combined, dried, and evaporated. The residue was chromatographed on a silica gel (140 mL) column with a linear ethyl–EtOAc gradient (0 → 33%, v/v; 2 × 500 mL) in hexane. The fractions containing individual products were collected and evaporated to afford the starting lyxoside **14a** [107 mg (43%)], the arabinoside **10a** [36 mg (14%)], and the riboside **13a** [45 mg (18%)].

*Methyl 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-α-*D*-ribofuranoside* (**15**).—Conventional benzoylation of **13a** (1.6 g, 6.24 mmol), followed by chromatography as described above, gave 1.96 g (87%) of the benzoate **13b** as a syrup; $R_f$ 0.48 (1,B). $^1$H NMR: δ 8.10–7.24 (m, 10 H, arom.), 5.44 (dt, 1 H, $J_{3,2}$ 6.5, $J_{3,4}$ 4.0, $J_{3,F}$ 6.0 Hz, H-3), 5.16 (d, 1 H, $J_{1,2}$ 4.0, $J_{1,F}$ < 1.0 Hz, H-1), 5.10 (ddd, 1 H, $J_{2,F}$ 50.0 Hz, H-2), 4.63 (d, 2 H, PhC$H_2$), 4.55 (d, 2 H, PhC$H_2$), 4.44 (dt, 1 H, $J_{4,5} = J_{4,5'} = 7.0$ Hz, H-4), 3.74 (d, 2 H, H-5 and H-5'), 3.54 (s, 3 H, OMe).

To a solution of **13b** (1.96 g, 5.44 mmol) in anhyd EtOH, 20% $Pd(OH)_2/C$ (2.0 g) and freshly distilled cyclohexene (100 mL) were added and the mixture was refluxed for 50 min. After cooling to room temperature, the catalyst was filtered off and washed with EtOH (150 mL), and the combined filtrates were evaporated. The residue was benzoylated and the crude product purified by silica gel (150 mL) column chromatography, using a linear EtOAc gradient (0 → 20%, v/v; 2 × 1.0 L) in hexane, to afford the syrupy dibenzoate **15** (2.0 g, 98%); $R_f$ 0.41 (1,B).

*1-*O*-Acetyl-3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-β-*D*-ribofuranose* (**16**).—Concentrated $H_2SO_4$ (0.32 mL) was added to a solution of **15** (0.56 g, 1.49 mmol) in HOAc (4.7 mL) and $Ac_2O$ (0.56 mL), the mixture was stirred for 20 h and poured into ice–water (50

mL). Processing by $CHCl_3$ extraction (4 × 80 mL) and chromatography (100 mL of $SiO_2$; linear EtOAc gradient [0 → 25%, v/v; 2 × 500 mL] in hexane) gave **16** (0.5 g, 83%) which was crystallized from diethyl ether; mp 105–106°C; $R_f$ 0.40 (1,B); (lit. [15] mp 90–92°C); $[\alpha]_D^{18}$ +32.8° (*c* 1.0, $CHCl_3$); FABMS: *m/z* 403 $[M + H]^+$, 343 $[M - AcO]^+$. Anal. Calcd for $C_{21}H_{19}FO_7$: C, 62.69; H, 4.76; F, 4.72. Found: C, 63.08; H, 5.10; F, 4.31. The $^1H$ NMR data for **16** (Tables 4 and 5) are in agreement with those reported [15].

*9-(2-Deoxy-2-fluoro-β-*D*-ribofuranosyl)adenine* (**17**) *and its α anomer* (**18**).—A mixture of **16** (0.47 g, 1.17 mmol), $SnCl_4$ (0.4 mL, 0.89 g, 3.42 mmol), and the bis(trimethylsilyl) derivative of $N^6$-benzoyladenine [obtained from 0.42 g (1.75 mmol) of $N^6$-benzoyladenine] in anhyd MeCN (15 mL) and dichloroethane (6 mL) was refluxed for 3 h. After standard work-up, the residue was purified by silica gel (60 mL) column chromatography with $CHCl_3$ as eluent, to afford 0.5 g of an unresolved mixture of benzoylated derivatives of **17** and **18**.

Standard debenzoylation of the above mixture and subsequent silica gel (90 mL) chromatography with a linear MeOH gradient (0 → 10%, v/v; 2 × 500 mL) in $CHCl_3$ afforded 0.15 g (48%) of the β-nucleoside **17** {mp 209–210°C (from MeOH); lit. [20] 209–212°C (from MeOH); $[\alpha]_D^{18}$ −22.0° (*c* 1.0, $H_2O$); $R_f$ 0.55 (2,C); $\lambda_{max}$ ($H_2O$) 260 nm (ε 14700); CD ($H_2O$), λ, nm ($[\Theta] \times 10^{-3}$): 217 (−18.0), 250 (−3.38), 280 (0); FABMS: *m/z* 270 $[M + H]^+$, and 40 mg (13%) of the α-nucleoside **18** as an amorphous powder $R_f$ 0.40 (2,C); $\lambda_{max}$ ($H_2O$) 260 nm (ε 14,700); FABMS: *m/z* 270 $[M + H]^+$}.

The $^1H$ NMR data recorded for **17** (Tables 4 and 5) are in agreement with those recently reported [20,21].

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