SYNTHESIS OF DEOXY, DIDEOXY AND DIDEHYDRODIDEOXY ANALOGS OF 9-(4-*C*-HYDROXYMETHYL-α-L-PENTOFURANOSYL)ADENINE

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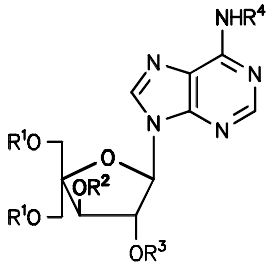
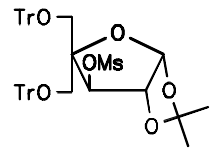
Condensation of 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-4-*C*-benzoyloxymethyl-L-arabinofuranose with N^6-benzoyladenine, catalyzed with tin tetrachloride, afforded nucleoside *I*, which upon partial deacetylation and subsequent mesylation was converted into 9-(3,5-di-*O*-benzoyl-4-*C*-benzoyloxymethyl-2-*O*-methanesulfonyl-α-L-arabinofuranosyl)adenine (*III*). 9-(2,5,6-Tri-*O*-acetyl-4-*C*-acetoxy methyl-3-*O*-methane sulfonyl-α-L-arabinofuranosyl)-N^6-benzoyladenine (*V*) was obtained by condensation of 1,2,5-tri-*O*-acetyl-4-*C*-acetoxymethyl-3-*O*-methanesulfonyl-L-arabinose with N^6-benzoyladenine. Reaction of mesyl derivatives *III* and *V* with methanolic sodium methoxide afforded 2′,3′-anhydro nucleosides *VIa* and *VIIa*, which were acetylated to give 9-(5-*O*-acetyl-4-*C*-acetoxymethyl-2,3-anhydro-α-L-ribofuranosyl)adenine (*VIb*) and 9-(5-*O*-acetyl-4-*C*-acetoxymethyl-2,3-anhydro-α-L-lyxofuranosyl)adenine (*VIIb*). Epoxy derivative *VIb* was cleaved with bromotrimethylsilane to 9-(5-*O*-acetyl-4-*C*-acetoxymethyl-2-bromo-2-deoxy-α-L-arabinofuranosyl)adenine (*VIIIa*); the same reaction with epoxy derivative *VIIb* afforded a mixture of 9-(5-*O*-acetyl-4-*C*-acetoxy methyl-2-bromo-2-deoxy-α-L-xylofuranosyl)adenine (*IXa*) and 9-(5-*O*-acetyl-4-*C*-acetoxymethyl-3-bromo-3-deoxy-α-L-arabinofuranosyl)adenine (*Xa*). Their dehalogenation with tributylstannane and subsequent deacetylation led to 9-(2-deoxy-4-*C*-hydroxymethyl-α-L-*erythro*-pentofuranosyl)adenine (*VIIIc*), 9-(2-deoxy-4-*C*-hydroxymethyl-α-L-*threo*-pentofuranosyl)adenine (*IXc*) and 9-(3-deoxy-4-*C*-hydroxymethyl-α-L-*threo*-pentofuranosyl)adenine (*Xc*). 9-(2,5-Di-*O*-acetyl-4-*C*-acetoxymethyl-2-bromo-2-deoxy-α-L-arabinofuranosyl)adenine (*VIIId*), prepared by acetylation of *VIIIa*, on reductive elimination with Cu/Zn couple and subsequent deacetylation afforded 9-(2,3-dideoxy-4-*C*-hydroxymethyl-α-L-*glycero*-pent-2-enofuranosyl)adenine (*XIb*). 9-(2,3-Dideoxy-4-*C*-hydroxymethyl-α-L-*glycero*-pentofuranosyl)-adenine (*XIIb*) was obtained either by catalytic hydrogenation of bromo derivative *VIIId*, followed by deacetylation, or by catalytic hydrogenation of didehydro derivative *XIb*. The nucleosides synthesized were tested for antiviral activity.

This study represents a continuation of our preceding communication dealing with the synthesis of 4-*C*-hydroxymethylpentofuranosyl derivatives[1] of 3′-azido-2′,3′-dideoxy, 2′,3′-dideoxy and 2′,3′-didehydro-2′,3′-dideoxy nucleosides having antiviral activity against HIV (see ref.[1] and references therein). The present communication describes the synthesis of the above-mentioned analogs containing adenine as the nucleoside base.

As the key compounds for the synthesis of deoxy derivatives of 9-(4-*C*-hydroxymethyl-α-L-pentofuranosyl)adenine we have chosen 2′,3′-anhydro nucleosides, which are easily accessible from the corresponding mesyl derivatives.





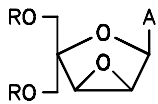
IV

I, $R^1 = R^2 = R^4 = Bz$; $R^3 = Ac$
II, $R^1 = R^2 = Bz$; $R^3 = R^4 = H$
III, $R^1 = R^2 = Bz$; $R^3 = Ms$; $R^4 = H$
V, $R^1 = R^3 = Ac$; $R^2 = Ms$; $R^4 = Bz$

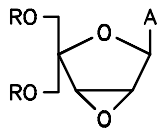
Condensation of 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-4-*C*-benzoyloxymethyl-L-arabinofuranose[1] with N^6-benzoyladenine in acetonitrile, catalyzed with tin tetrachloride, afforded nucleoside *I*. Its deacetylation with hydrazine hydrate in a mixture of acetic acid and pyridine[2] gave derivative *II* with fre hydroxyl in position 2′ which was mesylated to give mesyl derivative *III*. In the preparation of mesyl derivative *V*, the starting 1,2-*O*-isopropylidene-4-*C*-hydroxymethyl-β-L-arabinofuranose[3] was successively tritylated and mesylated to give dityrityl derivative *IV*. Its acetolysis afforded 1,2,5-tri-*O*-acetyl-4-*C*-acetoxymethyl-3-*O*-methanesulfonyl-L-arabinose, which on reaction with N^6-benzoyladenine furnished nucleoside *V*. Reaction of mesyl derivatives *III* and *V* with 0.5 M methanolic sodium methoxide afforded 2′,3′-anhydro nucleosides *VIa* and *VIIa*. The epoxy derivatives *VIa* and *VIIa* were acetylated with acetic anhydride in acetonitrile using 4-dimethylaminopyridine as catalyst, the acetic anhydride being added gradually to avoid acetylation of the base.

The obtained protected epoxides *VIb* and *VIIb* were cleaved with bromotrimethylsilane in the presence of boron trifluoride etherate. It is known that on treatment with hydrogen halide, 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine[4,5] and 9-(2,3-anhydro-β-D-ribofuranosyl)adenine[5,6] give rise to 3′-halogeno derivatives as the principal products. However, the cleavage of oxirane *VIb* with bromotrimethylsilane in the presence of boron trifluoride etherate led to the 2′-bromo derivative *VIIIa* as the sole product. In the case of epoxide *VIIb*, which has the opposite configuration, this reaction afforded a mixture of 2′-isomer *IXa* and 3′-isomer *Xa*. Because of very similar chromatographic

mobility of the bromo derivatives *IXa* and *Xa*, the individual isomers were not separated and their mixture was reduced with tributylstannane using 2,2′-azobis(2-propionitrile) as catalyst. The obtained deoxy derivatives were then separated by chromatography which afforded 34% of 2′-deoxy derivative *IXb* and 28% of 3′-deoxy derivative *Xb*. Bromo derivative *VIIIa* was also reduced with tributylstannane to 2′-deoxy compound *VIIIb*. The deoxy derivatives *VIIIb*, *IXb* and *Xb* were deacetylated with methanolic ammonia to give compounds *VIIIc*, *IXc* and *Xc*.

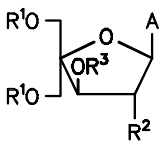


VI

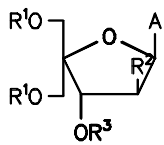


VII

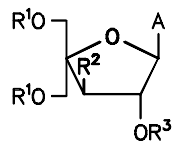
VIa, *VIIa*, R = H
VIb, *VIIb*, R = Ac
A = adenin-9-yl



VIII



IX



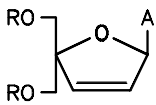
X

VIIIa – *Xa*, R^1 = Ac; R^2 = Br; R^3 = H
VIIIb – *Xb*, R^1 = Ac; R^2 = R^3 = H
VIIIc – *Xc*, R^1 = R^2 = R^3 = H
VIIId, R^1 = R^3 = Ac; R^2 = Br
A = adenin-9-yl

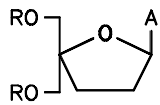
The 2′- and 3′-deoxy derivatives are easily distinguishable by ^{1}H NMR spectra. Spectra of the 2′-deoxy derivatives exhibit two multiplets of 2′-methylene protons: one centered at 2.32 – 2.33 ppm and the other at 2.84 – 2.94 ppm (*VIIIc*: 2.32 m, 2.94 m; *IXc*: 2.33 m, 2.84 m). The 3′-deoxy derivative *Xc* exhibits one doublet of doublets at 2.01 ppm and the second doublet of doublets at 2.34 ppm. The spectra of the synthesized deoxy nucleosides are in accord with those of 2′-deoxyadenosine[7], 9-(2-deoxy-β-D-*threo*-pentofuranosyl)adenine[8], 9-(3-deoxy-β-D-*erythro*-pentofuranosyl)adenine[9],

9-(3-deoxy-β-D-*threo*-pentofuranosyl)adenine[10] and also with spectra of analogs containing pyrimidine as base[1].

UV spectra of deoxy derivatives *VIIIc* and *Xc* display an absorption maximum at 260 nm. Its position shows that the sugar component is bound in the position N^9 of the adenine moiety. In the condensation of 1-*O*-acetyl sugar derivatives with N^6-benzoyladenine, we detected no N^3-isomer whose formation was described[11] in the reaction of protected ribofuranosyl bromide with adenine. Apparently, under conditions of the tin tetrachloride-catalyzed reaction, the primarily formed N^3-isomer is immediately rearranged into the N^9-isomer.



XI



XII

***XIa*, *XIIa*,** R = Ac
***XIb*, *XIIb*,** R = H
A = adenin-9-yl

For the preparation of 2′,3′-didehydro-2′,3′-dideoxy derivative *XIa* we made use of reductive elimination of tri-*O*-acetyl bromo derivative *VIIId* with Zn/Cu couple[12]. The compound *VIIId* was prepared by acetylation of bromo nucleoside *VIIIa*. Because of low stability of purine didehydrodideoxy nucleosides, and also because the reaction with 3′,5′-di-*O*-acetyl-2′-bromo-2′-deoxyuridine[13] is accompanied by significant cleavage of the nucleoside bond, we performed the reaction at 0 °C, the solution of the bromo derivative being slowly added to suspension of the Zn/Cu couple. In this way, we were able to prepare the 2′,3′-unsaturated nucleoside *XIa* in 84% yield. The free nucleoside *XIb* was obtained by methanolysis with methanolic ammonia. Hydrogenation of nucleoside *XIb* over Pd/C afforded dideoxy nucleoside *XIIb* in only 45% yield because the reaction was accompanied with significant cleavage of the nucleoside bond. Therefore, we tried also an alternative, already described, procedure[14] consisting in catalytic hydrogenation of bromo derivative *VIIId*. In this case, the yield of the dideoxy nucleoside *XIIa* was 57%. From the reaction mixture after hydrogenation of the bromo derivative *VIIId* we isolated 9-(3,5-di-*O*-acetyl-4-*C*-acetoxymethyl-2-deoxy-α-L-*erythro*-pentofuranosyl)adenine which upon methanolysis afforded the 2′-deoxy derivative *VIIIc* in 17% yield. Nucleoside *XIIb* was obtained from compound *XIIa* by methanolysis.

The synthesized compounds were tested for inhibitory activity against replication of HIV-1 and HIV-2. Activity has been found only for the 2′-deoxy derivative *IXc* (ref.[15]). Also the thymine analog[16] was found to be active against HIV.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. ^{1}H NMR spectra (δ, ppm; *J*, Hz) were measured on a Varian XL-200 (200 MHz) instrument in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. UV spectra were measured on a Beckman DU-65 spectrometer. Column chromatography was performed on silica gel (particle size 30 – 60 μm; Service Laboratories of this Institute) and thin-layer chromatography (TLC) on Silufol UV 254 sheets (Kavalier, Votice, The Czech Republic) in the following systems: S1, ethyl acetate–toluene (4 : 1); S2, ethyl acetate–acetone–ethanol–water (19 : 3 : 2 : 1); S3, ethyl acetate–acetone–ethanol–water (32 : 6 : 7 : 5); S4, ethyl acetate. The solvents were evaporated at bath temperature 30 – 60 °C/2 kPa and the compounds were dried over phosphorus pentoxide at 13 Pa.

9-(2-*O*-Acetyl-3,5-di-*O*-benzoyl-4-*C*-benzoyloxymethyl-α-L-arabinofuranosyl)-N^6-benzoyladenine (*I*)

Concentrated sulfuric acid (1.2 ml) was added during 30 min to an ice-cooled solution of 3,5-di-*O*-benzoyl-4-*C*-benzoyloxymethyl-1,2-*O*-isopropylidene-β-L-arabinofuranose[1] (5.33 g, 10 mmol) in a mixture of acetic acid (12.5 ml) and acetic anhydride (6.5 ml). After standing at room temperature overnight, the mixture was poured on ice (100 g), neutralized with solid sodium hydrogen carbonate and extracted with ethyl acetate (2 × 100 ml). The combined extracts were washed with 10% sodium hydrogen carbonate solution until the evolution of carbon dioxide ceased, dried over magnesium sulfate, and the solvent was evaporated. The residue was dried in vacuo (13 Pa) at 40 °C for 3 h and dissolved in acetonitrile (18 ml). After addition of N^6-benzoyladenine (2.4 g, 10 mmol), tin tetrachloride (2.3 ml, 20 mmol) was added dropwise with stirring which was continued until the mixture became homogeneous. The solution was set aside overnight at room temperature and then poured into stirred 10% sodium hydrogen carbonate solution (150 ml). The mixture was extracted with ethyl acetate (2 × 100 ml), the combined extracts were washed with 10% aqueous sodium hydrogen carbonate (2 × 100 ml) and dried over magnesium sulfate. The solvent was evaporated and the residue was column chromatographed on silica gel (600 g) in ethyl acetate–toluene (3 : 1) to give 5.5 g (73%) of protected nucleoside *I* as a solid foam; R_F 0.62 (S1). For $C_{41}H_{33}N_5O_{10}$ (755.7) calculated: 65.16% C, 4.40% H, 9.27% N; found: 65.13% C, 4.63% H, 8.98% N. ^{1}H NMR spectrum: 2.03 s, 3 H (CH_3CO); 4.78 d, 1 H, *J*(a,b) = 11.9 (CH^aH–O); 4.83 d, 1 H, *J*(c,d) = 11.8 (CH^cH–O); 4.92 d, 1 H (CH^dH–O); 5.02 d, 1 H (CH^bH–O); 6.22 d, 1 H, *J*(3′,2′) = 5.9 (H-3′); 6.67 – 6.79 m, 2 H (H-1′, H-2′); 7.37 – 8.07 m, 20 H (H-arom.); 8.71 s, 1 H (H-2); 8.83 s, 1 H (H-8); 11.26 s, 1 H (NH).

9-(3,5-Di-*O*-benzoyl-4-*C*-benzoyloxymethyl-α-L-arabinofuranosyl)adenine (*II*)

Hydrazine hydrate (80%, 1.8 ml) was added to a solution of acetyl derivative *I* (7.56 g, 10 mmol) in a mixture of acetic acid and pyridine (1 : 4, 90 ml) and the solution was allowed to stand at room temperature for 2 days. Acetone (40 ml) was added and, after standing for 2 h at room temperature, the solvent was evaporated. The residue was dissolved in ethyl acetate (250 ml) and the solution was washed successively with water (3 × 50 ml), 2% hydrochloric acid to acid reaction of the aqueous layer, water (50 ml), and 10% sodium hydrogen carbonate solution (2 × 50 ml). After drying over magnesium sulfate, the solvent was evaporated and the residue was crystallized from 2-propanol

(70 ml) to give 3.52 g (58%) of compound *II*. Chromatography of the mother liquors on a column of silica gel (100 g) in ethyl acetate, followed by crystallization from 2-propanol, afforded another crop (1.15 g; 19%) of compound *II*; m.p. 214 – 215 °C; R_F 0.59 (S4). For $C_{32}H_{27}N_5O_8$ (609.6) calculated: 63.05% C, 4.47% H, 11.49% N; found: 63.10% C, 4.55% H, 11.35% N. ^{1}H NMR spectrum: 4.63 d, 1 H, *J*(a,b) = 11.7 (CH^{a}H–O); 4.75 d, 1 H, *J*(c,d) = 11.9 (CH^{c}H–O); 4.83 d, 1 H (CH^{d}H–O); 4.92 d, 1 H (CH^{b}H–O); 5.57 m, 1 H, *J*(2′,1′) = 7.6, *J*(2′,3′) = 7.5, *J*(2′,OH) = 5.6 (H-2′); 5.90 d, 1 H (H-3′); 6.22 d, 1 H (H-1′); 6.38 d, 1 H (2′-OH); 7.33 – 7.75 m and 7.90 – 8.03 m, 13 H and 4 H (NH_2, H-arom.); 8.15 s, 1 H (H-2); 8.51 s, 1 H (H-8).

9-(3,5-Di-*O*-benzoyl-4-*C*-benzoyloxymethyl-3-*O*-methanesulfonyl-α-L-arabinofuranosyl)adenine (*III*)

Methanesulfonyl chloride (3 ml, 39 mmol) was added dropwise to a stirred and ice-cooled solution of nucleoside *II* (6.10 g, 10 mmol) in pyridine (50 ml). After standing for 5 h at room temperature, the mixture was cooled to 0 °C, water (2 ml) was added and after 15 min the mixture was concentrated. The residue was partitioned between water (50 ml) and ethyl acetate (400 ml), the organic layer was separated, washed with water (2 × 100 ml) and dried over magnesium sulfate. The solvent was evaporated and the residue was column chromatographed on silica gel (400 g) in ethyl acetate to give 5.14 g (75%) of mesyl derivative *III* as a solid foam; R_F 0.39 (S1). For $C_{33}H_{29}N_5O_{10}S$ (687.7) calculated: 57.63% C, 4.25% H, 10.18% N, 4.66% S; found: 57.35% C, 4.40% H, 9.95% N, 4.41% S. ^{1}H NMR spectrum: 3.12 s, 3 H (CH_3SO_2); 4.69 d, 1 H, *J*(a,b) = 11.9 (CH^{a}H–O); 4.84 d, 1 H, *J*(c,d) = 11.9 (CH^{c}H–O); 4.92 d, 1 H (CH^{d}H–O); 5.02 d, 1 H (CH^{b}H–O); 6.28 m, 1 H (H-3′); 6.61 – 6.71 m, 2 H (H-1′, H-2′); 7.33 – 7.74 m and 7.95 – 8.11 m, 13 H and 4 H (NH_2, H-arom.); 8.11 s, 1 H (H-2); 8.54 s, 1 H (H-8).

1,2-*O*-Isopropylidene-3-*O*-methanesulfonyl-5-*O*-triphenylmethyl-4-*C*-(triphenylmethoxymethyl)-β-L-arabinofuranose (*IV*)

A solution of 1,2-*O*-isopropylidene-4-*C*-hydroxymethyl-β-L-arabinofuranose[3] (5.5 g, 25 mmol) and triphenylmethyl chloride (15.89 g, 57 mmol) in pyridine (100 ml) was heated at 100 °C for 1 h. The solution was cooled to 0 °C, methanesulfonyl chloride (7.7 ml, 100 mmol) was added under stirring, the mixture was set aside at room temperature for 5 h, and transferred dropwise into ice-cold water (1.5 l). The precipitate was collected on filter, dried and crystallized from toluene to give 17.7 g (81%) of compound *IV* as a solvate with one molecule of crystal toluene. M.p. 108 – 111 °C. For $C_{48}H_{46}O_8S \cdot C_7H_8$ (875.1) calculated: 75.49% C, 6.22% H, 3.66% S; found: 75.44% C, 6.40% H, 3.45% S. ^{1}H NMR spectrum: 0.99 s and 1.16 s, 3 H and 3 H ($C(CH_3)_2$); 2.30 s, 3 H ($C_6H_4CH_3$); 2.95 s, 3 H (CH_3SO_2); 3.10 d, 1 H, *J*(a,b) = 8.4 (CH^{a}H–O); 3.24 d, 1 H, *J*(c,d) = 9.9 (CH^{c}H–O); 3.30 d, 1 H (CH^{d}H–O); 3.74 d, 1 H (CH^{b}H–O); 4.77 d, 1 H, *J*(2′,1′) = 4.1 (H-2′); 4.86 s, 1 H (H- 3′); 5.96 d, 1 H (H-1′); 7.10 – 7.47 m, 35 H (H-arom.).

9-(2,5-Di-*O*-acetyl-4-*C*-acetoxymethyl-3-*O*-methanesulfonyl-α-L-arabinofuranosyl)-N^6-benzoyladenine (*V*)

Concentrated sulfuric acid (3 ml) was added to an ice-cooled stirred solution of the sugar derivative *IV* (8.75 g, 10 mmol) in a mixture of acetic acid (35 ml) and acetic anhydride (10 ml). After standing at room temperature overnight, the mixture was poured on crushed ice (200 g), neutralized with solid sodium hydrogen carbonate and extracted with ethyl acetate (3 × 100 ml). The combined extracts were washed with 10% sodium hydrogen carbonate solution until the evolution of carbon dioxide ceased. The aqueous layer was extracted with ethyl acetate (2 × 100 ml) and all the combined extracts were dried over magnesium sulfate. The solvent was evaporated and the residue was chroma-

tographed on a column of silica gel (500 g). Ethyl acetate–toluene (1 : 4) washed out the trityl derivatives and subsequent elution with ethyl acetate–toluene (1 : 2) afforded 1,2,5-tri-*O*-acetyl-4-*C*-acetoxymethyl-3-*O*-methanesulfonyl-L-arabinose which was dried in vacuo (13 Pa) at 40 °C for 3 h and dissolved in acetonitrile (20 ml). After addition of N^6-benzoyladenine (2.39 g, 10 mmol), tin tetrachloride (2.3 ml, 20 mmol) was added dropwise with stirring which was continued until the mixture became homogeneous. The solution was set aside overnight at room temperature and then poured into stirred 10% solution of sodium hydrogen carbonate solution (150 ml). The mixture was extracted with ethyl acetate (3 × 100 ml) and the combined extracts were washed with 10% aqueous sodium hydrogen carbonate (60 ml). The aqueous layer was washed with ethyl acetate (50 ml) and the combined extracts were dried over magnesium sulfate. The solvent was evaporated and the residue was column chromatographed on silica gel (400 g). Ethyl acetate washed out the unreacted sugar, ethyl acetate–2-propanol (4 : 1) eluted the nucleoside *V* (4.54 g; 75%) as a solid foam; R_F 0.50 (S4). For $C_{25}H_{27}N_5O_{11}S$ (605.6) calculated: 49.58% C, 4.49% H, 11.57% N, 5.29% S; found: 49.29% C, 4.58% H, 11.30% N, 5.01% S. ^{1}H NMR spectrum: 2.04 s, 2.05 s and 2.12 s, 3 H, 3 H and 3 H (3 × CH_3CO); 3.37 s, 3 H (CH_3SO_2); 4.38 s, 2 H (CH_2O); 4.44 s, 2 H (CH_2O); 5.62 d, 1 H, J(3′,2′) = 6.4 (H-3′); 6.41 – 6.55 m, 2 H (H-1′, H-2′); 7.52 – 7.70 m and 8.02 – 8.07 m, 3 H and 2 H (H-arom.); 8.72 s, 1 H (H-2); 8.79 s, 1 H (H-8); 11.27 s, 1 H (NH).

9-(2,3-Anhydro-4-*C*-hydroxymethyl-α-L-ribofuranosyl)adenine (*VIa*)

A solution of mesyl derivative *III* (3.44 g, 5 mmol) in 0.5 M methanolic sodium methoxide (30 ml) was set aside at room temperature overnight. The mixture was neutralized with acetic acid and concentrated. Crystallization of the residue from water afforded 815 mg (59%) of anhydro nucleoside *VIa*, m.p. 272 °C (decomp.); R_F 0.36 (S3). For $C_{11}H_{13}N_5O_4$ (279.3) calculated: 47.31% C, 4.69% H, 25.08% N; found: 47.12% C, 4.69% H, 25.29% N. ^{1}H NMR spectrum: 3.42 – 3.49 m, 3.58 – 3.66 m and 3.75 – 3.85 m, 1 H, 2 H and 1 H (2 × CH_2O); 4.01 d, 1 H, J(3′,2′) = 3.1 (H-3′); 4.32 dd, 1 H, J(2′,1′) = 0.6 (H-2′); 5.00 t, 1 H, J(OH,CH_2) = 5.6 (CH_2OH); 5.10 t, 1 H, J(OH,CH_2) = 5.3 (CH_2OH); 6.46 d, 1 H (H-1′); 7.33 s, 2 H (NH_2); 8.14 s, 1 H (H-2); 8.17 s, 1 H (H-8).

9-(2,3-Anhydro-4-*C*-hydroxymethyl-α-L-lyxofuranosyl)adenine (*VIIa*)

Mesyl derivative *V* (3.03 g, 5 mmol) was converted into compound *VIIa* by procedure described for the preparation of anhydro nucleoside *VIa*. Yield of *VIIa* 1.03 g (74%), m.p. 202 – 204 °C; R_F 0.40 (S3). For $C_{11}H_{13}N_5O_4$ (279.3) calculated: 47.31% C, 4.69% H, 25.08% N; found: 47.08% C, 4.74% H, 24.81% N. ^{1}H NMR spectrum: 3.38 – 3.58 m and 3.76 dd, 3 H and 1 H (2 × CH_2O); 4.10 d, 1 H, J(3′,2′) = 2.7 (H-3′); 4.48 d, 1 H (H-2′); 4.98 t, 1 H, J(OH,CH_2) = 5.7 (CH_2OH); 5.04 t, 1 H, J(OH,CH_2) = 5.2 (CH_2OH); 6.18 s, 1 H (H-1′); 7.31 s, 2 H (NH_2); 8.16 s, 1 H (H-2); 8.36 s, 1 H (H-8).

9-(4-*C*-Acetoxymethyl-5-*O*-acetyl-2,3-anhydro-α-L-ribofuranosyl)adenine (*VIb*)

4-Dimethylaminopyridine (250 mg) and acetic anhydride (0.5 ml) were added to a stirred suspension of epoxide *VIa* (1.40 g, 5 mmol) in acetonitrile (15 ml). After 3 h, another portion (0.5 ml) of acetic anhydride was added and the mixture was stirred overnight at room temperature. The crystalline compound that separated was collected and washed with ethanol; yield 1.62 g (89%) of acetyl derivative *VIb*, m.p. 171 – 173 °C; R_F 0.67 (S3). For $C_{15}H_{17}N_5O_6$ (363.3) calculated: 49.58% C, 4.72% H, 19.28% N; found: 49.46% C, 4.73% H, 19.30% N. ^{1}H NMR spectrum: 2.06 s, 3 H (CH_3CO); 2.13 s, 3 H (CH_3CO); 4.22 d, 1 H, J(3′,2′) = 2.7 (H-3′); 4.26 d, 1 H, J(a,b) = 11.9 (CH^aH–O); 4.31 s, 2 H

(CH_2O); 4.39 d, 1 H (CH^bH–O); 4.46 dd, 1 H, *J*(2′,1′) = 0.6 (H-2′); 6.42 d, 1 H (H-1′); 7.38 s, 2 H (NH_2); 8.19 s, 2 H (H-2, H-8).

9-(4-*C*-Acetoxymethyl-5-*O*-acetyl-2,3-anhydro-α-L-lyxofuranosyl)adenine (*VIIb*)

Anhydro nucleoside *VIIa* (1.40 g, 5 mmol) was acetylated as described in the preceding experiment to give 1.49 g (82%) of compound *VIIb*, m.p. 127 – 128 °C; R_F 0.71 (S3). For $C_{15}H_{17}N_5O_6$ (363.3) calculated: 49.58% C, 4.72% H, 19.28% N; found: 49.39% C, 4.68% H, 19.31% N. ^{1}H NMR spectrum: 1.92 s, 3 H (CH_3CO); 2.05 s, 3 H (CH_3CO); 4.16 s, 2 H (CH_2O); 4.25 s, 2 H (CH_2O); 4.33 d, 1 H, *J*(3′,2′) = 2.8 (H-3′); 4.66 d, 1 H (H-2′); 6.30 s, 1 H (H-1′); 7.36 s, 2 H (NH_2); 8.16 s, 1 H (H-2); 8.32 s, 1 H (H-8).

9-(4-*C*-Acetoxymethyl-5-*O*-acetyl-2-bromo-2-deoxy-α-L-arabinofuranosyl)adenine (*VIIIa*)

Bromotrimethylsilane (1 ml) and boron trifluoride etherate (2 ml) were added to a solution of epoxide *VIb* (1.82 g, 5 mmol) in dioxane (20 ml). The mixture was stirred at room temperature for 3 h and then 1 M triethylammonium hydrogen carbonate solution (20 ml) was added. The mixture was concentrated to a half of the original volume and extracted with chloroform (2 × 50 ml). The combined chloroform extracts were dried over magnesium sulfate and the solvent was evaporated to give 2.02 g (91%) of bromo derivative *VIIIa* as a solid foam; R_F 0.56 (S2). For $C_{15}H_{18}BrN_5O_6$ (444.2) calculated: 40.55% C, 4.08% H, 17.99% Br, 15.77% N; found: 40.35% C, 4.11% H, 17.78% Br, 15.94% N. ^{1}H NMR spectrum: 2.04 s, 3 H (CH_3CO); 2.09 s, 3 H (CH_3CO); 4.13 – 4.42 m, 4 H (2 × CH_2O); 4.54 dd, 1 H, *J*(3′,2′) = 9.2, *J*(3′,OH) = 5.8 (H-3′); 5.40 t, 1 H, *J*(2′,1′) = 9.2 (H-2′); 6.25 d, 1 H (H-1′); 6.47 d, 1 H (3′-OH); 7.42 s, 2 H (NH_2); 8.17 s, 1 H (H-2); 8.44 s, 1 H (H-8).

9-(4-*C*-Acetoxymethyl-5-*O*-acetyl-2-deoxy-α-L-*erythro*-pentofuranosyl)adenine (*VIIIb*)

A solution of tributylstannane (1 M, 2 ml) in toluene and 2,2′-azobis(2-propionitrile) (30 mg) were added at 100 °C to a solution of bromo derivative *VIIIa* (444 mg, 1 mmol) in dioxane (3 ml). After heating for 20 min, the hot mixture was filtered and filtrate was taken down. The residue was chromatographed on a column of silica gel (40 g) in ethyl acetate–acetone–ethanol–water (36 : 6 : 5 : 3) to give 326 mg (89%) of deoxy derivative *VIIIb* as a solid foam; R_F 0.34 (S2). For $C_{15}H_{19}N_5O_6$ (365.3) calculated: 49.31% C, 5.24% H, 19.17% N; found: 49.03% C, 5.34% H, 18.89% N. ^{1}H NMR spectrum: 1.98 s, 3 H (CH_3CO); 2.07 s, 3 H (CH_3CO); 2.47 m, 1 H, *J*(2a′,1′) = 3.4, *J*(2a′,2b′) = 14.7, *J*(2a′,3′) = 2.8 (H-2a′); 3.02 m, 1 H, *J*(2b′,1′) = 8.1, *J*(2b′,3′) = 6.5 (H-2b′); 4.06 d, 1 H, *J*(a,b) = 11.4 (CH^aH–O); 4.11 d, 1 H (CH^bH–O); 4.23 d, 1 H, *J*(c,d) = 11.6 (CH^cH–O); 4.30 d, 1 H (CH^dH–O); 4.41 m, 1 H (H-3′); 6.35 dd, 1 H (H-1′); 6.47 d, 1 H, *J*(OH,3′) = 6.1 (3′-OH); 7.37 s, 2 H (NH_2); 8.16 s, 1 H (H-2); 8.37 s, 1 H (H-8).

9-(4-*C*-Acetoxymethyl-5-*O*-acetyl-2-deoxy-α-L-*threo*-pentofuranosyl)adenine (*IXb*)
and 9-(4-*C*-Acetoxymethyl-5-*O*-acetyl-3-deoxy-α-L-*threo*-pentofuranosyl)adenine (*Xb*)

Epoxy nucleoside *VIIb* (1.82 g, 5 mmol) was treated with bromotrimethylsilane as described for the preparation of bromo derivative *VIIIa*. The obtained mixture of bromo nucleosides *IXa* and *Xa* was dissolved in dioxane (20 ml), the solution was heated to the boil and 1 M solution of tributylstannane (10 ml) in toluene and 2,2′-azobis(2-propionitrile) (100 mg) were added under stirring. After boiling for 20 min, the mixture was cooled and the solvent was evaporated. The residue was mixed with light petroleum (100 ml) and the separated solid was collected and washed with light petroleum. Chromatography on a column of silica gel (500 g) in ethyl acetate–acetone–ethanol–water (8 : 6 : 4 : 2) and

crystallization of the first fraction from 2-propanol afforded 509 mg (28%) of compound *Xb*, m.p. 172 – 173 °C; R_F 0.38 (S2). For $C_{15}H_{19}N_5O_6$ (365.3) calculated: 49.31% C, 5.24% H, 19.17% N; found: 49.31% C, 5.25% H, 19.07% N. ^{1}H NMR spectrum: 1.98 s, 3 H (CH_3CO); 2.00 dd, 1 H (H-3a′);2.07 s, 3 H (CH_3CO); 2.58 dd, 1 H, *J*(3b′,2′) = 7.0, *J*(3b′,3a′) = 13.7 (H-3b′); 4.13 d, 1 H, *J*(a,b) = 11.6 (CH^aH–O); 4.14 d, 1 H, *J*(c,d) = 11.6 (CH^cH–O); 4.18 d, 1 H (CH^dH–O); 4.27 d, 1 H (CH^bH–O); 4.97 m, 1 H (H-2′); 5.78 d, 1 H, *J*(OH,2′) = 4.6 (2′-OH); 5.94 d, 1 H, *J*(1′,2′) = 4.3 (H-1′); 7.30 s, 2 H (NH_2); 8.15 s, 1 H (H-2); 8.31 s, 1 H (H-8).

The second fraction afforded 620 mg (34%) of deoxy derivative *IXb* as a solid foam; R_F 0.37 (S2). For $C_{15}H_{19}N_5O_6$ (365.3) calculated: 49.31% C, 5.24% H, 19.17% N; found: 49.08% C, 5.28% H, 18.92% N. ^{1}H NMR spectrum: 1.96 s, 3 H (CH_3CO); 2.03 s, 3 H (CH_3CO); 2.42 m, 1 H (H-2a′); 3.05 m, 1 H, *J*(2b′,1′) = 6.7, *J*(2b′,2a′) = 13.4, *J*(2b′,3′) = 6.7 (H-2b′); 4.09 – 4.27 m, 4 H (2 × CH_2O); 4.70 m, 1 H, *J*(3′,2a′) = 4.9, *J*(3′,OH) = 4.9 (H-3′); 5.65 d, 1 H (3′-OH); 6.39 t, 1 H, *J*(1′,2a′) = 6.5 (H-1′); 7.29 s, 2 H (NH_2); 8.14 s, 1 H (H-2); 8.32 s, 1 H (H-8).

9-(2-Deoxy-4-*C*-hydroxymethyl-α-L-*erythro*-pentofuranosyl)adenine (*VIIIc*)

A solution of acetyl derivative *VIIIb* (183 mg, 0.5 mmol) in methanolic ammonia was set aside at room temperature overnight. After evaporation of the solvent, the residue was crystallized from 2-propanol to give 125 mg (89%) of compound *VIIc*, m.p. 189 – 191 °C; R_F 0.24 (S3). For $C_{11}H_{15}N_5O_4$ (281.3) calculated: 46.97% C, 5.38% H, 24.90% N; found: 47.10% C, 5.40% H, 24.70% N. UV spectrum (water): λ_{max} 260 nm, ε_{max} 15 100. ^{1}H NMR spectrum: 2.32 m, 1 H, *J*(2a′,1′) = 3.4, *J*(2a′,2b′) = 14.1, *J*(2a′,3′) = 2.1 (H-2a′); 2.94 m, 1 H, *J*(2b′,1′) = 8.1, *J*(2b′,3′) = 6.7 (H-2b′); 3.33 – 3.70 m, 4 H (2 × CH_2O); 4.36 m, 1 H, *J*(3′,OH) = 6.1 (H-3′); 4.56 t, *J*(OH,CH_2) = 5.8 (OH); 4.83 t, 1 H, *J*(OH,CH_2) = 5.7 (OH); 5.91 d, 1 H (3′-OH); 6.31 dd, 1 H (H-1′); 7.34 s, 2 H (NH_2); 8.15 s, 1 H (H-2); 8.40 s, 1 H (H-8); after exchange with D_2O: 3.38 d, 1 H, *J*(a,b) = 11.3 (CH^aH–O); 3.49 d, 1 H (CH^bH–O); 3.58 d, 1 H, *J*(c,d) = 11.6 (CH^cH–O); 3.63 d, 1 H (CH^dH–O).

9-(2-Deoxy-4-*C*-hydroxymethyl-α-L-*threo*-pentofuranosyl)adenine (*IXc*)

Methanolysis of acetyl derivative *IXb* (183 mg, 0.5 mmol) with methanolic ammonia, followed by crystallization from 2-propanol, afforded 112 mg (80%) of compound *IXc*, m.p. 181 – 182.5 °C; R_F 0.27 (S3). For $C_{11}H_{15}N_5O_4$ (281.3) calculated: 46.97% C, 5.38% H, 24.90% N; found: 46.79% C, 5.45% H, 24.71% N. ^{1}H NMR spectrum: 2.33 m, 1 H, *J*(2a′,1′) = 6.4, *J*(2a′,2b′) = 13.4, *J*(2a′,3′) = 3.2 (H-2a′); 2.84 m, 1 H, *J*(2b′,1′) = 7.3, *J*(2b′,3′) = 6.2 (H-2b′): 3.57 d, 4 H, *J*(CH_2,OH) = 5.8 (2 × CH_2O); 4.42 – 4.53 m, 2 H (H-3′,OH); 5.19 d, 1 H, *J*(OH,3′) = 4.6 (3′-OH); 5.25 t, 1 H (OH); 6.37 dd, 1 H (H-1′); 7.31 s, 2 H (NH_2); 8.13 s, 1 H (H-2); 8.34 s, 1 H (H-8).

9-(3-Deoxy-4-*C*-hydroxymethyl-α-L-*threo*-pentofuranosyl)adenine (*Xc*)

Methanolysis of acetyl derivative *Xb* (183 mg, 0.5 mmol) with methanolic ammonia, followed by crystallization from 2-propanol, afforded 114 mg (81%) of compound *Xc*, m.p. 210 – 212 °C; R_F 0.31 (S3). For $C_{11}H_{15}N_5O_4$ (281.3) calculated: 46.97% C, 5.38% H, 24.90% N; found: 46.89% C, 5.32% H, 24.87% N. UV spectrum (water): λ_{max} 260 nm, ε_{max} 15 100. ^{1}H NMR spectrum: 2.01 dd, 1 H, *J*(3a′,2′) = 8.2, *J*(3a′,3b′) = 12.5 (H-3a′); 2.34 dd, 1 H, *J*(3b′,2′) = 7.9 (H-3b′); 3.34 – 3.59 m, 4 H (2 × CH_2O); 4.82 m, 1 H (H-2′); 4.99 t, 1 H, *J*(OH,CH_2) = 5.6 (OH); 5.50 t, 1 H, *J*(OH,CH_2) = 4.0 (OH); 5.56 d, 1 H, *J*(OH,2′) = 5.5 (2′-OH); 5.79 d, 1 H, *J*(1′,2′) = 6.1 (H-1′); 7.36 s, 2 H (NH_2); 8.13 s, 1 H (H-2); 8.32 s, 1 H (H-8).

9-(4-*C*-Acetoxymethyl-3,5-di-*O*-acetyl-2-bromo-2-deoxy-α-L-arabinofuranosyl)adenine (*VIIId*)

Acetic anhydride (0.25 ml) and 4-dimethylaminopyridine (0.2 g) were added to a solution of bromo derivative *VIIIa* (2.22 g, 5 mmol) in acetonitrile (10 ml). After 3 h, another portion of acetic anhydride (0.25 ml) was added and the reaction mixture was allowed to stand at room temperature for 3 h. Methanol (0.5 ml) was added and the solution was taken down. The residue was dissolved in chloroform (50 ml) and the solution was washed with water (2 × 5 ml), dried over magnesium sulfate, and the solvent was evaporated. Crystallization of the residue from 2-propanol afforded 1.97 g (81%) of triacetyl derivative *VIIId*, m.p. 76 – 79 °C; R_F 0.63 (S2). For $C_{17}H_{20}BrN_5O_7$ (486.3) calculated: 41.99% C, 4.15% H, 16.43% Br, 14.40% N; found: 41.71% C, 4.25% H, 16.15% Br, 14.11% N. ^{1}H NMR spectrum: 2.67 s, 6 H (2 × CH_3CO); 2.17 s, 3 H (CH_3CO); 4.21 – 4.40 m, 4 H (2 × CH_2O); 5.71 – 5.83 m, 2 H (H-2′, H-3′); 6.43 dd, 1 H, J(1′,2′) = 7.5, J = 1.4 (H-1′); 7.42 s, 2 H (NH_2); 8.19 s, 1 H (H-2); 8.47 s, 1 H (H-8).

9-(4-*C*-Acetoxymethyl-5-*O*-acetyl-2,3-dideoxy-α-L-*glycero*-pent-2-enofuranosyl)adenine (*XIa*)

A solution of bromo derivative *VIIId* (486 mg, 1 mmol) in dimethylformamide (7 ml) was added during 30 min at 0 °C to a stirred suspension of Cu/Zn couple (prepared from 0.55 g of cupric acetate and 3.4 g of zinc powder according to ref.[12]). After stirring for 15 min at 0 °C, the mixture was filtered through Celite, the insoluble material was washed with dimethylformamide (7 ml) and the combined filtrates were diluted with chloroform (250 ml). The solution was successively washed with saturated solution of disodium salt of ethylenediaminetetraacetic acid (2 × 15 ml) and 10% solution of sodium hydrogen carbonate (15 ml). After drying over magnesium sulfate, the solvent was evaporated, the residue was codistilled with xylene and crystallized from 2-propanol to give 291 mg (84%) of compound *XIa*, m.p. 139 – 140 °C; R_F 0.33 (S2). For $C_{15}H_{17}N_5O_5$ (347.3) calculated: 51.87% C, 4.93% H, 20.16% N; found: 51.61% C, 5.10% H, 19.98% N. ^{1}H NMR spectrum: 2.00 s, 3 H (CH_3CO); 2.07 s, 3 H (CH_3CO); 4.13 – 4.33 m, 4 H (2 × CH_2O); 6.34 – 6.42 m, 2 H (H-2′, H-3′); 6.98 bs, 1 H (H-1′); 7.33 s, 2 H (NH_2); 8.09 s, 1 H (H-2); 8.17 s, 1 H (H-8).

9-(2,3-Dideoxy-4-*C*-hydroxymethyl-α-L-*glycero*-pent-2-enofuranosyladenine (*XIb*)

Methanolysis of acetyl derivative *XIa* (174 mg, 0.5 mmol) with methanolic ammonia and crystallization from methanol–2-propanol afforded 115 mg (87%) of compound *XIb*, m.p. 196.5 – 197.5 °C; R_F 0.24 (S3). For $C_{11}H_{13}N_5O_3$ (263.3) calculated: 50.18% C, 4.98% H, 26.60% N; found: 50.01% C, 5.05% H, 26.48% N. ^{1}H NMR spectrum: 3.40 – 3.68 m, 4 H (2 × CH_2O); 4.87 t, 1 H, J(OH,CH_2) = 6.1 (OH); 5.06 t, 1 H, J(OH,CH_2) = 5.6 (OH); 6.13 dd, 1 H, J(3′,1′) = 1.0, J(3′,2′) = 5.9 (H-3′); 6.36 dd, 1 H, J(2′,1′) = 1.9 (H-2′); 6.97 m, 1 H (H-1′); 7.28 s, 2 H (NH_2); 8.14 s, 1 H (H-2); 8.20 s, 1 H (H-8).

9-(4-*C*-Acetoxymethyl-5-*O*-acetyl-2,3-dideoxy-α-L-*glycero*-pentofuranosyl)adenine (*XIIa*)

Magnesium oxide (80 mg) and 10% Pd/C (50 mg) were added to a solution of bromo derivative *VIIId* (486 mg, 1 mmol) in dimethylformamide (3 ml) and the mixture was hydrogenated at atmospheric pressure and room temperature for 30 h. The insoluble material was removed by filtration through Celite, washed with dimethylformamide and the combined filtrates were taken down. Chromatography on a column of silica gel (50 g) in ethyl acetate–acetone–ethanol–water (19 : 3 : 2 : 1) afforded two principal UV-absorbing fractions. The first on methanolysis gave 48 mg (17%) of deoxy derivative *VIIIc*.

The second fraction afforded 198 mg (57%) of compound *XIIa*, m.p. 143 – 144 °C; R_F 0.36 (S2). For $C_{15}H_{19}N_5O_5$ (349.3) calculated: 51.57% C, 5.48% H, 20.05% N; found: 51.71% C, 5.56% H,

20.23% N. ^{1}H NMR spectrum: 1.84 s, 3 H (CH_3CO); 2.07 s, 3 H (CH_3CO); 2.00 – 2.13 m and 2.32 – 2.73 m, 1 H and 3 H (2 × H-2′, 2 × H-3′); 4.09 s, 2 H (CH_2O); 4.15 s, 2 H (CH_2O); 6.31 dd, 1 H, J(1′,2a′) = 4.9, J(1′,2b′) = 6.1 (H-1′); 7.28 s, 2 H (NH_2); 8.15 s, 1 H (H-2); 8.32 s, 1 H (H-8).

9-(2,3-Dideoxy-4-*C*-hydroxymethyl-α-L-*glycero*-pentofuranosyl)adenine (*XIIb*)

A. Methanolysis of acetyl derivative *XIIa* (175 mg, 0.5 mmol) with methanolic ammonia and crystallization from 80% ethanol afforded 107 mg (81%) of dideoxy derivative *XIIb*, m.p. 199 – 201 °C; R_F 0.25 (S3). For $C_{11}H_{15}N_5O_3$ (265.3) calculated: 49.80% C, 5.70% H, 26.40% N; found: 49.63% C, 5.81% H, 26.31% N. ^{1}H NMR spectrum: 1.92 – 2.22 m and 2.41 – 2.52 m, 2 H and 2 H (2 × H-2′, 2 x H-3′); 3.37 d, 2 H, J(CH_2,OH) = 5.5 (CH_2O); 3.48 m, 2 H (CH_2O); 4.84 t, 1 H (OH); 5.16 dd, 1 H, J(OH,CH_2) = 5.3, J(OH,CH_2) = 6.5 (OH); 6.25 t, 1 H, J(1′,2a′) = J(1′,2b′) = 6.0 (H-1′); 7.29 s, 2 H (NH_2); 8.13 s, 1 H (H-2); 8.34 s, 1 H (H-8).

B. Didehydro dervative *XIb* (100 mg, 0.38 mmol) in dimethylformamide (2.5 ml) was hydrogenated over 10% Pd/C (10 mg) at room temperature for 30 h. The catalyst was removed by filtration through Celite, washed with dimethylformamide, and the combined filtrates were taken down. According to TLC (S3), the residue contained significant amount of adenine in addition to compound *XIIb*. The residue was dissolved in hot 2-propanol, filtered and allowed to crystallize overnight. Yield 45 mg (45%) of dideoxy derivative *XIIb*, identical with the product prepared according to procedure *A*.

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