[5-(ADENIN-9-YL)-5-DEOXYPENTOFURANOSYL]PHOSPHONATES – A NOVEL TYPE OF NUCLEOTIDE ANALOGS RELATED TO HPMPA. I. DERIVATIVES WITH L-*arabino*, D-*arabino*, 2-DEOXY-L-*erythro* AND 2-DEOXY-L-*threo* CONFIGURATION

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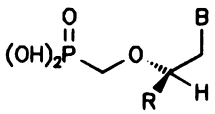
[5-(Adenin-9-yl)-5-deoxypentofuranosyl]phosphonates, a new type of nucleotide analogs with fixed HPMPA structure, have been prepared. The synthesis of compounds of L-*arabino* (*IIa*, *IIb*), D-*arabino* (*XIVa*, *XIVb*), 2-deoxy-L-*erythro* (*IIIa*, *IIIb*) and 2-deoxy-L-*threo* (*IVa*, *IVb*) configuration is based on the Michaelis–Arbuzov reaction of the fully protected methyl glycosides with triethyl phosphite and trimethylsilyl triflate which leads to anomeric mixture of diethyl (L-pentofuranosyl) phosphonates. The protected 5-*O*-tosyl derivatives react with sodium salt of adenine to give N^9-substituted products which after total deprotection afford the title nucleotide analogs. The fixation of the partial structure of HPMPA to form five-membered ring leads to a significant decrease, or a total loss, of biological activity.

A number of biologically active nucleotide analogs containing a phosphonate group have been described that are resistant against dephosphorylating enzymes[1 – 5]. To the most studied compounds of this type belong particularly two groups of acyclic analogs of nucleotides with the phosphonomethyl ether group: *N*-(*S*)-(2-phosphonomethoxy-3-hydroxypropyl) (HPMP; *Ia*) and *N*-(2-phosphonomethoxyethyl) (PME; *Ib*) derivatives of adenine, guanine, 2,6-diaminopurine and cytosine which show specific activity against DNA viruses (herpesviruses, adenoviruses, poxviruses). The PME compounds are also active against retroviruses (MSV, HIV) and exhibit a cytostatic effect to mice L-1210 leukemia cells (for a review see refs[1 – 4]).

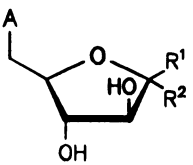
Within the framework of our systematic structure–biological activity investigations of these compounds, and a series of their possible structural modifications[4,5], we studied the synthesis of a novel type of cyclic nucleotide analogs derived from the structure of HPMP compounds in which the basic aliphatic chain, including the only chiral center, is a part of a five-membered ring.

The aim of the present work was to study the effect of fixation of the acyclic skeleton on biological activity. With this in mind, we prepared a series of [5-(adenin-9-yl)-5-deoxy-α- and β-L-pentofuranosyl]phosphonates *II* – *IV*, differing in the number and

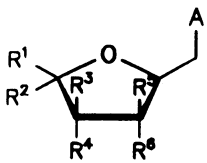
configuration of hydroxy groups in positions 2 and 3 of the sugar moiety, and in configuration of the carbon atom bearing the phosphonate group. Since our objective was to prepare derivatives with the same configuration of the chiral center as in the known effective antiviral (*S*)-9-(2-phosphonomethoxy-3-hydroxypropyl)adenine[1] ((*S*)-HPMPA, *Ia*, B = Ade), our synthesis of the cyclic analogs started predominantly from the L-sugars. As key synthons we used dialkyl L-pentofuranosyl phosphonates which were obtained from the fully protected methyl L-pentofuranoside by the Michaelis–Arbuzov reaction. This method represents a modification of the previously described methods utilizing protected 1-*O*-acetates[6,7] or 1-*O*-trichloroacetimidates[8] but, unlike them, it is not very stereospecific, enabling thus to obtain both the anomeric glycosyl phosphonates in preparatively acceptable relative ratios.



Ia, R = CH_2OH
Ib, R = H



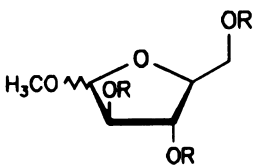
XIVa, R^1 = H; R^2 = $P(O)(OH)_2$
XIVb, R^1 = $P(O)(OH)_2$; R^2 = H



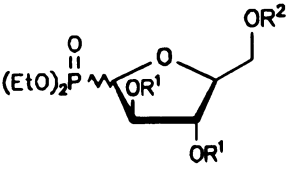
IIa, R^1 = R^4 = R^5 = H; R^2 = $P(O)(OH)_2$; R^3 = R^6 = OH
IIb, R^1 = $P(O)(OH)_2$; R^2 = R^4 = R^5 = H; R^3 = R^6 = OH
IIIa, R^1 = R^3 = R^4 = R^5 = H; R^2 = $P(O)(OH)_2$; R^6 = OH
IIIb, R^1 = $P(O)(OH)_2$; R^2 = R^3 = R^4 = R^5 = H; R^6 = OH
IVa, R^1 = R^3 = R^4 = R^6 = H; R^2 = $P(O)(OH)_2$; R^5 = OH
IVb, R^1 = $P(O)(OH)_2$; R^2 = R^3 = R^4 = R^6 = H; R^5 = OH

The synthesis of compounds of L-*arabino* configuration (*IIa*, *IIb*) started from methyl tri-*O*-benzyl-α- and β-L-arabinofuranosides[9,10] *V* which on reaction with triethyl phosphite and trimethylsilyl triflate in acetonitrile afforded 55% of an anomeric mixture of diethyl (2,3,5-tri-*O*-benzyl-L-arabinofuranosyl)phosphonates *VII* in the ratio α : β = 1 : 3.5. Hydrogenolytic removal of the benzyl groups gave diethyl (α- and β-L-arabinofuranosyl)phosphonates *VIII*. In the analogous reaction, methyl 2,3,5-tri-*O*-(trimethylsilyl)-α- and β-L-arabinofuranosides *VI* gave the desired phosphonates *VIII* directly but in a lower yield. The compounds *VIII* were selectively converted into diethyl (5-*O*-tosyl-α- and β-L-arabinofuranosyl)phosphonates *IX* by treatment with one equivalent of

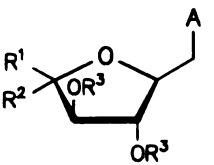
tosyl chloride in pyridine and compounds *IX* were subjected to acid-catalyzed reaction with 3,4-dihydro-2*H*-pyran to give 2,3-di-*O*-(tetrahydropyran-2-yl) derivatives *X*. Reaction of these compounds with sodium salt of adenine in *N*,*N*-dimethylformamide afforded N^9-substituted products *XIa* and *XIb* which were separated by column chromatography on silica gel and, after acid-catalyzed removal of the tetrahydropyranyl groups, furnished anomerically pure diethyl [5-(adenin-9-yl)-5-deoxy-α- and β-L-arabinofuranosyl]phosphonates *XIIa* and *XIIb*. These on boiling with 60% aqueous pyridine were converted into monoethyl esters *XIIIa* and *XIIIb*. The free acids *IIa* and *IIb* were obtained from their diesters by treatment with bromotrimethylsilane[11].



V, R = Bn
VI, R = $SiMe_3$



VII, $R^1 = R^2$ = Bn
VIII, $R^1 = R^2$ = H
IX, R^1 = H; R^2 = Ts
X, R^1 = THP; R^2 = Ts



XIa, R^1 = H; R^2 = P(O)$(OEt)_2$; R^3 = THP
XIb, R^1 = P(O)$(OEt)_2$; R^2 = H; R^3 = THP
XIIa, $R^1 = R^3$ = H; R^2 = P(O)$(OEt)_2$
XIIb, R^1 = P(O)$(OEt)_2$; $R^2 = R^3$ = H
XIIIa, $R^1 = R^3$ = H; R^2 = P(O)(OH)(OEt)
XIIIb, R^1 = P(O)(OH)(OEt); $R^2 = R^3$ = H

Bn = benzyl; THP = tetrahydropyran-2-yl

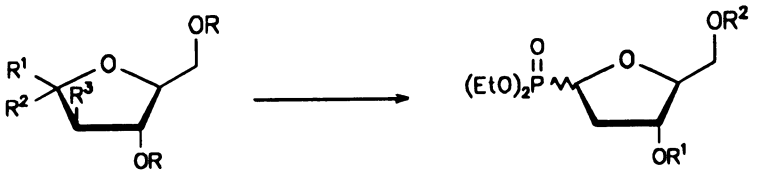
SCHEME 1

In analogous manner we also prepared the enantiomeric [5-(adenin-9-yl)-5-deoxy-α- and β-D-arabinofuranosyl]phosphonic acids *XIVa* and *XIVb* (see Scheme 1).

Synthesis of the above-mentioned nucleotide analogs with L-*erythro* configuration (*III*) started from an anomeric mixture of methyl L-arabinofuranosides[12] (α : β = 1 : 1) which on reaction with 1,3-dibromo-1,1,3,3-tetraisopropyldisiloxane[13] (prepared in situ from the corresponding silane and bromine in tetrachloromethane) afforded methyl 3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α- and β-L-arabinofuranosides *XVa* and *XVb*. Both the protected anomers were separated by chromatography on silica gel and, after conversion into the phenoxythiocarbonyl derivatives *XVIa* and *XVIb*, reduced with tributylstannane[14]. The protected α-anomer *XVIa*, in which the phenoxythiocarbonyl group is trans to the neighbouring methoxy group on C(1), afforded in a good yield the corresponding methyl 2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α-L-*erythro*-pentofuranoside *XVII*. In contrast, the β-anomer *XVIb* (with cis orientation of the phenoxythiocarbonyl and methoxy groups) gave a mixture of products from which we isolated in low yield only methyl 2-*O*-methyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-L-arabinofuranoside *XVIII*.

Using the above-mentioned procedure, the α-anomer *XVII* was converted into a mixture of [2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α- and β-L-*erythro*-pentofuranosyl]phosphonates *XIX* (α : β = 1 : 3) in 71% yield. Compounds *XIX* were then deblocked by treatment with tetrabutylammonium fluoride, affording diethyl (2-deoxy-α- and β-L-*erythro*-pentofuranosyl)phosphonates *XX*. Selective tosylation of their primary hydroxy groups led to both the anomeric diethyl (2-deoxy-5-*O*-tosyl-α- and β-L-*erythro*-pentofuranosyl)phosphonates *XXIa* and *XXIb* which were separated by chromatography on silica gel. Reaction with 3,4-dihydro-2*H*-pyran converted them into 3-*O*-(tetrahydropyran-2-yl) derivatives *XXIIa* and *XXIIb* which were reacted with sodium salt of adenine to give N^9-alkylation products *XXIIIa* and *XXIIIb*. Acid-catalyzed removal of the tetrahydropyranyl groups afforded diethyl [5-(adenin-9-yl)-2-deoxy-α- and β-L-*erythro*-pentofuranosyl]phosphonates *XXIVa* and *XXIVb* which were converted into monoesters *XXVa* and *XXVb* by reflux in 60% pyridine or into the free acids *IIIa* and *IIIb* by reaction with bromotrimethylsilane (see Scheme 2).

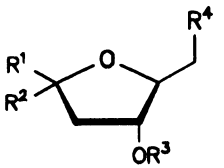
The synthesis of cyclic analogs of L-*threo* configuration (*IVa* and *IVb*) started from 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-L-xylofuranose *XXVI* (prepared by benzylation[15] of 1,2-*O*-isopropylidene-α-L-xylofuranose which in turn was obtained from L-xylose[16] according to a described procedure[17]). Reaction of compound *XXVI* with methanolic hydrogen chloride afforded first a mixture of methyl 3,5-di-*O*-benzyl-α- and β-L-xylofuranosides (*XXVIIa*, *XXVIIb*) from which the pure anomers were obtained by chromatography on silica gel, then separately converted into the 2-*O*-phenoxythiocarbonyl derivatives *XXVIIIa* and *XXVIIIb* which were deoxygenated by reduction with tributylstannane. The α-anomer *XXVIIIa* with phenoxythiocarbonyl group in cis relation to the neighbouring methoxy group on C(1) afforded only low yield of methyl



In formulae *XV–XVIII*
R = $Si(iPr)_2–O–Si(iPr)_2$

XIX, $R^1 + R^2 = R$
XX, $R^1 = R^2 = H$

XVa, $R^1 = H$; $R^2 = OCH_3$; $R^3 = OH$
XVb, $R^1 = OCH_3$; $R^2 = H$; $R^3 = OH$
XVIa, $R^1 = H$; $R^2 = OCH_3$; $R^3 = OC(S)(OPh)$
XVIb, $R^1 = OCH_3$; $R^2 = H$; $R^3 = OC(S)(OPh)$
XVII, $R^1 = R^3 = H$; $R^2 = OCH_3$
XVIII, $R^1 = R^3 = OCH_3$; $R^2 = H$



XXIa, $R^1 = R^3 = H$; $R^2 = P(O)(OEt)_2$; $R^4 = OTs$
XXIb, $R^1 = P(O)(OEt)_2$; $R^2 = R^3 = H$; $R^4 = OTs$
XXIIa, $R^1 = H$; $R^2 = P(O)(OEt)_2$; $R^3 = THP$; $R^4 = OTs$
XXIIb, $R^1 = P(O)(OEt)_2$; $R^2 = H$; $R^3 = THP$; $R^4 = OTs$
XXIIIa, $R^1 = H$; $R^2 = P(O)(OEt)_2$; $R^3 = THP$; $R^4 = Ade$
XXIIIb, $R^1 = P(O)(OEt)_2$; $R^2 = H$; $R^3 = THP$; $R^4 = Ade$
XXIVa, $R^1 = R^3 = H$; $R^2 = P(O)(OEt)_2$; $R^4 = Ade$
XXIVb, $R^1 = P(O)(OEt)_2$; $R^2 = R^3 = H$; $R^4 = Ade$
XXVa, $R^1 = R^3 = H$; $R^2 = P(O)(OH)(OEt)$; $R^4 = Ade$
XXVb, $R^1 = P(O)(OH)(OEt)$; $R^2 = R^3 = H$; $R^4 = Ade$

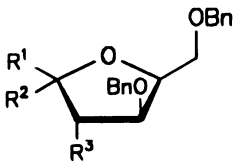
SCHEME 2

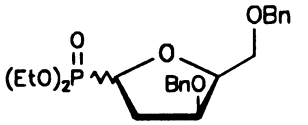
3,5-di-*O*-benzyl-2-deoxy-α-L-*threo*-pentofuranoside *XXIXa*. The β-anomer, in which these groups are in the trans relation, gave the product *XXIXb* in high yield. Both the methyl glycosides *XXIXa* and *XXIXb* were then converted into diethyl (3,5-di-*O*-benzyl-2-deoxy-α- and β-L-*threo*-pentofuranosyl)phosphonates *XXXa* and *XXXb* (α : β = 1 : 3). The mixture of phosphonates *XXX* was then hydrogenolytically debenzylated under formation of diethyl (2-deoxy-α- and β-L-*threo*-pentofuranosyl)phosphonates *XXXIa* and *XXXIb* and both anomers were then separated by chromatography on silica gel. These dihydroxy derivatives *XXXI* were selectively tosylated on the primary hydroxyl to give 5-*O*-tosylates *XXXIIa* and *XXXIIb*. The secondary hydroxyl on C(3) was protected with tetrahydropyranyl group, introduced by reaction with 3,4-dihydro-2*H*-pyran. The protected synthons *XXXIIIa* and *XXXIIIb* were then used in the alkylation of adenine under the above-mentioned conditions. Acid hydrolysis of the obtained N^9-substituted intermediates *XXXIVa* and *XXXIVb* afforded diethyl [5-(adenin-9-yl)-2,5-dideoxy-α- and β-L-*threo*-pentofuranosyl]phosphonates *XXXVa* and *XXXVb* which were converted into the free acids *IVa* and *IVb* by the usual reaction with bromotrimethylsilane (Scheme 3).

The structure of the studied compounds was determined on the basis of their ^1H and ^{13}C APT NMR spectra. Tables I and II show chemical shifts and coupling constants of protons of the (L-pentofuranosyl)phosphonate ring; Tables III and IV contain chemical shifts of carbon atom signals and the C–P coupling constants.

In substituted (L-arabinofuranosyl)phosphonates *IIa*, *IIb*, *VII* – *XIII* the observed data are in accord with the published ones[6]. In these compounds, the crucial parameter for determination of configuration at the anomeric center is the Karplus-like dependence of the vicinal coupling constant ^3J(PCCH) on the dihedral angle. According to ref.[6], the maximum coupling constant corresponds to dihedral angle 0° (^3J = 15 – 20 Hz) or 180° (^3J(PCCH) = 35 – 40 Hz) and the minimum one to an angle 90° (^3J(PCCH) = 0 Hz). On the basis of conformational analysis we estimated that in the α-anomer the dihedral angle H–CC(2)–C(1)–H is about 0 – 20° which corresponds to ^3J(H-2,P) of about 10 Hz. On the other hand, in the β-anomer this dihedral angle is 80 – 100° for which the corresponding ^3J(H-2,P) should be about 2 Hz. The measured values in Table II are in full accord with these assumptions. In the ^{13}C NMR spectrum, the coupling constant ^1J(C,P) is important for the determination of configuration at the anomeric center of (L-arabinofuranosyl)phosphonates. Its value depends on the axial or equatorial orientation of the phosphonate group, $^1J(P_{eq},C)$ being higher than $^1J(P_{ax},C)$. The data in Table IV for the pseudoequatorial orientation of the phosphonate functionality in the β-anomer also agree with those in ref.[6].

In the ^1H NMR spectra of (2-deoxy-L-*erythro*- and 2-deoxy-L-*threo*-pentofuranosyl)phosphonates *III*, *XIX* – *XXV* and *IV*, *XXX* – *XXXV* the anomers were distinguished on the basis of vicinal coupling constants. In accord with the general rules, the α-anomers are characterized by different values of ^3J(1,2) and ^3J(1,2′), non-zero value





XXVI, R^1 = H;
$R^2 + R^3$ = O–isopropylidene

XXX

XXVIIa, R^1 = H; R^2 = OCH_3; R^3 = OH

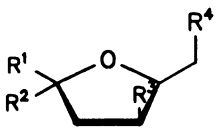
XXVIIb, R^1 = OCH_3; R^2 = H; R^3 = OH

XXVIIIa, R^1 = H; R^2 = OCH_3;
R^3 = OC(S)(OPh)

XXVIIIb, R^1 = OCH_3; R^2 = H;
R^3 = OC(S)(OPh)

XXIXa, $R^1 = R^3$ = H; R^2 = OCH_3

XXIXb, R^1 = OCH_3; $R^2 = R^3$ = H



XXXIa, $R^1 = R^3$ = H; R^2 = $P(O)(OEt)_2$; R^4 = OH

XXXIb, R^1 = $P(O)(OEt)_2$; $R^2 = R^3$ = H; R^4 = OH

XXXIIa, $R^1 = R^3$ = H; R^2 = $P(O)(OEt)_2$; R^4 = OTs

XXXIIb, R^1 = $P(O)(OEt)_2$; $R^2 = R^3$ = H; R^4 = OTs

XXXIIIa, R^1 = H; R^2 = $P(O)(OEt)_2$; R^3 = THP; R^4 = OTs

XXXIIIb, R^1 = $P(O)(OEt)_2$; R^2 = H; R^3 = THP; R^4 = OTs

XXXIVa, R^1 = H; R^2 = $P(O)(OEt)_2$; R^3 = THP; R^4 = Ade

XXXIVb, R^1 = $P(O)(OEt)_2$; R^2 = H; R^3 = THP; R^4 = Ade

XXXVa, $R^1 = R^3$ = H; R^2 = $P(O)(OEt)_2$; R^4 = Ade

XXXVb, R^1 = $P(O)(OEt)_2$; $R^2 = R^3$ = H; R^4 = Ade

SCHEME 3

of ^{2}J(1,P) and considerably different values of ^{3}J(2,P) and ^{3}J(2′,P) (refs[18 - 25]). The ^{13}C NMR spectra of the α-anomers in which, according to the conformational analysis, the phosphonate functionality should be pseudoequatorial, show higher coupling constants ^{1}J(C-1,P) than for the β-anomers; this represents another proof of our interpretation.

TABLE I
500 MHz ^{1}H NMR chemical shifts for prepared compounds

Compound	δ, ppm						
	H-1	H-2	H-2′	H-3	H-4	H-5	H-5′
IIa[a]	3.89	4.36	–	3.86	4.32	4.57	4.51
IIb[a]	4.07	4.22	–	4.15	4.26	4.51	4.51
IIIa[a]	4.10	2.15	1.97	4.21	4.06	4.27	3.98
IIIb[a]	4.09	2.31	1.92	4.04	4.08	4.33	4.14
IVa[a]	4.22	2.27	2.15	4.43	4.31	4.48	4.37
IVb[a]	4.10	2.62	2.22	4.49	4.26	4.54	4.42
VIIIb	4.13	4.05	–	3.90	3.75	3.53	3.49
XIIa	3.96	4.21	–	3.74	4.06	4.38	4.28
XIIb	4.24	4.20	–	3.99	4.10	4.37	4.37
XIIIa	3.90	4.21	–	3.74	4.11	4.40	4.31
XIIIb	4.12	4.15	–	3.99	4.06	4.44	4.39
XXa	4.20	2.05	1.91	4.16	3.75	3.33	3.25
XXb	4.19	2.36	1.92	4.00	3.63	3.49	3.36
XXIa	4.24	2.03	1.94	4.09	3.87	3.98	3.90
XXIb	4.28	2.46	1.94	4.05	4.01	4.35	4.16
XXIVa	4.28	2.17	2.01	4.23	4.14	4.25	4.02
XXIVb	4.16	2.34	1.96	4.02	4.04	4.35	4.16
XXXa	4.27	2.37	2.10	4.08	3.96	3.71	3.56
XXXb	4.07	2.42	2.07	4.21	3.96	3.74	3.59
XXXIa	4.25	2.13	2.00	4.26	3.76	3.58	3.46
XXXIb	4.05	2.42	1.93	4.24	4.08	3.62	3.48
XXXIIa	4.25	2.12	1.99	4.31	3.97	4.17	3.95
XXXIIb	4.11	2.41	1.87	4.32	3.91	4.20	3.96
XXXVa	4.37	2.19	2.09	4.31	4.18	4.31	4.28
XXXVb	4.13	2.48	2.03	4.38	4.06	4.38	4.21

[a] Measured in D_2O.

TABLE II
500 MHz ^{1}H NMR coupling constants for prepared compounds

Compound	*J*, Hz											
	1,2	1,2′	2,2′	2,3	2′,3	3,4	4,5	4,5′	5,5′	1,P	2,P	3,P
IIa[a]	5.8	–	–	4.9	–	5.8	3.9	7.3	14.6	3.4	10.7	–
IIb[a]	2.9	–	–	1.0	–	2.0	4.9	4.9	–	6.8	1.0	2.2
IIIa[a]	10.5	6.8	12.9	5.1	1.7	1.2	3.9	8.8	13.9	1.0	17.9	6.1
IIIb[a]	8.3	7.3	12.9	6.6	5.6	4.7	3.7	7.8	14.2	0	14.9	16.6
IVa[a]	10.8	6.8	13.7	4.9	1.4	3.4	4.9	7.3	14.2	0.5	16.5	5.4
IVb[a]	9.7	5.9	14.2	6.4	3.4	3.9	3.9	8.8	14.6	0	16.7	14.2
VIIIb	4.2	–	–	2.0	–	2.2	4.9	4.9	11.5	4.4	2.5	2.9
XIIa	6.0	–	–	5.1	–	6.6	3.6	8.3	14.4	2.0	14.2	–
XIIb	4.1	–	–	1.7	–	2.0	5.6	5.6	–	4.4	2.2	2.2
XIIIa	4.6	–	–	4.4	–	4.6	4.2	8.3	14.2	2.4	11.0	–
XIIIb	3.9	–	–	1.4	–	1.2	8.8	4.2	14.2	4.8	2.2	1.0
XXa	10.5	6.8	12.9	5.4	2.2	2.2	5.2	6.6	11.5	2.2	18.1	11.8
XXb	8.0	8.8	12.2	7.0	6.8	5.8	3.4	5.4	12.0	0	11.7	19.5
XXIa	9.5	6.8	12.9	5.8	2.9	2.7	3.7	6.1	10.0	1.5	17.1	9.8
XXIb	8.0	9.0	12.5	6.6	6.8	5.8	3.6	7.8	14.2	0	11.0	19.5
XXIVa	10.3	6.8	12.9	5.4	2.2	2.2	4.9	7.8	13.9	2.0	18.3	7.1

TABLE II
(*Continued*)

Compound	*J*, Hz											
	1,2	1,2′	2,2′	2,3	2′,3	3,4	4,5	4,5′	5,5′	1,P	2,P	3,P
XXIVb	8.1	8.3	12.7	6.6	6.4	4.9	3.4	7.8	14.2	0	12.2	17.3
XXXa	7.1	10.0	13.4	1.2	4.6	4.0	4.9	6.6	10.3	2.9	7.3	20.0
XXXb	8.5	8.8	13.2	6.6	3.7	4.9	4.2	7.1	10.5	0	10.0	18.8
XXXIa	10.5	7.1	12.9	4.6	1.2	3.2	5.6	6.1	11.5	3.4	20.2	6.8
XXXIb	9.3	6.8	13.2	6.1	2.9	3.9	4.7	7.0	10.0	0	16.8	17.1
XXXIIa	10.0	7.1	12.9	4.8	1.5	4.0	2.0	8.1	10.0	2.9	19.5	7.3
XXXIIb	8.6	7.8	13.2	6.6	3.9	4.9	2.2	8.3	9.8	0	14.8	17.3
XXXVa	10.3	6.8	13.5	4.9	2.0	2.9	5.4	7.8	14.1	2.9	18.7	7.0
XXXVb	8.3	8.3	13.2	6.3	3.9	4.9	3.4	8.8	14.2	0	14.6	18.0

[a] Measured in D_2O.

Biological studies revealed that neither the synthesized nucleotide analogs nor their mono- or diethyl esters are effective against RNA viruses and retroviruses[26]. Compounds *IIa*, *IIb*, *IIIa*, *IIIb*, *XIIa*, *XIIb*, *XXIVb*, *XXVa* and *XXVb* exhibit only low activity against some DNA viruses (herpes simplex virus type 1 and 2, vaccinia virus and varicella zoster virus) with only low cytotoxicity[26]. Neither of the described compounds is

TABLE III
^{13}C NMR chemical shifts

Compound	δ, ppm				
	C(1)	C(2)	C(3)	C(4)	C(5)
VIIIb	77.71	78.11	78.51	87.95	62.90
XIIa	77.69	77.87	79.20	81.70	44.49
XIIb	77.95	77.32	78.32	84.81	45.19
XXIVa	72.95	35.64	72.43	85.76	45.91
XXIVb	71.97	35.86	72.94	83.92	45.17
XXVb	72.91	35.65	72.88	83.73	45.43
XXXIb	71.61	37.04	70.38	85.14	59.87
XXXIIa	72.36	37.02	70.96	81.45	70.53
XXXIIb	72.54	36.40	71.07	81.10	70.74

TABLE IV
^{13}C NMR coupling constants

Compound	*J*, Hz			
	P,C(1)	P,C(2)	P,(C3)	P,C(4)
VIIIb	172.2	4.2	8.4	11.4
XIIa	164.1	2.3	8.1	4.9
XIIb	170.0	4.4	6.6	8.8
XXIVa	172.4	0	8.8	7.8
XXIVb	169.9	0	7.3	5.4
XXVb	164.8	0	6.1	4.6
XXXIb	171.4	0	5.9	4.4
XXXIIa	171.4	0	7.3	5.9
XXXIIb	154.6	0	6.6	9.5

as effective as the parent (*S*)-HPMPA (*Ia*, B = Ade). The enantiospecificity of the effect is apparently retained because (D-arabinofuranosyl)phosphonate derivatives *XIVa* and *XIVb* are inactive.

EXPERIMENTAL

Unless stated otherwise, the solvents were evaporated at 40 °C/2 kPa and the compounds were dried at 13 Pa over phosphorus pentoxide. In all the described procedures the reaction course was followed by TLC on Silufol UV 254 foils (Kavalier, The Czech Republic); detection in UV light, by heating or by spraying with 0.4% solution of 4-(4-nitrobenzyl)pyridine in ethanol, subsequent heating and exposure to ammonia vapours[27]. Preparative column chromatography was carried out on spherical silica gel 20 – 40 μm (Tessek, The Czech Republic; 20 – 40 times greater amount than that of the mixture to be separated), elution at 50 kPa overpressure. Analytical and preparative thin-layer chromatography (TLC) was performed in the following solvent systems (v/v): toluene (A); toluene–ethyl acetate 49 : 1 (B), 19 : 1 (D), 4 : 1 (E), 1 : 1 (F); chloroform–ethanol 49 : 1 (H), 19 : 1 (I), 9 : 1 (J), 17 : 3 (K), 4 : 1 (L); chloroform–methanol 4 : 1 (M); ethyl acetate–acetone–ethanol–water 4 : 1 : 1 : 1 (N), 6 : 1 : 1 : 1 (O), 12 : 2 : 2 : 1 (P); 2-propanol–concentrated aqueous ammonia–water 7 : 1 : 2 (Q). HPLC analyses were carried out on a reversed phase (C18) Separon SGX-RPS 10 μm (Laboratorní přístroje, Praha), elution with a linear gradient 10 – 40% (v/v) of methanol in 0.05 M triethylammonium acetate. The electrophoreses were done on a Whatman 3 MM paper in 0.1 M triethylammonium hydrogen carbonate (pH 7.5) at 20 V/cm. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer, using the EI (electron energy 70 eV), FAB (ionization by Xe, accelerating voltage 8 kV) and SIMS (ionization by Cs^+, accelerating voltage 35 kV) techniques; matrices glycerol and thioglycerol. ^1H NMR spectra were measured on Varian Unity 200 (200 MHz) and Varian Unity 500 (500 MHz) instruments in hexadeuteriodimethyl sulfoxide with tetramethysilane as internal standard, unless stated otherwise. Free phosphonic acids were measured in deuterium oxide containing sodium deuterioxide with sodium 3-(trimethylsilyl)-1-propanesulfonate (DSS) as internal standard. ^{13}C NMR spectra were obtained with a Varian Unity 200 (50.3 MHz) spectrometer in hexadeuteriodimethyl sulfoxide. The signals were referenced to the solvent signal and the chemical shifts were calculated using the relationship $\delta(CD_3SOCD_3) = 39.7$.

General Procedure 1: Removal of Benzyl Groups by Catalytic Hydrogenation

Palladium on charcoal (10%, 150 mg) was added under argon to a solution of the benzyl derivative (10 mmol) in ethanol (100 ml) and the mixture was hydrogenated at 20 kPa for 8 h. The catalyst was removed by filtration through Celite and the filtrate was concentrated under diminished pressure.

General Procedure 2: Selective Tosylation of Primary Hydroxy Group

A solution of tosyl chloride (2.0 g, 1.05 mmol) in pyridine (10 ml) was added dropwise at 0 °C in the course of 1 h to a solution of the hydroxy compound (10 mmol) in pyridine (70 ml). After standing at 0 °C overnight, the unreacted reagent was decomposed at 0 °C with an excess of water. The mixture was allowed to warm to room temperature, the solvent was evaporated and the residue was taken up in ethyl acetate. The extract was washed with saturated aqueous solution of sodium hydrogen carbonate, dried over magnesium sulfate and the solvent was evaporated. Traces of pyridine were removed by codistillation with toluene. The crude product was purified by column chromatography on silica gel.

General Procedure 3: Preparation of Tetrahydropyran-2-yl Derivatives

The hydroxy (10 mmol) or dihydroxy (5 mmol) compound and 3,4-dihydro-2*H*-pyran (1.8 ml, 19.9 mmol) were dissolved in dioxane (10 ml), the solution was cooled to 0 °C and several drops of a solution of hydrogen chloride in dioxane were added so as the solution was acid. After standing at ambient temperature for 2 – 4 h, the reaction mixture was taken up in ethyl acetate, the extract was washed with saturated solution of sodium hydrogen carbonate, dried over anhydrous sodium sulfate and the solvent was evaporated. The reaction was practically quantitative and the products were used directly in the next reaction step.

General Procedure 4: Removal of Tetrahydropyran-2-yl Groups

The deprotection was carried out by 4 h reflux with 80% acetic acid (10 ml per 1 mmol of compound). The solvent was evaporated under diminished pressure and traces of acetic acid were removed by codistillation with water. The product was purified by chromatography on silica gel.

General Procedure 5: Alkylation of Adenine

Sodium hydride (60% suspension in mineral oil, 84 mg, 2.1 mmol) was added to a solution of adenine (284 mg, 2.1 mmol) in dry dimethylformamide (16 ml). The mixture was sonicated for 20 min and then heated at 80 °C for 30 min. Then the protected tosylate (2 mmol) in small amount of dimethylformamide was added and the heating was continued for 8 h. After evaporation of the solvent, the residue was chromatographically separated on a column of silica gel.

General Procedure 6: Preparation of Monoesters of Phosphonic Acids

A solution of the dialkyl phosphonate (1 mmol) in a pyridine–water mixture (10 ml, 4 : 1) was refluxed for 8 h. The reaction course was followed by TLC in the system Q or by electrophoresis. The solvent was removed under diminished pressure and the residue was codistilled with water. The product was isolated by chromatography on a column of Dowex 1X2 (acetate form, 60 ml); elution with a linear gradient 0 – 0.35 M acetic acid (2 × 1 l).

General Procedure 7: Cleavage of Phosphonate Esters with Bromotrimethylsilane

Bromotrimethylsilane (1 equivalent per each group to be removed and per each active hydrogen in the molecule) was added to a solution of mono- or diester of phosphonic acid (1 mmol) in dry acetonitrile (3 ml). In case when the reaction mixture was not homogeneous, dimethylformamide was added to homogeneity. The reaction mixture was left aside overnight at room temperature. The reaction course was followed by TLC in the system Q or by electrophoresis. After evaporation of the solvent, the residue was codistilled with acetonitrile, traces of the unreacted reagent were decomposed by addition of an acetonitrile–water–triethylamine mixture (9 : 9 : 2, 5 ml) and the mixture was concentrated. The product was isolated by chromatography on a column of Dowex 1X2 (acetate form; 60 ml); elution with a linear gradient 0 – 0.75 M acetic acid (2 × 1 l).

Diethyl (2,3,5-Tri-*O*-benzyl-α- and β-L-arabinofuranosyl)phosphonates (*VIIa* and *VIIb*)

Trimethylsilyl triflate (1.3 ml, 6.6 mmol) was added at 0 °C to a mixture of methyl 2,3,5-tri-*O*-benzyl-α and β-L-arabinofuranoside[9,10] (α : β = 1 : 1) (*Va*, *Vb*; 2.17 g, 5 mmol), triethyl phosphite (1.7 ml, 10 mmol) and acetonitrile (30 ml). The mixture was set aside at room temperature for 4 h, and then the reaction was quenched by addition of an excess of triethylamine at 0 °C. The reaction mixture

was taken up in ethyl acetate, the solution washed with saturated solution of sodium hydrogen carbonate and dried over anhydrous sodium sulfate. After evaporation of the solvent, the product was isolated by column chromatography on silica gel in the system H. Yield 749 mg (28%) of a mixture of *VIIa* and *VIIb* (1 : 3.5); R_F 0.41 (I). Mass spectrum (FAB): 541 (MH^+). For $C_{30}H_{37}O_7P$ (540.6) calculated: 66.65% C, 6.90% H, 5.73% P; found: 65.94% C, 7.13% H, 5.59% P.

Diethyl (α- and β-L-Arabinofuranosyl)phosphonates (*VIIIa* and *VIIIb*)

A) A mixture of phosphonates *VIIa* and *VIIb* (700 mg, 1.29 mmol) was hydrogenolytically debenzylated according to procedure 1. Yield 292 mg (84%) of a mixture of *VIIIa* and *VIIIb* (1 : 3.5); R_F 0.42 (P). Mass spectrum (FAB): (MH^+). For $C_9H_{19}O_7P$ (270.2) calculated: 38.37% C, 7.82% H, 10.87% P; found: 38.51% C, 7.77% H, 10.68% P.

B) An anomeric mixture (1 : 1) of methyl L-arabinofuranosides[12] (1.64 g, 10 mmol), ammonium sulfate (2 mg) and 1,1,1,3,3,3-hexamethyldisilazane (50 ml) was refluxed for 5 h. The solvent was evaporated, the residue codistilled with toluene and mixed with triethyl phosphite (3.4 ml, 20 mmol) and acetonitrile (30 ml). Trimethylsilyl triflate (2.6 ml, 13.5 mmol) was then added at 0 °C and the mixture was set aside at room temperature for 4 h. An excess of 50% ethanolic triethylamine was added at 0 °C, the solvent was evaporated and the product isolated on a column of silica gel in the system J. Yield 854 mg (32%) of a mixture of *VIIIa* and *VIIIb* (1 : 3.5), identical with the product obtained according to procedure *A*.

Diethyl (5-*O*-Tosyl-α- and β-L-arabinofuranosyl)phosphonates (*IXa* and *IXb*)

A mixture of compounds *VIIIa* and *VIIIb* (780 mg, 2.9 mmol) was selectively tosylated according to procedure 2. Yield 850 mg (69%) of product *IXa* and *IXb* (1 : 3.5); R_F 0.49 (J). Mass spectrum (FAB): 425 (MH^+). For $C_{16}H_{25}O_9PS$ (424.4) calculated: 45.28% C, 5.94% H, 7.30% P, 7.55% S; found: 45.68% C, 5.98% H, 7.21% P, 7.71% S.

Diethyl [5-(Adenin-9-yl)-5-deoxy-α- and β-L-arabinofuranosyl]phosphonates (*XIIa* and *XIIb*)

A mixture of phosphonates *IXa* and *IXb* (849 mg, 2 mmol) was converted into tetrahydropyranyl derivatives *Xa* and *Xb* (R_F 0.37 in I) according to the procedure 3. The obtained compounds were directly used in the reaction with adenine according to the general procedure 5, yielding a mixture of compound *XIa* and *XIb* (R_F 0.58 and 0.64 in K). Chromatography on silica gel in the system J and removal of the tetrahydropyranyl groups according to the general procedure 4 afforded both anomers. α-Anomer *XIIa*: yield 66 mg (9% calculated for *IXa*, *IXb*); R_F 0.39 (L). Mass spectrum (FAB): 388 (MH^+). For $C_{14}H_{22}N_5O_6P$ (387.3) calculated: 43.41% C, 5.72% H, 18.08% N, 8.00% P; found: 43.84% C, 5.65% H, 17.87% N, 8.12% P. β-Anomer *XIIb*: yield 233 mg (30% calculated for *IXa*, *IXb*); R_F 0.41 (L). Mass spectrum (FAB): 388 (MH^+). For $C_{14}H_{22}N_5O_6P$ (387.3) calculated: 43.41% C, 5.72% H, 18.08% N, 8.00% P; found: 43.29% C, 5.82% H, 17.89% N, 8.08% P.

Ethyl [5-(Adenin-9-yl)-5-deoxy-α-L-arabinofuranosyl]phosphonate (*XIIIa*)

Compound *XIIa* (70 mg, 0.18 mmol) was converted according to general procedure 6 into monoester *XIIIa* (48 mg, 74%); R_F 0.55 (Q). Mass spectrum (FAB): 360 (MH^+). For $C_{12}H_{18}N_5O_6P$ (359.2) calculated: 40.12% C, 5.05% H, 19.49% N, 8.62% P; found: 40.31% C, 4.93% H, 19.28% N, 8.80% P.

Ethyl [5-(Adenin-9-yl)-5-deoxy-β-L-arabinofuranosyl]phosphonate (*XIIIb*)

Compound *XIIb* (194 mg, 0.5 mmol) was converted into monoester *XIIIb* (130 mg, 72%) according to general procedure 6; R_F 0.59 (Q). Mass spectrum (FAB): 360 (MH^+). For $C_{12}H_{18}N_5O_6P$ (359.2) calculated: 40.12% C, 5.05% H, 19.49% N, 8.62% P; found: 40.43% C, 5.19% H, 19.23% N, 8.58% P.

[5-(Adenin-9-yl)-5-deoxy-α-L-arabinofuranosyl]phosphonic Acid (*IIa*)

Compound *XIIa* (70 mg, 0.18 mmol) was processed according to the general procedure 7 to give 39 mg (65%) of the free acid *IIa*; R_F 0.36 (Q). Mass spectrum (FAB): 332 (MH^+). For $C_{10}H_{14}N_5O_6P$ (331.2) calculated: 36.26% C, 4.26% H, 21.14% N, 9.35% P; found: 36.56% C, 4.18% H, 20.94% N, 9.19% P.

[5-(Adenin-9-yl)-5-deoxy-β-L-arabinofuranosyl]phosphonic Acid (*IIb*)

Compound *XIIb* (194 mg, 0.5 mmol) was processed according to the general procedure 7 to give 138 mg (83%) of the free acid *IIb*; R_F 0.35 (Q). Mass spectrum (FAB): 332 (MH^+). For $C_{10}H_{14}N_5O_6P$ (331.2) calculated: 36.26% C, 4.26% H, 21.14% N, 9.35% P; found: 36.14% C, 4.35% H, 21.21% N, 9.29% P.

Methyl 3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-α- and β-L-arabinofuranosides (*XVa* and *XVb*)

Bromine (5.6 ml, 17.6 g, 110 mmol) was added dropwise at 0 °C during 30 min to a solution of 1,1,3,3-tetraisopropyldisiloxane[13] (12.3 g, 50 mmol) in dry tetrachloromethane (50 ml). After standing at room temperature for 4 h, the solvent was evaporated and the residue was codistilled with tetrachloromethane. A solution of methyl L-arabinofuranoside[12] (α : β = 1 : 1; 8.2 g, 50 mmol) in pyridine (50 ml) was then added at 0 °C and the resulting solution was set aside for 4 h at room temperature. The unreacted reagent was destroyed with water at 0 °C, the solution was concentrated to one third of the original volume and washed with saturated solution of sodium hydrogen carbonate. After drying over sodium sulfate and evaporation of the solvent, the anomers were separated by column chromatography on silica gel in the system C. α-Anomer *XVa*: 9.5 g (47%); R_F 0.33 (E). Mass spectrum (FAB): 407 (MH^+). For $C_{18}H_{38}O_6Si_2$ (406.7) calculated: 53.16% C, 9.42% H; found: 53.55% C, 9.61% H. ^1H NMR spectrum (200 MHz, hexadeuteriobenzene): 4.85 d, 1 H, $J(1,2)$ = 2.4 (H-1); 4.45 dd, 1 H, $J(3,2)$ = 5.6, $J(3,4)$ = 7.2 (H-3); 4.36 dd, 1 H, $J(2,1)$ = 2.4 (H-2); 4.15 m, 1 H (H-4); 4.14 dd, 1 H, $J(5,4)$ = 3.2, $J(5,5')$ = 12.4 (H-5); 4.06 dd, 1 H, $J(5',4)$ = 5.6 (H-5'); 3.29 s, 3 H (OCH_3); 1.83 m, 4 H (4 × CH); 1.10 s, 6 H (2 × CH_3); 1.08 s, 6 H (2 × CH_3); 1.06 s, (2 × CH_3); 1.01 s, 6 H (2 × CH_3). β-Anomer *XVb*: yield 6.90 g (34%); R_F 0.42 (E). Mass spectrum (FAB): 407 (MH^+). For $C_{18}H_{38}O_6Si_2$ (406.7) calculated: 53.16% C, 9.42% H; found: 53.09% C, 9.63% H. ^1H NMR spectrum (200 MHz, deuteriochloroform + hexadeuteriobenzene): 4.54 d, 1 H, $J(1,2)$ = 4.6 (H-1); 4.24 dd, 1 H, $J(3,2)$ = 7.4, $J(3,4)$ = 5.6 (H-3); 4.07 dd, 1 H, $J(2,1)$ = 4.6 (H-2); 3.98 dd, 1 H, $J(5,4)$ = 2.8, $J(5,5')$ = 10.0 (H-5); 3.88 ddd, 1 H, $J(4,3)$ = 5.6, $J(4,5')$ = 8.4 (H-4); 3.76 dd (H-5'); 3.39 s, 3 H (OCH_3); 1.82 m, 4 H (4 × CH); 1.10 s, 6 H (2 × CH_3); 1.08 s, 6 H (2 × CH_3); 1.04 s, 6 H (2 × CH_3); 1.01 s, 6 H (2 × CH_3).

Methyl 2-*O*-(Phenoxythiocarbonyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α-L-arabinofuranoside (*XVIa*)

Phenoxythiocarbonyl chloride (5.1 g, 29.7 mmol) was added at 0 °C to a solution of compound *XVa* (11.5 g, 28.3 mmol) in pyridine–dichloromethane (1 : 1, 60 ml) and the mixture was set aside overnight at room temperature[14]. The unreacted reagent was destroyed with an excess of water, the solu-

tion was concentrated to about one third of the original volume, diluted with ethyl acetate (100 ml) and washed with saturated solution of sodium hydrogen carbonate. The organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated. Column chromatography on silica gel in the system B afforded 10.0 g (65%) of the product *XVIa*; R_F 0.61 (C). Mass spectrum (FAB): 543 (MH^+). For $C_{25}H_{42}O_7SSi_2$ (542.8) calculated: 55.32% C, 7.80% H, 5.90% S; found: 54.79% C, 7.53% H, 5.71% S.

Methyl 2-*O*-(Phenoxythiocarbonyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-L-arabinofuranoside (*XVIb*)

Compound *XVb* (4.9 g, 12 mmol) was treated in the same manner as described in the preceding experiment. Yield 4.5 g (69%) of product *XVIb*; R_F 0.61 (C). Mass spectrum (FAB): 543 (MH^+). For $C_{25}H_{42}O_7SSi_2$ (542.8) calculated: 55.32% C, 7.80% H, 5.90% S; found: 55.37% C, 7.83% H, 5.83% S.

Methyl 2-Deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α-L-*erythro*-pentofuranoside (*XVII*)

Tributylstannane (1 M solution, 19.3 ml) in toluene was added under argon to a solution of compound *XVIa* (10.0 g, 18.4 mmol) and 2,2'-azobis(2-methylpropionitrile) (100 mg) in toluene (20 ml). The reaction mixture was heated at 80 °C for 2 h, the solvent was evaporated and the residue was chromatographed on a column of silica gel in the system B. Yield 6.5 g (90%) of product *XVII*; R_F 0.41 (C). Mass spectrum (FAB): 391 (MH^+). For $C_{18}H_{38}O_5Si_2$ (390.7) calculated: 55.34% C, 9.80% H; found: 54.91% C, 9.82% H. ^1H NMR spectrum (500 MHz): 4.90 dd, $J(1,2)$ = 5.6, $J(1,2')$ = 3.0 (H-1); 4.27 dt, 1 H, $J(3,2)$ = 8.6, $J(3,2')$ = 6.4, $J(3,4)$ = 8.6 (H-3); 3.94 dd, 1 H, $J(5,4)$ = 3.2, $J(5,5')$ = 12.0 (H-5); 3.78 dd, 1 H, $J(5',4)$ = 6.3 (H-5'); 3.69 ddd, 1 H (H-4); 3.25 s, 3 H (OCH_3); 2.51 ddd, 1 H, $J(2,2')$ = 13.4 (H-2); 1.71 ddd, 1 H (H-2'); 1.10 – 0.90 m, 28 H (4 × *i*-Pr).

Reduction of Methyl 2-*O*-(Phenoxythiocarbonyl)-2,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-L-arabinofuranoside (*XVIb*) with Tributylstannane

Compound *XVIb* (4.5 g, 8.3 mmol) was processed in the same manner as described in the preceding experiment. The crude product was subjected to column chromatography on silica gel in the system B which afforded 2.0 g (44%) of the starting compound *XVIb* and 517 mg (15%) of methyl 2-*O*-methyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-L-arabinofuranoside (*XVIII*); R_F 0.38 (C). Mass spectrum (FAB): 421 (MH^+). For $C_{19}H_{40}O_6Si_2$ (420.7) calculated: 54.25% C, 9.58% H; found: 54.21% C, 9.21% H. ^1H NMR spectrum (500 MHz): 4.85 d, 1 H, $J(1,2)$ = 4.4 (H-1); 4.16 dd, $J(3,2)$ = 6.8, $J(3,4)$ = 5.9 (H-3); 3.67 m, 1 H (H-4); 3.60 dd, 1 H (H-2); 3.53 dd, 1 H, $J(5,4)$ = 3.9, $J(5,5')$ = 11.5 (H-5); 3.36 dd, 1 H, $J(5',4)$ = 7.1 (H-5'); 3.32 s, 3 H (OCH_3); 3.24 s, 3 H (OCH_3); 1.10 – 0.90 m, 28 H (4 × *i*-Pr).

Diethyl [2-Deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α- and β-L-*erythro*-pentofuranosyl]phosphonates (*XIXa* and *XIXb*)

Trimethylsilyl triflate (4.2 ml, 21.7 mmol) was added to a mixture of compound *XVII* (6.7 g, 17 mmol), triethyl phosphite (5.8 ml, 33.8 mmol) and acetonitrile (50 ml) and the reaction mixture was allowed to stand at room temperature for 4 h. The reaction was quenched by addition of an excess of triethylamine at 0 °C, the solvent was evaporated and the residue was taken up in ethyl acetate. This solution was washed with saturated solution of sodium hydrogen carbonate, dried over sodium sulfate and the solvent was evaporated. The product was isolated by column chromatography on silica gel in

the system G; yield 5.9 g (70%) of product *XIXa* and *XIXb* (1 : 3); R_F 0.41 (I). Mass spectrum (FAB): 497 (MH^+). For $C_{21}H_{45}O_7PSi_2$ (496.7) calculated: 50.78% C, 9.13% H, 6.24% P; found: 51.07% C, 9.01% H, 6.32% P. ^{1}H NMR spectrum (500 MHz): α-anomer: 4.46 dt, 1 H, J(3,2) = 7.6, J(3,2′) = 7.6, J(3,4) = 6.8 (H-3); 4.30 dd, 1 H, J(1,2) = 5.1, J(1,2′) = 9.5 (H-1); 4.07 dq, 4 H, $J(CH_2,CH_3)$ = 7.1, $^3J(CH_2,P)$ = 8.1 (2 × $POCH_2$); 3.91 dd, 1 H, J(5,4) = 3.4, J(5,5′) = 12.0 (H-5); 3.82 dd, 1 H, J(5′,4) = 6.6 (H-5′); 3.59 ddd, 1 H (H-4); 2.31 dddd, 1 H, J(2,2′) = 12.9, ^3J(2,P) = 15.4 (H-2); 2.18 dddd, 1 H, ^3J(2′,P) = 21.0 (H-2′); 1.22 t, 6 H, J = 7.1 (2 × CH_3); 1.10 – 0.90 m, 28 H (4 × *i*-Pr); β-anomer: 4.36 dt, 1 H, J(3,2) = 7.6, J(3,2′) = 9.3, J(3,4) = 7.6 (H-3); 4.26 ddd, 1 H, J(1,2) = 7.3, J(1,2′) = 10.2, ^2J(1,P) = 1.0 (H-1); 4.04 dq, 4 H, $J(CH_2,CH_3)$ = 7.1, $^3J(CH_2,P)$ = 8.1 (2 × $POCH_2$); 3.87 dd, 1 H, J(5,4) = 3.4, J(5,5′) = 12.4 (H-5); 3.82 dd, 1 H, J(5′,4) = 5.1 (H-5′); 3.60 ddd, 1 H (H-4); 2.50 m, 1 H (H-2); 2.04 dddd, 1 H, J(2′,2) = 11.7, ^3J(2′,P) = 21.0 (H-2′); 1.24 t, 3 H, J = 7.1 (CH_3); 1.23 t, 3 H, J = 7.1 (CH_3); 1.10 – 0.90 m, 28 H (4 × *i*-Pr).

Diethyl (2-Deoxy-α- and β-L-*erythro*-pentofuranosyl)phosphonates (*XXa* and *XXb*)

A mixture of compounds *XIXa* and *XIXb* (5.9 g, 11.9 mmol) was dissolved in 0.5 M solution of tetrabutylammonium fluoride in tetrahydrofuran (50 ml). After standing overnight at room temperature, the solvent was evaporated and the product isolated by column chromatography on silica gel in the system I. Yield 2.3 g (76%) of a mixture of *XXa* and *XXb* (1 : 3). Mass spectrum (FAB): 255 (MH^+). For $C_9H_{19}O_6P$ (254.2) calculated: 42.52% C, 7.53% H, 12.18% P; found: 42.83% C, 7.62% H, 12.30% P.

Diethyl (2-Deoxy-5-*O*-tosyl-α- and β-L-*erythro*-pentofuranosyl)phosphonates (*XXIa* and *XXIb*)

A mixture of compounds *XXa* and *XXb* (2.3 g, 9 mmol) was selectively tosylated according to the general procedure 2. Chromatography on a column of silica gel in the system H separated both anomers. Yield of α-anomer *XXIa* 950 mg (26%); R_F 0.37 (I). Mass spectrum (FAB): 409 (MH^+). For $C_{16}H_{25}O_8PS$ (408.4) calculated: 47.06% C, 6.17% H, 7.58% P, 7.85% S; found: 47.38% C, 6.37% H, 7.77% P, 8.63% S. Yield of β-anomer 1.9 g (52%); R_F 0.44 (I). Mass spectrum (FAB): 409 (MH^+). For $C_{16}H_{25}O_8PS$ (408.4) calculated: 47.06% C, 6.17% H, 7.58% P, 7.85% S; found: 47.32% C, 6.08% H, 7.29% P, 8.41% S.

Diethyl [5-(Adenin-9-yl)-2,5-dideoxy-α-L-*erythro*-pentofuranosyl]phosphonate (*XXIVa*)

Compound *XXIa* (939 mg, 2.3 mmol) was converted into derivative *XXIIa* according to the general procedure 3. The reaction of *XXIIa* with adenine was carried out as described in the general procedure 5 and the obtained product *XXIIIa* was subjected to acid cleavage according to the general procedure 4. Chromatography on a column of silica gel in the system H afforded 323 mg (38%) of product *XXIVa*; R_F 0.51 (L). Mass spectrum (FAB): 372 (MH^+). For $C_{14}H_{22}N_5O_5P$ (371.3) calculated: 45.28% C, 5.97% H, 18.86% N, 8.34% P; found: 45.68% C, 6.02% H, 17.54% N, 8.11% P.

Diethyl [5-(Adenin-9-yl)-2,5-dideoxy-β-L-*erythro*-pentofuranosyl]phosphonate (*XXIVb*)

Compound *XXIb* (939 mg, 2.3 mmol) was converted into the product *XXIVb* (309 mg, 36%) using the same procedure as described for compound *XXIVa*; R_F 0.53 (L). Mass spectrum (FAB): 372 (MH^+). For $C_{14}H_{22}N_5O_5P$ (371.3) calculated: 45.28% C, 5.97% H, 18.86% N, 8.34% P; found: 42.10% C, 5.76% H, 18.23% N, 7.95% P.

Ethyl [5-(Adenin-9-yl)-2,5-dideoxy-α-L-*erythro*-pentofuranosyl]phosphonate (*XXVa*)

Compound *XXIVa* (50 mg, 0.13 mmol) was hydrolyzed according to the general procedure 6 to give 35 mg (78%) of monoester *XXVa*; R_F 0.61 (Q). Mass spectrum (FAB): 344 (MH^+).

Ethyl [5-(Adenin-9-yl)-2,5-dideoxy-β-L-*erythro*-pentofuranosyl]phosphonate (*XXVb*)

Compound *XXIVb* (50 mg, 0.13 mmol) was hydrolyzed according to the general procedure 6 to give 29 mg (65%) of monoester *XXVb*; R_F 0.60 (Q). Mass spectrum (FAB): 344 (MH^+).

[5-(Adenin-9-yl)-2,5-dideoxy-α-L-*erythro*-pentofuranosyl]phosphonic Acid (*IIIa*)

Diester *XXIVa* (200 mg, 0.54 mmol) was treated according to the general procedure 7 to give 132 mg (76%) of free acid *IIIa*; R_F 0.32 (Q). Mass spectrum (FAB): 316 (MH^+).

[5-(Adenin-9-yl)-2,5-dideoxy-β-L-*erythro*-pentofuranosyl]phosphonic Acid (*IIIb*)

Diester *XXIVb* (200 mg, 0.54 mmol) was treated according to the general procedure 7 to give 140 mg (82%) of free acid *IIIb*; R_F 0.32 (Q). Mass spectrum (FAB): 316 (MH^+).

3,5-Di-*O*-benzyl-1,2-*O*-isopropylidene-α-L-xylofuranoside (*XXVI*)

The title compound was prepared by benzylation[15] of 1,2-*O*-isopropylidene-α-L-xylofuranoside (13.9 g, 73.1 mmol) obtained from L-xylose[21] according to the described procedure[17]. Column chromatography on silica gel in the system B afforded 15.6 g (58%) of product *XXVI*; R_F 0.39 (D). Mass spectrum (FAB): 371 (MH^+). For $C_{22}H_{26}O_5$ (370.4) calculated: 71.33% C, 7.07% H; found: 71.76% C, 7.31% H. ^1H NMR spectrum (500 MHz): 7.32 m, 10 H (arom.); 5.87 d, 1 H, $J(1,2)$ = 3.9 (H-1); 4.71 dd, 1 H, $J(2,3)$ = 0.5 (H-2); 4.65 d, 1 H, J = 11.7 (OCH); 4.52 d, 1 H, J = 11.7 (OCH); 4.49 d, 1 H, J = 11.7 (OCH); 4.47 d, 1 H, J = 11.7 (OCH); 4.24 ddd, 1 H, $J(4,3)$ = 3.4, $J(4,5)$ = 4.9, $J(4,5')$ = 6.8 (H-4); 3.91 d, 1 H (H-3); 3.72 dd, 1 H, $J(5,5')$ = 10.2 (H-5); 3.60 dd, 1 H (H-5'); 1.39 s, 3 H (CH_3); 1.26 s, 3 H (CH_3).

Methyl 3,5-Di-*O*-benzyl-α- and β-L-xylofuranosides (*XXVIIa* and *XXVIIb*)

A solution of compound *XXVI* (7.4 g, 20 mmol) in 1 M solution of hydrogen chloride in methanol (60 ml) was set aside overnight. The reaction was quenched by addition of an excess of triethylamine at 0 °C, the solvent was evaporated and the residue taken up in ethyl acetate. The ethyl acetate extract was washed with saturated solution of sodium hydrogen carbonate, dried over anhydrous sodium sulfate and the solvent was evaporated. Column chromatography on silica gel in the system D separated the anomers. α-Anomer *XXVIIa*; 3.5 g (51%); R_F 0.41 (E). For $C_{20}H_{24}O_5$ (344.4) calculated: 69.75% C, 7.02% H; found: 69.68% C, 7.35% H. ^1H NMR spectrum (200 MHz): 7.31 m, 10 H (arom.); 5.07 d, 1 H, J(2,OH) = 6.4 (OH); 4.77 d, 1 H, $J(1,2)$ = 4.2 (H-1); 4.67 d, 1 H, J(CH,CH) = 12.0 (Ph-CH^a); 4.51 d, 1 H, J(CH,CH) = 12.0 (Ph-CH^a); 4.49 s, 2 H (2 × Ph-CH^b); 4.26 td, 1 H, $J(4,3)$ = 6.1, $J(4,5)$ = 4.2, $J(4,5')$ = 6.6 (H-4); 4.07 dd, 1 H, $J(2,3)$ = 5.4 (H-2); 4.00 dd, 1 H (H-3); 3.66 dd, 1 H, $J(5,5')$ = 10.5 (H-5); 3.50 dd, 1 H (H-5'); 3.30 s, 3 H (OCH_3). β-Anomer *XXVIIb*; 2.75 g (40%); R_F 0.36 (E). For $C_{20}H_{24}O_5$ (344.4) calculated: 69.75% C, 7.02% H; found: 69.51% C, 7.14% H. ^1H NMR spectrum (200 MHz): 7.30 m, 10 H (arom.); 5.49 d, 1 H, J(2,OH) = 4.6 (OH); 4.68 d, 1 H, $J(1,2)$ = 1.2 (H-1); 4.60 d, 1 H, J(CH,CH) = 12.0 (Ph-CH^a); 4.45 d, 1 H, J(CH,CH) = 12.0 (Ph-CH^a); 4.51 s, 2 H (2 × Ph-CH^b); 4.36 ddd, 1 H, $J(4,3)$ = 5.8, $J(4,5)$ = 4.6, $J(4,5')$ = 7.3 (H-4); 4.03 dd, 1 H, $J(2,3)$

= 2.4 (H-2); 3.85 dd, 1 H (H-3); 3.70 dd, 1 H, $J(5,5')$ = 10.2 (H-5); 3.55 dd, 1 H (H-5'); 3.24 s, 3 H (OCH_3).

Methyl 3,5-Di-*O*-benzyl-2-*O*-(phenoxythiocarbonyl)-α-L-xylofuranoside (*XXVIIIa*)

Phenoxythiocarbonyl chloride (1.8 g, 10.6 mmol) was added at 0 °C to a solution of compound *XVIIa* (3.5 g, 10.2 mmol) in a mixture of pyridine–dichloromethane (1 : 1, 20 ml). After standing at room temperature overnight[14], the unreacted reagent was destroyed by addition of an excess of water at 0 °C and the solution was concentrated to about one third of the original volume. After dilution with ethyl acetate, the solution was washed with saturated solution of sodium hydrogen carbonate, dried over anhydrous magnesium sulfate and the solvent was evaporated. The crude product was used directly in the reaction with tributylstannane.

Methyl 3,5-Di-*O*-benzyl-2-*O*-(phenoxythiocarbonyl)-β-L-xylofuranoside (*XXVIIIb*)

The title compound was obtained from compound *XXVIIb* (2.8 g, 8.1 mmol) in the same manner as described in the preceding experiment and the evaporation residue was used directly in the reaction with tributylstannane.

Methyl 3,5-Di-*O*-benzyl-2-deoxy-α-L-*threo*-pentofuranoside (*XXIXa*)

A solution of tributylstannane in toluene (1 M, 11.1 ml) was added under argon to a solution of the crude phenoxythiocarbonyl derivative *XXVIIIa* (10.1 mmol) and 2,2'-azobis(2-methylpropionitrile) (AIBN; 100 mg) in toluene (10 ml) and the reaction mixture was heated at 80 °C for 2 h. The solvent was evaporated and the product was isolated by column chromatography on silica gel in the system B. Yield 910 mg (27%) of product *XXIXa*; R_F 0.34 (B). For $C_{20}H_{24}O_4$ (328.4) calculated: 73.15% C, 7.37% H; found: 73.27% C, 7.15% H. ^{1}H NMR spectrum (500 MHz): 7.30 m, 10 H (arom.); 5.06 dd, 1 H, $J(1,2)$ = 5.6, $J(1,2')$ = 3.2 (H-1); 4.52 d, 2 H, J(CH,CH) = 12.0 (2 × Ph–CH^a); 4.48 d, 2 H, J(CH,CH) = 12.0 (2 × Ph–CH^b); 4.16 ddd, 1 H, $J(3,2)$ = 2.4, $J(3,2')$ = 6.1, $J(3,4)$ = 4.4 (H-3); 4.09 dt, 1 H, $J(4,5)$ = 4.4, $J(4,5')$ = 6.6 (H-4); 3.72 dd, 1 H, $J(5,5')$ = 10.3 (H-5); 3.58 dd, 1 H (H-5'); 3.22 s, 3 H (OCH_3); 2.22 ddd, 1 H, $J(2,2')$ = 14.2 (H-2); 1.94 ddd, 1 H (H-2').

Methyl 3,5-Di-*O*-benzyl-2-deoxy-β-L-*threo*-pentofuranoside (*XXIXb*)

The crude compound *XXVIIa* (3.84 g, 8 mmol) was treated in the same manner as described in the preceding experiment to give 2.04 g (78%) of the title compound *XXIXb*; R_F 0.34 (B). For $C_{20}H_{24}O_4$ (328.4) calculated: 73.15% C, 7.37% H; found: 73.21% C, 7.11% H. ^{1}H NMR spectrum (500 MHz): 7.30 m, 10 H (arom.); 4.95 dd, 1 H, $J(1,2)$ = 6.1, $J(1,2')$ = 1.7 (H-1); 4.52 s, 2 H (2 × Ph–CH^a); 4.52 d, 1 H, J(CH,CH) = 12.2 (Ph–CH^b); 4.38 d, 1 H, J(CH,CH) = 12.2 (Ph–CH^b); 4.17 ddd, 1 H, $J(4,3)$ = 5.6, $J(4,5)$ = 4.6, $J(4,5')$ = 7.1 (H-4); 4.11 ddd, 1 H, $J(3,2)$ = 6.4, $J(3,2')$ = 2.7 (H-3); 3.74 dd, 1 H, $J(5,5')$ = 10.3 (H-5); 3.58 dd, 1 H (H-5'); 3.22 s, 3 H (OCH_3); 2.16 ddd, 1 H, $J(2,2')$ = 14.2 (H-2); 1.98 ddd, 1 H (H-2').

Diethyl (3,5-Di-*O*-benzyl-2-deoxy-α- and β-L-*threo*-pentofuranosyl)phosphonates (*XXXa* and *XXXb*)

A) Trimethylsilyl triflate (0.7 ml, 3.6 mmol) was added at 0 °C under argon to a mixture of compound *XXIXa* (910 mg, 2.8 mmol), triethyl phosphite (0.9 ml, 5.2 mmol) and acetonitrile (8 ml) and the mixture was allowed to stand at room temperature for 4 h. The reaction was quenched by addition of an excess of triethylamine at 0 °C, the solvent was evaporated and the residue was taken up in ethyl acetate. The extract was washed with saturated solution of sodium hydrogen carbonate, dried

over anhydrous magnesium sulfate and the solvent was evaporated. Column chromatography on silica gel in the system H afforded 801 mg (66%) of a mixture of *XXXa* and *XXXb* (1 : 3); R_F α: 0.36, β: 0.38 (I). Mass spectrum (FAB): 435 (MH^+). For $C_{23}H_{31}O_6P$ (434.5) calculated: 63.58% C, 7.19% H, 7.13% P; found: 63.62% C, 7.01% H, 7.29% P.

B) Compound *XXIXb* (1.7 g, 5.2 mmol) was treated as described under *A*) and afforded 2 g (89%) of a mixture of *XXXa* and *XXXb* (1 : 3).

Diethyl (2-Deoxy-α- and β-L-*threo*-pentofuranosyl)phosphonates (*XXXIa* and *XXXIb*)

A mixture of compounds *XXXa* and *XXXb* (3.0 g, 6.9 mmol) was hydrogenolytically debenzylated according to the general procedure 1. The anomers were separated by chromatography on a column of silica gel in the system I. α-Anomer *XXXIa*: 328 mg (19%); R_F 0.25 (J). Mass spectrum (FAB): 255 (MH^+). For $C_9H_{19}O_6P$ (254.2) calculated: 42.52% C, 7.53% H, 12.58% P; found: 42.83% C, 7.13% H, 12.51% P. β-Anomer *XXXIb*: 880 mg (50%); R_F 0.35 (J). Mass spectrum (FAB): 255 (MH^+). For $C_9H_{19}O_6P$ (254.2) calculated: 42.52% C, 7.53% H, 12.58% P; found: 42.71% C, 7.11% H, 12.45% P.

Diethyl (2-Deoxy-5-*O*-tosyl-α-L-*threo*-pentofuranosyl)phosphonate (*XXXIIa*)

Compound *XXXIa* (328 mg, 1.3 mmol) was tosylated according to the general procedure 2, affording 369 mg (69%) of compound *XXXIIa*; R_F 0.31 (J). Mass spectrum (FAB): 409 (MH^+). For $C_{16}H_{25}O_8PS$ (408.4) calculated: 47.06% C, 6.17% H, 7.58% P, 7.85% S; found: 47.38% C, 6.27% H, 7.41% P, 7.64% S.

Diethyl (2-Deoxy-5-*O*-tosyl-β-L-*threo*-pentofuranosyl)phosphonate (*XXXIIb*)

Compound *XXXIb* (692 mg, 2.7 mmol) was tosylated according to the general procedure 2 to give 893 mg (81%) of compound *XXXIIb*; R_F 0.39 (J). Mass spectrum (FAB): 409 (MH^+). For $C_{16}H_{25}O_8PS$ (408.4) calculated: 47.06% C, 6.17% H, 7.58% P, 7.85% S; found: 47.41% C, 6.35% H, 7.33% P, 7.63% S.

Diethyl [5-(Adenin-9-yl)-2,5-dideoxy-α-L-*threo*-pentofuranosyl]phosphonate (*XXXVa*)

Compound *XXXIIa* (300 mg, 0.73 mmol) was treated as described in the general procedure 3 to give derivative *XXXIIIa* which on reaction with adenine according to the general procedure 5 was converted into compound *XXXIVa*. This was cleaved according to the general procedure 4 and the product was chromatographed on a column of silica gel in the system K. Yield 117 mg (43%) of compound *XXXVa*; R_F 0.54 (M). Mass spectrum (FAB): 372 (MH^+).

Diethyl [5-(Adenin-9-yl)-2,5-dideoxy-β-L-*threo*-pentofuranosyl]phosphonate (*XXXVb*)

Compound *XXXIIb* (830 mg, 2 mmol) was treated in the same way as described for compound *XXXVa*, yielding 283 mg (38%) of the title compound *XXXVb*; R_F 0.51 (M). Mass spectrum (FAB): 372 (MH^+).

[5-(Adenin-9-yl)-2,5-dideoxy-α-L-*threo*-pentofuranosyl]phosphonic Acid (*IVa*)

Diester *XXXVa* (80 mg, 0.22 mmol) was treated as described in the general procedure 7, yielding 47 mg (68%) of product *IVa*; R_F 0.32. Mass spectrum (FAB): 316 (MH^+).

[5-(Adenin-9-yl)-2,5-dideoxy-β-L-*threo*-pentofuranosyl]phosphonic Acid (*IVb*)

Diester *XXXVb* (220 mg, 0.6 mmol) was treated as described for compound *IVa*, yielding 144 mg (78%) of product *IVb*; R_F 0.31. Mass spectrum (FAB): 316 (MH^+).

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