TETROFURANOSE NUCLEOSIDE PHOSPHONIC ACIDS: SYNTHESIS AND PROPERTIES

Ivana POLÁKOVÁ[1], Miloš BUDĚŠÍNSKÝ[2], Zdeněk TOČÍK[3] and Ivan ROSENBERG[4,*]

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, v.v.i., Flemingovo 2, 16610 Prague 6, Czech Republic; e-mail: [1] ivana.polakova@uochb.cas.cz, [2] budesinsky@uochb.cas.cz, [3] tocik@uochb.cas.cz, [4] ivan@uochb.cas.cz

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Dedicated to Professor Antonín Holý on the occasion of his 75th birthday.

New isoelectronic, non-isosteric phosphonate analogues of nucleoside 5′-phosphates featuring the phosphorus moiety directly attached on the sugar ring in the C4′ position are described. The analogues were synthesised by a nucleosidation reaction from tetrofuranosyl phosphonate synthons and silylated nucleobases. The pyrimidine compounds with *erythro* and *threo* configuration in both D- and L-series were prepared, and the structures were assigned by NMR spectroscopy. The results of NMR conformational studies show that all calculated conformers have a maximum pucker in the range typical for nucleosides. In all compounds, the S-type conformer is preferred and is more significant in α-D-*threo*-compounds. Studies on inhibition of thymidine phosphorylase revealed that one of the prepared phosphonic acids was a competitive inhibitor of the enzyme (K_i = 4 μM).

Keywords: Tetrofuranosyl phosphonate; Nucleotide analogues; NMR spectroscopy; Nucleotides; Phosphorus; Oxidation; Synthesis design; Tetrofuranosyl phosphonate; Nucleotide analogues; Sugar hydroxyphosphonates.

Numerous attempts have been made over past few decades to synthesise suitable analogues of nucleotides that would be able to perform differently in various biological processes and become therapeutically exploitable. The search for novel analogues was governed, in addition to other factors, by the necessity to overcome the susceptibility of the natural phosphoester bond for cleavage by phosphomonoesterases. A prominent role belongs to the nucleoside phosphonic acids containing a bridging P–C bond. Significant effort devoted to the synthesis of these compounds and their biological evaluation has led to the discovery of remarkable antiviral properties of acyclic nucleoside phosphonic acids of general formula **1a** (Fig. 1). Among

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them, Vistide (B = cytosine, R′ = CH_2OH), Hepsera (B = adenine, R′ = H), and Viread (B = adenine, R′ = CH_3) are in clinical use for the treatment of CMV-induced retinitis, hepatitis B, and HIV, respectively[1–5].

The biological activities of these compounds have stimulated additional synthetic work, which has provided a number of novel compounds, such as a 5-azacytosine derivative[6,7] (**1a**, B = 5-azacytosine, R′ = CH_2OH) efficient against DNA viruses and a phosphonate GS-9219 (Gilead Sci, Ltd.) (**1a**, B = 2-amino-6-*N*-cyclopropylaminopurine, R′ = H), a prodrug of cytostatic PMEG (**1a**, B = guanine, R′ = H) against leukaemia and non-Hodgkin's lymphoma in dogs[8]. Recently, the prodrugs of phosphonate **1b** [9,10] mimicking the 2′,3′-dideoxydidehydronucleosides, were recognised as efficient compounds against DNA viruses.

Attention was also devoted to the synthesis of the cyclic structures, such as the pentofuranose and cyclopentane ring-containing phosphonate nucleotide analogues[11–17]. Out of them, the compounds GS-9148 **2a** [18], 2′-azido-2′-deoxyerythrose-based nucleoside phosphonate **2b** [19], and 4′-substituted carbocyclic nucleoside phosphonate **2c** [20] (R = C≡CH) have been found to be efficient HIV-RT inhibitors. Surprisingly, diethyl esters of isoxazolidine nucleoside phosphonates **2d** [21] were reported to be very potent antiretroviral compounds although there was no proof of the mechanism of action.

In contrast to the success in development of antiviral compounds against DNA and retroviruses, the use of nucleoside phosphonates for treatment of the RNA viruses, such as HCV, has not been fully explored[16]; however, some potent HCV nucleoside inhibitors have been evaluated in clinical studies[22–25]. The recently published substrate specificity study on HCV RNA polymerase and diphosphoryl derivatives of several types of ribonucleoside phosphonic acids revealed two chain terminators competing with ATP (**3a**: X = O or CH_2, Y = O, R = H)[26]. Compound **3b** (PSI-7977, Pharmasset),

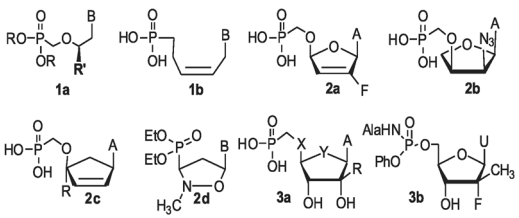


FIG. 1
Examples of nucleoside phosphonates with marked biological effects

a very potent HCV RNA polymerase inhibitor containing phosphoester (not phosphonate) moiety, is in phase II clinical development[27]. Despite important achievements in the area of antivirals, the demand for novel substances with anticancer, antiviral, and other specific activities remains strong. The chemistry of phosphonate analogues of nucleoside phosphates is a fruitful, not yet fully explored field.

In our Laboratory, we have synthesised and evaluated a number of structurally diverse nucleoside phosphonic acids such as **4a–4d** (Fig. 2), differing in the number of bridging atoms of the phosphoester mimic[28–41]. Some nucleoside phosphonic acids exhibited interesting biological properties[42–48].

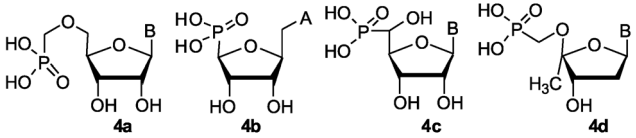


FIG. 2
Examples of structurally diverse nucleoside phosphonic acids

In continuation of our work, we attempted the synthesis of the additional compounds **9**, **20**, **34**, and **50** related to the published adenine derivative **5** [36]. The compounds differ in the configuration on the asymmetric centres of the sugar ring and nucleobases (Fig. 3).

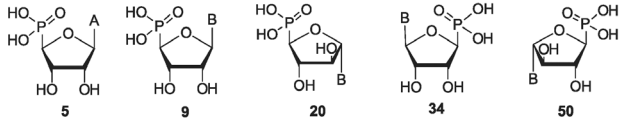


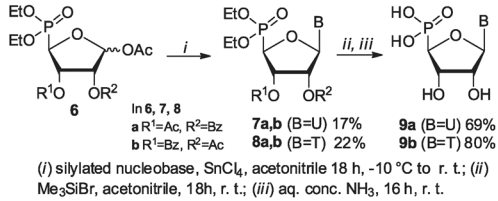
FIG. 3
Phosphonic acids representing synthetic targets

RESULTS AND DISCUSSION

Preparation of D-*Erythrofuranose Nucleoside Phosphonates*

The nucleosidation reaction of of D-erythrofuranosylphosphonates **6** (newly prepared according to the published procedure[36] providing a mixture of both 2′,3′ regioisomers and anomers) with silylated uracil and thymine in the presence of $SnCl_4$ as a Lewis acid catalyst provided a low yield of the protected derivatives **7a**, **7b** and **8a**, **8b** (Scheme 1). The free

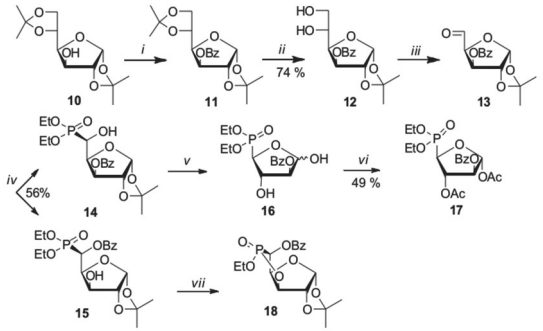
phosphonic acids **9a** and **9b** were easily obtained upon deprotection with bromotrimethylsilane, followed by ammonia treatment (Scheme 1).



SCHEME 1
Preparation of nucleoside phosphonates with D-*erythro* configuration

Preparation of D-*Threofuranose Nucleoside Phosphonates*

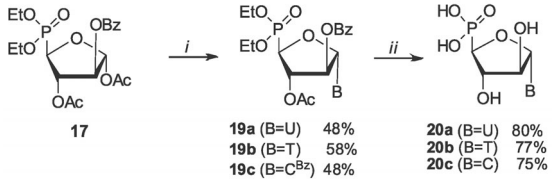
Synthesis of the key synthon, D-threofuranosylphosphonate **17**, was accomplished starting from 1,2:5,6-di-*O*-isopropylideneglucofuranose (**10**) which was benzoylated to **11**. Removal of the 5,6-*O*-isopropylidene group of **11** with 60% aqueous acetic acid, followed by periodate cleavage and the addition of diethyl phosphite to aldehyde **13** (Scheme 2), proceeded without difficulty to exclusively provide the desired *R*-epimer **14**. As the phosphite addition was performed in the presence of triethylamine, a partial migration (ca. 25%) of the benzoyl group from the 3-OH onto 5-OH under formation of **15** was observed. The migration of the benzoyl group likely proceeded in an intramolecular manner through a six-membered intermediate. The attempt to achieve a reversed migration back to 3-hydroxyl



SCHEME 2
The path to the phosphonate precursor for nucleosidation in D-*threo* series

using 5% Et_3N in DCM led to a mixture of both benzoates **14** (26%) and **15** (23%), cyclic phosphonate **18** (36%), and several other undefined products (15%). The formation of cyclic product **18** could be explained by an intramolecular transesterification. Phosphonate **14** was subjected to a cleavage-oxidation step with HIO_4 followed by acetylation to provide synthon **17** as an α-anomer.

In contrast to D-erythrofuranosylphosphonate **6**, the nucleosidation reaction (Scheme 3) performed with D-threofuranosylphosphonate **17** and three silylated pyrimidine nucleobases proceeded with good yields (approx. 50%). The deprotection of **19a–19c** with bromotrimethylsilane, followed by ammonia treatment, afforded free phosphonic acids **20a–20c**.

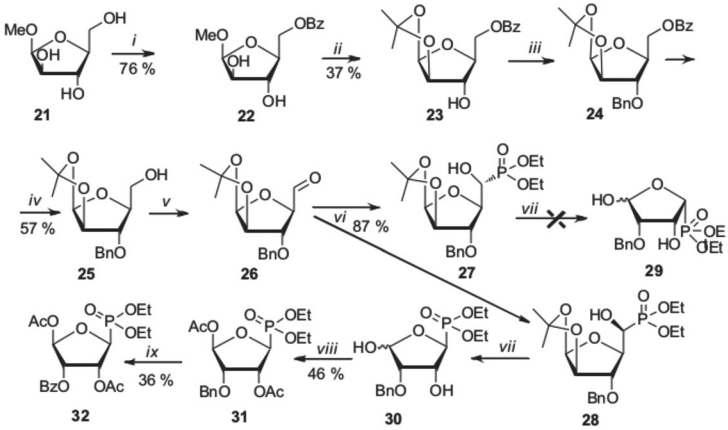


SCHEME 3
Preparation of nucleoside phosphonates with D-*threo* configuration

Preparation of L-*Erythrofuranose Nucleoside Phosphonates*

The synthesis of key synthon **32** started from methyl L-arabinoside (**21**). The benzoylation with benzoyl chloride at –78 °C afforded the 5′-*O*-benzoyl derivative **22** in very good yield of 76% (Scheme 4). Introduction of the isopropylidene group[30] took place in relatively low yield, and the obtained compound **23** with a free 3-hydroxyl group was reacted with benzyl bromide–sodium hydride to provide compound **24**. The 5-*O*-benzoyl moiety was then removed under basic conditions whereby 3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-arabinose (**25**) was obtained. This compound was subjected to Moffatt oxidation and provided 5-aldehyde **26**. The addition of diethyl phosphite to the carbonyl group of **26** gave rise to a mixture of *R*- and *S*-epimers **27** and **28**, respectively, which were not separated (a ratio of minor to major epimers, 22:78). The attempt to assign the 5*R*- and 5*S*-epimers by NMR was not successful. Oxidation of the epimeric mixture of **27** and **28** with HIO_4 afforded the phosphonate derivative **30**. Similar to isomer **14** (Scheme 2), only the *S*-epimer **28** conformed to these conditions, while the

R-epimer **27** underwent an oxidative decomposition. After acetylation of free 1- and 3-hydroxyls of **30** to acetyl derivative **31**, it was necessary to oxidise the 3-*O*-benzyl group of compound **31** by RuO_2 to the benzoyl group, which was capable of providing the desired derivative **32**. We encountered problems when monitoring the oxidation. On TLC analysis, compounds **31** and **32** were not distinguishable, and information about the course of reaction could only be obtained from HPLC or NMR verification.



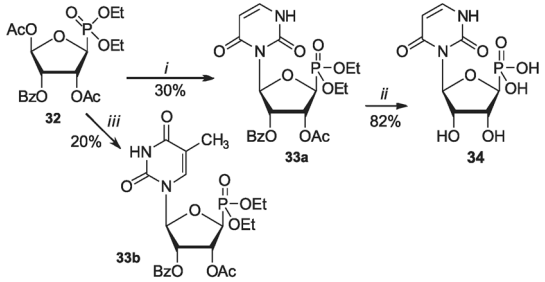
(i) BzCl, triethylamine, CH_2Cl_2, 18 h, -78 °C; (ii) H_2SO_4, $CuSO_4$, acetone, 24 h, r. t.; (iii) NaH, THF, BnBr, 24 h, 0 °C; (iv) CH_3ONa-MeOH, 24 h, r. t.; (v) DCC, DMSO, TFA, pyridine, 18 h, r. t.; (vi) $HP(O)(OEt)_2$, Et_3N, CH_2Cl_2, 18 h, 0 °C; (vii) HIO_4, 50% aq. dioxane, 48 h, 50 °C; (viii) Ac_2O, DMAP, pyridine, 30 min, r. t.; (ix) $NaIO_4$, RuO_2, CCl_4 : acetonitrile : water 2 : 3 : 3, 52 h, r. t.

SCHEME 4
The path to the phosphonate synthon **32** for nucleosidation in L-*erythro* series

The quantification of the conversion of **31** to **32** by UV detection was difficult. Because of the very different extinction coefficients of benzyl and benzoyl derivatives, **31** and **32**, the reaction mixture looked as if it contained an apparent excess of compound **32** at all times. Interestingly, there were no by-products observed with UV absorption and only starting compound **31** and product **32** were identified in the reaction mixture. Thus, compounds **31** and **32** were obtained in a mixture (27:73 by NMR). The prolonged time of oxidation for an additional two days neither influenced a ratio of **31** and **32** nor decreased the total amount of both compounds.

The nucleosidation reaction (Scheme 5) performed with the mixture of the 2-*O*-benzoyl **32** and 2-*O*-benzyl **31** derivatives and the silylated uracil surprisingly provided the 3-*N*-isomer **33a** exclusively, however, the use of

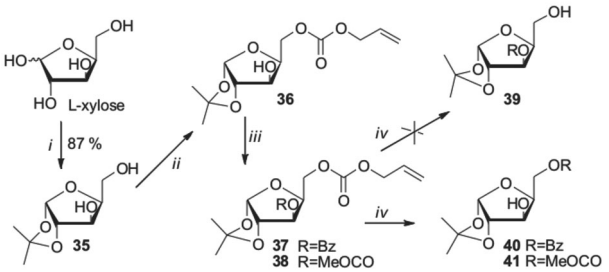
silylated thymine afforded the desired 1-*N*-isomer **33b** though in a low yield of 20%. The compounds **33a** (the sole product obtained from the nucleosidation reaction) was subsequently deprotected to yield phosphonic acid **34** in 82% yield. The mechanism of exclusive formation of the 3-*N*-derivative in case of only uracil and not thymine nucleobase remained unclear. We also examined the use of trimethylsilyl triflate as an alternative Lewis acid in the nucleosidation reaction with silylated uracil, but in this case, an unresolvable mixture of various products was obtained.



SCHEME 5
Preparation of nucleoside phosphonate with L-*erythro* configuration

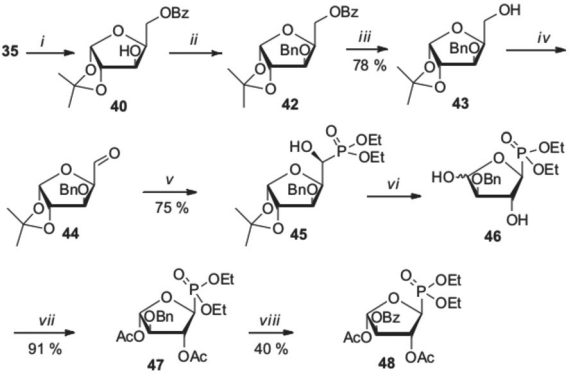
Preparation of L-*Threofuranose Nucleoside Phosphonates*

To prepare the L-threofuranosylphosphonate **48** (Scheme 7) synthon, we examined two synthetic pathways. The first pathway (Scheme 6) utilised 1,2-*O*-isopropylidene-L-xylose (**35**), which was easily accessible from L-



SCHEME 6
Sugar protections in the search for active species for phosphonylations and subsequent nucleosidations in L-*threo* series

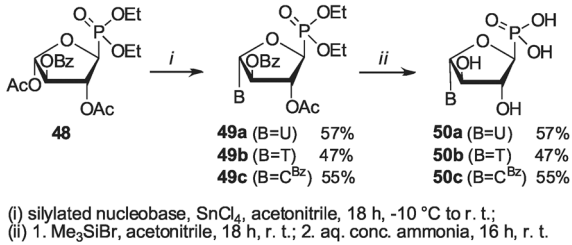
xylose upon isopropylidenation, followed by a selective hydrolysis of the 3,5-*O*-isopropylidene group of 1,2:3,5-di-*O*-isopropylidene-L-xylose in 60% aqueous acetic acid[36]. We further protected the 5-hydroxyl of **35** with an allyloxycarbonyl group. The subsequent acylation of the formed compound **36** with benzoyl cyanide and methoxycarbonyltetrazole afforded the 3-*O*-benzoyl and 3-*O*-methoxycarbonyl derivatives **37** and **38**, respectively. The treatment of **37** and **38** with tetrakistriphenylphosphine palladium in dichloromethane in the presence of tri-*n*-butylammonium formate to remove the allyloxycarbonyl moiety[49] afforded in both cases almost quantitative yield of the 5-*O*-acyl derivatives **40** and **41** instead of the desired 3-*O*-derivatives **39**. In both cases, the complete 3→5 migration of benzoyl and methoxycarbonyl groups occurred.



SCHEME 7
Pathway to the phosphonate precursor **48** for nucleosidations in L-*threo* series

An alternative route (Scheme 7) was contemplated, starting with direct benzoylation of the 5-hydroxy group of compound **35** to provide derivative **40**, which was easier than the one depicted in Scheme 6. The subsequent benzylation of the 3-hydroxy group afforded compound **42**, and the removal of the 5-*O*-benzoyl group under basic conditions provided product **43**. After Moffatt oxidation to the aldehyde **44** and the addition of diethyl phosphite, only product **45** with an *S*-configuration on the C5 atom formed. Oxidative treatment with HIO_4 followed by acetylation afforded **47**. The benzyl derivative was further oxidised with RuO_2 to the final benzoyl compound, **48**, in a moderate yield. The separation of the benzyl **47** and benzoyl **48** derivatives was successfully performed. The nucleosidation reaction (Scheme 8) proceeded in good yield, providing nucleoside phos-

phonates **49a–49c**, which were deprotected to yield free phosphonic acids **50a–50c**.



SCHEME 8
Preparation of nucleoside phosphonates with L-*threo* configuration

*Conformation of the Furanose Ring in **5**, **9a**, **9b**, **20a–20c***

It was realised that the compounds prepared in this work possessed specific structural features, such as the "shortened" carbon backbone in the sugar portion and the attachment of the phosphonate moiety directly to the tetrofuranose ring. These properties were evaluated by determining their prevailing conformational forms with an NMR study. Compounds **5**, **9a**, **9b**, **20a–20c** were selected for the measurement and computation, and they represented several related configurational types differing in the orientation of the nucleobase and adjacent hydroxy group (Fig. 4).

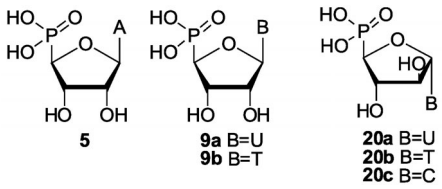


FIG. 4
The NMR-evaluated β-D-erythrose (**5**, **9a**, **9b**) and α-D-threose (**20a–20c**) nucleotide analogues

The ^3J(H,H)s and PSEUROT program[50], based on the concept of pseudorotation[51], were used to obtain information on conformation of furanose ring. The NMR conformational studies showed that when nucleotides were in solution, two preferred conformers (N- and S-type) of the furanose ring were present in fast equilibrium and could be fully described by five parameters (phase angles P(N), P(S), puckering amplitudes (ϕ_m(N), ϕ_m(S)), and the molar concentration of one conformer X(N) or X(S)). As there are only

TABLE I

Experimental vicinal *J*(H,H)s and the ranges of calculated pseudorotation parameters for β-D-*erythro*- (**5**, **9a**, **9b**) and α-D-*threo*-nucleotides (**20a–20c**). Pseudorotation parameters of the conformers after energy minimisation and calculated conformer populations (with PSEUROT) are given in red

Comp. (base)	*J*(1′,2′)	*J*(2′,3′)	*J*(3′,4′)	ϕ_m(N)	P(N)	X(N)	ϕ_m(S)	P(S)	X(S)	rms
5 (A)	7.4	5.3	2.2	32 to 40	–11 to –55	0.14 to 0.24	32 to 40	155 to 142	0.86 to 0.76	
				33	–23	0.20	36	159	0.80	0.220
9a (U)	7.0	4.9	2.2	36 to 42	–28 to –48	0.24 to 0.31	36 to 42	161 to 148	0.76 to 0.69	
				39	–32	0.25	38	156	0.75	0.107
9b (T)	6.8	5.1	2.6	34 to 42	–18 to –47	0.24 to 0.33	34 to 42	157 to 142	0.76 to 0.67	
				39	–31	0.29	38	155	0.71	0.147
20a (U)	1.7	1.9	2.2	32 to 44	10 to 28	0.17 to 0.07	32 to 44	166 to 142	0.83 to 0.93	
				36	0	0.13	35	151	0.87	0.100
20b (T)	1.1	1.5	1.6	32 to 42	16 to 56	0.10 to 0.03	32 to 42	173 to 148	0.90 to 0.97	
				36	16	0.05	35	151	0.95	0.178
20c (C)	1.9	1.9	2.4	32 to 44	–12 to 0	0.20 to 0.07	32 to 44	167 to 140	0.80 to 0.93	
				38	–45	0.16	36.0	148	0.84	0.277

three ^3J(H,H)s in the furanose ring in this case, the PSEUROT calculation was started by assuming $\phi_m(N) = \phi_m(S)$, and the values were changed in 2° steps from 30 to 46°. The P(N), P(S), and X(N) were calculated to obtain a best fit between the calculated and observed ^3J(H,H) values. Table I shows the observed ^3J(H,H) values and the ranges of calculated combinations of P(N), P(S), and X(N) that give an excellent agreement between the calculated and observed ^3J(H,H)s (rms ≤ 0.001).

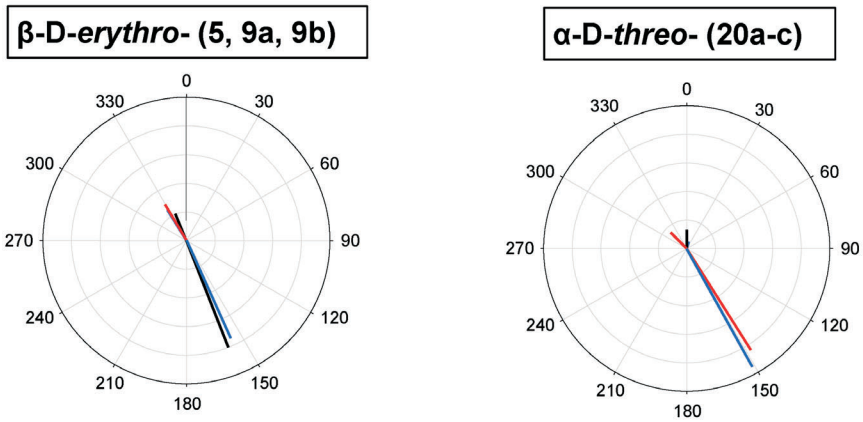


FIG. 5
Graphical presentation of the geometry optimisation of the N- and S-type conformers of compounds **5**, **9a**, **9b** and **20a**–**20c**. The individual compounds are distinguished by colour: black, **5** and **20a**; blue, **9a** and **20b**; red, **9b** and **20c**. The length of the lines indicates the relative populations of conformers from PSEUROT calculations

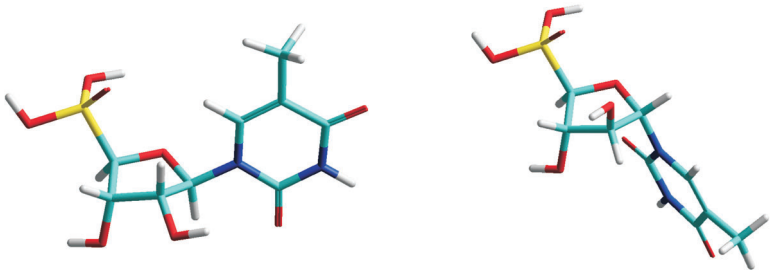


FIG. 6
The energy-minimised conformations of thymine derivatives **9b** and **20b** with 8b-D-*erythro* and α-D-*threo* configuration, respectively

The results showed that all calculated conformers had a maximum pucker Φm in the range typical for nucleosides, and all compounds indicated that the S-type conformer was preferred (more significantly in α-D-*threo*-compounds).

To verify if the calculated conformers corresponded to the energy minima, molecular modeling was used. For each compound, we constructed the model of its N- and S-type conformer using previously calculated (PSEUROT) geometry parameters with a maximum pucker of $\phi_m = 38°$. Each molecule was allowed to "relax" without any restraints to optimize the geometry by energy minimisation (using the AMBER version of molecular mechanics in the HYPERCHEM 8.0 program). The calculated geometry data (P(N), ϕ_m(N), P(S), ϕ_m(S)) were further used as the fixed input data in the PSEUROT program for the estimation of the conformer populations ratio (X(N):X(S) as the only variable. The results were summarised in Table I (in red) and presented using the pseudorotation wheel in Fig. 5. It was concluded that the S-conformer (type ^2E to $^2T_1$) was significantly preferred in all six compounds and it existed in aqueous solution in a fast equilibrium with a small amount of the N-conformer. The energy-minimised, preferred S-type conformers of thymine derivatives **9b** and **20b** are shown in Fig. 6.

Inhibition of Thymidine Phosphorylase

Free phosphonic acids **9a**, **9b**, **20a–20c**, **34**, and **50a–50c** were tested as potential bi-substrate inhibitors of recombinant thymidine phosphorylase ($^{dThd}K_m$ = 60 μM) (for methodology, see Experimental). It was found that none of these analogues exerted any significant inhibition activity, except for compound **34**, which acted as a competitive inhibitor of thymidine phosphorylase with a K_i value of 4 μM; compound **34** is a 3-*N* substituted uracil derivative. Synthesis of the 1-*N* uracil derivative was not successfully resolved to check and compare the inhibitory activity of both compounds.

CONCLUSION

The presented work described the synthesis of tetrofuranose nucleoside phosphonic acids, the new isopolar phosphonate analogues of nucleoside 5′-phosphates. These analogues are distinguished for direct attachment of the phosphoryl group to the C4 atom of the tetrofuranose ring. The key synthons, *erythro*- and *threo*-configured tetrofuranosyl phosphonates in the D- and L-series, were synthesised from pentofuranosyl 5′-hydroxyphosphonates through oxidative cleavage of the C1-C2 bond. Four such

synthons were prepared and found to yield desired compounds in the nucleosidation reaction with silylated pyrimidine nucleobases. The course of the reaction for particular tetrofuranose phosphonate synthons and nucleobases was found to be far from uniform. Nevertheless, we were able to prepare the representative compounds from all four groups, defined by the variants of the tetrofuranosyl ring. NMR conformational studies with a series of selected compounds, employing molecular modelling, showed that with nucleotides in solution, the two preferred conformers (N- and S-type) of the furanose ring were present in a fast equilibrium. All calculated conformers had a maximum pucker Φm in a range typical for nucleosides. In all compounds, the S-type conformer significantly prevailed (especially in α-D-*threo*-compounds).

Free nucleoside phosphonic acids were subjected to screening for inhibition of human thymidine phosphorylase. Of the group, (4*S*)-[1-deoxy-1-(uracil-3-yl)-β-L-erythrofuranos-4-yl]phosphonic acid was found to be competitive inhibitor of the enzyme with a K_i value of 4 μM. Another compound from the prepared series was found to inhibit human cytosolic and mitochondrial pyrimidine specific 5′-nucleotidases but that recent data will be published separately in a new context. The synthesis of diphosphoryl derivatives of tetrose nucleoside phosphonic acids as NTP analogues and a study with viral polymerases are underway.

EXPERIMENTAL

General

The solvents were evaporated at 30 °C in vacuo using a rotatory evaporator, and the products were dried over phosphorus pentoxide at 40–50 °C and 13 Pa. The course of the reactions was checked by TLC on silica gel UV 254 foils (Merck), whereby the products were detected by UV monitoring upon spraying with 1% ethanolic solution of 4-(4-nitrobenzyl)-pyridine followed by heating and treating with gaseous ammonia (blue colour of diesters of phosphonic acids), and by spraying with 10% aqueous sulfuric acid followed by heating (sugar derivatives). For flash column chromatography, silica gel 40–60 μm (Fluka) was used. The TLC and the preparative silica gel chromatography were carried out in the following solvent systems (v/v): chloroform–ethanol 19:1 (C1), chloroform–ethanol 9:1 (C2), ethyl acetate–acetone–ethanol–water 4:1:1:1 (H1), ethyl acetate–acetone–ethanol–water 6:1:1:1 (H3), 2-propanol–conc. aq. ammonia–water 7:1:2 (I), ethyl acetate–toluene 1:1 (T1) and ethyl acetate–toluene 1:5 (T2). Analytical HPLC was performed on an LC 5000 liquid chromatograph (INGOS, Czech Republic) with a Luna C18 5 μm (4.6 × 150 mm; Phenomenex) reversed phase column using a linear gradient of methanol in 0.1 M triethylammonium acetate (TEAA) buffer. Preparative reversed-phase chromatography was carried out on a spherical octadecyl silica gel column (25 × 250 mm, 20 to 40 μm), compounds were eluted with a linear gradient of methanol in water at 10 ml min^{-1}. Mass spec-

tra (*m/z*), as well as HR-FAB MS, were recorded on a ZAB-EQ (VG Analytical) instrument using FAB in both the positive and negative modes (ionisation by Xe, accelerating voltage 8 kV) with thioglycerol–glycerol (3:1) and 2-hydroxyethyldisulfide as matrices.

The ^{1}H and ^{13}C NMR spectra were measured on a Varian Unity 500 instrument (^{1}H at 500 MHz, ^{13}C at 125.7 MHz) or on a Bruker Avance 600 spectrometer (^{1}H at 600 MHz, ^{13}C at 150.9 MHz) in DMSO-d_6 (referenced to the solvent signals δ_H 2.50 and δ_C 39.7), $CDCl_3$ (referenced to TMS), and D_2O (referenced to DSS) at 20 °C. Proton signals in the ^{1}H NMR spectra were assigned on the basis of chemical shifts, observed multiplicities, and homonuclear 2D-COSY experiments. The exchange of hydroxyl protons for deuterium was carried out using several drops of tetradeuterioacetic acid. Assignments of signals in the ^{13}C NMR spectra were accomplished using *J*-modulated spectra (APT), and in some cases, confirmed by 2D-^{1}H,^{13}C-HSQC and 2D-^{1}H,^{13}C-HBMC spectra.

Optical rotations were measured on an Autopol IV (Rudolph) instrument at 20 °C and 589 nm.

The thymidine phosphorylase activity was measured using an Infinite F500 (Tecan) reader.

Synthetic Methods

Method A: *Oxidative cleavage of pentofuranose 5′-hydroxyphosphonates and acetylation of formed terofuranosylphosphonates*. Periodic acid dihydrate (340 mg, 1.5 mmol) was added to a solution of the respective pentofuranose 5′-hydroxyphosphonate (**14**, **28**, **45**; 1 mmol) in 50% aqueous dioxane (7 ml) and the reaction mixture was set aside at 50 °C in the dark for 2 days (TLC in C1). The solution was treated with Dowex 1x2 in acetate form (4 ml) under stirring for 10 min to remove periodate and iodate anions. The resin was filtered off and washed with methanol, and the combined filtrates were evaporated. The residue was co-distilled several times with water to remove acetic acid, and finally treated with 0.1 M TEAB (10 ml) for 20 min. The aqueous solution was evaporated to dryness, the crude tetrofuranosylphosphonate (**16**, **30**, **46**) was co-distilled with pyridine, and treated with acetic anhydride (0.42 ml, 4.4 mmol) and DMAP (7 mg, 0.06 mmol) in pyridine (4 ml) for 30 min (TLC in C1). The reaction mixture was quenched by the addition of water (0.4 ml) at 0 °C, the solvent was evaporated in vacuo, and the acetyl derivative (**17a**, **17b**, **31a**, **31b**, **47a**, **47b**) was purified on silica gel by elution with a linear gradient of ethyl acetate in toluene.

Method B: *Nucleosidation reaction*. The nucleobase (4-*N*-benzoylcytosine, thymine, uracil; 4 mmol) in hexamethyldisilazane (HMDS; 12 ml, 56 mmol) was refluxed in the presence of a catalytical amount of ammonium sulfate under stirring and exclusion of moisture overnight. Volatile components were removed under reduced pressure and the resulting oil was co-distilled twice with xylene and twice with acetonitrile to remove traces of HMDS. A solution of the sugar phosphonate (**6**, **17**, **32**, **48**; 440 mg, 1 mmol) in acetonitrile (2 ml) was then added via septum under argon to the silylated nucleobase followed by the addition of tin tetrachloride (0.24 ml, 2 mmol) at –10 °C. The mixture was stored at r.t. for 12 h (TLC in C1, H1). Into the reaction mixture, 2 M TEAB (2 ml) was added. The reaction was diluted with chloroform and filtered through Celite, washed with chloroform, and the solvents were removed under reduced pressure. The residue was purified on silica gel by elution with a linear gradient of ethanol in chloroform.

Method C: *Oxidation of the benzyl group to the benzoyl group*. Sodium periodate (900 mg, 4.2 mmol) and ruthenium(IV) oxide (3 mg, 0.02 mmol) was added at r.t. to the mixture of a given phosphonate (**31**, **47**; 1 mmol) and tetrachloromethane–acetonitrile– water (2:2:3; 35 ml). The reaction was set aside in the dark for 3 days (monitored by HPLC). The solution was diluted with ethyl acetate, extracted twice with water, and the organic layers were dried, evaporated, and finally purified on a silica gel column by a linear gradient of ethyl acetate in toluene.

Method D: *Removal of the protecting groups*. Bromotrimethylsilane (0.66 ml, 5 mmol) was added to a solution of the respective nucleotide (**7a**, **7b**, **8a**, **8b**, **19a–19c**, **33a**, **33b**, **49a–49c**; 1 mmol) in acetonitrile (5 ml), the mixture was stored at r.t. for 48 h (TLC in C2, H1 and I), and then concentrated in vacuo. Concentrated aqeuous ammonia (20 ml) was added and the reaction was stored overnight. The solution was concentrated and the residue was co-distilled several times with water. The phosphonic acid was obtained by purification using chromatography on DEAE-Sephadex A-25 $(HCO_3)^-$. The compounds were eluted with a linear gradient of 0 to 0.3 M TEAB. The fractions were pooled and evaporated and the residue was co-distilled several times with methanol and then applied onto a C18 column (25 × 300 mm). The products were eluted by a linear gradient of methanol in water (0 to 5%), transformed into sodium salts on a column of Dowex 50 (Na^+), and finally freeze-dried from water.

Diethyl (4*R*)-[3-*O*-Acetyl-2-*O*-benzoyl-1-deoxy-1-(uracil-1-yl)-β-D-erythrofuranos-4-yl]-phosphonate (**7a**) and Diethyl (4*R*)-[2-*O*-Acetyl-3-*O*-benzoyl-1-deoxy-1-(uracil-1-yl)-β-D-erythrofuranos-4-yl]phosphonate (**7b**)

A mixture of phosphonates **7a**, **7b** was obtained from silylated uracil (630 mg, 5.6 mmol) and the phosphonate **6** (410 mg, 0.9 mmol) according to the Method *B*. Yield 155 mg (17%, white lyophilizate) of **7** (**a**:**b** = 63:37). HR-FAB calculated for $C_{21}H_{26}N_2O_{10}P$ $(M + H)^+$: 497.1325; found 497.1308. IR ($CHCl_3$, cm^{-1}): **U**: ν (NH-free) 3390w; ν (NH-bonded) 3171w, br; ν (C=O) 1723s, 1699vs; ν (C=C) 1638w; ν (ring) 1460m, sh, 1391m, 1262s. **–OAc**: ν (C=O) 1752s; ν (C–O) 1229s, 1036s; γ (CCOO) 595w; δ_s (CH_3) 1376m. **OBz**: β (C=O) 712m; ν (C–O) 1277s, sh, 964m; ν (=CH) 3065w, 3028m; ν (ring) 1603w, 1586w, 1493vw, 1445w, sh, 1317w, 1178w, 1068m, 686w. **PO(OEt)$_2$**: ν (P=O) 1249s, ν_{as} (POCC) 1036s, 978m; δ (POC) 562m; β_s (CH_2) 1479w, sh; δ_{as} (CH_3) 1454m; δ_{as} (CH_3) 1163w, 1097m.

7a: ^{1}H NMR (500 MHz, $CDCl_3$): 8.385 bd, 1 H, *J*(NH,5) = 2.3 (NH); 8.21 dd, 1 H, *J*(6,5) = 8.3 (H-6); 7.97 m, 2 H, 7.59 m, 1 H and 7.45 m, 2 H (C_6H_5); 6.60 dd, 1 H, *J*(1′,2′) = 7.8 and *J*(1′,3′) = 1.5 (H-1′); 5.88 dd, 1 H, *J*(5,6) = 8.3 and *J*(5,NH) = 2.3 (H-5); 5.85 ddd, 1 H, *J*(3′,2′) = 5.0, *J*(3′,4′) = 1.7 and *J*(3′,1′) = 1.5 (H-3′); 5.76 dd, 1 H, *J*(2′,1′) = 7.8 and *J*(2′,3′) = 5.0 (H-2′); 4.43 dd, 1 H, *J*(4′,3′) = 1.7 and *J*(4′,P) = 5.5 (H-4′); 4.31–4.21 m, 4 H and 1.42 t, 3 H, *J* = 7.0 and 1.415 t, 3 H, *J* = 7.0 ($P(OEt)_2$); 2.13 s, 3 H (OAc).

7b: ^{1}H NMR (500 MHz, $CDCl_3$): 8.38 bd, 1 H, *J*(NH,5) = 2.3 (NH); 8.215 dd, 1 H, *J*(6,5) = 8.3 (H-6); 8.09 m, 2 H, 7.51 m, 1 H and 7.64 m, 2 H (C_6H_5); 6.54 dd, 1 H, *J*(1′,2′) = 8.1 and *J*(1′,3′) = 1.6 (H-1′); 5.88 dd, 1 H, *J*(5,6) = 8.3 and *J*(5,NH) = 2.3 (H-5); 5.68 dd, 1 H, *J*(2′,1′) = 8.1 and *J*(2′,3′) = 5.1 (H-2′); 5.95 ddd, 1 H, *J*(3′,2′) = 5.1, *J*(3′,4′) = 1.4 and *J*(3′,1′) = 1.6 (H-3′); 4.52 dd, 1 H, *J*(4′,3′) = 1.4 and *J*(4′,P) = 5.75 (H-4′); 4.31–4.21 m, 4 H and 1.42 t, 3 H, *J* = 7.0 and 1.415 t, 3 H, *J* = 7.0 ($P(OEt)_2$); 2.01 s, 3 H (OAc).

Diethyl (4*R*)-[3-*O*-Acetyl-2-*O*-benzoyl-1-deoxy-1-(thymin-1-yl)-β-D-erythrofuranos-4-yl]-phosphonate (**8a**) and Diethyl (4*R*)-[2-*O*-Acetyl-3-*O*-benzoyl-1-deoxy-1-(thymin-1-yl)-β-D-erythrofuranos-4-yl]phosphonate (**8b**)

Phosphonates **8a** and **8b** were obtained from silylated thymine (1.1 g, 8.6 mmol) and phosphonate **6** (950 mg, 2.1 mmol) according to the Method *B*. Yield 240 mg (22%, white lyophilizate) of **8** (**a**:**b** = 74:26). HR-FAB calculated for $C_{22}H_{28}N_2O_{10}P$ $(M + H)^+$: 511.1482; found 511.1473. IR ($CHCl_3$, cm^{-1}): **T**: ν (C=O) 1717s, 1696vs; ν (C=C) 1658w, sh; ν (ring) 1466w, 1435w, sh; δ_s (CH_3) 1381w, sh. **OAc**: ν (C=O) 1752m; ν (C–O) 1249s, 1027s; δ_s (CH_3) 1375w. **OBz**: ν (C=O) 1731s, sh; ν (C–O) 1261s; β (C=O) 711m; ν (ring) 1603w, 1586vw, 1493vw, 1453w, 1317w, 1178w, 1121m, 1070m, sh, 1027s, 1002w, sh, 686w. **PO(OEt)$_2$**: ν_{as} (POCC) 1038s, 1027s, 979w; δ (POC) 559w; δ_{as} (CH_3) 1444w, sh; γ_s (CH_2) 1391w; δ_{as} (CH_3) 1164w, 1097m.

8a: ^{1}H NMR (600 MHz, $CDCl_3$): 8.00 q, 1 H, J(6,CH_3) = 1.2 (H-6); 7.98 m, 2 H, 7.595 m, 1 H and 7.45 m, 2 H (OBz); 6.59 dd, 1 H, J(1′,2′) = 7.8 and J(1′,P) = 1.5 (H-1′); 5.86 ddd, 1 H, J(3′,2′) = 5.1, J(3′,4′) = 1.7 and J(3′,P) = 7.0 (H-3′); 5.76 dd, 1 H, J(2′,1′) = 7.8 and J(2′,3′) = 5.1 (H-2′); 4.43 dd, 1 H, J(4′,3′) = 1.7 and J(4′,P) = 5.5 (H-4′); 4.25 m, 4 H, 1.42 t, 3 H and 1.38 t, 3 H (P(OEt)$_2$); 2.12 s, 3 H (OAc); 1.98 d, 3 H, J(CH_3,6) = 1.2 (CH_3-5). ^{13}C NMR (150.9 MHz, $CDCl_3$): 169.29 and 20.64 (OAc); 164.93, 133.86, 129.87(2), 128.63(2) and 128.31 (OBz); 162.94 (C-4); 150.50 (C-2); 135.56 (C-6); 112.42 (C-5); 85.56 d, J(C,P) = 2.9 (C-1′); 77.98 d, J(C,P) = 168.1 (C-4′); 72.87 (C-2′); 70.91 d, J(C,P) = 10.1 (C-3′); 64.07 d, J(C,P) = 6.6, 63.51 d, J(C,P) = 7.2, 16.47 d, J(C,P) = 5.7 and 16.46 d, J(C,P) = 5.7 (P(OEt)$_2$).

8b: ^{1}H NMR (600 MHz, $CDCl_3$): 8.02 q, 1 H, J(6,CH_3) = 1.2 (H-6); 7.98 m, 2 H, 7.595 m, 1 H and 7.45 m, 2 H (OBz); 6.54 dd, 1 H, J(1′,2′) = 8.0 and J(1′,P) = 1.5 (H-1′); 5.68 dd, 1 H, J(2′,1′) = 8.0 and J(2′,3′) = 5.1 (H-2′); 5.95 ddd, 1 H, J(3′,2′) = 5.1, J(3′,4′) = 1.5 and J(3′,P) = 7.0 (H-3′); 4.52 dd, 1 H, J(4′,3′) = 1.5 and J(4′,P) = 5.7 (H-4′); 4.29 m, 4 H, 1.425 t, 3 H and 1.37 t, 3 H (P(OEt)$_2$); 2.12 s, 3 H (OAc); 1.987 d, 3 H, J(CH_3,6) = 1.2 (CH_3-5).

(4*R*)-[1-Deoxy-1-(uracil-1-yl)-β-D-erythrofuranos-4-yl]phosphonic Acid (**9a**)

Phosphonic acid **9a** was obtained from phosphonates **7a**, **7b** (60 mg, 0.12 mmol) according to the Method *D*. Yield 28 mg (69%, white lyophilizate) of **9a**, $[\alpha]^{20}$ –8.6. HR-FAB calculated for $C_8H_{10}N_2O_8P$ $(M + H)^+$: 293.0175; found 293.0178. IR (KBr, cm^{-1}): ν (OH, NH) 3423s, br, 3255m, br, sh, 2807w, br, ν (C–OH) 1117s, 1085s, ν $(PO_3)^{2-}$ 972m, δ $(PO_3)^{2-}$ 577m. **U**: ν (C=O) 1697vs; ν (ring) 1637m, sh, 1466w, 1396w, 1273m; γ (=CH) 821w, 769w. ^{1}H NMR (600 MHz, D_2O): 8.39 d, 1 H, J(6,5) = 8.1 (H-6); 6.04 dd, 1 H, J(1′,2′) = 7.0 and J(1′,P) = 1.2 (H-1′); 5.93 d, 1 H, J(5,6) = 8.1 (H-5); 4.42 bt, 1 H, J(2′,1′) = 7.0 and J(2′,3′) = 4.9 (H-2′); 4.39 ddd, 1 H, J(3′,2′) = 4.9, J(3′,4′) = 2.2 and J(3′,P) = 6.6 (H-3′); 4.05 dd, 1 H, J(4′,3′) = 2.2 and J(4′,P) = 5.6 (H-4′). ^{13}C NMR (150.9 MHz, D_2O): 167.04 (C-4); 152.87 (C-2); 143.50 (C-6); 103.19 (C-5); 87.73 d, J(C,P) = 3.2 (C-1′); 84.65 d, J(C,P) = 147.6 (C-4′); 75.47 d, J(C,P) = 2.3 (C-2′); 72.27 d, J(C,P) = 5.7 (C-3′).

(4*R*)-[1-Deoxy-1-(thymin-1-yl)-β-D-erythrofuranos-4-yl]phosphonic Acid (**9b**)

Title phosphonic acid **9b** was obtained from phosphonates **8a**, **8b** (120 mg, 0.23 mmol) according to the Method *D*. Yield 65 mg (80 %, white lyophilizate) of **9b**, $[\alpha]^{20}$ –12.8. HR-FAB calculated for $C_9H_{12}N_2O_8P$ $(M + H)^+$: 307.0331; found 307.0336. IR (KBr, cm^{-1}) ν (C–OH) 1122w, br, 1077w, br; ν (OH, NH) 3436vs, br; ν_{as} $(PO_3)^{2-}$ 971w, br, δ_s $(PO_3)^{2-}$ 597w.

T: ν (C=O) 1700w, br; ν (ring) 1636m, br, 1476w, br, 1435w, br, sh, 1393w, br, 1273w, br. ^{1}H NMR (600 MHz, D_2O): 8.09 q, 1 H, *J*(6,CH_3) = 1.2 (H-6); 6.04 dd, 1 H, *J*(1′,2′) = 6.8 and *J*(1′,P) = 1.1 (H-1′); 4.41 ddd, 1 H, *J*(3′,2′) = 5.1, *J*(3′,4′) = 2.6 and *J*(3′,P) = 7.5 (H-3′); 4.38 dd, 1 H, *J*(2′,1′) = 6.8 and *J*(2′,3′) = 5.1 (H-2′); 4.09 dd, 1 H, *J*(4′,3′) = 2.6 and *J*(4′,P) = 5.2 (H-4′); 1.92 d, 3 H, *J*(CH_3,6) = 1.2 (CH_3-5). ^{13}C NMR (150.9 MHz, D_2O): 169.36 (C-4); 155.02 (C-2); 140.59 (C-6); 114.59 (C-5); 89.73 d, *J*(C,P) = 4.1 (C-1′); 85.40 d, *J*(C,P) = 152.4 (C-4′); 77.01 d, *J*(C,P) = 3.0 (C-2′); 73.82 d, *J*(C,P) = 5.6 (C-3′); 14.38 (CH_3-5).

Diethyl (5*R*)-(3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranos-5-*C*-yl)-phosphonate (**14**) and Diethyl (5*R*)-(5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranos-5-*C*-yl)phosphonate (**15**)

1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**10**; 31.9 g, 122 mmol) was treated with benzoyl chloride (17 ml, 146 mmol) and triethylamine (34.2 ml, 244 mmol) in dichloromethane (146 ml) at 0 °C under exclusion of moisture (TLC in T1) overnight. The reaction was quenched by addition of methanol (12 ml) and the solvent was evaporated in vacuo. The residue was dissolved in chloroform and the organic layer was washed with water several times. After evaporation of the solvent, the crude benzoyl derivative **11** was treated with 60% aqueous acetic acid (1500 ml) at r.t. for 3 days. The acid was evaporated in vacuo, the residue taken into chloroform, and the organic layer was washed with saturated aqueous solution of NaCl. The organic layer was washed with saturated aqueous solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, and evaporated. Yield 29.4 g (74%; yellowish syrup) of 3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**12**). The saturated aqueous solution of sodium periodate (23.5 g, 108 mmol) was then added at 0 °C to a stirred solution of this compound (29.4 g, 90.5 mmol) in 70% aqueous acetone (905 ml) (TLC in C1). After 1 h, the crystals of iodate were filtered off, the filter cake was washed with 70% aqueous acetone, and the solvents were evaporated. The residue was dissolved in acetone, filtered once more, evaporated, and co-distilled repeatably with toluene. To a solution of the formed aldehyde in CH_2Cl_2 (90.5 ml), diethyl phosphite (23.5 ml, 181 mmol) and triethylamine (63.3 ml, 452 mmol) were added at 0 °C and the mixture was stirred overnight (TLC in C2). The reaction mixture was then diluted with chloroform, filtered through Celite, and the filtrate was extracted with water. The organic layer was dried over anhydrous Na_2SO_4. Chromatography of the crude product on silica gel (elution with a linear gradient of 0–10% ethanol in chloroform) afforded a mixture of both regioisomeric phosphonates **14** and **15** (67:33). Yield 21.1 g (56%, colourless sirup). HR-FAB calculated for $C_{19}H_{28}O_9P$ $(M + H)^+$: 431.1471; found 431.1453. IR ($CHCl_3$, cm^{-1}): ν (OH) 3573w, br, 3441w, br, 3251w, br. **PO(OEt)$_2$**: ν (P=O) 1250s, sh; ν_{as} (POCC) 1050vs, 1026vs; ν (C–C) 974s, 963s; δ (POC) 554m, 543m; β_s (CH_2) 1478w; δ_{as} (CH_3) 1453m; γ_s (CH_2) 1395m, sh; δ_{as} (CH_3) 1164s, 1096vs; ν_{as} (CH_3) 2996s. **OBz**: ν (C=O) 1726s; ν (C–O) 1269vs; β (C=O) 712s; ν (=CH) 3093w, 3065w, 3028m; ν (ring) 1602w, 1586w, 1493w, 1445w, 1316m, 1178s, 1112s, 1072vs, 1002m, sh, 686w, 617vs. **CMe$_2$**: δ_s (CH_3) 1386m, 1377m; ν_s (CMe_2) 861m; γ_s (CMe_2) 521w.

14: ^{1}H NMR (500 MHz, DMSO): 7.98 m, 2 H, 7.69 m, 1 H and 7.56 m, 2 H (C_6H_5); 5.98 d, 1 H, *J*(1,2) = 3.8 (H-1); 5.98 dd, 1 H, *J*(OH,5) = 7.4 and *J*(OH,P) = 5.3 (H-5); 5.31 bd, 1 H, *J*(3,2) < 0.5 and *J*(3,4) = 2.8 (H-3); 4.66 bdd, 1 H, *J*(2,1) = 3.8, *J*(2,P) = 2.0 and *J*(2,3) < 0.5 (H-2); 4.40 ddd, 1 H, *J*(4,3) = 2.8, *J*(4,5) = 9.8 and *J*(4,P) = 8.9 (H-4); 4.06 m, 4 H, 1.24 t, 3 H, *J* = 7.1 and 1.23 t, 3 H, *J* = 7.1 (P(OEt)$_2$); 4.00 ddd, 1 H, *J*(5,4) = 9.8, *J*(5,OH) = 7.4 and *J*(5,P) = 4.3 (H-5); 1.46 s, 3 H and 1.27 s, 3 H (1,2-O*i*Pr). ^{13}C NMR (125.8 MHz, DMSO):

164.96, 133.77, 129.57(2), 129.55 and 128.93(2) (OBz); 111.47, 26.58 and 26.19 (1,2-O*i*Pr); 105.11 (C-1); 81.92 (C-2); 77.87 d, *J*(C,P) = 3.5 (C-4); 76.33 d, *J*(C,P) = 10.4 (C-3); 63.99 d, *J*(C,P) = 164.9 (C-5); 62.18 d, *J*(C,P) = 6.8, 61.95 d, *J*(C,P) = 6.7, 16.52 d, *J*(C,P) = 5.4 and 16.50 d, *J*(C,P) = 5.3 ($P(OEt)_2$).

15: ^{1}H NMR (500 MHz, DMSO): 7.98 m, 2 H, 7.69 m, 1 H and 7.55 m, 2 H (C_6H_5); 5.91 d, 1 H, *J*(1,2) = 3.6 (H-1); 5.49 dd, 1 H, *J*(5,4) = 10.0 and *J*(5,P) = 4.1 (H-5); 4.49 ddd, 1 H, *J*(4,3) = 2.9, *J*(4,5) = 10.0 and *J*(4,P) = 8.5 (H-4); 4.42 bdd, 1 H, *J*(2,1) = 3.6, *J*(2,P) = 2.2 and *J*(2,3) ≤ 0.5 (H-2); 4.06 m, 4 H, 1.19 t, 3 H, *J* = 7.2 and 1.16 t, 3 H, *J* = 7.2 ($P(OEt)_2$); 4.04 bd, 1 H, *J*(3,2) ≤ 0.5 and *J*(3,4) = 2.9 (H-3); 1.43 s, 3 H and 1.26 s, 3 H (1,2-O*i*Pr). ^{13}C NMR (125.8 MHz, DMSO): 163.76 d, *J*(C,P) = 2.0, 133.79, 129.54(2), 129.28 and 129.03(2) (OBz); 111.23, 26.91 and 26.31 (1,2-O*i*Pr); 105.12 (C-1); 84.38 (C-2); 78.12 (C-4); 73.25 d, *J*(C,P) = 9.8 (C-3); 65.33 d, *J*(C,P) = 164.0 (C-5); 62.60(2) d, *J*(C,P) = 6.8, 16.37 d, *J*(C,P) = 5.2 and 16.32 d, *J*(C,P) = 5.5 ($P(OEt)_2$).

Diethyl (4*R*)-(1,3-di-*O*-Acetyl-2-*O*-benzoyl-α-D-threofuranos-4-yl)phosphonate (**17**)

Phosphonate **17** was obtained from diethyl (5*R*)-(3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranos-5-*C*-yl)phosphonate (**14**; 3.42 g, 8.0 mmol) according to the Method *A*. Yield 1.76 g (49%, colourless sirup) of **17**. HR-FAB calculated for $C_{19}H_{26}O_{10}P$ $(M + H)^+$: 445.1264; found 445.1258. IR ($CHCl_3$, cm^{-1}): **OBz**: ν (C=O) 1730s; ν (C–O) 1266s, sh; β (C=O) 712s; ν (=CH) 3030m; ν (ring) 1603w, 1585w, 1493w, 1452w, 1317m, 1179m, 1297m, sh, 1100s, 686w. **OAc**: ν (C=O) 1755vs; ν (C–O, P=O) 1257s, 1232vs, sh; γ (CCO) 602w; δ_s (CH_3) 1370m. **$PO(OEt)_2$**: β_s (CH_2) 1479w; δ_{as} (CH_3) 1444w; γ_s (CH_2) 1393w; δ_{as} (CH_3) 1164w, 1097s; ν_{as} (POCC) 1046s, 1028vs, 963s; δ (POC) 574w. ^{1}H NMR (500 MHz, $CDCl_3$): 8.08 m, 2 H, 7.59 m, 1 H and 7.46 m, 2 H (OBz); 6.40 q, *J*(1,2) = 0.65, *J*(1,3) = 0.65 and *J*(1,P) = 0.7 (H-1); 5.72 dddd, *J*(3,2) = 1.6, *J*(3,4) = 5.8, *J*(3,1) = 0.65 and *J*(3,P) = 13.3 (H-3); 5.395 dt, *J*(2,1) = 0.65, *J*(2,3) = 1.6 and *J*(2,4) = 0.55 (H-2); 4.46 ddd, 1 H, *J*(4,3) = 5.8, *J*(4,P) = 4.3 and *J*(4,2) = 0.55 (H-4); 4.23 m, 4 H, 1.34 t, 3 H, *J* = 7.2 and 1.335 t, 3 H, *J* = 7.2 ($P(OEt)_2$); 2.15 s, 6 H (2 × OAc). ^{13}C NMR (125.8 MHz, $CDCl_3$): 169.18, 168.75, 20.96 and 20.70 (2 × OAc); 165.18, 133.69, 130.03(2), 128.70 and 128.48(2) (OBz); 63.40(2) d, *J*(CH_2,P) = 6.5, 16.42 d, *J*(CH_3,P) = 5.5 and 16.39 d, *J*(CH_3,P) = 5.5 ($P(OEt)_2$); 99.58 d, *J*(1,P) = 12.6 (C-1); 76.24 d, *J*(C,P) = 4.0 (C-3); 81.48 d, *J*(C,P) = 8.2 (C-2); 78.14 d, *J*(C,P) = 175.5 (C-4).

Diethyl (4*R*)-[3-*O*-Acetyl-2-*O*-benzoyl-1-deoxy-1-(uracil-1-yl)-α-D-threofuranos-4-yl]-phosphonate (**19a**)

The title phosphonate was obtained from silylated uracil (3.1 g, 28 mmol) and the phosphonate **17** (2.5 g, 5.6 mmol) according to the Method *B*. Yield 1.3 g (48%, white lyophilizate) of **19a**, $[\alpha]^{20}$ +55.6. HR-FAB calculated for $C_{21}H_{26}N_2O_{10}P$ $(M + H)^+$: 497.1325; found 497.1303. IR ($CHCl_3$, cm^{-1}): **OAc**: ν (C=O) 1754s; ν (C–O) 1261s, 1029s; γ (CCOO) 600w; δ_s (CH_3) 1377m. **OBz**: ν (C=O) 1727vs; β (C=O) 712s; ν (C–O) 1261s, 965m, sh; ν (=CH) 3065w, 3026m; ν (ring) 1603w, 1586w, 1493w, 1453m, 1317w, 1179w, 1111s, 1071m, sh, 686w, 547w. **U**: ν (NH-free) 3389w; ν (NH-bonded) 3170w, br; ν (C=O) 1697vs; ν (C=C) 1636w; ν (ring) 1425w, sh. **$PO(OEt)_2$**: β_s (CH_2) 1480w, sh; δ_{as} (CH_3) 1445w, sh; γ_s (CH_2) 1391m; δ_s (CH_3) 1371m; δ_{as} (CH_3) 1064w, 1097m; ν_{as} (POCC) 1048s, 1029s, 978m; δ (POC) 571m. ^{1}H NMR (600 MHz, DMSO): 7.99 m, 2 H, 7.71 m, 1 H and 7.56 m, 2 H (C_6H_5); 7.80 d, 1 H, *J*(6,5) = 8.1 (H-6); 6.16 d, 1 H, *J*(1′,2′) = 4.6 (H-1′); 5.81 t, 1 H, *J*(2′,1′) = 4.6 and *J*(2′,3′) = 4.6 (H-2′); 5.78 ddd, 1 H, *J*(3′,4′) = 6.6, *J*(3′,P) = 13.1 and *J*(3′,2′) = 4.6

(H-3′); 5.72 d, 1 H, *J*(5,6) = 8.1 (H-5); 4.88 dd, 1 H, *J*(4′,3′) = 6.6 and *J*(4′,P) = 1.5 (H-4′); 4.11 m, 4 H, 1.264 t, 3 H, *J* = 7.0 and 1.262 t, 3 H, *J* = 7.0 ($P(OEt)_2$); 2.09 s, 3 H (OAc). ^{13}C NMR (150.9 MHz, DMSO): 169.39 and 20.76 (OAc); 165.16, 134.27, 129.78(2), 129.09(2) and 128.64 (OBz); 163.38 (C-4); 150.70 (C-2); 142.59 (C-6); 102.41 (C-5); 90.84 d, *J*(C,P) = 6.9 (C-1′); 79.41 d, *J*(C,P) = 7.1 (C-2′); 76.84 d, *J*(C,P) = 169.9 (C-4′); 74.76 d, *J*(C,P) = 4.4 (C-3′); 63.06 d, *J*(C,P) = 6.6, 62.93 d, *J*(C,P) = 6.6, 16.49 d, *J*(C,P) = 5.3 and 16.47 d, *J*(C,P) = 5.3 ($P(OEt)_2$).

Diethyl (4*R*)-[3-*O*-Acetyl-2-*O*-benzoyl-1-deoxy-1-(thymin-1-yl)-α-D-threofuranos-4-yl]-phoshonate (**19b**)

Phosphonate **19b** was obtained from silylated thymine (1.02 g, 8.1 mmol) and phosphonate **17** (900 mg, 2.02 mmol) according to the Method *B*. Yield 600 mg (58%, white lyophilizate) of **19b**, $[\alpha]^{20}$ +71.0. HR-FAB calculated for $C_{22}H_{28}N_2O_{10}P$ $(M + H)^+$: 511.1482; found 511.1463. IR ($CHCl_3$, cm^{-1}): **T**: ν (NH-free) 3389w; ν (NH-bonded) 3185vw, br; ν (C=O) 1722vs, 1697vs; ν (C=C) 1659m, sh; ν (ring) 1465w, 1435w; δ_s (CH_3) 1386w. **OAc**: ν (C=O) 1756m; ν (C–O) 1229s, 1029s; γ (CCOO) 602w; δ_s (CH_3) 1370m. **OBz**: ν (C–O) 1261s; β (C=O) 712m; ν (ring) 1603w, 1586w, 1494w, sh, 1452m, 1317w, 1179w, 1112m, 1072m, sh, 1001w, sh, 686w. **$PO(OEt)_2$**: ν (P=O) 1247s, sh; ν_{as} (POCC) 1047s, 1029s, 976m; δ (POC) 572w; δ_{as} (CH_3) 1444w, sh; γ_s (CH_2) 1393w, sh; δ_{as} (CH_3) 1164w, 1097m. ^1H NMR (600 MHz, $CDCl_3$): 8.67 bs, 1 H (NH); 8.07 m, 2 H, 7.60 m, 1 H and 7.46 m, 2 H (C_6H_5); 7.13 q, 1 H, *J*(6,CH_3) = 1.2 (H-6); 6.14 d, 1 H, *J*(1′,2′) = 4.8 (H-1′); 5.94 ddd, 1 H, *J*(3′,4′) = 5.4, *J*(3′,P) = 12.7 and *J*(3′,2′) = 3.9 (H-3′); 5.76 ddd, 1 H, *J*(2′,1′) = 4.8, *J*(2′,3′) = 3.9 and *J*(2′,P) = 0.8 (H-2′); 4.69 dd, 1 H, *J*(4′,3′) = 5.4 and *J*(4′,P) = 3.6 (H-4′); ~4.25 m, 4 H, 1.37 t, 3 H, *J* = 7.1 and 1.36 t, 3 H, *J* = 7.0 ($P(OEt)_2$); 2.15 s, 3 H (OAc); 1.96 d, 3 H, *J*(CH_3,6) = 1.2 (CH_3-5). ^{13}C NMR (150.9 MHz, $CDCl_3$): 169.20 and 20.74 (OAc); 165.69, 133.86, 130.08(2), 128.57(2) and 128.37 (OBz); 163.36 (C-4); 150.00 (C-2); 136.44 (C-6); 111.70 (C-5); 91.25 d, *J*(C,P) = 5.3 (C-1′); 79.88 d, *J*(C,P) = 5.4 (C-2′); 78.25 d, *J*(C,P) = 171.4 (C-4′); 75.80 d, *J*(C,P) = 6.2 (C-3′); 63.52 d, *J*(C,P) = 6.8, 63.42 d, *J*(C,P) = 6.9 and 16.45 d, *J*(C,P) = 5.4 ($P(OEt)_2$); 12.60 (CH_3-5).

Diethyl (4*R*)-[3-*O*-Acetyl-2-*O*-benzoyl-1-(4-*N*-benzoylcytosin-1-yl)-1-deoxy-α-D-threofuranos-4-yl]phosphonate (**19c**)

The title phosphonate was obtained from silylated 6-*N*-benzoylcytosine (970 mg, 4.5 mmol) and phosphonate **17** (500 mg, 1.12 mmol) according to the Method *D*. Yield 320 mg (48%, white lyophilizate) of **19c**, $[\alpha]^{20}$ +48.1. HR-FAB calculated for $C_{28}H_{31}N_3O_{10}P$ $(M + H)^+$: 600.1747; found 600.1754. IR ($CHCl_3$, cm^{-1}): **OAc**: ν (C=O) 1754m; ν (C–O) 1238s, sh, 1028s; γ (CCOO) 600w; δ_s (CH_3) 1368m. **OBz**: ν (C=O) 1728m; β (C=O) 712m; ν (C–O) 1259s; ν (ring) 1316m, 1299w, 1112m, 1002w, 829w. **NHBz**: ν (NH) 3406w; ν (amide I) 1705m; ν (amide II) 1554m. **OBz** and **NHBz**: ν (C–H) 3092vw, 3066vw; ν (ring) 1603m, 1583w, 1497w, 1452w, 1180w, 1071m, sh, 1028s, 686w, 616vw. **$PO(OEt)_2$**: ν (P=O) 1248s; ν (POC) 1069s, 1028s, 976w; δ (POC) 567w; δ_{as} (CH_3) 1445w; γ_s (CH_2) 1392w; δ_{as} (CH_3) 1165w, 1097m. **–C**: ν (C=O) 1674s; ν (ring) 1629m, 1480vs, 1404w, 1287m, sh. ^1H NMR (600 MHz, $CDCl_3$): 8.78 b, 1 H (NH); 8.10 m, 2 H, 7.60 m, 1 H and 7.46 m, 2 H (O-Bz); 7.90 m, 2 H, 7.63 m, 1 H and 7.53 m, 2 H (N-Bz); 7.74 bd, 1 H, *J*(6,5) ~ 7.0 (H-6); 7.63 bd, 1 H, *J*(5,6) ~ 7.0 (H-5); 6.11 dd, 1 H, *J*(1′,2′) = 3.4 and *J*(1′,P) = 0.8 (H-1′); 5.95 ddd, 1 H, *J*(3′,4′) = 5.4, *J*(3′,P) = 12.3 and *J*(3′,2′) = 3.4 (H-3′); 5.89 bt, 1 H, *J*(2′,1′) = 3.4 and *J*(2′,3′) =

3.4 (H-2′); 4.89 dd, 1 H, *J*(4′,3′) = 5.4 and *J*(4′,P) = 3.3 (H-4′); 4.23 m, 4 H, 1.35 t, 3H, *J* = 7.0 and 1.34 t, 3 H, *J* = 7.0 ($P(OEt)_2$); 2.13 s, 3 H (OAc). ^{13}C NMR (150.9 MHz, $CDCl_3$): 169.17 and 20.76 (OAc); 165.65, 133.76, 130.15(2), 128.51(2) (OBz); 133.36, 129.10(2), 128.58 and 127.54(2) (NBz); 154.65 (C-2); 145.80 (C-6); 94.80 (C-1′); 80.65 d, *J*(C,P) = 6.0 (C-2′); 80.03 d, *J*(C,P) = 181.5 (C-4′); 75.90 d, *J*(C,P) = 5.1 (C-3′); 63.48 d, *J*(C,P) = 6.8, 63.39 d, *J*(C,P) = 6.8 and 16.45 d, *J*(C,P) = 5.6 ($P(OEt)_2$).

(4*R*)-[1-Deoxy-1-(uracil-1-yl)-α-D-threofuranos-4-yl]phosphonic Acid (**20a**)

Phosphonic acid **20a** was obtained from phosphonate **19a** (300 mg, 0.6 mmol) according to the Method *D*. Yield 160 g (80%, white lyophilizate) of **20a**, $[\alpha]^{20}$ –3.2. HR-FAB calculated for $C_8H_9N_2O_8Na_3P$ $(M + Na)^+$: 360.9790; found 360.9786. IR (KBr, cm^{-1}): ν (OH, NH) 3424s, br, 3109m, br, 2802m, br; ν (C=O) 1696vs, br; ν (C=C) 1625m, sh; ν (ring) 1470m, 1439m, 1400w, 1272m; γ (=CH) 766w; ν (C–OH) 1077s, br, 1062s, sh; ν_{as} $(PO_3)^{2-}$ 978m; ν_s $(PO_3)^{2-}$ 912w, br; δ_s (PO_3^{2-}) 584m. ^1H NMR (600 MHz, D_2O): 7.82 d, 1 H, *J*(6,5) = 8.1 (H-6); 5.89 d, 1 H, *J*(1′,2′) = 1.7 (H-1′); 5.84 d, 1 H, *J*(5,6) = 8.1 (H-5); 4.49 ddd, 1 H, *J*(3′,4′) = 2.2, *J*(3′,P) = 6.5 and *J*(3′,2′) = 1.9 (H-3′); 4.41 dd, 1 H, *J*(4′,3′) = 2.2, *J*(4′,2′) ~ 0.6 and *J*(4′,P) = 5.6 (H-4′); 4.22 m, 1 H, *J*(2′,1′) = 1.7, *J*(2′,3′) = 1.9, *J*(2′,4′) ~ 0.6 and *J*(2′,P) ~ 0.5 (H-2′). ^{13}C NMR (150.9 MHz, D_2O): 169.48 (C-4); 154.24 (C-2); 145.21 (C-6); 103.44 (C-5); 96.03 d, *J*(C,P) = 3.8 (C-1′); 89.42 d, *J*(C,P) = 149.1 (C-4′); 83.70 d, *J*(C,P) = 1.8 (C-2′); 78.75 d, *J*(C,P) = 7.1 (C′-3).

(4*R*)-[1-Deoxy-1-(thymin-1-yl)-α-D-threofuranos-4-yl]phosphonic Acid (**20b**)

The title phosphonic acid was obtained from phosphonate **19b** (190 g, 0.37 mmol) according to the Method *D*. Yield 100 mg (77%, white lyophilizate) of **20b**, $[\alpha]^{20}$ +9.5. HR-FAB calculated for $C_9H_{12}N_2O_8Na_2P$ $(M + H)^+$: 353.0127; found 353.0135. IR (KBr, cm^{-1}): ν (C–OH) 1116m, br, 1078m, br; ν_{as} $(PO_3)^{2-}$ 980w; δ_s $(PO_3)^{2-}$ 596m. **T**: ν (C=O) 1692m, br; ν (ring) 1643m, br, 1473w, 1437w, 1399w, 1274w; γ (=CH) 769vw; δ_s (CH_3) 1374w. ^1H NMR (600 MHz, D_2O): 7.64 q, 1 H, *J*(6,CH_3) = 1.2 (H-6); 5.88 t, 1 H, *J*(1′,2′) = 1.1 and *J*(1′,P) = 1.1 (H-1′); 4.475 dt, 1 H, *J*(3′,P) = 5.75, *J*(3′,4′) = 1.6 and *J*(3′,2′) = 1.5 (H-3′); 4.40 ddd, 1 H, *J*(4′,3′) = 1.6, *J*(4′,2′) ~ 0.7 and *J*(4′,P) = 6.0 (H-4′); 4.15 m, 1 H, *J*(2′,1′) = 1.1, *J*(2′,3′) = 1.5 and *J*(2′,4′) ~ 0.7 (H-2′); 1.89 d, 3 H, *J*(CH_3,6) = 1.2 (CH_3-5). ^{13}C NMR (150.9 MHz, D_2O): 167.63 (C-4); 152.11 (C-2); 138.15 (C-6); 110.17 (C-5); 94.12 d, *J*(C,P) = 3.0 (C-1′); 88.52 d, *J*(C,P) = 145.6 (C-4′); 81.91 (C-2′); 76.85 d, *J*(C,P) = 8.0 (C-3′); 12.92 (CH_3-5).

(4*R*)-[1-(Cytosin-1-yl)-1-deoxy-α-D-threofuranos-4-yl]phosphonic Acid (**20c**)

Phosphonic acid **20c** was obtained from the phosphonate derivative **19c** (150 mg, 0.25 mmol) according to the Method *D*. Yield 63 mg (75%, white lyophilizate) of **20c**, $[\alpha]^{20}$ +6.7. HR-FAB calculated for $C_8H_{11}N_3O_7P$ $(M + H)^+$: 292.0335; found 292.0322. IR (KBr, cm^{-1}): ν (C–OH) 1110m, br, 1079m, br; ν_{as} (PO_3^{2-}) 979w; δ_s (PO_3^{2-}) 584m, br. **C**: β_s (NH_2) + ν (C=O) 1651s; ν (ring) 1605m, sh, 1530w, 1494w; ν (C-N) 1288w, br; γ (=CH) 787w. ^1H NMR (600 MHz, D_2O): 7.79 d, 1 H, *J*(6,5) = 7.6 (H-6); 6.03 d, 1 H, *J*(5,6) = 7.6 (H-5); 5.88 dd, 1 H, *J*(1′,2′) = 1.9 and *J*(1′,P) = 0.9 (H-1′); 4.48 ddd, 1 H, *J*(3′,4′) = 2.4, *J*(3′,P) = 7.0 and *J*(3′,2′) = 1.9 (H-3′); 4.42 ddd, 1 H, *J*(4′,3′) = 2.4, *J*(4′,2′) = 0.6 and *J*(4′,P) = 5.4 (H-4′); 4.22 tt, 1 H, *J*(2′,1′) = 1.9, *J*(2′,3′) = 1.9, *J*(2′,4′) = 0.6 and *J*(2′,P) = 0.9 (H-2′). ^{13}C NMR (150.9 MHz, D_2O): 168.74 (C-4); 159.78 (C-2); 145.14 (C-6); 97.81 (C-5); 96.60 d, *J*(C,P) =

3.9 (C-1′); 88.90 d, *J*(C,P) = 150.9 (C-4′); 83.96 d, *J*(C,P) = 2.3 (C-3′); 79.02 d, *J*(C,P) = 6.8 (C-2′).

Methyl 5-*O*-Benzoyl-β-L-arabinoside (**22**)

Methyl β-L-arabinoside (**21**; 1 g, 6.1 mmol) was treated with benzoyl chloride (0.84 ml, 7.1 mmol) and triethylamine (1.7 ml, 12 mmol) in dichloromethane (11.3 ml) at –78 °C under exclusion of moisture (TLC in T1) for 18 h. The reaction was quenched by addition of methanol (0.5 ml) and the solvents were evaporated in vacuo. The residue was dissolved in chloroform and the organic layer was washed several times with saturated aqueous $NaHCO_3$. The crude product was purified on silica gel column with a linear gradient of ethanol in chloroform. Yield 1.24 g (76 %, colourless sirup) of **22**. HR-FAB calculated for $C_{13}H_{17}O_6$ $(M + H)^+$: 269.1025; found 269.1018. ^{1}H NMR (500 MHz, DMSO): 7.99 m, 2 H, 7.67 m, 1 H and 7.55 m, 2 H (OBz); 5.45 d, 1 H, *J*(OH,2) = 4.8 (OH-2); 5.36 d, 1 H, *J*(OH,3) = 5.3 (OH-3); 4.68 d, 1 H, *J*(1,2) = 2.0 (H-1); 4.49 dd, 1 H, *J*(5a,4) = 3.1 and *J*(5a,5b) = 11.9 (H-5a); 4.41 dd, 1 H, *J*(5b,4) = 6.0 and *J*(5b,5a) = 11.9 (H-5b); 4.01 ddd, 1 H, *J*(4,3) = 7.0, *J*(4,5a) = 3.1 and *J*(4,5b) = 6.0 (H-4); 3.83 ddd, 1 H, *J*(2,1) = 2.0, *J*(2,OH) = 4.8 and *J*(2,3) = 4.0 (H-2); 3.80 ddd, 1 H, *J*(3,2) = 4.0, *J*(3,OH) = 5.3 and *J*(3,4) = 7.0 (H-3); 3.26 s, 3 H (OMe). ^{13}C NMR (125.8 MHz, DMSO): 165.77, 133.58, 129.70, 129.38(2) and 128.95(2) (OBz); 109.29 (C-1); 81.91 (C-2); 80.60 (C-4); 77.52 (C-3); 64.44 (C-5); 54.67 (OMe).

5-*O*-Benzoyl-1,2-*O*-isopropylidene-β-L-arabinose (**23**)

Copper sulfate (1.2 g, 7.4 mmol) followed by concentrated sulfuric acid (0.052 ml, 0.96 mmol) were added to a solution of methyl-5-*O*-benzoyl-L-arabinoside (**22**; 1 g, 3.7 mmol) in acetone (11.1 ml). The suspension was stirred overnight (TLC in C1). The reaction was set on pH 7 with the concentrated aqueous ammonia, diluted with chloroform and extracted with saturated solution of aqueous sodium hydrogen carbonate. The organic layer was dried with anhydrous sodium sulfate and the solvents were evaporated. Yield 370 mg (37%, white crystals) of **23**, m.p. 138–141 °C, $[\alpha]^{20}$ –14.5. HR-FAB calculated for $C_{15}H_{19}O_6$ $(M + H)^+$: 295.1182; found 295.1178. IR ($CHCl_3$, cm^{-1}): ν (OH-free) 3611w; ν (OH-bonded) 3483w, br; ν (C–OH) 1085s, sh. **OBz**: ν (C=O) 1720s; β (C=O) 713vs; ν (C–O) 1275vs; ν (=CH) 3092vs, 3065w, 3026m; ν (ring) 1603w, 1585w, 1493w, 1452m, 1317m, 1178m, 1110s, sh, 1070s, 1026s, 687w, 617vw. **CMe_2**: δ_s (CH_3) 1385m, 1377m; ν_s (CMe_2) 859w; γ_s (CMe_2) 517w; δ_{as} 1019s. **1,3–Dioxolane**: ν_s (COCOC) 1096s. ^{1}H NMR (600 MHz, $CDCl_3$): 8.06 m, 2 H, 7.57 m, 1 H and 7.44 m, 2 H (OBz); 5.97 d, 1 H, *J*(1,2) = 3.9 (H-1); 4.60 ddd, 1 H, *J*(2,1) = 3.9, *J*(2,3) = 1.0 and *J*(2,4) = 0.6 (H-2); 4.37 m, 1 H, *J*(3,2) = 1.0, *J*(3,4) = 2.6 and *J*(3,OH) = 4.6 (H-3); 4.31 tdd, 1 H, *J*(4,5a) ~ *J*(4,5b) = 6.2, *J*(4,3) = 2.6 and *J*(4,2) = 0.6 (H-4); 4.54 m, 2 H (H-5a + H-5b); 2.31 d, 1 H, *J*(OH,3) = 4.6 (OH-3); 1.57 bs, 3 H and 1.34 bs, 3 H (1,2-O*i*Pr). ^{13}C NMR (150.9 MHz, $CDCl_3$): 166.39, 133.22, 129.75(2), 129.63 and 128.38(2) (OBz); 112.97, 26.93 and 26.10 (1,2-O*i*Pr); 105.72 (C-1); 86.77 (C-2); 84.95 (C-4); 76.28 (C-3); 64.36 (C-5).

3-*O*-Benzyl-1,2-*O*-isopropylidene-β-L-arabinose (**25**)

The sugar derivative **23** (3.5 g, 12 mmol) was co-distilled with THF, then dissolved in 60 ml THF, and sodium hydride (576 mg, 14.4 mmol) was added at 0 °C under argon atmosphere. After 0.5 h, benzyl bromide (1.7 ml, 14.4 mmol) was added dropwise. The mixture was

stirred overnight (TLC in T2). The mixture was diluted with chloroform (pH must be neutral; adjustment with acetic acid) and extracted three times with water. The organic layer was evaporated and the residue was purified on a silica gel column by elution with a linear gradient of ethyl acetate in toluene. The so-obtained, pure intermediary product **24** was dissolved in a 0.05 M solution of sodium methoxide in dry methanol (30 ml). The reaction was left to stand for 16 h (TLC in T1). The mixture was neutralized with solid CO_2, evaporated, and purified on a silica gel column by elution with a linear gradient of ethyl acetate in toluene. Yield 1.92 g (57%, white crystals) of **25**, m.p. 73–77 °C, $[\alpha]^{20}$ –22.4. HR-FAB calculated for $C_{15}H_{21}O_5$ $(M + H)^+$: 281.1389; found 281.1385. IR ($CHCl_3$, cm^{-1}): ν (OH) 3630w, sh, 3595w, 3500w, br; ν (C–OH) 1049s. **OBn**: ν_{as} (COC) 1076vs; ν (=CH) 3091w, 3068w; ν (ring) 1606w, 1588vw, 1497w, 1455m, 1027vs, 699s. **1,3-Dioxolane**: δ_s (CH_3) 1385s, 1376s; ν_{as} (COCOC) 1163s, 1049s; δ_{as} (CH_3) 1020s, sh; ν_s (CMe_2) 864m; γ_s (CH_2) 517w. ^{1}H NMR (600 MHz, $CDCl_3$): 7.38–7.31 m, 5 H, 4.72 bd, 1 H, *J*(gem) = 12.0 and 4.495 bd, 1 H, *J*(gem) = 12.0 (OBn); 5.99 d, 1 H, *J*(1,2) = 3.9 (H-1); 4.65 bd, 1 H, *J*(2,1) = 3.9 and *J*(2,3) ~ 0.6 (H-2); 4.28 ddd, 1 H, *J*(4,5a) = 5.2, *J*(4,5b) = 4.8 and *J*(4,3) = 3.6 (H-4); 4.02 dt, 1 H, *J*(3,2) ~ 0.6, *J*(3,4) = 3.6 and *J*(3,5b) ~ 0.6 (H-3); 3.945 dd, 1 H, *J*(5a,4) = 5.2 and *J*(5a,5b) = 12.0 (H-5a); 3.86 bdd, 1 H, *J*(5b,4) = 4.8 and *J*(5b,5a) = 12.0, *J*(5b,3) ~ 0.6 (H-5b); 1.49 bs, 3 H and 1.33 bs, 3 H (1,2-O*i*Pr). ^{13}C NMR (150.9 MHz, $CDCl_3$): 136.97, 128.64(2), 128.18, 127.71(2) and 71.84 (OBn); 111.74, 26.75 and 26.25 (1,2-O*i*Pr); 105.02 (C-1); 82.69 (C-3); 82.37 (C-2); 80.00 (C-4); 60.93 (C-5).

Diethyl (5*R*)-(3-*O*-Benzyl-1,2-*O*-isopropylidene-β-L-arabinofuranos-5-*C*-yl)-phosphonate (**27**) and Diethyl (5*S*)-(3-*O*-Benzyl-1,2-*O*-isopropylidene-β-L-arabinofuranos-5-*C*-yl)phosphonate (**28**)

Pyridine (0.45 ml, 5.6 mmol) followed by TFA (0.22 ml, 2.8 mmol) was added at r.t. to a stirred solution of 3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-arabinose (**25**; 1.5 g, 5.6 mmol) and DCC (3.6 g, 16.8 mmol) in DMSO (22.4 ml) (TLC in C2). After 16 h, diethyl phosphite (1.5 ml, 11.2 mmol) and trietylamine (3.9 ml, 28 mmol) were added and the mixture was stirred overnight (TLC in C1). The reaction mixture was diluted with chloroform, filtered through Celite, and the filtrate was extracted with water. The organic layer was dried over anhydrous sodium sulfate. Chromatography of the crude product on silica gel (elution with a linear gradient of 0–10% ethanol in chloroform) afforded the expected phosphonate. Yield 2.04 g (87%, white crystals) of a mixture of **27** and **28** (major epimer:minor epimer, 78:22), m.p. 77–80 °C. HR-FAB calculated for $C_{19}H_{30}O_8P$ $(M + H)^+$: 417.1678; found 417.1686. IR ($CHCl_3$, cm^{-1}): ν (OH) 3550w, br; ν (C–OH) 1075s. **PO(OEt)$_2$**: ν (P=O) 1245s; β_s (CH_2) 1479w; δ_{as} (CH_3) 1454m; γ_s (CH_2) 1393w, sh; δ_s (CH_3) 1370w, sh; δ_{as} (CH_3) 1164m, 1097s, sh; ν_{as} (POCC) 1051s, 1028vs, 974m; δ (POC) 561w. **1,3–Dioxolan**: δ_s (CH_3) 1386m, 1377m; ν_s (CMe_2) 861w; γ_s (CMe_2) 521w. **OBn**: ν (=CH) 3091vw, 3067w, 3029w; ν (ring) 1498w, 1287w, 699w.

Major epimer: ^{1}H NMR (500 MHz, $CDCl_3$): 7.37–7.26 m, 5 H, 4.67 d, 1 H, *J*(gem) = 11.6 and 4.59 d, 1 H, *J*(gem) = 11.6 (OBn); 5.91 d, 1 H, *J*(1,2) = 3.7 (H-1); 4.63 bd, 1 H, *J*(2,1) = 3.7 and *J*(2,3) ~ 0.5 (H-2); 4.48 ddd, 1 H, *J*(4,5) = 6.8, *J*(4,3) = 2.1 and *J*(4,P) = 5.6 (H-4); 4.42 dd, 1 H, *J*(3,2) ~ 0.5 and *J*(3,4) = 2.1 (H-3); 4.20 m, 4 H, 1.34 t, 3 H, *J* = 7.1 and 1.31 t, 3 H, *J* = 7.1 (P(OEt)$_2$); 4.12 dt, 1 H, *J*(5,4) = 6.8, *J*(5,P) = 6.8 and *J*(5,OH) = 4.0 (H-5); 3.33 dd, 1 H, *J*(OH,5) = 4.0 and *J*(OH,P) = 12.6 (5-OH); 1.55 bs, 3 H and 1.32 bs, 3 H (1,2-O*i*Pr). ^{13}C NMR (150.9 MHz, $CDCl_3$): 137.52, 128.39(2), 127.86(2), 127.81 and 71.89 (OBn);

112.79, 26.77 and 25.95 (1,2-O*i*Pr); 105.97 (C-1); 85.53 d, *J*(C,P) = 3.9 (C-4); 84.88 (C-2); 82.31 d, *J*(C,P) = 8.2 (C-3); 68.12 d, *J*(C,P) = 161.6 (C-5); 62.99 d, *J*(C,P) = 6.7, 62.87 d, *J*(C,P) = 6.9, 16.46 and 16.42 ($P(OEt)_2$).

Minor epimer: ^{1}H NMR (500 MHz, $CDCl_3$): 7.37–7.26 m, 5 H, 4.64 d, 1 H, *J*(gem) = 11.6 and 4.60 d, 1 H, *J*(gem) = 11.6 (OBn); 5.95 d, 1 H, *J*(1,2) = 4.0 (H-1); 4.68 dd, 1 H, *J*(2,1) = 4.0 and *J*(2,3) ~ 0.8 (H-2); 4.49 ddd, 1 H, *J*(4,5) = 6.5, *J*(4,3) = 2.1 and *J*(4,P) = 5.6 (H-4); 4.40 dd, 1 H, *J*(3,2) ~ 0.8 and *J*(3,4) = 2.1 (H-3); 4.20 m, 4 H, 1.34 t, 3 H, *J* = 7.1 and 1.31 t, 3 H, *J* = 7.1 ($P(OEt)_2$); 4.06 dt, 1 H, *J*(5,4) = 6.5, *J*(5,P) = 9.5 and *J*(5,OH) = 5.6 (H-5); 2.93 dd, 1 H, *J*(OH,5) = 5.6 and *J*(OH,P) = 15.6 (5-OH); 1.53 bs, 3 H and 1.38 bs, 3 H (1,2-O*i*Pr). ^{13}C NMR (150.9 MHz, $CDCl_3$): 137.30, 128.48(2), 127.93, 127.71(2) and 72.00 (OBn); 112.90, 26.92 and 26.10 (1,2-O*i*Pr); 105.78 (C-1); 84.12 d, *J*(C,P) = 3.3 (C-4); 85.00 (C-2); 83.30 d, *J*(C,P) = 6.3 (C-3); 67.23 d, *J*(C,P) = 162.7 (C-5); 63.21 d, *J*(C,P) = 6.7, 62.64 d, *J*(C,P) = 6.7, 16.48 and 16.44 ($P(OEt)_2$).

Diethyl (4*S*)-(1,3-di-*O*-Acetyl-2-*O*-benzyl-β-L-erythrofuranos-4-yl)phoshonate (**31**)

The title phosphonate was obtained from the mixture of epimers **27** and **28** (2 g, 4.8 mmol) according to the Method *A*. Yield 950 mg (46%, colourless sirup) of **31**. ^{1}H NMR (600 MHz, $CDCl_3$): 7.36–7.29 m, 5 H, 4.63 bd, 1 H, *J*(gem) = 11.6 and 4.58 bd, 1 H, *J*(gem) = 11.6 (OBn); 6.17 d, 1 H, *J*(1,2) = 2.0 and *J*(1,3) = 1.0 (H-1); 5.51 m, 1 H, *J*(3,1) = 1.0, *J*(3,2) = 4.8, *J*(3,4) = 6.6 and *J*(3,P) = 12.8 (H-3); 4.32 ddd, 1 H, *J*(2,1) = 2.0, *J*(2,3) = 4.8 and *J*(2,4) = 0.5 (H-2); 4.40 m, 1 H, *J*(4,2) = 0.5, *J*(4,3) = 6.6 and *J*(4,P) = 1.4 (H-4); 4.18 m, 4 H, 1.33 dt, 3 H, $J(CH_3,CH_2)$ = 7.1, $J(CH_3,P)$ = 0.6 and 1.32 dt, 3 H, $J(CH_3,CH_2)$ = 7.1, $J(CH_3,P)$ = 0.6 ($P(OEt)_2$); 2.11 s, 3 H and 2.08 s, 3 H (2 × OAc). ^{13}C NMR (150.9 MHz, $CDCl_3$): 169.89, 169.65, 21.04 and 20.65 (2 × OAc); 136.96, 128.46(2), 128.10 and 127.79(2) (OBn); 98.88 d, *J*(1,P) = 1.8 (C-1); 79.73 d, *J*(2,P) = 5.7 (C-2); 76.19 d, *J*(4,P) = 172.0 (C-4); 71.73 d, *J*(3,P) = 5.1 (C-3); 63.39 d, *J*(C,P) = 6.6, 62.85 d, *J*(C,P) = 6.8 and 16.39(2) d, *J*(C,P) = 5.7 ($P(OEt)_2$).

Mixture of Diethyl (4*S*)-(1,3-di-*O*-Acetyl-2-*O*-benzoyl-β-L-erythrofuranos-4-yl)-phosphonate (**32**) and Diethyl (4*S*)-(1,3-di-*O*-Acetyl-2-*O*-benzyl-β-L-erythrofuranos-4-yl)phoshonate (**31**)

Oxidation of the 2-*O*-benzyl group of diethyl (5*S*)-(1,3-di-*O*-acetyl-2-*O*-benzyl-L-erythrofuranos-4-yl)phosphonate (**31**; 950 mg, 2.2 mmol) to 2-*O*-benzoyl was performed according to the Method *C*. Yield 350 mg (~36%, colourless sirup) of a mixture of the desired **32** and unreacted **31** (73:27).

32: HR-FAB calculated for $C_{19}H_{26}O_{10}P$ $(M + H)^+$: 445.1264; found 445.1283. IR ($CHCl_3$, cm^{-1}): **OAc**: ν (C=O) 1751vs; ν (C–O) 1232vs, sh; γ (CCOO) 598w; δ_s (CH_3) 1370m. **OBz**: ν (C=O) 1731s, sh; ν (C–O) 1270s; β (C=O) 712s; ν (=CH) 3092vw, 3064w, 3030m. ν (ring) 1603w, 1586w, 1494w, 1453w, 1317w, 1178m, 1071s, sh, 1109m, 697w, 617vw. **$PO(OEt)_2$**: ν (P=O) 1249s; β_s (CH_2) 1479w; δ_{as} (CH_3) 1443w, 1437w; γ_s (CH_2) 1393w; δ_{as} (CH_3) 1164w, 1097m; ν_{as} (POCC) 1048s, 1028vs, 977m; δ (POC) 571w, 557w. ^{1}H NMR (600 MHz, $CDCl_3$): 8.04 m, 2 H, 7.62 m, 1 H and 7.48 m, 2 H (OBz); 6.34 m, 1 H, *J*(1,2) = 1.1, *J*(1,3) = 0.4 and *J*(1,4) = 0.6 (H-1); 5.90 m, 1 H, *J*(3,1) = 0.4, *J*(3,2) = 4.6, *J*(3,4) = 8.0 and *J*(3,P) = 14.2 (H-3); 5.64 ddd, 1 H, *J*(2,1) = 1.1, *J*(2,3) = 4.6 and *J*(2,4) = 0.5 (H-2); 4.44 m, 1 H, *J*(4,1) = 0.6, *J*(4,2) = 0.5, *J*(4,3) = 8.0 and *J*(4,P) = 0.9 (H-4); 4.22 m, 4 H, 1.355 dt, 3 H, $J(CH_3,CH_2)$ = 7.1, $J(CH_3,P)$ = 0.6 and 1.350 dt, 3 H, $J(CH_3,CH_2)$ = 7.1, $J(CH_3,P)$ = 0.6 (2 × OEt); 2.15 s, 6 H (2 ×

OAc). ^{13}C NMR (150.9 MHz, $CDCl_3$): 169.26, 169.10, 20.96 and 20.37 (2 × OAc); 164.90, 133.75, 129.80(2), 128.68 and 128.60(2) (OBz); 98.30 d, *J*(1,P) = 2.4 (C-1); 75.37 d, *J*(4,P) = 174.7 (C-4); 74.08 d, *J*(2,P) = 7.2 (C-2); 70.50 d, *J*(3,P) = 3.9 (C-3); 63.41 d, *J*(C,P) = 6.6, 62.98 d, *J*(C,P) = 6.8 and 16.43(2) d, *J*(C,P) = 5.7 ($P(OEt)_2$).

Diethyl (4*S*)-[3-*O*-Acetyl-2-*O*-benzoyl-1-deoxy-1-(uracil-3-yl)-β-L-erythrofuranos-4-yl]-phosphonate (**33a**)

Phosphonate **33a** was obtained from silylated uracil (560 mg, 5 mmol) and the mixture of sugar phosphonate **32** + **31** (700 mg, 1.6 56 mmol of **32**) according to the Method *B*. Yield 240 mg (30%, white lyophilizate) of **33a**. HR-FAB calculated for $C_{21}H_{26}N_2O_{10}P$ $(M + H)^+$: 497.1325; found 497.1340. IR ($CHCl_3$, cm^{-1}): **OAc**: ν (C=O) 1751s, sh; ν (C–O) 1231s; γ (CCOO) 597w; δ_s (CH_3) 1377m. **OBz**: ν (C=O) 1736vs; ν (C–O) 1271s, 963m, br; β (C=O) 712m; ν (ring) 1603w, 1585w, 1494w, sh, 1452w, 1314w, 1178w, 1110m, 1070s, 686w. **U**: ν (NH) 3426w, 3318w, br, sh, 3245w, 3188w, 3109w, br; ν (C=O) 1736vs, 1680vs, sh, 1671vs; ν (C=C) 1643m, sh; ν (ring) 1477w, 1425w. **$PO(OEt)_2$**: ν (P=O) 1248s; ν_{as} (POCC) 1050s, 1027vs, 978m; δ (POC) 564w; δ_{as} (CH_3) 1444w, sh; γ_s (CH_2) 1394w, sh; δ_{as} (CH_3) 1164w, 1096m. ^{1}H NMR (600 MHz, $CDCl_3$ + DMSO 4:1): 11.16 bd, 1 H, *J*(NH,6) = 5.8 and *J*(NH,5) = 1.5 (NH); 8.03 m, 2 H, 7.61 m, 1 H and 7.47 m, 2 H (OBz); 7.22 dd, 1 H, *J*(6,5) = 7.6 and *J*(6,NH) = 5.8 (H-6); 6.56 bd, 1 H, *J*(1′,2′) = 4.6 (H-1′); 6.03 dd, 1 H, *J*(2′,1′) = 4.6 and *J*(2′,3′) = 5.0 (H-2′); 5.64 dd, 1 H, *J*(5,6) = 7.6 and *J*(5,NH) = 1.5 (H-5); 5.51 bd, 1 H, *J*(OH,3′) ~ 7.0; 4.85 m, 1 H, *J*(3′,4′) = 8.0, *J*(3′,P) = 13.0, *J*(3′,OH) ~ 7.0 and *J*(3′,2′) = 5.0 (H-3′); 4.70 dd, 1 H, *J*(4′,3′) = 8.0 and *J*(4′,P) = 1.2 (H-4′); 4.21 m, 4 H, 1.363 t, 3 H, *J* = 7.0 and 1.354 t, 3 H, *J* = 7.0 ($P(OEt)_2$). ^{13}C NMR (150.9 MHz, $CDCl_3$ + DMSO 4:1): 165.67, 133.16, 129.36(2), 128.78 and 128.16(2) (OBz); 163.00 (C-2); 151.10 (C-4); 140.37 (C-6); 100.52 (C-5); 85.43 (C-1′); 81.65 d, *J*(C,P) = 11.2 (C-2′); 79.68 d, *J*(C,P) = 169.2 (C-4′); 76.41 (C-3′); 62.46 d, *J*(C,P) = 6.5 and 16.17 d, *J*(C,P) = 4.7 ($P(OEt)_2$).

Diethyl (4*S*)-[3-*O*-Acetyl-2-*O*-benzoyl-1-deoxy-1-(thymin-1-yl)-β-L-erythrofuranos-4-yl]-phosphonate (**33b**)

Phosphonate **33b** was obtained from silylated thymine (220 mg, 1.7 mmol) and the mixture of sugar phosphonate **32** + **31** (190 mg, 0.42 mmol of **32**) according to the Method *B*. Yield 40 mg (20%, white foam) of **33b**. For $C_{22}H_{28}N_2O_{10}P$ $(M + H)^+$ calculated 511.1482, found 511.1495. IR ($CHCl_3$, cm^{-1}): T: ν (NH-free) 3391w; ν (NH-bonded) 3184w, br; ν (C=O) 1716s, 1696vs; ν (ring) 1655m, sh, 1466m, 1435w, sh; δ_s (CH_3) 1376m. **$PO(OEt)_2$**: ν (P=O) 1249s; ν_{as} (POCC) 1055s, sh, 1038s, 979m; δ (POC) 560m; γ_s (CH_2) 1391m; δ_{as} (CH_3) 1163w, 1097m. **OAc**: ν (C=O) 1751s; ν (C–O) 1249s, 1027s; γ (CCOO) 596w; δ_s (CH_3) 1376m. **OBz**: ν (C=O) 1731s, sh; ν (C–O) 1262s, 961m; β (C=O) 711m; ν (=CH) 3064w, 3026m; ν (ring) 1603w, 1585w, 1495w, sh, 1453m, 1317w, 1178w, 1122m, 1073m, sh, 1027s, 686w, 615vw. ^{1}H NMR (600 MHz, $CDCl_3$): 8.40 bs, 1 H (NH); 8.00 q, 1 H, *J*(6,CH_3) = 1.2 (H-6); 7.98 m, 2 H, 7.59 m, 1 H and 7.45 m, 2 H (OBz); 6.60 dd, 1 H, *J*(1′,2′) = 7.8 a *J*(1′,P) = 1.5 (H-1′); 5.86 ddd, 1 H, *J*(3′,4′) = 1.6, *J*(3′,P) = 6.9 and *J*(3′,2′) = 5.1 (H-3′); 5.76 dd, 1 H, *J*(2′,1′) = 7.8 and *J*(2′,3′) = 5.1 (H-2′); 4.42 dd, 1 H, *J*(4′,3′) = 1.6 and *J*(4′,P) = 5.2 (H-4′); 4.28 m, 2 H, 4.25 m, 2 H, 1.42 t, 3H, *J*(CH_3,CH_2) = 7.0 and 1.38 t, 3 H, *J*(CH_3,CH_2) = 7.0 ($P(OEt)_2$); 2.12 s, 3 H (OAc); 1.98 q, 3 H, *J*(CH_3,6) = 1.2 (CH_3-5). ^{13}C NMR (150.9 MHz, $CDCl_3$): 169.29 and 20.63 (OAc); 164.92, 133.84, 129.87(2), 128.61(2) and 128.30 (OBz); 163.14 (C-4); 150.64 (C-2); 135.54 (C-6); 112.44 (C-5); 85.53 d, *J*(C,P) = 3.0 (C-1′); 77.95 d, *J*(C,P) = 168.1 (C-4′);

72.85 d, *J*(C,P) = 1.4 (C-2′); 70.89 d, *J*(C,P) = 9.8 (C-3′); 64.07 d, *J*(C,P) = 6.6, 63.50 d, *J*(C,P) = 7.2, 16.45 d, *J*(C,P) = 5.6 and 16.17 d, *J*(C,P) = 5.6 ($P(OEt)_2$); 12.58 (CH_3-5).

(4*S*)-[1-Deoxy-1-(uracil-3-yl)-β-L-erythrofuranos-4-yl]phosphonic Acid (**34**)

The title phosphonic acid was obtained from phosphonate mixture **33** (300 mg, 0.56 mmol) according to the Method *D*. Yield 150 mg (82%, white lyophilizate) of **34**, $[\alpha]^{20}$ +12.9. HR-FAB calculated for $C_8H_{10}N_2O_8Na_2P$ $(M + H)^+$: 338.9970; found 338.9979. IR (KBr, cm^{-1}): ν (CH, NH) 3427 vs, br, 3250m, br, sh; ν (C–OH) 1081s; ν_{as} $(PO_3)^{2-}$ 975m; δ $(PO_3)^{2-}$ 570m. **U**: ν (C=O) 1717s, 1653vs; ν (C=C) 1601m, sh; γ (=CH) 815w, 769w. ^{1}H NMR (600 MHz, D_2O): 7.48 d, 1 H, *J*(6,5) = 7.8 (H-6); 6.40 d, 1 H, *J*(1′,2′) = 5.3 (H-1′); 5.83 d, 1 H, *J*(5,6) = 7.8 (H-5); 4.825 dd, 1 H, *J*(2′,1′) = 5.3 and *J*(2′,3′) = 4.8 (H-2′); 4.38 ddd, 1 H, *J*(3′,2′) = 4.8, *J*(3′,4′) = 6.5 and *J*(3′,P) = 10.0 (H-3′); 4.19 dd, 1 H, *J*(4′,3′) = 6.5 and *J*(4′,P) = 2.7 (H-4′). ^{13}C NMR (150.9 MHz, D_2O): 166.61 (C-4); 153.12 (C-2); 142.63 (C-6); 101.84 (C-5); 85.13 d, *J*(C,P) = 5.7 (C-1′); 82.74 d, *J*(C,P) = 151.7 (C-4′); 78.82 d, *J*(C,P) = 7.1 (C-2′); 78.60 d, *J*(C,P) = 2.7 (C-3′).

1,2-*O*-Isopropylidene-α-L-xylofuranose (**35**)

Copper sulfate (16.3 g, 102 mmol) and then concentrated sulfuric acid (0.71 ml, 13.3 mmol) were added to a solution of L-xylose (7.6 g, 51 mmol) in acetone (153 ml). The suspension was stirred overnight (TLC in C1). The reaction was set to pH 7 using concentrated aqueous ammonia, diluted with chloroform, and the solution was extracted with saturated solution of aqueous sodium hydrogen carbonate. The organic layer was dried over anhydrous sodium sulfate, and evaporated. To the crude 1,2;3,5-di-*O*-isopropylidene-α-L-xylofuranose, the 60% aqueous acetic acid (500 ml) was added and the whole was set overnight. The reaction mixture was evaporated and the residue co-distilled several times with water. The product was purified on the Dowex 1 column in OH^- form using the elution with water. Yield 8.4 g (87%, yellow sirup) of **35**, $[\alpha]^{20}$ +22.1. HR-FAB calculated for $C_8H_{14}O_5Na$ $(M + Na)^+$: 213.0739; found 213.0730. IR ($CHCl_3$, cm^{-1}): ν (OH) 3587w, 3446m, br; ν (C–OH) 1076vs, 1041s. **CMe_2**: δ_s (CH_3) 1385s, 1376s; δ_{as} (CH_3) 1014vs; ν_s (CMe_2) 860m; γ_s (CMe_2) 522m; **1,3–Dioxolane**: ν_{as} (COCOC) 1164s, 1076vs; ν_s (COCOC) 1105s. ^{1}H NMR (600 MHz, DMSO): 5.79 dd, 1 H, *J*(1,2) = 3.8 and *J*(1,3) ~ 0.6 (H-1); 4.37 dd, 1 H, *J*(2,1) = 3.8 and *J*(2,3) ~ 0.6 (H-2); 3.97 ddd, 1 H, *J*(4,3) = 2.8, *J*(4,5a) = 5.5 and *J*(4,5b) = 6.1 (H-4); 3.95 dt, 1 H, *J*(3,4) = 2.8, *J*(3,2) ~ 0.6 and *J*(3,1) ~ 0.6 (H-3); 3.60 dd, 1 H, *J*(5a,4) = 5.5, *J*(5a,5b) = 11.2 (H-5a); 3.49 dd, 1 H, *J*(5b,4) = 6.1, *J*(5b,5a) = 11.2 (H-5b); 1.35 s, 3 H and 1.22 s, 3 H (1,2-O*i*Pr). ^{13}C NMR (150.9 MHz, DMSO): 110.48, 26.86 and 26.31 (1,2-O*i*Pr); 104.45 (C-1); 81.56 (C-4); 85.25 (C-2); 73.56 (C-3); 58.97 (C-5).

5-*O*-Allyloxycarbonyl-1,2-*O*-isopropylidene-α-L-xylofuranose (**36**)

1,2-*O*-Isopropylidene-α-L-xylofuranose **35** (1 g, 5.3 mmol) was repeatedly co-evaporated with dichloromethane and then dissolved in a 1:1 dichlormethane–pyridine mixture (10 ml). After cooling of the solution to –78 °C, allyloxycarbonyl chloride (0.58 ml, 5.5 mmol) was added. The reaction was monitored on TLC in T1 system using a 10% H_2SO_4 detection. After 30 min, the reaction was quenched with methanol (0.2 ml), diluted with chloroform, and the whole was extracted with water. The organic washings were evaporated and the crude product was purified on silica gel using a linear gradient of ethyl acetate in toluene. Yield

1.0 g (68%, white foam) of **36**, $[\alpha]^{20}$ +5.0. HR-FAB calculated for $C_{12}H_{19}O_7$ $(M + H)^+$: 275.1131; found 275.1134. IR ($CHCl_3$, cm^{-1}): ν (OH) 3603w, br, 3441m, br; ν (C–OH) 1076vs. **CMe$_2$**: δ_s (CH_3) 1385s, 1376s; δ_{as} (CH_3) 1011vs; ν_s (CMe_2) 860m; γ_s (CMe_2) 522w. **1,3–Dioxolane**: ν_{as} (COCOC) 1164s, 1076vs; ν_s (COCOC) 1105s. Carbonyl: ν (C=O) 1746m; ν_{as} (OCO) 1268s, 1258s. **Vinyl**: ν (C=C) 1649vw; ν_{as} (=CH_2) 3090vw; β_s (=CH_2) 1410w; β (=CH) 1294m; γ_s (=CH_2) 906w. ^{1}H NMR (500 MHz, DMSO): 5.93 ddt, 1 H, *J* = 17.25, 10.5, 5.5 (2×), 5.33 dq, 1 H, *J* = 17.25 and 1.5 (3×), 5.25 dq, 1 H, *J* = 10.5 and 1.5 (3×) and 4.61 dt, 2 H, *J* = 5.5 and 1.5 (2×) (O-CH_2-CH=CH_2); 5.86 d, 1 H, *J*(1,2) = 3.7 (H-1); 5.46 d, 1 H, *J*(OH,3) = 4.4 (OH-3); 4.41 dd, 1 H, *J*(2,1) = 3.7 and *J*(2,3) = 0.6 (H-2); 4.30 m (H-4); 4.19 m, 1 H and 4.16 m, 1 H (H-5a + H-5b); 4.04 m, 1 H (H-3); 1.38 bs, 3 H and 1.23 bs, 3 H (1,2-O*i*Pr). ^{13}C NMR (125.8 MHz, DMSO): 154.44, 68.10, 132.31 and 118.58 (O-CO-O-CH_2-CH=CH_2); 110.86, 26.83 and 26.24 (1,2-O*i*Pr); 104.76 (C-1); 85.10 (C-2); 78.16 (C-4); 73.86 (C-3); 66.42 (C-5).

5-*O*-Allyloxycarbonyl-1,2-*O*-isopropylidene-3-*O*-methoxycarbonyl-α-L-xylofuranose (**38**)

A solution of methoxycarbonyl chloride was added dropwise, under exclusion of atmospheric moisture and 0 °C, to a solution of tetrazole (1.4 g, 20 mmol) in THF (60 ml) and triethylamine (2.8 ml, 20 mmol). The mixture was left to react for 3 h. After filtering off the deposited triethylamine hydrochloride, a solution of 5-*O*-allyloxycarbonyl-1,2-*O*-isopropylidene-α-L-xylofuranose (**36**; 1.1 g, 4 mmol) in THF (28 ml) and DMAP (1.7 g, 16 mmol) was added to the obtained filtrate (which contained methoxycarbonyl tetrazolide). The reaction was monitored on TLC (system T1) and the detection was carried out by spraying with a 10% H_2SO_4 solution. Upon quenching of the reaction (18 h) with methanol (0.64 ml), the mixture was diluted with chloroform and the whole was extracted several times with 10% aqueous solution of citric acid and once with water. The combined organic washings were evaporated and the residue was chromatographed on silica gel using a linear gradient of ethyl acetate in toluene. Yield 0.86 g (93%, white crystals) of **38**, m.p. 112–117 °C, $[\alpha]^{20}$ +4.8. HR-FAB calculated for $C_{14}H_{21}O_9$ $(M + H)^+$: 333.1186; found 333.1178. IR ($CHCl_3$, cm^{-1}): **CMe$_2$**: δ_s (CH_3) 1385w, 1376m; δ_{as} (CH_3) 1026m; ν_s (CMe_2) 859w. **1,3-Dioxolane**: ν_{as} (COCOC) 1163m, 1069m; ν_s (COCOC) 1095m. **Carbonyl**: ν (C=O) 1753vs; ν_{as} (OCO) 1279vs, 1261vs; δ_s (CH_3) 1444m. **Vinyl**: ν (C=C) 1650vw; ν_{as} (=CH_2) 3089vw; β_s (=CH_2) 1414w; β (=CH) 1293s; γ_s (=CH_2) 913w. ^{1}H NMR (500 MHz, $CDCl_3$): 5.95 bd, 1 H, *J*(1,2) = 3.7, *J*(1,3) ~ 0.6 and *J*(1,4) ~ 0.6 (H-1); 5.93 ddt, 1 H, *J* = 17.2, 10.4, 5.8 (2×), 5.37 dq, 1 H, *J* = 17.2 and 1.5 (3×), 5.28 dq, 1 H, *J* = 10.4 and 1.5 (3×) and 4.63 dt, 2 H, *J* = 5.8 and 1.5 (2×) (O-CH_2-CH=CH_2); 5.13 dt, 1 H, *J*(3,4) = 3.0, *J*(3,2) ~ 0.6 and *J*(3,1) ~ 0.6 (H-3); 4.61 bd, 1 H, *J*(2,1) = 3.7 and *J*(2,3) ~ 0.6 (H-2); 4.53 ddd, *J*(4.3) = 3.0, *J*(4,5a) = 6.1 and *J*(4,5b) = 5.8 (H-4); 4.37 m, 2 H (H-5a + H-5b); 3.82 s, 3 H (OCO-OCH_3); 1.51 bs, 3 H and 1.32 bs, 3 H (1,2-O*i*Pr). ^{13}C NMR (125.8 MHz, $CDCl_3$): 154.64, 68.75, 131.31 and 119.08 (O-CO-O-CH_2-CH=CH_2); 154.59 and 55.33 (O-CO-OCH_3); 112.45, 26.65 and 26.20 (1,2-O*i*Pr); 104.79 (C-1); 83.15 (C-2); 79.48 (C-3); 76.46 (C-4); 64.43 (C-5).

5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-L-xylofuranose (**40**)

Route A: To a solution of 5-*O*-allyloxycarbonyl-1,2-*O*-isopropylidene-α-L-xylofuranose (**36**; 1.1 g, 4 mmol) in dry acetonitrile (30 ml) containing 0.112 ml (0.8 mmol, 0.2 equiv.) of triethylamine, benzoyl cyanide (1.051 g, 8 mmol, 2 equiv.) was added at 0 °C and the mixture was left to react at r.t. for 8 h (TLC checking in T1). The solvent was evaporated and

the residue containing the 3″-*O*-benzoyl derivative **40** was processed by flash chromatography on silica gel using a linear gradient of ethyl acetate in toluene to afford the 3′-*O*-benzoyl derivative **37** (1.29 g, 85%), HR-FAB calculated for $C_{19}H_{22}O_8$ $(M + H)^+$: 379.1348; found 379.1360), as amorphous solid which was submitted for further reaction. The so-obtained product (3.4 mmol) was co-evaporated with toluene and dichloromethane, and dissolved in the latter (15 ml). To the solution, triphenylphosphine (0.34 g, 1.27 mmol), tetrakistriphenylphosphinepalladium (0.25 g, 0.21 mmol) and butylammonium formate (1.10 ml, 9.2 mmol) were added, and the reaction was set to proceed (TLC checking in T1) until disappearance of the starting material (16 h). The mixture was evaporated in vacuo and the residue was chromatographed on silica gel using a linear gradient of ethyl acetate in toluene. Yield 0.90 g (90%, sirup, based on **37**) of **40**.

Route B: 1,2-*O*-Isopropylidene-α-L-xylofuranose (**35**; 860 mg, 4.5 mmol) was treated with benzoyl chloride (0.53 ml, 4.5 mmol) and pyridine (7.8 ml, 55 mmol) in dichloromethane (31 ml) at –78 °C under exclusion of moisture (TLC in T1) overnight. The reaction was quenched by addition of methanol (1 ml) and the solvent was evaporated in vacuo. The residue was dissolved in chloroform and the organic layer was washed several times with saturated aqueous $NaHCO_3$. The crude product was purified on a silica gel column using a linear gradient of ethanol in chloroform. Yield 1.17 g (88%, colorless sirup) of **40**. HR-FAB calculated for $C_{15}H_{19}O_6$ $(M + H)^+$: 295.1182; found 295.1173. ^{1}H NMR (500 MHz, DMSO): 7.98 m, 2 H, 7.67 m, 1 H and 7.54 m, 2 H (OBz); 5.89 d, 1 H, *J*(1,2) = 3.7 (H-1); 5.49 d, 1 H, *J*(OH,3) = 5.0 (OH-3); 4.47 m, 1 H and 4.36 m, 1 H (H-5a + H-5b); 4.455 dd, 1 H, *J*(2,1) = 3.7 and *J*(2,3) ~ 0.5 (H-2); 4.34 m, 1 H (H-4); 4.13 ddd, 1 H, *J*(3,4) = 3.6, *J*(3,2) ~ 0.5 and *J*(3,OH) = 5.0 (H-3); 1.40 s, 3 H and 1.25 s, 3 H (1,2-O*i*Pr). ^{13}C NMR (125.8 MHz, DMSO): 165.79, 133.57, 129.78, 129.40(2) and 128.94(2) (OBz); 110.84, 26.86 and 26.23 (1,2-O*i*Pr); 104.78 (C-1); 85.17 (C-2); 78.35 (C-4); 73.91 (C-3); 63.32 (C-5).

1,2-*O*-Isopropylidene-5-*O*-methoxycarbonyl-α-L-xylofuranose (**41**)

Triphenylphosphine (0.23 g, 0.86 mmol), tetrakistriphenylphosphinepalladium (0.17 g, 0.14 mmol), and butylammonium formate (0.74 ml, 6.2 mmol) were added to a solution of compound **38** (0.77 g, 2.3 mmol) in dichloromethane (12 ml). The reaction was followed on TLC in the system T1 and the detection was done by spraying with a 10% H_2SO_4 solution. After completion of the reaction (16 h), the mixture was evaporated in vacuo and the residue was chromatographed on silica gel using a linear gradient of ethyl acetate in toluene. Yield 0.60 g (92%, white crystals) of **41**, m.p. 130–135 °C, $[\alpha]^{20}$ +7.5. HR-FAB calculated for $C_{10}H_{17}O_7$ $(M + H)^+$: 249.0974; found 249.0971. IR ($CHCl_3$, cm^{-1}): ν (OH) 3617w, 3580w, sh, 3492m, br; ν (C–OH) 1076vs. **CMe_2**: δ_s (CH_3) 1385s, 1376s; δ_{as} (CH_3) 1015vs; ν_s (CMe_2) 860s; γ_s (CMe_2) 520m. **1,3-Dioxolane**: ν_{as} (COCOC) 1164vs, 1076vs; ν_s (COCOC) 1109s. **Methoxycarbonyl**: ν (C=O) 1747vs, br; ν_{as} (OCO) 1281vs, br; δ_s (CH_3) 1444vs. ^{1}H NMR (500 MHz, $CDCl_3$): 5.93 bd, 1 H, *J*(1,2) = 3.7 and *J*(1,3) ~ 0.6 (H-1); 4.20 ddt,1 H, *J*(3,4) = 2.25, *J*(3,OH) = 4.6, *J*(3,2) ~ 0.6 and *J*(3,1) ~ 0.6 (H-3); 4.56 bd, 1 H, *J*(2,1) = 3.7 and *J*(2,3) ~ 0.6 (H-2); 4.50 m, 1 H (H-5a); 4.325 m, 2 H (H-4 + H-5b); 3.815 s, 3 H (O-$COOCH_3$); 2.82 bd, 1 H, *J*(OH,3) = 4.6 (OH-3); 1.50 bs, 3 H and 1.32 bs, 3 H (1,2-O*i*Pr). ^{13}C NMR (125.8 MHz, $CDCl_3$): 156.26 and 55.27 (O-CO-OCH_3); 111.93, 26.75 and 26.16 (1,2-O*i*Pr); 104.67 (C-1); 85.06 (C-2); 77.95 (C-4); 74.44 (C-3); 64.10 (C-5).

Diethyl (5*S*)-(3-*O*-Benzyl-1,2-*O*-isopropylidene-α-L-xylofuranos-5-*C*-yl)phoshonate (**45**)

The sugar derivative **40** (3 g, 10 mmol) was co-distilled with THF, then dissolved in 44 ml THF, and sodium hydride (480 mg, 12 mmol) was added at 0 °C under argon atmosphere. After 0.5 h, benzyl bromide (6.5 ml, 12 mmol) was added dropwise. The mixture was stirred overnight (TLC in T2), then diluted with chloroform (pH must be neutral) and extracted three times with water. The organic layer was evaporated and the residue was purified on a silica gel column by elution with a linear gradient of ethyl acetate in toluene. The pure product **42** was dissolved in 0.05 M solution of sodium methoxide in dry methanol (60 ml). The reaction was set overnight (TLC in T1). The mixture was neutralized with solid CO_2, evaporated, and purified on a silica gel column by elution with a linear gradient of ethyl acetate in toluene. Yield 2.2 g (78%, yellowish sirup) of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-L-xylofuranose (**43**), $[\alpha]^{20}$ +67.4. HR-FAB calculated for $C_{15}H_{21}O_5$ $(M + H)^+$: 281.1389; found 281.1385. This compound was used for further reaction without any additional characterization.

Pyridine (0.13 ml, 1.6 mmol) followed by TFA (0.064 ml, 0.8 mmol) was added at r.t. to a stirred solution of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-L-xylofuranose (**43**; 430 mg, 1.6 mmol) and DCC (1.1 g, 4.8 mmol) in DMSO (6.4 ml) (TLC in C2). After 16 h, diethyl phosphite (0.42 ml, 3.2 mmol) and trietylamine (1.12 ml, 8 mmol) were added and the whole was stirred overnight (TLC in C1). The reaction mixture was diluted with chloroform and filtered through Celite. The filtrate was then extracted with water and the organic layer was dried over anhydrous sodium sulfate. Chromatography of the crude product on silica gel (elution with a linear gradient of 0–10% ethanol in chloroform) afforded the expected phosphonate. Yield 480 mg (75%, colourless sirup) of **45**, $[\alpha]^{20}$ +29.5. HR-FAB calculated for $C_{19}H_{30}O_8P$ $(M + H)^+$: 417.1678; found 417.1674. IR ($CHCl_3$, cm^{-1}): ν (OH)3451w, br, 3240w, br; **OBn**: ν (=CH) 3092w, 3068w, 3027m; ν (ring) 1604vw, 1588vw, 1498w, 1456m, 699m; ν_{as} (CH_2) 2911m; ν_s (CH_2) 2872w. **1,3-Dioxolane**: δ_s (CH_3) 1386m, 1376m; ν_{as} (COCOC) 1132m, sh, 1075vs; ν_s (COCOC) 1098s, sh; ν_s (CMe_2) 859w; γ_s (CMe_2) 523m. **PO(OEt)$_2$**: ν (P=O) 1245s, br; β_s (CH_2) 1478w; δ_{as} (CH_3) 1444w; γ_s (CH_2) 1394m, sh; δ_{as} (CH_3) 1164s, 1098s, sh; ν_{as} (POCC) 1049vs, 1028vs, 974s; δ (POC) 567m. ^{1}H NMR (600 MHz, $CDCl_3$): 6.00 bd, 1 H, *J*(1,2) = 3.8 (H-1); 7.37–7.30 m, 5 H, 4.72 d, 1 H, *J*(gem) = 10.8 and 4.65 d, 1 H, *J*(gem) = 10.8 (OBn); 4.60 d, 1 H, *J*(2,1) = 3.8 and *J*(2,3) ~ 0 (H-2); 4.41 m, 1 H, *J*(4,3) = 3.2 (H-4); 4.39 d, 1 H, *J*(3,4) = 3.2, *J*(3,2) ~ 0 (H-3); 4.37 m, 1 H (H-5); 4.23 m, 2 H, 4.19 m, 2 H, 1.353 t, 3 H, *J* = 7.0 and 1.347 t, 3 H, *J* = 7.0 (P(OEt)$_2$); 4.14 b, 1 H (OH-5′); 1.50 bs, 3 H and 1.32 bs, 3 H (1,2-O*i*Pr). ^{13}C NMR (150.9 MHz, $CDCl_3$): 136.76, 128.52(2), 128.16, 127.98(2) and 72.83 (OBn); 117.80, 26.67 and 26.16 (1,2-O*i*Pr); 104.77 (C-1); 84.37 d, *J*(C,P) = 3.9 (C-3); 81.98 (C-2); 77.16 d, *J*(C,P) = 11.8 (C-4); 67.44 d, *J*(C,P) = 161.0 (C-5); 63.23 d, *J*(C,P) = 7.1, 62.48 d, *J*(C,P) = 7.1, 16.47 d, *J*(C,P) = 5.6 and 16.41 d, *J*(C,P) = 5.6 (P(OEt)$_2$).

Diethyl (4*S*)-(1,3-Di-*O*-acetyl-2-*O*-benzyl-α-L-threofuranos-4-yl)phosphonate (**47**)

The title phosphonate was obtained from diethyl (5*S*)-(3-*O*-benzyl-1,2-di-*O*-isopropylidene-α-L-xylofuranos-5-*C*-yl)phosphonate (**45**; 1 g, 2.4 mmol) according to the Method *A*. Yield 940 mg (91%, colourless syrup) of **47**. HR-FAB calculated for $C_{19}H_{28}O_9P$ $(M + H)^+$: 431.1471; found 431.1467. IR ($CHCl_3$, cm^{-1}): **OBn**: ν (=CH) 3091vw, 3067w, 3030w; ν (ring) 1604vw, 1497w, 1455w, 699w; ν_{as} (CH_2) 2912w, ν_s (CH_2) 2871w. **OAc**: ν (C=O) 1749s, ν (C–O) 1255s, sh, 1229vs; γ (CCOO) 604w; δ_s ((CH_3) 1374m. **PO(OEt)$_2$**: β_s (CH_2) 1478w; δ_{as} (CH_3) 1443w;

γ_s (CH_2) 1393w; δ_{as} (CH_3) 1164w, 1103m; ν (POCC) 1043vs, 1029vs; δ (POC) 575w. ^{1}H NMR (500 MHz, $CDCl_3$): 7.38–7.28 m, 5 H, 4.80 d, 1 H, *J*(gem) = 12.0 and 4.67 d, 1 H, *J*(gem) = 12.0 (OBn); 6.30 p, 1 H, *J*(1,2) = 0.5; *J*(1,3) = 0.6; *J*(1,4) = 0.4 and *J*(1,P) = 0.8 (H-1); 3.98 m, 1 H, *J*(2,1) = 0.5, *J*(2,3) = 1.0 and *J*(2,P) = 0.5 (H-2); 5.56 m, 1 H, *J*(3,4) = 5.0, *J*(3,2) = 1.0, *J*(3,1) = 0.6 and *J*(3,P) = 13.2 (H-3); 4.44 m, 1 H, *J*(4,3) = 5.0, *J*(4,1) = 0.4 and *J*(4,P) = 4.5 (H-4); 2.105 s, 3 H (1-OAc); 2.07 s, 3 H (3-OAc); ~4.18 m, 4 H, 1.305 td, 3 H, *J*(CH_3,CH_2) = 7.1 and *J*(CH_3,P) = 0.4 and 1.27 td, 3 H, *J*(CH_3,CH_2) = 7.1 and *J*(CH_3,P) = 0.4 ($P(OEt)_2$). ^{13}C NMR (125.8 MHz, $CDCl_3$): 169.15 and 20.88 (1-OAc); 169.71 and 21.02 (3-OAc); 136.97, 128.38(2), 127.90(3) and 71.67 (OBn); 100.72 d, *J*(C,P) = 12.1 (C-1); 86.25 d, *J*(C,P) = 6.9 (C-2); 78.55 d, *J*(C,P) = 174.1 (C-4); 76.41 d, *J*(C,P) = 4.2 (C-3); 63.46 d, *J*(C,P) = 6.5, 63.40 d, *J*(C,P) = 6.3, 16.35 d, *J*(C,P) = 5.7 and 16.32 d, *J*(C,P) = 5.8 ($P(OEt)_2$).

Diethyl (4*S*)-(1,3-Di-*O*-acetyl-2-*O*-benzoyl-α-L-threofuranos-4-yl)phosphonate (**48**)

The title phosphonate was obtained from diethyl (4*S*)-(1,3-*O*-acetyl-2-*O*-benzyl-L-threofuranos-4-yl)phosphonate (**47**; 6 g, 14 mmol) according to the Method *C*. Yield 2.5 g (40%, colourless sirup) of **48**. HR-FAB calculated for $C_{19}H_{26}O_{10}P$ $(M + H)^+$: 445.1264; found 445.1279. IR ($CHCl_3$, cm^{-1}): **OAc**: ν (C=O) 1755s; ν (C–O) 1232s, sh; γ (CCOO) 603w; δ_s (CH_3) 1370w. **OBz**: ν (C=O) 1729m; ν (C–O) 1270s; β (C=O) 712m; ν (=CH) 3033w; ν (ring) 1585vw, 1494vw, 1444w, 1317w, 1179w, 1110m, 1070m, sh, 855w, 687w, 617vw. **$PO(OEt)_2$**: ν (P=O) 1261s; ν_{as} (POCC) 1045s, 1028vs; ν (C–C) 963m; δ (POC) 574w; ν_{as} (CH_3) 2990w, sh; β_s (CH_2) 1479vw; δ_{as} (CH_3) 1452w; γ_s (CH_2) 1393w; δ_{as} 1163w, 1097m. ^{1}H NMR (500 MHz, $CDCl_3$): 8.09 m, 2 H, 7.59 m, 1 H and 7.46 m, 2H (OBz); 6.40 m, 1 H, *J*(1,2) = 0.6, *J*(1,3) = 0.65 and *J*(1,4) = 0.4 (H-1); 5.72 m, 1 H, *J*(3,1) = 0.65, *J*(3,2) = 1.6, *J*(3,4) = 5.8 and *J*(3,P) = 13.3 (H-3); 5.40 dt, 1 H, *J*(2,1) = 0.6, *J*(2,3) = 1.6 and *J*(2,P) = 0.6 (H-2); 4.46 ddd, 1 H, *J*(4,1) = 0.4, *J*(4,3) = 5.8 and *J*(4,P) = 4.3 (H-4); 4.24 m, 4 H and 1.34 dt, 6 H, *J*(CH_3,CH_2) = 7.1, *J*(CH_3,P) = 0.4 (2 × OEt); 2.15 s, 6 H (2 × OAc). ^{13}C NMR (125.8 MHz, $CDCl_3$): 169.20, 168.77, 20.98 and 20.71 (2 × OAc); 165.20, 133.71, 130.05(2), 128.71 and 128.49(2) (OBz); 99.60 d, *J*(1,P) = 12.6 (C-1); 81.50 d, *J*(2,P) = 8.2 (C-2); 79.25 d, *J*(3,P) = 4.0 (C-3); 78.15 d, *J*(4,P) = 175.3 (C-4); 63.42(2) d, *J*(C,P) = 6.7, 16.43 d, *J*(C,P) = 5.5 and 16.40 d, *J*(C,P) = 5.8 ($P(OEt)_2$).

Diethyl (4*S*)-[3-*O*-Acetyl-2-*O*-benzoyl-1-deoxy-1-(uracil-1-yl)-α-L-threofuranos-4-yl]-phosphonate (**49a**)

The title phosphonate was obtained from silylated uracil (2.14 g, 19 mmol) and the phosphonate **48** (2.1 g, 4.8 mmol) according to the Method *B*. Yield 1.3 g (57%, white lyophilizate) of **49a**, $[\alpha]^{20}$ –40.0. HR-FAB calculated for $C_{21}H_{26}N_2O_{10}P$ $(M + H)^+$: 497.1325; found 497.1332. IR ($CHCl_3$, cm^{-1}): **U**: ν (NH-free) 3389w; ν (NH-bonded) 3171w, br; ν (C=O) 1727vs, 1697vs; ν (C=C)1635m; ν (ring) 1480w, sh, 1427w, sh. **OAc**: ν (C=O) 1756s, sh; ν (C–O) 1232vs, sh; γ (CCOO) 600w; δ_s (CH_3) 1376m, 1372m. **OBz**: ν (C–O) 1260vs, β (C=O) 712s; ν (=CH) 3064w, 3027m; ν (ring) 1603w, 1586w, 1493w, 1453s, 1317m, 1179m, 1111s, 1071s, sh, 686w, 617vw. **$PO(OEt)_2$**: ν (P=O) 1250vs, sh; ν_{as} (POCC) 1047vs, 1029vs, 978s; δ (POC) 572m; δ_{as} (CH_3) 1444m, sh; γ_s (CH_2) 1391m; δ_{as} (CH_3) 1164m, 1097s. ^{1}H NMR (600 MHz, $CDCl_3$): 8.82 bs, 1 H (NH); 8.07 m, 2 H, 7.60 m, 1 H and 7.46 m, 2 H (OBz); 7.32 d, 1 H, *J*(6,5) = 8.2 (H-6); 6.11 d, 1 H, *J*(1′,2′) = 4.5 (H-1′); 5.93 ddd, 1 H, *J*(3′,4′) = 5.4, *J*(3′,P) = 12.6 and *J*(3′,2′) = 3.8 (H-3′); 5.81 d, 1 H, *J*(5,6) = 8.2 (H-5); 5.74 m, 1 H, *J*(2′,1′) = 4.5, *J*(2′,3′) = 3.8 and *J*(2′,P) = 0.9 (H-2′); 4.71 dd, 1 H, *J*(4′,3′) = 5.4 and *J*(4′,P) = 3.7 (H-4′);

~4.25 m, 4 H, 1.362 t, 3 H, $J(CH_3,CH_2)$ = 7.0 and 1.358 t, 3 H, $J(CH_3,CH_2)$ = 7.0 $(P(OEt)_2)$; 2.15 s, 3 H (OAc). ^{13}C NMR (150.9 MHz, $CDCl_3$): 169.21 and 20.73 (OAc); 165.68, 133.89, 130.09(2), 128.58(2) and 128.32 (OBz); 162.68 (C-4); 149.86 (C-2); 140.81 (C-6); 103.13 (C-5); 91.91 d, J(C,P) = 7.2 (C-1′); 80.14 d, J(C,P) = 5.4 (C-2′); 78.61 d, J(C,P) = 171.6 (C-4′); 75.78 d, J(C,P) = 6.2 (C-3′); 63.55 d, J(C,P) = 6.8, 63.42 d, J(C,P) = 6.8 and 16.45(2) d, J(C,P) = 5.6 $(P(OEt)_2)$.

Diethyl (4*S*)-[3-*O*-Acetyl-2-*O*-benzoyl-1-deoxy-1-(thymin-1-yl)-α-L-threofuranos-4-yl]-phosphonate (**49b**)

The title phosphonate was obtained from silylated thymine (1.23 g, 9.8 mmol) and phosphonate **48** (900 mg, 2.4 mmol) according to the Method *B*. Yield 480 mg (47%, white lyophilizate) of **49b**, $[\alpha]^{20}$ –55.5. HR-FAB calculated for $C_{22}H_{28}N_2O_{10}P$ $(M + H)^+$: 511.1482; found 511.1490. IR ($CHCl_3$, cm^{-1}): **T**: ν (NH) 3389w; ν (C=O) 1723vs, 1697vs; ν (C=C) 1657m, sh; ν (ring) 1465m, 1435w; δ_s (CH_3) 1387m. **OAc**: ν (C=O) 1756s; ν (C–O) 1245s, sh, 1029vs; δ_s (CH_3) 1370m; γ (CCOO) 600w. **OBz**: ν (C=O) 1723vs; ν (C–O) 1261s; ν (ring) 1603w, 1586w, 1493w, 1452m, 1317m, 1179m, 1112m, 1029vs, 1072m, sh, 1002m, sh; β (C=O) 712s. **PO(OEt)$_2$**: ν (P=O) 1245s, sh; ν_{as} (POCC) 1048s, 1029vs, 977m; δ (POC) 572w; δ_{as} (CH_3) 1444w, sh; γ_s (CH_2) 1394w, sh; δ_{as} (CH_3) 1164w, 1097m. ^1H NMR (600 MHz, $CDCl_3$): 8.24 bs, 1 H (NH); 8.07 m, 2 H, 7.61 m, 1 H and 7.46 m, 2 H (OBz); 7.13 q, 1 H, $J(6,CH_3)$ = 1.2 (H-6); 6.15 d, 1 H, J(1′,2′) = 4.8 (H-1′); 5.93 ddd, 1 H, J(3′,2′) = 3.95, J(3′,4′) = 5.4 and J(3′,P) = 12.7 (H-3′); 5.75 bdd, 1 H, J(2′,1′) = 4.8, J(2′,3′) = 3.95 and J(2′,P) < 1 (H-2); 4.68 dd, 1 H, J(4′,3′) = 5.4 and J(4′,P) = 3.7 (H-4′); 4.25 m, 4 H, 1.37 t, 3 H, $J(CH_3,CH_2)$ = 7.1 and 1.34 t, 3 H, $J(CH_3,CH_2)$ = 7.1 $(P(OEt)_2)$; 2.16 s, 3 H (OAc); 1.97 d, 3 H, $J(CH_3,6)$ = 1.2 (5-CH_3). ^{13}C NMR (150.9 MHz, $CDCl_3$): 169.20 and 20.75 (OAc); 165.71, 133.89, 130.10(2), 128.59(2) and 128.37 (OBz); 163.11 (C-4); 149.89 (C-2); 136.38 (C-6); 111.73 (C-5); 91.23 (C-1′); 79.89 d, J(2′,P) = 5.3 (C-2′); 78.28 d, J(4,P) = 171.3 (C-4′); 75.82 d, J(3′,P) = 6.5 (C-3′); 63.52 d, J(C,P) = 6.8, 63.42 d, J(C,P) = 6.9 and 16.47(2) d, J(C,P) = 5.6 $(P(OEt)_2)$; 12.61 (5-CH_3).

Diethyl (4*S*)-[3-*O*-Acetyl-2-*O*-benzoyl-1-(4-*N*-benzoylcytosin-1-yl)-1-deoxy-α-L-threofuranos-4-yl]phosphonate (**49c**)

The title phosphonate was obtained from silylated 4-*N*-benzoylcytosine (0.97 g, 4.5 mmol) and the phosphonate **48** (0.5 g, 1.12 mmol) according to the Method *B*. Yield 370 mg (55%, white lyophilizate) of **49c**, $[\alpha]^{20}$ –36.5. HR-FAB calculated for $C_{28}H_{31}N_3O_{10}P$ $(M + H)^+$: 600.1747; found 600.1722. IR ($CHCl_3$, cm^{-1}): **OAc**: ν (C=O) 1754m; ν (C–O) 1239s, sh, 1028s; γ (CCOO) 600w; δ_s (CH_3) 1368m. **OBz**: ν (C=O) 1728m; β (C=O) 712m; ν (C–O) 1259s; ν (ring) 1316m, 1298m, 1112m, 1002w, 829w. **NHBz**: ν (NH) 3406w; ν (amide I) 1705m; ν (amide II) 1554m. **OBz** and **NHBz**: ν (=CH) 3092vw, 3066vw, 3027w; ν (ring) 1603m, 1583w, 1497w, sh, 1452w, 1180w, 1071m, sh, 1028s, 686w, 616vw. **PO(OEt)$_2$**: ν (P=O) 1248s; ν_{as} (POCC) 1049s, 1028s, 976w; δ (POC) 567w; δ_{as} (CH_3) 1445w; γ_s (CH_2) 1392w; δ_{as} (CH_3) 1165w, 1097m. **C**: ν (C=O) 1674s; ν (ring) 1629m, 1480vs, 1404w, 1285m, sh. ^1H NMR (600 MHz, $CDCl_3$ + DMSO 9:1): 10.22 bs, 1 H (NH); 8.09 m, 2 H, 7.61 m, 1 H and 7.47 m, 2 H (OBz); 8.01 m, 2 H, 7.60 m, 1 H and 7.51 m, 2 H (NBz); 7.845 bd, 1 H, J(6,5) = 7.5 (H-6); 7.64 bd, 1 H, J(5,6) = 7.5 (H-5); 6.16 d, 1 H, J(1′,2′) = 3.3 (H-1′); 5.91 m, 2 H (H-3′ and H-4′); 4.94 dd, 1 H, J(2′,1′) = 3.3 and J(2′,3′) = 5.0 (H-2);

4.23 m, 4 H, 1.35 t, 3 H, $J(CH_3,CH_2)$ = 7.0 and 1.335 t, 3 H, $J(CH_3,CH_2)$ = 7.0 ($P(OEt)_2$); 2.12 s, 3 H (OAc). ^{13}C NMR (150.9 MHz, $CDCl_3$ + DMSO 9:1): 168.69 and 20.36 (OAc); 165.01, 133.32, 129.65(2), 128.26 and 128.09(2) (OBz); 166.70, 132.62, 128.30(2), 128.26 and 127.75(2) (NBz); 163.40 (C-4); 154.50 (C-2); 145.17 (C-6); 96.60 (C-5); 93.65 (C-1′); 79.98 d, J(2′,P) = 5.9 (C-2′); 79.54 d, J(4′,P) = 171.6 (C-4′); 75.38 d, J(3′,P) = 5.4 (C-3′); 63.00 d, J(C,P) = 6.8, 62.88 d, J(C,P) = 6.8 and 16.03(2) d, J(C,P) = 5.6 ($P(OEt)_2$).

(4*S*)-[1-Deoxy-1-(uracil-1-yl)-α-L-threofuranos-4-yl]phosphonic Acid (**50a**)

The title phosphonic acid was obtained from the phosphonate **49a** (300 mg, 0.6 mmol) according to the Method *D*. Yield 0.16 g (83%, white lyophilizate) of **50a**, $[\alpha]^{20}$ +7.6. HR-FAB calculated for $C_2H_{10}N_2O_8Na_2P$ $(M + H)^+$: 338.9970; found 338.9958. IR (KBr, cm^{-1}): ν (C–OH) 1114m, 1047m, br; ν_{as} $(PO_3)^{2-}$ 1011m, br, sh; ν_s $(PO_3)^{2-}$ 935w, br, sh; δ_s $(PO_3)^{2-}$ 582w, sh. **U**: ν (C=O) 1698m, br; ν (ring) 1472w, 1404w, 1271w; γ (CH) 815w, 770w. ^1H NMR (600 MHz, D_2O): 7.81 d, 1 H, J(6,5) = 8.1 (H-6); 5.82 d, 1 H, J(5,6) = 8.1 (H-5); 5.88 t, 1 H, J(1′,2′) = 1.1 and J(1′,P) = 1.1 (H-1′); 4.48 dt, 1 H, J(3′,2′) = 1.6, J(3′,4′) = 5.8 and J(3′,P) = 1.6 (H-3′); 4.40 dt, 1 H, J(4′,2′) = 1.6, J(4′,3′) = 5.8 and J(4′,P) = 1.6 (H-4); 4.18 m, 1 H, J(2′,1′) = 1.1, J(2′,3′) = 1.6 and J(2′,4′) = 1.6 (H-2′). ^{13}C NMR (150.9 MHz, D_2O): 167.39 (C-4); 152.08 (C-2); 143.12 (C-6); 101.11 (C-5); 94.18 d, J(1′,P) = 3.3 (C-1′); 88.12 d, J(4,P) = 146.8 (C-4′); 81.66 (C-2′); 76.68 d, J(3,P) = 7.5 (C-3′).

(4*S*)-[1-Deoxy-1-(thymin-1-yl)-α-L-threofuranos-4-yl]phosphonic Acid (**50b**)

The title phosphonic acid was obtained from the phosphonate **49b** (220 mg, 0.42 mmol) according to the Method *D*. Yield 120 mg (79%, white lyophilizate) of **50b**, $[\alpha]^{20}$ +11.0. HR-FAB calculated for $C_9H_{12}N_2O_8Na_2P$ $(M + H)^+$: 353.0127; found 353.0118. IR (KBr, cm^{-1}): ν (C–OH) 1116s, br, sh, 1081s, br; ν_{as} ($(PO_3)^{2-}$ 979m; δ_s $(PO_3)^{2-}$ 599m. **T**: ν (C=O) 1683s, br; ν (C=C and ring) 1646s, br, sh, 1476w, 1437w, sh, 1395w, br, 1274w; γ (=CH) 769w; δ_s (CH_3) 1374w. ^1H NMR (600 MHz, D_2O): 7.64 q, 1 H, J(6,CH_3) = 1.2 (H-6); 5.88 t, 1 H, J(1′,2′) = 1.1 and J(1′,P) = 1.1 (H-1′); 4.475 dt, 1 H, J(3′,2′) = 1.5, J(3′,4′) = 1.6 and J(3′,P) = 5.75 (H-3′); 4.15 m, 1 H, J(2′,1′) = 1.1, J(2′,3′) = 1.5 and J(2′,4′) = 0.7 (H-2); 4.40 ddd, 1 H, J(4′,3′) = 1.6, J(4′,2′) = 0.7 and J(4′,P) = 6.0 (H-4′); 1.89 d, 3 H, J(CH_3,6) = 1.2 (5-CH_3). ^{13}C NMR (150.9 MHz, D_2O): 167.63 (C-4); 152.11 (C-2); 138.15 (C-6); 110.17 (C-5); 94.12 d, J(1′,P) = 3.0 (C-1′); 81.91 (C-2′); 88.52 d, J(4,P) = 145.6 (C-4′); 76.85 d, J(3′,P) = 8.0 (C-3′); 12.92 (5-CH_3).

(4*S*)-[1-(Cytosin-1-yl)-1-deoxy-α-L-threofuranos-4-yl]phosphonic acid (**50c**)

The title phosphonic acid was obtained from the phosphonate **49c** (200 mg, 0.34 mmol) according to the Method *D*. Yield 94 mg (82%, white lyophilizate) of **50c**, $[\alpha]^{20}$ +4.6. HR-FAB calculated for $C_8H_{11}N_3O_7P$ $(M + H)^+$: 292.0335; found 292.0342. IR (KBr, cm^{-1}): ν (C–OH) 1111w, br, 1080w, br; ν_{as} $(PO_3)^{2-}$ 980w, br; δ_s $(PO_3)^{2-}$ 582m, br. **C**: ν (C=O) + β_s (NH) 1644m; ν (ring) 1605m, sh, 1530w, 1493w; ν (C–N) 1287w. br; γ (=CH) 785w. ^1H NMR (600 MHz, D_2O): 7.79 d, 1 H, J(6,5) = 7.6 (H-6); 6.03 d, 1 H, J(5,6) = 7.6 (H-5); 5.88 dd, 1 H, J(1′,2′) = 1.9 and J(1′,P) = 0.9 (H-1′); 4.48 ddd, 1 H, J(3′,4′) = 2.4, J(3′,P) = 7.0 and J(3′,2′) = 1.9 (H-3′); 4.42 ddd, 1 H, J(4′,3′) = 2.4, J(4′,2′) = 0.6 and J(4′,P) = 5.4 (H-4′); 4.22 tt, 1 H, J(2′,1′) = 1.9, J(2′,3′) = 1.9, J(2′,4′) = 0.6 and J(2′,P) = 0.9 (H-2′). ^{13}C NMR (150.9 MHz, D_2O): 168.74 (C-4); 159.78 (C-2); 145.14 (C-6); 97.81 (C-5); 96.60 d, J(C,P) =

3.9 (C-1′); 88.90 d, J(C,P) = 150.9 (C-4′); 83.96 d, J(C,P) = 2.3 (C-3′); 79.02 d, J(C,P) = 6.8 (C-2′).

Determination of K_m Value for 5-Nitrodeoxyuridine as TP Substrate

The reaction mixture (200 μl) contained 300 μM 5-nitrodeoxyuridine, 300 μM potassium dighydrogen phosphate (pH 6.5), 0.018 units of TP. The real time assay was performed at 37 °C in 96-well plates by measuring the absorption at 340 nm for 5 min ($\Delta\varepsilon_{340}$ = 9200 M^{-1} cm^{-1}). Michaelis constant K_m for phosphorolysis of 5-nitrodeoxyuridine was 60 μM.

Determination of K_i Values for Tetrofuranose Nucleoside Phosphonic Acids

The reaction mixture (200 μl) contained 150 and 300 μM 5-nitrodeoxyuridine, 300 μM potassium dihydrogen phosphate (pH 6.5), 0.018 units of TP, and variable concentration of the appropriate nucleotide analogs **9**, **20**, **34** and **50** in the range of 0–35 μM [I]. The real time assay was performed at 37 °C in 96-well plates by measuring the absorption at 340 nm for 5 min ($\Delta\varepsilon_{340}$ = 9200 M^{-1} cm^{-1}). Only compound **34** exhibited competitive inhibition of the enzyme with K_i = 4 μM (Dixon–Webb plot 1/v vs [I]; data not shown).

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