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Electrophile-promoted addition of hydroxymethylphosphonate to 4′,5′-didehydronucleosides: a way to novel isosteric analogues of 5′-nucleotides

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Abstract—An electrophile-promoted addition of dialkyl-hydroxymethylphosphonate to the protected 4′,5′-didehydronucleosides resulted in an epimeric mixture of 4′-dialkylphosphonomethoxy derivatives of 2′,5′-dideoxynucleosides, novel analogues of 2′-deoxynucleoside 5′-monophosphates. Several types of electrophiles (pyridinium tosylate, NIS, NBS, MCPBA and others) were evaluated in addition reactions with 4′,5′-didehydrothymidine. Out of them, pyridinium tosylate was found to have a practical usefulness in these transformations. Its use has led to the preparation of a series of 4′-phosphonomethoxy derivatives of common 2′-deoxynucleosides. On biological screening, these free phosphonic acids exerted no significant cytostatic or antiviral activity.

1. Introduction

There have been numerous attempts to accomplish structural alterations of the phosphate moiety in nucleotides and oligonucleotides, stimulated especially by the need to overcome its inherent susceptibility to in vivo cleavage by phosphomonoesterases, nucleotidases and nucleases.[1,2] The phosphonate analogues containing the enzyme-stable ether *P–C–O* moiety instead of the ester *P–O* emerged as promising candidates in this respect. Isopolarity and isostericity of these compounds with natural 5′-nucleotides, as well as the presence of an oxygen atom-containing moiety mimicking the phosphoester oxygen atom in the proximity of the phosphoryl residue, seems to be of key importance for biological activity of these compounds.[3,4] This was proved on finding remarkable antiviral properties of a family of acyclic nucleoside phosphonic acids,[5–7] analogues of 5′-nucleotides. Among them, three phosphonate drugs bearing just the *P–C–O* moiety are in clinical use (Fig. 1): *Vistide* [(*S*)-1-(1-cytosinyl)-3-hydroxy-2-propoxymethylphosphonic acid (**1**)] for the treatment of CMV-induced retinitis, *Viread* [(*R*)-1-(9-adeninyl)-2-propoxymethylphosphonic acid (**2**)] for the treatment of HIV and *Hepsera* [2-(9-adeninyl)ethoxymethylphosphonic acid (**3**)] for the treatment of chronic Hepatitis B. In addition, the isosteric phosphonate analogues of 2′-dideoxynucleoside 5′-phosphate **4a** and 2′,3′-dideoxydidehydronucleoside 5′-phosphate **5a**,[4,8] bearing 4′*C–O–C–P* linkage were found to possess antiretroviral activity, and their

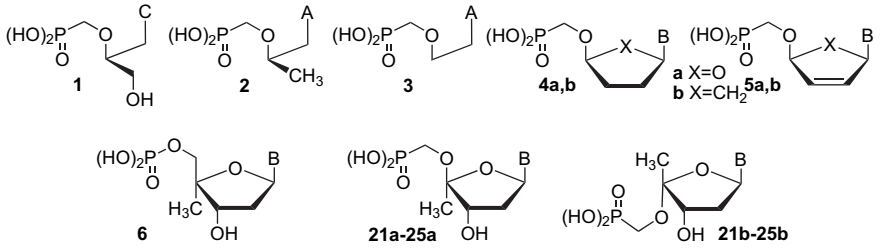

Figure 1. Examples of structurally diverse nucleoside phosphonic acids.

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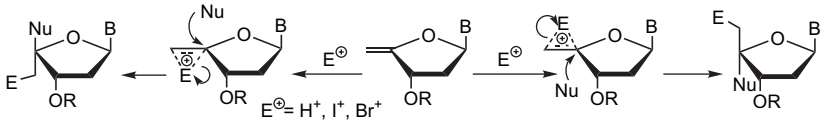
carba congeners **4b** and **5b**[9] were also prepared (Fig. 1). Over recent years we have been dealing extensively with both the synthetic methods leading to a range of novel phosphonate-based analogues of mono- and oligonucleotides,[10–17] and with their biochemical and biophysical evaluation.[18–22] We describe here the compounds **21**–**25** (Fig. 1) isosteric with 4′-methyl-2′-deoxynucleoside 5′-phosphates **6**[23] and bearing 4′-phosphonomethoxy moiety (*P*–*C*–*O*), similar to compound **4a**.

2. Results and discussion

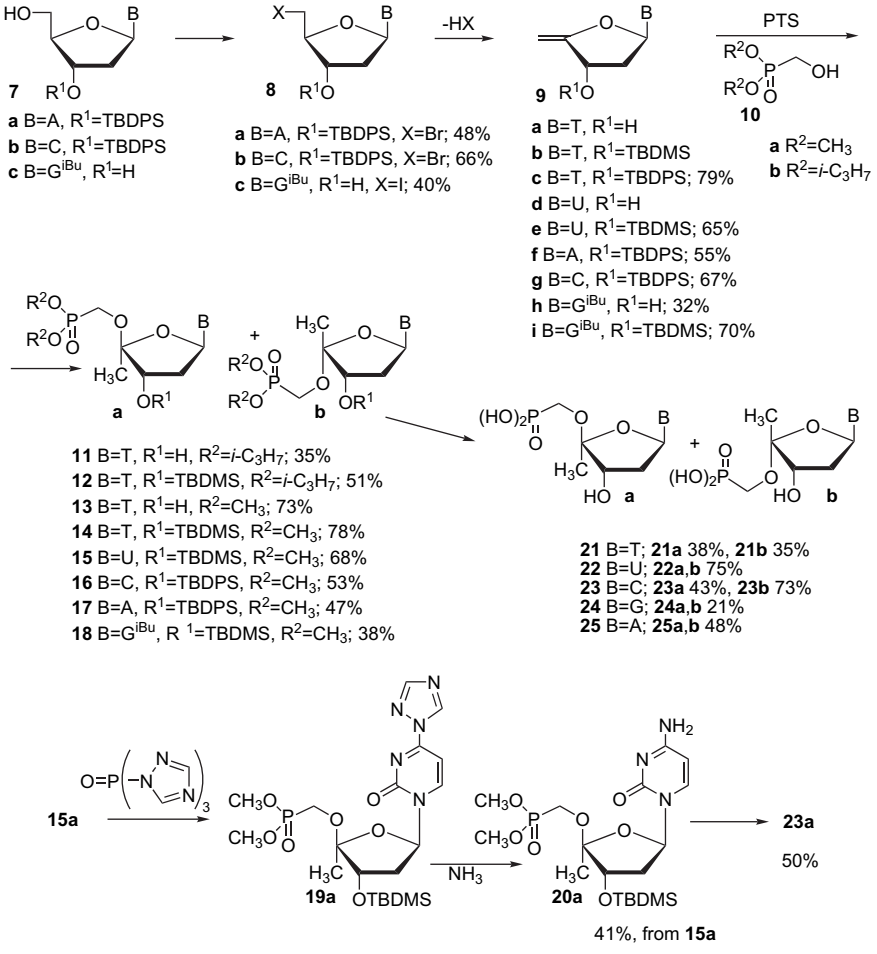
In general, electrophilic addition (Scheme 1) of a nucleophile to 4′,5′-didehydronucleosides proceeds via electrophile-mediated formation of 4′-epimeric three-membered spiro-intermediates, which subsequently undergo an attack by a nucleophile on the 4′-position to provide the desired product as a mixture of 4′-epimers. A plausible synthetic route to the preparation of 4′-phosphonomethoxy derivatives of nucleosides was seen, therefore, in the exploitation of 4′,5′-didehydronucleosides **9** (Schemes 1 and 2)[24] studied by Moffatt,[25,26] and also by Prisbe,[27] Lerner,[28] Robins,[29] and Reese.[30] We expected compounds **9**, in keeping with results of reactions performed earlier with nucleosidic compounds having the acyclic type of vinyl ether linkage,[31] cyclic type,[4,8] or exocyclic double bond of the vinyl ether moiety,[32,33] to be suitable for an electrophile-promoted addition of hydroxymethylphosphonate. In our study, we explored the use of pyridinium *p*-toluenesulfonate (PTS), *N*-iodosuccinimide (NIS), *N*-bromosuccinimide (NBS) and *m*-chloroperoxybenzoic acid (MCPBA) as electrophiles, and dialkyl-hydroxymethylphosphonates as nucleophiles.

2.1. Phosphonylation reactions in thymidine series

The starting compounds 1-(2,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)thymine (4′,5′-didehydrothymidine) **9a**[27] (Scheme 2) and the 3′-*O*-*tert*-butyldimethylsilyl derivative **9b**[27] reacted smoothly with an excess of dialkyl-



Scheme 1. Electrophile-mediated addition of nucleophile to exocyclic vinyl ether moiety.



Scheme 2. Synthesis of 4′-*C*-phosphonomethoxynucleosides.

hydroxymethylphosphonate **10a** or **10b** in dichloromethane at rt in the presence of PTS as a proton source added as the last component, to provide expected phosphonates **11**–**14** as 4′-epimeric mixtures. Considerably better yields of the products were obtained with dimethyl ester **10a**. A slight advantage over the use of the unprotected starting compound **9a** has been observed (somewhat better yields) in the use of 3′-*O*-silylated derivative **9b** (may be due to a better solubility of **9b** than **9a** in dichloromethane). Resulting pairs of diastereoisomers **11a**,**b**–**14a**,**b** were all separable on silica gel. The yields and isomeric ratios for the products **11**–**14**, along with the data obtained with non-thymidine compounds **15**–**18** (see below) are provided in Table 1.

The assignments of the 3′-*O*-silylated diastereoisomers with the configuration α-L-*threo* and β-D-*erythro*, respectively, was made by 2D-ROESY NMR spectroscopy, as is shown for compounds **14a** and **14b** in Figure 2. The observed NOE contacts between H-6 of the base and pentose proton H-2′ and H-3′confirm β-orientation of base in both diastereoisomers **14a**, **14b**, and allow for distinguishing the hydrogens H-2′ and H-2″. Configuration of the C(4)-methyl group could be derived from NOE contacts of its protons with H-1′ and H-2′ in diastereoisomer **14a** and/or with H-3′ and H-6 in diastereoisomer **14b**. The vicinal coupling pattern of the pentose ring protons shows significant difference in diastereoisomeric pairs. Although the absence of H-4′ does not allow for the use of complete pseudorotational conformation calculation for the pentose ring, the application of empirical relation (Eq. 1) suggested by Rinkel and Altona[34] and applied under similar conditions by Chattopadhyaya[33] allowed us to estimate the S-type (80–95% of C2′-*endo*) as preferred for all α-L-*threo* diastereoisomers and the N-type (70–90% of C3′-*endo*) for β-D-*erythro* diastereoisomers **11**–**18**, as it is illustrated in Figure 3.

Table 1. Yields and 4′-epimeric ratios of dimethyl-phosphonates **11**–**18**

Compound	Base	Yield (%)	Ratio (**a**:**b**)[a]
11	T	35	17:83[b]
12	T	51	44:56[b]
13	T	73	29:71[b]
14	T	78	40:60[b]
15	U	68	49:51[b]
16	C	53	20:80[c]
17	A	47	8:92[c]
18	$G^{i\text{-Bu}}$	38	40:60[c]

[a] Epimers assigned from NMR spectra.
[b] Silica gel separable.
[c] Silica gel unseparable.

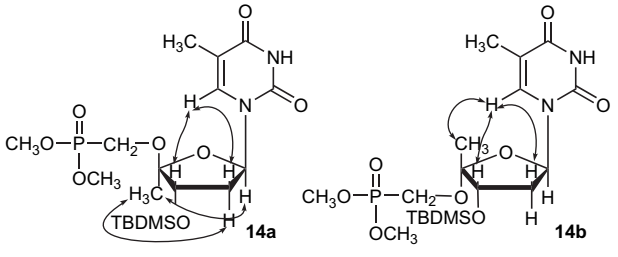


Figure 2. The observed proton NOE contacts (shown with arrows) important for structure determination of diastereoisomers **14a** and **14b**.

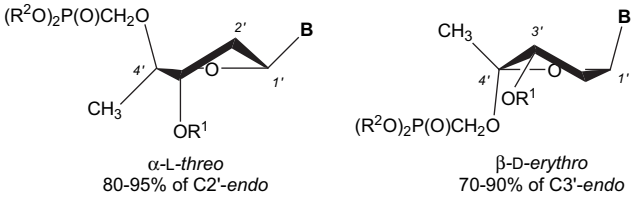
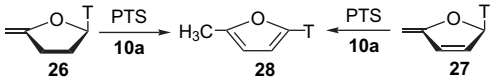


Figure 3. Preferred conformations of pentose ring for α-L-*threo* and β-D-*erythro* diastereoisomers **11**–**18**.

$$\%S = [(J(1',2') + J(1',2'') - 9.8)/5.9] \times 100 \quad (1)$$

It is worth mentioning that compounds **14a** and **14b** proved exploitable for obtaining the building blocks for the preparation of modified thymidine oligonucleotides.[35]

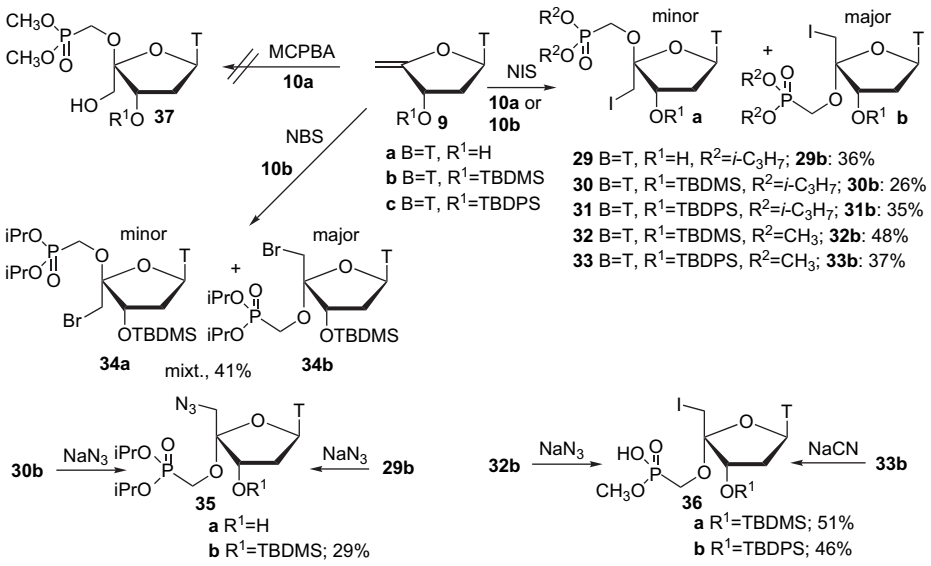
Attempts to employ tetrazole, BF_3–etherate, or *N*-methylimidazolium trifluoromethanesulfonate in the role of PTS did not afford the phosphonate compounds, and led to decomposition of the starting 4′,5′-didehydrothymidine derivative. An attempt to convert the 4′,5′-didehydro-2′,3′-dideoxythymidine (**26**)[27] and (2-methylene-5(*R*)-(thymin-1-yl))-2,5-dihydrofuran (**27**)[36] into the corresponding 4′-phosphonomethoxy derivatives using PTS and **10a** completely failed (Scheme 3). Only 2-methyl-5-(thymin-1-yl)-furan (**28**) as a predominant product, along with thymine as a minor product, were identified by ^{1}H NMR. It is known that ddT and d4T are acid-sensitive compounds; in the case of compound **27**, Reese[37] reported its lability in both basic and acidic conditions, with formation of furan derivative **28** in a high yield in both cases. Assuming this, and the results observed, we did not go into further studies and quantification of the reactions with **26** and **27**.



Scheme 3.

In general, PTS activation was clearly the most straightforward, considering the practical accessibility of the desired phosphonate compounds. It was found difficult to modulate favourably the yield and epimeric composition by the conditions influencing the PTS-mediated electrophilic addition, e.g., by increasing the acidity of the PTS (prolonged drying in vacuo), the presence of molecular sieves in the reactions, etc. No conclusions on the positive role of such changes could be drawn.

In a similar way as with the PTS activation, though with somewhat lower overall yields (26–48%), the reactions of **9a**–**c** with **10a** and **10b** promoted by NIS were carried out to give (Scheme 4) the desired 5′-deoxy-5′-halo derivatives **29**–**33**, and in the same way, **9b** afforded **34a**,**b** in reaction promoted by NBS (41%). The principal difference from the above-mentioned reactions using PTS was the high predominance of the β-D-*erythro* isomers **29b**–**33b** over α-L-*threo* isomers **29a**–**33a**. Actually, with a single exception of the 5′-bromo derivative **34** (with the ratio of isomers **34a**–**34b**=1:5) all other minor isomers **29a**–**33a** could not be fully characterized by NMR spectra due to their too low



Scheme 4. Reaction of 4′,5′-didehydrothymidine derivatives with various electrophiles.

population (<10%). Obviously, the predominant type of the supposed epiiodonium (epibromonium) intermediate (Scheme 1) strongly favours the form with halogen atom orientated to β-face, which governs the opening of the three-membered cycle from α-face by the hydroxy function of **10**. The presence of iodine atom at C-5′ in compounds **29**–**33** is manifested by characteristic upfield signal of CH_2–I in the ^{13}C NMR spectra around 5 ppm. A characteristic feature in the ^1H NMR spectra for the compounds **29**–**33** is the coupling pattern of the pentose protons in positions 1′,2′ and 3′, which corresponds to that observed for **b** isomers (β-D-*erythro*) of the above discussed series **11**–**18**, and indicates a preference of N-type pentose conformer (60–70% of C3′-*endo*). The bromine atom at C-5′ in diastereoisomeric pair **34a**, **34b** is evidenced in the ^{13}C NMR spectra ($\delta_{CH_2-Br} \sim 31.5$).

Unfortunately, with the reactions employing NIS/NBS, the obtained mixtures were very difficult to separate, although both silica gel and reversed-phase separations were used. In addition, the products **29**–**34**, although providing (for single main isomers **b**) the MS FAB (molecular ions) and NMR data as expected, underwent gradual decomposition on attempted deblocking reactions, further purifications, and even on storage. That was also why we were not able to proceed in this case to the preparation of the free 5′-iodo and 5′-bromo compounds **29**–**34** as free phosphonic acids. Attempts were made, nevertheless, to find out whether the prepared 5′-deoxy-5′-iodo derivatives **29b**–**31b** (diisopropyl esters; their better stability over dimethyl esters assumed) could be converted to the corresponding azido derivatives **35a**–**35c** on substitution reaction with sodium azide (Scheme 4). After several days in DMF at elevated temperature, the reaction mixtures still showed, as seen from ^1H NMR spectra, the presence of the starting compound, which was not separable by means of chromatography. The formation of **35a** from **29b** was supported only by finding azido group bands at 2112 and 1288 cm^{-1} in the IR spectrum while interpretation of ^1H NMR spectrum was not successful. Likewise, reaction of **31b** with sodium azide yielded no spectrally characterizable azido compound **35c**. In case of product **35b**, obtained in a low yield and contaminated, the IR, ^1H and ^{13}C NMR spectra were obtained and could be interpreted; in the latter, δ_{CH_2-N} at 50.22 ppm confirms the presence of the azido derivative. On treatment of dimethyl ester **32b** with sodium azide in DMSO at rt, as well as of **33b** with sodium cyanide in DMF at elevated temperature, no substitution of the iodo group was observed and the reactions afforded only the appropriate monoesters **36a** and **36b**.

Finally, a possibility was checked to accomplish the MCPBA-promoted phosphonylation reaction, and thus achieve the formation of a product **37** that would possess the both 4′-phosphonomethoxy and 4′-hydroxymethyl moieties. In our hands, reaction of 4′,5′-didehydrothymidine derivatives **9a**–**c** with **10a** and MCPBA provided thymine in all cases and no expected products **37**. To this point, neither purification of MCPBA to remove *m*-chlorobenzoic acid nor the use of base (K_2CO_3) to suppress acidity was any help in attempts to obtain **37** (recently, Haraguchi et al. reported[38] the dimethyldioxirane epoxidation of 4′,5′ double bond in **9a**). The failure of this reaction to provide the desired product is in contrast to the successful preparation of several 4′-alkoxythymidine derivatives using the same methodology.[27,33] Obviously there is a considerable difference between the reactivity of simple alcohols and dialkylhydroxymethylphosphonate **10a** as a nucleophile with 4′,5′-oxirane intermediate, and with longer reaction times, the competing side reactions (decomposition) finally prevail.

2.2. PTS-mediated phosphonylation reactions in the dA, dC, dG and dU series

In general, the so far reported ways to the synthesis of 4′,5′-didehydronucleosides **9** as starting compounds were based on a simple scheme involving 5′-halogenation of the nucleoside **7** and subsequent basic elimination of **8** (Scheme 2). Maag et al.[27] described the Ph_3P/I_2 iodination–MeONa elimination approach as usable for all 2′-deoxynucleosides (except for dC, which was not mentioned). In turning to this

approach, however, we found its use straightforward in the case of 4′,5′-didehydrodeoxyuridine **9d** only and prepared its 3′-*O*-TBDMS derivative **9e**; it proved necessary to adjust the syntheses of starting compounds first (Scheme 4).

With *N*-protected 2′-deoxyguanosine, iodination–elimination reactions gave complex mixtures under varied conditions, and we failed to obtain any preparatively sufficient yields of 4′,5′-didehydrodeoxyguanosine (much later, we found that direct iodination of 2′-deoxyguanosine with Ph_3P–I_2 followed by elimination using sodium methoxide in methanol at elevated temperature gives satisfactory yield of unprotected 2′-deoxy-4′,5′-didehydroguanosine). We partially succeeded in starting with 2′-deoxy-*N*-isobutyryl guanosine (**7c**), converting it to the 5′-iodo derivative **8c** with Ph_3P–I_2, and subsequently using *t*-BuOK in DMF for elimination at low temperature and short reaction time to obtain the product **9h** (32%), which was then silylated to afford **9i** (70%) as a starting compound for phosphonylation. Elimination of HI can be a tricky reaction accompanied by elimination of the nucleobase.

With deoxyadenosine, similarly, the reported[27] iodination yield of 29% proved to be inaccessible. The product was difficult to purify, and in turn the subsequent MeONa elimination (16 h heating) gave very unsatisfactory results. Following the report by Lerner[28] on the use of DBU in DMF at rt for the elimination reaction with 3′-*O*-acetyl-5′-bromo-2′,5′-dideoxyadenosine (53%), and an earlier communication by Moffatt[26] on the use of Ph_3P–CBr_4 in dimethylacetamide when brominating 4-*N*-benzoyl-2′-deoxycytidine, we therefore tested the combination of the bromination of the readily available 6-*N*-benzoyl-3′-*O*-*tert*-butyldiphenylsilyl-2′-deoxyadenosine with Ph_3P–CBr_4 in dioxane and the DBU–DMF elimination, but found that the obtained 4′,5′-didehydro product was repeatedly anomerized (to ca. 20–30%; the use of *t*-BuOK caused the same, and partial decomposition was observed). The anomerization, as evidenced on the ^1H NMR spectra, was attributable to the elimination step. Similarly, we observed partial anomerization and decomposition when carrying out the same reactions with 4-*N*-benzoyl-3′-*O*-*tert*-butyldiphenylsilyl-2′-deoxycytidine. This may relate to the comment in the paper by Verheyden and Moffatt[26] that 4-*N*-benzoyl-1-(2,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)cytosine, which they prepared, was characterized as just ‘essentially pure’. The NMR spectra were not provided; the authors described its further alkaline deblocking to the free 4′,5′-didehydro derivative, unless they mentioned anomerization, but the ambiguous term ‘essentially pure’ may refer to the fact that the purity of the compound could have been affected by the presence of certain amount of the anomerized product. We concluded that the observed partial anomerization/decomposition was probably due to the presence of *N*-protecting groups, since we finally succeeded in obtaining the correct products from the *N*-unprotected starting compounds, as follows. To prepare the key 5′-halogeno compound for elimination, two approaches were used (as an alternative to procedure[28] describing 29% yield of bromination by thionyl bromide).

In Method A, the described 6-*N*-benzoyl-3′-*O*-*tert*-butyldiphenylsilyl-2′-deoxyadenosine[39] was converted, using bromination with Ph_3P–CBr_4 in dioxane, to its 5′-bromo derivative (45%), which in turn furnished the *N*-deblocked compound **8a** (31%) on treatment with methanolic ammonia (Scheme 2).

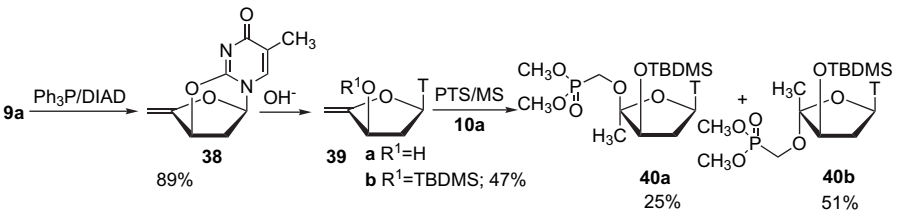
In Method B using an altered reaction sequence, 5′-*O*-dimethoxytrityl-3′-*O*-*tert*-butyldiphenylsilyl-2′-deoxyadenosine[40] was treated with 80% aq acetic acid to remove the 5′-protecting group to give compound **7a** (89%). This was converted to the desired 5′-bromo derivative **8a** on reaction with Ph_3P–CBr_4 in dioxane (48%). Compound **8a** was subsequently subjected to the elimination by prolonged treatment with DBU in DMF (47%), giving the 4′,5′-didehydro derivative **9f**. No anomerization was observed.

In the 2′-deoxycytidine case, the 5′-bromo derivative **8b** was obtained by reaction sequence starting from 4-*N*-benzoyl-2′-deoxy-5′-*O*-dimethoxytritylcytidine. This compound was first silylated to produce the 3′-*O*-*tert*-butyldiphenylsilyl derivative, which was debenzoylated in methanolic ammonia, and then dimethoxytrityl group was removed in 80% aq acetic acid to afford compound **7b** (75%, three steps), which was brominated in 5′-position with CBr_4/Ph_3P in dioxane to give **8b** (66%). This compound, on prolonged treatment with DBU–DMF at rt, afforded the 4′,5′-didehydro precursor **9g** smoothly, also without anomerization.

Phosphonylation reactions with the 3′-silylated precursors **9e**, **9f**, **9g** and **9i** (Scheme 2) using **10a** and PTS were carried out as described above for thymidine compounds **9a**,**b**. Thus, the dA derivative **9f** furnished a 47% yield of phosphonate mixture of **17a** and **17b** showing (on NMR checking) the predominance of 12:1 of the β-D-*erythro* compound **17b** over the α-L-*threo* isomer **17a**. The isomers were not separable either on silica gel or on reversed-phase chromatography, but both were characterized by NMR spectroscopy. They were submitted for further deprotection treatment as a mixture.

The deoxycytidine precursor **9g** afforded two expected isomers **16a** and **16b**, which were separated by column chromatography on silica. They gave a combined yield of 53%, and were characterized by NMR. The isomer of the β-D-*erythro* configuration **16b** showed a more pronounced predominance in this case (ratio 4:1). In connection with the initial difficulties in dC series in preparing a suitable derivative for the elimination reaction and subsequent phosphonylation, we also sought help in the utilization of the dU-precursor for the preparation of deoxycytidine phosphonate. Thus, the deoxyuridine derivative **9e** was phosphonylated, and a diastereoisomeric mixture of **15a** and **15b** (1:1 ratio, as of HPLC) was obtained, from which we were able to isolate the more desired α-L-*threo* isomer **15a** in pure form (while the remaining mixture was left for final deblocking). Compound **15a** was then converted to a triazolide intermediate **19a** by the reaction with triazole–$POCl_3$ according to the approach described by Brown,[41] which in turn was converted on treatment with aq ammonia, without isolation, to the 2′-deoxycytidine compound **20a** in 40% overall yield. It was submitted for deblocking (see below) as a separate sample.

The dG derivative **9i** provided a mixture of 4′-diastereoisomers **18a** and **18b** in 30% overall yield, with a 1.5:1 majority of the β-D-*erythro* isomer **18b**, as revealed by HPLC. The



Scheme 5.

compounds could not be fully separated by repeated chromatography on silica and, in order to avoid losing and decomposing the material, the isomeric mixture was left unresolved for further deblocking steps. Both 4′-epimers **18a**,**b** were analyzed by ^{1}H NMR in the mixture.

Apart from testing the accessibility of 4′-phosphonomethoxy derivatives **11**–**18**, i.e. those originating from the natural nucleosidic precursors possessing the β-D-*erythro* configuration of the pentofuranose ring, we also attempted the preparation of analogues with reverse configuration of the 3′-hydroxy group, i.e. β-D-*threo* or α-L-*erythro* compounds, for potential further exploitation in oligonucleotide chemistry. To achieve this (Scheme 5), we made use of the thymidine derivative **9a**, which was converted in a high yield (~85%) to the 2,3′-cyclonucleoside **38** under Mitsunobu conditions, using triphenyl phosphine and diisopropyl-azodicarboxylate in DMF. This compound was treated with alkali to afford 1-(2,5-dideoxy-β-D-*threo*-pent-4-enofuranosyl)thymine (**39a**),[42] and this in turn was immediately silylated to give the derivative **39b** (47%, in two steps) as the starting compound for phosphonylation in the presence of PTS (**39b** was reported[43] recently, without data, as obtainable from 1-(2,5-dideoxy-5-iodo-β-D-*threo*-pentofuranosyl)thymine in four steps). With **10a**, the reaction furnished (in the presence of molecular sieves) the phosphonates **40a** and **40b** in a 1:2 ratio (76%), separable on silica. In an attempt to accomplish formation of 2,3′-anhydro bridge with the phosphonate **13a** via Mitsunobu reaction, we obtained 3-*N*-methylated phosphonate **13a** without the 2,3′-anhydro bridge, as single product.

The configuration at carbon atom C-4′ in the isomers **40a** and **40b** was derived from their 2D-ROESY spectra. In compound **40a** the observed NOE contacts between the C4′-methyl protons and protons H-3′, H-2″ and H-1′ indicate the cis-orientation of C4′-methyl group. On the other hand, in compound **40b** the C4′-methyl protons show NOE contact with proton H-6 of thymine, which indicates the cis-orientation of C4′-methyl group and thymine base. Additional NOE contacts support the above suggested configurations in both isomers. Further exploitation of these compounds is underway.

2.3. Deprotection

All the 3′-silylated phosphonate dimethyl esters in dT, dC, dA, dU and dG series **11**–**18**, and **20** were subjected to a standard procedure leading to completely deblocked phosphonate derivatives **21**–**25** (Scheme 2). The deprotection included, first, the removal of the nucleobase-acyl protecting groups using ammonia-saturated methanol (case of the dG^{ib} derivative **18**), then the removal of the methylester groups of the phosphonate moiety with bromotrimethylsilane in acetonitrile in the presence of 2,6-lutidine, and finally, the splitting of the 3′-*O*-silyl group with tetrabutylammonium fluoride in tetrahydrofuran. The use of 2,6-lutidine during the bromotrimethylsilane treatment was absolutely necessary to avoid the rapid cleavage of nucleosidic bond. After complete deprotection, the compounds were subjected to ion-exchange purification on DEAE-Sephadex with a gradient of triethylammonium hydrogen carbonate, followed by reversed-phase column re-purification and desalting. The obtained phosphonate compounds were converted, after reversed-phase treatment, into sodium salts by Dowex 50 (Na^+) and adjusted by lyophilization from water. These samples were submitted to the confirmation of structure by MS and NMR spectra. All compounds provided the expected HRMS data from the respective molecular ions, and the ^{1}H and ^{13}C NMR spectra in D_2O were all interpretable and in accordance with the expected structures. No anomerization was observed. The configuration at C-4′ in diastereoisomeric pairs **21**–**25** was derived from 2D-ROESY spectra and showed characteristic coupling pattern of pentose ring protons, as with the above discussed compounds **11**–**18**. NMR spectra of 4′-epimers of dT-phosphonates **21a**,**b** and dC-phosphonates **23a**,**b** were recorded from the pure epimers, while the remaining ones (dU-phosphonates, **22a**,**b**; dG-phosphonates, **24a**,**b**; dA-phosphonates, **25a**,**b**) were obtained from the respective epimeric mixtures.

2.4. Screening for biological activity

The free 4′-phosphonomethoxy compounds **21a**,**b** and **23a**,**b**, as individual isomers, and **22a**,**b**, **24a**,**b** and **25a**,**b**, as mixtures of the α-L-*threo* and β-D-*erythro* isomers, were evaluated for potential cytostatic and antiviral activity. It was found in tests (Dr. I. Votruba, IOCB, Prague) with L929, L1210 and HeLa cells that none of the compounds exerted any significant cytostatic effect. Likewise, no activity was found (Prof. E. DeClercq, Rega Inst., Leuven) on the screening with CMV, VZV, HSV and HIV viruses.

3. Conclusion

We have succeeded in the verification of the practical utility of the general reaction leading to 4′-dialkylphosphonomethoxy derivatives of 2′,5′-dideoxynucleosides (Schemes 1 and 2). The novel structural features introduced in 4′-position were considered worth examining as plausible modifying elements in nucleotide (and potentially, oligonucleotide) analogues. The syntheses elaborated with 4′,5′-didehydrothymidine derivatives were applied to analogous reactions

with the corresponding 4′,5′-didehydro derivatives of the protected 2′-deoxycytidine, 2′-deoxyuridine, 2′-deoxyguanosine and 2′-deoxyadenosine, whereby the preparative availability of these didehydronucleosides was evaluated and revised. New knowledge concerning the use of the individual electrophiles (showing positive results with PTS, NIS and NBS activation, and negative results on attempts with MCPBA) for the addition of dialkyl-hydroxymethylphosphonates to the 4′,5′-didehydronucleosides was obtained. The deprotected compounds of the most promising (PTS-promoted) series (**21**–**25**) submitted for biological testing showed no significant cytostatic effect or antiviral activity, and thus the assumption on the possible biological activity was not confirmed. It seems that the mere presence of the isopolar, isosteric phosphonomethoxy group in the molecule of such a nucleotide analogue may not be sufficient for exerting activity, although this grouping was found to be the key structural feature in some antivirals.[4,8,9] When considering the absence of antiviral and cytostatic activity, nevertheless, we cannot exclude the possibility that the tested compounds are not transported into cells and phosphorylated to the 5′-triphosphates. It would be of interest to prepare a suitable prodrug to evaluate the biological properties at such a stage as well. In addition, in vitro experiments with triphosphate analogues and DNA polymerases should provide information on substrate or inhibitory properties of the compounds. These studies are underway.

4. Experimental

4.1. General

Unless stated otherwise, the solvents were concentrated at 40 °C using a rotatory evaporator. The products were dried over phosphorus pentoxide at 40–50 °C and 13 Pa. The course of the reactions was followed by TLC on silica gel Silufol UV 254 foils (Kavalier Glassworks, Votice, Czech Republic) and the products were visualized both by UV monitoring and (where applicable) by spraying with a 1% ethanolic solution of 4-(4-nitrobenzyl)pyridine which, after short heating and exposing to ammonia vapours, showed the di- (and partly mono-) alkyl phosphonates as blue spots. Preparative column chromatography (PLC) was performed on silica gel (40–60 μm, Fluka) whereby the amount of adsorbent used was 20–40 times the weight of the mixture separated. Elution was performed under a 50 kPa overpressure at the rate of 40 mL min^{-1}. For TLC and PLC runs, the following solvent systems were used (v/v): toluene–ethyl acetate 1:1 (T1), chloroform–ethanol 9:1 (C1), chloroform–ethanol 95:5 (C2), ethyl acetate–acetone–ethanol–water 4:1:1:1 (H1), 12:2:2:1 (H3), H3–ethyl acetate 1:4 (E1), 2-propanol–concd aq ammonia–water 7:1:2 (IPAW, for charged compounds). The HPLC analyses were performed on a DuPont 850 Liquid Chromatograph instrument using a column of reverse phase (4.6×150 mm) Nucleosil 100-5 C18 (Macherey-Nagel), either isocratically at various concentrations of methanol in 0.1 M triethylammonium acetate (TEAA) or by gradients of methanol in the same buffer. The electrophoresis was made on Whatman No. 1 paper in 0.1 M triethylammonium hydrogen carbonate (pH 7.5) at 20 V cm^{-1}. The UV spectra were recorded on a Pye-Unicam SP 8000 spectrophotometer in water or in a 1:1 (v/v) methanol–water mixture at pH 2, pH 7 and pH 12. Mass spectra (*m*/*z*) were recorded on a ZAB-EQ (VG Analytical) instrument, using FAB in both positive and negative mode (ionization by Xe, accelerating voltage 8 kV) with glycerol–thioglycerol (3:1) and 2-hydroxyethyldisulfide as matrices. Infrared spectra (cm^{-1}) were measured on a Nicolet 740 spectrometer in chloroform or in KBr pellet. Elemental analyses were carried out on a PE 2400 Series II analyzer. In cases of compounds where the elemental analyses are not presented and the HRMS data are used instead, it is understood that no peaks were observed in their NMR spectra additional to those expected for the target compounds; the HRMS values thus refer to the uncontaminated species. The optical rotations (α_D values) were measured on an Autopol IV polarimeter (Rudolph Research Analytical) at 20 °C. ^1H and ^{13}C NMR spectra were measured on a Varian Unity 500 instrument (^1H at 500 MHz, ^{13}C at 125.7 MHz) in DMSO-d_6 (referenced to the solvent signal δ_H=2.50, δ_C=39.7) and/or $CDCl_3$ (referenced to TMS). Sodium salts of phosphonic acids were measured in deuterium oxide, free phosphonic acids in deuterium oxide containing sodium deuteroxide, with DSS as internal standard. Signals in the ^1H NMR spectra were assigned to protons on the basis of chemical shifts, observed multiplicities and homonuclear 2D-COSY experiments. Chemical shifts and coupling constants were obtained by a first-order analysis of spectra. The exchange of hydroxy protons for deuterium was carried out by addition of several drops of tetradeuterioacetic acid. Assignments of signals in ^{13}C NMR spectra were accomplished on the basis of *J*-modulated spectra (APT) enabling to discriminate between C, CH, CH_2 and CH_3 signals, characteristic chemical shifts and in some cases confirmed by ^1H, ^{13}C-correlated HMQC spectra. Pyridinium *p*-toluenesulfonate (PTS) was prepared according to Miyashita et al.,[44] and *m*-chloroperoxybenzoic acid containing a 95% active species was prepared according to Schwartz and Blumbergs.[45] 1-(2,5-Dideoxy-β-D-*glycero*-pent-4-enofuranosyl)-thymine (**9a**) was repeatedly prepared according to Ref. 27 in 70–80% yields. 1-(3-*O*-*tert*-Butyldimethylsilyl-2,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)thymine (**9b**), described without experimental details by Reese,[30] was prepared in repeated yields of 70–75% by silylation of **9a** using the procedure provided for 9-(3-*O*-*tert*-butyldimethylsilyl-2,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)adenine.[27]

4.2. Deblocking of the fully protected phosphonate derivatives—general procedures

(a) Removal of phosphorus protecting groups: The phosphonate diesters **11**–**17**, **20a** and the deacylated (by 16 h treatment with satd ammonia in methanol) **18** in dry acetonitrile (10 mL $mmol^{-1}$) were treated with 2,6-lutidine (2-fold molar equivalent of trimethylbromosilane), and then trimethylbromosilane (6 M equiv per mmol of diester) was added dropwise under stirring at rt. The mixture was stirred overnight (TLC in IPAW and H1), then evaporated in the presence of triethylamine (1.5 equiv of bromotrimethylsilane), and the residue was co-evaporated with 5% triethylamine in acetonitrile.

(b) Removal of silyl protecting groups: The residue obtained in (a) was treated with 0.5 M TBAF in tetrahydrofuran (5 equiv, based on starting phosphonate diester) at rt

overnight (TLC in IPAW; completion of reaction was checked by electrophoretic comparison with AMP or UMP as reference). The solvent was evaporated with several drops of triethylamine.

(c) Anion exchange chromatography: The products from (b) containing crude free phosphonic acids **21**–**25** were applied onto a column of DEAE-Sephadex A25 (16×200 mm), the column was washed with water (150 mL), and then a gradient elution with aq triethylammonium hydrogen carbonate (0–0.2 M, 2×1000 mL) was applied. Fractions (10 mL) containing the product were pooled and evaporated repeatedly with several drops of triethylamine, and finally co-evaporated three times with 1% triethylamine–methanol. In cases when TLC checking of the residue (IPAW) showed, on gentle heating of the eluted TLC sheet, the presence of a carbonized by-product not detectable in UV light, the anion exchange chromatography was repeated with somewhat slower elution to remove it.

(d) Reversed-phase chromatography: The free phosphonic acids from (c) were subjected to preparative chromatography on octadecyl silica column (25×300 mm, 20–40 μm, IOCB Prague); compounds were eluted with a linear gradient of methanol in water at a rate of 10 mL min^{-1}. Fractions with product were evaporated.

(e) Adjustment of phosphonic acids **21**–**25**: The pure phosphonic acids from (d) were converted into the sodium salt by passing through a Dowex 50 (Na^+) column. Final adjustment was made by lyophilization of the compound from water and drying over phosphorus pentoxide in vacuo.

4.2.1. 3′-*O*-*tert*-Butyldiphenylsilyl-2′-deoxyadenosine (7a). 5′-*O*-Dimethoxytrityl-3′-*O*-*tert*-butyldiphenylsilyl-2′-deoxyadenosine[40] (39.6 g, 50 mmol) was treated with 80% aq acetic acid (400 mL) for 4 h at rt, the solution was evaporated to dryness, and the residue was chromatographed on silica gel using gradient elution from A to 8:92 A–B (where A=ethyl acetate, B=ethyl acetate–H3 9:1). Obtained: 21.82 g (44.5 mmol, 89%) of **7a** as an amorphous solid. ^{1}H NMR (DMSO): 8.09 and 8.29 (2×s, 2×1H, H-2 and H-8), 7.43–7.51 m, 6H and 7.64 m, 4H (2×C_6H_5), 5.30 (dd, 1H, $J_{OH,5'}$=7.0, $J_{OH,5''}$=4.7 Hz, OH), 6.45 (dd, 1H, $J_{1',2''}$=5.8, $J_{1',2'}$=8.8 Hz, H-1′), 4.57 (dt, 1H, $J_{3',2''}$=1.8, $J_{3',2'}$=5.3, $J_{3',4'}$=1.6 Hz, H-3′), 4.02 (ddd, 1H, $J_{4',3'}$=1.6, $J_{4',5'}$=3.8, $J_{4',5''}$=4.3 Hz, H-4′), 3.43 (ddd, 1H, $J_{5'',4'}$=4.3, $J_{5'',5'}$=12.0, $J_{5'',OH}$=4.7 Hz, H-5″), 3.18 (ddd, 1H, $J_{5',4'}$=3.8, $J_{5',5''}$=12.0, $J_{5',OH}$=7.0 Hz, H-5′), 2.68 (ddd, 1H, $J_{2',1'}$=8.8, $J_{2',2''}$=13.2, $J_{2',3'}$=5.3 Hz, H-2′), 2.29 (ddd, 1H, $J_{2'',1'}$=5.8, $J_{2'',2'}$=13.2, $J_{2'',3'}$=1.8 Hz, H-2″), 1.07 (s, 9H, *t*-Bu). ^{13}C NMR (DMSO): 156.30 (C-6), 152.48 (C-2), 148.98 (C-4), 139.75 (C-8), 128.12 (4), 130.21 (2), 133.11 (2) and 135.45 (4) (2×C_6H_5), 119.47 (C-5), 88.43 (C-1′), 84.36 (C-4′), 74.52 (C-3′), 61.74 (C-5′), ~39.7 (C-2′, overlapped with DMSO), 18.83 and 26.92 (*t*-Bu). HRMS FAB+ calcd for $C_{26}H_{32}N_5O_3Si$ $(M+H)^+$ 490.2274, found 490.2260.

4.2.2. 5′-Bromo-3′-*O*-*tert*-butyldiphenylsilyl-2′,5′-dideoxyadenosine (8a). Method A: 6-*N*-benzoyl-3′-*O*-*tert*-butyldiphenylsilyl-2′-deoxyadenosine[39] (10.7 g, 18.1 mmol) in dioxane (130 mL) was treated with triphenyl phosphine (5.3 g, 19.9 mmol) and tetrabromomethane (5.1 g, 15.4 mmol) at rt for 4 d (after 2 d, half portions of both reagents were added). The reaction mixture was quenched by methanol (1 mL), the solution was concentrated in vacuo to one third, diluted with ethyl acetate (300 mL), and the organic layer was washed with satd aq sodium hydrogen carbonate (3×100 mL), dried over Na_2SO_4 and evaporated. Gradient chromatography of the residue on silica gel (0–10% of acetone in toluene) afforded 5.4 g (8.2 mmol, 45%) of 6-*N*-benzoyl-5′-bromo-3′-*O*-*tert*-butyldiphenylsilyl-2′,5″-dideoxyadenosine as TLC-pure compound, which was used for further reaction without characterization. It was treated with satd (0 °C) ammonia in anhydrous methanol (150 mL) at rt for 48 h, the solvent was evaporated, and the residue chromatographed on silica gel in chloroform–ethanol (0–10%). Yield: 1.4 g (2.5 mmol, 31%) of **8a** as a solid.

Method B: 3′-*O*-*tert*-butyldiphenylsilyl-2′-deoxyadenosine (**7a**) (21.8 g, 44.5 mmol) was brominated with triphenyl phosphine and tetrabromomethane in the same manner as described for *N*-benzoyl derivative in Method A, and the product was chromatographed on silica gel (0–10% ethanol in chloroform). Yield: 11.81 g (21.4 mmol, 48%) of crystalline **8a** (crystallized from ethanol). Mp 172 °C (decomp.). For $C_{26}H_{30}N_5O_2SiBr$ calcd C 56.52%, H 5.47%, N 12.67%, Br 14.46%; found C 56.54%, H 5.67%, N 12.34%, Br 14.79%. IR spectrum (KBr): ν_{max} (cm^{-1}) 3300 (s), 3280 (s, sh), 3246 (s), 3160 (s, br), 3133 (s), 3121 (s) and 1643 all NH_2; 3075 (s) =C–H; 1605 (vs), 1574 (s), 1514 (w), 1472 (m), 1370 (m) and 1335 (s) all adenine ring; 1302 (s), 1252 (m), 1237 (m), 1216 (m), 1050 (vs), 1035 (m, sh), 824 (m), 797 (m) and 724 (m) all adenine; 1472 (m), 1391 (w) and 1363 (w, sh) all CH_3 from TBDPS; 1426 (s), 1112 (vs), 1105 (s), 995 (m), 744 (m), 701 (vs), 692 (s), 622 (m), 616 (m), 504 (s) and 490 (m) all ring from TBDPS; 1078 (m, sh) COSi; 648 (w, sh) and 606 (w, sh) all C–Br. ^{1}H NMR (DMSO): 8.29 and 8.12 (2×s, 2×1H, H-2 and H-8), 7.66 m, 4H and 7.50 m, 6H (2×C_6H_5), 7.30 (br s, 2H, NH_2), 6.49 (dd, 1H, $J_{1',2''}$=6.1, $J_{1',2'}$=8.3 Hz, H-1′), 4.63 (dt, 1H, $J_{3',2''}$=2.4, $J_{3',4'}$=2.0, $J_{3',2'}$=5.4 Hz, H-3′), 4.17 (td, 1H, $J_{4',3'}$=2.0, $J_{4',5'}$=6.8, $J_{4',5''}$=6.1 Hz, H-4′), 3.49 (dd, 1H, $J_{5',4'}$=6.8, $J_{5',5''}$=10.5 Hz, H-5′), 3.42 (dd, 1H, $J_{5'',4'}$=6.1, $J_{5'',5'}$=10.5 Hz, H-5″), 2.95 (ddd, 1H, $J_{2',3'}$=5.4, $J_{2',1'}$=8.3, $J_{2',2''}$=13.7 Hz, H-2′), 2.36 (ddd, 1H, $J_{2'',3'}$=2.4, $J_{2'',1'}$=6.1, $J_{2'',2'}$=13.7 Hz, H-2″), 1.08 s, 9H, *t*-Bu. HRMS FAB+ calcd for $C_{26}H_{31}BrN_5O_2Si$ $(M+H)^+$ 552.1430, found 552.1492.

4.2.3. 5′-Bromo-3′-*O*-*tert*-butyldiphenylsilyl-2′,5′-dideoxycytidine (8b). 3′-*O*-*tert*-Butyldiphenylsilyl-2′-deoxycytidine (**7b**): 4-*N*-benzoyl-2′-deoxy-5′-*O*-dimethoxytrityl-cytidine (15.8 g, 25 mmol) and dried imidazole (3.4 g, 50 mmol) in pyridine (100 mL) were treated with *tert*-butylchlorodiphenylsilane (8.25 g, 30 mmol) at rt for 16 h (TLC in 50% ethyl acetate–toluene). The reaction was quenched with methanol (2 mL) and the solution was evaporated. The solution of the residue in ethyl acetate (300 mL) was washed with satd aq sodium hydrogen carbonate (3×100 mL), dried (Na_2SO_4) and evaporated. The residue was treated with satd (0 °C) ammonia in anhydrous methanol (300 mL) in a stoppered vessel at rt for 16 h, and the solvent was carefully evaporated. The residue was co-evaporated with toluene (2×100 mL), treated with 80% aq acetic acid (300 mL) at rt for 1 h to remove the dimethoxytrityl

group, and the solution concentrated to dryness. Gradient chromatography of the residue on silica gel (0–10% of ethanol in chloroform) afforded a TLC-pure silyl derivative **7b** (8.7 g, 18.7 mmol, 75%), which was used without characterization for subsequent reactions.

Bromination: Compound **7b** (1.9 g, 4.08 mmol) was treated with triphenyl phosphine (1.31 g, 5 mmol) and tetrabromomethane (1.72 g, 5.2 mmol) in dioxane (40 mL) at rt for 16 h. The reaction was quenched with methanol (0.5 mL), the solution concentrated in vacuo, then ethyl acetate (100 mL) was added, and the organic layer was washed with satd aq sodium hydrogen carbonate (3×60 mL), dried over Na_2SO_4 and evaporated. Gradient chromatography of the residue on silica gel (0–10% of ethanol in chloroform) afforded TLC-pure title compound **8b** (1.43 g, 2.7 mmol, 66%) as an amorphous solid. ^{1}H NMR (DMSO): 7.62 m, 4H and 7.48 m, 6H (2×C_6H_5), 7.53 (d, 1H, $J_{6,5}$=7.6 Hz, H-6); 7.22 and 7.19 (2×br s, 2×1H, NH_2), 6.35 (dd, 1H, $J_{1',2''}$=5.6, $J_{1',2'}$=8.8 Hz, H-1′), 5.71 (d, 1H, $J_{5,6}$=7.6 Hz, H-5), 4.35 (dt, 1H, $J_{3',2''}$=2.2, $J_{3',4'}$=2.0, $J_{3',2'}$=5.4 Hz, H-3′), 4.08 (td, 1H, $J_{4',3'}$=2.0, $J_{4',5'}$=6.2, $J_{4',5''}$=5.6 Hz, H-4′), 3.37 (dd, 1H, $J_{5',4'}$=6.2, $J_{5',5''}$=10.7 Hz, H-5′), 3.31 (dd, 1H, $J_{5'',4'}$=5.6, $J_{5'',5'}$=10.7 Hz, H-5″), 2.13 (ddd, 1H, $J_{2'',3'}$=2.2, $J_{2'',1'}$=5.6, $J_{2'',2'}$=13.7 Hz, H-2″), 2.03 (ddd, 1H, $J_{2',3'}$=5.4, $J_{2',1'}$=8.8, $J_{2',2''}$=13.7 Hz, H-2′), 1.05 (s, 9H, *t*-Bu). HRMS FAB+ calcd for $C_{25}H_{31}BrN_3O_3Si$ $(M+H)^+$ 528.1318, found 528.1313.

4.2.4. 1-(3-*O*-*tert*-Butyldiphenylsilyl-2,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)thymine (9c). To a solution of compound **9a**[27] (2.24 g, 10 mmol) and imidazole (6.15 g, 90 mmol) in dimethylformamide (20 mL), *tert*-butyldiphenylsilyl chloride (10.24 mL, 40 mmol) was gradually added and the whole was stirred at rt overnight. On checking the end of reaction by TLC (in C2 and T1), methanol (2 mL) was added and the stirring continued for 1 h. The mixture was then diluted with ethyl acetate (200 mL) and washed with a satd solution of sodium hydrogen carbonate (270 mL). The organic phase was separated and the aqueous layer washed with ethyl acetate (2×100 mL). The pooled extracts were washed with a satd solution of NaCl (80 mL), dried over anhydrous $MgSO_4$ and evaporated. The resulting mixture was chromatographed on a silica gel column (120 g) with chloroform as an eluent. Yield: 3.63 g (79%) of product **9c** in the form of a solid foam, R_f=0.87 (C2). For $C_{26}H_{30}N_2O_4Si$ (462.61) calcd 67.65% C, 6.54% H, 6.06% N; found, 68.02% C, 6.66% H, 5.73% N. MS (FAB): 463.4 $(M+H)^+$. ^{1}H NMR (DMSO): 11.40 (br s, 1H, NH), 7.64 and 7.45–7.50 (2×m, 4H and 6H, 2×C_6H_5), 7.38 (q, 1H, J_{6,CH_3} = 1.2 Hz, H-6), 6.47 (br t, 1H, $J_{1',2'}$=6.7 Hz, H-1′), 4.83 (dd, 1H, $J_{3',2''}$=2.9, $J_{3',2'}$=6.3 Hz, H-3′), 4.23 (br d, 1H, $J_{5',5''}$=2.0 Hz, H-5′), 3.72 (d, 1H, $J_{5'',5'}$=2.0 Hz, H-5″), 2.36 (ddd, 1H, $J_{2',1'}$=7.1, $J_{2',3'}$=6.3, $J_{2',2''}$=13.7 Hz, H-2′), 2.27 (ddd, 1H, $J_{2'',1'}$=6.3, $J_{2'',3'}$=2.9, $J_{2'',2'}$=13.7 Hz, H-2″), 1.76 (d, 3H, $J_{CH_3,6}$ = 1.2 Hz, CH_3), 1.03 (s, 9H, *t*-Bu).

4.2.5. 1-(3-*O*-*tert*-Butyldimethylsilyl-2,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)uracil (9e). Compound **9d**[27] (3.99 g, 16.75 mmol) was co-evaporated with pyridine, then pyridine (120 mL) and imidazole (3.42 g, 50.3 mmol, 3 equiv) were added followed by *tert*-butyldimethylchlorosilane (3.03 g, 20.1 mmol, 1.2 equiv), and the whole was left to react at rt overnight. On TLC checking (C1), additional 0.2 equiv of both *tert*-butyldimethylchlorosilane and imidazole were added to complete the reaction (8 h). Abs methanol was then added (0.5 mL) and after 30 min, the solvent was evaporated, the residue co-evaporated with toluene, and partitioned between chloroform (2×150 mL) and satd aq sodium hydrogen carbonate (150 mL). The organic layer was dried with $MgSO_4$, the solvent evaporated and the residue chromatographed on silica using a gradient of 0–3.5% ethanol in chloroform. Yield: 3.53 g (65%) of **9e** as a foam. IR spectrum (KBr): ν_{max} (cm^{-1}) 3117 (w) NH; 1688 (vs) C=O; 1472 (w, sh), 1463 (w), 1388 (m), 1363 (w), 1268 (m), 1253 (w, sh) and 837 (m) all CH_3 from TBDMS; 1418 (w) ring; 873 (w) =CH_2; 764 (w, sh) =CH. ^{1}H NMR (DMSO): 11.41 (br s, 1H, NH), 7.57 (d, 1H, $J_{6,5}$=8.2 Hz, H-6), 6.34 (dd, 1H, $J_{1',2'}$=5.9, $J_{1',2''}$=7.0 Hz, H-1′), 5.65 (d, 1H, $J_{5,6}$=8.2 Hz, H-5), 4.91 (m, 1H, H-3′), 4.34 (dd, 1H, $J_{5',3'}$=1.2, $J_{5',5''}$=1.8 Hz, H-5′), 4.10 (dd, 1H, $J_{5'',3'}$=1.2, $J_{5'',5'}$=1.8 Hz, H-5″), 2.49 (ddd, 1H, $J_{2',1'}$=5.9, $J_{2',3'}$=6.8, $J_{2',2''}$=13.7 Hz, H-2′), 2.21 (ddd, 1H, $J_{2'',3'}$=4.2, $J_{2'',1'}$=7.0, $J_{2'',2'}$=13.7 Hz, H-2″), 0.88 (s, 9H, *t*-Bu), 0.12 and 0.11 (2×s, 2×3H, $Si(CH_3)_2$). ^{13}C NMR (DMSO): 164.60 (C-4), 163.98 (C-4′), 150.58 (C-2), 141.29 (C-6), 102.59 (C-5), 86.07 (C-1′), 83.51 (C-5′), 70.66 (C-3′), 37.16 (C-2′), 25.86 (3×CH_3 (*t*-Bu)), 17.99 (>C<(*t*-Bu)), −4.60 ($Si(CH_3)_2$). HRMS FAB+ calcd for $C_{15}H_{25}N_2O_4Si$ $(M+H)^+$ 325.1584, found 325.1571.

4.2.6. 9-(3-*O*-*tert*-Butyldiphenylsilyl-2,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)adenine (9f). Using the procedure described for preparation of **9g**, the deoxyadenosine compound was prepared from **8a** (3.0 g, 5.44 mmol) in DMF (30 mL) by treatment with DBU (4 equiv) for 4 d (checked by HPLC). Work-up and column chromatography on silica gel using gradient elution from A to 8:92 A–B (where A=ethyl acetate, B=ethyl acetate–H3 9:1) afforded 1.41 g (2.99 mmol, 55%) of **9f** as a solid foam. IR spectrum (KBr): ν_{max} (cm^{-1}) 3421 (s, br), 3358 (s), 3310 (s) and 3161 (s) all NH_2, H_2O, OH; 3074 (m) =C–H; 1641 (s) NH_2; 1604 (vs), 1573 (s), 1511 (w), 1472 (m), 1371 (m) and 1333 all adenine ring; 1303 (m) adenine; 1076 (s); 1472 (m) and 1391 (w, sh) all CH_3; 1427 (s), 1113 (s), 999 (w, sh), 743 (m), 703 (vs), 693 (m, sh), 617 (m), 505 (s) and 482 (m) all arom. ring of TBDPS. ^{1}H NMR (DMSO): 8.26 and 8.03 (2×s, 2×1H, H-2 and H-8), 7.68 and 7.47 (2×m, 4H and 6H, 2×C_6H_5), 7.32 (br s, 2H, NH_2), 6.64 (dd, 1H, $J_{1',2'}$=6.2, $J_{1',2''}$=6.8 Hz, H-1′), 5.25 (m, 1H, H-3′), 4.20 (dd, 1H, $J_{5',3'}$=1.5, $J_{5',5''}$=1.8 Hz, H-5′), 3.80 (dd, 1H, $J_{5'',3'}$=1.0, $J_{5'',5'}$=1.8 Hz, H-5″), 2.90 (dt, 1H, $J_{2',1'}$= 6.2, $J_{2',3'}$=6.4, $J_{2',2''}$=13.2 Hz, H-2′), 2.51 (ddd, 1H, $J_{2'',3'}$= 4.4, $J_{2'',1'}$=6.8, $J_{2'',2'}$=13.2 Hz, H-2″), 1.08 (s, 9H, *t*-Bu). ^{13}C NMR (DMSO): 162.69 (C-4′), 156.31 (C-6), 152.86 (C-2), 149.06 (C-4), 140.21 (C-8), 135.66(2), 135.65(2), 133.04, 132.96, 130.34, 130.31, 128.19(2) and 128.11(2) (2×C_6H_5), 119.45 (C-5), 84.09 (C-1′), 83.57 (C-5′), 71.82 (C-3′), 37.95 (C-2′), 26.98 (3×CH_3 (*t*-Bu)), 19.01 (>C<(*t*-Bu)), −4.60 ($Si(CH_3)_2$). HRMS FAB+ calcd for $C_{26}H_{30}N_5O_2Si$ $(M+H)^+$ 472.2169, found 472.2207.

4.2.7. 1-(3-*O*-*tert*-Butyldiphenylsilyl-2,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)cytosine (9g). To the 5′-bromo compound **8b** (1.13 g, 2.14 mmol) in dry DMF (23 mL), DBU (1.28 mL, 8.55 mmol, 4 equiv) was added and the whole was stirred at rt for 4 d (HPLC) until

completion. Solvent was evaporated in vacuo at 45 °C and the chloroform solution (100 mL) of the residue was washed with 5% aq citric acid (2×100 mL). The chloroform layer was washed with 0.5 M aq triethylammonium hydrogen carbonate (100 mL), separated, dried ($MgSO_4$) and evaporated. Chromatography of the residue on silica gel using a gradient elution with 0–7% ethanol in chloroform afforded 0.641 g (67%) of **9g** as an amorphous solid. IR spectrum (KBr): ν_{max} (cm^{-1}) 3412 (w, br) and 3177 (w, br) all NH_2; 3072 (w) and 3051 (w) =C–H; 1647 (vs) NH_2 and C=O; 1610 (m) C=C; 1525 (w) and 1404 (w) all cytosine ring; 1280 (w) C–N; 823 (w), 856 (w), 788 (w), 1473 (m, sh), 1465 (w, sh), 1393 (w) and 1362 (w) all CH_3; 1428 (m), 1113 (s), 1105 (m, sh), 1029 (m), 999 (w), 742 (w), 703 (m), 615 (w), 507 (w) and 491 (w) all arom. ring of TBDPS; 1080 (m) COSi. ^{1}H NMR (DMSO): 7.65 and 7.50 (2×m, 4H and 6H, 2×C_6H_5), 7.39 (d, 1H, $J_{6,5}$=7.4 Hz, H-6), 7.26 and 7.23 (2×br s, 2×1H, NH_2), 6.47 (t, 1H, $J_{1',2''}$=6.6, $J_{1',2'}$=6.6 Hz, H-1′), 5.69 (d, 1H, $J_{5,6}$=7.4 Hz, H-5), 4.84 (br dd, 1H, $J_{3',2''}$=3.4, $J_{3',2'}$=6.0 Hz, H-3′), 4.22 (br d, 1H, $J_{5',3'}$=1.0, $J_{5',5''}$=1.7 Hz, H-5′), 3.73 (br d, 1H, $J_{5'',3'}$=1.0, $J_{5'',5'}$=1.7 Hz, H-5″), 2.26 (ddd, 1H, $J_{2'',3'}$=3.4, $J_{2'',1'}$=6.6, $J_{2'',2'}$=13.6 Hz, H-2″), 2.19 (dt, 1H, $J_{2',1'}$=$J_{2',3'}$=6.3, $J_{2',2''}$= 13.6 Hz, H-2′), 1.04 (s, 9H, *t*-Bu). ^{13}C NMR (DMSO): 165.82 (C-4), 162.84 (C-4′), 154.91 (C-2), 141.56 (C-6), 94.96 (C-5), 135.60(4), 133.01, 132.95, 130.36, 130.30, 128.22(2) and 128.11(2) (2×C_6H_5), 86.87 (C-1′), 83.76 (C-5′), 72.04 (C-3′), 39.17 (C-2′), 26.92 (3×CH_3 (*t*-Bu)), 18.94 (>C< (*t*-Bu)). HRMS FAB+ calcd for $C_{25}H_{30}N_3O_3Si$ $(M+H)^+$ 448.2056, found 448.2005.

4.2.8. 9-(2,5-Dideoxy-β-D-*glycero*-pent-4-enofuranosyl)-2-*N*-isobutyrylguanine (9h). 2′,5′-Dideoxy-5′-iodo-2-*N*-isobutyrylguanosine (**8c**): Iodine (7.61 g, 60 mmol) was added at 0 °C to a stirred mixture of 2′-deoxy-2-*N*-isobutyrylguanosine (16.87 g, 50 mmol), triphenyl phosphine (15.74 g, 60 mmol) and pyridine (5 mL) in DMF (200 mL), and the reaction mixture was further stirred at rt for 16 h. Water (10 mL) was added and the mixture was concentrated in vacuo. The residue was shortly refluxed in methanol (200 mL), silica gel (100 g) was added and methanol was removed in vacuo. Silica gel with adsorbed compound was applied on a dry column of silica gel (300 g) and the compound was eluted using a linear gradient of H1 in ethyl acetate. The obtained TLC- and HPLC-pure **8c** (17.9 g, 40%) was used for further reactions without characterization.

Elimination reaction: Compound **8c** (6.96 g, 15.56 mmol) in DMF (15 mL) was treated with potassium *tert*-butoxide (2.34 g, 20.9 mmol; in 8 mL of DMF) under stirring at 0 °C for 5 min, and then the reaction was quenched by adding Dowex 50 $(Et_3N)^+$ in 50% aq ethanol. The pooled washings were evaporated, and the residue was submitted to a short column of Dowex 1X8 $(HCO_3)^-$. The bound product was released from the resin by washing with a 30:70 mixture of 1 M aq triethylammonium hydrogen carbonate–ethanol, the washings were concentrated, and the aq solution of the residue was applied onto preparative reversed-phase column. Elution with water afforded the traces of starting product while 10% aq methanol eluted the title product. Yield of the amorphous solid **9h**: 1.59 g (4.98 mmol, 32%). IR spectrum (KBr): ν_{max} (cm^{-1}) 3500 (m, br, sh) OH, 3454 (s, br) H_2O, 3227 (w, br) NH, 1721 (m, br, sh) C=O, 1608 (s), 1563 (m), 1402 (w) and 1391 (w) all ring; 1688 (vs) amide I, 1538 (w, sh) amide II, 1102 (m) and 1054 (w) all C–OH. ^{1}H NMR (DMSO): 12.10 (br s, 1H, NH), 11.65 (br s, 1H, NH), 8.21 (s, 1H, H-8), 6.46 (dd, 1H, $J_{1',2'}$=6.2, $J_{1',2''}$= 6.6 Hz, H-1′), 5.63 (d, 1H, $J_{OH,3'}$=4.9 Hz, OH), 4.93 (m, 1H, H-3′), 4.27 (t, 1H, $J_{5',3'}$=1.5, $J_{5',5''}$=1.5 Hz, H-5′), 4.17 (t, 1H, $J_{5'',3'}$=1.5, $J_{5'',5'}$=1.5 Hz, H-5″), 2.87 (dt, 1H, $J_{2',1'}$= $J_{2',3'}$=6.3, $J_{2',2''}$=13.4 Hz, H-2′), 2.73 (sept, 1H, J=6.8 Hz, CH), 2.40 (ddd, 1H, $J_{2'',3'}$=4.9, $J_{2'',1'}$=6.6, $J_{2'',2'}$=13.4 Hz, H-2″), 1.12 (d, 6H, J=6.8 Hz, CH_3). HRMS FAB+ calcd for $C_{14}H_{18}N_5O_4$ $(M+H)^+$ 320.1357, found 320.2005.

4.2.9. 9-(3-*O*-*tert*-Butyldimethylsilyl-2,5-dideoxy-β-D-*glycero*-pent-4-eno-furanosyl)-2-*N*-isobutyrylguanine (9i). Compound **9h** (1.58 g, 4.95 mmol) was co-evaporated with pyridine and silylated with *tert*-butyldimethylchlorosilane in pyridine in the presence of imidazole in the same manner as described for **9e**. Chromatography on silica gel using a gradient of 0–8% ethanol in chloroform yielded 1.51 g (3.48 mmol, 70%) of **9i** as an amorphous solid. ^{1}H NMR (DMSO): 12.12 (s, 1H, NH), 11.67 (s, 1H, NH), 8.26 (s, 1H, H-8), 6.45 (t, 1H, $J_{1',2'}$=6.4, $J_{1',2''}$=6.4 Hz, H-1′), 5.02 (ddt, 1H, $J_{3',5'}$=1.0, $J_{3',5''}$=1.0, $J_{3',2''}$=4.2, $J_{3',2'}$=6.2 Hz, H-3′), 4.31 (dd, 1H, $J_{5',3'}$=1.0, $J_{5',5''}$=2.0 Hz, H-5′), 4.13 (dd, 1H, $J_{5'',3'}$=1.0, $J_{5'',5'}$=2.0 Hz, H-5″), 2.93 (dt, 1H, $J_{2',1'}$= 6.4, $J_{2',3'}$=6.2, $J_{2',2''}$=13.6 Hz, H-2′), 2.77 (sept, 1H, J=6.8 Hz, CH), 2.44 (ddd, 1H, $J_{2'',3'}$=4.2, $J_{2'',1'}$=6.4, $J_{2'',2'}$=13.6 Hz, H-2″), 1.125 and 1.12 (2×d, 2×3H, J=6.8 Hz, 2×CH_3), 0.90 (s, 9H, *t*-Bu), 0.16 and 0.15 (2×s, 2×3H, $Si(CH_3)_2$).

^{13}C NMR (DMSO): 180.50 (C=O (^{i}Bu)), 162.91 (C-4′), 155.02 (C-6), 148.93 (C-4), 141.84 (C-2), 137.75 (C-8), 120.64 (C-5), 83.83 (C-5′), 83.22 (C-1′), 70.65 (C-3′), 38.41 (C-2′), 25.94 (3×CH_3 (*t*-Bu)), 17.92 (>C< (*t*-Bu)), −4.59 and −4.57 ($Si(CH_3)_2$). HRMS FAB+ calcd for $C_{20}H_{32}N_5O_4Si$ $(M+H)^+$ 434.2224, found 434.2188.

4.2.10. Diisopropyl-(1-thymin-1-yl-1,2,5-trideoxy-α-L-*threo*-pentofuranos-4-yloxy)methylphosphonate (11a) and diisopropyl-(1-thymin-1-yl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxy)methylphosphonate (11b). To a solution of compound **9a** (436 mg, 1.946 mmol; co-evaporated with dioxane–dichloromethane) in dry dichloromethane (20 mL), **10b** (1.144 g, 5.838 mmol) was added and then, under stirring, PTS (1.465 g, 5.838 mmol). The whole was stirred at rt for 3 h (TLC in C2 and E1). The mixture was then diluted with dichloromethane (50 mL) and washed with water (50 mL). The aqueous layer was extracted with dichloromethane (3×30 mL), and the pooled organic washings were dried with Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column (50 g) using a 0–5% chloroform–ethanol gradient. Overall yield of the obtained isomers **11a** and **11b**, 290 mg (35%) as colourless sirups; ca. 1:5 weight ratio. HRMS FAB+ calcd for $C_{17}H_{30}N_2O_8P$ $(M+H)^+$ 421.1740, found 421.1755.

Isomer **11a**: 48 mg, R_f=0.17 in C2. ^{1}H NMR (DMSO): 11.35 (br s, 1H, NH), 7.50 (br q, 1H, J=1.0 Hz, H-6), 6.48 (dd, 1H, $J_{1',2'}$=9.0, $J_{1',2''}$=6.3 Hz, H-1′), 5.62 (d, 1H, $J_{OH,3'}$=4.9 Hz, 3′-OH), 4.63 (m, 2H, 2×P–OCH), 4.01 (br t, 1H, H-3′), 3.74 (dd, 1H, $J_{P,CHa}$=11.5, J_{gem}=12.9 Hz, P–CHa), 3.62 (dd, 1H, $J_{P,CHb}$=10.7, J_{gem}=12.9 Hz, P–CHb), 2.26 (ddd, 1H,

$J_{2',1'}$=9.0, $J_{2',3'}$=4.4, $J_{2',2''}$=13.4 Hz, H-2′), 2.11 (br dd, 1H, $J_{2'',1'}$=6.3, $J_{2'',3'}$=1.0, $J_{2'',2'}$=13.4 Hz, H-2″), 1.87 (d, 3H, J=1.0 Hz, CH_3), 1.26, 1.25 and 1.23 (3×d, 6H, 3H and 3H, J=6.1 Hz, 4×CH_3), 1.36 (s, 3H, CH_3). ^{13}C NMR (DMSO): 163.86 (C-4), 151.01 (C-2), 135.59 (C-6), 111.48 (d, $J_{C,P}$=13.7 Hz, C-4′), 111.18 (C-5), 84.33 (C-1′), 75.17 (C-3′), 70.77 and 70.61 (2×d, $J_{C,P}$=6.8 Hz, 2×P–OCH), 56.21 (d, $J_{C,P}$=172.9 Hz, P–C), 37.52 (C-2′), 23.96 (d, 2C, $J_{C,P}$=3.9 Hz, 2×CH_3), 23.86 and 23.83 (2×d, $J_{C,P}$=4.9 Hz, 2×CH_3), 16.37 (CH_3), 11.86 (CH_3).

Isomer **11b**: 242 mg, R_f=0.22 in C2. ^{1}H NMR (DMSO): 11.30 (br s, 1H, NH), 7.36 (br q, 1H, J=1.0 Hz, H-6), 6.11 (dd, 1H, $J_{1',2''}$=8.5, $J_{1',2'}$=2.9 Hz, H-1′), 5.11 (d, 1H, $J_{OH,3'}$=6.1 Hz, 3′-OH), 4.65 and 4.63 (2×d sept, 2×1H, $J_{H,H}$=6.1, $J_{P,OCH}$=7.6 Hz, 2×P–OCH), 4.29 (br td, 1H, $J_{3',2''}$=9.5, $J_{3',2'}$=8.8, $J_{3',OH}$=6.1 Hz, H-3′), 3.74 (dd, 1H, $J_{P,CHa}$=12.2, J_{gem}=13.4 Hz, P–CHa), 3.67 (dd, 1H, $J_{P,CHb}$=8.3, J_{gem}=13.4 Hz, P–CHb), 2.23 (ddd, 1H, $J_{2'',1'}$=8.5, $J_{2'',3'}$=9.5, $J_{2'',2'}$=13.2 Hz, H-2″), 2.13 (ddd, 1H, $J_{2',1'}$=2.9, $J_{2',3'}$=8.8, $J_{2',2''}$=13.2 Hz, H-2′), 1.80 (d, 3H, J=1.0 Hz, CH_3), 1.27 (d, 12H, J=6.1 Hz, 4×CH_3), 1.41 (s, 3H, CH_3). ^{13}C NMR (DMSO): 163.96 (C-4), 150.48 (C-2), 136.58 (C-6), 110.39 (C-5), 106.18 (d, $J_{C,P}$=11.7 Hz, C-4′), 81.79 (C-1′), 74.27 (C-3′), 70.50 and 70.45 (2×d, $J_{C,P}$=6.8 Hz, 2×P–OCH), 55.80 (d, $J_{C,P}$=170.9 Hz, P–C), 36.23 (C-2′), 24.03, 24.00, 23.93 and 23.88 (4×d, $J_{C,P}$=4.9 Hz, 4×CH_3), 18.49 (CH_3), 12.20 (CH_3).

4.2.11. Diisopropyl-(3-*O*-*tert*-butyldimethylsilyl-1-thymin-1-yl-1,2,5-trideoxy-α-L-*threo*-pentofuranos-4-yloxy)methylphosphonate (12a) and diisopropyl-(3-*O*-*tert*-butyldimethylsilyl-1-thymin-1-yl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxy)methylphosphonate (12b). Compound **9b** (100 mg, 0.296 mmol), co-evaporated with dioxane–dichloromethane, was dissolved in dichloromethane (5 mL). Compound **10b** (175 mg, 0.888 mmol) was added and then, under stirring, PTS (223 mg, 0.888 mmol). The mixture was stirred for 4 h (TLC in C2 and T1) and then partitioned between dichloromethane (40 mL) and water (40 mL). Aqueous layer was extracted with dichloromethane (3×30 mL), the organic washings were combined, dried with Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column (40 g) using a 0–2.5% ethanol–chloroform gradient. Combined yield of isomers **12a** and **12b** (in 1:1.25 ratio), 81 mg (51%); solid foams. HRMS FAB+ calcd for $C_{23}H_{44}N_2O_8PSi$ $(M+H)^+$ 535.2604, found 535.2626. Isomer **12a**: 36 mg, R_f=0.27 in C2. ^{1}H NMR (DMSO): 11.37 (br s, 1H, NH), 7.50 (br s, 1H, H-6), 6.43 (dd, 1H, $J_{1',2'}$=9.0, $J_{1',2''}$=6.1 Hz, H-1′), 4.63 (m, 2H, 2×P–OCH), 4.18 (br d, 1H, $J_{3',2'}$=4.2, $J_{3',2''}$=1.0 Hz, H-3′), 3.78 (dd, 1H, $J_{P,CHa}$=11.5, J_{gem}=12.9 Hz, P–CHa), 3.64 (dd, 1H, $J_{P,CHb}$=11.0, J_{gem}=12.9 Hz, P–CHb), 2.32 (ddd, 1H, $J_{2',1'}$=9.0, $J_{2',3'}$=4.2, $J_{2',2''}$=13.4 Hz, H-2′), 2.08 (br dd, 1H, $J_{2'',1'}$=6.1, $J_{2'',3'}$=1.0, $J_{2'',2'}$=13.4 Hz, H-2″), 1.86 (br s, 3H, CH_3), 1.26, 1.255 and 1.23 (3×d, 6H, 3H and 3H, J=6.1 Hz, 4×CH_3), 1.35 (s, 3H, CH_3), 0.89 (s, 9H, *t*-Bu), 0.11 and 0.10 (2×s, 2×3H, $Si(CH_3)_2$).

Isomer **12b**: 45 mg, R_f=0.14 in C2. ^{1}H NMR (DMSO): 11.31 (br s, 1H, NH), 7.40 (br q, 1H, J=1.2 Hz, H-6), 6.08 (dd, 1H, $J_{1',2'}$=3.7, $J_{1',2''}$=8.0 Hz, H-1′), 4.65 and 4.63 (2×d sept, 2×1H, $J_{H,H}$=6.1, $J_{P,OCH}$=7.6 Hz, 2×P–OCH), 4.45 (t, 1H, $J_{3',2'}$=$J_{3',2''}$=9.0 Hz, H-3′), 3.74 (dd, 1H, $J_{P,CHa}$=15.4, J_{gem}=13.4 Hz, P–CHa), 3.72 (t, 1H, $J_{P,CHb}$=13.4, J_{gem}=13.4 Hz, P–CHb), 2.15–2.25 (m, 2H, H-2′ and H-2″), 1.81 (d, 3H, J=1.2 Hz, CH_3) 1.27 and 1.26 (2×d, 2×3H, J=6.1 Hz, 4×CH_3), 1.40 (s, 3H, CH_3), 0.87 (s, 9H, *t*-Bu), 0.10 and 0.07 (2×s, 2×3H, $Si(CH_3)_2$).

4.2.12. Dimethyl-(1-thymin-1-yl-1,2,5-trideoxy-α-L-*threo*-pentofuranos-4-yloxy)methylphosphonate (13a) and dimethyl-(1-thymin-1-yl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxy)methylphosphonate (13a). Compound **9a** (1.345 g, 6 mmol) was co-evaporated with dichloromethane–dioxane, dichloromethane (25 mL) and the finely powdered molecular sieves A3 (1 g) were added, and the whole was stirred. To the mixture, **10a** (2.52 g, 18 mmol) and then PTS (4.52 g, 18 mmol) were added. The whole was stirred at rt for 36 h (TLC in C1, HPLC). The mixture was treated with water (0.3 mL), filtered through Celite, the washings were evaporated and co-distilled with toluene. The residue was chromatographed on silica gel using a gradient of ethyl acetate to 10% H3 in ethyl acetate. Obtained: 0.457 g of the faster product α-L-*threo* **13a** and 1.144 g of slower β-D-*erythro* **13b** as colourless sirups; total yield, 1.601 g (73%); ratio, ca. 1:2.5. HRMS FAB+ calcd for $C_{13}H_{22}N_2O_8P$ $(M+H)^+$ 365.1114, found 365.1115.

Isomer α-L-threo **13a**: ^{1}H NMR (DMSO): 11.31 (br s, 1H, NH), 7.45 (br q, 1H, J=1.2 Hz, H-6), 6.47 (dd, 1H, $J_{1',2''}$=6.2, $J_{1',2'}$=9.1 Hz, H-1′), 5.62 (d, 1H, $J_{OH,3'}$=4.8 Hz, OH), 4.04 (br t, 1H, $J_{3',2''}$~1.0, $J_{3',2'}$=4.8, $J_{3',OH}$=4.8 Hz, H-3′), 3.87 (dd, 1H, $J_{P,CHa}$=11.0, J_{gem}=13.2 Hz, P–CHa), 3.74 (dd, 1H, $J_{P,CHb}$=10.8, J_{gem}=13.2 Hz, P–CHb), 3.69 and 3.68 (2×d, 2×3H, $J_{P,H}$=10.6 Hz, $P(OCH_3)_2$), 2.28 (ddd, 1H, $J_{2',3'}$=4.8, $J_{2',1'}$=9.1, $J_{2',2''}$=13.4 Hz, H-2′), 2.11 (ddd, 1H, $J_{2'',3'}$=1.0, $J_{2'',1'}$=6.2, $J_{2'',2'}$=13.4 Hz, H-2″), 1.84 (d, 3H, J=1.2 Hz, CH_3), 1.36 (s, 3H, CH_3).

Isomer β-D-erythro **13b**: ^{1}H NMR (DMSO): 11.31 (br s, 1H, NH), 7.36 (br q, 1H, J=1.2 Hz, H-6), 6.08 (dd, 1H, $J_{1',2'}$=3.1, $J_{1',2''}$=8.5 Hz, H-1′), 5.14 (d, 1H, $J_{OH,3'}$=6.4 Hz, OH), 4.29 (td, 1H, $J_{3',OH}$=6.4, $J_{3',2''}$=9.6, $J_{3',2'}$=8.8 Hz, H-3′), 3.88 (dd, 1H, $J_{P,CHa}$=12.0, J_{gem}=13.7 Hz, P–CHa), 3.80 (dd, 1H, $J_{P,CHb}$=8.3, J_{gem}=13.7 Hz, P–CHb), 3.715 and 3.71 (2×d, 2×3H, $J_{P,OCH}$=10.6 Hz, $P(OCH_3)_2$), 2.23 (ddd, 1H, $J_{2'',1'}$=8.5, $J_{2'',3'}$=9.6, $J_{2'',2'}$=13.4 Hz, H-2″), 2.15 (ddd, 1H, $J_{2',1'}$=3.1, $J_{2',3'}$=8.8, $J_{2',2''}$=13.4 Hz, H-2′), 1.79 (d, 3H, J=1.2 Hz, CH_3), 1.40 (s, 3H, CH_3).

4.2.13. Dimethyl-(3-*O*-*tert*-butyldimethylsilyl-1-thymin-1-yl-1,2,5-trideoxy-α-L-*threo*-pentofuranos-4-yloxy)methylphosphonate (14a) and dimethyl-(3-*O*-*tert*-butyldimethylsilyl-1-thymin-1-yl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxy)methylphosphonate (14b). To a solution of **9b** (1.69 g, 5 mmol, co-evaporated with dioxane–dichloromethane) in dichloromethane (30 mL), **10a** (2.1 g, 15 mmol) was added and then, under stirring, PTS (3.76 g, 15 mmol). The mixture was stirred at rt overnight (TLC in C2), dichloromethane was added (30 mL), and the whole washed with water (100 mL). On re-extraction of the aqueous layer with dichloromethane (2×50 mL), the organic washings were combined, dried with Na_2SO_4 and evaporated. The syrupy residue was subjected to column

chromatography on silica gel (100 g) and the elution by a gradient of 0–2.5% methanol in chloroform provided a 1.860 g (78%) combined yield of isomers **14a** (0.76 g) and **14b** (1.10 g) as solid foams; weight ratio, ca. 1:1.5. For $C_{19}H_{35}O_8N_2PSi$ (478.55) calcd 47.69% C, 7.37% H, 5.85% N; found: 47.75% C, 7.39% H, 5.56% N. MS (FAB): 479.3 $(M+H)^+$.

Isomer **14a**: R_f=0.56 in C2. $[\alpha]_D^{20}$ −45.3 (*c* 0.063, $CHCl_3$). IR spectrum (KBr): ν_{max} (cm^{-1}) 3180 (w, br) NH; 2897 (w), 1472 (m), 1464 (m, sh), 1389 (w, sh), 1364 (w), 1261 (s) and 837 (s) all CH_3 from TBDMS; 1718 (s, sh) and 1693 (vs) all C═O; 1648 (m, sh) C═C; 1432 (m, sh), 1404 (w), 1289 (m), 1007 (m) and 764 (m, sh) all ring; 1381 (w) CH_3 from thymine; 1107 (s) C–O–C; 1047 (s), 1030 (s) and 780 (m) all P–O–C. ^{1}H NMR (DMSO): 11.37 (br s, 1H, NH), 7.46 (br s, 1H, H-6), 6.42 (dd, 1H, $J_{1',2'}$=9.3, $J_{1',2''}$=6.1 Hz, H-1′), 4.22 (br d, 1H, $J_{3',2'}$=4.0, $J_{3',2''}$=1.0 Hz, H-3′), 3.91 (dd, 1H, $J_{P,CHa}$=11.0, J_{gem}=13.2 Hz, P–CHa), 3.77 (dd, 1H, $J_{P,CHb}$=11.2, J_{gem}=13.2 Hz, P–CHb), 3.70 and 3.695 (2×d, 2×3H, $J_{P,OCH}$=10.5 Hz, $P(OCH_3)_2$), 2.34 (ddd, 1H, $J_{2',1'}$=9.3, $J_{2',3'}$=4.0, $J_{2',2''}$=13.4 Hz, H-2′), 2.06 (br dd, 1H, $J_{2'',1'}$=6.1, $J_{2'',3'}$=1.0, $J_{2'',2'}$=13.4 Hz, H-2″), 1.84 (br s, 3H, CH_3), 1.36 (s, 3H, CH_3), 0.89 (s, 9H, *t*-Bu), 0.12 and 0.11 (2×s, 2×3H, $Si(CH_3)_2$). ^{13}C NMR (DMSO): 163.79 (C-4), 150.98 (C-2), 135.44 (C-6), 111.33 (d, $J_{C,P}$=13.7 Hz, C-4′), 111.10 (C-5), 84.23 (C-1′), 76.59 (C-3′), 55.02 (d, $J_{C,P}$=169.9 Hz, P–C), 53.04 and 52.99 (2×d, $J_{C,P}$=6.8 and 5.9 Hz, $P(OCH_3)_2$), 37.83 (C-2′), 25.73 and 17.81 (*t*-Bu), 16.58 (CH_3), 11.82 (CH_3), −4.81 and −5.03 ($Si(CH_3)_2$).

Isomer **14b**: R_f=0.46 in C2. $[\alpha]_D^{20}$ +10.1 (*c* 0.188; $CHCl_3$). IR spectrum (KBr): ν_{max} (cm^{-1}) 3180 (w, br) NH, 2898 (w), 1473 (m), 1464 (m, sh), 1363 (w, sh), 1251 (s), 1185 (m), 939 (w) and 840 (s) all CH_3 from TBDMS, 1705 (vs) and 1687 (vs) all C═O, 1646 (m, sh) C═C, 1424 (w), 1317 (w), 1288 (m, sh) and 1066 (s) all ring, 1385 (m) and 1368 (w) all CH_3 from thymine, 1260 (s) P═O, 1134 (s) C–O–C, 1101 (w, sh) C–O–Si, 1041 (s), 802 (m) and 778 (m) all P–O–C, 765 (m) ═CH. ^{1}H NMR (DMSO): 11.32 (br s, 1H, NH), 7.41 (br q, 1H, *J*=1.2 Hz, H-6), 6.06 (dd, 1H, $J_{1',2'}$=3.4, $J_{1',2''}$=8.3 Hz, H-1′), 4.48 (t, 1H, $J_{3',2'}$=8.8, $J_{3',2''}$= 8.8 Hz, H-3′), 3.88 (dd, 1H, $J_{P,CHa}$=11.2, J_{gem}=13.7 Hz, P–CHa), 3.85 (dd, 1H, $J_{P,CHb}$=9.5, J_{gem}=13.7 Hz, P–CHb), 3.72 and 3.71 (2×d, 2×3H, $J_{P,OCH}$=10.5 Hz, $P(OCH_3)_2$), 2.16–2.30 (m, 2H, H-2′ and H-2″), 1.81 (d, 3H, *J*=1.2 Hz, CH_3), 1.41 (s, 3H, CH_3), 0.86 (s, 9H, *t*-Bu), 0.10 and 0.07 (2×s, 2×3H, $Si(CH_3)_2$). ^{13}C NMR (DMSO): 163.96 (C-4), 150.38 (C-2), 137.14 (C-6), 110.17 (C-5), 105.97 (d, $J_{C,P}$=11.7 Hz, C-4′), 82.68 (C-1′), 75.42 (C-3′), 54.97 (d, $J_{C,P}$=168.0 Hz, P–C), 53.17 and 53.11 (2×d, $J_{C,P}$=7.8 and 6.8 Hz, $P(OCH_3)_2$), 36.73 (C-2′), 25.75 and 17.80 (*t*-Bu), 18.59 (CH_3), 12.22 (CH_3), −4.59 and −4.71 ($Si(CH_3)_2$).

4.2.14. Dimethyl-(3-*O*-*tert*-butyldimethylsilyl-1,2,5-trideoxy-1-uracil-1-yl-α-L-*threo*-pentofuranos-4-yloxy)methylphosphonate (15a). To the compound **9e** (1.657 g, 5.11 mmol) co-evaporated with dry dioxane–dichloromethane was added dichloromethane (35 mL) followed by **10a** (2.15 g, 15.33 mmol) and then, under stirring, by PTS (3.85 g, 15.33 mmol). The mixture was stirred at rt overnight (TLC in C2), dichloromethane was added (60 mL) and the whole washed with water (100 mL). On re-extraction of the aqueous layer with dichloromethane (50 mL), the organic washings were dried with Na_2SO_4 and evaporated. The residue was subjected to column chromatography on silica gel and the elution by a gradient of 0–6% ethanol in chloroform provided isomers **15a** and **15b** in a 1:1 ratio (TLC in C1, HPLC) of which the faster-moving compound was isolated (in the form of a solid foam) and characterized as pure α-L-*threo* isomer **15a** (0.783 g, 33%), while the remaining sirupy mixture of isomers **15a**,**b** (0.830 g, 35%) was not further resolved and brought to additional NMR characterization in the form of fully deprotected isomers **22a**,**b**.

Isomer α-L-threo **15a**: R_f=0.53 in C2. ^{1}H NMR (DMSO): 11.38 (d, 1H, $J_{NH,5}$=2.0 Hz, NH), 7.69 (d, 1H, $J_{6,5}$= 8.2 Hz, H-6), 6.39 (dd, 1H, $J_{1',2''}$=6.2, $J_{1',2'}$=8.8 Hz, H-1′), 5.63 (dd, 1H, $J_{5,NH}$=2.0, $J_{5,6}$=8.2 Hz, H-5), 4.21 (dd, 1H, $J_{3',2''}$=1.5, $J_{3',2'}$=4.5 Hz, H-3′), 3.90 (dd, 1H, $J_{P,CHa}$=10.5, J_{gem}=13.4 Hz, P–CHa), 3.77 (dd, 1H, $J_{P,CHb}$=11.5, J_{gem}= 13.4 Hz, P–CHb), 3.70 and 3.69 (2×d, 2×3H, J_{P,OCH_3} = 10.6 Hz, $P(OCH_3)_2$), 2.33 (ddd, 1H, $J_{2',3'}$=4.5, $J_{2',1'}$=8.8, $J_{2',2''}$=13.6 Hz, H-2′), 2.12 (ddd, 1H, $J_{2'',3'}$=1.5, $J_{2'',1'}$=6.2, $J_{2'',2'}$=13.6 Hz, H-2″), 1.36 (s, 3H, CH_3), 0.89 (s, 9H, *t*-Bu); 0.12 and 0.10 (2×s, 2×3H, $Si(CH_3)_2$). HRMS FAB+ calcd for $C_{18}H_{34}N_2O_8PSi$ $(M+H)^+$ 465.1822, found 465.1852.

4.2.15. Dimethyl-(3-*O*-*tert*-butyldiphenylsilyl-1-cytosin-1-yl-1,2,5-trideoxy-α-L-*threo*-pentofuranos-4-yloxy)methylphosphonate (16a) and dimethyl-(3-*O*-*tert*-butyldiphenylsilyl-1-cytosin-1-yl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxy)methylphosphonate (16b). Compound **9g** (0.240 g, 0.536 mmol) was co-evaporated with dioxane, and dichloromethane was added (7 mL) followed by **10a** (0.225 g, 1.608 mmol, 3 equiv) and then by PTS (0.404 g, 1.608 mmol, 3 equiv). The mixture was stirred at rt for 2 d (TLC in C2, HPLC), and 1 equiv each of the reagents were added to completion (8 h). Dichloromethane was added (30 mL), and the whole washed with water (50 mL). On re-extraction of the aqueous layer with dichloromethane (40 mL), the organic washings were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel using a gradient of 0–10% ethanol in chloroform to afford isomers **16a** (32 mg) as the faster, and **16b** (132 mg) as the slower moving product (ratio 1:4); overall yield, 164 mg (53%) in the form of solid foams.

Isomer α-L-threo **16a**: R_f=0.50 in C2. $[\alpha]_D^{20}$ +5.0 (*c* 0.039, $CHCl_3$). IR spectrum (KBr): ν_{max} (cm^{-1}) 3073 (w) ═C–H; 1651 (s) NH_2 and C═O, 1612 (m, sh) C═C, 1530 (w) and 1291 (m) all cytosine ring, 1590 (w, sh), 1486 (w), 1428 (m), 1113 (s), 1105 (s), 998 (w, sh), 740 (w), 704 (m), 613 (m), 514 (s) and 488 (m) all arom. ring of TBDPS; 1468 (m), 1392 (w), 1365 (w) and 1379 (w) all CH_3, 1260 (m) and 1207 (m) all P═O, 1046 (s) POC. ^{1}H NMR (DMSO): 7.62 and 7.45 (2×m, 4H and 6H, 2×C_6H_5), 7.55 (d, 1H, $J_{6,5}$=7.5 Hz, H-6), 7.23 and 7.20 (2×br s, 2×1H, NH_2), 6.58 (dd, 1H, $J_{1',2'}$=8.8, $J_{1',2''}$=6.5 Hz, H-1′), 5.72 (d, 1H, $J_{5,6}$=7.5 Hz, H-5), 4.23 (dd, 1H, $J_{3',2'}$=4.7, $J_{3',2''}$= 1.5 Hz, H-3′), 3.83 (dd, 1H, $J_{P,CHa}$=10.5, J_{gem}=13.4 Hz, P–CHa), 3.70 (dd, 1H, $J_{P,CHb}$=11.4, J_{gem}=13.4 Hz, P–CHb), 3.63 (d, 6H, $J_{P,OCH}$=10.7 Hz, $P(OCH_3)_2$), 2.02 (ddd, 1H, $J_{2',3'}$=4.7, $J_{2',1'}$=8.8, $J_{2',2''}$=13.4 Hz, H-2′), 1.95 (ddd, 1H, $J_{2'',3'}$=1.5, $J_{2'',1'}$=6.5, $J_{2'',2'}$=13.4 Hz, H-2″), 1.39 (s,

3H, CH_3), 1.07 (s, 9H, *t*-Bu). ^{13}C NMR (DMSO): 165.54 (C-2), 141.21 (C-6), 135.58(2), 135.54(2), 132.92, 132.42, 130.50, 130.46, 128.31(2) and 128.27(2) (2×C_6H_5), 111.40 (C-4′), 84.90 (C-1′), 77.96 (C-3′), 54.89 d, *J*(C,P)=169.8 Hz (P–CH_2–O), 53.05 d, *J*(C,P)=6.2 Hz and 53.00 d, *J*(C,P)=6.2 Hz (P(OCH_3)$_2$), 38.20 (C-2′), 26.92 (3×CH_3 (*t*-Bu)), 19.05 (>C< (*t*-Bu)), 17.12 (C-5′). HRMS FAB+ calcd for $C_{28}H_{39}N_3O_7PSi$ $(M+H)^+$ 588.2295, found 588.2270.

Isomer β-D-erythro **16b**: R_f=0.40 in C2. IR spectrum (KBr): ν_{max} (cm^{-1}) 3072 (m) and 3049 (m) all =C–H, 1653 (vs) NH_2 and C=O, 1527 (m) and 1291 (m) all cytosine ring; 1590 (m), 1480 (m), 1428 (m), 113 (vs), 1105 (s, sh), 999 (m), 742 (m) 703 (s), 612 (m), 507 (s) and 489 (s) all arom. ring of TBDPS; 1472 (m), 1465 (m), 1390 (m), 1381 (m) and 1362 (m) all CH_3, 1272 (m), 1225 (s, sh) P=O, 1078 (s, sh) COSi, 1047 (vs), 760 (m) and 545 (m) all POC. ^1H NMR (DMSO): 7.65 and 7.45 (2×m, 4H and 6H, 2×C_6H_5), 7.32 (d, 1H, $J_{6,5}$=7.6 Hz, H-6), 7.17 and 7.12 (2×br s, 2×1H, NH_2), 5.99 (dd, 1H, $J_{1',2'}$=2.9, $J_{1',2''}$=8.4 Hz, H-1′), 5.64 (d, 1H, $J_{5,6}$=7.6 Hz, H-5), 4.43 (t, 1H, $J_{3',2''}$=8.8, $J_{3',2'}$=8.4 Hz, H-3′), 3.92 (dd, 1H, $J_{P,CHa}$=11.1, J_{gem}= 13.6 Hz, P–CHa), 3.88 (dd, 1H, $J_{P,CHb}$=9.5, J_{gem}=13.6 Hz, P–CHb), 3.75 and 3.745 (2×d, 2×3H, $J_{P,OCH}$=10.6 Hz, P(OCH_3)$_2$), 2.28 (dt, 1H, $J_{2'',1'}$=8.4, $J_{2'',3'}$=8.8, $J_{2'',2'}$= 13.4 Hz, H-2″), 1.78 (ddd, 1H, $J_{2',1'}$=2.9, $J_{2',3'}$=8.4 Hz, H-2′), 1.25 (s, 3H, CH_3), 1.02 (s, 9H, *t*-Bu).

4.2.16. Dimethyl-(1-adenin-9-yl-3-*O*-*tert*-butyldiphenylsilyl-1,2,5-trideoxy-α-L-*threo*-pentofuranos-4-yloxy)methylphosphonate (17a) and dimethyl-(1-adenin-9-yl-3-*O*-*tert*-butyldiphenylsilyl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxy)methylphosphonate (17b). Compound **9f** (1.40 g, 2.97 mmol) was phosphonylated following the procedure described for **16a**,**b** under the use of 4 equiv of both **10a** and PTS for 4 d (TLC in C1, HPLC). After work-up, the silica gel chromatography using a gradient of 0–8% ethanol in chloroform afforded the isomeric mixture of **17a** (faster moving, minor product) and **17b** (slower, major product) in a 1:12 ratio (NMR reading). The mixture remained unresolved after an attempt for separation on preparative RP column (elution, 100% water to 100% methanol). Yield of **17a**,**b**: 0.86 g (47%); amorphous solid. IR spectrum (KBr): ν_{max} (cm^{-1}) 3072 (w) =C–H, 1642 (m, sh) NH_2, 1611 (vs), 1566 (m), 1517 (w), 1437 (m) all adenine ring; 1314 (w), 1216 (m), 1160 (m, sh), 824 (m), 798 (w) and 648 (w) all adenine; 1590 (m, sh), 1488 (w, sh), 1428 (m), 1113 (s), 742 (w), 703 (s), 622 (m), 613 (m), 508 (m), 504 (m) and 487 (m) all arom. ring of TBDPS; 1365 (w, sh) CH_3, 1230 (m) P=O, 1082 (m) COSi, 1039 (w) POC. HRMS FAB+ calcd for $C_{29}H_{39}N_5O_6PSi$ $(M+H)^+$ 612.2407, found 612.2379.

Isomer α-L-threo **17a**: ^1H NMR (DMSO): 8.22 and 8.14 (2×s, 2×1H, H-2 and H-8), 7.67 and 7.45 (2×m, 4H and 6H, 2×C_6H_5), 7.31 (s, 2H, NH_2), 6.53 (dd, 1H, $J_{1',2''}$=6.9, $J_{1',2'}$=7.6 Hz, H-1′), 4.45 (dd, 1H, $J_{3',2''}$=1.5, $J_{3',2'}$=4.5 Hz, H-3′), 3.77 (dd, 1H, $J_{P,CHa}$=10.6, J_{gem}=13.4 Hz, P–CHa), 3.59 (d, 6H, J_{P,OCH_3} = 10.5 Hz, P(OCH_3)$_2$), 3.40 (dd, 1H, $J_{P,CHb}$=11.4, J_{gem}=13.4 Hz, P–CHb), 2.59 (ddd, 1H, $J_{2',3'}$=4.5, $J_{2',1'}$=7.6, $J_{2',2''}$=13.4 Hz, H-2′), 2.26 (ddd, 1H, $J_{2'',3'}$=1.5, $J_{2'',1'}$=6.9, $J_{2'',2'}$=13.4 Hz, H-2″), 1.42 (s, 3H, CH_3), 1.09 (s, 9H, *t*-Bu).

Isomer β-D-erythro **17b**: ^1H NMR (DMSO): 8.08 and 7.97 (2×s, 2×1H, H-2 and H-8), 7.73, 7.69 and 7.45 (3×m, 2H, 2H and 6H, 2×C_6H_5), 7.24 (s, 2H, NH_2), 6.23 (dd, 1H, $J_{1',2'}$=2.0, $J_{1',2''}$=8.7 Hz, H-1′), 5.16 (dd, 1H, $J_{3',2'}$=8.3, $J_{3',2''}$=9.2 Hz, H-3′), 3.99 (dd, 1H, $J_{P,CHa}$=11.1, J_{gem}= 13.6 Hz, P–CHa), 3.93 (dd, 1H, $J_{P,CHb}$=9.6, J_{gem}=13.6 Hz, P–CHb), 3.80 and 3.78 (2×d, 2×3H, J_{P,OCH_3} = 10.5 Hz, P(OCH_3)$_2$), 2.56 (ddd, 1H, $J_{2'',1'}$=8.7, $J_{2'',3'}$=9.2, $J_{2'',2'}$= 12.9 Hz, H-2″), 2.37 (ddd, 1H, $J_{2',1'}$=2.0, $J_{2',3'}$=8.3, $J_{2',2''}$=12.9 Hz, H-2′), 1.18 (s, 3H, CH_3); 1.06 (s, 9H, *t*-Bu).

4.2.17. Dimethyl-(3-*O*-*tert*-butyldimethylsilyl-1-guanin-9-yl-1,2,5-trideoxy-α-L-*threo*-pentofuranos-4-yloxy)methylphosphonate (18a) and dimethyl-(3-*O*-*tert*-butyldimethylsilyl-1-guanin-9-yl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxy)methylphosphonate (18b). Using the procedure described for **16a**,**b**, compound **9i** (1.273 g, 2.94 mmol) was phosphonylated with 4 equiv of both **10a** and PTS for 2 d to completion (TLC in C1, HPLC). After work-up, the silica gel chromatography using a gradient of 0–6% ethanol in chloroform, which was repeated once more with a 0–4% run, afforded 0.635 g (1.107 mmol, 38%) of **18a**,**b** as unresolved mixture of isomers in the form of a sirupy residue. They were identified by ^1H NMR spectra, using the enriched fractions, as the faster-moving α-L-*threo* **18a** isomer and the slower β-D-*erythro* **18b** isomer in ca. 1:1.5 ratio. HRMS FAB+ calcd for $C_{23}H_{41}N_5O_8PSi$ $(M+H)^+$ 574.2462, found 574.2494.

Isomer α-L-threo **18a**: ^1H NMR (DMSO): 12.09 (s, 1H, NH), 11.64 (s, 1H, NH), 8.17 (s, 1H, H-8), 6.33 (dd, 1H, $J_{1',2''}$=6.4, $J_{1',2'}$=8.6 Hz, H-1′), 4.31 (dd, 1H, $J_{3',2''}$=1.0, $J_{3',2'}$=4.5 Hz, H-3′); 3.82 (dd, 1H, $J_{P,CHa}$=11.0, J_{gem}=13.4 Hz, P–CHa), 3.675 and 3.67 (2×d, 2×3H, J_{P,OCH_3} = 10.7 Hz, P(OCH_3)$_2$), 3.47 (dd, 1H, $J_{P,CHb}$=10.6, J_{gem}=13.4 Hz, P–CHb), 2.96 (ddd, 1H, $J_{2',3'}$=4.5, $J_{2',1'}$=8.6, $J_{2',2''}$=13.9 Hz, H-2′), 2.76 (sept, 1H, *J*=6.8 Hz, CH), 2.35 (ddd, 1H, $J_{2'',3'}$=1.0, $J_{2'',1'}$=6.4, $J_{2'',2'}$=13.9 Hz, H-2″), 1.35 (s, 3H, CH_3), 1.12 (d, 6H, *J*=6.8 Hz, 2×CH_3), 0.91 (s, 9H, *t*-Bu), 0.15 and 0.13 (2×s, 2×3H, Si(CH_3)$_2$).

Isomer β-D-erythro **18b**: ^1H NMR (DMSO): 12.09 (s, 1H, NH), 11.64 (s, 1H, NH), 8.26 (s, 1H, H-8), 6.18 (dd, 1H, $J_{1',2'}$=3.4, $J_{1',2''}$=7.0 Hz, H-1′), 4.64 (t, 1H, $J_{3',2''}$=8.8, $J_{3',2'}$=8.4 Hz, H-3′), 3.91 (d, 2H, $J_{P,CH2}$=10.5 Hz, P–CH_2), 3.75 and 3.71 (2×d, 2×3H, J_{P,OCH_3} = 10.7 Hz, P(OCH_3)$_2$), 2.77 (sept, 1H, *J*=6.8 Hz, CH), 2.50 (m, 2H, H-2′ and H-2″), 1.44 (s, 3H, CH_3), 1.12 (d, 6H, *J*=6.8 Hz, 2×CH_3), 0.87 (s, 9H, *t*-Bu), 0.14 and 0.10 (2×s, 2×3H, Si(CH_3)$_2$).

4.2.18. Dimethyl-(3-*O*-*tert*-butyldimethylsilyl-1,2,5-trideoxy-1-cytosin-1-yl-α-L-*threo*-pentofuranos-4-yloxy)-methylphosphonate (20a). Phosphorylchloride (0.69 mL, 7.4 mmol) followed by triethylamine (5.45 mL, 74 mmol) were added to an ice-cold suspension of triazole (2.26 g, 33 mmol) in dry acetonitrile (55 mL). After 30 min stirring, compound **15a** (0.773 g, 1.664 mmol) in acetonitrile (8 mL) was added dropwise. The whole was stirred for 5 h (TLC in C2), evaporated to dryness, and the residue partitioned between chloroform and a satd solution of sodium hydrogen carbonate. The organic washings were pooled, evaporated and the residue submitted to short-column chromatography on silica (gradient of 0–7% ethanol in chloroform) to give

the residue of a single main product, which was immediately used, without characterization, for treatment in satd (0 °C) ammonia-dry dioxane (15 mL) in a sealed vessel for 80 °C for 2 d (TLC in H1). The mixture, upon cooling, was carefully evaporated, the residue partitioned between chloroform and a satd solution of sodium hydrogen carbonate, the organic washings collected and evaporated, and the residue chromatographed on a silica gel column (gradient, 0–5% ethanol in chloroform). Obtained: 0.316 g of **20a** (0.682 mmol, 41%) as a solid foam. UV spectrum (nm): pH2: ν_{max}=275, ν_{min}=244; pH7: ν_{max}=265, ν_{min}=253; pH12: ν_{max}=270, ν_{min}=255. ^{1}H NMR (DMSO): 7.66 (d, 1H, H-6), 7.23 and 7.19 (2×br s, 2×1H, NH_2), 6.51 (dd, 1H, $J_{1',2'}$=8.9, $J_{1',2''}$=6.1 Hz, H-1′), 5.78 (d, $J_{5,6}$=7.4 Hz, H-5), 4.18 (br d, 1H, $J_{3',2'}$=4.4, $J_{3',2''}$∼1.0 Hz, H-3′), 3.89 (dd, 1H, $J_{P,CHa}$=10.5, J_{gem}=13.3 Hz, P–CHa), 3.77 (dd, 1H, $J_{P,CHb}$=11.6, J_{gem}=13.3 Hz, P–CHb), 3.70 and 3.69 (2×d, 2×3H, $J_{P,OCH}$=10.6 Hz, $P(OCH_3)_2$), 2.22 (ddd, 1H, $J_{2',3'}$=4.4, $J_{2',1'}$=8.9, $J_{2',2''}$=13.4 Hz, H-2′), 2.08 (br dd, 1H, $J_{2'',3'}$∼1.0, $J_{2'',1'}$=6.1, $J_{2'',2'}$=13.4 Hz, H-2″), 1.35 (s, 3H, CH_3), 0.89 (s, 9H, *t*-Bu), 0.12 and 0.105 (2×s, 2×3H, $Si(CH_3)_2$). Product was further characterized in its fully deprotected form **23a**.

4.2.19. 1-Thymin-1-yl-1,2,5-trideoxy-α-L-*threo*-pentofuranos-4-yloxymethylphosphonic acid (21a). On application of the general deprotection procedure provided above, compound **14a** (0.900 g, 1.88 mmol) afforded the free phosphonic acid **21a** (0.243 g, 0.723 mmol) in 38% yield as a solid lyophilisate from water. $[\alpha]_D^{20}$ +24.8 (*c* 0.177, H_2O). IR spectrum (KBr): ν_{max} (cm^{-1}) 3437 (vs, br), 3260 (w, br, sh) and 2795 all OH, NH, H_2O; 1696 (vs, br) C═O; 1476 (w) and 1284 (m) all ring; 1040 (m, sh), 1016 (m), 972 (m), 908 (w), 564 (m) and 480 (w, br) all $[PO_3]^{2-}$, 1388 (w) and 1379 (w) all CH_3, 1107 (m) C–O–C, 1079 (s) C–OH, 769 (w) ═C–H. ^{1}H NMR (D_2O): 7.78 (q, 1H, J_{6,OCH_3} = 1.3 Hz, H-6), 6.56 (dd, 1H, $J_{1',2'}$=8.5, $J_{1',2''}$=6.5 Hz, H-1′), 4.21 (br d, 1H, $J_{3',2'}$=6.0, $J_{3',2''}$<1 Hz, H-3′), 3.66 (dd, 1H, $J_{P,CHa}$= 11.5, $J_{CHa,CHb}$=12.2 Hz, P–CHa), 3.53 (dd, 1H, $J_{P,CHb}$=10.0, $J_{CHb,CHa}$=12.2 Hz, P–CHb), 2.66 (ddd, 1H, $J_{2',1'}$=8.5, $J_{2',2''}$=14.2, $J_{2',3'}$=5.0 Hz, H-2′), 2.35 (bdd, 1H, $J_{2'',1'}$=6.5, $J_{2'',2'}$=14.2, $J_{2'',3'}$<1 Hz, H-2″), 1.89 (d, 3H, $J_{CH_3,6}$ = 1.2 Hz, 5-CH_3), 1.50 (s, 3H, 4′-CH_3). ^{13}C NMR (D_2O): 169.52 (C-4), 154.64 (C-2), 141.55 (C-6), 114.66 (d, $J_{C,P}$=11.7 Hz, C-4′), 114.35 (C-5), 87.77 (C-1′), 76.98 (C-3′), 61.04 (d, $J_{C,P}$=157.2 Hz, P–CH_2–O), 40.92 (C-2′), 18.06 (4′-CH_3), 14.47 (5-CH_3). HRMS FAB+ calcd for $C_{11}H_{18}N_2O_8P$ $(M+H)^+$ 337.0801, found 337.0813.

4.2.20. 1-Thymin-1-yl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxymethylphosphonic acid (21b). On standard deprotection of **14b** (0.220 g, 0.606 mmol), product **21b** 0.071 g (0.211 mmol) was obtained in 35% overall yield as a solid lyophilisate from water. $[\alpha]_D^{20}$ +80.0 (*c* 0.074, H_2O).

IR spectrum (KBr): ν_{max} (cm^{-1}) 3425 (s, br), 3260 (br, sh) and 2816 (w, vbr) all OH, NH, H_2O, 1692 (vs, br) C═O, 1477 (m) and 1282 (m) all ring; 1387 (w) and 1383 (w) all CH_3, 1108 (s) COC, 1087 (m, sh) C–OH, 1041 (s), 1014 (m, sh), 960 (m), 908 (m), 551 (m) and 477 (m, sh) all $[PO3]^{2-}$, 766 (w) ═C–H. ^{1}H NMR (D_2O): 7.39 (q, 1H, J_{6,CH_3} = 1.2 Hz, H-6), 6.14 (dd, 1H, $J_{1',2'}$=3.0, $J_{1',2''}$=8.5 Hz, H-1′), 4.39 (dd, 1H, $J_{3',2'}$=8.9, $J_{3',2''}$=9.3 Hz, H-3′), 3.57 (dd, 1H, J_{gem}=12.3, $J_{CH,P}$=9.4 Hz, P–C*Ha*Hb–O), 3.68 (dd, 1H, J_{gem}=12.3, $J_{CH,P}$=11.5 Hz, P–CHa*Hb*–O), 2.54 (ddd, 1H, $J_{2'',1'}$=8.5, $J_{2'',2'}$=13.8, $J_{2'',3'}$=9.3 Hz, H-2″), 2.45 (ddd, 1H, $J_{2',1'}$=3.0, $J_{2',2''}$=13.8, $J_{2',3'}$=8.9 Hz, H-2′), 1.88 (d, 3H, $J_{CH_3,6}$ = 1.2 Hz, 5-CH_3), 1.53 (s, 3H, 4′-CH_3). ^{13}C NMR (D_2O): 169.41 (C-4), 154.32 (C-2), 141.22 (C-6), 114.59 (C-5), 108.93 (d, $J_{C,P}$=11.2 Hz, C-4′), 86.80 (C-1′), 77.61 (C-3′), 60.13 (d, $J_{C,P}$=163.7 Hz, P–CH_2–O), 38.40 (C-2′), 20.27 (4′-CH_3), 14.30 (5-CH_3). HRMS FAB+ calcd for $C_{11}H_{18}N_2O_8P$ $(M+H)^+$ 337.0801, found 337.0819.

4.2.21. 1,2,5-Trideoxy-1-uracil-1-yl-pentofuranos-4-yloxymethylphosphonic acid (22a,b). Standard deprotection of epimeric mixture **15a**,**b** (0.283 g, 0.609 mmol) afforded 0.147 g (0.456 mmol, 75%) of epimeric mixture **22a**,**b** in the form of a solid lyophilisate from water. IR spectrum (KBr): ν_{max} (cm^{-1}) 3427 (s, br), 3250 (m, br, sh) and 2805 (w, br) all OH, NH, H_2O; 1697 (s) and 1685 (s, sh) all C═O, 1628 (m, sh) C═C, 1473 (w), 1437 (w), 1398 (w) and 1282 (m) all ring, 1387 (w) CH_3, 1072 (m) C–OH, 1040 (m), 1015 (m), 985 (w, sh), 911 (w), 891 (w), 541 (w) and 472 (w, br) all $[PO_3]^{2-}$, 817 (w) and 767 (w) ═C–H. HRMS FAB+ calcd for $C_{10}H_{16}N_2O_8P$ $(M+H)^+$ 323.0644, found 323.0829. Isomer α-L-*threo* **22a**: ^{1}H NMR (D_2O): 7.98 (d, 1H, $J_{6,5}$=8.0 Hz, H-6); 6.57 (dd, 1H, $J_{1',2'}$=8.5, $J_{1',2''}$=6.6 Hz, H-1′), 5.95 (d, 1H, $J_{5,6}$=8.0 Hz, H-5), 4.33 (dd, 1H, $J_{3',2''}$=1.0, $J_{3',2'}$=5.0 Hz, H-3′), 3.54 (dd, 1H, J_{gem}= 12.4, $J_{CH,P}$=10.5 Hz, P–C*Ha*Hb–O), 3.66 (dd, 1H, J_{gem}= 12.4, $J_{CH,P}$=5.8 Hz, P–CHa*Hb*–O), 2.62 (ddd, 1H, $J_{2',1'}$=8.5, $J_{2',2''}$=14.3, $J_{2',3'}$=5.0 Hz, H-2′), 2.37 (ddd, 1H, $J_{2'',2'}$=14.3, $J_{2'',1'}$=6.6, $J_{2'',3'}$=1.0 Hz, H-2″), 1.50 (s, 3H, 4′-CH_3). ^{13}C NMR (D_2O): 169.04 (C-4), 154.94 (C-2), 145.68 (C-6), 115.17 (d, $J_{C,P}$=12.7 Hz, C-4′), 106.06 (C-5), 87.86 (C-1′), 78.60 (C-3′), 61.16 (d, $J_{C,P}$=160.3 Hz, P–CH_2–O), 39.87 (C-2′), 18.23 (4′-CH_3). Isomer β-D-*erythro* **22b**: ^{1}H NMR (D_2O): 7.64 (d, 1H, $J_{6,5}$=8.1 Hz, H-6), 6.12 (dd, 1H, $J_{1',2'}$=2.9, $J_{1',2''}$=8.5 Hz, H-1′), 5.86 (d, 1H, $J_{5,6}$= 8.1 Hz, H-5), 4.35 (dd, 1H, $J_{3',2'}$=8.7, $J_{3',2''}$=9.4 Hz, H-3′), 3.63 (dd, 1H, J_{gem}=12.0, $J_{CH,P}$=11.2 Hz, P–C*Ha*Hb–O), 3.53 (dd, 1H, J_{gem}=12.0, $J_{CH,P}$=9.7 Hz, P–CHa*Hb*–O), 2.58 (ddd, 1H, $J_{2'',1'}$=8.5, $J_{2'',2'}$=13.8, $J_{2'',3'}$=9.4 Hz, H-2″), 2.45 (ddd, 1H, $J_{2',1'}$=2.9, $J_{2',2''}$=13.8, $J_{2',3'}$=8.7 Hz, H-2′), 1.53 (s, 3H, 4′-CH_3). ^{13}C NMR (D_2O): 170.20 (C-4), 154.42 (C-2), 145.84 (C-6), 114.88 (d, $J_{C,P}$=12.7 Hz, C-4′), 104.96 (C-5), 88.03 (C-1′), 76.74 (C-3′), 60.42 (d, $J_{C,P}$=159.3 Hz, P–CH_2–O), 40.98 (C-2′), 17.91 (4′-CH_3).

4.2.22. 1-Cytosin-1-yl-1,2,5-trideoxy-α-L-*threo*-pentofuranos-4-yloxymethylphosphonic acid (23a). From **16a**: On standard deblocking, compound **16a** (0.027 g, 0.058 mmol) afforded 0.008 g (0.025 mmol, 43%) of **23a** as a solid lyophilisate from water.

From **20a**: On standard deblocking, 0.306 g of compound **20a** (0.660 mmol) afforded 0.106 g (0.330 mmol, 50%) of **23a** (lyophilisate from water). $[\alpha]_D^{20}$ −7.8 (*c* 0.348, H_2O). IR spectrum (KBr): ν_{max} (cm^{-1}) 3430 (vs, br) and 3205 (m, br, sh) all OH, NH_2, H_2O, 1722 (w, sh) C═O, 1645 (s) C═O, NH_2, 1607 (m, sh), 1531 (w), 1485 (w), 1423 (w), and 1335 (w) all ring, 1380 (w) CH_3, 1290 (w, br), 1206 (w), 1155 (m), 1043 (w), 1102 (m) C–O–C; 1080 (m, br, sh) C–OH; 1043 (w), 1013 (w), 970 (w), 945 (w), 899 (w, br), 570 (w, br, sh), 536 (w, br) and 467 (w, br) all $[PO_3]^{2-}$,

799 (w) =C–H. ^{1}H NMR (D_2O): 7.99 (d, 1H, $J_{6,5}$=7.5 Hz, H-6), 6.60 (dd, 1H, $J_{1',2''}$=6.5, $J_{1',2'}$=8.4 Hz, H-1′), 6.13 (d, 1H, $J_{5,6}$=7.5 Hz, H-5), 4.33 (dd, 1H, $J_{3',2''}$=1.2, $J_{3',2'}$= 4.8 Hz, H-3′), 3.50 (dd, 1H, J_{gem}=12.0, $J_{CHa,P}$=10.4 Hz, P–C*Ha*Hb–O), 3.60 (dd, 1H, J_{gem}=12.0, $J_{CHb,P}$=11.2 Hz, P–CHa*Hb*–O), 2.58 (ddd, 1H, $J_{2',1'}$=8.4, $J_{2',2''}$=14.2, $J_{2',3'}$=4.8, H-2′), 2.37 (ddd, 1H, $J_{2'',1'}$=6.5, $J_{2'',2'}$=14.2, $J_{2'',3'}$=1.2 Hz, H-2″), 1.50 (s, 3H, 4′-CH_3). ^{13}C NMR (D_2O): 168.93 (C-2), 160.82 (C-4), 145.64 (C-6), 115.07 (d, $J_{C,P}$=13.2 Hz, C-4′), 100.18 (C-5), 88.65 (C-1′), 78.76 (C-3′), 61.44 (d, $J_{C,P}$=157.2 Hz, P–CH_2–O), 40.40 (C-2′), 18.37 (4′-CH_3). HRMS FAB+ calcd for $C_{10}H_{17}N_3O_7P$ $(M+H)^+$ 322.0804, found 322.0902.

4.2.23. 1-Cytosin-1-yl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxymethylphosphonic acid (23b). On standard deblocking, 0.127 g (0.216 mmol) of **16b** afforded 0.051 g (0.159 mmol, 73%) of **23b** as a solid lyophilisate from water. $[\alpha]_D^{20}$ +64.0 (*c* 0.033, H_2O). IR spectrum (KBr): ν_{max} (cm^{-1}) 3427 (vs, br) OH, NH_2, H_2O, 1722 (w) C=O, 1651 (s) C=O and NH_2, 1613 (m, sh), 1530 (w), 1493 (w) and 1411 (w) all ring, 1388 (vw) CH_3, 1289 (w), 1210 (w, sh), 1093 (m) C–O–C, C–OH, 1044 (m), 960 (w), 907 (w), 570 (m, br), 481 (m, br) all $[PO_3]^{2-}$, 784 (w) =C–H.

^{1}H NMR (D_2O): 7.60 (d, 1H, $J_{6,5}$=7.5 Hz, H-6), 6.10 (dd, 1H, $J_{1',2'}$=2.6, $J_{1',2''}$=8.4 Hz, H-1′), 6.02 (d, 1H, $J_{5,6}$=7.5 Hz, H-5), 4.33 (dd, 1H, $J_{3',2'}$=8.5, $J_{3',2''}$=9.6 Hz, H-3′), 3.58 (dd, 1H, J_{gem}=12.2, $J_{CHa,P}$=9.4 Hz, P–C*Ha*Hb–O), 3.69 (dd, 1H, J_{gem}=12.2, $J_{CHb,P}$=11.4 Hz, P–CHa*Hb*–O), 2.56 (ddd, 1H, $J_{2'',1'}$=8.4, $J_{2'',2'}$=13.6, $J_{2'',3'}$=9.6 Hz, H-2″), 2.39 (ddd, 1H, $J_{2',1'}$=2.6, $J_{2',2''}$=13.6, $J_{2',3'}$=8.5 Hz, H-2′), 1.52 (s, 3H, 4′-CH_3). ^{13}C NMR (D_2O): 169.07 (C-2), 160.12 (C-4), 145.29 (C-6), 108.99 (d, $J_{C,P}$=12.2 Hz, C-4′), 99.17 (C-5), 87.72 (C-1′), 77.53 (C-3′), 60.16 (d, $J_{C,P}$=159.2 Hz, P–CH_2–O), 39.06 (C-2′), 20.39 (4′-CH_3). HRMS FAB+ calcd for $C_{10}H_{17}N_3O_7P$ $(M+H)^+$ 322.0804, found 322.0922.

4.2.24. 1-Guanin-9-yl-1,2,5-trideoxypentofuranos-4-yloxymethylphosphonic acid (24a,b). Standard deprotection of compound mixture **18a**,**b** (0.618 g, 1.077 mmol) afforded 0.080 g (0.221 mmol, 21%) of epimeric mixture **24a**,**b** in the form of a solid lyophilisate from water. IR spectrum (KBr): ν_{max} (cm^{-1}) 3433 (vs, br) and 3132 (w, br, sh) all OH, NH, NH_2, H_2O, 1694 (m) C=O, 1627 (m, br) NH_2, 1605 (m, sh), 1532 (w), 1484 (w), 1412 (vw, sh) and 1324 (w) all ring, 1177 (w), 1381 (w) CH_3, 1110 (w) C–O–C, 1082 (w, sh) C–OH, 1040 (w), 970 (w, sh), 907 (w, br), 560 (w, br), 470 (w, br) all $[PO_3]^{2-}$, 783 (vw) =C–H.

Isomer α-L-threo **24a**: ^{1}H NMR (D_2O): 8.15 (s, 1H, H-8), 6.38 (dd, 1H, $J_{1',2''}$=7.0, $J_{1',2'}$=8.0 Hz, H-1′), 4.43 (dd, 1H, $J_{3',2''}$<1.0, $J_{3',2'}$=5.0 Hz, H-3′), 3.20 (dd, 1H, J_{gem}=12.2, $J_{CHa,P}$=9.3 Hz, P–C*Ha*Hb–O), 3.55 (t, 1H, J_{gem}=12.2, $J_{CHb,P}$=12.2 Hz, P–CHa*Hb*–O), 3.06 (ddd, 1H, $J_{2',1'}$=8.0, $J_{2',2''}$=14.4, $J_{2',3'}$=5.0 Hz, H-2′), 2.55 (bdd, 1H, $J_{2'',1'}$=7.0, $J_{2'',2'}$=14.4, $J_{2'',3'}$<1.0 Hz, H-2″), 1.50 (s, 3H, 4′-CH_3). ^{13}C NMR (D_2O): 85.44 (C-1′), 78.74 (C-3′), 40.37 (C-2′), 18.16 (4′-CH_3).

Isomer β-D-erythro **24b**: ^{1}H NMR (D_2O): 7.89 (s, 1H, H-8), 6.19 (dd, 1H, $J_{1',2'}$=3.3, $J_{1',2''}$=8.0 Hz, H-1′), 4.62 (dd, 1H, $J_{3',2'}$=8.6, $J_{3',2''}$=9.5 Hz, H-3′), 3.58 (dd, 1H, J_{gem}=12.2, $J_{CHa,P}$=9.2 Hz, P–C*Ha*Hb–O), 3.72 (dd, 1H, J_{gem}=12.2, $J_{CHb,P}$=11.4 Hz, P–CHa*Hb*–O), 2.71 (ddd, 1H, $J_{2'',1'}$=8.0, $J_{2'',2'}$=13.8, $J_{2'',3'}$=9.5 Hz, H-2″), 2.67 (ddd, 1H, $J_{2',1'}$=3.3, $J_{2',2''}$=13.8, $J_{2',3'}$=8.6 Hz, H-2′), 1.51 (s, 3H, 4′-CH_3). ^{13}C NMR (D_2O): 161.78 (C-6), 156.64 (C-2), 119.16 (C-5), 109.04 (C-4′), 83.84 (C-1′), 77.65 (C-3′), 60.27 (d, $J_{C,P}$=158.7 Hz, P–CH_2–O), 38.78 (C-2′), 20.45 (4′-CH_3), signals of C-4 and C-8 were not detected. HRMS FAB+ calcd for $C_{11}H_{17}N_5O_7P$ $(M+H)^+$ 362.0866, found 362.0856.

4.2.25. 1-Adenin-9-yl-1,2,5-trideoxypentofuranos-4-yloxymethylphosphonic acid (25a,b). Standard deprotection of compound mixture **17a**,**b** (0.350 g, 0.572 mmol) afforded 0.095 g (0.275 mmol, 48%) of epimeric mixture **25a**,**b** as a solid lyophilisate from water. IR spectrum (KBr): ν_{max} (cm^{-1}) 3435 (vs, br) and 3180 (m, br, sh) all OH, NH_2, H_2O, 1644 (s) NH_2, 1607 (m), 1579 (w), 1579 (w), 1506 (w), 1480 (w), 1423 (w) and 1335 (w) all ring, 1305 (w), 1210 (w) and 647 (w) all C–NH_2, 1386 (w, CH_3), 1230 (w, br), 1176 (w), 1106 (m, C–O–C), 1085 (m, sh, C–OH); 1040 (m), 951 (w), 903 (w), 565 (w, br) and 464 (w, br) all $[PO_3]^{2-}$, 798 (w), 734 (w) =C–H.

Isomer α-L-threo **25a**: ^{1}H NMR (D_2O): 8.17 and 8.49 (2×s, 2×1H, H-2 and H-8), 6.56 (dd, 1H, $J_{1',2''}$=7.0, $J_{1',2'}$=7.8 Hz, H-1′), 4.47 (dd, 1H, $J_{3',2''}$≈1.0, $J_{3',2'}$=5.2 Hz, H-3′), 3.17 (dd, 1H, J_{gem}=12.2, $J_{CHa,P}$=9.3 Hz, P–C*Ha*Hb–O), 3.53 (t, 1H, J_{gem}=$J_{CHb,P}$=12.2 Hz, P–CHa*Hb*–O), 3.13 (ddd, 1H, $J_{2',1'}$=7.8, $J_{2',2''}$=14.3, $J_{2',3'}$=5.2 Hz, H-2′), 2.62 (ddd, 1H, $J_{2'',1'}$=7.0, $J_{2'',2'}$=14.3, $J_{2'',3'}$≈1.0 Hz, H-2″), 1.51 (s, 3H, 4′-CH_3). ^{13}C NMR (D_2O): 85.64 (C-1′), 78.76 (C-3′), 40.70 (C-2′), 18.17 (4′-CH_3).

Isomer β-D-erythro **25b**: ^{1}H NMR (D_2O): 8.17 and 8.22 (2×s, 2×1H, H-2 and H-8), 6.35 (dd, 1H, $J_{1',2'}$=3.0, $J_{1',2''}$=8.0 Hz, H-1′), 4.58 (dd, 1H, $J_{3',2'}$=8.4, $J_{3',2''}$=9.6 Hz, H-3′), 3.59 (dd, 1H, J_{gem}=12.2, $J_{CHa,P}$=9.4 Hz, P–C*Ha*Hb–O), 3.73 (t, 1H, J_{gem}=12.2, $J_{CHb,P}$=12.2 Hz, P–CHa*Hb*–O), 2.77 (ddd, 1H, $J_{2'',1'}$=8.0, $J_{2'',2'}$=13.5, $J_{2'',3'}$=9.6 Hz, H-2″), 2.73 (ddd, 1H, $J_{2',1'}$=3.0, $J_{2',2''}$=13.5, $J_{2',3'}$=8.4 Hz, H-2′), 1.54 (s, 3H, 4′-CH_3). ^{13}C NMR (D_2O): 158.35 (C-6), 155.61 (C-2), 151.21 (C-4), 143.01 (C-8), 121.61 (C-5), 109.08 (d, $J_{C,P}$=11.7 Hz, C-4′), 84.12 (C-1′), 77.62 (C-3′), 60.49 (d, $J_{C,P}$=158.3 Hz, P–CH_2–O), 38.89 (C-2′), 20.55 (4′-CH_3). HRMS FAB+ calcd for $C_{11}H_{17}N_5O_6P$ $(M+H)^+$ 346.0917, found 346.0883.

4.2.26. Diisopropyl-(5-iodo-1-thymin-1-yl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxy)methylphosphonate (29b). To a solution of **9a** (1.120 g, 5 mmol; dried by co-evaporation with toluene) in 20 mL of dichloromethane, 1.96 g (10 mmol) of **10b** was added. Then NIS (1.463 g, 6.5 mmol) was added under stirring and the mixture was stirred at rt overnight (TLC in C2, HPLC). After the starting compound had disappeared, the mixture was diluted with dichloromethane (150 mL) and washed with aq sodium thiosulfate (150 mL). The aqueous layer was washed with dichloromethane (2×80 mL), the pooled organic washings were treated with satd NaCl solution (150 mL), dried with anhydrous $MgSO_4$ and evaporated. The residue was purified using the preparative reversed-phase chromatography under elution with a linear gradient of water–methanol (0–50% in

150 min, 50–100% in 150 min, 10 mL min^{-1}) to furnish 984 mg (36%) of **29b** as an amorphous solid. MS (FAB): 547.2 $(M+H)^+$. ^1H NMR (DMSO): 11.36 (br s, 1H, NH), 7.49 (br q, 1H, J_{6,CH_3} = 1.2 Hz, H-6), 6.22 (dd, 1H, $J_{1',2'}$= 3.7, $J_{1',2''}$=8.0 Hz, H-1′), 5.32 (d, 1H, $J_{OH,3'}$=5.9 Hz, 3′-OH), 4.65 (d sept, 2H, J_{CH,CH_3} = 6.1, $J_{P,OCH}$=7.6 Hz, $P(OCH)_2$), 4.59 (t, 1H, $J_{3',2'}$=8.8 Hz, H-3′), 3.85 (dd, 1H, $J_{P,CHa}$=12.0, J_{gem}=13.4 Hz, P–CHa), 3.79 (dd, 1H, $J_{P,CHb}$= 8.8, J_{gem}=13.4 Hz, P–CHb), 3.75 and 3.45 (2×d, 2×1H, J_{gem}=11.2 Hz, I–CH_2), 2.18–2.40 (m, 2H, H-2′ and H-2″), 1.80 (d, 3H, $J_{CH_3,6}$ = 1.2 Hz, 5-CH_3), 1.27 (d, 12H, $J_{CH_3,CH}$ = 6.3 Hz, 4×CH_3); ^{13}C NMR (DMSO): 163.96 (C-4), 150.60 (C-2), 136.87 (C-6), 110.36 (C-5), 104.47 (d, $J_{C,P}$=11.7 Hz, C-4′), 82.66 (C-1′), 72.40 (C-3′), 70.94 and 70.87 (2×d, $J_{C,P}$=6.8 Hz, $P(OCH)_2$), 56.40 (d, $J_{C,P}$= 169.9 Hz, P–C), 36.51 (C-2′), 24.15, 24.10, 24.06 and 24.02 (4×d, $J_{C,P}$=4.9 Hz, 4×CH_3), 12.37 (CH_3), 5.34 (CH_2–I).

4.2.27. Diisopropyl-(3-*O*-*tert*-butyldimethylsilyl-5-iodo-1-thymin-1-yl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxy)methylphosphonate (30b). Compound **9b** (845 mg, 2.5 mmol) was co-evaporated with dioxane–dichloromethane, dissolved in dichloromethane (10 mL), and **10b** (980 mg, 5 mmol) was added. Then 730 mg (3.25 mmol) of NIS was added, and the reaction and subsequent work-up were carried out as described for **29b**. Chromatography of the residue on silica (100 g) using a 0–5% ethanol–chloroform gradient followed by rechromatography in the same system (0–2.5%) afforded 424 mg (26%) of **30b** as a sirup besides 50 mg of a mixture of three compounds unresolved by NMR. For $C_{23}H_{42}N_2O_8ISiP$ (660.55) calcd 41.82% C, 6.41% H, 4.24% N; found, 41.77% C, 6.23% H, 4.47% N. MS (FAB) 661.3 $(M+H)^+$. ^1H NMR (DMSO): 11.37 (br s, 1H, NH), 7.48 (br q, 1H, J_{6,CH_3} = 1.2 Hz, H-6), 6.19 (dd, 1H, $J_{1',2'}$=3.2, $J_{1',2''}$=8.3 Hz, H-1′), 4.71 (t, 1H, $J_{3',2'}$=8.2 Hz, H-3′), 4.65 and 4.63 (2×d sept, 2×1H, J_{CH,CH_3} = 6.1, $J_{P,OCH}$=7.8 Hz, $P(OCH)_2$), 3.84 (dd, 1H, $J_{P,CHa}$=11.2, J_{gem}=13.4 Hz, P–CHa), 3.835 (dd, 1H, $J_{P,CHb}$=9.8, J_{gem}=13.4 Hz, P–CHb), 3.78 and 3.35 (2×d, 2×1H, J_{gem}=11.5 Hz, I–CH_2), 2.44 (ddd, 1H, $J_{2',1'}$=3.2, $J_{2',3'}$=8.1, $J_{2',2''}$=13.2 Hz, H-2′), 2.21 (dt, 1H, $J_{2'',1'}$=8.3, $J_{2'',3'}$=8.3, $J_{2'',2'}$=13.2 Hz, H-2″), 1.275, 1.270 and 1.26 (3×d, 3H, 3H and 6H, $J_{CH_3,CH}$ = 6.1 Hz, 4×CH_3), 0.88 s, 9H, *t*-Bu), 0.15 and 0.10 (2×s, 2×3H, $Si(CH_3)_2$). ^{13}C NMR (DMSO): 164.11 (C-4), 150.86 (C-2), 138.11 (C-6), 110.35 (C-5), 104.41 (d, $J_{C,P}$=11.7 Hz, C-4′), 82.59 (C-1′), 72.48 (C-3′), 71.06 and 70.96 (2×d, $J_{C,P}$=5.9 Hz, $P(OCH)_2$), 56.31 (d, $J_{C,P}$=169.0 Hz, P–C), 36.45 (C-2′), 24.16, 24.13, 24.08 and 24.04 (4×d, $J_{C,P}$=4.0 Hz, 4×CH_3), 26.12 and 18.09 (*t*-Bu), 12.38 (CH_3), 5.23 (CH_2–I), −2.92 ($SiCH_3$).

4.2.28. Diisopropyl-(3-*O*-*tert*-butyldiphenylsilyl-5-iodo-1-thymin-1-yl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxy)methylphosphonate (31b). Compound **9c** (924 mg, 2 mmol) was co-evaporated with dioxane, dissolved in dichloromethane (5 mL), treated with **10b** (784 mg, 4 mmol), and then NIS (585 mg, 2.6 mmol) was added under stirring. On carrying out the reaction and work-up as described for **29b**, the obtained syrupy residue was chromatographed on silica (gradient, 0–3% chloroform–methanol) to give 530 mg (35%) of **31b** as an amorphous solid, besides trace by-products unresolved by NMR. MS (FAB): 785.3 $(M+H)^+$. ^1H NMR (DMSO): 11.32 (br s, 1H, NH), 7.69 and 7.46 (2×m, 4H and 6H, 2×C_6H_5), 7.03 (br q, 1H, J_{6,CH_3} = 1.0 Hz, H-6), 6.15 (dd, 1H, $J_{1',2''}$=8.3, $J_{1',2'}$= 3.2 Hz, H-1′), 4.71 (t, 1H, $J_{3',2'}$=$J_{3',2''}$=8.3 Hz, H-3′), 4.65 (m, 2H, $P(OCH)_2$), 3.89 (d, 2H, $J_{P,CH}$=10.3 Hz, P–CH_2), 3.75 and 3.22 (2×d, 2×1H, J_{gem}=11.5 Hz, I–CH_2), 2.28 (dt, 1H, $J_{2'',1'}$=$J_{2'',3'}$=8.3, $J_{2'',2'}$=13.4 Hz, H-2″), 1.92 (ddd, 1H, $J_{2',1'}$=3.2, $J_{2',3'}$=8.3, $J_{2',2''}$=13.4 Hz, H-2′), 1.67 (d, 3H, $J_{CH_3,6}$ = 1.0 Hz, CH_3), 1.29, 1.28 and 1.275 (3×d, 3H, 3H and 6H, $J_{CH_3,CH}$ = 6.1 Hz, 4×CH_3), 1.04 (s, 9H, *t*-Bu).

4.2.29. Dimethyl-(3-*O*-*tert*-butyldimethylsilyl-5-iodo-1-thymin-1-yl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxy)methylphosphonate (32b). Compound **9b** (1.69 g, 5 mmol) was co-evaporated with dioxane, dissolved in dichloromethane (20 mL), and treated with dimethyl hydroxymethylphosphonate (1.4 g, 10 mmol). NIS (1.463 g, 6.5 mmol) was added under stirring and after 90 min (TLC in C2 and T1) of stirring at rt, the mixture was worked up as described for **29a**. Column chromatography on silica (100 g; elution with 0–3% chloroform–ethanol) afforded 1.451 g (48%) of **32b** as an amorphous solid, along with a minor product (ca. 1:20, as from NMR; its spectrum not resolved). MS (FAB) 603.1 $(M+H)^+$. ^1H NMR (DMSO): 11.40 (br s, 1H, NH), 7.48 (br q, 1H, J_{6,CH_3} = 1.2 Hz, H-6), 6.18 (dd, 1H, $J_{1',2'}$=4.1, $J_{1',2''}$=8.1 Hz, H-1′), 4.72 (t, 1H, $J_{3',2'}$=8.3, $J_{3',2''}$=7.8 Hz, H-3′), 3.96 (d, 2H, $J_{P,CH}$=10.0 Hz, P–CH_2), 3.73 and 3.40 (2×d, 2×1H, J_{gem}=11.2 Hz, I–CH_2), 3.73 and 3.72 (2×d, 2×3H, J_{P,OCH_3} = 10.5 Hz, $P(OCH_3)_2$), 2.48 (ddd, 1H, $J_{2',1'}$=4.1, $J_{2',3'}$=8.3, $J_{2',2''}$=12.7 Hz, H-2′), 2.23 (dt, 1H, $J_{2'',1'}$=$J_{2'',3'}$=7.8, $J_{2'',2'}$=12.7 Hz, H-2″), 1.80 (d, 3H, $J_{CH_3,6}$ = 1.2 Hz, CH_3), 0.88 (s, 9H, *t*-Bu), 0.15 and 0.11 (2×s, 2×3H, $Si(CH_3)_2$). ^{13}C NMR (DMSO): 163.89 (C-4), 150.43 (C-2), 137.12 (C-6), 110.02 (C-5), 104.56 (d, $J_{C,P}$=12.7 Hz, C-4′), 83.51 (C-1′), 73.82 (C-3′), 55.44 (d, $J_{C,P}$=167.0 Hz, P–C), 53.25 and 53.19 (2×d, $J_{C,P}$=6.8 Hz, $P(OCH_3)_2$), 37.36 (C-2′), 25.78 and 17.78 (*t*-Bu), 12.29 (CH_3), 5.13 (CH_2–I), −4.50 and −4.57 ($Si(CH_3)_2$).

4.2.30. Dimethyl-(3-*O*-*tert*-butyldiphenylsilyl-5-iodo-1-thymin-1-yl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxy)methylphosphonate (33b). Using the same procedure and stoichiometry as for **32b** (reaction time, 90 min), compound **9c** (693 mg, 1.5 mmol) was treated with **10a** and NIS to afford, after similar work-up and column chromatography (50 g silica, 0–3% chloroform–ethanol gradient), 410 mg (37%) of **33b** (R_f=0.25 in C2) as a thick oil, along with a minor (ca. 1:10, NMR) product (the signals in ^1H NMR were not fully resolvable). MS (FAB): 728.3 $(M+H)^+$. ^1H NMR (DMSO): 11.35 (br s, 1H, NH), 7.66–7.72 and 7.30–7.52 (2×m, 4H and 6H, 2×C_6H_5), 7.12 (br s, 1H, H-6), 6.15 (dd, 1H, $J_{1',2''}$=8.3, $J_{1',2'}$=3.4 Hz, H-1′), 4.75 (t, 1H, $J_{3',2'}$=8.1, $J_{3',2''}$=8.1 Hz, H-3′), 4.03 (d, 2H, $J_{P,CH}$=10.5 Hz, P–CH_2), 3.76 (d, 6H, J_{P,OCH_3} = 10.5 Hz, $P(OCH_3)_2$), 3.65 and 3.22 (2×d, 2×1H, J_{gem}=11.2 Hz, I–CH_2), 2.28 (dt, 1H, $J_{2'',1'}$=8.3, $J_{2'',3'}$=8.3, $J_{2'',2'}$=13.4 Hz, H-2″), 2.04 (ddd, 1H, $J_{2',1'}$=3.4, $J_{2',3'}$=8.1, $J_{2',2''}$=13.4 Hz, H-2′), 1.70 (br s, 3H, 5-CH_3), 1.04 (s, 9H, *t*-Bu). ^{13}C NMR (DMSO): 163.72 (C-4), 150.28 (C-2), 136.69 (C-6), 132.91, 132.74, 135.66, 135.64, 130.39, 130.36, 128.16 (arom. C), 109.99 (C-5), 104.50 (d, $J_{C,P}$=11.7 Hz, C-4′), 83.21 (C-1′), 74.37 (C-3′), 55.13 (d, $J_{C,P}$=167.0 Hz, P–C),

53.22 and 53.12 (2×d, $J_{C,P}$=5.9 Hz, $P(OCH_3)_2$), 36.75 (C-2′), 26.79 and 19.93 (*t*-Bu), 12.23 (5-CH_3), 4.85 (CH_2–I).

4.2.31. Diisopropyl-(5-bromo-3-*O*-*tert*-butyldimethylsilyl-1-thymin-1-yl-1,2,5-trideoxy-α-L-*threo*-pentofuranos-4-yloxy)methylphosphonate (34a) and diisopropyl-(5-bromo-3-*O*-*tert*-butyldimethylsilyl-1-thymin-1-yl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxy)-methylphosphonate (34b). Compound **9b** (563 mg, 1.67 mmol) was co-evaporated with dioxane, dissolved in dichloromethane (10 mL), and **10b** (655 mg, 3.34 mmol) was added. NBS (386 mg, 2.17 mmol) was added under stirring and the whole was left to react for 5 h at rt (TLC in C2). The mixture was diluted with dichloromethane (150 mL) and washed with a 5% solution of $NaHCO_3$ (150 mL). The aqueous layer was treated with dichloromethane (2×50 mL), the combined organic washings were washed with water (100 mL), dried with $MgSO_4$ and evaporated. The residue was purified by preparative reversed-phase chromatography under elution with a linear gradient of water–methanol (0–50% in 180 min, 50–100% in 120 min, 10 mL min^{-1}). The obtained product was rechromatographed on silica gel column (50 g) using a 0–3% chloroform–ethanol gradient elution. Yield: 423 mg (41%) of a 5:1 **34b**–**34a** isomeric mixture (as of NMR) in the form of a thick oil, MS (FAB) 614.1 $(M+H)^+$.

Isomer **34a**, α-L-threo, minor: ^{1}H NMR (DMSO): 11.12 (br s, 1H, NH), 7.64 (br q, 1 H, J_{6,CH_3} = 1.0 Hz, H-6), 6.20 (dd, 1 H, $J_{1',2''}$=6.3, $J_{1',2'}$=9.0 Hz, H-1′), 5.87 (br d, 1H, $J_{3',2''}$<0.5, $J_{3',2'}$=5.0 Hz, H-3′), 4.60 (m, 2H, $P(OCH)_2$), 3.90 and 3.51 (2×d, 2×1H, J_{gem}=11.2 Hz, CH_2–Br), 3.68 (dd, 1H, $J_{P,CHa}$=11.5, J_{gem}=13.2 Hz, P–CHa), 3.61 (dd, 1H, $J_{P,CHb}$=7.1, J_{gem}=13.2 Hz, P–CHb), 2.54 and 2.10 (2×m, 2×1H, H-2′ and H-2″), 1.87 (d, 3H, $J_{CH_3,6}$ = 1.0 Hz, 5-CH_3), further CH_3 signals overlapped.

Isomer **34b**, ß-D-erythro, major: ^{1}H NMR (DMSO): 11.37 (br s, 1H, NH), 7.46 (br q, 1H, J_{6,CH_3} = 1.2 Hz, H-6), 6.25 (dd, 1H, $J_{1',2'}$=3.7, $J_{1',2''}$=8.3 Hz, H-1′), 4.57–4.70 (m, 3H, H-3′ and $P(OCH)_2$), 3.92 and 3.68 (2×d, 2×1H, J_{gem}=11.2 Hz, Br–CH_2), 3.89 (dd, 1H, $J_{P,CHa}$=12.0, J_{gem}=13.2 Hz, P–CHa), 3.80 (dd, 1H, $J_{P,CHb}$=8.7, J_{gem}=13.2 Hz, P–CHb), 2.32 (ddd, 1H, $J_{2',1'}$=3.7, $J_{2',3'}$=8.3, $J_{2',2''}$=13.4 Hz, H-2′), 2.27 (dt, 1H, $J_{2'',1'}$=8.3, $J_{2'',3'}$=8.3, $J_{2'',2'}$=13.4 Hz, H-2″), 1.79 (d, 3H, $J_{CH_3,6}$ = 1.2 Hz, 5-CH_3), 1.27 and 1.26 (2×d, 2×6H, $J_{CH_3,CH}$ = 6.3 Hz, 4×CH_3). ^{13}C NMR (DMSO): 163.85 (C-4), 150.50 (C-2), 136.52 (C-6), 110.16 (C-5), 104.75 (d, $J_{C,P}$=10.7 Hz, C-4′), 82.66 (C-1′), 71.38 (C-3′), 70.66 and 70.61 (2×d, $J_{C,P}$=5.9 Hz, $P(OCH)_2$), 56.47 (d, $J_{C,P}$=169.9 Hz, P–C), 36.23 (C-2′), 31.60 (CH_2–Br), 23.91 and 23.88 (2×d, $J_{C,P}$=3.9 Hz, 2×CH_3), 25.0 and 18.0 (*t*-Bu), 12.25 (5-CH_3), −5.0 ($Si(CH_3)_2$).

4.2.32. Diisopropyl-(5-azido-3-*O*-*tert*-butyldimethylsilyl-1-thymin-1-yl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxy)methylphosphonate (35b). Compound **30b** (234 mg, 0.35 mmol) was co-evaporated with dioxane, dissolved in dry DMF (15 mL) and sodium azide (300 mg, 4.61 mmol) was added. The mixture was heated at 100 °C for 48 h (TLC in C2), then the solvent was removed under reduced pressure at 50 °C, and the residue partitioned between dichloromethane (50 mL) and water (2×50 mL). The organic layer was dried (Na_2SO_4), evaporated and chromatographed on silica (50 g) under elution with a 0–5% chloroform–ethanol gradient.

The desired azido derivative **35b** (58.5 mg, 29%), obtained as a thick oil, was contaminated by the starting compound and could not be separated from it by reversed-phase purification. MS (FAB): 598.2 (M^++Na). IR spectrum (cm^{-1}): 3392, 3178 (NH); 2960, 2900, 1254, 844, 1411 (CH_3, $SiMe_2$); 2109 (–N_3); 1692, 1713 (C=O); 1382, 1374 (CH_3, isopropyl); 1361 (CH_3, *t*-Bu); 1144, 1133 (C–O); 999, 1055 (C–O–P–O–C). ^{1}H NMR (DMSO): 11.36 (br s, 1H, NH), 7.42 (br q, 1H, J_{6,CH_3} = 1.2 Hz, H-6), 6.21 (dd, 1H, $J_{1',2'}$=3.2, $J_{1',2''}$=8.8 Hz, H-1′), 4.74 (t, 1H, $J_{3',2'}$=$J_{3',2''}$=8.5 Hz, H-3′), 4.64 (m, 2H, $P(OCH)_2$), 3.68–3.94 (m, 4H, P–CH_2 and N–CH_2), 2.22–2.44 (m, 2H, H-2′ and H-2″), 1.79 (d, 3H, $J_{CH_3,6}$ = 1.2 Hz, 5-CH_3), 1.27 and 1.26 (2×d, 2×6H, $J_{CH_3,CH}$ = 6.3 Hz, 4×CH_3), 0.87 (s, 9H, *t*-Bu), 0.10 and 0.08 (2×s, 2×3H, $Si(CH_3)_2$). ^{13}C NMR (DMSO): 163.98 (C-4), 150.41 (C-2), 137.50 (C-6), 109.99 (C-5), 105.98 (d, $J_{C,P}$=11.7 Hz, C-4′), 84.38 (C-1′), 72.39 (C-3′), 70.51 (d, $J_{C,P}$=5.9 Hz, $P(OCH)_2$), 56.20 (d, $J_{C,P}$=169.0 Hz, P–C), 50.22 (CH_2–N), 36.63 (C-2′), 25.74 and 17.81 (*t*-Bu), 24.10 and 23.96 (2×d, $J_{C,P}$=4.9 Hz, 4×CH_3), 12.23 (5-CH_3), −4.52 and −4.69 ($Si(CH_3)_2$).

4.2.33. Methyl-(3-*O*-*tert*-butyldimethylsilyl-5-iodo-1-thymin-1-yl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxy)methylphosphonate (36a). Compound **32b** (604 mg, 1 mmol) was dissolved in dry DMSO (10 mL) and 650 mg (10 mmol) of sodium azide was added. The mixture was stirred and on disappearance of the starting product (3 d, TLC in C2), the solvent was removed and the residue was chromatographed on preparative reversed phase column using a water–methanol linear gradient (0–50% in 30 min, 50–100% in 240 min, 10 mL min^{-1}). Obtained: 302 mg (51%) of **36a** as an oil. MS (FAB): 613.2 (M^++Na). ^{1}H NMR (DMSO): 11.40 (br s, 1H, NH), 7.45 (br q, 1H, J_{6,CH_3} = 1.2 Hz, H-6), 6.20 (t, 1H, $J_{1',2'}$=$J_{1',2''}$=6.3 Hz, H-1′), 4.66 (t, 1H, $J_{3',2'}$=$J_{3',2''}$=8.5 Hz, H-3′), 3.73 and 3.26 (2×d, 2×1H, J_{gem}=11.5 Hz, I–CH_2), 3.48 (br t, 1H, $J_{P,CHa}$=J_{gem}=12.0 Hz, P–CHa), 3.43 (d, 3H, J_{P,OCH_3} = 9.8 Hz, P–OCH_3), 3.39 (dd, 1H, $J_{P,CHb}$=8.5, J_{gem}=12.2 Hz, P–CHb), 2.29 (dd, 2H, $J_{2',1'}$=$J_{2'',1'}$=6.3, $J_{2',3'}$=$J_{2'',3'}$=8.5 Hz, H-2′+H-2″), 1.80 (d, 3H, $J_{CH_3,6}$ = 1.2 Hz, 5-CH_3), 0.87 (s, 9H, *t*-Bu), 0.14 and 0.10 (2×s, 2×3H, $Si(CH_3)_2$). ^{13}C NMR (DMSO): 164.07 (C-4), 150.53 (C-2), 137.09 (C-6), 109.92 (C-5), 103.27 (d, $J_{C,P}$=8.8 Hz, C-4′), 82.63 (C-1′), 73.41 (C-3′), 58.48 (d, $J_{C,P}$=155.3 Hz, P–C), 51.93 (d, $J_{C,P}$=4.9 Hz, OCH_3), 36.81 (C-2′), 25.91 and 17.89 (*t*-Bu), 12.41 (5-CH_3), 4.69 (CH_2–I), −4.41 and −4.44 ($Si(CH_3)_2$).

4.2.34. Methyl-(3-*O*-*tert*-butyldiphenylsilyl-5-iodo-1-thymin-1-yl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxy)methylphosphonate (36b). Compound **33b** (259 mg, 0.36 mmol) in dry DMF (5 mL) was heated with 176 mg (3.6 mmol) of sodium cyanide at 100 °C for 3 d (TLC in C2). The solvent was removed, and the residue chromatographed on preparative reversed phase column using a water–methanol linear gradient (0–50% in 90 min, 50–100% in 150 min, 10 mL min^{-1}). Obtained: 118 mg (46%) of title product in the form of an oil. MS (FAB): 737.1 (M^++Na). ^{1}H NMR (DMSO): 11.35 br s, 1H, NH), 7.70 and

7.42–7.52 (2×m, 4H and 6H, 2×C_6H_5), 6.91 (br s, 1H, H-6), 6.22 (dd, 1H, $J_{1',2'}$=2.5, $J_{1',2''}$=9.0 Hz, H-1′), 4.61 (t, 1H, $J_{3',2''}$=8.8, $J_{3',2'}$=8.8 Hz, H-3′), 3.72 and 3.15 (2×d, 2×1H, J_{gem}=11.5 Hz, I–CH_2), 3.51 (dd, 1H, $J_{P,CHa}$=11.0, J_{gem}= 12.2 Hz, P–CHa), 3.50 (d, 3H, J_{P,OCH_3} = 9.5 Hz, P–OCH_3), 3.44 (dd, 1H, $J_{P,CHb}$=8.0, J_{gem}=12.2 Hz, P–CHb), 2.37 (dt, 1H, $J_{2'',1'}$=9.0, $J_{2'',3'}$=8.8, $J_{2'',2'}$=13.2 Hz, H-2″), 1.71 (m, 1H, H-2′), 1.66 (br s, 3H, 5-CH_3), 1.02 (s, 9H, *t*-Bu). ^{13}C NMR (DMSO): 164.95 (C-4), 151.18 (C-2), 135.98 (C-6), 132.99, 132.92, 135.72, 135.65, 128.13, 128.10, 130.28 and 130.24 (arom. C), 110.09 (C-5), 103.21 (d, $J_{C,P}$=8.8 Hz, C-4′), 81.83 (C-1′), 73.95 (C-3′), 58.61 (d, $J_{C,P}$=155.3 Hz, P–C), 51.97 (d, $J_{C,P}$=4.9 Hz, P–OCH_3), 36.28 (C-2′), 26.85 and 18.94 (*t*-Bu), 12.50 (5-CH_3), 4.85 (CH_2–I).

4.2.35. 2,3′-Anhydro-1-(3-*O*-*tert*-butyldimethylsilyl-2,5-dideoxy-β-L-*glycero*-pent-4-enofuranosyl)thymine (38). To the compound **9a** (2.24 g, 10 mmol) in DMF (10 mL), triphenyl phosphine (3.93 g, 15 mmol) was added and then, under stirring, diisopropyl-azodicarboxylate (2.93 mL, 15 mmol; in 10 mL of DMF) was added dropwise while keeping the reaction temperature below 20 °C. The whole was then stirred at rt for 30 min (TLC in H-1). The product was then precipitated by dropping the mixture into stirred ether (400 mL), and the solid was collected on sintered glass and washed with ether. On evaporating the solvents from the filtrate, the residue was re-precipitated in ether (100 mL). Total yield from two crops, 1.848 g (89%) of **38** as a white amorphous solid. HRMS FAB+ calcd for $C_{10}H_{11}N_2O_3$ $(M+H)^+$ 207.0770, found 207.0799. ^{1}H NMR (DMSO): 7.65 (br q, 1H, J_{6,CH_3} = 1.2 Hz, H-6), 6.18 (dd, 1H, $J_{1',2'}$=1.0, $J_{1',2''}$= 4.0 Hz, H-1′), 5.54 (dt, 1H, $J_{3',2'}$=$J_{3',5''}$=1.2, $J_{3',2''}$=2.9 Hz, H-3′), 4.69 (br d, 1H, J_{gem}=2.5 Hz, H-5′), 4.61 (dd, 1H, $J_{5'',3'}$=1.2, $J_{5'',5'}$=2.5 Hz, H-5″), 2.66 (br d, 1H, $J_{2',1'}$= $J_{2',3'}$=1.1, $J_{2',2''}$=13.2 Hz, H-2′), 2.47 (ddd, 1H, $J_{2'',3'}$=2.9, $J_{2'',1'}$=4.0, $J_{2'',2'}$=13.2 Hz, H-2″), 1.76 (d, 3H, $J_{CH_3,6}$ = 1.2 Hz, 5-CH_3). ^{13}C NMR (DMSO): 170.70 (C-4), 158.97 (C-2), 136.94 (C-6), 116.62 (C-5), 89.55 (C-4′), 87.43 (C-1′), 75.77 (C-3′), 32.92 (C-2′), 13.15 (CH_3).

4.2.36. 1-(3-*O*-*tert*-Butyldimethylsilyl-2,5-dideoxy-β-L-*glycero*-pent-4-enofuranosyl)thymine (39b). Compound **38** (1.031; 5 mmol) was set with 0.1 M NaOH (60 mL, 6 mmol) for 36 h at rt. A single reaction product was then detected on TLC checking in H3. For work-up, first the Na^+ ions were exchanged for py^+ by treatment with Dowex 50 (py^+) in cooled (0 °C) 50% aq pyridine. The solvents were evaporated, and the residue **39a** (ca. 0.90 g, 4 mmol) was immediately used for subsequent reaction without further purification to avoid decomposition. It was made anhydrous by repeated co-vaporation with pyridine, then dry pyridine (4 mL) was added followed by *tert*-butyldimethylsilyl imidazole (2.19 g, 12 mmol, 3 equiv) and the mixture was stirred for 3 h at rt (TLC in C2). After quenching with anhydrous methanol (0.5 mL) and stirring for 30 min, the solvents were evaporated and the residue partitioned between 2 M triethylammonium hydrogen carbonate and chloroform. The organic layer was dried by $MgSO_4$, the solvent evaporated, and the resulting sirup chromatographed on silica gel (50 g) using elution with toluene to 1:1 toluene–acetone gradient. Obtained: 634 mg of compound **39b** (47%, based on **38**) as an amorphous solid. HRMS FAB+ calcd for $C_{16}H_{27}N_2O_4Si$ $(M+H)^+$ 339.1740, found 339.1727. ^{1}H NMR ($CDCl_3$): 9.71 (br s, 1H, NH), 7.44 (q, 1H, J_{6,CH_3} = 1.2 Hz, H-6), 6.47 (dd, 1H, $J_{1',2'}$=3.3, $J_{1',2''}$= 7.1 Hz, H-1′), 4.68 (ddt, 1H, $J_{3',2'}$=3.3, $J_{3',2''}$=6.7, $J_{3',5'}$= $J_{3',5''}$∼1.0 Hz, H-3′), 4.25 (dd, 1H, $J_{5',5''}$=2.2, $J_{5',3'}$∼1.0 Hz, H-5′), 4.57 (dd, 1H, $J_{5',5''}$=2.2, $J_{5',3'}$=$J_{5'',3'}$∼1.0 Hz, H-5″), 2.65 (dt, 1H, $J_{2'',1'}$=7.1, $J_{2'',2'}$=14.2, $J_{2'',3'}$=6.7 Hz, H-2″), 2.04 (dt, 1H, $J_{2',1'}$=3.3, $J_{2',2''}$=14.2, $J_{2',3'}$=3.3 Hz, H-2′), 1.92 (d, 3H, $J_{CH_3,6}$ = 1.2 Hz, 5-CH_3), 0.88 s, 9H, *t*-Bu), 0.11 and 0.14 (2×s, 2×3H, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): 164.01 (C-4), 163.09 (C-4′), 150.54 (C-2), 135.72 (C-6), 110.77 (C-5), 85.36 (C-5′), 85.03 (C-1′), 69.83 (C-3′), 40.22 (C-2′), 17.87 and 25.49 (*t*-Bu), 12.56 (5-CH_3), 4.78 and −5.04 ($Si(CH_3)_2$).

4.2.37. Dimethyl-(3-*O*-*tert*-butyldimethylsilyl-1-thymin-1-yl-1,2,5-trideoxy-α-L-*threo*-pentofuranos-4-yloxy)methylphosphonate (40a) and dimethyl-(3-*O*-*tert*-butyldimethylsilyl-1-thymin-1-yl-1,2,5-trideoxy-β-D-*erythro*-pentofuranos-4-yloxy)methylphosphonate (40b). To a solution of **39b** (169 mg, 0.5 mmol) in dichloromethane (3 mL), **10a** (140 mg, 1 mmol, 2 equiv) and A3 molecular sieves (Merck) (0.7 g) were added followed by PTS (377 mg, 1.5 mmol) and the whole was stirred overnight under argon (TLC in C2). The solids were filtered off on Celite, the washings were pooled, the solvent evaporated and the residue chromatographed on a silica gel column using elution by a 0–5% chloroform–ethanol gradient to provide 60 mg (25%) of **40a** and 122 mg (51%) of **40b** as solid foams.

Isomer **40a**: HRMS FAB+ calcd for $C_{19}H_{36}N_2O_8SiP$ 478.1900, found 479.1979 $(M+H)^+$. ^{1}H NMR ($CDCl_3$): 9.40 (br s, 1H, NH), 7.71 (q, 1H, J_{6,CH_3} = 1.2 Hz, H-6), 6.36 (dd, 1H, $J_{1',2'}$=6.4, $J_{1',2''}$=8.7 Hz, H-1′), 4.07 (ddd, 1H, $J_{3',2'}$=6.5, $J_{3',2''}$=10.2, $J_{3',P}$=1.1 Hz, H-3′), 3.91 (dd, 1H, J_{gem}=12.8, $J_{P,CHa}$=11.0 Hz, P–CHa), 4.00 (dd, 1H, J_{gem}=12.8, J_{P-CHb}=11.6 Hz, P–CHb), 3.86 and 3.82 (2×d, 2×3H, J_{P,OCH_3} = 10.6 Hz, P(OCH_3)$_2$), 2.45 (dt, 1H, $J_{2',1'}$=6.4, $J_{2',2''}$=12.3, $J_{2',3'}$=6.5 Hz, H-2′), 2.25 (dt, 1H, $J_{2'',1'}$=8.7, $J_{2'',2'}$=12.3, $J_{2'',3'}$=10.2 Hz, H-2″), 2.03 (d, 3H, J_{6,CH_3} = 1.2 Hz, 5-CH_3), 1.47 (s, 3H, 4′-CH_3), 0.92 (s, 9H, *t*-Bu), 0.12 and 0.09 (2×s, 2×3H, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): 163.85 (C-4), 150.97 (C-2), 136.03 (C-6), 112.20 (C-5), 105.54 (d, $J_{C,P}$=14.2 Hz, C-4′), 80.89 (C-1′), 76.53 (C-3′), 56.75 (d, $J_{C,P}$=172.4 Hz, P–CH_2–O), 53.48 and 52.83 (2×d, $J_{C,P}$=6.4 Hz, P(OCH_3)$_2$), 36.35 (C-2′), 19.34 (4′-CH_3), 17.91 and 25.51 (*t*-Bu), 11.95 (5-CH_3), −4.91 and −5.07 ($Si(CH_3)_2$).

Isomer **40b**: ^{1}H NMR ($CDCl_3$): 9.75 (br s, 1H, NH), 7.56 (q, 1H, J_{6,CH_3} = 1.2 Hz, H-6), 6.33 (dd, 1H, $J_{1',2'}$=2.2, $J_{1',2''}$=8.5 Hz, H-1′), 4.11 (d, 1H, $J_{3',2'}$∼0, $J_{3',2''}$=5.4 Hz, H-3′), 3.73 (dd, 1H, J_{gem}=13.6, $J_{P,CHa}$=8.0 Hz, P–CHa), 3.95 (dd, 1H, J_{gem}=13.6, $J_{P,CHb}$=12.9 Hz, P–CHb), 3.82 (d, 6H, J_{P,OCH_3} = 10.8 Hz, P(OCH_3)$_2$), 2.91 (ddd, 1H, $J_{2'',1'}$=8.5, $J_{2'',2'}$=14.5, $J_{2'',3'}$=5.4 Hz, H-2″), 1.90 (d, 3H, $J_{CH_3,6}$ = 1.2 Hz, 5-CH_3), 1.74 (dd, 1H, $J_{2',1'}$=2.2, $J_{2',2''}$=14.5, $J_{2',3'}$∼0 Hz, H-2′), 1.48 (s, 3H, 4′-CH_3), 0.90 (s, 9H, *t*-Bu), 0.11 and 0.07 (2×s, 2×3H, $Si(CH_3)_2$).

^{13}C NMR ($CDCl_3$): 163.97 (C-4), 150.57 (C-2), 136.41 (C-6), 111.61 (d, $J_{C,P}$=10.8 Hz, C-4′), 110.98 (C-5), 83.76 (C-1′), 75.34 (C-3′), 54.33 (d, $J_{C,P}$=173.4 Hz, P–CH_2–O), 53.06 and 53.01 (2×d, $J_{C,P}$=6.6 Hz, P(OCH_3)$_2$), 40.28 (C-2′),

17.85 and 25.53 (*t*-Bu), 16.13 (4′-CH_3), 12.45 (5-CH_3), −5.00 and −5.06 ($Si(CH_3)_2$).

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References and notes

1. Scheit, K. H. *Nucleotide Analogues. Synthesis and Biological Function*; Wiley-Interscience: New York, NY, 1980.
2. Freier, S. M.; Altmann, K. H. *Nucleic Acids Res.* **1997**, *25*, 4429–4443.
3. Holý, A. *Advances in Antiviral Drug Design*; JAI: Greenwich, CT, 1993; Vol. 1, p 179.
4. Kim, C. U.; Luh, B. Y.; Martin, J. C. *J. Org. Chem.* **1991**, *56*, 2642–2647.
5. De Clercq, E.; Holý, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P. C. *Nature* **1986**, *323*, 464–467.
6. Holý, A.; Rosenberg, I. *Collect. Czech. Chem. Commun.* **1987**, *52*, 2801–2809.
7. Holý, A.; Gunter, J.; Dvořáková, H.; Masojídková, M.; Andrei, G.; Snoeck, R.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1999**, *42*, 2064–2068.
8. Kim, C. U.; Luh, B. Y.; Misco, P. F.; Martin, J. C. *Nucleosides Nucleotides* **1991**, *10*, 371–375.
9. Jähne, G.; Müller, A.; Kroha, H.; Rösner, M.; Holzhäuser, O.; Meichsner, C.; Helsberg, M.; Winkler, I.; Riess, G. *Tetrahedron Lett.* **1992**, *33*, 5335–5338.
10. Endová, M.; Masojídková, M.; Buděšínský, M.; Rosenberg, I. *Tetrahedron* **1998**, *54*, 11151–11186.
11. Endová, M.; Masojídková, M.; Buděšínský, M.; Rosenberg, I. *Tetrahedron* **1998**, *54*, 11187–11208.
12. Králíková, Š.; Buděšínský, M.; Masojídková, M.; Rosenberg, I. *Nucleosides Nucleotides Nucleic Acids* **2000**, *19*, 1159–1183.
13. Králíková, Š.; Buděšínský, M.; Masojídková, M.; Rosenberg, I. *Tetrahedron Lett.* **2000**, *41*, 955–958.
14. Snášel, J.; Rejman, D.; Liboska, R.; Točík, Z.; Ruml, T.; Rosenberg, I.; Pichová, I. *Eur. J. Biochem.* **2001**, *268*, 980–986.
15. Rejman, D.; Erbs, J.; Rosenberg, I. *Org. Process Res. Dev.* **2000**, *4*, 473–476.
16. Rejman, D.; Masojídková, M.; De Clercq, E.; Rosenberg, I. *Nucleosides Nucleotides Nucleic Acids* **2001**, *20*, 1497–1522.
17. Hanuš, J.; Chmelová, K.; Štěpánek, J.; Turpin, P.-Y.; Bok, J.; Rosenberg, I.; Točík, Z. *J. Raman Spectrosc.* **1999**, *30*, 667–676.
18. Zachová, J.; Císařová, I.; Buděšínský, M.; Liboska, R.; Točík, Z.; Rosenberg, I. *Nucleosides Nucleotides* **1999**, *18*, 2581–2599.
19. Rejman, D.; Snášel, J.; Liboska, R.; Točík, Z.; Pačes, O.; Králíková, Š.; Rinnová, M.; Koiš, P.; Rosenberg, I. *Nucleosides Nucleotides Nucleic Acids* **2001**, *20*, 819–823.
20. Hanuš, J.; Barvík, I.; Ruszová-Chmelová, K.; Štěpánek, J.; Turpin, P.-Y.; Bok, J.; Rosenberg, I.; Petrová-Endová, M. *Nucleic Acids Res.* **2001**, *29*, 5182–5194.
21. Pressová, M.; Endová, M.; Točík, Z.; Liboska, R.; Rosenberg, I. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1225–1230.
22. Rosenberg, I. *Frontiers in Nucleosides and Nucleic Acids*; Schinazi, R. F., Liotta, D. C., Eds.; IHL: Tucker, GA, 2004; pp 519–548.
23. Summerer, D.; Marx, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3693–3695.
24. Ueda, T. *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum: New York, NY, 1988; Vol. 1, pp 83–87.
25. Verheyden, J. P. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1975**, *97*, 4386–4395.
26. Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 3573–3579.
27. Maag, H.; Rydzewski, R. M.; McRoberts, M. J.; Crawford-Ruth, D.; Verheyden, J. P. H.; Prisbe, E. J. *J. Med. Chem.* **1992**, *35*, 1440–1451.
28. Suciu, N.; Lerner, L. *Carbohydr. Res.* **1975**, *44*, 112–115.
29. Robins, M. J.; Wnuk, S. F.; Mullah, K. B.; Dalley, N. K. *J. Org. Chem.* **1994**, *59*, 544–555.
30. Joshi, B. V.; Reese, C. B. *Tetrahedron Lett.* **1993**, *34*, 5807–5810.
31. Kim, C. U.; Luh, B. Y.; Misco, P. F.; Martin, J. C. *Nucleosides Nucleotides* **1991**, *10*, 483–485.
32. Nicotra, F.; Panza, L.; Russo, G. *Tetrahedron Lett.* **1991**, *32*, 4035–4038.
33. Tong, W.; Agback, P.; Chattopadhyaya, J. *Acta Chem. Scand.* **1993**, *47*, 145–156.
34. Rinkel, L. J.; Altona, C. *J. Biomol. Struct. Dyn.* **1987**, *4*, 621–649.
35. Točík, Z.; Barvík, I., Jr.; Buděšínský, M.; Rosenberg, I. *Biopolymers* **2006**, *83*, 400–413.
36. Wang, Y.; Hogencamp, H. P. C. *J. Org. Chem.* **1978**, *43*, 3324–3326.
37. Joshi, B. V.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 441–443.
38. Haraguchi, K.; Takeda, S.; Tanaka, H. *Org. Lett.* **2003**, *5*, 1399–1402.
39. Henningfeld, K. A.; Arslan, T.; Hecht, S. M. *J. Am. Chem. Soc.* **1996**, *118*, 11701–11714.
40. Bhat, B.; Sanghvi, Y. *Tetrahedron Lett.* **1997**, *38*, 8811–8814.
41. Lin, P. K. T.; Brown, D. M. *Nucleic Acids Res.* **1989**, *17*, 10373–10383.
42. Urjasz, W.; Celewicz, L.; Golankiewicz, K. *Nucleosides Nucleotides* **1996**, *15*, 1189–1202.
43. Haraguchi, K.; Takeda, S.; Tanaka, H.; Nitanda, T.; Baba, M.; Dutschman, G. E.; Cheng, Y.-C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3775–3777.
44. Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772–3774.
45. Schwartz, N. N.; Blumbergs, J. H. *J. Org. Chem.* **1964**, *29*, 1976–1979.