

Ex-Chiral-Pool Synthesis of β -Hydroxyphosphonate Nucleoside AnaloguesFranck Gallier,^[a] Suzanne Peyrottes,^{*[a]} and Christian Périgaud^[a]**Keywords:** Nucleotides / Phosphorus / Carbohydrates / Glycosylation

A new series of mononucleotide analogues bearing a nonhydrolysable P–C bond instead of the P–O phosphate linkage is presented. We intend to set up an approach that allows the synthesis of β -hydroxyphosphonate nucleoside analogues as a single diastereoisomer. In this respect, the key “sugar-phosphonate” intermediate was obtained through an Arbu-

sov reaction from an iodosugar derivative in which the stereochemistry of the β -hydroxy group is determined by the choice of the starting material and remains in the resulting nucleotide analogues.

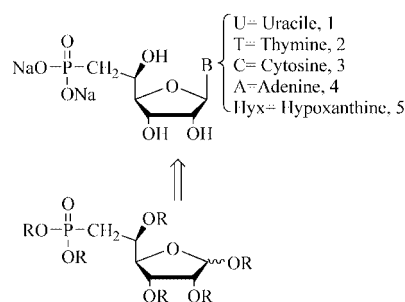
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Introduction

In the search for more effective antiviral/anticancer agents, various modifications of nucleotides have been proposed.^[1–3] As part of our ongoing research on nucleoside 5'-monophosphate analogues (mononucleotides),^[4,5] we recently focused on the development of phosphonate derivatives. This family of compounds, in which the hydrolysable P–O bond is replaced by a chemically and enzymatically stable P–C bond, is very important among the arsenal of biologically active molecules. The most potent structures are acyclic nucleoside phosphonate derivatives developed by Holy and coworkers^[2,6,7] and exhibit broad antiviral activities. In the mean time, only a few examples of phosphonate derivatives incorporating a furanose ring have been reported, although these structures could present interesting biological properties.^[8–10] This prompted us to explore new hydroxyphosphonate analogues isosteric to 5'-mononucleotide.

Synthetic approaches to α -hydroxyalkanphosphonates include the addition of dialkylphosphites to aldehydes, the reduction of ketophosphonates and the opening of 1,3-dioxane acetals with triethylphosphite.^[11–13] A few examples have also been applied to the synthesis of the corresponding α -hydroxyphosphonate nucleosidic derivatives.^[14–17] Regarding the preparation of β -hydroxyphosphonates, only a few synthetic pathways are available. They include the reaction of aldehydes with the lithium salt of dialkylmethylphosphonates generated in situ^[18] or dialkyliodomethylphosphonates in the presence of a samarium catalyst,^[19] followed by the reduction of the corresponding ketophosphonates.^[20] Such methodologies usually lead to racemic mixtures of α - or β -hydroxyphosphonates and then involved

their chemical or enzymatic resolutions.^[21] Only, the asymmetric reduction in the presence of chiral catalysts gives rise to chiral α - or β -hydroxyalkanphosphonates.^[12,20,22] Because no report dealing with the synthesis of a pure diastereoisomer of the corresponding β -hydroxyphosphonate nucleoside analogues has been described, we decided to evaluate the potentiality of such constructs (Scheme 1, compounds 1–5) over a large panel of enzymes involved in the anabolism of nucleic acids. The presence of an additional hydroxy group may help to increase the affinity of these analogues in the binding site of various enzymatic systems, and can also be considered as a precursor of a large number of modifications in the β position, which allows for a SAR study to be performed.



Scheme 1.

The development of a practical synthesis of β -hydroxyphosphonate nucleoside analogues would require (1) an efficient preparation of the β -ketophosphonic esters followed by an asymmetric hydrogenation or (2) an addition of dialkylmethyl- or iodomethylphosphonate carbanions^[18,19] to nucleoside 5'-aldehydes leading to the racemic mixture and followed by the search of suitable conditions for its efficient resolution. However, these two approaches presented major drawbacks: the availability of the precursors; β -ketophosphonic ester of nucleosidic derivatives are not yet

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described in the literature, and both synthetic pathways are well-documented only for simple substrates such as β -hydroxyalkan- or β -hydroxyarylphosphinic derivatives.^[12,13,19,21–23] Consequently, we intended to set up an ex-chiral-pool synthesis using an extended sugar derivative (allofuranose) in which the stereochemistry of the β -hydroxy group would remain unchanged during the synthesis (Scheme 1). The choice of setting the synthetic approach on the (5*S*)-isomer relies on the availability of the starting material, indeed diacetone D-glucose is a cheap and commercially available derivative.

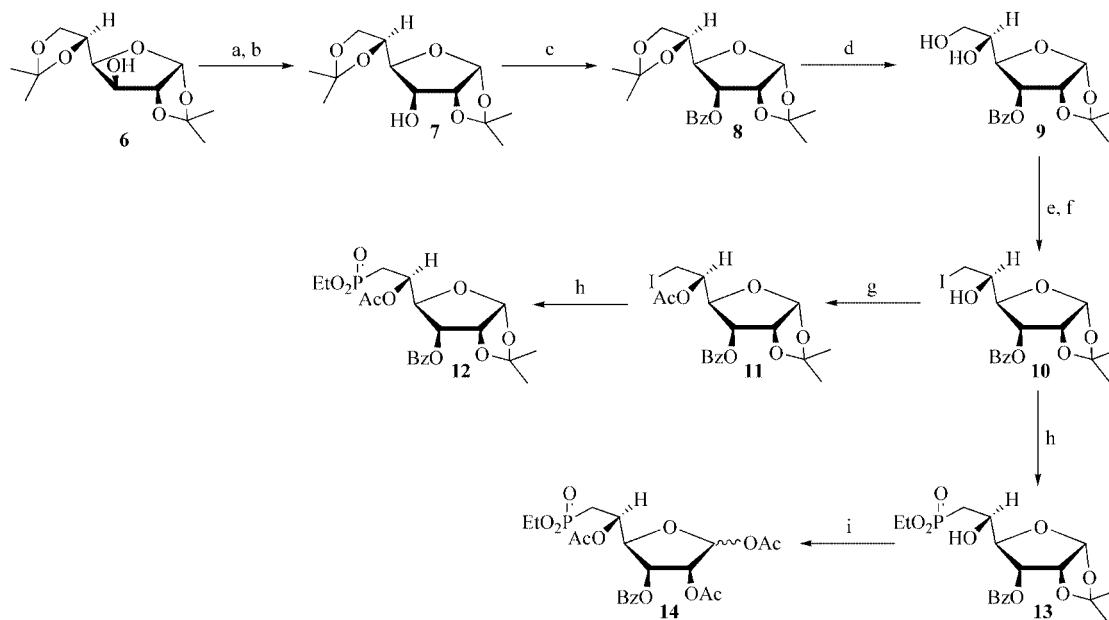
Results and Discussion

The target nucleotide analogues (Scheme 1, compounds 1–5) were obtained by coupling various nucleobases to the appropriate sugar-phosphonate intermediate (Scheme 2, compound 14). Hence, 1,2:5,6-di-*O*-isopropylidene-D-allofuranose (7) was obtained in two steps from commercial diacetone-D-glucose (6) using a well-known oxidation^[24,25] and stereoselective reduction^[26] procedure leading to the inversion at the C-3 centre. Subsequent benzylation and hydrolytic removal of the terminal isopropylidene group^[27] afforded α -D-allofuranose derivative 9 in 66% overall yield from starting material 6. Selective tosylation of the primary hydroxy group was achieved, and in situ displacement of this leaving group was performed by using sodium iodide in acetone, leading to compound 10.

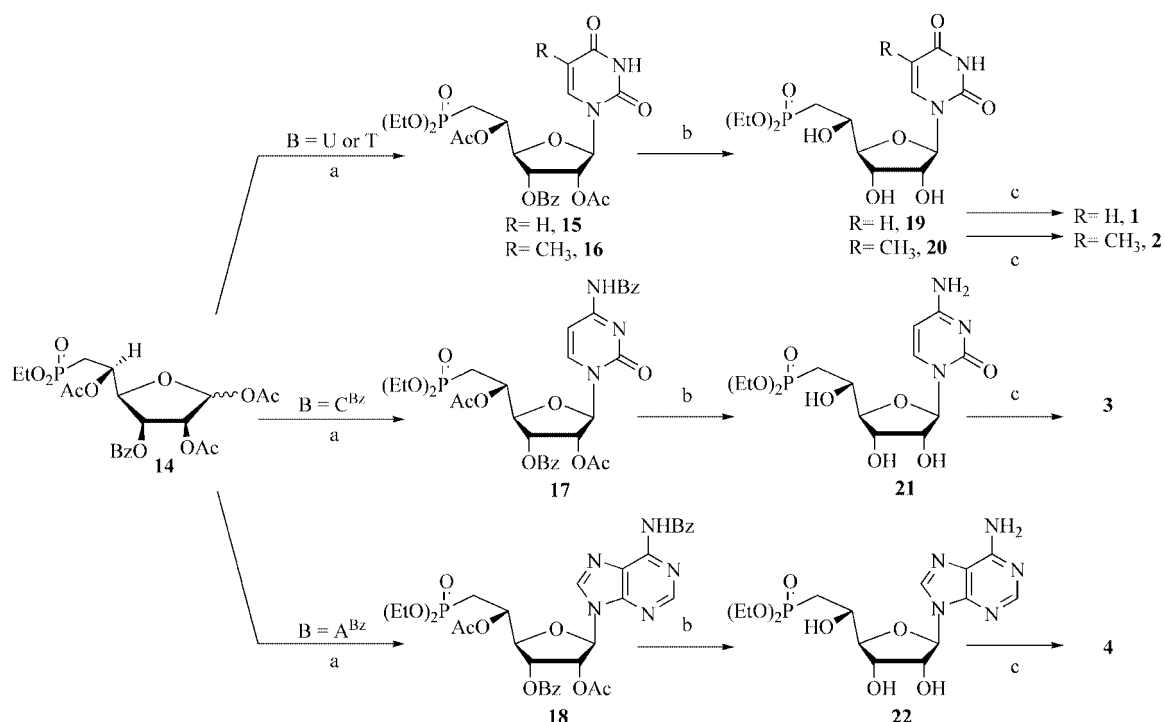
At this stage, we suspected carrying out the Michaelis–Arbusov reaction^[28–30] on compound 10 bearing a vicinal hydroxy group in the 5-position could be problematic. Consequently, the 5-hydroxy was acetylated under standard conditions (acetic anhydride in pyridine) and few attempts

were performed to obtain sugar phosphonate derivative 12. Unfortunately, heating derivative 11 in triethylphosphite led to a complex crude mixture from which 12 was isolated in very low yield (less than 20%). Thus, we decided to perform a similar reaction on intermediate 10 and found out that the Michaelis–Arbusov reaction proceeded well even in presence of the unprotected vicinal hydroxy group. This reaction is among the most versatile ones to introduce a P–C bond, but it presents some drawbacks such as the length of reaction time, the high temperature and the removal of the excess trialkylphosphite. Consequently, we explored the use of microwave (MW) irradiation for the preparation of sugar-phosphonate 13. Indeed, despite the considerable and still growing interest in the application of MW irradiation in organic synthesis,^[31,32] only a few reports have been made in the field of organophosphorus chemistry.^[33–35] Reaction progress was monitored with the use of TLC and ³¹P NMR, and various experimental conditions were studied, such as temperature (range of 160 to 220 °C), reaction time, power of the irradiation (up to 300W) and quantity of triethylphosphite used. Finally, the use of MW irradiation led to a small decrease in the isolated compound yield (63% instead of 70%) but allowed to significantly reduce the amount of triethylphosphite (from 25 to 5 equiv.) and to considerably shorten the reaction time (from a few days to half an hour).

Phosphonate 13 was converted into desired sugar-phosphonate 14, ready for the glycosylation step, with the use of a one-pot procedure with concomitant removal of the 1,2-isopropylidene group and acetolysis. Compound 14 was obtained in good yield as a mixture of α - and β -anomers (ratio α/β , 36:64 as determined by ¹H NMR spectroscopy). The use of Vorbrüggen conditions for the glycosylation and trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a



Scheme 2. Preparation of key “sugar-phosphonate” intermediate 14. a) CrO₃, Ac₂O, pyr., CH₂Cl₂; b) NaBH₄, EtOH_{abs}; c) BzCl, pyr.; d) AcOH_{aq} 90%, 60 °C; e) TsCl, DMAP, pyr.; f) NaI, acetone, reflux; g) Ac₂O, pyr.; h) P(OEt)₃, 110 °C or MW irradiation; i) Ac₂O, AcOH, conc. H₂SO₄.

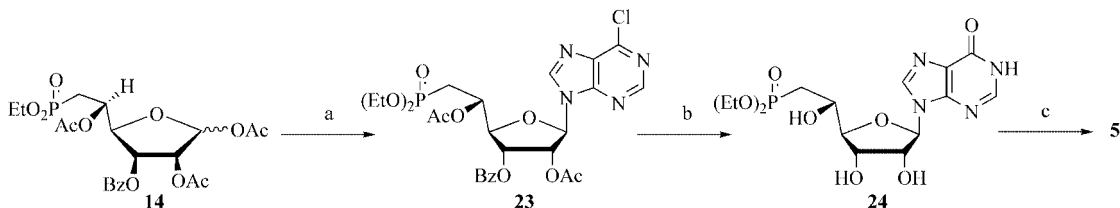


Scheme 3. Synthesis of β -hydroxyphosphonate nucleoside analogues, **1–4**. a) Nucleic base ($\text{B} = \text{U}$ or T or N^4 -benzoylcytosine or N^6 -benzoyladenine), BSA, CH_3CN , reflux then SnCl_4 ; b) NH_3 , MeOH ; c) TMSBr , DMF , then water or TEAB (1 M, pH 7).

catalyst^[36] resulted in the degradation of the ethyl phosphonate moiety and side reactions as previously mentioned.^[37] Thus, bis(trimethylsilyl) derivatives of uracil, thymine and N^4 -benzoylcytosine were glycosylated (Scheme 3) in the presence of excess tin(IV) chloride in acetonitrile.^[38] Yields of protected nucleotides **15–17** vary from 60 to 80%, and removal of the sugar and base protecting groups was achieved through methanolic ammonia treatment to afford compounds **19–21** in high yields. Finally, the ethyl phosphonate protecting groups were eliminated by using bromotrimethylsilane (TMSBr) in dimethylformamide, and after purification by reverse phase (RP-C18) chromatography and ionic exchange, desired β -hydroxyphosphonate nucleoside analogues **1–3** were obtained as their sodium salts.

Synthesis of N -glycosides incorporating pyrimidines was obvious but condensation of purines were less straightforward. Whereas, N^6 -benzoyladenine could be glycosylated in similar conditions as used for pyrimidines with good yield (compound **18**, 70%) leading to compound **22**, and then derivative **4** following a similar pathway (Scheme 3). The

same glycosylation step performed with 2- N -acetyl, 6- O -diphenylcarbamoylguanine, 2-amino-6-chloropurine or hypoxanthine did not afford the expected nucleotide derivatives. Thus, we developed another approach to inosine analogue **5** adapted from the literature (Scheme 4).^[39] It consisted of the condensation of silylated 6-chloropurine, as its 6-oxopurine precursor, onto sugar intermediate **14** and gave rise to desired nucleotide analogue **23** in 64% yield. Finally, substitution of chlorine at the 6-position of the purine and concomitant removal of the sugar protecting groups was performed with the use of 2-mercaptoethanol in the presence of sodium methoxide. Desired inosine nucleotide analogue **24** was isolated in good yield (70%) along with a second compound (12%) that was identified as the 6-(2-mercaptoethyl)purine derivative (on the basis of NMR and MS spectroscopic data). Finally, the ethyl phosphonate protecting groups were eliminated as described previously (TMSBr in dimethylformamide), and purification by reverse phase (RP-C18) chromatography and ionic exchange afforded β -hydroxyphosphonate inosine analogue **5** as its sodium salt.



Scheme 4. Preparation of inosine analogue **5**. a) 6-Chloropurine, HMDS , $(\text{NH}_4)_2\text{SO}_4$, reflux then SnCl_4 ; b) 2-mercaptoethanol, NaOMe , MeOH , reflux; c) TMSBr , DMF , then TEAB (1 M, pH 7).

Conclusions

In summary, we have described a stereoselective pathway to β -hydroxyphosphonate nucleoside analogues involving the preparation of a key "sugar-phosphonate" intermediate in which the chirality of the carbon atom in the β position to the phosphorus atom is embedded in the starting material. Thus, pyrimidine and purine analogues (**1** to **5**) were conveniently prepared from this key intermediate and biological activity of these compounds is currently being evaluated.

The utility of such optically pure phosphonate derivatives is not limited to the synthetic application described herein. They can indeed be viewed as new chiral blocks for the enantioselective synthesis of various phosphorus containing bioactive nucleotide analogues as well as the corresponding oligomers. Related work is currently in progress.

Experimental Section

General Remarks: Unless otherwise stated, ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz with proton decoupling at ambient temperature. Chemical shifts are given in δ values referenced to the residual solvent peak ($[\text{D}_6]\text{DMSO}$ at $\delta = 2.49$ ppm and 39.5 ppm) relative to TMS. Deuterium exchange, decoupling and COSY experiments were performed in order to confirm proton assignments. Coupling constants, J , are reported in Hertz. 2D ^1H - ^{13}C heteronuclear COSY were recorded for the attribution of ^{13}C signals. Unless otherwise stated, ^{31}P NMR spectra were recorded at ambient temperature at 121 MHz with proton decoupling. Chemical shifts are reported relative to external H_3PO_4 . FAB mass spectra were recorded in the positive-ion or negative-ion mode with the use of thioglycerol/glycerol (1:1 v/v, GT) as matrix. Specific rotations were measured with a Perkin-Elmer Model 241 spectropolarimeter (path length 1 cm). Elemental analyses were carried out by the Service de Microanalyses du CNRS, Division de Vernaison (France). TLC was performed on precoated aluminium sheets of silica gel 60 F₂₅₄ (Merck, Art. 9385), visualisation of products being accomplished by UV absorbance followed by charring with 5% ethanolic sulfuric acid with heating for carbohydrates and nucleotides. Flash chromatography was carried out with 63–100 μm silica gel (Merck Art. no. 115101) otherwise 40–63 μm silica gel (Merck Art. no. 109385) was used. Thin layer chromatography was carried out with the use of aluminium-supported silica gel 60 plates (Merck Art. no. 105554). MW experiments were carried out by using a single mode cavity synthesizer to ensure reproducibility and safety and were performed in a sealed Pyrex glass vessel (2–5 mL content) under an argon atmosphere, with the use of a microwave synthesizer Initiator 2.0 from Biotage (Biotage AB, Sweden) set at 300 W (frequency 2.45 GHz) with a 10 s premixing time. The temperature was monitored with an internal infrared probe. Solvents were reagent grade or purified by distillation prior to use, and solids were dried with P_2O_5 under reduced pressure at room temp. Moisture sensitive reactions were performed under an argon atmosphere with the use of oven-dried glassware. All aqueous (aq.) solutions were saturated with the specified salt unless otherwise indicated. Organic solutions were dried with Na_2SO_4 after work up and solvents were removed by evaporation at reduced pressure. Starting material such as diacetone-D-glucose was purchased from Acros Organics.

1,2:5,6-Di-O-isopropylidene-D-allofuranose (7):^[40] Chromium(VI) oxide (11.8 g, 118 mmol) was suspended in anhydrous dichloro-

methane (200 mL). After 15 min stirring, acetic anhydride (11.5 mL) and then pyridine (20 mL) were added dropwise, at 0 °C. A solution of diacetone-D-glucose (**6**; 10 g, 38.4 mmol) in dichloromethane (100 mL) was added at 0 °C over 30 min. The reaction mixture was stirred for 1 h, the chromium salts were precipitated in cold ethyl acetate (1.5 L) and the resulting suspension was filtered over silica gel. The crude solution was concentrated under reduced pressure, coevaporated with toluene and dried with P_2O_5 . This oily residue was then dissolved in absolute ethanol (150 mL) under an argon atmosphere, and a solution of sodium borohydride (4.26 g, 115 mmol) in absolute ethanol (200 mL) was added dropwise at 0 °C. The mixture was stirred for 30 min. The reaction mixture was diluted with water (100 mL) and neutralised with HCl (1 N, $\approx$ 50 mL). The resulting aqueous layer was extracted with dichloromethane, and the organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give compound **7** as a white solid (8.0 g, 80%). $[\alpha]_{\text{D}}^{20} = +35$ ($c = 0.96$, MeOH). $R_f = 0.4$ ($\text{CH}_2\text{Cl}_2/\text{AcOEt}$, 8/2 v/v). ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): $\delta = 1.27$, 1.32, 1.44 (3s, 12 H, CH_3), 3.7–3.9 (m, 3 H, 6-H, 4-H, 3-H), 3.93 (t, $J = 7.5$ Hz, 1 H, 6'-H), 4.23 (dt, $J = 2.6$ and 7.1 Hz, 1 H, 5-H), 4.46 (t, $J = 4.0$ Hz, 1 H, 2-H), 5.11 (d, $J = 7.1$ Hz, 1 H exchangeable, 3-OH), 5.66 (d, $J = 3.6$ Hz, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): $\delta = 25.4$, 26.1, 26.4, 26.6 (CH_3), 63.7 (C-6), 71.2 (C-3), 74.8 (C-5), 77.8 (C-4), 79.4 (C-2), 103.2 (C-1), 108.4, 111.4 [Cq , $\text{C}(\text{CH}_3)_2$] ppm. MS (FAB, GT): $m/z = 521$ $[\text{2M} + \text{H}]^+$, 261 $[\text{M} + \text{H}]^+$, 203 $[\text{M} + \text{H} - (\text{CH}_3)_2\text{CO}]^+$.

3-O-Benzoyl-1,2:5,6-di-O-isopropylidene-D-allofuranose (8): Benzoyl chloride (4.3 mL, 36.9 mmol) was added at 0 °C to a solution of derivative **7** (8 g, 30.7 mmol) in pyridine (62 mL) under an argon atmosphere. The mixture was warmed to room temperature and stirred for 20 h. Ice-water was then added, and the resulting aqueous phase was extracted with dichloromethane. The organic layer was washed with HCl (1 N), saturated NaHCO_3 and water then dried with Na_2SO_4 . After concentration under reduced pressure, the crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate 1 to 7%) to give compound **8** as a white solid (10.1 g, 90%). $[\alpha]_{\text{D}}^{20} = +112$ ($c = 1.03$, MeOH).^[41] $R_f = 0.6$ ($\text{CH}_2\text{Cl}_2/\text{AcOEt}$, 9:1 v/v). ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): $\delta = 1.24$, 1.26, 1.29, 1.44 (4s, 12 H, CH_3), 3.85 (m, 1 H, 5-H), 4.06 (dd, $J = 7.0$ and 7.7 Hz, 1 H, 6-H), 4.25–4.35 (m, 2 H, 4-H, 6'-H), 4.9–5.0 (m, 2 H, 3-H, 2-H), 5.88 (d, $J = 3.6$ Hz, 1 H, 1-H), 7.54 (m, 2 H, H-Ar), 7.70 (m, 1 H, H-Ar), 8.00 (m, 2 H, H-Ar) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): $\delta = 24.9$, 26.1, 26.5, 26.6 (CH_3), 65.04 (C-6), 72.9 (C-5), 74.6 (C-3), 77.2 (C-2), 77.4 (C-4), 104.0 (C-1), 108.9, 112.2 [Cq , $\text{C}(\text{CH}_3)_2$], 128.8, 128.9, 129.2, 133.7 (C-Ar), 164.8 (C=O) ppm. MS (FAB, GT): $m/z = 365$ $[\text{M} + \text{H}]^+$, 307 $[\text{M} + \text{H} - (\text{CH}_3)_2\text{CO}]^+$. UV (EtOH, 95°): λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 229 (13200), 272 (700) nm; λ_{min} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 248 (400) nm. $\text{C}_{19}\text{H}_{24}\text{O}_7$ (364.39): calcd. C 62.63, H 6.64; found C 62.63, H 6.67.

3-O-Benzoyl-1,2-O-isopropylidene-D-allofuranose (9): A solution of 3-O-benzoyl-1,2:5,6-di-O-isopropylidene-D-allofuranose (**8**; 11.3 g, 31 mmol) in aqueous acetic acid (9:1 v/v, 155 mL) was warmed for 45 min at 60 °C. The solution was then concentrated and coevaporated with toluene three times. Column chromatography of the crude material on silica gel (petroleum ether/ethyl acetate 30 to 50%) gave title compound **9** as a white solid (9.1 g, 91%). $[\alpha]_{\text{D}}^{20} = +116.5$ ($c = 1.09$, MeOH).^[41] $R_f = 0.1$ ($\text{CH}_2\text{Cl}_2/\text{AcOEt}$, 8:2 v/v). ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): $\delta = 1.32$, 1.49 (2s, 6 H, CH_3), 3.3–3.5 (m, 2 H, 6-H, 6'-H), 3.80 (m, 1 H, 5-H), 4.40 (dd, $J = 3.0$ and 8.2 Hz, 1 H, 4-H), 4.77 (dd, $J = 5.4$ and 5.6 Hz, 1 H exchangeable, 6-OH), 4.96 (dd, $J = 5.2$ and 4.0 Hz, 1 H, 2-H), 5.09 (dd, $J = 5.3$ and 8.2 Hz, 1 H, 3-H), 5.66 (d, $J = 5.1$ Hz, 1 H ex-

changeable, 5-OH), 5.94 (d, $J = 3.8$ Hz, 1 H, 1-H), 7.63 (m, 2 H, H-Ar), 7.77 (m, 1 H, H-Ar), 8.06 (m, 2 H, H-Ar) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): $\delta = 26.5$, 26.7 (CH_3), 62.6 (C-6), 70.6, 72.0 (C-5, C-3), 77.3, 78.2 (C-2, C-4), 104.1 (C-1), 111.9 [Cq , $\text{C}(\text{CH}_3)_2$], 128.8, 129.2, 129.3, 133.6 (C-Ar), 164.9 (C=O) ppm. MS (FAB, GT): $m/z = 649$ [$2\text{M} + \text{H}$] $^+$, 325 [$\text{M} + \text{H}$] $^+$, 267 [$\text{M} + \text{H} - (\text{CH}_3)_2\text{CO}$] $^+$, and 647 [$2\text{M} - \text{H}$] $^-$, 323 [$\text{M} - \text{H}$] $^-$. UV (EtOH, 95°): λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 229 (12500) nm. $\text{C}_{16}\text{H}_{20}\text{O}_7$ (324.33): calcd. C 59.25, H 6.22; found C 58.35, H 6.24.

3-O-Benzoyl-6-deoxy-6-iodo-1,2-O-isopropylidene-D-allofuranose (10): 3-O-Benzoyl-1,2-O-isopropylidene-D-allofuranose (**9**; 4.2 g, 1.3 mmol) was dissolved in anhydrous pyridine (130 mL). At 0 °C, *N,N*-dimethylaminopyridine (1.58 g, 1.3 mmol) was added, the solution was stirred for 15 min and then tosylchloride (4.95 g, 2.6 mmol) was added. The solution was warmed to room temperature and stirred overnight. The reaction mixture was cooled with an ice bath and then water and ethyl acetate were added. After decantation and extraction with ethyl acetate, the combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Coevaporations were done with toluene, the pasty residue was partially dissolved in acetone and the insoluble salts were removed by filtration. The filtrate was concentrated to give a yellow oil which was dried with P_2O_5 . The resulting residue was dissolved in anhydrous acetone (26 mL) under an argon atmosphere, sodium iodide (2.53 g, 1.7 mmol) was added, and the mixture was heated at reflux overnight. The salts were filtered, and the filtrate was concentrated under reduced pressure. Column chromatography of the crude material on silica gel (petroleum ether/ethyl acetate, 8:2) gave iodo derivative **10** as a colourless oil (2.88 g, 51% from **9**). $[\alpha]_{\text{D}}^{20} = +77.5$ ($c = 1.02$, MeOH). $R_f = 0.4$ (petroleum ether/ethyl acetate, 7:3 v/v). ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): $\delta = 1.26$, 1.43 (2s, 6 H, CH_3), 3.20 (m, 1 H, 6-H), 3.37 (m, 1 H, 6'-H), 3.68 (m, 1 H, 5-H), 4.30 (dd, $J = 4.9$ and 8.0 Hz, 1 H, 4-H), 4.92 (dd, $J = 5.1$ and 4.0 Hz, 1 H, 2-H), 5.00 (dd, $J = 5.2$ and 8.0 Hz, 1 H, 3-H), 5.66 (d, $J = 5.7$ Hz, 1 H exchangeable, 5-OH), 5.87 (d, $J = 3.8$ Hz, 1 H, 1-H), 7.57 (m, 2 H, H-Ar), 7.70 (m, 1 H, H-Ar), 7.98 (m, 2 H, H-Ar) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): $\delta = 10.6$ (C-6), 26.6, 26.8 (CH_3), 70.2 (C-5), 73.1 (C-3), 77.5 (C-2), 79.4 (C-4), 104.1 (C-1), 112.2 [Cq , $\text{C}(\text{CH}_3)_2$], 128.8, 129.2, 129.3, 133.6 (C-Ar), 164.8 (C=O) ppm. MS (FAB, GT): $m/z = 435$ [$\text{M} + \text{H}$] $^+$, 377 [$\text{M} + \text{H} - (\text{CH}_3)_2\text{CO}$] $^+$, 307 [$\text{M} - \text{I}$] $^+$. UV (EtOH, 95°) λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 229 (12100) nm. $\text{C}_{16}\text{H}_{19}\text{IO}_6$ (434.22): calcd. C 44.26, H 4.41; found C 44.29, H 4.52.

5-O-Acetyl-3-O-benzoyl-6-iodo-1,2-O-isopropylidene-D-allofuranose (11): Compound **10** (2.87 g, 6.6 mmol) was dissolved in pyridine (60 mL) under an argon atmosphere. Acetic anhydride (6.2 mL, 66 mmol) was added at 0 °C, and the mixture was stirred for 5 h at room temp. Ice-water was then added at 0 °C. Dichloromethane was added to the solution, and the resulting layer was washed with saturated NaHCO_3 . The aqueous layer was extracted with dichloromethane, and the resulting organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was coevaporated with toluene, chromatographed on silica gel (petroleum ether/ethyl acetate, 8:2) to lead to desired derivative **11** as a colourless oil (2.91 g, 92%). $[\alpha]_{\text{D}}^{20} = +96.4$ ($c = 1.12$, MeOH). $R_f = 0.5$ ($\text{CH}_2\text{Cl}_2/\text{AcOEt}$, 8:2 v/v). ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): $\delta = 1.27$, 1.46 (2s, 6 H, CH_3), 1.92 (s, 3 H, Ac), 3.40 (m, 1 H, 6-H under peak of water), 3.57 (dd, $J = 3.8$ and 11.0 Hz, 1 H, 6'-H), 4.37 (dd, $J = 5.6$ and 8.7 Hz, 1 H, 4-H), 4.90–4.95 (m, 1 H, 2-H), 5.00–5.07 (m, 2 H, 3-H, 5-H), 5.88 (d, $J = 3.7$ Hz, 1 H, 1-H), 7.57 (m, 2 H, H-Ar), 7.70 (m, 1 H, H-Ar), 7.98 (m, 2 H, H-Ar) ppm. ^{13}C NMR (300 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): $\delta = 4.8$ (C-6),

20.5 (CH_3 , Ac) 26.6 (2s, CH_3), 71.6, 73.5 (C-3, C-5), 77.3 (2s, C-4, C-2), 104.0 (C-1), 112.6 [Cq , $\text{C}(\text{CH}_3)_2$], 128.8, 129.2, 129.3, 133.6 (C-Ar), 164.6, 169.3 (C=O) ppm. MS (FAB, GT): $m/z = 477$ [$\text{M} + \text{H}$] $^+$, 419 [$\text{M} + \text{H} - (\text{CH}_3)_2\text{CO}$] $^+$. UV (EtOH, 95°): λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 229 (13400) nm. $\text{C}_{18}\text{H}_{21}\text{IO}_7$ (476.26): calcd. C 45.39, H 4.44; found C 45.10, H 4.53.

3-O-Benzoyl-6-deoxy-6-diethylphosphono-1,2-O-isopropylidene-D-allofuranose (13): Thermal conditions: A solution of 3-O-benzoyl-6-deoxy-6-iodo-1,2-O-isopropylidene-D-allofuranose (**10**; 1.03 g, 2.4 mmol) in triethylphosphite (4 mL) was heated at 110 °C for 2 d. The solution was evaporated under high vacuum at 70 °C. Column chromatography of the crude mixture on silica gel (ethyl acetate) gave expected phosphonate derivative **13** as a colourless oil (0.74 g, 70%). MW conditions: A heterogeneous mixture of iodo derivative **10** (1.21 g, 2.8 mmol) in triethylphosphite (2.4 mL, 5 equiv.) was sealed under an argon atmosphere in the specific reactor. Under stirring, microwave irradiations were applied for 30 min at 180 °C with a power of 300 Watts. Column chromatography of the crude mixture on silica gel (ethyl acetate) gave expected phosphonate derivative **13** as a colourless oil (0.77 g, 63%). $[\alpha]_{\text{D}}^{20} = +92.9$ ($c = 1.12$, MeOH). $R_f = 0.3$ (AcOEt). ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): $\delta = 1.21$ (t, $J = 7.0$ Hz, 6 H, POCH_2CH_3), 1.26, 1.42 (2s, 6 H, CH_3), 1.9–2.1 (m, 2 H, 6-H, 6'-H), 3.98 (m, 4 H, POCH_2CH_3), 4.05 (m, 1 H, 5-H), 4.33 (m, 1 H, 4-H), 4.92 (m, 1 H, 2-H), 5.01 (m, 1 H, 3-H), 5.35 (d, $J = 5.6$ Hz, 1 H, 5-OH), 5.87 (d, $J = 3.8$ Hz, 1 H, 1-H), 7.59 (m, 2 H, H-Ar), 7.72 (m, 1 H, H-Ar), 8.01 (m, 2 H, H-Ar) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): $\delta = 16.1$, 16.2 (POCH_2CH_3), 26.5, 26.8 (CH_3), 29.4 (d, $J = 138.0$ Hz, C-6), 60.8, 61.1 (2d, $J = 6.8$ Hz, POCH_2CH_3), 65.1 (C-5), 72.2 (C-3), 77.5 (C-2), 80.5 (d, $J = 12.8$ Hz, C-4), 104.1 (C-1), 112.1 [Cq , $\text{C}(\text{CH}_3)_2$], 128.8, 129.1, 129.3, 133.6 (C-Ar), 164.7 (C=O) ppm. ^{31}P NMR (121 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): $\delta = 28.9$ ppm. MS (FAB, GT): $m/z = 467$ [$\text{M} + \text{Na}$] $^+$, 445 [$\text{M} + \text{H}$] $^+$. UV (EtOH, 95°): λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 229 (11400) nm. $\text{C}_{20}\text{H}_{29}\text{O}_9\text{P}$ (444.41)·0.1PO(OEt) $_3$: calcd. C 53.48, H 6.65, P 7.36; found C 53.08, H 6.80, P 7.49.

1,2,5-Tri-O-acetyl-3-O-benzoyl-6-deoxy-6-diethylphosphono-(5S)-(α,β)-D-ribohexofuranose (14): A solution of 3-O-benzoyl-6-deoxy-6-diethylphosphono-1,2-O-isopropylidene-D-allofuranose (**13**; 1.2 g, 2.7 mmol) in glacial acetic acid (10.3 mL), acetic anhydride (3.8 mL) and concentrated sulfuric acid (0.4 mL) was stirred overnight at room temperature. The reaction mixture was diluted with dichloromethane, washed with aqueous saturated NaHCO_3 solution and then water. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 95:5) of the crude materials gave key sugar-phosphonate derivative **14** as a mixture of α/β anomers (ratio α/β , 36:64), as a colourless oil (1.1 g, 75%). $R_f = 0.7$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 95:5 v/v). ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): $\delta = 1.20$ (m, 6 H, POCH_2CH_3), 1.93, 2.05, 2.16 (3s, 9 H, Ac, α anomer), 1.99, 2.03, 2.10 (3s, 9 H, Ac, β anomer), 2.1–2.4 (m, 2 H, 6-H, 6'-H), 3.95 (m, 4 H, POCH_2CH_3), 4.55 (m, 1 H, 4-H), 5.22 (m, 1 H, 2-H, α anomer), 5.30 (m, 1 H, 5-H), 5.40 (m, 1 H, 2-H, β anomer), 5.65 (m, 1 H, 3-H), 6.12 (d, $J = 0.9$ Hz, 1 H, 1-H, β anomer), 6.41 (d, $J = 4.5$ Hz, 1 H, 1-H, α anomer), 7.59 (m, 2 H, H-Ar), 7.72 (m, 1 H, H-Ar), 8.01 (m, 2 H, H-Ar) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): $\delta = 16.05$, 16.13 (POCH_2CH_3 , β anomer), 16.02, 16.10 (POCH_2CH_3 , α anomer), 20.0, 20.2, 20.7, 20.8 (5s, Ac), 26.3, 26.4 (2d, $J = 140.0$ Hz, C-6), 61.2, 61.3, 61.4 (4s, POCH_2CH_3), 67.0 (d, $J < 1.0$ Hz, C-5, α anomer), 67.2 (d, $J = 3.7$ Hz, C-5, β anomer), 68.5 (C-3, α anomer), 70.1 (C-2, α anomer), 70.4 (C-3, β anomer), 74.1 (C-2, β anomer), 82.4 (d, $J = 14.3$ Hz, C-4, β anomer), 84.6 (d, $J = 11.3$ Hz, C-4, α anomer), 93.4 (C-1, α anomer), 97.9 (C-1,

β anomer), 128.4, 128.9, 129.2, 129.3, 133.9, 134.0 (C-Ar), 164.4, 168.8, 169.0, 169.1 (C=O, β anomer), 164.6, 169.1 (2s), 169.4 (C=O, α anomer) ppm. ^{31}P NMR (121 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): δ = 25.8 (α anomer), 26.1 (β anomer) ppm. MS (FAB, GT): m/z = 553 $[\text{M} + \text{Na}]^+$, 289 $[\text{M} - \text{Ac} - \text{BzOH} - \text{AcOH}]^+$. UV (EtOH, 95°): λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 230 (12700) nm. $\text{C}_{23}\text{H}_{31}\text{O}_{12}\text{P}$ (530.46): calcd. C 52.08, H 5.89, P 5.84; found C 51.91, H 6.06, P 5.80.

General Glycosylation Procedure: The nucleobase (2 equiv.) was dissolved in anhydrous acetonitrile (2 mL/mmol) and *N,O*-bis(trimethylsilyl)acetamide (4 equiv.) was added. The solution was heated at reflux for 1.5 h, and the reaction mixture was cooled to room temperature. A solution of 1,2,5-tri-*O*-acetyl-3-*O*-benzoyl-6-deoxy-6-diethylphosphono-(5*S*)-(α,β)-D-ribohexofuranose (**14**; 1 equiv.) in acetonitrile (5 mL/mmol) was added, followed by tin(IV) chloride (4 equiv.). The resulting solution was stirred for 30 h, and then eventually warmed at 50 °C for few hours. The reaction mixture was powdered onto a cold saturated NaHCO_3 solution and filtered through celite. The celite was washed with AcOEt. The organic layer was extracted with saturated NaHCO_3 and brine, dried with Na_2SO_4 and concentrated under reduced pressure.

1-(5*S*)-[2,5-Di-*O*-acetyl-3-*O*-benzoyl-6-deoxy-6-diethylphosphono- β -D-ribohexofuranosyl]uracil (15**):** Column chromatography of the crude material on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 97:3) gave protected nucleotide derivative **15** as a white foam (0.86 g, 79%). $[\alpha]_{\text{D}}^{20}$ = -21.7 (c = 1.06, MeOH). R_f = 0.3 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 95:5 v/v). ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): δ = 1.19 (m, 6 H, POCH_2CH_3), 1.94, 1.97 (2s, 6 H, CH_3 , Ac), 2.0–2.4 (m, 2 H, 6'-H, 6''-H), 3.96 (m, 4 H, POCH_2CH_3), 4.37 (dd, J = 4.6 and 6.1 Hz, 1 H, 4'-H), 5.41 (m, 1 H, 5'-H), 5.63 (dd, J = 4.6 and 6.7 Hz, 1 H, 2'-H), 5.73 (m, 2 H, 3'-H, 5-H), 5.86 (d, J = 4.6 Hz, 1 H, 1'-H), 7.59 (m, 2 H, H-Ar), 7.72 (m, 2 H, H-Ar, 6-H), 8.01 (m, 2 H, H-Ar), 11.51 (sl, 1 H exchangeable, NH) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): δ = 16.0, 16.1 (POCH_2CH_3), 20.2, 20.6 (CH_3 , Ac), 25.9 (d, J = 140.4 Hz, C-6'), 61.2, 61.3 (POCH_2CH_3), 66.8 (d, J = 3.8 Hz, C-5'), 69.4 (C-3'), 71.8 (C-2'), 81.1 (d, J = 12.8 Hz, C-4'), 89.7 (C-1'), 102.2 (C-5), 128.5, 128.9, 129.3, 134.0 (C-Ar), 142.8 (C-6), 150.2 (C-2), 163.1 (C-4), 164.4, 169.1, 169.3 (C=O) ppm. ^{31}P NMR (121 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): δ = 26.4 ppm. MS (FAB, GT): m/z = 583 $[\text{M} + \text{H}]^+$, 289 $[\text{M} - \text{B} - \text{BzOH} - \text{AcOH}]^+$, and 581 $[\text{M} - \text{H}]^-$, 111 $[\text{B}]^-$. UV (EtOH, 95°) λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 231 (14700), 253 (10400) nm; λ_{min} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 247 (10100) nm. $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_{12}\text{P}$ (582.49): calcd. C 51.55, H 5.36, N 4.81, P 5.32; found C 51.58, H 5.50, N 4.45, P 5.16.

1-(5*S*)-[2,5-Di-*O*-acetyl-3-*O*-benzoyl-6-deoxy-6-diethylphosphono- β -D-ribohexofuranosyl]thymine (16**):** Column chromatography of the crude material on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 98:2) gave protected nucleotide derivative **16** as a white foam (1.2 g, 62%). $[\alpha]_{\text{D}}^{20}$ = -30.6 (c = 1.11, MeOH). R_f = 0.4 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 95:5 v/v). ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): δ = 1.27 (m, 6 H, POCH_2CH_3), 1.87 (s, 3 H, CH_3), 2.01, 2.07 (2s, 6 H, CH_3 , Ac), 2.45–2.10 (m, 2 H, 6'-H, 6''-H), 4.05 (m, 4 H, POCH_2CH_3), 4.44 (dd, J = 5.6 and 5.0 Hz, 1 H, 4'-H), 5.50 (m, 1 H, 5'-H), 5.68 (dd, J = 5.3 and 6.4 Hz, 1 H, 2'-H), 5.81 (dd, J = 6.5 and 6.3 Hz, 1 H, 3'-H), 5.96 (d, J = 4.9 Hz, 1 H, 1'-H), 7.68 (m, 3 H, H-Ar, 6-H), 7.81 (m, 1 H, H-Ar), 8.10 (m, 2 H, H-Ar), 11.6 (sl, 1 H exchangeable, NH) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): δ = 11.8 (CH_3), 16.0, 16.1 (POCH_2CH_3), 20.1, 20.6 (CH_3 , Ac), 25.9 (d, J = 140.0 Hz, C-6'), 61.2, 61.3 (2d, J = 6.3 Hz, POCH_2CH_3), 66.8 (d, J = 3.8 Hz, C-5'), 69.3 (C-3'), 71.7 (C-2'), 81.2 (d, J = 12.8 Hz, C-4'), 88.8 (C-1'), 109.9 (C-5), 128.5, 128.9, 129.3, 134.0 (C-Ar), 137.9 (C-6), 150.2 (C-2), 163.7 (C-4), 164.3, 169.1, 169.3 (C=O) ppm. ^{31}P NMR (121 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): δ = 26.4 ppm. MS (FAB,

GT): m/z = 1193 $[\text{2M} + \text{H}]^+$, 597 $[\text{M} + \text{H}]^+$, 289 $[\text{M} - \text{B} - \text{BzOH} - \text{AcOH}]^+$ and 1191 $[\text{2M} - \text{H}]^-$, 595 $[\text{M} - \text{H}]^-$, 125 $[\text{B}]^-$. UV (EtOH, 95°) λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 229 (16100), 260 (11100) nm; λ_{min} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 247 (9100) nm. $\text{C}_{26}\text{H}_{33}\text{N}_2\text{O}_{12}\text{P}$ (596.52): calcd. C 52.35, H 5.58, N 4.70, P 5.19; found C 52.07, H 5.65, N 4.57, P 5.06.

***N*⁴-Benzoyl-1-(5*S*)-[2,5-di-*O*-acetyl-3-*O*-benzoyl-6-deoxy-6-diethylphosphono- β -D-ribohexofuranosyl]cytidine (**17**):** Column chromatography of the crude material on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 98:2) gave protected nucleotide derivative **17** as a white foam (2 g, 76%). $[\alpha]_{\text{D}}^{20}$ = -29.4 (c = 1.09, MeOH). R_f = 0.3 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 95:5 v/v). ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): δ = 1.22–1.14 (m, 6 H, POCH_2CH_3), 1.94, 1.96 (2s, 6 H, CH_3 , Ac), 2.40–2.10 (m, 2 H, 6'-H, 6''-H), 3.96 (m, 4 H, POCH_2CH_3), 4.43 (dd, J = 4.5 and 6.8 Hz, 1 H, 4'-H), 5.44 (m, 1 H, 5'-H), 5.74 (dd, J = 3.6 and 6.6 Hz, 1 H, 2'-H), 5.81 (dd, J = 6.7 and 6.8 Hz, 1 H, 3'-H), 5.90 (d, J = 3.6 Hz, 1 H, 1'-H), 7.36 (d, J = 7.6 Hz, 1 H, 5-H), 7.60 (m, 6 H, H-Ar), 8.00 (m, 4 H, H-Ar), 8.17 (d, J = 7.6 Hz, 1 H, 6-H), 11.4 (sl, 1 H exchangeable, NH) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): δ = 16.0, 16.1 (POCH_2CH_3), 20.1, 20.6 (CH_3 , Ac), 25.8 (d, J = 140.0 Hz, C-6'), 61.2, 61.3 (POCH_2CH_3), 66.8 (d, J = 3.8 Hz, C-5'), 69.8 (C-3'), 72.3 (C-2'), 81.4 (d, J = 12.8 Hz, C-4'), 92.4 (C-1'), 96.8 (C-5), 128.4, 128.5, 128.9, 129.3, 132.8, 133.0, 134.0 (C-Ar), 148.2 (C-6), 154.0 (C-2), 164.0 (C-4), 164.4, 169.1, 169.3 (C=O) ppm. ^{31}P NMR (121 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): δ = 26.5 ppm. MS (FAB, GT): m/z = 686 $[\text{M} + \text{H}]^+$, 289 $[\text{M} - \text{B} - \text{BzOH} - \text{AcOH}]^+$, and 1369 $[\text{2M} - \text{H}]^-$, 684 $[\text{M} - \text{H}]^-$, 214 $[\text{B}^{\text{Bz}} - \text{H}]^-$. UV (EtOH, 95°): λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 230 (21600), 261 (28000), 300 (9100) nm; λ_{min} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 243 (18500), 291 (8600) nm. $\text{C}_{32}\text{H}_{36}\text{N}_3\text{O}_{12}\text{P}$ (685.62): calcd. C 56.06, H 5.29, N 6.13, P 4.52; found C 55.99, H 5.24, N 5.85, P 4.48.

***N*⁶-Benzoyl-9-(5*S*)-[2,5-di-*O*-acetyl-3-*O*-benzoyl-6-deoxy-6-diethylphosphono- β -D-ribohexofuranosyl]adenine (**18**):** Column chromatography of the crude material on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 98:2) gave protected nucleotide derivative **18** as a white foam (0.22 g, 69%). $[\alpha]_{\text{D}}^{20}$ = -47.8 (c = 0.9, MeOH). R_f = 0.2 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 95:5 v/v). ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): δ = 1.16 (m, 6 H, POCH_2CH_3), 1.92, 2.01 (2s, 6 H, CH_3 , Ac), 2.10–2.40 (m, 2 H, 6'-H, 6''-H), 3.96 (m, 4 H, POCH_2CH_3), 4.56 (t, J = 4.4 Hz, 1 H, 4'-H), 5.50 (m, 1 H, 5'-H), 5.74 (dd, J = 4.5 and 5.9 Hz, 1 H, 3'-H), 6.26 (t, J = 6.0 Hz, 1 H, 2'-H), 6.46 (d, J = 5.9 Hz, 1 H, 1'-H), 7.60 (m, 6 H, H-Ar), 8.05 (m, 4 H, H-Ar), 8.68, 8.79 (2s, 2 H, 2-H, 8-H), 11.3 (sl, 1 H exchangeable, NH) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): δ = 16.0, 16.1 (POCH_2CH_3), 20.1, 20.7 (CH_3 , Ac), 26.2 (d, J = 139.4 Hz, C-6'), 61.32, 61.34 (2d, J = 6.2 Hz, POCH_2CH_3), 66.7 (d, J = 3.8 Hz, C-5'), 69.7 (C-3'), 71.3 (C-2'), 82.4 (d, J = 12.7 Hz, C-4'), 85.7 (C-1'), 126.0, 128.5, 129.0, 129.4, 132.5, 133.1, 134.1 (C-Ar), 144.2, 151.9 (C-2, C-8), 150.7, 151.7 (Cq), 164.5, 165.7, 169.19, 169.20 (C=O) ppm. ^{31}P NMR (121 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): δ = 26.2 ppm. MS (FAB, GT): m/z = 710 $[\text{M} + \text{H}]^+$, 289 $[\text{M} - \text{B}^{\text{Bz}} - \text{BzOH} - \text{AcOH}]^+$, 240 $[\text{B}^{\text{Bz}} + \text{H}]^+$, and 708 $[\text{M} - \text{H}]^-$, 238 $[\text{B}^{\text{Bz}} - \text{H}]^-$. UV (EtOH, 95°): λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 230 (25100), 277 (22500) nm; λ_{min} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 250 (12700) nm. $\text{C}_{33}\text{H}_{36}\text{N}_5\text{O}_{11}\text{P}$ (709.64): calcd. C 55.85, H 5.11, N 9.87, P 4.36; found C 55.36, H 5.53, N 9.36, P 4.21.

Removal of Sugar and Nucleobase Protecting Groups: The protected nucleotide derivative was dissolved in methanolic ammonia (20 mL/mmol) at room temperature and stirred overnight. The solution was then concentrated.

1-(5*S*)-[6-Deoxy-6-diethylphosphono- β -D-ribohexofuranosyl]uracil (19**):** Reverse phase column chromatography of the crude material ($\text{H}_2\text{O}/\text{CH}_3\text{CN}$ 0 to 50%) gave title compound **19** as a white solid

(0.58 g, 92%) after freeze-drying. $[\alpha]_D^{20} = -5.8$ ($c = 1.04$, MeOH). $R_f = 0.2$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1 v/v). ^1H NMR (300 MHz, $[\text{D}_6]$ -DMSO, 20 °C): $\delta = 1.23$ (t, $J = 7.0$ Hz, 6 H, POCH_2CH_3), 1.80–2.10 (m, 2 H, H-6', 6''-H), 3.80 (t, $J = 3.0$ Hz, 1 H, 4'-H), 3.9–4.1 (m, 7 H, 3'-H, 2'-H, 5'-H, POCH_2CH_3), 5.10 (sl, 1 H exchangeable, 3'-OH), 5.36 (sl, 1 H exchangeable, 2'-OH), 5.50 (d, $J = 5.0$ Hz, 1 H exchangeable, 5'-OH), 5.63 (d, $J = 8.1$ Hz, 1 H, 5-H), 5.78 (d, $J = 6.4$ Hz, 1 H, 1'-H), 7.80 (d, $J = 8.1$ Hz, 1 H, 6-H), 11.3 (sl, 1 H exchangeable, NH) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]$ -DMSO, 20 °C): $\delta = 16.1$, 16.2 (POCH_2CH_3), 29.5 (d, $J = 137.3$ Hz, C-6'), 60.8, 61.1 (2d, $J = 6.0$ Hz, POCH_2CH_3), 65.6 (d, $J = 3.0$ Hz, C-5'), 68.5 (C-3'), 73.1 (C-2'), 86.9 (C-1'), 87.3 (d, $J = 14.3$ Hz, C-4'), 101.9 (C-5), 140.9 (C-6), 150.8 (C-2), 163.0 (C-4) ppm. ^{31}P NMR (121 MHz, $[\text{D}_6]$ -DMSO, 20 °C): $\delta = 29.2$ ppm. MS (FAB, GT): 789 $[2\text{M} + \text{H}]^+$, 395 $[\text{M} + \text{H}]^+$ and 787 $[2\text{M} - \text{H}]^-$, 393 $[\text{M} - \text{H}]^-$. UV (EtOH, 95°) λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 260 (10000) nm; λ_{min} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 228 (2000) nm. $\text{C}_{14}\text{H}_{23}\text{N}_2\text{O}_9\text{P}$ (394.31): calcd. C 42.64, H 5.88, N 7.10; found C 42.53, H 6.14, N 7.03.

1-(5S)-[6-Deoxy-6-diethylphosphono- β -D-ribohexofuranosyl]thymine (20): Reverse phase column chromatography of the crude material ($\text{H}_2\text{O}/\text{CH}_3\text{CN}$, 0 to 50%) gave title compound **20** as a white solid (0.64 g, 93%) after freeze-drying. $[\alpha]_D^{20} = -11.2$ ($c = 1.16$, MeOH). $R_f = 0.1$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1 v/v). ^1H NMR (300 MHz, $[\text{D}_6]$ -DMSO, 20 °C): $\delta = 1.24$ (t, $J = 7.0$ Hz, 6 H, POCH_2CH_3), 1.79 (s, 3 H, CH_3), 1.80–2.10 (m, 2 H, 6'-H, 6''-H), 3.77 (t, $J = 2.8$ Hz, 1 H, 4'-H), 3.9–4.1 (m, 7 H, 3'-H, 2'-H, 5'-H, POCH_2CH_3), 5.08 (d, $J = 4.6$ Hz, 1 H exchangeable, 3'-OH), 5.31 (d, $J = 6.0$ Hz, 1 H exchangeable, 2'-OH), 5.59 (d, $J = 5.7$ Hz, 1 H exchangeable, 5'-OH), 5.78 (d, $J = 6.6$ Hz, 1 H, 1'-H), 7.62 (s, 1 H, 6-H), 11.3 (sl, 1 H exchangeable, NH) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]$ -DMSO, 20 °C): $\delta = 10.9$ (CH_3), 15.0, 15.1 (POCH_2CH_3), 28.4 (d, $J = 138.1$ Hz, C-6'), 59.7, 60.0 (2d, $J = 6.0$ Hz, POCH_2CH_3), 64.5 (d, $J = 3.0$ Hz, C-5'), 67.4 (C-3'), 71.7 (C-2'), 85.4 (C-1'), 86.1 (d, $J = 15.1$ Hz, C-4'), 108.4 (C-5), 135.1 (C-6), 149.7 (C-2), 162.5 (C-4) ppm. ^{31}P NMR (121 MHz, $[\text{D}_6]$ -DMSO, 20 °C): $\delta = 29.3$ ppm. MS (FAB, GT): $m/z = 409$ $[\text{M} + \text{H}]^+$, and 815 $[2\text{M} - \text{H}]^-$, 407 $[\text{M} - \text{H}]^-$, 125 $[\text{B}]^-$. UV (EtOH, 95°): λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 265 (9600) nm; λ_{min} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 232 (2000) nm. $\text{C}_{15}\text{H}_{25}\text{N}_2\text{O}_9\text{P}$ (408.34): calcd. C 44.12, H 6.17, N 6.86; found C 44.06, H 6.46, N 6.78.

1-(5S)-[6-Deoxy-6-diethylphosphono- β -D-ribohexofuranosyl]cytidine (21): Reverse phase column chromatography of the crude material ($\text{H}_2\text{O}/\text{CH}_3\text{CN}$, 0 to 50%) gave title compound **21** as a white solid (1.04 g, 91%) after freeze-drying. $[\alpha]_D^{20} = +13.9$ ($c = 1.01$, MeOH). $R_f = 0.1$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 8:2 v/v). ^1H NMR (300 MHz, $[\text{D}_6]$ -DMSO, 20 °C): $\delta = 1.23$ (t, $J = 7.0$ Hz, 6 H, POCH_2CH_3), 1.79 (s, 3 H, CH_3), 1.80–2.10 (m, 2 H, 6'-H, 6''-H), 3.77 (t, $J = 3.4$ Hz, 1 H, 4'-H), 3.9–4.1 (m, 7 H, 3'-H, 2'-H, 5'-H, POCH_2CH_3), 5.01 (sl, 1 H exchangeable, 3'-OH), 5.25 (sl, 1 H exchangeable, 2'-OH), 5.49 (d, $J = 5.0$ Hz, 1 H exchangeable, 5'-OH), 5.71 (d, $J = 8.4$ Hz, 1 H, 5-H), 5.74 (d, $J = 5.8$ Hz, 1 H, 1'-H), 7.16, 7.20 (2sl, 2 H exchangeable, NH_2), 7.74 (d, $J = 8.4$ Hz, 1 H, 6-H) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]$ -DMSO, 20 °C): $\delta = 16.1$, 16.2 (POCH_2CH_3), 29.3 (d, $J = 138.1$ Hz, C-6'), 60.8, 61.1 (2d, $J = 6.0$ Hz, POCH_2CH_3), 65.6 (d, $J = 3.0$ Hz, C-5'), 68.5 (C-3'), 73.3 (C-2'), 86.6 (d, $J = 15.1$ Hz, C-4'), 88.9 (C-1'), 94.1 (C-5), 142.0 (C-6), 155.4 (C-2), 165.5 (C-4) ppm. ^{31}P NMR (121 MHz, $[\text{D}_6]$ -DMSO, 20 °C): $\delta = 29.4$ ppm. MS (FAB, GT): $m/z = 787$ $[2\text{M} + \text{H}]^+$, 394 $[\text{M} + \text{H}]^+$, and 785 $[2\text{M} - \text{H}]^-$, 392 $[\text{M} - \text{H}]^-$. UV (EtOH, 95°): λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 235 (8000), 271 (8800) nm; λ_{min} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 226 (7800), 252 (7200) nm. $\text{C}_{14}\text{H}_{24}\text{N}_3\text{O}_8\text{P}$ (393.33)·0.5 H_2O : calcd. C 41.79, H 6.26, N 10.44; found C 41.55, H 6.24, N 10.38.

9-(5S)-[6-Deoxy-6-diethylphosphono- β -D-ribohexofuranosyl]adenine (22): Column chromatography of the crude material on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1) gave title compound **22** as a white solid (0.23 g, 85%) after freeze-drying. $[\alpha]_D^{20} = -40.2$ ($c = 0.92$, MeOH). $R_f = 0.1$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1 v/v). ^1H NMR (300 MHz, $[\text{D}_6]$ -DMSO, 20 °C): $\delta = 1.23$ (t, $J = 7.0$ Hz, 6 H, POCH_2CH_3), 1.80–2.10 (m, 2 H, 6'-H, 6''-H), 3.9–4.1 (m, 6 H, 5'-H, POCH_2CH_3 , 4'-H), 4.20 (m, 1 H, 3'-H), 4.64 (m, 1 H, 2'-H), 5.19 (d, $J = 4.2$ Hz, 1 H exchangeable, 3'-OH), 5.43 (d, $J = 6.6$ Hz, 1 H exchangeable, 2'-OH), 5.84 (d, $J = 7.2$ Hz, 1 H, 1'-H), 6.12 (d, $J = 5.0$ Hz, 1 H exchangeable, 5'-OH), 7.40 (sl, 2 H exchangeable, NH_2), 8.12, 8.31 (2s, 2 H, 2-H, 8-H) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]$ -DMSO, 20 °C): $\delta = 16.1$, 16.2 (POCH_2CH_3), 29.2 (d, $J = 138.8$ Hz, C-6'), 60.8, 61.1 (2d, $J = 6.1$ Hz, POCH_2CH_3), 66.1 (d, $J = 3.3$ Hz, C-5'), 69.3 (C-3'), 72.9 (C-2'), 87.9 (C-1'), 88.8 (d, $J = 14.5$ Hz, C-4'), 119.5, 148.8, 156.2 (Cq), 140.3, 152.2 (C-2, C-8) ppm. ^{31}P NMR (121 MHz, $[\text{D}_6]$ -DMSO, 20 °C): $\delta = 29.4$ ppm. MS (FAB, GT): $m/z = 835$ $[2\text{M} + \text{H}]^+$, 418 $[\text{M} + \text{H}]^+$, and 833 $[2\text{M} - \text{H}]^-$, 416 $[\text{M} - \text{H}]^-$, 134 $[\text{B}]^-$. UV (EtOH, 95°): λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 258 (15600) nm; λ_{min} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 226 (2600) nm. $\text{C}_{15}\text{H}_{24}\text{N}_5\text{O}_7\text{P}$ (417.35)·0.8 H_2O : calcd. C 41.73, H 5.98, N 16.22, P 7.17; found C 42.16, H 6.19, N 15.82, P 6.83.

6-Chloro-9-(5S)-[2,5-di-O-acetyl-3-O-benzoyl-6-deoxy-6-diethylphosphono- β -D-ribohexofuranosyl]purine (23): 6-Chloropurine (0.12 g, 0.75 mmol) and ammonium sulfate (catalytic amount) were dissolved in hexamethyldisilazane (7 mL). The solution was heated at reflux overnight, and then evaporated to dryness to give a pale yellow solid which was dissolved in anhydrous acetonitrile (3 mL). At room temperature, a solution of sugar-phosphonate **14** (0.2 g, 0.4 mmol) in acetonitrile (3 mL) was added followed by tin(IV) chloride (0.18 mL, 1.5 mmol). The resulting solution was stirred for 2.5 h. The reaction mixture was poured into cold saturated aq. NaHCO_3 and filtered through celite. The celite was washed with AcOEt. The organic layer was extracted with saturated aq. NaHCO_3 , brine, dried with Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the crude material on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 97:3) gave protected nucleotide derivative **23** as a pale yellow foam (0.15 g, 64%). $[\alpha]_D^{20} = -11.1$ ($c = 1.08$, MeOH). $R_f = 0.5$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1 v/v). ^1H NMR (300 MHz, $[\text{D}_6]$ -DMSO, 20 °C): $\delta = 1.20$ (m, 6 H, POCH_2CH_3), 1.97 (s, 6 H, CH_3 , Ac), 2.10–2.40 (m, 2 H, 6'-H, 6''-H), 3.96 (m, 4 H, POCH_2CH_3), 4.63 (t, $J = 5.0$ Hz, 1 H, 4'-H), 5.46 (m, 1 H, 5'-H), 5.90 (m, 2 H, 2'-H, 3'-H), 6.70 (d, $J = 4.9$ Hz, 1 H, 1'-H), 7.61 (m, 2 H, H-Ar), 7.75 (m, 1 H, H-Ar), 8.04 (m, 2 H, H-Ar), 8.91, 9.18 (2s, 1 H, 2-H, 8-H) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]$ -DMSO, 20 °C): $\delta = 16.0$, 16.1 (POCH_2CH_3), 20.0, 20.6 (Ac), 26.1 (d, $J = 139.6$ Hz, C-6'), 61.3, 61.4 (POCH_2CH_3), 66.9 (d, $J = 3.8$ Hz, C-5'), 69.1 (C-3'), 73.2 (C-2'), 82.1 (d, $J = 12.1$ Hz, C-4'), 86.8 (C-1'), 121.9, 142.2, 161.8 (Cq), 128.4, 129.0, 129.3, 134.1 (C-Ar), 148.2, 152.3 (C-2, C-8), 164.3, 169.1, 169.2 (C=O) ppm. ^{31}P NMR (121 MHz, $[\text{D}_6]$ -DMSO, 20 °C): $\delta = 26.1$ ppm. MS (FAB, GT): $m/z = 1249$ $[2\text{M} + \text{H}]^+$, 625 $[\text{M} + \text{H}]^+$, 289 $[\text{M} - \text{B} - \text{BzOH} - \text{AcOH}]^+$. UV (EtOH, 95°): λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 231 (18000), 269 (9400) nm; λ_{min} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 253 (7200) nm. $\text{C}_{26}\text{H}_{30}\text{ClN}_4\text{O}_{10}\text{P}$ (624.96): calcd. C 49.97, H 4.84, N 8.96, P 4.96; found C 50.19, H 5.00, N 8.74, P 4.75.

9-(5S)-[6-Deoxy-6-diethylphosphono- β -D-ribohexofuranosyl]hypoxanthine (24): Compound **23** (1.3 g, 2.1 mmol) was dissolved in anhydrous methanol (40 mL). To this solution, 2-mercaptoethanol (0.72 mL, 10.2 mmol) and sodium methoxide (0.67 g, 12.4 mmol) were added, and the mixture was warmed at 60 °C and stirred for 4 h. The solution was neutralised with aqueous acetic acid (7:3 v/v) and solvents were evaporated. Reverse phase column chro-

matography of the resulting oily residue ($\text{H}_2\text{O}/\text{CH}_3\text{CN}$ 0 to 50%) gave the nucleotide analogue of inosine **24** as a white solid (0.61 g, 70%) after freeze-drying. A second compound (0.1 g) was isolated from this reaction and may correspond to the intermediate bearing the mercaptoethyl group in the 6-position of the purine. The structure of this compound was assigned on the basis of NMR and MS data. $[\alpha]_{\text{D}}^{20} = -4.4$ ($c = 0.9$, MeOH). $R_f = 0.2$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 8:2 v/v). ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): $\delta = 1.23$ (t, $J = 7.0$ Hz, 6 H, POCH_2CH_3), 1.80–2.10 (m, 2 H, 6'-H, 6''-H), 3.88 (m, 1 H, 4'-H), 3.94–4.05 (m, 5 H, 5'-H, POCH_2CH_3), 4.19 (m, 1 H, 3'-H), 4.39 (m, 1 H, 2'-H), 5.18 (sl, 1 H, 3'-OH), 5.45 (sl, 1 H, 2'-OH), 5.56 (sl, 1 H, 5'-OH), 6.11 (d, $J = 6.7$ Hz, 1 H, 1'-H), 8.04, 8.56 (2s, 1 H, 2-H, 8-H) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): $\delta = 17.0$, 17.1 (POCH_2CH_3), 30.2 (d, $J = 139.0$ Hz, C-6'), 61.6, 61.9 (2d, $J = 6.1$ Hz, POCH_2CH_3), 66.4 (d, $J = 3.4$ Hz, C-5'), 69.4 (C-3'), 75.6 (C-2'), 88.8 (d, $J = 14.7$ Hz, C-4'), 89.4 (C-1'), 115.5, 155.2, 158.7 (Cq), 143.8, 146.0 (C-2, C-8) ppm. ^{31}P NMR (121 MHz, $[\text{D}_6]\text{DMSO}$, 20 °C): $\delta = 29.4$ ppm. MS (FAB, GT): $m/z = 837$ $[\text{2M} + \text{H}]^+$, 419 $[\text{M} + \text{H}]^+$, and 835 $[\text{2M} - \text{H}]^-$, 417 $[\text{M} - \text{H}]^-$, 135 $[\text{B}]^-$. UV (EtOH, 95°): λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 255 (8000) nm; λ_{min} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 229 (4000) nm. $\text{C}_{15}\text{H}_{23}\text{N}_4\text{O}_8\text{P}$ (418.34), H_2O : calcd. C 41.29, H 5.77, N 12.84, P 7.10; found C 41.16, H 5.47, N 12.76, P 6.93.

Removal of Phosphonic Ester Protecting Groups: The nucleoside diethylphosphonate derivative was dissolved in anhydrous dimethylformamide (20 mL/mmol), then trimethylsilyl bromide (10 or 15 equiv.) was added at 0 °C, and the mixture was stirred at room temperature until completion of the reaction was indicated by TLC.

1-(5S)-[6-Deoxy-6-phosphono- β -D-ribohexofuranosyl]uracil (1, Disodium Salt): The reaction mixture was neutralised with aqueous triethylammonium hydrogencarbonate (1 M) and concentrated to dryness under high vacuum. Reverse phase column chromatography of the crude material (H_2O) gave the corresponding phosphonic acid and title compound **1**, which was obtained as a white solid (0.25 g, 82%) after ion exchange with DOWEX Na^+ and freeze-drying. $[\alpha]_{\text{D}}^{20} = -22.7$ ($c = 0.88$, H_2O). $R_f = 0.2$ ($i\text{PrOH}/\text{NH}_4\text{OH}$ 30%/H₂O, 7:1:2 v/v/v). ^1H NMR (300 MHz, D_2O , 20 °C): $\delta = 1.70$ –1.95 (m, 2 H, 6'-H, 6''-H), 4.03 (t, $J = 3.2$ Hz, 1 H, 4'-H), 4.10 (m, 1 H, 5'-H), 4.2–4.3 (m, 2 H, 3'-H, 2'-H), 5.83 (d, $J = 8.1$ Hz, 1 H, 5-H), 5.87 (d, $J = 5.3$ Hz, 1 H, 1'-H), 7.83 (d, $J = 8.1$ Hz, 1 H, 6-H) ppm. ^{13}C NMR (75 MHz, D_2O , 20 °C): $\delta = 31.6$ (d, $J = 131.4$ Hz, C-6'), 67.2 (d, $J = 3.1$ Hz, C-5'), 68.7 (C-3'), 73.5 (C-2'), 87.5 (d, $J = 14.1$ Hz, C-4'), 87.9 (C-1'), 102.6 (C-5), 141.9 (C-6), 151.9 (C-2), 166.1 (C-4) ppm. ^{31}P NMR (121 MHz, D_2O , 20 °C): $\delta = 20.6$ ppm. MS (FAB, GT): $m/z = 359$ $[\text{M} - \text{Na}]^-$, 337 $[\text{M} - 2\text{Na} + \text{H}]^-$. UV (H_2O): λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 259 (10600) nm; λ_{min} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 228 (2300) nm. $\text{C}_{10}\text{H}_{13}\text{N}_2\text{Na}_2\text{O}_9\text{P}$ (382.17)·0.4H₂O: calcd. C 30.85, H 3.57, N 7.19, P 7.95; found C 31.15, H 4.08, N 7.26, P 8.19.

1-(5S)-[6-Deoxy-6-phosphono- β -D-ribohexofuranosyl]thymine (2, Diacidic Salt): The solution was evaporated to dryness under high vacuum. Reverse phase column chromatography of the crude material (H_2O) gave compound **2** as a white solid (0.12 g, 80%) after freeze-drying. $[\alpha]_{\text{D}}^{20} = -27.6$ ($c = 0.87$, H_2O). $R_f = 0.2$ ($i\text{PrOH}/\text{NH}_4\text{OH}$ 30%/H₂O, 7:1:2 v/v/v). ^1H NMR (300 MHz, D_2O , 20 °C): $\delta = 1.89$ (d, $J = 1.0$ Hz, 3 H, CH_3), 1.90–2.15 (m, 2 H, 6'-H, 6''-H), 4.05 (t, $J = 3.4$ Hz, 1 H, 4'-H), 4.21 (m, 1 H, 5'-H), 4.3–4.4 (m, 2 H, 2'-H, 3'-H), 5.93 (d, $J = 5.4$ Hz, 1 H, 1'-H), 7.66 (d, $J = 1.0$ Hz, 1 H, 6-H) ppm. ^{13}C NMR (75 MHz, D_2O , 20 °C): $\delta = 11.5$ (CH_3), 31.0 (d, $J = 134.6$ Hz, C-6'), 66.6 (d, $J = 3.9$ Hz, C-5'), 68.7, 73.1 (C-2', C-3'), 87.1 (d, $J = 15.1$ Hz, C-4'), 87.9 (C-1'), 111.7 (C-5), 137.4 (C-6), 152.0 (C-2), 166.4 (C-4) ppm. ^{31}P NMR (121 MHz,

D_2O , 20 °C): $\delta = 23.9$ ppm. MS (FAB, GT): $m/z = 353$ $[\text{M} + \text{H}]^+$, and 351 $[\text{M} - \text{H}]^-$, 125 $[\text{B}]^-$. UV (H_2O): λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 265 (9300) nm; λ_{min} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 232 (2200) nm. $\text{C}_{11}\text{H}_{17}\text{N}_2\text{O}_9\text{P}$ (352.23)·0.5H₂O: calcd. C 36.57, H 5.02, N 7.75; found C 36.17, H 5.21, N 7.69.

1-(5S)-[6-Deoxy-6-phosphono- β -D-ribohexofuranosyl]cytidine (3, Sodium Salt): The reaction mixture was neutralised with triethylammonium hydrogencarbonate (1 M) and concentrated to dryness under high vacuum. Reverse phase column chromatography of the crude material (H_2O) gave the corresponding phosphonic acid and title compound **3**, which was obtained as a white solid (0.12 g, 85%) after ion exchange with DOWEX Na^+ and freeze-drying. $[\alpha]_{\text{D}}^{20} = -11.3$ ($c = 0.53$, H_2O). $R_f = 0.1$ ($i\text{PrOH}/\text{NH}_4\text{OH}$ 30%/H₂O, 7:1:2 v/v/v). ^1H NMR (300 MHz, D_2O , 20 °C): $\delta = 1.80$ –2.00 (m, 2 H, 6'-H, 6''-H), 4.11 (t, $J = 3.4$ Hz, 1 H, 4'-H), 4.20 (m, 1 H, 5'-H), 4.2–4.4 (m, 2 H, 3'-H, 2'-H), 5.96 (d, $J = 5.4$ Hz, 1 H, 1'-H), 6.07 (d, $J = 7.6$ Hz, 1 H, 5-H), 7.88 (d, $J = 7.6$ Hz, 1 H, 6-H) ppm. ^{13}C NMR (75 MHz, D_2O , 20 °C): $\delta = 31.5$ (d, $J = 131.1$ Hz, C-6'), 67.2 (d, $J = 3.1$ Hz, C-5'), 68.7 (C-3'), 73.7 (C-2'), 87.1 (d, $J = 14.1$ Hz, C-4'), 88.9 (C-1'), 96.5 (C-5), 141.9 (C-6), 157.8 (C-2), 166.1 (C-4) ppm. ^{31}P NMR (121 MHz, D_2O , 20 °C): $\delta = 20.5$ ppm. MS (FAB, GT): $m/z = 358$ $[\text{M} - \text{Na}]^-$, 336 $[\text{M} - 2\text{Na} + \text{H}]^-$. UV (H_2O): λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 268 (8800) nm; λ_{min} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 248 (6400) nm. $\text{C}_{10}\text{H}_{14}\text{N}_3\text{Na}_2\text{O}_8\text{P}$ (381.19)·0.5H₂O: calcd. C 30.78, H 3.87, N 10.77, P 7.94; found C 30.59, H 4.10, N 10.62, P 7.77.

9-(5S)-[6-Deoxy-6-phosphono- β -D-ribohexofuranosyl]adenine (4, Sodium Salt): The reaction mixture was neutralised with triethylammonium hydrogencarbonate (1 M) and concentrated to dryness under high vacuum. Reverse phase column chromatography of the crude material (H_2O) gave the corresponding phosphonic acid and title compound **4**, which was obtained as a white solid (0.15 g, 77%) after ion exchange with DOWEX Na^+ and freeze-drying. $[\alpha]_{\text{D}}^{20} = -44.9$ ($c = 0.98$, H_2O). $R_f = 0.2$ ($i\text{PrOH}/\text{NH}_4\text{OH}$ 30%/H₂O, 7:1:2 v/v/v). ^1H NMR (300 MHz, D_2O , 20 °C): $\delta = 1.80$ –2.10 (m, 2 H, 6'-H, 6''-H), 4.25 (m, 1 H, 5'-H), 4.34 (m, 1 H, 4'-H), 4.50 (dd, $J = 1.9$ and 5.4 Hz, 1 H, 3'-H), 4.8 (m, under H₂O signal, 1 H, 2'-H), 6.04 (d, $J = 7.2$ Hz, 1 H, 1'-H), 8.24 (s, 1 H, 8-H), 8.33 (s, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, D_2O , 20 °C): $\delta = 31.3$ (d, $J = 131.7$ Hz, C-6'), 67.6 (d, $J = 3.1$ Hz, C-5'), 69.1 (C-3'), 73.5 (C-2'), 88.0 (C-1'), 89.3 (d, $J = 12.2$ Hz, C-4'), 119.3 (C-4, Cq), 140.9, 152.5 (C-2, C-8), 148.5, 155.7 (Cq) ppm. ^{31}P NMR (121 MHz, D_2O , 20 °C): $\delta = 20.4$ ppm. MS (FAB, GT): $m/z = 382$ $[\text{M} - \text{Na}]^-$, 360 $[\text{M} - 2\text{Na} + \text{H}]^-$. UV (H_2O): λ_{max} (ϵ , $\text{L mol}^{-1} \text{cm}^{-1}$) = 258 (15200) nm; λ_{min} = 225 (2500) nm. $\text{C}_{11}\text{H}_{14}\text{N}_5\text{Na}_2\text{O}_7\text{P}$ (405.21)·0.6H₂O: calcd. C 31.76, H 3.68, N 16.83, P 7.45; found C 31.54, H 4.02, N 16.47, P 7.51.

9-(5S)-[6-Deoxy-6-phosphono- β -D-ribohexofuranosyl]hypoxanthine (5, Sodium Salt): The reaction mixture was neutralised with triethylammonium hydrogencarbonate (1 M) and concentrated to dryness under high vacuum. Reverse phase column chromatography of the crude material (H_2O) gave the corresponding phosphonic acid and title compound **5**, which was obtained as a white solid (0.1 g, 68%) after ion exchange with DOWEX Na^+ and freeze-drying. $[\alpha]_{\text{D}}^{20} = -16.7$ ($c = 0.9$, H_2O). $R_f = 0.2$ ($i\text{PrOH}/\text{NH}_4\text{OH}$ 30%/H₂O, 7:1:2 v/v/v). ^1H NMR (300 MHz, D_2O , 20 °C): $\delta = 1.70$ –1.90 (m, 2 H, 6'-H, 6''-H), 4.15 (m, 2 H, 5'-H, 4'-H), 4.37 (dd, $J = 3.8$ and 5.6 Hz, 1 H, 3'-H), 4.50 (t, $J = 5.8$ Hz, 1 H, 2'-H), 6.15 (d, $J = 5.9$ Hz, 1 H, 1'-H), 8.08, 8.48 (2s, 1 H, 2-H, 8-H) ppm. ^{13}C NMR (75 MHz, D_2O , 20 °C): $\delta = 30.8$ (d, $J = 131.7$ Hz, C-6'), 67.1 (d, $J = 2.7$ Hz, C-5'), 68.4 (C-3'), 74.8 (C-2'), 87.8 (d, $J = 13.4$ Hz, C-4'), 89.2 (C-1'), 114.7 (Cq), 143.6, 145.8 (C-2, C-8), 155.3, 157.4

(Cq) ppm. ^{31}P NMR (121 MHz, D_2O , 20 °C): δ = 20.4 ppm. MS (FAB, GT): m/z = 361 $[\text{M} - 2\text{Na} + \text{H}]^+$. UV (H_2O): λ_{max} (ϵ , $\text{L mol}^{-1}\text{cm}^{-1}$) = 255 (8000) nm, λ_{min} (ϵ , $\text{L mol}^{-1}\text{cm}^{-1}$) = 226 (2000) nm. $\text{C}_{11}\text{H}_{13}\text{N}_4\text{Na}_2\text{O}_8\text{P}$ (406.20): calcd. C 32.53, H 3.23, N 13.79, P 7.63; found C 32.47, H 4.17, N 13.64, P 7.42.

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