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SYNTHESIS AND ANTI-HIV ACTIVITY OF NEW 3'-*O*-PHOSPHONOMETHYL NUCLEOSIDES

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Abstract – The synthesis of 4'(*S*)-ethynyl-2'-deoxythreosyl and β-D-galactofuranose nucleosides starting from D-galactose is described. The nucleobase is introduced using Vorbruggen glycosylation. The 4'(*S*)-ethynyl derivatives are obtained by selective oxidation of vicinal diol to the aldehyde and subsequent Bestmann modification of Seyferth-Gilbert homologation. All compounds were evaluated for activity against HIV (MT4 cells), RSV (Hep2 cells) and HCV (HCV replicon cells), however, none of these compounds demonstrate biological activity.

INTRODUCTION

The human immunodeficiency virus (HIV) is the causative agent of the acquired immune deficiency syndrome (AIDS). It is a life threatening infection, which is effectively suppressed by using highly active antiretroviral therapy (HAART). This treatment consists of a combination of two or more reverse transcriptase inhibitors and/or protease inhibitors. Seven of these reverse transcriptase inhibitors are nucleoside analogues and one is a nucleotide analogue.[1] Although HAART improves prognosis of survival of infected patients,[2] drug-resistant mutant viruses emerge during long time therapy. Therefore, the development of new HIV RT inhibitors, especially against drug-resistant variants, is necessary.

Among the nucleoside analogues, nucleoside phosphonates are the most effective anti-HIV compounds. Nucleoside phosphonates are effective therapeutic agents known to have a broad spectrum of antiviral activity.[3] These phosphonates are intracellularly metabolized to the phosphonodiphosphates by cellular

This paper is dedicated to Professor Dr. Albert Eschenmoser on the occasion of his 85th birthday.

kinases. The mimic of natural triphosphates allows them the incorporation into viral DNA. Their incorporation in the viral DNA leads to termination of DNA chain elongation.[4] A nucleoside phosphonate has the advantage that only two phosphorylation steps are needed to convert the compound in the active metabolite. The first phosphorylation reaction is an inefficient and often rate-limiting step, in the metabolic activation of modified nucleosides. Likewise, a nucleoside phosphonate has the advantage over its phosphate counterpart of being metabolically stable, as its phosphorus-carbon bond is not susceptible to phosphatase hydrolysis.[5]

There are two main categories of nucleoside phosphonates. The acyclic nucleoside phosphonates, (ANP) were discovered by Holy and De Clercq in 1986.[6] The most important ANP is tenofovir (a prodrug of (*R*)-9-[2-(phosphonomethoxy)propyl]adenine PMPA) (**1**, Figure 1) which has been approved for treatment of HIV infections.[7] Until now, there are no phosphonate nucleosides with a cyclic sugar moiety available for antiviral therapy although a few cyclic phosphonate nucleosides have been reported with potent antiviral activity.[8] The D-d4AP (**2**, Figure 1) nucleoside shows potent anti-HIV activity, unfortunately, also mitochondrial toxicity.[9a] D-2'Fd4AP (**3**, Figure 1) is a somewhat less active compound but with an optimal resistance profile.[9b,10] PMDTA and PMDTT (**4**, **5**, Figure 1) were described as selective anti-HIV-1 and HIV-2 phosphonate nucleosides while no cytotoxicity was observed at the highest concentration tested.[11]

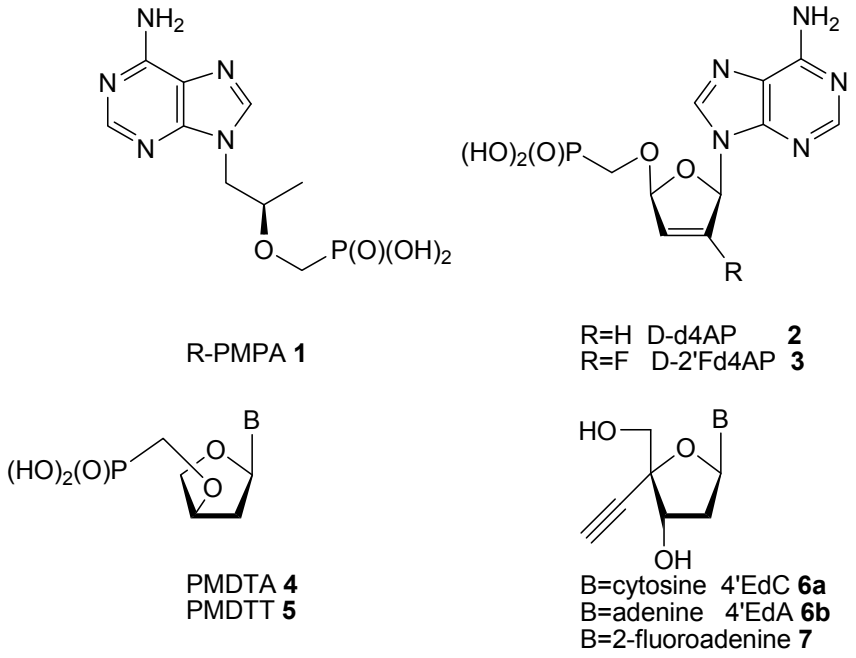


Figure 1. Structure of some antiviral nucleoside and nucleotide analogues

This study is part of a structure activity relationship of 3'-*O*-phosphonoalkyl nucleosides. We investigated the influence of combining a 3'-*O*-phosphonomethyl substituent with a 4'-C-ethynyl

functional group, on a 2'-deoxythreosyl scaffold, on the activity against HIV. Therefore we synthesized three 4'-ethynyl nucleoside phosphonates (Figure 2). This approach has its precedent with the introduction of a 4'-ethynyl group on d4AP.[12] The compound had 3 fold improved antiviral activity compared to the 4'-H analogue. 4'-C-Ethynyl nucleosides are known to be strong inhibitors of HIV, which is due to the presence of a hydrophobic (4') binding pocket in HIV reverse transcriptase.[12] 4'EdC (**6a**, Figure 1) and 4'EdA (**6b**, Figure 1) are examples of compounds with a 4'-ethynyl substituent possessing strong inhibitory activity against HIV[13], but also cytotoxicity. The most promising ethynyl nucleoside is 2'-deoxy-4'-C-ethynyl-2-fluoroadenosine[14] (**7**, Figure 1) and its 2-chloro congener which possess strong anti-HIV activity either against wild type of virus or wide spectrum of HIV-1 strains and also very low cytotoxicity.

The antiviral activity of L-2'-deoxythreosyl nucleosides with a 3'-*O*-phosphonomethyl substituent is explained by intracellular phosphorylation to its diphosphate and subsequent incorporation of the phosphonate nucleotide into viral DNA. As the phosphonoalkoxy group of PMDTA/PMDTT are bound at the 3'-position, the phosphorus atom and the nucleobase are closer to each other than in previously synthesized nucleoside phosphonates where the phosphonate group is bound at the primary hydroxyl group of the nucleoside.[15] In order to investigate the importance of the stereochemistry in the 1'- and 3'-position of PMDTA, isomeric analogs of PMDTA were synthesized.[16] However, none of these compounds showed activity in an HIV-assay. Likewise, the elongation of the phosphonoalkyl chain led to the lost of antiviral activity.[17]

Besides the 4'-ethynyl analogues of the previously mentioned threosyl nucleosides, we have also synthesized and evaluated the 3'-*O*-(phosphonomethyl)-β-D-galactofuranose (Figure 2) congeners.

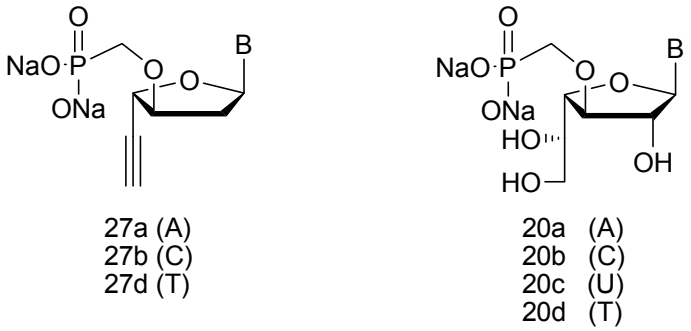


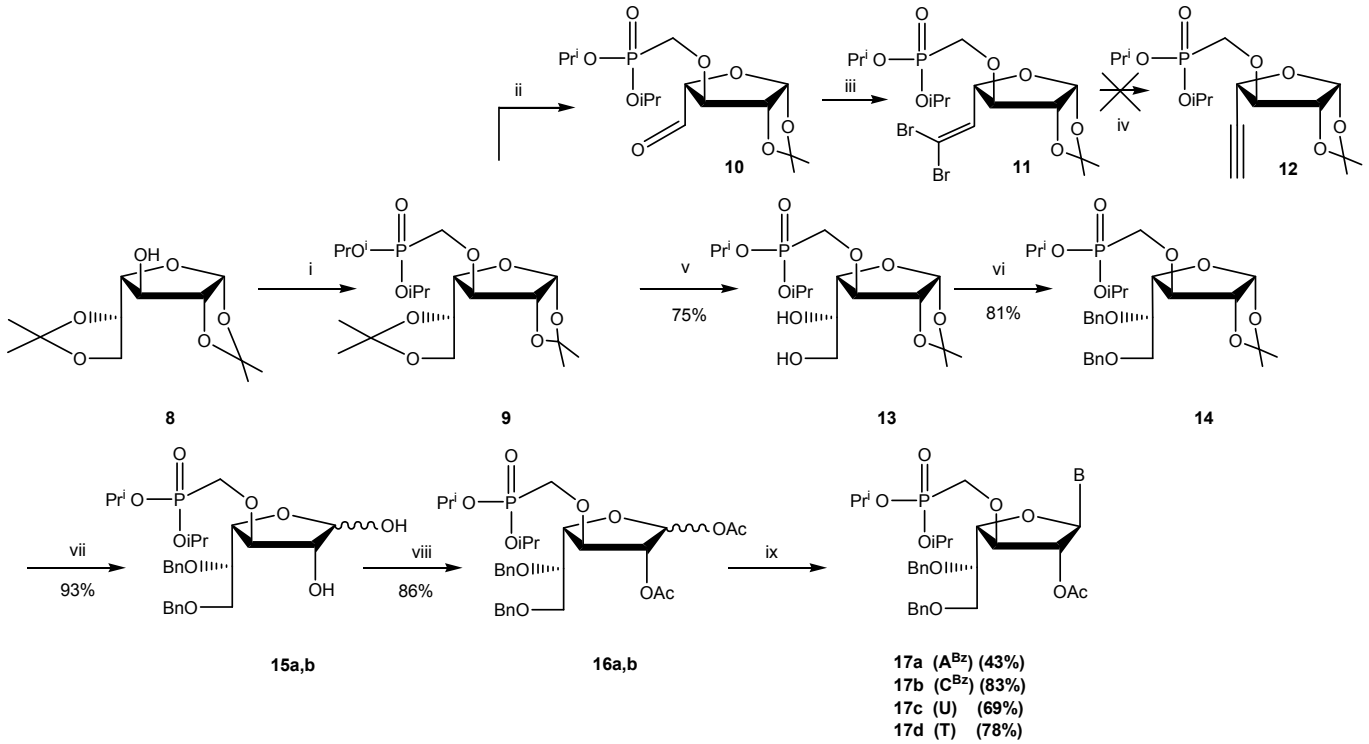
Figure 2. Structure of 4'-substituted analogues of PMDTT and PMDTA

RESULTS AND DISCUSSION

Synthesis

As shown in Scheme 1, key intermediates **16a, b** were synthesized starting from 1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose (**8**), which was obtained by the reaction of D-galactose with an excess

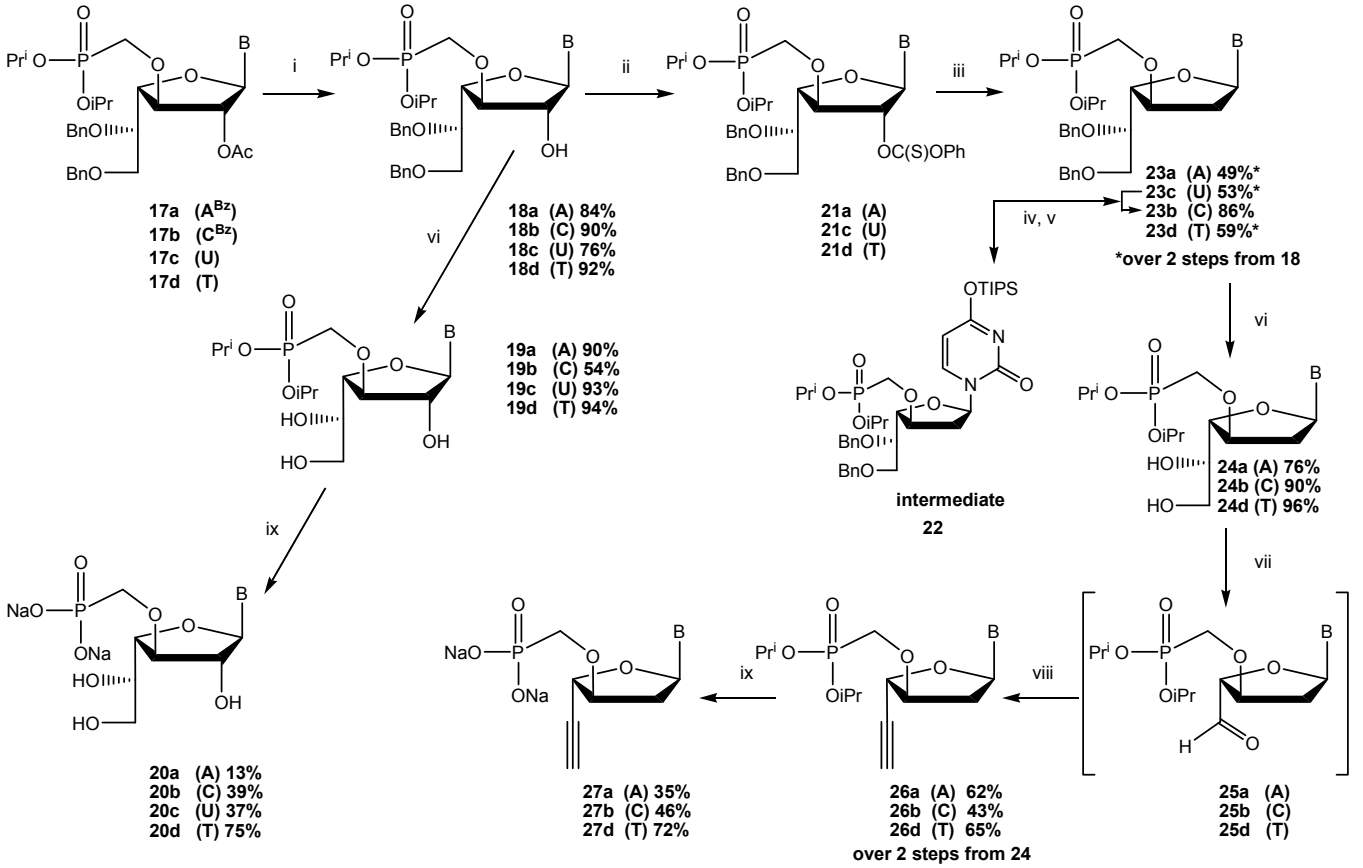
of 2,2-dimethoxypropane (DMP) in the presence of p-toluenesulfonic acid (PTSA) in DMF. The elevated temperature of the reaction mixture is crucial for obtaining the D-galactofuranose derivative. The reaction of D-galactose with DMP and PTSA at room temperature leads to 1,2:3,4-galactopyranose in almost quantitative yield.[18] The phosphonate function was introduced using (diisopropoxyphosphonyl)methyl trifluoromethanesulfonate[19] and NaH in dry THF.[11] Selective oxidation of compound **9** by a mixture of periodic acid and sodium periodate[16] gives the aldehyde **10**, which was converted into the 6,6-dibromoalkene derivative **11** by Corey-Fuchs reaction.[20] Unfortunately, the elimination reaction to obtain the 4-ethynyl sugar using BuLi or *tert*-BuOK led to a complex reaction mixture. Therefore, we decided to introduce the triple bond at the end of the synthetic scheme.



Scheme 1. i) NaH, THF, $TfOCH_2P(O)(OiPr)_2$, -78 °C, room temperature; ii) H_5IO_6, $NaIO_4$, EtOAc, room temperature; iii) PPh_3, CBr_4, Et_3N, CH_2Cl_2; room temperature iv) BuLi or MeONa; v) 70% AcOH, room temperature 20 h; vi) NaH, BnBr, DMF; vii) CF_3CO_2H, 1 h; viii) Ac_2O, pyridine, 0 °C; ix) HMDS, $(NH_4)_2SO_4$, $SnCl_4$ in CH_2Cl_2, room temperature.

Selective hydrolysis of the 5,6-isopropylidene protecting group of compound **9** using 70% acetic acid gave the vicinal diol **13**. Benzylation of thus obtained derivative **13** was performed at room temperature. A decomposition was observed when the compound 13 was treated with sodium hydride and subsequently with benzyl bromide at higher temperature.[21] The 1,2-isopropylidene protecting group of **14** was hydrolyzed with CF_3CO_2H and then the resulting compounds **15a**, **b** were transformed to diacetyl

derivatives **16a**, **b**. The presence of a 2-*O*-acetyl group allowed β-selective introduction of the base moieties (N^6-benzoyladenine, N^4-benzoylcytosine, N^3-benzoyluracil and thymine) using $SnCl_4$ as a Lewis acid. The obtained compounds, **17a-d** were deacetylated and debenzoylated using ammonia in methanol. From these compounds the galactofuranoside phosphonate nucleosides **20a-d** were obtained by transfer hydrogenation on Pd hydroxide [22] and subsequent transfer esterification using iodotrimethylsilane as shown in Scheme 2. The 4'-alkynyl substituted compounds **27a**,**b**,**d** were prepared in five steps starting from compounds **18a-d**. These compounds were transformed into the 2'-deoxygenated congeners by Barton deoxygenation.[11] In contrast to the results obtained with the adenine (**23a**) and thymine (**23d**) derivatives,[23] deoxygenation of cytosine **23b** failed. Therefore, the cytosine congener was synthesized via the uracil analogue. The uracil derivative **23c** was transformed to the 2-oxo-1,2-dihydropyrimidin-4-(2,4,6-triisopropylbenzenesulfonate) derivative, **22**, by reaction with 2,4,6-triisopropylbenzenesulfonyl chloride, Et_3N and DMAP in CH_2Cl_2,[24] followed by treatment of the intermediate **22** with concentrated aqueous ammonia in dioxane, to afford the desired deoxygenated cytosine product **23b**.



Scheme 2. i) MeOH/NH_3 overnight, RT; ii) PhOC(S)Cl, DMAP, MeCN, 0 °C; iii) AIBN, Bu_3SnH, toluene, reflux; iv) DMAP, E_3N, TIPSCl, CH_2Cl_2, RT overnight; 88% yield; v) NH_3 solution in dioxane, RT, 5 h; vi) cyclohexene, $Pd(OH)_2$, MeOH, 80 °C; vii) $NaIO_4$, aq MeOH RT; viii) $MeCOC(N_2)P(O)(OMe)_2$ (**28**), K_2CO_3, MeOH, RT; ix) TMSI, 2,6-lutidine, MeCN;

The 2'-deoxygenated products **23a**,**b**,**d** were debenzylated by transfer hydrogenation and converted into the aldehyde derivatives **25a**,**b**,**d** by reaction with $NaIO_4$ in 50% aqueous methanol. The aldehydes were converted by Bestmann modification of Seyferth-Gilbert homologation[25,26,27] into the appropriate 4'-ethynyl derivatives **26a**,**b**,**d**.

The final transesterification reaction under mild conditions using TMSI and 2,6-lutidine, afforded the nucleoside phosphonates **27a**,**b**,**d** in moderate to good yields.

BIOLOGICAL RESULTS

All compounds were evaluated for antiviral activity against HIV (MT4 cells), RSV (Hep2 cells) and HCV (HCV replicon cells at 88 μM). Unfortunately, none of the synthesized compounds shows antiviral activity against HIV, HCV and RSV. The addition of 4'-ethynyl substituent to the PMDTA/PMDTT has a detrimental effect on its antiviral activity. It is not clear if the loss of anti-HIV activity is caused by the lack of intracellular phosphorylated or if the 4'-ethynyl substituent is not able to reach the hydrophobic binding pocket in the HIV reverse transcriptase.

CONCLUSION

Three 4'-ethynyl-2'-deoxythreosyl nucleosides and four β-D-galactofuranose derivatives with a 3'-*O*-phosphonomethyl substituent were synthesized. A new efficient synthetic method for preparation of 4'-ethynyl-2'-deoxythreosyl phosphonates was developed. The stereoselective introduction of the base moiety was ensured by using galactofuranosides as starting material. The 2'-OH group was removed by Barton deoxygenation. The alkynyl group was obtained by the selective oxidation of the exocyclic vicinal diol to aldehyde and subsequent Bestman-Ohira modification of the Seyfert-Gilbert reaction. The sodium salts of phosphonates were obtained by a transesterification reaction with iodotrimethylsilane in the presence of 2,6-lutidine as a base. Unfortunately, the obtained compounds did not show activity against HIV and HCV.

EXPERIMENTAL

All the synthesized compounds were characterized by NMR and Mass Spectroscopy. ^{1}H and ^{13}C NMR spectra were acquired on Bruker Avance 300 UtraShield spectrometer, locked on deuterium frequency ^{1}H, 300 MHz and 75 MHz for ^{13}C NMR spectra. The samples were dissolved in $CDCl_3$, DMSO-d_6 using the solvent residual peak as reference (7.26 ppm and 2.50 ppm respectively). For the experiments in D_2O, 1% dioxane was used as internal reference for ^{1}H and ^{13}C NMR spectra (3.75 ppm and 67.3 ppm respectively). Exact mass measurements were performed on a quadrupole time-of-flight mass spectrometer (Q-Tof-2, Micromass, Manchester, UK) equipped with a standard electrospray-ionization (ESI) interface; samples

were infused in iPrOH/H_2O 1 : 1 at 3 μL/min.

Preparative HPLC purifications were performed on a column packed with 5 μm C18 reversed phase Xbridge^{TM}- Waters 19 x 150 mm in ca. 50 mg batches of mixtures using a linear gradient of 0.05 M tetraethyl ammonium hydrogen carbonate buffer in H_2O/MeCN (1–50% MeCN) as eluent. The purifications were performed on Waters 1525 binary HPLC pump system.

Precoated aluminum sheets (Fluka Silica gel/TLC-cards, 254 nm) were used for TLC. The spots were examined with UV light and visualized with Ceric Ammonium Molybdate (CAM) or p-Anisaldehyde spray. Column chromatography was performed on ICN silica gel 63-200 A.

For all reactions, analytical grade solvents were used. All moisture sensitive reactions were carried out in oven-dried glassware (135 °C) under argon atmosphere. Anhydrous THF was refluxed over sodium/benzophenone and distilled. Toluene was refluxed over sodium and distilled. Acetonitrile was distilled over P_2O_5.

1,2:5,6-Di-*O*-isopropylidene-α-D-galactofuranose (8)

D-Galactose (3 g, 16.6 mmol), molecular sieves and p-toluenesulfonic acid (0.2 g, 1.05 mmol) were dissolved in DMF (72 mL) and the reaction mixture was placed into hot oil bath (90 °C). When the slurry was completely dissolved, 2,2-dimethoxypropane (20 mL, 162 mmol) was added. The resulting reaction mixture was stirred at 90 °C for 1 h. After cooling to room temperature solid K_2CO_3 (0.2 g) was added and after 10 min the reaction mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was coevaporated with toluene (3 x 50 mL) and partitioned between Et_2O (100 mL) and brine (150 mL). The aqueous layer was extracted with Et_2O (5 x 30 mL). The organic layer was dried over Na_2SO_4, concentrated *in vacuo* and purified by column chromatography on a silicagel column (Hex : CH_2Cl_2 : MeOH, 6 : 4 : 0.05) to afford **8** (1.73 g, 40%). The data were identical to those described in the literature.[28]

1,2-*O*-Isopropylidene-3-*O*-(diisopropylphosphonomethyl)-α-D-galactofuranose (13)

Compound **9** (4 g, 9.1 mmol) was dissolved in 70% acetic acid (60 mL) and stirred at room temperature for 16 h. This solution was diluted by water (10 mL) and neutralized with solid $NaHCO_3$. The resulting slurry was filtered and the filtrate was extracted with Et_2O (3 x 30 mL). The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography (Hex : EtOAc, 50 : 50) to afford an oily product (2.7 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.31-1.37 (m, 12H, CH_3) and (s, 3H, CH_3-isopropylidene); 1.54 (s, 3H, CH_3-isopropylidene); 2.98 and 3.07 2 x (brs, 1H, OH); 3.72-3.94 (m, 5H, PCH_2, H-6'a, H-6'b, H-3', H-4'); 4.09 (m, 1H, H-6'a); 4.18 (m, 1H, H-5'); 4.64 (d, J = 4.1 Hz, 1H, H-2'); 4.68-4.83 (m, 2H, POCH); 5.87 (d, J = 4.1 Hz, 1H, H-1'). ^{13}C NMR (75 MHz, $CDCl_3$): 23.99

(CH_3 iPr); 26.37 and 27.04 (2 x CH_3 isopropylidene); 63.59 (C-6'); 64.80 (d, $J_{P,C}$ = 169.8 Hz, PCH_2); 70.76 (C-5'); 71.48(POCH); 71.58 (POCH); 84.95 (C-2'); 85.37 (C-4'); 85.71 (d, $J_{P,C}$ = 9.1 Hz, C-3'); 105.29 (C-1'); 113.28 (C-isopropylidene). Exact mass calcd for $C_{16}H_{31}O_9P$ $[M+H]^+$: 399.1778, found 399.1793.

5,6-Di-*O*-benzyl-1,2-*O*-isopropylidene-3-*O*-(diisopropylphosphonomethyl)-α-D-galactofuranose (14)

Compound **13** (2.27 g, 5.7 mmol) was coevaporated with dry toluene (3 x 50 mL), dissolved in dry DMF (40 mL) and cooled to 0 °C. To this solution benzyl bromide (1.46 mL, 12.4 mmol) and NaH (60% suspension in mineral oil) (0.5 g, 12.5 mmol) were added. The resulting slurry was allowed to heat to room temperature and stirred overnight. The solvent was evaporated *in vacuo* and to the residue was added saturated aqueous $NaHCO_3$ (5 mL). The mixture was partitioned between EtOAc (100 mL) and brine (50 mL). The organic layer was washed with brine (2 times), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica (EtOAc : Hexane, 95 : 5) to afford compound **14** (2.67 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.28 (d, J = 6.2 Hz, 6H, CH_3), 1.31 (d, J = 6.2 Hz, 6H, CH_3) 1.34 (s, 3H, CH_3-isopropylidene); 1.47 (s, 3H, CH_3-isopropylidene); 3.60 (dd, J_1 = 13.3 Hz, J_2 = 9.5 Hz, 1H, PCH_{2a}); 3.72 (dd, J_1 = 13.3 Hz, J_2 = 9.5 Hz, 1H, PCH_{2b}); 3.67-3.73 (m, 2H, H-6'); 3.76-3.85 (m, 1H, H-5'); 3.99 (dd, J_1 = 4.8 Hz, J_2 = 1.3 Hz, 1H, H-3'); 4.06 (t, J = 5.2 Hz, 1H, H-4'); 4.55 (s, 2H, CH_2Bn); 4.60 (dd, J_1 = 4.2 Hz, J_2 = 1.3 Hz, 1H, H-2'); 4.64-4.78 (m, 2H, PCH); 4.73 (d, J = 11.8 Hz, 1H, CH_{2a}Bn); 4.79 (d, J = 11.8 Hz, 1H, CH_{2b}Bn); 5.81 (d, J = 4.2 Hz, 1H, H-1'); 7.27-7.39 (m, 10H, H-arom). ^{13}C NMR (75 MHz, $CDCl_3$): 24.03 (CH_3 iPr); 26.76 and 27.25 (2 x CH_3 isopropylidene); 64.72 (d, $J_{P,C}$ = 170.5 Hz, PCH_2); 70.65 (C-6'); 71.21 (POCH); 71.09 (POCH); 73.21 (CH_2Bn); 73.40 (CH_2Bn); 76.85 (C-5'); 83.94 (C-2'); 85.25 (C-4'); 85.33 (d, $J_{P,C}$ = 13.8 Hz, C-3'); 104.89 (C-1'); 113.48 (C-isopropylidene); 127.54, 127.60, 127.61, 128.10, 128.24, 128.35, (C-arom); 138.06 (C-Bn); 138.48 (C-Bn). Exact mass calcd for $C_{30}H_{43}O_9P$ $[M+H]^+$: 579.2723, found 579.2717.

5,6-Di-*O*-benzyl-3-*O*-(diisopropylphosphonomethyl)-α-D-galactofuranose (15a) and 5,6-di-*O*-benzyl-3-*O*-(diisopropylphosphonomethyl)-β-D-galactofuranose (15b)

Compound **14** (2.56 g, 4.4 mmol) was dissolved in 12 mL of concentrated trifluoroacetic acid : H_2O (3 : 1) and the solution was stirred at room temperature for 1 h. The resulting mixture was neutralized with solid $NaHCO_3$. The mixture was partitioned between CH_2Cl_2 (100 mL) and brine (50 mL) and the organic layer was extracted twice by CH_2Cl_2 and concentrated *in vacuo*. The residue was coevaporated with dry toluene (3 x 50 mL) to afford an oily product **15a**,**b** (2.21g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.28 (m, 24H, CH_3 - iPr); 3.62-3.86 (m, 12H, 2xPCH_2, H-5', H-6', H-4'); 3.99 (t, J = 4.0 Hz, 1H, H-3'α); 4.00 (s,

1H, H-3'β); 4.09 (dd, J_1 = 4.0 Hz, J_2 = 1.8 Hz, 1H, H-2'α); 4.39 (t, J = 1.9 Hz, 1H, H-2'β); 4.56 (s, 2H, CH_2Bn) and 4.57 (s, 2H, CH_2Bn); 4.64-4.80 (m, 4H, PCH); 4.61 (d, J = 11.3 Hz, 1H, CH_{2a}Bn); 4.66 (d, J = 11.4 Hz, 1H, CH_{2a}Bn); 4.84 (d, J = 11.3 Hz, 1H, CH_{2b}Bn); 4.88 (d, J = 11.4 Hz, 1H, CH_{2b}Bn); 5.17 (d, J = 4.0 Hz, 1H, H-1'α); 5.20 (d, J = 1.9 Hz, 1H, H-1'β); 7.28-7.40 (m, 20H, H-arom). ^{13}C NMR (75 MHz, $CDCl_3$): 23.93-24.08 (CH_3 iPr); 64.70 (d, $J_{P,C}$ = 169.1 Hz, PCH_2-α); 65.16 (d, $J_{P,C}$ = 168.4 Hz, PCH_2-β); 70.27 (C-6'α); 70.31 (C-6'β); 71.35 (d, $J_{P,C}$ = 6.8 Hz, POCH-β); 71.38 (d, $J_{P,C}$ = 6.8 Hz, POCH-β); 71.53 (d, $J_{P,C}$ = 7.0 Hz, POCH-α); 71.70 (d, $J_{P,C}$ = 7.0 Hz, POCH-α); 73.39 (CH_2Bn-α); 73.56, 73.59, 73.62 3 x (CH_2Bn) 2x β 1x α; 76.13, 76.40 and 76.80 (C-2'α, C-5'α, β); 81.63 and 81.64 (C-2'β and C-4'α); 83.69 (C-4'β); 87.54 (d, $J_{P,C}$ = 10.0 Hz, C-3'α); 88.31 (d, $J_{P,C}$ = 10.0 Hz, C-3'β); 97.53 (C-1'α); 103.73 (C-1'β); 127.64, 127.71, 127.74, 127.76, 128.38, 128.41, 128.42, 128.43, 128.60, 128.67, 128.72, 128.82 (C-arom); 136.66, 136.87, 137.84, 137.87 (C-Bn). Exact mass calcd for $C_{27}H_{39}O_9P$ $[M+H]^+$: 539.2404, found 539.2402.

1,2-Di-*O*-acetyl-5,6-di-*O*-benzyl-3-*O*-(diisopropylphosphonomethyl)-α-D-galactofuranose (16a) and 1,2-di-*O*-acetyl-5,6-di-*O*-benzyl-3-*O*-(diisopropylphosphonomethyl)-β-D-galactofuranose (16b)

To a solution of **15a**,**b** (2.21 g, 3.5 mmol) in pyridine (12 mL) was added dropwise acetic anhydride (3.34 mL, 35 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was evaporated *in vacuo* and coevaporated with toluene. The residue was partitioned between EtOAc (100 mL) and H_2O (50 mL). The organic layer was washed with brine (2 x 50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica (Et_2O : EtOH, 99 : 1) to afford **16a (**α-anomer), (0.74 g) as a colorless oil in 29% yield. ^{1}H NMR (300 MHz, $CDCl_3$): 1.28-1.33 (m, 12H, CH_3 - iPr); 1.89 (s, 3H, CH_3); 2.07 (s, 3H, CH_3); 3.66 (dd, J_1 = 13.3 Hz, J_2 = 9.8 Hz, 1H, PCH_{2a}); 3.64-3.77 (m, 3H, H-5', H-6'); 3.79 (dd, J_1 = 13.3 Hz, J_2 = 9.8 Hz, 1H, PCH_{2b}); 4.10 (dd, J_1 = 6.7 Hz, J_2 = 3.9 Hz, 1H, H-4'); 4.37 (t, J = 7.2 Hz, 1H, H-3'); 4.55 (s, 2H, CH_2Bn); 4.66 (d, J = 11.7 Hz, 1H, CH_2Bn); 4.66-4.80 (m, 2H, POCH); 4.84 (d, J = 11.7 Hz, 1H, CH_2Bn); 5.15 (dd, J_1 = 7.2 Hz, J_2 = 4.5 Hz, 1H, H-2'); 6.29 (d, J = 4.5 Hz, 1H, H-1'). ^{13}C NMR (75 MHz, $CDCl_3$); 20.49 (CH_3CO); 20.89 (CH_3CO); 23.95 (iPr-CH_3); 65.12 (d, $J_{P,C}$ = 168.6 Hz, PCH_2); 69.98 (C-6'); 70.23 (POCH); 73.02 (CH_2Bn); 73.43 (CH_2Bn); 76.94 and 77.08 (C-2' and C-5'); 81.14 (C-4'); 81.37 (d, $J_{P,C}$ = 13.9 Hz, C-3'); 93.91 (C-1'); 127.57, 127.62, 127.67, 127.96, 128.29, 128.36, 128.44 (C-arom); 138.07, 138.38 (C-Bn). Exact mass calcd for $C_{31}H_{43}O_{11}P$ $[M+Na]^+$: 645.2421, found 645.2419.

(1.45 g, 57%) of **16b** (β-anomer). ^{1}H NMR (300 MHz, $CDCl_3$): beta 1.31-1.35 (m, 12H, CH_3 - iPr); 1.97 (s, 3H, CH_3); 2.08 (s, 3H, CH_3); 3.62 (dd, J_1 = 13.5 Hz, J_2 = 9.0 Hz, 1H, PCH_{2a}); 3.69-3.79 (m, 2H, H-6'); 3.85-3.90 (m, 1H, H-5'); 3.91 (dd, J_1 = 13.5 Hz, J_2 = 9.0 Hz, 1H, PCH_{2b}); 3.97 (m, 1H, H-3'); 4.33 (dd, J_1 = 5.1 Hz, J_2 = 3.5 Hz, 1H, H-4'); 4.58 (s, 2H, CH_2Bn); 4.66 (d, J = 11.7 Hz, 1H, CH_{2a}Bn); 4.68-4.80 (m,

2H, POCH); 4.84 (d, J = 11.7 Hz, 1H, CH_{2b}Bn); 5.07 (d, J = 0.8 Hz, 1H, H-2'); 6.22 (s, 1H, H-1'); 7.29-7.39 (m, 10H, H-arom). ^{13}C NMR (75 MHz, $CDCl_3$): 20.62 (CH_3CO); 21.01 (CH_3CO); 23.99 (iPr-CH_3); 65.16 (d, $J_{P,C}$ = 168.2 Hz, PCH_2); 70.29 (C-6'); 70.99 (d, $J_{P,C}$ = 6.5 Hz, POCH); 71.06 (d, $J_{P,C}$ = 6.5 Hz, POCH); 73.33 (CH_2Bn); 73.37 (CH_2Bn); 76.23 (C-5'); 80.53 (C-2'); 85.01 (C-4'); 85.62 (d, $J_{P,C}$ = 13.4 Hz, C-3'); 99.66 (C-1'); 127.48, 127.59, 127.80, 128.29, 128.35 (C-arom); 138.10, 138.16 (C-Bn). Exact mass calcd for $C_{31}H_{43}O_{11}P$ $[M+Na]^+$: 645.2421, found 645.2384.

2-*O*-Acetyl-1-(N^6-benzoyladenin-9-yl)-5,6-di-*O*-benzyl-3-*O*-(diisopropylphosphonomethyl)-β-D-galactofuranose (17a)

N^6-Benzoyladenine (1.3 g, 5.6 mmol), ammonia sulfate (70 mg, 0.7 mmol), and 15 mL of HMDS were added to a dried flask. The mixture was refluxed overnight under argon. Volatile parts were removed *in vacuo* and the residue was dried in high vacuum for 1 h. A solution of **16a, b** (1.74 g, 2.8 mmol) in 25 mL of dry MeCN was added to the previous dried residue, followed by dropwise addition of $SnCl_4$ (0.91 mL, 8.4 mmol) under Ar at room temperature. The reaction mixture was stirred for 5 h and additional $SnCl_4$ (0.30 mL, 2.8 mmol) was added. After 2 h at room temperature the reaction was quenched with solid $NaHCO_3$ and 4 mL H_2O, filtered and the filtrate was concentrated to a small volume. The residue was partitioned between H_2O (30 mL) and CH_2Cl_2 (150 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on a silica gel column (CH_2Cl_2 : MeOH, 98 : 2) to afford **17a** (1.57 g) as a colorless amorphous solid in 43% yield. ^{1}H NMR (300 MHz, $CDCl_3$): 1.25-1.34 (m, 12H, CH_3), 1.95 (s, 3H, CH_3CO); 3.64-3.78 (m, 3H, PCH_{2a}, H-6'); 3.82-3.91 (m, 2H, PCH_{2b}, H-5'); 4.35 (dd, J_1 = 3.9 Hz, J_2 = 1.8 Hz, 1H, H-3'); 4.53 (s, 2H, CH_2Bn); 4.58 (t, J = 4.0 Hz, 1H, H-4'); 4.67 (d, J = 11.7 Hz, 1H, CH_{2a}Bn); 4.84 (d, J = 11.7 Hz, 1H, CH_{2b}Bn); 4.66-4.78 (m, 2H, POCH); 5.70 (t, 1H, J = 2.0 Hz, H-2'); 6.40 (d, 1H, J = 2.0 Hz, H-1'); 8.02 (d, 2H, J = 7.6 Hz, H-arom Bz); 7.28-7.42 (m, 10H, ArH); 7.47-7.64 (m, 3H, ArH); 8.36 (s, 1H, H-8); 8.82 (s, 1H, H-2); 9.23 (brs, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): 20.47 (CH_3CO); 23.99 (CH_3); 64.97 (d, $J_{P,C}$ = 168.6 Hz, PCH_2); 69.45 (C-6'); 71.24 (POCH); 71.33(POCH), 73.20 (CH_2-Bn); 73.46 (CH_2-Bn); 76.63 (C-5'); 80.60 (C-2'), 85.24 (d, $J_{P,C}$ = 11.6 Hz, C-3'); 85.65 (C-4'); 87.76 (C-1'); 122.73 (C-5); 127.60, 127.71, 127.80, 127.91, 128.19, 128.35, 128.41, 128.76 (C-arom); 132.63 (C-Bn); 133.72 (C-Bn); 137.72 (C-Bn); 137.89 (C-Bn); 141.80 (C-8); 149.51 (C-6); 151.60 (C-4); 152.92 (C-2); 164.51 (OBzCO); 169.70 (AcCO). Exact mass calcd for $C_{41}H_{48}N_5O_{10}P$ $[M+Na]^+$: 824.3037, found 824.3055.

2-*O*-Acetyl-1-(N^4-benzoylcytosin-1-yl)-5,6-di-*O*-benzyl-3-*O*-(diisopropylphosphonomethyl)-β-D-galactofuranose (17b)

N^4-Benzoylcytosine (1.05 g, 4.9 mmol), ammonia sulfate (0.1 g, 0.8 mmol), and 21 mL of HMDS were

added to a dried flask. The mixture was refluxed overnight under argon. Volatile parts were removed *in vacuo* and the residue was dried in high vacuum for 1 h. A solution of **16a**,**b** (2 g, 3.2 mmol) in 32 mL of dry MeCN was added to the previous residue, followed by dropwise addition of $SnCl_4$ in CH_2Cl_2 (1M solution, 9.8 mL, 9.8 mmol) under Ar at room temperature. The reaction mixture was stirred for 5 h and quenched with solid $NaHCO_3$ and 4 mL H_2O, filtered and the filtrate was concentrated to a small volume. The residue was partitioned between H_2O (30 mL) and CH_2Cl_2 (150 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica (CH_2Cl_2:MeOH, 97:3) to afford **17b** (2.09 g) as a colorless amorphous solid in 83% yield. ^{1}H NMR (300 MHz, $CDCl_3$): 1.25-1.30 (m, 12H, CH_3); 1.89 (s, 3H, CH_3CO); 3.66-3.79 (m, 4H, PCH_{2a}, H-6', H-5'); 3.81 (dd, J_1 = 13.8 Hz, J_2 = 9.5 Hz, 1H, PCH_{2b}); 4.26 (dd, J_1 = 2.2 Hz, J_2 = 1.6 Hz, 1H, H-3'); 4.54 (s, 2H, CH_2Bn); 4.68 (d, J = 11.7 Hz, 1H, $CH_{2a}Bn$); 4.61-4.73 (m, 3H, POCH, H-4'); 4.78 (d, J = 11.7 Hz, 1H, $CH_{2b}Bn$); 5.26 (t, J = 1.7 Hz, 1H, H-2'); 6.15 (d, 1H, J = 1.7 Hz, H-1'); 7.29-7.40 (m, 10H, arom H); 7.88 (d, J = 7.5 Hz, 1H, H-6); 7.47-7.63 (m, 5H, arom H); 8.90 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): 20.48 (CH_3CO); 23.84 (CH_3); 64.65 (d, $J_{P,C}$ = 167.5 Hz, PCH_2); 69.06 (C-6'); 71.02 (POCH); 71.11 (POCH); 73.02 (CH_2Bn); 73.42 (CH_2Bn); 76.92 (C-5'); 80.30 (C-2'); 84.35 (d, $J_{P,C}$ = 11.0 Hz, C-3'); 87.83 (C-4'); 91.30 (C-1'); 96.46 (C-5); 127.47, 127.75, 127.80, 127.81, 128.03, 128.33, 128.36, 128.87 (C-arom); 133.02 (C-arom); 137.52 (C-Bn); 137.73 (C-Bn); 144.39 (C-6); 154.55 (CH_3CO); 162.34 (C-2); 166.59 (BzCO); 169.55 (C-4). Exact mass calcd. for $C_{40}H_{48}N_3O_{11}P$ $[M+H]^+$: 778.3099, found 778.3097.

2-*O*-Acetyl-5,6-di-*O*-benzyl-3-*O*-(diisopropylphosphonomethyl)-1-(uracil-1-yl)-β-D-galactofuranose (17c)

3-Benzoyluracil[29] (0.52 g, 2.4 mmol), ammonia sulfate (0.016 g, 0.13 mmol), and 8.2 mL of HMDS were added to a dried flask. The mixture was refluxed overnight under argon. Volatile parts were removed *in vacuo* and the residue was dried in high vacuum for 1 h. A solution of **16a**,**b** (1 g, 1.6 mmol) in 22 mL of dry MeCN was added to the previous dried residue, followed by dropwise addition of $SnCl_4$ in CH_2Cl_2 (1M solution, 4.8 mL, 4.8 mmol) under Ar at room temperature. The reaction mixture was stirred for 6 h and quenched with solid $NaHCO_3$ and 2 mL H_2O, filtered and the filtrate was concentrated to a small volume. The residue was partitioned between H_2O (30 mL) and EtOAc (150 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica (Hexane:CH_2Cl_2:MeOH, 6:4:0.5) to afford **17c** (1.5 g) as a colorless oil in 69% yield. ^{1}H NMR (300 MHz, $CDCl_3$): 1.27-1.32 (m, 12H, CH_3); 1.89 (s, 3H, CH_3CO); 3.63-3.76 (m, 4H, PCH_{2a}, H-6', H-5'); 3.81 (dd, J_1 = 13.6 Hz, J_2 = 9.9 Hz, 1H, PCH_{2b}); 4.22 (t, J = 2.4 Hz, H-3'); 4.51 (dd, J_1 = 4.2 Hz, J_2 = 1.2 Hz, 1H, H-4'); 4.53 (s, 2H, CH_2Bn); 4.64 (d, J = 11.8 Hz, 1H, $CH_{2a}Bn$); 4.66-

4.76 (m, 2H, POCH); 4.78 (d, J = 11.8 Hz, 1H, CH_{2b}Bn); 5.18 (dd, J_1 = 2.9 Hz, J_2 = 2.1 Hz, 1H, H-2'); 5.72 (d, J = 8.1 Hz, 1H, H-5); 6.11 (d, 1H, J = 2.9 Hz, H-1'); 7.27-7.36 (m, 10H, ArH); 7.48 (d, J = 8.1 Hz, 1H, H-6); 8.44 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): 20.45 (CH_3CO); 24.01 (CH_3); 64.83 (d, $J_{P,C}$ = 168.7 Hz, PCH_2); 69.14 (C-6'); 71.33 2 x (POCH); 73.05 (CH_2-Bn); 73.56 (CH_2-Bn); 76.58 (C-5'); 80.76 (C-2'), 84.94 (d, $J_{P,C}$ = 11.6 Hz, C-3'); 86.25 (C-4'); 89.67 (C-1'); 102.67 (C-5); 127.76, 127.87, 127.94, 128.07, 128.46 (C-arom); 137.67 (C-Bn); 137.81 (C-Bn); 140.04 (C-6); 150.02 (C-2); 162.65 (C-4); 169.78 (CH_3CO). Exact mass calcd. for $C_{33}H_{43}N_2O_{11}P$ $[M+H]^+$: 675.2677, found 675.2653.

2-*O*-Acetyl-5,6-di-*O*-benzyl-3-*O*-(diisopropylphosphonomethyl)-1-(thymin-1-yl)-β-D-galacto-furanose (17d)

Thymine (0.6 g, 4.8 mmol), ammonia sulfate (0.016 g, 0.13 mmol), and 10.8 mL of HMDS were added to a dried flask. The mixture was refluxed overnight under argon. Volatile parts were removed *in vacuo* and the residue was dried in high vacuum for 1 h. A solution of **16a, b** (2 g, 3.2 mmol) in 44 mL of dry MeCN was added to the previous dried residue, followed by dropwise addition of $SnCl_4$ in CH_2Cl_2 (1M, 12.8 mL, 12.8 mmol) under Ar at room temperature. The reaction mixture was stirred for 3.5 h and quenched with solid $NaHCO_3$ and 4 mL H_2O, filtered and the filtrate was concentrated to a small volume. The residue was partitioned between brine (50 mL) and EtOAc (150 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica (CH_2Cl_2 : MeOH, 97 : 3) to afford **17d** (1.74 g) as a colorless amorphous solid in 78% yield. ^{1}H NMR (300 MHz, $CDCl_3$): 1.27-1.33 (m, 12H, CH_3); 1.90 (s, 3H, CH_3CO); 1.94 (d, J = 1.0 Hz, 3H, CH_3-T); 3.62-3.77 (m, 4H, PCH_{2a}, H-6', H-5'); 3.81 (dd, J_1 = 13.4 Hz, J_2 = 9.9 Hz, 1H, PCH_{2b}); 4.21 (dd, J_1 = 3.0 Hz, J_2 = 2.5 Hz, 1H, H-3'); 4.50 (dd, J_1 = 3.0 Hz, J_2 = 2.5 Hz, 1H, H-4'); 4.53 (s, 2H, CH_2Bn); 4.63 (d, J = 11.8 Hz, 1H, CH_{2a}Bn); 4.67-4.76 (m, 2H, POCH); 4.79 (d, J = 11.8 Hz, 1H, CH_{2b}Bn); 5.19 (dd, J_1 = 3.4 Hz, J_2 = 2.5 Hz, 1H, H-2'); 6.16 (d, 1H, J = 3.4 Hz, H-1'); 7.29 (d, J = 1.0 Hz, 1H, H-6); 7.29-7.42 (m, 10H, ArH); 8.33 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): 12.55 (CH_3-T); 20.47 (CH_3CO); 24.01 (CH_3); 64.90 (d, $J_{P,C}$ = 169.5 Hz, PCH_2); 69.20 (C-6'); 71.21 (POCH); 71.30 (POCH); 73.04 (CH_2-Bn); 73.55 (CH_2-Bn); 77.13 (C-5'); 80.79 (C-2'), 85.22 (d, $J_{P,C}$ = 12.2 Hz, C-3'); 85.67 (C-4'); 89.18 (C-1'); 111.36 (C-5); 127.72, 127.84, 127.92, 128.07, 128.45 (C-arom); 135.65 (C-6); 137.72 (C-Bn); 137.83 (C-Bn); 150.15 (C-2); 163.35 (C-4); 169.84 (C-2); 169.84 (CH_3CO). Exact mass calcd. for $C_{34}H_{45}N_2O_{11}P$ $[M+H]^+$: 689.2834, found 689.2836.

1-(Adenin-9-yl)-5,6-di-*O*-benzyl-3-*O*-(diisopropylphosphonomethyl)-β-D-galactofuranose (18a)

A solution of **17a** (0.25 g, 0.3 mmol) in MeOH saturated with ammonia (15 mL) was stirred at room temperature overnight. The mixture was concentrated, and the residue was purified by column

chromatography (CH_2Cl_2 : MeOH, 96 : 4) to give compound **18a** (0.172 g) as a colorless oil in 84% yield. ^{1}H NMR (300 MHz, $CDCl_3$): 1.27 (d, 6H, J = 6.2 Hz, CH_3); 1.30 (d, 6H, J = 6.2 Hz, CH_3); 3.61 (dd, J_1 = 14.6 Hz, J_2 = 7.1 Hz, 1H, PCH_{2a}); 3.66-3.89 (m, 4H, PCH_{2b}, H-5', H-6'); 4.12 (dd, J_1 = 5.7 Hz, J_2 = 4.8 Hz, 1H, H-3'); 4.55 (d, J = 1.2 Hz, 2H, CH_2Bn); 4.57 (dd, J_1 = 5.7 Hz, J_2 = 2.1 Hz, 1H, H-4'); 4.65 (d, J = 11.8 Hz, 1H, CH_{2a}Bn); 4.60-4.77 (m, 2H, POCH); 4.85 (d, J = 11.8 Hz, 1H, CH_{2b}Bn); 4.89 (t, J = 4.5 Hz, 1H, H-2'); 5.92 (brs, 2H, NH_2); 5.99 (d, 1H, J = 4.5 Hz, H-1'); 7.28-7.52 (m, 10H, ArH); 7.95 (s, 1H, H-8); 8.27 (s, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 23.98 (CH_3); 65.76 (d, $J_{P,C}$ = 167.9 Hz, PCH_2); 69.71 (C-6'); 71.41 (POCH); 71.70 (POCH); 73.21 (CH_2-Bn); 73.54 (CH_2-Bn); 76.22 (C-5'); 79.26 (C-2'); 83.43 (C-4'); 87.56 (d, $J_{P,C}$ = 7.6 Hz, C-3'); 90.50 (C-1'); 120.01 (C-5); 127.65, 127.75, 128.18, 128.40, 128.58, 128.67 (C-arom); 137.45 (C-Bn); 137.87 (C-Bn); 139.49 (C-8); 149.57 (C-6); 152.68 (C-4); 155.35 (C-2). Exact mass calcd for $C_{32}H_{42}N_5O_8P$ $[M+H]^+$: 656.2844, found 565.2836.

5,6-Di-*O*-benzyl-1-(cytosin-1-yl)-3-*O*-(diisopropylphosphonomethyl)-β-D-galactofuranose (18b)

A solution of **17b** (0.24 g, 0.3 mmol) in MeOH saturated with ammonia (3 mL) was stirred at room temperature overnight. The mixture was concentrated, and the residue was purified by column chromatography (CH_2Cl_2 : MeOH, 94 : 6) to give compound **18b** (0.175 g) as a colorless oil in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$): 1.24-1.31 (m, 12H, CH_3); 3.65 (dd, J_1 = 13.5 Hz, J_2 = 9.6 Hz, 1H, PCH_{2a}); 3.72-3.84 (m, 3H, H-5', H-6'); 3.85 (dd, J_1 = 13.5 Hz, J_2 = 9.6 Hz, 1H, PCH_{2b}); 4.08 (dd, J_1 = 5.3 Hz, J_2 = 4.5 Hz, 1H, H-3'); 4.30 (t, J_2 = 3.5 Hz, 1H, H-2'); 4.39 (dd, J_1 = 5.5 Hz, J_2 = 3.5 Hz, 1H, H-4'); 4.56 (d, 2H, J = 3.6 Hz, CH_2Bn); 4.60-4.71 (m, 2H, POCH); 4.67 (d, J = 11.7 Hz, 1H, CH_{2a}Bn); 4.77 (d, J = 11.7 Hz, 1H, CH_{2b}Bn); 5.13 (brs, 1H, OH); 5.69 (d, 1H, J = 3.5 Hz, H-1'); 5.68 (d, 1H, J = 7.5 Hz, H-5); 7.29-7.38 (m, 10H, arom-H); 7.45 (d, 1H, J = 7.5 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$): 23.99 (CH_3); 64.80 (d, $J_{P,C}$ = 168.6 Hz, PCH_2); 69.43 (C-6'); 71.17 (d, $J_{P,C}$ = 6.6 Hz, POCH); 71.21 (d, $J_{P,C}$ = 6.6 Hz, POCH); 73.36 (CH_2-Bn); 73.43 (CH_2-Bn); 76.58 (C-5'); 81.45 (C-2'); 83.63 (C-4'); 86.08 (d, $J_{P,C}$ = 13.2 Hz, C-3'); 93.84 and 94.05 (C-1' and C-5); 127.65, 127.71, 127.97, 128.29, 128.42, 128.48 (C-arom); 137.71 (C-Bn); 137.92 (C-Bn); 140.46 (C-6); 156.80 (C-2); 165.95 (C-4). Exact mass calcd. for $C_{31}H_{42}N_3O_9P$ $[M+H]^+$: 632.2731, found 632.2741.

5,6-Di-*O*-benzyl-3-*O*-(diisopropylphosphonomethyl)-1-(uracil-1-yl)-β-D-galactofuranose (18c)

A solution of **17c** (2 g, 2.96 mmol) in MeOH saturated with ammonia (30 mL) was stirred at room temperature for 3 h. The mixture was concentrated, and the residue was purified by column chromatography (hexane : CH_2Cl_2 : MeOH, 6 : 4 : 0.5) to give compound **18c** (1.43 g) as a colorless oil in 76% yield. ^{1}H NMR (300 MHz, $CDCl_3$): 1.26-1.32 (m, 12H, CH_3); 3.58 (dd, J_1 = 14.0 Hz, J_2 = 7.8 Hz, 1H, PCH_{2a}); 3.68 (dd, J_1 = 14.0 Hz, J_2 = 7.8 Hz, 1H, PCH_{2b}); 3.72-3.81 (m, 3H, H-5', H-6'); 3.98 (dd, J_1

= 4.0 Hz, J_2 = 3.3 Hz, 1H, H-3'); 4.31 (m, 1H, H-2'); 4.47 (dd, J_1 = 4.0 Hz, J_2 = 2.2 Hz, 1H, H-4'); 4.56 (s, 2H, CH_2Bn); 4.61 (d, J = 11.5 Hz, 1H, CH_{2a}Bn); 4.60-4.76 (m, 2H, POCH); 4.81 (d, J = 11.5 Hz, 1H, CH_{2b}Bn); 5.65 (d, 1H, J = 8.1 Hz, H-5); 5.80 (d, 1H, J = 3.3 Hz, H-1'); 7.29-7.42 (m, 11H, arom-H, H-6); 8.61 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): 24.00 (CH_3); 65.45 (d, $J_{P,C}$ = 167.6 Hz, PCH_2); 69.19 (C-6'); 71.56 (d, $J_{P,C}$ = 10.9 Hz, POCH); 71.47 (d, $J_{P,C}$ = 10.9 Hz, POCH); 73.21 (CH_2-Bn); 73.58 (CH_2-Bn); 76.55 (C-5'); 79.69 (C-2'); 84.73 (C-4'); 87.64 (d, $J_{P,C}$ = 8.6 Hz, C-3'); 93.09 (C-1'); 101.94 (C-5); 127.71, 127.87, 128.37, 128.48, 128.66 (C-arom); 136.93 (C-Bn); 137.72 (C-Bn); 140.38 (C-6); 150.28 (C-2); 162.98 (C-4). Exact mass calcd. for $C_{31}H_{41}N_2O_{10}P$ $[M+H]^+$: 633.2571, found 633.2551.

5,6-di-*O*-benzyl-3-*O*-(diisopropylphosphonomethyl)-1-(thymin-1-yl)-β-D-galactofuranose (18d)

A solution of **17d** (1.96 g, 2.8 mmol) in MeOH saturated with ammonia (50 mL) was stirred at room temperature for 5 h. The mixture was concentrated, and the residue was purified by column chromatography (CH_2Cl_2 : MeOH, 97 : 3) to give compound **18d** (1.69 g) as a colorless oil in 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$): 1.26-1.32 (m, 12H, CH_3); 1.90 (d, J = 1.2 Hz, 3H, CH_3-T); 3.58 (dd, J_1 = 14.0 Hz, J_2 = 7.6 Hz, 1H, PCH_{2a}); 3.70 (dd, J_1 = 14.0 Hz, J_2 = 7.6 Hz, 1H, PCH_{2b}); 3.73-3.82 (m, 3H, H-6', H-5'); 3.99 (dd, J_1 = 4.3 Hz, J_2 = 3.7 Hz, 1H, H-3'); 4.33 (m, 1H, H-2'); 4.46 (dd, J_1 = 4.3 Hz, J_2 = 2.7 Hz, 1H, H-4'); 4.56 (s, 2H, CH_2Bn); 4.62 (d, J = 11.7 Hz, 1H, CH_{2a}Bn); 4.62-4.77 (m, 2H, POCH); 4.81 (d, J = 11.7 Hz, 1H, CH_{2b}Bn); 4.86 (brs, 1H, OH); 5.83 (d, 1H, J = 3.8 Hz, H-1'); 7.21 (d, J = 1.2 Hz, 1H, H-6); 7.30-7.37 (m, 10H, ArH); 8.79 (brs, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): 12.49 (CH_3-T); 23.98 (CH_3); 65.51 (d, $J_{P,C}$ = 167.4 Hz, PCH_2); 69.40 (C-6'); 71.43 (d, J = 9.5 Hz, POCH); 71.51 (d, J = 9.5 Hz, POCH); 73.15 (CH_2-Bn); 73.55 (CH_2-Bn); 76.71 (C-5'); 79.77 (C-2'); 84.23 (C-4'); 87.72 (d, $J_{P,C}$ = 8.7 Hz, C-3'); 92.48 (C-1'); 110.58 (C-5); 127.64, 127.80, 128.25, 128.44, 128.61 (C-arom); 136.16 (C-6); 137.16 (C-Bn); 137.78 (C-Bn); 150.46 (C-2); 163.70 (C-4). Exact mass calcd. for $C_{32}H_{43}N_2O_{10}P$ $[M+H]^+$: 647.2728, found 647.2692.

1-(Adenin-9-yl)-3-*O*-(diisopropylphosphonomethyl)-β-D-galactofuranose (19a)

To a degassed solution of protected galactofuranose **18a** (0.23 g, 0.35 mmol) and cyclohexene (11.3 mL) in a mixture of MeOH (23 mL) and water (1.6 mL) under argon was added $Pd(OH)_2$ (20% on carbon, 0.4 g), and the mixture was stirred at 80 °C for 10 h. The mixture was filtered through Cellite and washed with aqueous methanol and 1% of aqueous ammonia in methanol. The combined filtrates were evaporated *in vacuo* and the residue was purified by chromatography (CH_2Cl_2 : MeOH, 90 : 10) to afford compound **19a** (0.15 g) as a colorless solid in 90% yield. ^{1}H NMR (300 MHz, DMSO-d_6): 1.24-1.28 (m, 12H, CH_3); 3.36-3.46 (m, 2H, H-6'); 3.56-3.59 (m, 1H, H-5'); 3.89 (dd, 1H, J_1 = 13.6 Hz, J_2 = 9.5 Hz, PCH_{2a}); 4.04 (dd, 1H, J_1 = 13.6 Hz, J_2 = 9.5 Hz, PCH_{2b}); 4.17-4.23 (m, 1H, H-3'); 4.28 (dd, J_1 = 6.3 Hz,

J_2 = 2.4 Hz, 1H, H-4'); 4.56-4.68 (m, 2H, POCH); 4.64 (t, 1H, J = 5.5 Hz, OH-6'); 4.94-4.99 (m, 1H, H-2'); 5.09 (d, 1H, J = 5.8 Hz, OH-5'); 5.93 (d, 1H, J = 5.8, 1H, OH-2'); 5.87 (d, 1H, J = 5.6 Hz, 1H, H-1'); 7.27 (s, 2H, NH_2); 8.15 (s, 1H, H-2); 8.31 (s, 1H, H-8). ^{13}C NMR (75 MHz, DMSO-d_6): 23.67 (CH_3); 61.94 (C-6'); 64.04 (d, $J_{P,C}$ = 165.4 Hz, PCH_2); 70.27 (POCH); 70.35 (POCH); 70.76 (C-2'); 77.41 (C-5'); 81.30 (C-4'); 85.23 (d, $J_{P,C}$ = 12.9 Hz, C-3'); 88.20 (C-1'); 119.05 (C-5); 139.80 (C-8); 149.30 (C-4); 152.49 (C-2); 155.95 (C-4). Exact mass calcd. for $C_{18}H_{30}N_5O_8P$ $[M+H]^+$: 476.1905**,** found 476.1902.

1-(Cytosin-1-yl)-3-*O*-(diisopropylphosphonomethyl)-β-D-galactofuranose (19b)

This compound was prepared as described for **19a**, using **18b** (0.36 g, 0.58 mmol) as starting material. Column chromatographic purification (CH_2Cl_2:MeOH, 90:10) gave compound **19b** (0.14 g) as a colorless amorphous solid in 54% yield. ^{1}H NMR (300 MHz, D_2O): 1.25-1.31 (m, 12H, CH_3); 3.65-3.78 (m, 2H, H-6'); 3.88-3.95 (m, 1H, H-5'); 3.63-3.67 (m, 2H, PCH_2); 4.12 (t, J_1 = 2.4 Hz, 1H, H-3'); 4.20 (t, J = 1.8 Hz, 1H, H-2'); 4.54 (dd, J_1 = 5.3 Hz, J_2 = 2.4 Hz, 1H, H-4'); 4.28-4.36 (m, 2H, POCH); 5.51 (d, 1H, J = 1.8 Hz, 1H, H-1'); 5.70 (d, 1H, J = 7.5 Hz, H-5); 7.35 (d, 1H, J = 7.5 Hz, H-6). ^{13}C NMR (75 MHz, D_2O+dioxane): 23.73 (CH_3); 62.98 (C-6'); 64.34 (d, $J_{P,C}$ = 165.8 Hz, PCH_2); 71.97 (C-2'); 74.44 (POCH); 74.52 (POCH); 78.85 (C-5'); 87.23 (C-4'); 87.25 (d, $J_{P,C}$ = 14.7 Hz, C-3'); 94.22 (C-1'); 96.01 (C-5); 142.24 (C-6); 157.97 (C-2); 166.92 (C-4). Exact mass calcd. for $C_{17}H_{30}N_3O_9P$ $[M+H]^+$: 452.1792, found 452.1789.

3-*O*-(Diisopropylphosphonomethyl)-1-(uracil-1-yl)-β-D-galactofuranose (19c)

This compound was prepared as described for **19a**, using **18c** (0.15 g, 0.24 mmol) as starting material. Reaction time was 3 h. Column chromatographic purification (CH_2Cl_2 : MeOH, 90 : 10) gave **19c** (0.1 g) as a colorless amorphous solid in 93% yield: ^{1}H NMR (300 MHz, D_2O): 1.28-1.33 (m, 12H, CH_3); 3.64-3.77 (m, 2H, H-6'); 3.89-3.94 (m, 1H, H-5'); 4.01-4.04 (m, 2H, PCH_2); 4.16 (t, J_1 = 2.7 Hz, 1H, H-3'); 4.50-4.53 (m, 2H, H-2', H-4'); 4.65-4.74 (m, 2H, POCH); 5.85 (d, 1H, J = 1.7 Hz, 1H, H-1'); 5.86 (d, 1H, J = 8.1 Hz, H-5); 7.72 (d, 1H, J = 8.1 Hz, H-6). ^{13}C NMR (75 MHz, D_2O+dioxane): 23.82 (CH_3); 63.04 (C-6'); 64.50 (d, $J_{P,C}$ = 166.2 Hz, PCH_2); 71.93 (C-2'); 74.53 (POCH); 74.62 (POCH); 78.75 (C-5'); 86.88 (C-4'); 86.97 (d, $J_{P,C}$ = 14.2 Hz, C-3'); 93.52 (C-1'); 102.15 (C-5); 142.75 (C-6); 152.12 (C-2); 167.20 (C-4). Exact mass calcd. for $C_{17}H_{29}N_2O_{10}P$ $[M+H]^+$: 453.1632, found 453.1628.

3-*O*-(Diisopropylphosphonomethyl)-1-(thymin-1-yl)-β-D-galactofuranose (19d)

This compound was prepared as described for **19a**, using **18d** (0.327 g, 0.51 mmol) as starting material. Reaction time was 4.5 h. Column chromatographic purification (CH_2Cl_2:MeOH, 90 : 10) gave compound **19d** (0.221 g) as a colorless amorphous solid in 94% yield: ^{1}H NMR (300 MHz, DMSO-d_6): 1.23-1.26 (m,

12H, CH_3); 1.80 (d, 3H, J = 0.9 Hz, CH_3-T); 3.26-3.41 (m, 2H, H-6'); 3.51-3.55 (m, 1H, H-5'); 3.85 (dd, 1H, J_1 = 13.7 Hz, J_2 = 9.3 Hz, PCH_{2a}); 3.97 (dd, 1H, J_1 = 13.7 Hz, J_2 = 9.3 Hz, PCH_{2b}); 4.11 (t, J_1 = 5.3 Hz, 1H, H-3'); 4.21 (dd, J_1 = 5.5 Hz, J_2 = 2.4 Hz, 1H, H-4'); 4.24-4.29 (m, 1H, H-2'); 4.54-4.58 (m, 2H, POCH); 4.67 (t, 1H, J = 5.5 Hz, OH-6'); 5.14 (d, 1H, J = 5.5 Hz, OH-5'); 5.76 (d, 1H, J = 5.5 Hz, 1H, OH-2'); 5.81 (d, 1H, J = 5.9 Hz, 1H, H-1'); 7.56 (d, 1H, J = 1.1 Hz, H-6); 11.27 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 12.20 (CH_3-T); 23.92 (CH_3); 62.21 (C-6'); 64.22 (d, $J_{P,C}$ = 165.1 Hz, PCH_2); 70.48 (d, $J_{P,C}$ = 6.2 Hz, POCH); 70.55 (d, $J_{P,C}$ = 6.2 Hz, POCH); 71.12 (C-2'); 77.67 (C-5'); 81.78 (C-4'); 85.21 (d, $J_{P,C}$ = 13.6 Hz, C-3'); 89.15 (C-1'); 109.71 (C-5); 136.83 (C-6); 150.85 (C-2); 163.94 (C-4). Exact mass calcd. for $C_{18}H_{31}N_2O_{10}P$ $[M+Na]^+$: 489.1614, found 489.1620.

1-(Adenin-9-yl)-3-*O*-(phosphonomethyl)-β-D-galactofuranose sodium salt (20a)

To a solution of **19a** (0.14 g, 0.3 mmol) and 2,6-lutidine (0.28 mL, 2.4 mmol) in dry acetonitrile (3 mL) was added iodotrimethylsilane (0.34 mL, 2.4 mmol) at room temperature. The reaction mixture was stirred for 3 h. The reaction was quenched with 2.5% aqueous ammonia solution. The mixture was concentrated *in vacuo*, coevaporated with 2.5% aqueous ammonia (2x) and the residue was purified by column chromatography (CH_2Cl_2 : MeOH : H_2O, 5 : 4 : 1) to give the crude title compound. Purification using reverse phase gradient HPLC (0.05M TEAB to 50% MeCN) and ion exchanges (Dowex-Na^+ resin) offered **20a** (15 mg) as a colorless solid after lyophylization in 13% yield. ^{1}H NMR (300 MHz, D_2O): 3.65-3.78 (m, 4H, PCH_2, H-6'); 3.95-3.99 (m, 1H, H-5'); 4.30 (dd, J_1 = 6.7 Hz, J_2 = 5.7 Hz, 1H, H-3'); 4.39 (dd, J_1 = 6.7 Hz, J_2 = 3.3 Hz, 1H, H-4'); 5.04 (d, J = 5.7 Hz, 1H, H-2'); 6.08 (d, J = 5.7 Hz, 1H, H-1'); 8.25 (s, 1H, H-8); 8.44 (s, 1H, H-2). ^{13}C NMR (75 MHz, D_2O+dioxane): 63.16 (C-6'); 69.98 (d, $J_{P,C}$ = 148.2 Hz, PCH_2); 71.74 (C-5'); 78.57 (C-2'); 83.15 (C-4'); 86.27 (d, $J_{P,C}$ = 8.4 Hz, C-3'); 88.48 (C-1'); 119.61 (C-5); 141.52 (C-8); 149.75 (C-4); 153.66 (C-2); 156.44 (C-6). Exact mass calcd. for $C_{12}H_{18}N_5O_8P$ $[M+H]^+$: 414.0791, found 414.0773.

1-(Cytosin-1-yl)-3-*O*-(phosphonomethyl)-β-D-galactofuranose sodium salt (20b)

This compound was prepared as described for **20a**, using **19b** (0.11 g, 0.24 mmol) as starting material. Reaction time was overnight. Compound **20b** (35 mg) was obtained as a white solid after lyophylization in 39% yield. ^{1}H NMR (300 MHz, D_2O+dioxane): 3.59-3.67 (m, 4H, PCH_2, H-6'); 3.83-3.88 (m, 1H, H-5'); 4.10 (dd, J_1 = 4.6 Hz, J_2 = 4.3 Hz, 1H, H-3'); 4.95 (dd, J_1 = 4.8 Hz, J_2 = 4.6 Hz, 1H, H-4'); 4.48 (t, J = 3.9 Hz, 1H, H-2'); 5.84 (d, J = 3.9 Hz, 1H, H-1'); 5.97 (d, J = 7.5 Hz, 1H, H-5); 7.67 (d, J = 7.5 Hz, 1H, H-6). ^{13}C NMR (75 MHz, D_2O+dioxane): 63.01 (C-6'); 67.29 (d, $J_{P,C}$ = 154.4 Hz, PCH_2); 71.78 (C-5'); 78.73 (C-2'); 84.82 (C-4'); 86.34 (d, $J_{P,C}$ = 11.2 Hz, C-3'); 92.57 (C-1'); 96.72 (C-5); 142.84 (C-6); 158.21 (C-2); 166.84 (C-4). Exact mass calcd. for $C_{11}H_{18}N_3O_9P$ $[M+H]^-$: 366.0708, found 366.0711.

3-*O*-(Phosphonomethyl)-1-(uracil-1-yl)-β-D-galactofuranose sodium salt (20c)

This compound was prepared as described for **20a**, using **19c** (0.1 g, 0.22 mmol) as starting material. Reaction time was 4 h. Compound **20c** (30 mg) was obtained as a white solid after lyophylization in 37% yield. ^{1}H NMR (300 MHz, D_2O+dioxane): 3.63-3.72 (m, 4H, PCH_2, H-6'); 3.88-3.95 (m, 1H, H-5'); 4.18 (dd, J_1 = 5.2 Hz, J_2 = 4.6 Hz, 1H, H-3'); 4.42 (dd, J_1 = 5.2 Hz, J_1 = 4.3 Hz, 1H, H-4'); 4.58 (t, J = 4.3 Hz, 1H, H-2'); 5.90 (d, J = 4.3 Hz, 1H, H-1'); 5.89 (d, J = 8.1 Hz, 1H, H-5); 7.78 (d, J = 8.1 Hz, 1H, H-6). ^{13}C NMR (75 MHz, D_2O+dioxane): 63.09 (C-6'); 67.70 (d, $J_{P,C}$ = 154.1 Hz, PCH_2); 71.78 (C-5'); 78.77 (C-2'); 84.69 (C-4'); 86.21 (d, $J_{P,C}$ = 10.8 Hz, C-3'); 91.90 (C-1'); 102.85 (C-5); 143.20 (C-6); 152.41 (C-2); 167.10 (C-4). Exact mass calcd. for $C_{11}H_{17}N_2O_{10}P$ $[M-H]^-$: 367.0548, found: 367.0543

3-*O*-(Phosphonomethyl)-1-(thymin-1-yl)-β-D-galactofuranose sodium salt (20d)

This compound was prepared as described for **20a**, using **19d** (0.144 g, 0.31 mmol) as starting material. The temperature was 0 °C and the reaction time was 6 h. Purification gave compound **20d** (88 mg) as a white solid after lyophylization in 75% yield. ^{1}H NMR (300 MHz, D_2O+dioxane): 1.90 (d, 3H, J = 1.1 Hz, CH_3-T); 3.62-3.85 (m, 4H, H-6', PCH_2); 3.89-3.94 (m, 1H, H-5'); 4.19 (t, J = 5.3 Hz, 1H, H-3'); 4.37 (dd, J_1 = 6.2 Hz, J_2 = 3.7 Hz, 1H, H-4'); 4.58 (t, 1H, J = 5.4 Hz, H-2'); 5.91 (d, 1H, J = 5.4 Hz, H-1'); 7.60 (d, 1H, J = 1.2 Hz, H-6). ^{13}C NMR (75 MHz, D_2O + dioxane): 12.23 (CH_3-T); 63.09 (C-6'); 68.14 (d, $J_{P,C}$ = 153.2 Hz, PCH_2); 71.73 (C-2'); 78.68 (C-5'); 83.66 (C-4'); 85.88 (d, $J_{P,C}$ = 10.6 Hz, C-3'); 90.75 (C-1'); 112.29 (C-5); 138.59 (C-6); 152.58 (C-2); 167.31 (C-4). Exact mass calcd. for $C_{12}H_{19}N_2O_{10}P$ $[M-H]^-$: 381.0704, found: 381.0738.

5,6-Di-*O*-benzyl-2-deoxy-1-{[2-oxo-1,2-dihydropyrimidin-4-(2,4,6-triisopropylbenzenesulfonate)-4-yl]-1-yl}-3-*O*-(phosphonomethyl-β-D-galactofuranose (22)

To a solution of compound **23c** (0.686 g, 1.08 mmol) in dried CH_2Cl_2 (14.4 mL) under Ar, DMAP (0.275 g, 2.25 mmol), E_3N (0.61 mL, 4.48 mmol) and TIPSCl (0.679 g, 2.24 mmol) were added subsequently. The reaction mixture was stirred at room temperature overnight. The solvents were evaporated and the residue was partitioned between H_2O (50 mL) and Et_2O (150 mL). The organic layer was washed with water (3 x 50 mL) and dried over Na_2SO_4. The residue was purified by column chromatography (CH_2Cl_2 : MeOH, 99 : 1) to give compound **22** (0.865 g), as a colorless solid in 88% yield (not stable at room temperature). ^{1}H NMR (300 MHz, $CDCl_3$): 1.20-1.32 (m, 12H, CH_3); 2.13 (d, 1H, J = 15.0 Hz, H-2'a); 2.70 (ddd, J_1 = 15.0 Hz, J_2 = 7.3 Hz, J_3 = 5.7 Hz, 1H, H-2'b); 2.86-2.95 (m, 1H, CH-iPr TIPS); 3.49-3.52 (m, 2H, PCH_2); 3.61-3.66 (m, 3H, H-5', H-6'); 4.00 (d, J = 5.7 Hz, 1H, H-3'); 4.21-4.30 (m, 2H, CH-iPr TIPS); 4.48 (d, J = 11.7 Hz, 1H, CH_{2a}Bn); 4.53 (s, 2H, CH_2Bn); 4.66-4.68 (m, 1H, H-4'); 4.57-4.71 (m, 2H, POCH); 4.70 (d, J = 11.7 Hz, 1H, CH_{2b}Bn); 6.05 (d, J = 7.3 Hz, 1H, H-5); 6.12 (dd, 1H, J_1

= 7.3 Hz, J_2 = 1.2 Hz, H-1'); 7.23-7.36 (m, 12H, arom-H); 8.01 (d, J = 7.3 Hz, 1H, H-6). ^{13}C NMR (75 MHz, $CDCl_3$): 24.05 (CH_3); 29.65 (2C, CH-iPr TIPS); 34.25 (CH-iPr TIPS); 39.17 (C-2'); 64.02 (d, $J_{P,C}$ = 169.2 Hz, PCH_2); 68.83 (C-6'); 71.16 (d, $J_{P,C}$ = 11.9 Hz, POCH); 71.25 (d, $J_{P,C}$ = 11.9 Hz, POCH); 72.87 (CH_2-Bn); 73.63 (CH_2-Bn); 77.60 (C-5'); 83.15 (d, $J_{P,C}$ = 11.7 Hz, C-3'); 86.98 (C-4'); 89.38 (C-1'); 94.40 (C-5); 124.01, 127.72, 127.85, 127.90, 128.03, 128.47 and 128.55 (C-arom); 137.60 and 137.77 (C-Bn); 146.53 (C-6); 154.04 (C-arom); 154.08 (C-arom); 151.20 (C-2); 166.99 (C-4).

1-(Adenin-9-yl)-5,6-di-*O*-benzyl-2-deoxy-3-*O*-(diisopropylphosphonomethyl)-β-D-galactofuranose (23a)

To a solution of compound **18a** (0.5 g, 0.75 mmol) in dried MeCN (25 mL) was added DMAP (0.275 g, 2.25 mmol) and phenyl thionochloroformate (0.155 mL, 1.125 mmol) at 0 °C. The reaction mixture was stirred for 2 h at the same temperature. The resulted solution was concentrated, and the residue was purified by column chromatography (CH_2Cl_2 : MeOH, 96 : 4) to afford 1-(adenin-9-yl)-5,6-di-*O*-benzyl-2-*O*-phenoxythiocarbonyl-3-*O*-(diisopropylphosphonomethyl)-β-D-galactofuranose (**21a**) (0.495 g) as a colorless oil in 82% yield. To a solution of **21a** (0.43 g, 0.54 mmol) (previously codistilled with dry toluene) in dried degassed toluene (18 mL) under argon were added tributytin hydride (0.24 mL, 1.08 mmol) and AIBN (22.2 mg, 0.136 mmol). The reaction mixture was refluxed for 1 h and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2 : MeOH, 96 : 4) to afford compound **23a**, 0.21 g, as a colorless oil in 60% yield (49% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$): 1.26-1.33 (m, 12H, CH_3); 2.44 (d, 1H, J = 15.6 Hz, H-2'a); 2.82 (ddd, J_1 = 15.3 Hz, J_2 = 7.8 Hz, J_3 = 6.5 Hz, 1H, H-2'b); 3.57-3.75 (m, 5H, PCH_2, H-5', H-6'); 4.21 (d, 1H, J = 5.7 Hz, H-3'); 4.54-4.60 (m, 4H, CH_{2a}Bn CH_2Bn, H-4'); 4.63-4.76 (m, 2H, POCH); 4.78 (d, J = 11.7 Hz, 1H, CH_{2b}Bn); 5.68 (s, 2H, NH_2); 6.53 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.6 Hz, H-1'); 7.29-7.39 (m, 10H, arom-H); 8.30 (s, 1H, H-8); 8.35 (s, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 23.98 (CH_3); 38.88 (C-2'); 64.26 (d, $J_{P,C}$ = 168.6 Hz, PCH_2); 69.30 (C-6'); 71.23 (POCH); 71.30 (POCH); 72.87 (CH_2-Bn); 73.60 (CH_2-Bn); 77.77 (C-5'); 83.43 (d, $J_{P,C}$ = 12.2 Hz, C-3'); 84.52 (C-4'); 85.84 (C-1'); 119.51 (C-5); 127.67, 127.76, 127.96, 128.00, 128.43 and 128.52 (C-arom); 137.86 and 137.87 (C-Bn); 139.80 (C-8); 149.77 (C-4); 152.94 (C-2); 155.37 (C-6). Exact mass calcd. for $C_{32}H_{42}N_5O_7P$ $[M+H]^+$: 640.2894, found 640.2894.

5,6-Di-*O*-benzyl-2-deoxy-3-*O*-(diisopropylphosphonomethyl)-1-(uracil-1-yl)-β-D-galactofuranose (23c)

This compound was prepared as described for **23a**, using **18c** (1.44 g, 2.3 mmol) as starting material. The reaction time was 3 h. Chromatography purification (CH_2Cl_2 : MeOH, 97 : 3) gave compound **21c** (1.48 g) which was transformed to **23c**. Compound **23c** was, likewise, purified by column chromatography

(CH_2Cl_2 : MeOH, 97 : 3) **23c** (0.683 g) as a colorless oil in 61% yield (53% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$): 1.26-1.32 (m, 12H, CH_3); 2.02 (ddd, 1H, J = 15.0 Hz, H-2'a); 2.71 (ddd, 1H, J_1 = 15.0 Hz, J_2 = 8.0 Hz, J_3 = 6.2 Hz, H-2'b); 3.57-3.69 (m, 5H, PCH_2, H-5', H-6'); 4.01 (d, 1H, J = 6.2 Hz, H-3'); 4.49 (d, J = 11.7 Hz, 1H, CH_{2a}Bn); 4.54 (d, J = 1.1 Hz, 2H, CH_2Bn); 4.59 (m, 1H, H-4'); 4.65-4.76 (m, 2H, POCH); 4.73 (d, J = 11.7 Hz, 1H, CH_{2b}Bn); 5.69 (d, J = 8.1 Hz, 1H, H-5); 6.31 (dd, 1H, J_1 = 8.0 Hz, J_2 = 2.0 Hz, H-1'); 7.29-7.36 (m, 10H, arom-H); 7.69 (d, J = 8.1 Hz, 1H, H-6). ^{13}C NMR (75 MHz, $CDCl_3$): 24.03 (CH_3); 38.98 (C-2'); 64.14 (d, $J_{P,C}$ = 169.6 Hz, PCH_2); 68.99 (C-6'); 71.28 (2C POCH); 72.85 (CH_2-Bn); 73.63 (CH_2-Bn); 77.93 (C-5'); 83.44 (d, $J_{P,C}$ = 12.5 Hz, C-3'); 86.07 (C-4'); 86.83 (C-1'); 102.07 (C-5); 127.70, 127.82, 127.97, 128.03, 128.45 and 128.55 (C-arom); 137.67 and 137.80 (C-Bn); 141.04 (C-6); 150.33 (C-2); 163.06 (C-4). Exact mass calcd. for $C_{31}H_{41}N_2O_9P$ $[M+H]^+$: 617.2622, found 617.2638.

5,6-Di-*O*-benzyl-1-(cytosin-1-yl)-2-deoxy-3-*O*-(diisopropylphosphonomethyl)-β-D-galactofuranose (23b)

To a solution of **22** (0.86 g, 0.97 mmol) in dioxane (48 mL) was added a 25% solution of aqueous NH_3 (16 mL). The reaction mixture was stirred at room temperature for 5 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (Hexane : CH_2Cl_2 : MeOH, 6 : 4 : 1) to afford compound **23b** (0.486 g), as a colorless solid in 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$): 1.25-1.30 (m, 12H, CH_3); 2.12 (d, 1H, J = 14.7 Hz, H-2'a); 2.69 (ddd, J_1 = 14.7 Hz, J_2 = 7.4 Hz, J_3 = 6.2 Hz, 1H, H-2'b); 3.52-3.69 (m, 5H, H-5', H-6', PCH_2); 4.01 (d, J = 6.2 Hz, 1H, H-3'); 4.51 (d, J = 11.8 Hz, 1H, CH_{2a}Bn); 4.54 (s, 2H, CH_2Bn); 4.57-4.61 (m, 1H, H-4'); 4.58-4.73 (m, 2H, POCH); 4.73 (d, J = 11.8 Hz, 1H, CH_{2b}Bn); 5.69 (d, J = 7.4 Hz, 1H, H-5); 6.36 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.7 Hz, H-1'); 7.29-7.39 (m, 10H, arom-H); 7.68 (d, J = 7.4 Hz, 1H, H-6). ^{13}C NMR (75 MHz, $CDCl_3$): 24.03 (CH_3); 39.10 (C-2'); 63.95 (d, $J_{P,C}$ = 169.3 Hz, PCH_2); 69.16 (C-6'); 71.08 (d, $J_{P,C}$ = 13.2 Hz, POCH); 71.17 (d, $J_{P,C}$ = 13.2 Hz, POCH); 72.84 (CH_2-Bn); 73.58 (CH_2-Bn); 77.83 (C-5'); 83.30 (d, $J_{P,C}$ = 12.7 Hz, C-3'); 86.35 (C-4'); 88.12 (C-1'); 93.25 (C-5); 127.68, 127.76, 127.91, 128.43 and 128.49 (C-arom); 137.79 and 137.87 (C-Bn); 142.14 (C-6); 155.92 (C-2); 165.48 (C-4). Exact mass calcd. for $C_{31}H_{42}N_3O_8P$ $[M+H]^+$: 616.2782, found 616.2786.

5,6-Di-*O*-benzyl-2-deoxy-3-*O*-(diisopropylphosphonomethyl)-1-(thymin-9-yl)-β-D-galactofuranose (23d)

This compound was prepared as described for **23a**, using **18d** (1.32 g, 2.04 mmol) as starting material. Reaction time was 3 h. Purification (CH_2Cl_2 : MeOH, 97:3) gave compound **21d** (1.19 g) which was transformed to **23d (**reaction time 1.5 h) which was purified by column chromatography (CH_2Cl_2 : MeOH,

97:3) gave compound **23d** (0.755 g) as a colorless oil in 79% yield (59% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$): 1.26-1.32 (m, 12H, CH_3); 1.96 (s, 3H, CH_3-T); 1.97 (d, 1H, J = 15.4 Hz, H-2'a); 2.66-2.78 (m, 1H, H-2'b); 3.59-3.70 (m, 5H, PCH_2, H-5', H-6'); 4.01 (d, 1H, J = 6.5 Hz, H-3'); 4.49 (d, J = 11.9 Hz, 1H, CH_{2a}Bn); 4.50-4.58 (m, 3H, CH_2Bn, H-4'); 4.64-4.78 (m, 2H, PCH); 4.74 (d, J = 11.9 Hz, 1H, CH_{2b}Bn); 6.36 (dd, 1H, J_1 = 8.1 Hz, J_2 = 2.5 Hz, H-1'); 7.29-7.39 (m, 10H, arom-H); 7.54 (s, 1H, H-6); 8.46 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): 12.54 (CH_3-T); 23.98 (CH_3); 38.89 (C-2'); 64.26 (d, $J_{P,C}$ = 170.4 Hz, PCH_2); 69.08 (C-6'); 71.14 (d, J = 6.7Hz, POCH); 71.22 (d, J = 6.7Hz, POCH); 72.81 (CH_2-Bn); 73.61 (CH_2-Bn); 78.08 (C-5'); 83.59 (d, $J_{P,C}$ = 12.9 Hz, C-3'); 85.68 (C-4'); 86.31 (C-1'); 110.84 (C-5); 127.68, 127.79, 127.96, 128.00, 128.44 and 128.53 (C-arom); 136.66 (C-6); 137.70 and 137.82 (C-Bn); 150.44 (C-2); 163.68 (C-4). Exact mass calcd. for $C_{32}H_{43}N_2O_9P$ $[M+H]^+$: 631.2779, found 631.2781.

1-(Adenin-9-yl)-2-deoxy-3-*O*-(diisopropylphosphonomethyl)-β-D-galactofuranose (24a)

To a solution of **23a** (0.195 g, 0.3 mmol) in methanol (23 mL) and H_2O (1.72 mL) was added cyclohexene (11.4 mL, 112 mmol). The reaction mixture was degassed (using argon) and $Pd(OH)_2$ (20% on charcoal) (0.204 g, 0.3 mmol) was added to the flask. The resulted mixture was stirred at 80 °C for 11 h. Insoluble particles were filtered and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2 : MeOH, 90 : 10) to give compound **24a** (0.106 g) as colorless oil in 76% yield. ^{1}H NMR (300 MHz, $CDCl_3$): 1.33 (m, 12H, CH_3); 2.60 (d, 1H, J = 14.8 Hz, H-2'a); 2.87-2.93 (m, 1H, H-2'b); 3.77-3.82 (m, 5H, PCH_2, H-5', H-6'); 4.51-4.53 (m, 2H, H-4', H-3'); 4.72-4.76 (m, 2H, POCH); 5.91 (s, 2H, NH_2); 6.57 (dd, 1H, J_1= 7.5 Hz, J_2 = 1.6 Hz, H-1'); 8.30 (s, 1H, H-8); 8.32 (s, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 24.03 (iPrCH_3); 38.20 (C-2'); 64.67 (d, $J_{P,C}$ = 169.04 Hz, PCH_2); 63.63 (C-6'); 71.57 (POCH); 71.67 (POCH); 77.20 (C-5'); 82.76 (d, $J_{P,C}$ = 9.3 Hz, C-3'); 84.30 (C-4'); 86.75 (C-1'); 119.54 (C-5); 139.57 (C-8); 149.73 (C-4); 152.95 (C-2); 155.35 (C-6). Exact mass calcd. for $C_{18}H_{30}N_5O_7P$ $[M+H]^+$: 460.1955, found 460.1923.

1-(Cytosin-1-yl)-2-deoxy-3-*O*-(diisopropylphosphonomethyl)-β-D-galactofuranose (24b)

This compound was prepared as described for **24a**, using **23b** (0.52 g, 0.85 mmol) as starting material. Reaction time was 18 h. Column chromatographic purification (CH_2Cl_2: MeOH, 85: 15) gave compound **24b** (0.33 g) as a colorless solid in 90% yield. ^{1}H NMR (300 MHz, DMSO-d_6): 1.26-1.30 (m, 12H, CH_3); 1.91 (d, 1H, J = 14.5 Hz, H-2'a); 2.57 (ddd, J_1 = 14.5 Hz, J_2 = 7.6 Hz, J_3 = 6.2 Hz, 1H, H-2'b); 3.27-3.51 (m, 3H, H-5', H-6'); 3.73-3.80 (m, 2H, PCH_2); 4.18 (d, J = 6.2 Hz, 1H, H-3'); 4.44 (s, 1H, H-4'); 4.54-4.64 (m, 2H, POCH); 4.66 (t, 1H, J = 5.4 Hz, OH-6'); 4.87 (d, 1H, J = 5.6 Hz, OH-5'); 5.68 (d, J = 7.4 Hz, 1H, H-5); 6.16 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.9 Hz, H-1'); 7.08 (brs, 2H, NH_2); 7.62 (d, J = 7.4 Hz, 1H, H-6). ^{13}C NMR (75 MHz, DMSO-d_6): 23.90 (CH_3); 30.84 (C-2'); 62.28 (C-6'); 62.98 (d, $J_{P,C}$ = 165.9 Hz,

PCH_2); 70.35 (POCH); 70.43 (POCH); 72.21 (C-5'); 83.09 (d, $J_{P,C}$ = 13.1 Hz, C-3'); 85.45 (C-4'); 86.78 (C-1'); 93.61 (C-5); 141.36 (C-6); 155.31 (C-2); 165.72 (C-4). Exact mass calcd. for $C_{17}H_{30}N_3O_8P$ $[M+H]^+$: 438.1843, found 438.1845.

2-Deoxy-3-*O*-(diisopropylphosphonomethyl)-4-(*S*)-ethynyl(thymin-1-yl)-L-threose (24d)

This compound was prepared as described for **24a**, using **23d** (0.66 g, 1.05 mmol) as starting material. Reaction time was 3 h. Column chromatographic purification (CH_2Cl_2 : MeOH, 92 : 8) gave compound **24d** (0.453 g) as a colorless solid in 96% yield. ^{1}H NMR (300 MHz, DMSO-d_6): 1.21-1.25 (m, 12H, CH_3); 1.80 (d, 3H, J = 0.9 Hz, CH_3-T); 1.97 (d, 1H, J = 14.5 Hz, H-2'a); 2.63 (ddd, J_1 = 14.5 Hz, J_2 = 8.1 Hz, J_3 = 6.2 Hz, 1H, H-2'b); 3.27-3.48 (m, 3H, H-5', H-6'); 3.79-3.82 (m, 2H, PCH_2); 4.19 (d, J = 6.2 Hz, 1H, H-3'); 4.44 (s, 1H, H-4'); 4.55-4.66 (m, 2H, POCH); 4.66 (t, 1H, J = 5.6 Hz, OH-6'); 4.90 (d, 1H, J = 5.5 Hz, OH-5'); 6.22 (dd, 1H, J_1 = 8.1 Hz, J_2 = 2.3 Hz, H-1'); 7.57 (d, 1H, J = 1.1 Hz, H-6); 11.23 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 12.46 (CH_3-T); 23.92 (CH_3); 38.16 (C-2'); 62.23 (C-6'); 63.30 (d, $J_{P,C}$ = 166.1 Hz, PCH_2); 70.40 (POCH); 70.48 (POCH); 72.30 (C-5'); 83.38 (d, $J_{P,C}$ = 13.8 Hz, C-3'); 85.18 (C-4'); 85.62 (C-1'); 109.44 (C-5); 136.78 (C-6); 150.72 (C-2); 164.02 (C-4). Exact mass calcd. for $C_{18}H_{31}N_2O_9P$ $[M+H]^+$: 451.1840, found 451.1844.

1-(Adenin-9-yl)-2-deoxy-3-*O*-(diisopropylphosphonomethyl)-4-(*S*)-ethynyl-L-threose (26a)

To a solution of **24a** (0.117 g, 0.25 mmol) in 50% aqueous MeOH (1.5 mL), sodium periodate (58 mg, 0.27 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and concentrated *in vacuo,* the residue was partitioned between brine (10 mL) and CH_2Cl_2 (25 mL). The organic layer was extracted with brine (3 x 10 mL). The organic layer was dried over Na_2SO_4, and concentrated *in vacuo* to afford **25a** as colorless oil (0.108 g, 0.25 mmol), which was immediately dissolved in absolute MeOH (18 mL) and degassed. Compound **28** (0.144 g, 0.75 mmol) prepared according to literature[27] was added dropwise to this solution followed by solid K_2CO_3 (0.103 g, 0.75 mmol). The reaction mixture was stirred at room temperature overnight. The solution was partitioned between H_2O (20 mL) and EtOAc (150 mL) and the aqueous layer was extracted (3 x 50 mL) with ethylacetate. The organic layers were dried over Na_2SO_4 and, after evaporation, purified by column chromatography (CH_2Cl_2 : MeOH, 97 : 3) to afford compound **26a**, (0.066 g) as a colorless solid in 62% yield. ^{1}H NMR (300 MHz, $CDCl_3$): 1.31 (d, 6H, J = 6.2 Hz, CH_3); 1.35 (d, 6H, J = 6.2 Hz, CH_3); 2.52 (d, 1H, J = 15.6 Hz, H-2'a); 2.60 (d, 1H, J = 2.2 Hz, H-6'); 2.99 (ddd, 1H, J_1= 15.6 Hz, J_2 = 8.2 Hz, J_3 = 5.6 Hz, H-2'b); 3.78-3.84 (m, 2H, PCH_2); 4.43 (d, 1H, J = 5.6 Hz, H-3'); 4.70-4.82 (m, 2H, POCH); 5.08-5.12 (m, 1H, H-4'); 5.58 (s, 2H, NH_2); 6.62 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.2 Hz, H-1'); 8.25 (s, 1H, H-8); 8.36 (s, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 24.03 (CH_3); 37.96 (C-2'); 64.68 (d, $J_{P,C}$ = 169.06 Hz, PCH_2); 71.45 (POCH); 71.54 (POCH);

73.76 (C-4'); 77.20 (C-6'); 79.28 (C-5'); 83.17 (C-1'); 85.49 (d, $J_{P,C}$ = 10.9 Hz, C-3'); 119.44 (C-5); 139.72 (C-8); 149.72 (C-4); 153.04 (C-2); 155.26 (C-6). Exact mass calcd for $C_{18}H_{26}N_5O_5P$ $[M+H]^+$: 424.1744, found 424.1758.

1-(Cytosin-1-yl)-2-deoxy-3-*O*-(diisopropylphosphonomethyl)-4-(*S*)-ethynyl-L-threose (26b)

This compound was prepared as described for **26a,** using **24b** (0.15 g, 0.35 mmol) as starting material. The reaction time was 4 h and the obtained compound **25b** was transformed (2 h) to **26b**. Column chromatographic purification (CH_2Cl_2 : MeOH, 93 : 7) gave compound **26b** (0.061 g) as a colorless oil in 43% yield over 2 steps. ^{1}H NMR (300 MHz, $CDCl_3$): 1.26-1.34 (m, 12H, CH_3); 2.21 (d, 1H, J = 15.4 Hz, H-2'a); 2.57 (d, 1H, J = 2.2 Hz, H-6'); 2.83 (ddd, 1H, J_1 = 15.4 Hz, J_2 = 7.7 Hz, J_3 = 5.3 Hz, H-2'b); 3.68-3.71 (m, 2H, PCH_2); 4.26 (d, J = 5.3 Hz, 1H, H-3'); 4.65-4.76 (m, 2H, POCH); 5.06 (s, 1H, H-4'); 5.72 (d, 1H, J = 7.4 Hz, H-5); 6.39 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.9 Hz, H-1'); 7.72 (d, 1H, 7.4 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$): 24.04 (CH_3); 37.89 (C-2'); 64.35 (d, $J_{P,C}$ = 169.2 Hz, PCH_2); 71.36 (POCH); 71.46 (POCH); 74.03 (C-4'); 75.93 (C-6'); 79.11 (C-5'); 85.34 (d, $J_{P,C}$ = 11.3 Hz, C-3'); 86.48 (C-1'); 93.45 (C-5); 142.26 (C-6); 155.72 (C-2); 165.35 (C-4). Exact mass calcd. for $C_{17}H_{26}N_3O_6P$ $[M+Na]^+$: 422.1457, found 422.1464.

2-Deoxy-3-*O*-(diisopropylphosphonomethyl)-4-(*S*)-ethynyl-1-(thymin-1-yl)-L-threose (26d)

This compound was prepared as described for **26a**, using **24a** (0.25 g, 0.56 mmol) as starting material for the first step. Reaction time was 2 h and the purification gave compound **25d** which was transformed in the second step (4 h) to **26d**. Column chromatographic purification (CH_2Cl_2: MeOH, 97:3) gave compound **26d** (0.15 g) as a colorless oil in 65% yield over 2 steps: ^{1}H NMR (300 MHz, $CDCl_3$): 1.32 (d, 6H, J = 6.4 Hz, CH_3); 1.33 (d, 6H, J = 6.4 Hz, CH_3); 1.96 (d, 3H, J = 1.1 Hz, CH_3-T); 2.07 (d, 1H, J = 15.6 Hz, H-2'a); 2.57 (d, 1H, J = 2.2 Hz, H-6'); 2.85 (ddd, 1H, J_1 = 15.6 Hz, J_2 = 8.4 Hz, J_3 = 5.6 Hz, H-2'b); 3.77-3.82 (m, 2H, PCH_2); 4.28 (d, J = 5.6 Hz, 1H, H-3'); 4.71-4.82 (m, 2H, POCH); 5.02 (s, 1H, H-4'); 6.46 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.8 Hz, H-1'); 7.54 (d, 1H, J = 1.2 Hz, H-6); 9.02 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): 12.52 (CH_3-T); 24.00 (CH_3); 37.33 (C-2'); 64.60 (d, $J_{P,C}$ = 169.03 Hz, PCH_2); 71.39 (d, $J_{P,C}$ = 6.5 Hz, POCH); 71.46 (d, $J_{P,C}$ = 6.5 Hz, POCH); 73.10 (C-4'); 76.00 (C-6'); 78.81 (C-5'); 84.24 (C-1'); 85.12 (d, $J_{P,C}$ = 11.6 Hz, C-3'); 111.27 (C-5); 136.37 (C-6); 150.50 (C-2); 163.73 (C-4). Exact mass calcd. for $C_{18}H_{27}N_2O_7P$ $[M+H]^+$: 415.1629, found 415.1634.

1-(Adenin-9-yl)-2-deoxy-3-*O*-(phosphonomethyl)-4-(*S*)-ethynyl-L-threose sodium salt (27a)

To a solution of **26a** (66 mg, 0.16 mmol) and 2,6-lutidine (0.14 mL, 1.27 mmol) in MeCN (3 mL) cooled to 0 °C, iodotrimethylsilane (0.179 mL, 1.27 mmol) was added. The reaction mixture was stirred at 0 °C for 24 h in the dark. The reaction mixture was quenched with 2.5% aqueous ammonia, the volatiles were

evaporated and the residue was coevaporated with 2.5% aqueous ammonia. The residue was purified by short column of SiO_2 (CH_2Cl_2 : MeOH : H_2O, 50 : 40 : 10) to give the crude title compound. Purification using HPLC. A linear gradient of 0.05 M tetraethyl ammonium hydrogen carbonate buffer (TEAB) in H_2O/MeCN (1–50% MeCN) as eluent and ion exchanges by Dowex-Na^+ resin gave **27a**, (21 mg) as a colorless solid after lyophilization in 35% yield. ^{1}H NMR (300 MHz, D_2O+dioxane): 2.65 (d, J = 15.4 Hz, 1H, H-2'a); 3.09 (d, J = 2.2 Hz, 1H, H-6'); 3.08 (ddd, J_1= 15.4 Hz, J_2 = 8.2 Hz, J_3 = 5.6 Hz, 1H, H-2'b); 3.65 (dd, J_1 = 12.8 Hz, J_2 = 9.5 Hz, 1H, PCH_{2a}); 3.73 (dd, J_1 = 12.8 Hz, J_2 = 9.5 Hz, 1H, PCH_{2b}); 4.52 (d, J = 5.6 Hz, 1H, H-3'); 5.21 (s, 1H, H-4'); 6.53 (dd, J_1 = 8.2 Hz, J_2 = 2.0 Hz, 1H, H-1'); 8.18 (s, 1H, H-8); 8.48 (s, 1H, H-2). ^{13}C NMR (75 MHz, D_2O+dioxane): 37.20 (C-2'); 66.15 (d, $J_{P,C}$ = 155.4 Hz, PCH_2); 74.77 (C-4'); 77.58 (C-6'); 80.15 (C-5'); 84.19 (C-1'); 85.61 (d, $J_{P,C}$ = 12.3 Hz, C-3'); 118.98 (C-5); 141.81 (C-8); 149.24 (C-4); 153.24 (C-2); 156.07 (C-6). Exact mass calcd. for $C_{12}H_{14}N_5O_5P$ $[M-H]^-$: 338.0660, found 338.0643.

1-(Cytosin-1-yl)-2-deoxy-3-*O*-(phosphonomethyl)-4-(*S*)-ethynyl-L-threose sodium salt (27b)

This compound was prepared as described for **27a,** using **26b** (61 mg, 0.15 mmol) as starting material. Reaction time was 7 h and compound **27b** (22 mg) was obtained as a white solid after lyophylization in 46% yield. ^{1}H NMR (300 MHz, D_2O+dioxane): 2.26 (d, J = 15.3 Hz, 1H, H-2'a); 2.86 (ddd, J_1 = 15.3 Hz, J_2 = 8.2 Hz, J_3 = 5.5 Hz, 1H, H-2'b); 3.04 (d, J = 2.1 Hz, 1H, H-6'); 3.63 (dd, J_1 = 11.4 Hz, J_2 = 8.1 Hz, 1H, PCH_{2a}); 3.56 (dd, J_1 = 11.4 Hz, J_2 = 8.1 Hz, 1H, PCH_{2b}); 4.39 (d, J = 5.5 Hz, 1H, H-3'); 5.23 (s, 1H, H-4'); 6.04 (d, J = 7.6 Hz, H-5'); 6.37 (dd, J_1 = 8.1 Hz, J_2 = 2.2 Hz, 1H, H-1'); 7.93 (d, J = 7.6 Hz, 1H, H-6). ^{13}C NMR (75 MHz, D_2O+dioxane): 36.98 (C-2'); 66.30 (d, $J_{P,C}$ = 155.4 Hz, PCH_2); 74.86 (C-4'); 77.46 (C-6'); 79.99 (C-5'); 85.31 (d, $J_{P,C}$ = 12.4 Hz, C-3'); 86.96 (C-1'); 96.92 (C-5); 143.51 (C-6); 158.18 (C-2); 166.79 (C-4). Exact mass calcd. for $C_{11}H_{14}N_3O_6P$ $[M-H]^-$: 314.0547, found: 314.0547

2-Deoxy-3-*O*-(phosphonomethyl)-4-(*S*)-ethynyl-1-(thymin-1-yl)-L-threose sodium salt (27d)

This compound was prepared as described for **27a,** using **26d** (0.14 g, 0.34 mmol) as starting material. Reaction time was 48 h and compound **27d** (80 mg) was obtained as a white solid after lyophylization in 72% yield. ^{1}H NMR (300 MHz, D_2O+dioxane): 1.90 (d, J = 0.9 Hz, 3H, CH_3-T); 2.27 (d, J = 15.5 Hz, 1H, H-2'a); 2.89 (ddd, J_1 = 15.5 Hz, J_2 = 8.3 Hz, J_3 = 5.6 Hz, 1H, H-2'b); 3.04 (d, J = 2.2 Hz, 1H, H-6'); 3.63 (dd, J_1 = 11.4 Hz, J_2 = 8.3 Hz, 1H, PCH_{2a}); 3.70 (dd, J_1 = 11.4 Hz, J_2 = 8.3 Hz, 1H, PCH_{2b}); 4.41 (d, J_1 = 6.5 Hz, 1H, H-3'); 5.20 (s, 1H, H-4'); 6.38 (dd, J_1 = 8.3 Hz, J_2 = 2.8 Hz, 1H, H-1'); 7.78 (d, 1H, H-6). ^{13}C NMR (75 MHz, D_2O+dioxane): 12.37 (CH_3-T); 36.62 (C-2'); 66.29 (d, $J_{P,C}$ = 155.4 Hz, PCH_2); 74.50 (C-4'); 77.52 (C-6'); 79.86 (C-5'); 85.26 (d, $J_{P,C}$ = 12.5 Hz, C-3'); 85.91 (C-1'); 112.15 (C-5); 139.15 (C-6); 152.50 (C-2); 167.38 (C-4). Exact mass calcd. for $C_{12}H_{15}N_2O_7P$ $[M-H]^-$: 329.0544, found: 329.0551.

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