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.\textsuperscript{1} Although HAART improves prognosis of survival of infected patients,\textsuperscript{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.\textsuperscript{3} These phosphonates are intracellularly metabolized to the phosphonodiphosphates by cellular
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. 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.

There are two main categories of nucleoside phosphonates. The acyclic nucleoside phosphonates, (ANP) were discovered by Holy and De Clercq in 1986. 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. 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. The D-d4AP (2, Figure 1) nucleoside shows potent anti-HIV activity, unfortunately, also mitochondrial toxicity. D-2’Fd4AP (3, Figure 1) is a somewhat less active compound but with an optimal resistance profile. 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.

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. 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. 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, but also cytotoxicity. The most promising ethynyl nucleoside is 2′-deoxy-4′-C-ethynyl-2-fluoroadenosine (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. In order to investigate the importance of the stereochemistry in the 1′- and 3′-position of PMDTA, isomeric analogs of PMDTA were synthesized. 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.

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](image-url)

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. The phosphonate function was introduced using (diisopropoxyphosphonyl)methyl trifluoromethanesulfonate and NaH in dry THF. Selective oxidation of compound 9 by a mixture of periodic acid and sodium periodate gives the aldehyde 10, which was converted into the 6,6-dibromoalkene derivative 11 by Corey-Fuchs reaction. 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.

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. The 1,2-isopropylidene protecting group of 14 was hydrolyzed with CF₃CO₂H and then the resulting compounds 15a, 16a were transformed to diacetyl
derivatives 16a, b. The presence of a 2-O-acetyl group allowed β-selective introduction of the base moieties (N6-benzoyleadenine, N4-benzoylecytosine, N3-benzoyluracil and thymine) using SnCl4 as a Lewis acid. The obtained compounds, 17a-d were deacetylated and debenzyolated 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 iodostrimethylsilane 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'-deoxygentated 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, Et3N and DMAP in CH2Cl2, 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/NH3 overnight, RT; ii) PhOC(S)Cl, DMAP, MeCN, 0 °C; iii) AIBN, Bu3SnH, toluene, reflux; iv) DMAP, Et3N, TIPSCI, CH2Cl2, RT overnight; 88% yield; v) NH3 solution in dioxane, RT, 5 h; vi) cyclohexene, Pd(OH)2, MeOH, 80 °C; vii) NaIO4, aq MeOH RT; viii) MeCOC(N2)P(O)(OMe)2 (28), K2CO3, MeOH, RT; ix) TMSI, 2,6-lutidine, MeCN;
The 2’-deoxygenated products 23\textsubscript{a,b,d} were debenzylated by transfer hydrogenation and converted into the aldehyde derivatives 25\textsubscript{a,b,d} by reaction with NaIO\textsubscript{4} in 50\% aqueous methanol. The aldehydes were converted by Bestmann modification of Seyferth-Gilbert homologation\textsuperscript{25,26,27} into the appropriate 4’-ethynyl derivatives 26\textsubscript{a,b,d}. The final transesterification reaction under mild conditions using TMSI and 2,6-lutidine, afforded the nucleoside phosphonates 27\textsubscript{a,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 \textmu M). 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 \beta-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. \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were acquired on Bruker Avance 300 UltraShield spectrometer, locked on deuterium frequency \textsuperscript{1}H, 300 MHz and 75 MHz for \textsuperscript{13}C NMR spectra. The samples were dissolved in CDCl\textsubscript{3}, DMSO-d\textsubscript{6} using the solvent residual peak as reference (7.26 ppm and 2.50 ppm respectively). For the experiments in D\textsubscript{2}O, 1\% dioxane was used as internal reference for \textsuperscript{1}H and \textsuperscript{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/H2O 1:1 at 3 μL/min.

Preparative HPLC purifications were performed on a column packed with 5 μm C18 reversed phase Xbridge™- 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 H2O/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 P2O5.

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 K2CO3 (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 Et2O (100 mL) and brine (150 mL). The aqueous layer was extracted with Et2O (5 x 30 mL). The organic layer was dried over Na2SO4, concentrated in vacuo and purified by column chromatography on a silicagel column (Hex: CH2Cl2: 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 NaHCO3. The resulting slurry was filtered and the filtrate was extracted with Et2O (3 x 30 mL). The organic layer was dried over Na2SO4 and evaporated in vacuo. The residue was purified by column chromatography (Hex:EtOAc, 50 : 50) to afford an oily product (2.7 g, 75%). 1H NMR (300 MHz, CDCl3): 1.31-1.37 (m, 12H, CH3) and (s, 3H, CH3-isopropylidene); 1.54 (s, 3H, CH3-isopropylidene); 2.98 and 3.07 2 x (brs, 1H, OH); 3.72-3.94 (m, 5H, PCH2, 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’). 13C NMR (75 MHz, CDCl3): 23.99
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 NaHCO₃ (5 mL). The mixture was partitioned between EtOAc (100 mL) and brine (50 mL). The organic layer was washed with brine (2 times), dried (Na₂SO₄) 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, CDCl₃): 1.28 (d, $J = 6.2$ Hz, 6H, CH₃); 1.31 (d, $J = 6.2$ Hz, 6H, CH₃); 1.34 (s, 3H, CH₃-isopropylidene); 1.47 (s, 3H, CH₃-isopropylidene); 3.60 (dd, $J_1 = 13.3$ Hz, $J_2 = 9.5$ Hz, 1H, PCH₂); 3.72 (dd, $J_1 = 13.3$ Hz, $J_2 = 9.5$ Hz, 1H, PCH₂); 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, CH₂Bn); 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, CH₂Bn); 4.79 (d, $J = 11.8$ Hz, 1H, CH₂Bn); 5.81 (d, $J = 4.2$ Hz, 1H, H-1'); 7.27-7.39 (m, 10H, H-arom).

$^{13}$C NMR (75 MHz, CDCl₃): 24.03 (CH₃ iPr); 26.76 and 27.25 (2 x CH₃ isopropylidene); 64.72 (d, $J_{P,C} = 170.5$ Hz, PCH₂); 70.65 (C-6'); 71.21 (POCH); 71.09 (POCH); 73.21 (CH₂Bn); 73.40 (CH₂Bn); 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 C₃₀H₄₃O₉P [M+H]⁺: 579.2723, found 579.2717.

5,6-Di-O-benzyl-1,2-O-isopropylidene-3-O-(diisopropylphosphonomethyl)-α-D-galactofuranose (14) and 5,6-di-O-benzyl-3-O-(diisopropylphosphonomethyl)-β-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 : H₂O (3 : 1) and the solution was stirred at room temperature for 1 h. The resulting mixture was neutralized with solid NaHCO₃. The mixture was partitioned between CH₂Cl₂ (100 mL) and brine (50 mL) and the organic layer was extracted twice by CH₂Cl₂ and concentrated in vacuo. The residue was coevaporated with dry toluene (3 x 50 mL) to afford an oily product 15a,b (2.21 g, 93%).

$^{1}$H NMR (300 MHz, CDCl₃): 1.28 (m, 24H, CH₃ - iPr); 3.62-3.86 (m, 12H, 2xPCH₂, 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, \(J = 4.0\) 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, CH₂Bn) and 4.57 (s, 2H, CH₂Bn); 4.64-4.80 (m, 4H, PCH); 4.61 (d, \(J = 11.3\) Hz, 1H, CH₂Bn); 4.66 (d, \(J = 11.4\) Hz, 1H, CH₂Bn); 4.88 (d, \(J = 11.4\) Hz, 1H, CH₂Bn); 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). 13C NMR (75 MHz, CDCl₃): 23.93-24.08 (CH₃ iPr); 64.70 (d, \(J_{P,C} = 169.1\) Hz, PCH₂-α); 65.16 (d, \(J_{P,C} = 168.4\) Hz, PCH₂-β); 70.27 (C-6’α); 70.31 (C-6’β); 71.35 (d, \(J_{P,C} = 6.8\) Hz, PCH-β); 71.38 (d, \(J_{P,C} = 6.8\) Hz, PCH-β); 71.53 (d, \(J_{P,C} = 7.0\) Hz, PCH-α); 71.70 (d, \(J_{P,C} = 7.0\) Hz, PCH-α); 73.39 (CH₂Bn-α); 73.56, 73.59, 73.62 (3 x CH₂Bn) 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); 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 calcld for C_{27}H_{39}O_{9}P \[M+H\]⁺: 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 H₂O (50 mL). The organic layer was washed with brine (2 x 50 mL), dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by column chromatography on silica (Et₂O : EtOH, 99 : 1) to afford 16a (α-anomer), (0.74 g) as a colorless oil in 29% yield. 1H NMR (300 MHz, CDCl₃): 1.28-1.33 (m, 12H, CH₃ - iPr); 1.89 (s, 3H, CH₃); 2.07 (s, 3H, CH₃); 3.66 (dd, \(J_1 = 13.3\) Hz, \(J_2 = 9.8\) Hz, 1H, PCH₂a); 3.64-3.77 (m, 3H, H-5’, H-6’); 3.79 (dd, \(J_1 = 13.3\) Hz, \(J_2 = 9.8\) Hz, 1H, PCH₂b); 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, CH₂Bn); 4.66 (d, \(J = 11.7\) Hz, 1H, CH₂Bn); 4.66-4.80 (m, 2H, POCH); 4.84 (d, \(J = 11.7\) Hz, 1H, CH₂Bn); 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’). 13C NMR (75 MHz, CDCl₃): 20.49 (CH₃CO); 20.89 (CH₃CO); 23.95 (iPr-CH₃); 65.12 (d, \(J_{P,C} = 168.6\) Hz, PCH₂); 69.98 (C-6’); 70.23 (POCH); 73.02 (CH₂Bn); 73.43 (CH₂Bn); 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 calcld for C_{31}H_{43}O_{11}P \[M+Na\]⁺: 645.2421, found 645.2419.

(1.45 g, 57%) of 16b (β-anomer). 1H NMR (300 MHz, CDCl₃): beta 1.31-1.35 (m, 12H, CH₃ - iPr); 1.97 (s, 3H, CH₃); 2.08 (s, 3H, CH₃); 3.62 (dd, \(J_1 = 13.5\) Hz, \(J_2 = 9.0\) Hz, 1H, PCH₂a); 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, PCH₂b); 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, CH₂Bn); 4.66 (d, \(J = 11.7\) Hz, 1H, CH₂Bn); 4.68-4.80 (m, 2H, H-arom).
2H, POCH); 4.84 (d, J = 11.7 Hz, 1H, CH2Bn); 5.07 (d, J = 0.8 Hz, 1H, H-2'); 6.22 (s, 1H, H-1'); 7.29-7.39 (m, 1H, H-arom). 13C NMR (75 MHz, CDCl3): 20.62 (CH3CO); 21.01 (CH3CO); 23.99 (iPr-CH3); 65.16 (d, J_{P,C} = 168.2 Hz, PCH2); 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 (CH3Bn); 73.37 (CH3Bn); 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 C31H43O11P [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 SnCl4 (0.91 mL, 8.4 mmol) under Ar at room temperature. The reaction mixture was stirred for 5 h and additional SnCl4 (0.30 mL, 2.8 mmol) was added. After 2 h at room temperature the reaction was quenched with solid NaHCO3 and 4 mL H2O, filtered and the filtrate was concentrated to a small volume. The residue was partitioned between H2O (30 mL) and CH2Cl2 (150 mL). The organic layer was washed with water and brine, dried over Na2SO4, and concentrated in vacuo. The residue was purified by chromatography on a silica gel column (CH2Cl2 : MeOH, 98 : 2) to afford 17a (1.57 g) as a colorless amorphous solid in 43% yield. 1H NMR (300 MHz, CDCl3): 1.25-1.34 (m, 12H, CH3); 3.64-3.78 (m, 3H, PCH2a, H-6'); 3.82-3.91 (m, 2H, PCH2b, H-5'); 4.35 (dd, J1 = 3.9 Hz, J2 = 1.8 Hz, 1H, H-3'); 4.53 (s, 2H, CH2Bn); 4.58 (t, J = 4.0 Hz, 1H, H-4'); 4.67 (d, J = 11.7 Hz, 1H, CH2Bn); 4.84 (d, J = 11.7 Hz, 1H, CH2Bn); 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). 13C NMR (75 MHz, CDCl3): 20.47 (CH3CO); 64.97 (d, J_{P,C} = 168.6 Hz, PCH2); 69.45 (C-6'); 71.24 (POCH); 71.33 (POCH), 73.20 (CH2-Bn); 73.46 (CH2-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 C41H48N5O10P [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 (1.74 g, 2.8 mmol) in 25 mL of dry MeCN was added to the previous dried residue, followed by dropwise addition of SnCl4 (0.91 mL, 8.4 mmol) under Ar at room temperature. The reaction mixture was stirred for 5 h and additional SnCl4 (0.30 mL, 2.8 mmol) was added. After 2 h at room temperature the reaction was quenched with solid NaHCO3 and 4 mL H2O, filtered and the filtrate was concentrated to a small volume. The residue was partitioned between H2O (30 mL) and CH2Cl2 (150 mL). The organic layer was washed with water and brine, dried over Na2SO4, and concentrated in vacuo. The residue was purified by chromatography on a silica gel column (CH2Cl2 : MeOH, 98 : 2) to afford 17b (1.57 g) as a colorless amorphous solid in 43% yield. 1H NMR (300 MHz, CDCl3): 1.25-1.34 (m, 12H, CH3); 3.64-3.78 (m, 3H, PCH2a, H-6'); 3.82-3.91 (m, 2H, PCH2b, H-5'); 4.35 (dd, J1 = 3.9 Hz, J2 = 1.8 Hz, 1H, H-3'); 4.53 (s, 2H, CH2Bn); 4.58 (t, J = 4.0 Hz, 1H, H-4'); 4.67 (d, J = 11.7 Hz, 1H, CH2Bn); 4.84 (d, J = 11.7 Hz, 1H, CH2Bn); 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). 13C NMR (75 MHz, CDCl3): 20.47 (CH3CO); 64.97 (d, J_{P,C} = 168.6 Hz, PCH2); 69.45 (C-6'); 71.24 (POCH); 71.33 (POCH), 73.20 (CH2-Bn); 73.46 (CH2-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 C41H48N5O10P [M+Na]^+: 824.3037, found 824.3055.
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 SnCl4 in CH2Cl2 (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 NaHCO3 and 4 mL H2O, filtered and the filtrate was concentrated to a small volume. The residue was partitioned between H2O (30 mL) and CH2Cl2 (150 mL). The organic layer was washed with water and brine, dried over Na2SO4, and concentrated in vacuo. The residue was purified by chromatography on silica (CH2Cl2 : MeOH, 97 : 3) to afford 17b (2.09 g) as a colorless amorphous solid in 83% yield. 1H NMR (300 MHz, CDCl3): 1.25-1.30 (m, 12H, CH3); 1.89 (s, 3H, CH3CO); 3.66-3.79 (m, 4H, PCH2a, H-6’, H-5’); 3.81 (dd, J1 = 13.8 Hz, J2 = 9.5 Hz, 1H, PCH2b); 4.26 (dd, J1 = 2.2 Hz, J2 = 1.6 Hz, 1H, H-3’); 4.54 (s, 2H, CH2Bn); 4.68 (d, J = 11.7 Hz, 1H, CH2Bn); 4.61-4.73 (m, 3H, POCH, H-4’); 4.78 (d, J = 11.7 Hz, 1H, CH2Bn); 5.26 (t, J = 1.7 Hz, 1H, H-2’); 6.15 (d, 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); 7.90 (s, 1H, NH). 13C NMR (75 MHz, CDCl3): 20.48 (CH3CO); 23.84 (CH3); 64.65 (d, JPC = 167.5 Hz, PCH2); 69.06 (C-6’); 71.02 (POCH); 71.11 (POCH); 73.02 (CH2Bn); 73.42 (CH2Bn); 76.92 (C-5’); 80.30 (C-2’); 84.35 (d, JPC = 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 (CH3CO); 162.34 (C-2); 166.59 (BzCO); 169.55 (C-4). Exact mass calcd. for C40H48N3O11P [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-Benzoyluracil29 (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 SnCl4 in CH2Cl2 (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 NaHCO3 and 2 mL H2O, filtered and the filtrate was concentrated to a small volume. The residue was partitioned between H2O (30 mL) and EtOAc (150 mL). The organic layer was washed with water and brine, dried over Na2SO4, and concentrated in vacuo. The residue was purified by chromatography on silica (Hexane:CH2Cl2:MeOH, 6:4:0.5) to afford 17c (1.5 g) as a colorless oil in 69% yield. 1H NMR (300 MHz, CDC13): 1.27-1.32 (m, 12H, CH3); 1.89 (s, 3H, CH3CO); 3.63-3.76 (m, 4H, PCH2a, H-6’, H-5’); 3.81 (dd, J1 = 13.6 Hz, J2 = 9.9 Hz, 1H, PCH2b); 4.22 (t, J = 2.4 Hz, H-3’); 4.51 (dd, J1 = 4.2 Hz, J2 = 1.2 Hz, 1H, H-4’); 4.53 (s, 2H, CH2Bn); 4.64 (d, J = 11.8 Hz, 1H, CH2Bn); 4.66-
4.76 (m, 2H, POCH); 4.78 (d, J = 11.8 Hz, 1H, CH₂Bn); 5.18 (dd, J₁ = 2.9 Hz, J₂ = 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). ¹³C NMR (75 MHz, CDCl₃): 20.45 (CH₃CO); 24.01 (CH₃); 64.83 (d, Jₚ,C = 168.7 Hz, PCH₂); 69.14 (C-6’); 71.33 2 x (POCH); 73.05 (CH₂-Bn); 73.56 (CH₂-Bn); 76.58 (C-5’); 80.76 (C-2’), 84.94 (d, Jₚ,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-Bn); 140.04 (C-Bn); 140.04 (C-Bn); 162.65 (C-4); 169.78 (CH₃CO).  Exact mass calcd. for C₃₃H₄₃N₂O₁₁P [M+H]+: 675.2677, found 675.2653.

2-O-Acetyl-5,6-di-O-benzyl-3-O-(diisopropylphosphonomethyl)-1-(thymin-1-yl)-β-D-galactofuranose (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 SnCl₄ in CH₂Cl₂ (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 NaHCO₃ and 4 mL H₂O, 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 Na₂SO₄, and concentrated in vacuo. The residue was purified by chromatography on silica (CH₂Cl₂ : MeOH, 97 : 3) to afford 17d (1.74 g) as a colorless amorphous solid in 78% yield. ¹H NMR (300 MHz, CDCl₃): 1.27-1.33 (m, 12H, CH₃); 1.90 (s, 3H, CH₃CO); 1.94 (d, J = 1.0 Hz, 3H, CH₃-T); 3.62-3.77 (m, 4H, PCH₂a, H-6’, H-5’); 3.81 (dd, J₁ = 13.4 Hz, J₂ = 9.9 Hz, 1H, H-3’); 4.21 (dd, J₁ = 3.0 Hz, J₂ = 2.5 Hz, 1H, H-4’); 4.50 (dd, J₁ = 3.0 Hz, J₂ = 2.5 Hz, 1H, H-4’); 4.53 (s, 2H, CH₂Bn); 4.63 (d, J = 11.8 Hz, 1H, CH₂Bn); 4.67-4.76 (m, 2H, POCH); 4.79 (d, J = 11.8 Hz, 1H, CH₂Bn); 5.19 (dd, J₁ = 3.4 Hz, J₂ = 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). ¹³C NMR (75 MHz, CDCl₃): 12.55 (CH₃-T); 20.47 (CH₃CO); 24.01 (CH₃); 64.90 (d, Jₚ,C = 169.5 Hz, PCH₂); 69.20 (C-6’); 71.21 (POCH); 71.30 (POCH); 73.04 (CH₂-Bn); 73.55 (CH₂-Bn); 77.13 (C-5’); 80.79 (C-2’), 85.22 (d, Jₚ,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 (CH₃CO).  Exact mass calcd. for C₃₄H₄₅N₂O₁₁P [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$_2$Cl$_2$ : 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$_2$a); 3.66-3.89 (m, 4H, PCH$_2$b, 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$_2$Bn); 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$_2$Bn); 4.60-4.77 (m, 2H, POCH); 4.85 (d, $J = 11.8$ Hz, 1H, CH$_2$Bn); 4.89 (t, $J = 4.5$ Hz, 1H, H-2’); 5.92 (brs, 2H, NH$_2$); 5.99 (d, $J = 4.5$ Hz, 1H, 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$_2$); 69.61 (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$_5$O$_8$P [M+H]$^+$: 656.2844, found 656.2836.

5,6-Di-O-benzyl-1-(cytosin-1-yl)-3-O-(diisopropylphosphonomethyl)-$\beta$-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$_2$Cl$_2$ : 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$_2$a); 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$_2$b); 4.08 (dd, $J_1 = 5.3$ Hz, $J_2 = 4.5$ Hz, 1H, H-3’); 4.30 (t, $J = 3.5$ 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$_2$Bn); 4.60-4.71 (m, 2H, POCH); 4.67 (d, $J = 11.7$ Hz, 1H, CH$_2$Bn); 4.77 (d, $J = 11.7$ Hz, 1H, CH$_3$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$_3$O$_9$P [M+H]$^+$: 632.2731, found 632.2741.

5,6-Di-O-benzyl-3-O-(diisopropylphosphonomethyl)-1-(uracil-1-yl)-$\beta$-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$_2$Cl$_2$ : 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$_2$a); 3.68 (dd, $J_1 = 14.0$ Hz, $J_2 = 7.8$ Hz, 1H, PCH$_2$b); 3.72-3.81 (m, 3H, H-5’, H-6’); 3.98 (dd, $J_1 = 5.7$ Hz, $J_2 = 2.1$ Hz, 1H, H-4’); 4.65 (d, $J = 11.8$ Hz, 1H, CH$_2$Bn); 4.60-4.71 (m, 2H, POCH); 4.85 (d, $J = 11.8$ Hz, 1H, CH$_2$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$_3$): 23.99 (CH$_3$); 65.76 (d, $J_{P,C} = 167.9$ Hz, PCH$_2$); 69.61 (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$_{31}$H$_{42}$N$_3$O$_9$P [M+H]$^+$: 632.2731, found 632.2741.
= 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, \( 1H, CH_3Bn \)); 4.60-4.76 (m, \( 2H, POCH \)); 4.81 (d, \( J = 11.5 \) Hz, \( 1H, CH_2Bn \)); 5.65 (d, \( J = 8.1 \) Hz, \( H-5 \)); 5.80 (d, \( J = 3.3 \) Hz, \( H-1' \)); 7.29-7.42 (m, \( 11H, arom-H, H-6 \)); 8.61 (s, \( 1H, NH \)). 

\( ^1\)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'); 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).

**5,6-di-O-benzyl-3-O-(diisopropylphosphonomethyl)-1-(thymin-1-yl)-\( \beta \)-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\(_2\)Cl\(_2\): 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, \( 1H, CH_2Bn \)); 4.62-4.77 (m, \( 2H, POCH \)); 4.81 (d, \( J = 11.7 \) Hz, \( 1H, CH_2Bn \)); 4.86 (brs, \( 1H, OH \)); 5.83 (d, \( J = 3.8 \) Hz, \( H-1' \)); 7.21 (d, \( J = 1.2 \) Hz, \( 1H, H-6 \)); 7.30-7.37 (m, \( 10H, ArH \)); 8.79 (brs, \( 1H, NH \)). 

\( ^1\)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, \( J_{P,C} = 8.6 \) Hz, C-3'); 92.48 (C-1'); 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\(_{31}\)H\(_{41}\)N\(_2\)O\(_{10}\)P \([M+H]\): 633.2571, found 633.2551.

**1-(Adenin-9-yl)-3-O-(diisopropylphosphonomethyl)-\( \beta \)-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 \( ^\circ \)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 \textit{in vacuo} and the residue was purified by chromatography (CH\(_2\)Cl\(_2\): 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\(_2b\)); 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,
$J_2 = 2.4 \text{ Hz, } 1\text{H, H-4'}$; 4.56-4.68 (m, 2H, POCH); 4.64 (t, 1H, $J = 5.5 \text{ Hz, OH-6'}$); 4.94-4.99 (m, 1H, H-2'); 5.09 (d, 1H, $J = 5.8 \text{ Hz, OH-5'}$); 5.93 (d, 1H, $J = 5.8$, 1H, OH-2'); 5.87 (d, 1H, $J = 5.6 \text{ Hz, } 1\text{H, H-1'}$); 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, $J_{P,C} = 165.4 \text{ Hz, PCH}_2$); 70.27 (POCH); 70.35 (POCH); 70.76 (C-2'); 77.41 (C-5'); 81.30 (C-4'); 85.23 (d, $J_{P,C} = 12.9 \text{ Hz, C-3'}$); 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$_5$O$_8$P [M+H]$^+$: 476.1905, found 476.1902.

1-(Cytosin-1-yl)-3-O-(diisopropylphosphonomethyl)-$\beta$-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$_2$Cl$_2$ : MeOH, 90:10) gave compound 19b (0.14 g) as a colorless amorphous solid in 54% yield. $^1$H NMR (300 MHz, D$_2$O): 1.25-1.31 (m, 12H, CH$_3$); 3.65-3.78 (m, 2H, H-6'); 3.88-3.95 (m, 1H, H-5'); 4.12 (t, $J_1 = 2.4 \text{ Hz, } 1\text{H, H-3'}$); 4.20 (t, $J = 1.8 \text{ Hz, } 1\text{H, H-2'}$); 4.54 (dd, $J_1 = 5.3 \text{ Hz, } J_2 = 2.4 \text{ Hz, } 1\text{H, H-4'}$); 4.28-4.36 (m, 2H, POCH); 5.51 (d, 1H, $J = 1.8 \text{ Hz, } 1\text{H, H-1'}$); 5.70 (d, 1H, $J = 7.5 \text{ Hz, H-5}$); 7.35 (d, 1H, $J = 7.5 \text{ Hz, H-6}$). $^{13}$C NMR (75 MHz, D$_2$O+dioxane): 23.73 (CH$_3$); 62.98 (C-6'); 64.34 (d, $J_{P,C} = 165.8 \text{ Hz, PCH}_2$); 71.93 (C-2'); 74.44 (POCH); 78.85 (C-5'); 87.23 (C-4'); 87.25 (d, $J_{P,C} = 14.7 \text{ Hz, C-3'}$); 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$_3$O$_9$P [M+H]$^+$: 452.1792, found 452.1789.

3-O-(Diisopropylphosphonomethyl)-1-(uracil-1-yl)-$\beta$-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$_2$Cl$_2$ : MeOH, 90 : 10) gave compound 19c (0.1 g) as a colorless amorphous solid in 93% yield: $^1$H NMR (300 MHz, D$_2$O): 1.28-1.33 (m, 12H, CH$_3$); 3.64-3.77 (m, 2H, H-6'); 3.89-3.95 (m, 1H, H-5'); 4.01-4.04 (m, 2H, PCH$_2$); 4.16 (t, $J_1 = 2.7 \text{ Hz, } 1\text{H, H-3'}$); 4.50-4.53 (m, 2H, H-2', H-4'); 4.65-4.74 (m, 2H, POCH); 5.85 (d, 1H, $J = 1.7 \text{ Hz, } 1\text{H, H-1'}$); 5.86 (d, 1H, $J = 8.1 \text{ Hz, H-5}$); 7.72 (d, 1H, $J = 8.1 \text{ Hz, H-6}$). $^{13}$C NMR (75 MHz, D$_2$O+dioxane): 23.82 (CH$_3$); 63.04 (C-6'); 64.50 (d, $J_{P,C} = 166.2 \text{ Hz, PCH}_2$); 71.93 (C-2'); 74.53 (POCH); 74.62 (POCH); 78.75 (C-5'); 86.88 (C-4'); 87.97 (d, $J_{P,C} = 14.2 \text{ Hz, C-3'}$); 93.52 (C-1'); 102.15 (C-5); 142.25 (C-6); 166.92 (C-4). Exact mass calcd. for C$_{17}$H$_{29}$N$_2$O$_9$P [M+H]$^+$: 453.1632, found 453.1628.

3-O-(Diisopropylphosphonomethyl)-1-(thymin-1-yl)-$\beta$-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$_2$Cl$_2$ : 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, CH3); 1.80 (d, 3H, J = 9.3 Hz, PCH2a); 3.97 (dd, 1H, J1 = 13.7 Hz, J2 = 9.3 Hz, PCH2b); 4.11 (t, J1 = 5.3 Hz, 1H, H-3’); 4.21 (dd, J1 = 5.5 Hz, J2 = 2.4 Hz, 1H, H-4’); 4.24-4.29 (m, 1H, CH2); 4.54-4.58 (m, 2H, PCH); 4.67 (t, J = 5.5 Hz, OH-6’); 5.14 (d, J = 5.5 Hz, OH-5’); 5.76 (d, J = 5.5 Hz, OH-2’); 5.81 (d, J = 5.9 Hz, 1H, H-1’); 7.56 (d, J = 1.1 Hz, H-6’); 11.27 (s, 1H, NH). 13C NMR (75 MHz, DMSO-d6): 12.20 (CH3); 23.92 (CH3); 62.21 (C-6’); 64.22 (d, Jp,C = 165.1 Hz, PCH2); 70.48 (d, Jp,C = 6.2 Hz, POCH); 70.55 (d, Jp,C = 6.2 Hz, POCH); 71.12 (C-2’); 77.67 (C-5’); 81.78 (C-4’); 89.15 (C-1’); 109.71 (C-5); 136.83 (C-6); 150.85 (C-2); 163.94 (C-4).

**Exact mass calcd. for C18H31N2O10P [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 ioddotrimethylsilane (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 (CH2Cl2 : MeOH : H2O, 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 lyophilization in 13% yield.

1H NMR (300 MHz, D2O): 3.65-3.78 (m, 4H, PCH2, H-6’); 3.95-3.99 (m, 1H, H-5’); 4.30 (dd, J1 = 6.7 Hz, J2 = 5.7 Hz, 1H, H-3’); 4.39 (dd, J1 = 6.7 Hz, J2 = 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). 13C NMR (75 MHz, D2O+dioxane): 63.16 (C-6’); 67.29 (d, Jp,C = 154.4 Hz, PCH2); 71.74 (C-5’); 78.57 (C-2’); 83.15 (C-4’); 86.27 (d, Jp,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 C12H18N5O8P [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 lyophilization in 39% yield. 1H NMR (300 MHz, D2O+dioxane): 3.59-3.67 (m, 4H, PCH2, H-6’); 3.83-3.88 (m, 1H, H-5’); 4.10 (dd, J1 = 4.6 Hz, J2 = 4.3 Hz, 1H, H-3’); 4.95 (dd, J1 = 4.8 Hz, J2 = 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’). 13C NMR (75 MHz, D2O+dioxane): 63.01 (C-6’); 67.29 (d, Jp,C = 154.4 Hz, PCH2); 71.78 (C-5’); 78.73 (C-2’); 84.82 (C-4’); 86.34 (d, Jp,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 C12H18N3O8P [M+H]+: 366.0791, found 366.0773.
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. 1H NMR (300 MHz, D2O+dioxane): 3.63-3.72 (m, 4H, PCH2, H-6'); 3.88-3.95 (m, 1H, H-5'); 4.18 (dd, J1 = 5.2 Hz, J2 = 4.3 Hz, 1H, H-4'); 4.42 (dd, J1 = 5.2 Hz, J2 = 1.0 Hz, 1H, H-3'); 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). 13C NMR (75 MHz, D2O+dioxane): 63.09 (C-6'); 67.70 (d, Jp,c = 154.1 Hz, PCH2); 71.78 (C-5'); 78.77 (C-2'); 84.69 (C-4'); 86.21 (d, Jp,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 C11H17N2O10P [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. 1H NMR (300 MHz, D2O+dioxane): 1.90 (d, 3H, J = 1.1 Hz, CH3-T); 3.62-3.85 (m, 4H, H-6', PCH2); 3.89-3.94 (m, 1H, H-5'); 4.19 (t, J = 5.3 Hz, 1H, H-3'); 4.37 (dd, J1 = 6.2 Hz, J2 = 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). 13C NMR (75 MHz, D2O+dioxane): 12.23 (CH3-T); 63.09 (C-6'); 68.14 (d, Jp,c = 153.2 Hz, PCH2); 71.73 (C-2'); 78.68 (C-5'); 83.66 (C-4'); 85.88 (d, Jp,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 C12H19N2O10P [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 CH2Cl2 (14.4 mL) under Ar, DMAP (0.275 g, 2.25 mmol), E3N (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 H2O (50 mL) and Et2O (150 mL). The organic layer was washed with water (3 x 50 mL) and dried over Na2SO4. The residue was purified by column chromatography (CH2Cl2: MeOH, 99:1) to give compound 22 (0.865 g), as a colorless solid in 88% yield (not stable at room temperature). 1H NMR (300 MHz, CDCl3): 1.20-1.32 (m, 12H, CH3); 2.13 (d, 1H, J = 15.0 Hz, H-2'a); 2.70 (ddd, J1 = 15.0 Hz, J2 = 7.3 Hz, J3 = 5.7 Hz, 1H, H-2'b); 2.86-2.95 (m, 1H, CH-iPr TIPS); 3.49-3.52 (m, 2H, PCH2); 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, CH2aBn); 4.53 (s, 2H, CH2Bn); 4.66-4.68 (m, 1H, H-4'); 4.57-4.71 (m, 2H, POCH); 4.70 (d, J = 11.7 Hz, 1H, CH2aBn); 6.05 (d, J = 7.3 Hz, 1H, H-5); 6.12 (dd, 1H, J1.
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 thionochlorofor mate (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 (CH2Cl2 : 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 (CH2Cl2 : MeOH, 96 : 4) to afford compound 23a, 0.21 g, as a colorless oil in 60% yield (49% over two steps). 1H NMR (300 MHz, CDCl3): 1.26-1.33 (m, 12H, CH3); 2.44 (d, 1H, J = 15.6 Hz, H-2’a); 2.82 (ddd, J1 = 15.3 Hz, J2 = 7.8 Hz, J3 = 6.5 Hz, 1H, H-2’b); 3.57-3.75 (m, 5H, PCH2, H-5’, H-6’); 4.21 (d, 1H, J = 5.7 Hz, H-3’); 4.54-4.60 (m, 4H, CH2aBn CH2Bn, H-4’); 4.63-4.76 (m, 2H, POCH); 4.78 (d, J = 11.7 Hz, 1H, CH2bBn); 5.68 (s, 2H, NH2); 6.53 (dd, 1H, J1 = 8.0 Hz, J2 = 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). 13C NMR (75 MHz, CDCl3): 23.98 (CH3); 38.88 (C-2’); 64.26 (d, JPC = 166.8 Hz, PCH2); 69.30 (C-6’); 71.23 (POCH); 71.30 (POCH); 72.87 (CH2-Bn); 73.60 (C-6’); 83.43 (d, JPC = 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); 149.77 (C-4); 152.94 (C-2); 155.37 (C-6).

Exact mass calcd. for C32H42N5O7P [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 (CH2Cl2:MeOH, 97 : 3) gave compound 21c (1.48 g) which was transformed to 23c. Compound 23c was, likewise, purified by column chromatography
(CH₂Cl₂:MeOH, 97:3) **23c** (0.683 g) as a colorless oil in 61% yield (53% over two steps). ¹H NMR (300 MHz, CDCl₃): 1.26-1.32 (m, 12H, CH₃); 2.02 (ddd, 1H, J = 15.0 Hz, H-2’a); 3.57-3.69 (m, 5H, PCH₂, H-5’, H-6’); 4.01 (d, 1H, J = 6.2 Hz, H-3’); 4.49 (d, J = 11.7 Hz, 1H, CH₂aBn); 4.54 (d, J = 1.1 Hz, 2H, CH₂Bn); 4.59 (m, 1H, H-4’); 4.65-4.76 (m, 2H, POCH); 4.73 (d, J = 11.7 Hz, 1H, CH₂Bn); 5.69 (d, J = 8.1 Hz, 1H, H-5); 6.31 (dd, 1H, J₁ = 8.0 Hz, J₂ = 2.0 Hz, H-1’); 6.31 (dd, 1H, J₁ = 8.0 Hz, J₂ = 2.0 Hz, H-1’); 7.29-7.36 (m, 10H, arom-H); 7.69 (d, J = 7.4 Hz, 1H, H-6). ¹³C NMR (75 MHz, CDCl₃): 24.03 (CH₃); 38.98 (C-2’); 64.14 (d, Jₚ,C = 169.6 Hz, PCH₂); 68.99 (C-6’); 71.28 (2C POCH); 72.85 (CH₂-Bn); 73.63 (CH₂-Bn); 77.93 (C-5’); 83.44 (d, Jₚ,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); 165.48 (C-4). Exact mass calcd. for C₃₁H₄₁N₂O₉P [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 NH₃ (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 : CH₂Cl₂ : MeOH, 6:4:1) to afford compound 23b (0.486 g), as a colorless solid in 86% yield. ¹H NMR (300 MHz, CDCl₃): 1.25-1.30 (m, 12H, CH₃); 2.12 (d, 1H, J = 14.7 Hz, H-2’a); 2.69 (ddd, J₁ = 14.7 Hz, J₂ = 7.4 Hz, J₃ = 6.2 Hz, 1H, H-2’b); 3.52-3.69 (m, 5H, H-5’, H-6’, PCH₂); 4.01 (d, J = 6.2 Hz, 1H, H-3’); 4.51 (d, J = 11.8 Hz, 1H, CH₂aBn); 4.54 (s, 2H, CH₂Bn); 4.57-4.61 (m, 1H, H-4’); 4.58-4.73 (m, 2H, POCH); 4.73 (d, J = 11.8 Hz, 1H, CH₂Bn); 5.69 (d, J = 7.4 Hz, 1H, H-5); 6.36 (dd, 1H, J₁ = 7.4 Hz, J₂ = 1.7 Hz, H-1’); 7.68 (d, J = 7.4 Hz, 1H, H-6). ¹³C NMR (75 MHz, CDCl₃): 24.03 (CH₃); 39.10 (C-2’); 63.95 (d, Jₚ,C = 169.3 Hz, PCH₂); 69.16 (C-6’); 71.08 (d, Jₚ,C = 13.2 Hz, POCH); 71.17 (d, Jₚ,C = 13.2 Hz, POCH); 72.84 (CH₂-Bn); 73.58 (CH₂-Bn); 77.83 (C-5’); 83.30 (d, Jₚ,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); 150.33 (C-2); 165.48 (C-4). Exact mass calcd. for C₃₁H₄₁N₂O₆P [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 (CH₂Cl₂ : 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 (CH₂Cl₂ : 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\(_2\)Bn); 4.50-4.58 (m, 3H, CH\(_2\)Bn, H-4’); 4.64-4.78 (m, 2H, PCH); 4.74 (d, J = 11.9 Hz, 1H, CH\(_2\)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). \(^1\)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\(_{POCH} = 6.7\) Hz, PCH); 71.22 (d, J\(_{POCH} = 6.7\) Hz, PCH); 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\(_2\)O\(_9\)P [M+H]\(^+\): 631.2779, found 631.2781.

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

To a solution of 23a (0.195 g, 0.3 mmol) in methanol (23 mL) and H\(_2\)O (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\(_2\)Cl\(_2\) : 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, PPOCH); 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). \(^1\)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’); 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\(_5\)O\(_7\)P [M+H]\(^+\): 460.1955, found 460.1923.

1-(Cytosin-1-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-\(\beta\)-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\(_2\)Cl\(_2\): 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\(_3\)); 4.18 (d, J = 6.2 Hz, 1H, H-3’); 4.44 (s, 1H, H-4’); 4.54-4.64 (m, 2H, PPOCH); 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). \(^1\)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,
PCH₂; 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 C₁₇H₃₀N₃O₈P [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 (CH₂Cl₂: MeOH, 92 : 8) gave compound 24d (0.453 g) as a colorless solid in 96% yield. ¹H NMR (300 MHz, DMSO-d₆): 1.21-1.25 (m, 12H, CH₃); 1.80 (d, 3H, J = 0.9 Hz, CH₃-T); 1.97 (d, 1H, J = 14.5 Hz, H-2'a); 2.63 (ddd, J₁ = 14.5 Hz, J₂ = 8.1 Hz, J₃ = 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, J₁ = 8.1 Hz, J₂ = 2.3 Hz, H-1'); 7.57 (d, 1H, J = 1.1 Hz, H-6); 11.23 (s, 1H, NH). ¹³C NMR (75 MHz, DMSO-d₆): 12.46 (CH₃-T); 23.92 (CH₃); 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 C₁₈H₃₁N₂O₉P [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 CH₂Cl₂ (25 mL). The organic layer was extracted with brine (3 x 10 mL). The organic layer was dried over Na₂SO₄, 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 literature²⁷ was added dropwise to this solution followed by solid K₂CO₃ (0.103 g, 0.75 mmol). The reaction mixture was stirred at room temperature overnight. The solution was partitioned between H₂O (20 mL) and EtOAc (150 mL) and the aqueous layer was extracted (3 x 50 mL) with ethylacetate. The organic layers were dried over Na₂SO₄ and, after evaporation, purified by column chromatography (CH₂Cl₂: MeOH, 97 : 3) to afford compound 26a, (0.066 g) as a colorless solid in 62% yield. ¹H NMR (300 MHz, CDCl₃): 1.31 (d, 6H, J = 6.2 Hz, CH₃); 1.35 (d, 6H, J = 6.2 Hz, CH₃); 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, J₁ = 15.6 Hz, J₂ = 8.2 Hz, J₃ = 5.6 Hz, H-2'b); 3.78-3.84 (m, 2H, PCH₂); 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, NH₂); 6.62 (dd, 1H, J₁ = 8.2 Hz, J₂ = 2.2 Hz, H-1'); 8.25 (s, 1H, H-8); 8.36 (s, 1H, H-2). ¹³C NMR (75 MHz, CDCl₃): 24.03 (CH₃); 37.96 (C-2'); 64.68 (d, J_P,C = 169.06 Hz, PCH₂); 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\(_2\)Cl\(_2\): 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, \( J = 7.4 \) 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\(_2\)Cl\(_2\): 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\(_3\)): 1.26-1.34 (m, 12H, CH\(_3\)); 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\(_3\)); 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 \( C_{18}H_{26}N_3O_6P \) [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, iodo(trimethyl)silane (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$_2$Cl$_2$: MeOH : H$_2$O, 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$_2$O/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$_2$O+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$_2$O+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’); 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$_5$O$_5$P [M-H]$: 338.0660, found: 338.0643.

1-(Cytosin-1-yl)-2-deoxy-3-O-(phosphonomethyl)-4-(S)-ethylidyne-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$_2$O+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$_2$O+dioxane): 36.98 (C-2’); 66.30 (d, $J_{P,C}$ = 155.4 Hz, PCH$_2$); 74.77 (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$_3$O$_6$P [M-H]$: 314.0547, found: 314.0547.

2-Deoxy-3-O-(phosphonomethyl)-4-(S)-ethylidyne-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$_2$O+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$_2$O+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$_{13}$N$_2$O$_6$P [M-H]$: 329.0544, found: 329.0551.
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