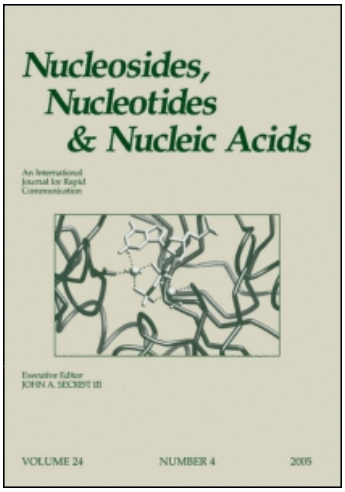

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Synthesis of 3'-*O*-Phosphonoethyl Nucleosides with an Adenine and a Thymine Base Moiety

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SYNTHESIS OF 3′-*O*-PHOSPHONOETHYL NUCLEOSIDES WITH AN ADENINE AND A THYMINE BASE MOIETY

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□ *The synthesis and antiviral evaluation of new 3′-O-phosphonoethyl modified phosphonate nucleosides related to PMDTA and PMDTT is described. The reaction scheme starts from protected L-threose and the phosphonate group is introduced by the Arbuzov reaction. The 2′-OH as well as the 2′-deoxygenated nucleosides have been obtained. Unfortunately, none of these synthesized compounds shows activity against HIV and HCV.*

Keywords Phosphonate nucleosides; PMDTA; PMDTT; Arbuzov reaction

INTRODUCTION

Nucleotide phosphonates are widely used therapeutic agents known to have a broad spectrum of antiviral activity.[1] Upon intracellular conversion to the active mono- and diphosphates by cellular kinases, they are incorporated into viral DNA, eventually leading to termination of DNA chain elongation.[2] Unlike nucleoside agents, a phosphonate nucleoside has the advantage of skipping the requisite first phosphorylation step, which is an inefficient and often rate-limiting step, to reach its active metabolic form. 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.[3] Since the acyclic nucleoside phosphonates (ANPs) were first discovered in 1986 by Holy and De Clercq,[4]

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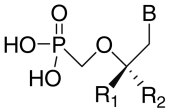
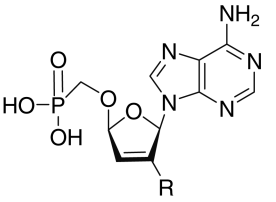
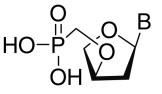


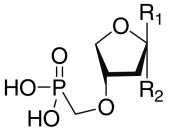
Ia $R_1 = R_2 = H$, B = adenin-9-yl **PMEA**
Ib $R_1 = CH_3$, $R_2 = H$, B = adenin-9-yl (***R***)-**PMPA**
Ic $R_1 = CH_2OH$, $R_2 = H$, B = cytosin-1-yl (***S***)-**HPMPC**
Id $R_1 = R_2 = -CH_2-CH_2-$, B = guanin-9-yl **PMCG**



IIa R = H **D-d4AP**
IIb R = F **D-2'Fd4AP**



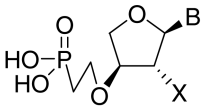
IIIa B = adenin-9-yl **PMDTA**
IIIb B = thymin-1-yl **PMDTT**



IVa R_1 = adenin-9-yl $R_2 = H$
IVb $R_1 = H$ R_2 = adenin-9-yl

FIGURE 1 Structure of representative phosphonate nucleosides.

three ANPs have been licensed for antiviral therapy: cidofovir ((S)-1-[3-hydroxy-2-(phosphonomethoxy)propyl]cytosine (S)-HPMPC), which has been approved for treatment of CMV retinitis in AIDS patients; adefovir (a prodrug of 9-[2-(phosphonomethoxy)ethyl]adenine PMEA), which has been approved for treatment of chronic HBV infection; and tenofovir (a prodrug of (R)-9-[2-(phosphonomethoxy)propyl]adenine PMPA), which has been approved for treatment of HIV infections (Figure 1).[5] Some limitations of these currently used phosphonate nucleoside drugs (cidofovir, adefovir, and tenofovir), that need to be surpassed are their long-term side effects, the emergency of resistance, and the presence of drug-drug interactions.[6] Recently, a novel phosphonate nucleoside, 9-[(1-phosphonomethoxycylcopropyl)methyl]-guanine (PMCG) was reported with highly potent and selective anti-HBV activity ($EC_{50} = 0.5$ μM), while exhibiting no significant cytotoxicity in several human cell lines (up to 1.0 mM). By contrast to the classic PMEA analogs, the introduction of a cyclopropyl moiety at the 2′-position restricts conformational mobility of the acyclic phosphonate chain and a highly potent, specific, and selective anti-HBV activity is obtained.[7] Until now, there are no phosphonate nucleosides with a cyclic sugar moiety available for antiviral therapy. A few cyclic phosphonate nucleosides have been described with potent antiviral activity. The D-d4AP nucleoside was described by Kim et al. in 1991, which shows potent anti-HIV activity (EC_{50}) of 0.6–2 μM with an excellent resistance profile, unfortunately, commensurate with mitochondrial toxicity.[8–10] D-2′Fd4AP (Figure 1) is a somewhat less active compound (EC_{50}: 12 μM) but with an excellent resistance profile.[10,11] PMDTA and PMDTT (Figure 1) were described as selective anti-HIV-1/HIV-2 phosphonate nucleosides



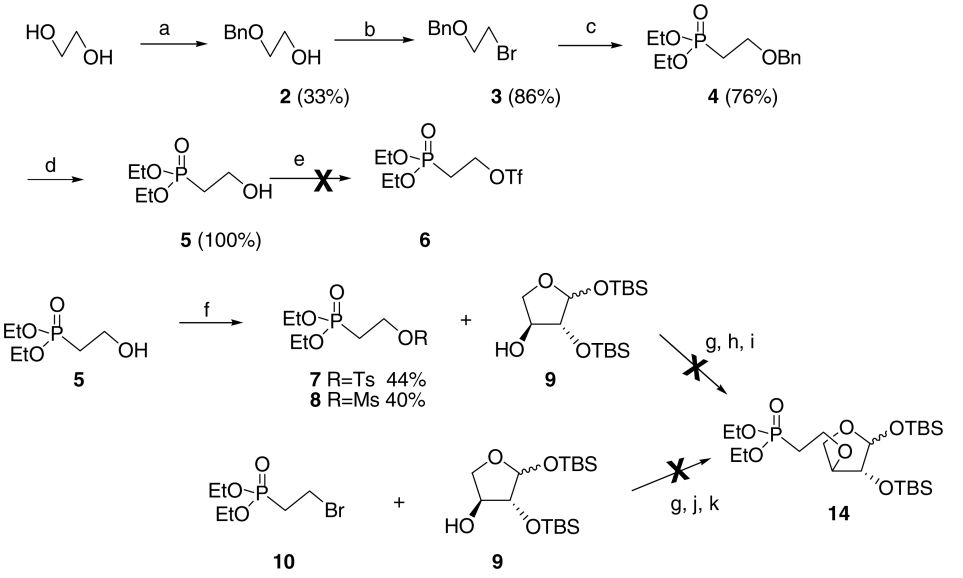
1a X = OH, B = adenin-9-yl
1b X = OH, B = thymin-1-yl
1c X = H, B = adenin-9-yl
1d X = H, B = thymin-1-yl

FIGURE 2 Structure of target nucleoside phosphonates.

with an activity of 2.5 μM and 6.6 μM respectively (EC_{50} values),[12] while no cytotoxicity was observed at the highest concentration tested. PMDTA has a phosphonomethyl moiety at the 3′-position of the furanose ring and no substituent at the 4′-position. The absence of a 4′-hydroxymethyl group avoids problems of steric hindrance during phosphorylation reaction by kinases. In order to investigate the importance of the stereochemistry in the 1′- and 3′-position of PMDTA, compound IVa and IVb, the isomeric analogs of PMDTA, were synthesized and evaluated (Figure 1). However, none of these compounds showed activity in an HIV-assay.[13] In this study, we would like to keep the L-threosyl nucleoside scaffold intact and pay specific attention to the 3′-phosphonate linkage. Therefore, we have synthesized a series of 3′-*O*-phosphonoethyl modified analogs (**1a-1d**) of PMDTA and PMDTT (Figure 2).

RESULT AND DISCUSSION

As shown in Scheme 1, diethylphosphonoethanol **5** was synthesized starting from ethylene glycol. Unfortunately, by reaction of diethylphosphonoethanol **5** with trifluoromethanesulfonyl chloride using NaH as base, the formation of triflate **6** could not be observed. Therefore, the more stable tosylate **7** and mesylate **8** were synthesized by sulfonylation of the free hydroxyl group of **5**. However, reaction of the tosylate **7** or the mesylate **8** with **9** did not lead to the expected alkylation of the 3′-hydroxyl group of **9**. Likewise, using the less reactive bromide **10**, we were unable to observe the formation of compound **14**. The reason of the unsuccessful attempts could be the β-elimination reaction of **7**, **8** and **10** under basic condition to give rise to the α, β-unsaturated phosphonate. As shown in Scheme 2, an alternative strategy was used by first introducing the mono-protected ethylene glycol chain to the 3′-oxygen position of L-threosyl sugar moiety, followed by introducing the phosphonate function. The nucleosides **1a-d** were synthesized starting from 1,2-di-*O*-*tert*-butyldimethylsilyl-L-threose (**9**) (Scheme 2).[12] Reaction of 3′-hydroxyl group of compound **9** with the triflate of monobenzylglycol using NaH in THF gave compound **11**. Removal

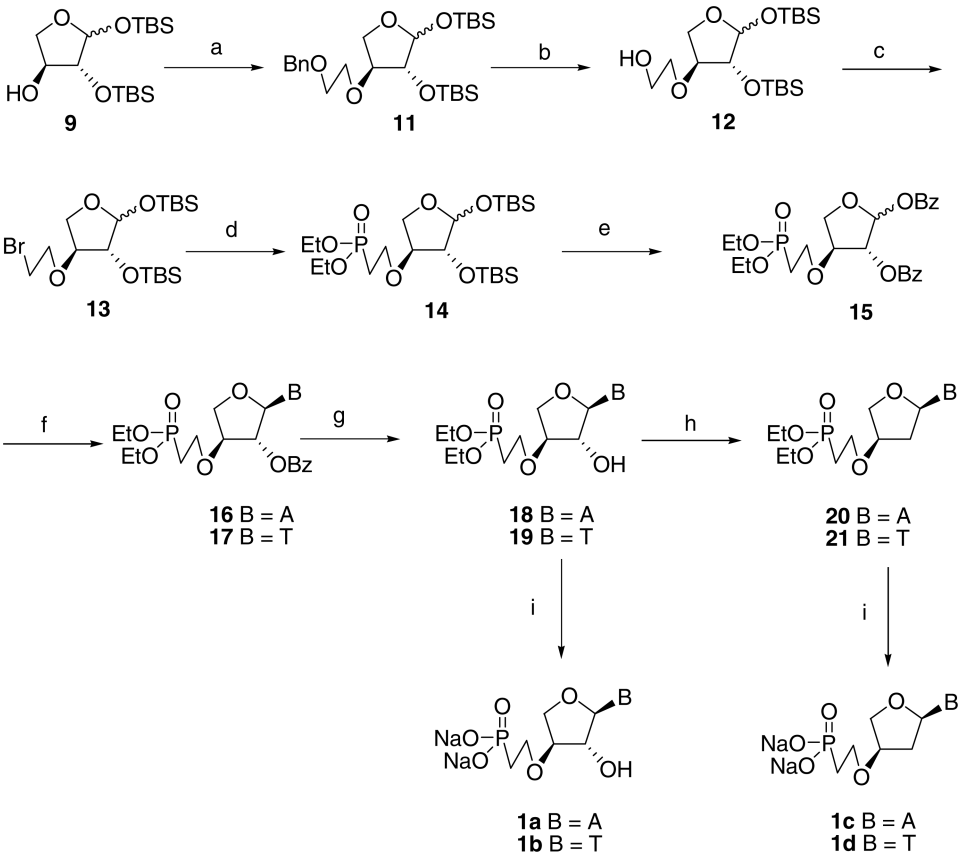


SCHEME 1 (a) NaH, BnBr, DMF-THF; (b) NBS, PPh_3, DCM; (c) Triethylphosphite, 165–170°C; (d) H_2, Pd-C (10%), EtOH; (e) trifluoromethanesulfonylchloride, NaH, diethyl ether; (f) TsCl or MsCl, TEA, DMAP, DCM; (g) NaH, THF; (h) ^{t}BuLi, THF; (i) ^{t}BuOK, THF; (j) Ag_2CO_3, Celite, DCM; (k) Ag_2O, DCM.

of the benzyl group of **11** by hydrogenation with 10% Pd-C afforded compound **12**. The free hydroxyl group of **12** was converted into bromine with NBS and PPh_3 to give compound **13**. The phosphonate function was introduced by the Arbuzov reaction of **13** with triethylphosphite to give **14**. The two silyl protecting groups of **14** were removed and replaced with two benzoyl protecting groups. The presence of a 2′-*O*-benzoyl group allows selective introduction of the base moiety in the α-configuration. The nucleobase adenine and thymine were introduced after silylation and using $SnCl_4$ as Lewis catalyst (giving **16** and **17**). Deprotection of **16** and **17** was done in two steps, firstly, removal of the benzoyl protecting groups with ammonia in methanol (yielding **18** and **19**) and, secondly, hydrolysis of the diethyl protecting groups with TMSI at 0°C (giving **1a** and **1b**). To obtain the 2′-deoxygenated ananlogues, the 2′-hydroxyl group of **18** and **19** was removed by Barton deoxygenation,[14] giving **20** and **21**. Hydrolysis of the phosphonate ester function of **20** and **21** was carried out with TMSI at 0°C. After purification by silica gel chromatography, reverse phase C_{18} HPLC and Dowex-sodium ion-exchange resin, nucleoside phosphonates **1c** and **1d** were obtained.

BIOLOGICAL RESULTS

Phosphonate nucleosides **1a**, **1b**, **1c**, and **1d**, in their sodium form, were evaluated in vitro for their cytotoxicity in MT4 cell-line and for their activity



SCHEME 2 (a) triflate of monobenzylglycol, NaH, THF; (b) Pd/C (10%), H_2, ethanol; (c) N-bromosuccinimide, PPh_3, CH_2Cl_2; (d) triethylphosphite, refluxed; (e) (1) TFA/H_2O; (2) BzCl, pyridine; (f) $SnCl_4$, A^{Bz} or T(Si), MeCN; (g) saturated NH_3 in MeOH; (h) (1) phenyl(chloro)thionocarbonate, DMAP, MeCN; (2) Bu_3SnH, AIBN, toluene; (i) (1) TMSI, CH_2Cl_2; (2) reverse phase C_{18} HPLC, Dowex-Na^+.

against HIV and HCV. PMDTT was used as a reference compound for anti-HIV activity,[12] and 2′-*C*-Me-A was used as a reference compound for anti-HCV activity.[15] None of the compounds shows activity against HIV and HCV as well as cytotoxicity at the highest concentration tested (250 μM; see Table 1).

CONCLUSION

A synthetic scheme has been developed for the synthesis of 3′-*O*-phosphonoethyl-L-threosyl nucleosides (**1a** and **1b**) as well as their 2′-deoxy analogs (**1c**, **1d**). Replacement of the methyl group in the 3′-*O*-phosphonomethyl group of PMDTA with an ethyl congener results in loss of biological activity. The reason for the loss of activity may be that these

TABLE 1 Summary of biological activities tested for compounds **1a**, **1b**, **1c**, **1d**

Compound	HCV	HIV	MT-4
	EC_{50}[a] (μM)	EC_{50}[a] (μM)	CC_{50}[b] (μM)
1a	>250	>250	>250
1b	>250	>250	>250
1c	>250	>250	>250
1d	>250	140	>250
PMDTT	—	6.59	>343
2′-C-Me-A	0.256	—	—

[a]EC_{50} = 50% effective concentration, or concentration required to protect 50% of the cells against viral cytopathicity.

[b]CC_{50} = 50% cytotoxic concentration, or concentration reducing the number of viable cells by 50%.

compounds are poor substrates for kinases, and therefore fail to be further converted into their metabolic diphosphate form.

EXPERIMENTAL SECTION

For all reactions, analytical grade solvents were used. All moisture-sensitive reactions were carried out in oven-dried glassware (135°C) under a nitrogen atmosphere. Anhydrous THF was refluxed over sodium/benzophenone and distilled. A Varian Unity 500 MHz spectrometer and a 300 MHz Varian Gemini apparatus were used for ^{1}H, ^{13}C, and ^{31}P NMR; TMS was used as internal reference for all ^{1}H NMR. Exact mass measurements were performed on a guadrupole time-of-flight mass spectrometer (Q-Tof -2, Micromass, Manchester, UK) equipped with a standard electrospray-ionization (EI) interface; samples were infused in CH_3CN/H_2O (1:1) at 3 μL/min. 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) stain. Column chromatography was performed on ICN silica gel 63–200, 60 Å. For the sake of clarity, NMR signals of sugar protons and carbons are indicated with a prime, and signals of base protons and carbons are given without a prime.

1,2-Di-*O*-*tert*-butyldimethylsilyl-3-*O*-(2-benzyloxyethyl)-L- threose (11)

To a suspension of NaH (60% dispersion in mineral oil, 228 mg, 5.7 mmol) in 5 mL of dried THF was added dropwise 1,2-Di-*O*-*tert*-butyldimethylsilyl-L-threose (**9**) (414 mg, 1.19 mmol) in 5 mL of dried THF at −20°C under nitrogen. The stirred solution was slowly warmed to room temperature and maintained for 10 minutes, then cooled to −78°C and the

solution of the triflate of 2-benzylglycol (0.94 g, 3.31 mmol) generated in situ in 5 mL of dried THF was added dropwise. The reaction mixture was slowly warmed to room temperature and continuously stirred overnight. The reaction was quenched with saturated $NaHCO_3$ and concentrated. The residue was partitioned between H_2O and EtOAc. 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 (n-Hexane:EtOAc = 19:1) to afford **11** (462 mg, 0.952 mmol, 80%) as a light yellow oil. Data for **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.07–0.09 (m, 24H, $SiCH_3$), 0.89–0,90 (m, 36H, CH_3), 3.53–3.76 (m, 10H, (OCH_2, 8H), (C(3′)H, 2H)), 3.82–3.93 (m, 2H, C(4′)H_a), 4.02–4.19 (m, 4H, (C(4′)H_b, 2H), (C(2′)H, 2H)), 4.56 (s, 4H, $BnCH_2O$), 5.11 (s, 1H, C(1′)H), 5.12 (d, J = 3.1 Hz, 1H, C(1′)H), 7.27–7.35 (m, 10H, Ar H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C -5.17 ($SiCH_3$), -5.01 ($SiCH_3$), -4.88 ($SiCH_3$), −4.75 ($SiCH_3$), −4.60 ($SiCH_3$), −4.45 ($SiCH_3$), −4.26 ($SiCH_3$), 17.88 ($C(CH_3)_3$), 18.00 ($C(CH_3)_3$), 18.11 ($C(CH_3)_3$), 25.71 ($C(CH_3)_3$), 25.74 ($C(CH_3)_3$), 25.76 ($C(CH_3)_3$), 25.82 ($C(CH_3)_3$), 69.09 (OCH_2), 69.47 (OCH_2), 69.54 (OCH_2), 69.61 (OCH_2), 69.92 (C-4′), 70.51 (C-4′), 73.27 ($BnCH_2O$), 73.31 ($BnCH_2O$), 78.93 (C-2′), 82.84 (C-2′), 83.79 (C-3′), 86.06 (C-3′), 97.30 (C-1′), 104.09 (C-1′), 127.59 (aroma-C), 127.67 (aroma-C), 127.71 (aroma-C), 128.31 (aroma-C), 128.35 (aroma-C), 138.25 (aroma-C); exact mass calcd. for $C_{25}H_{47}O_5Si_2$ $[M+H]^+$ 483.296, found 483.297.

1,2-Di-*O*-*tert*-butyldimethylsilyl-3-*O*-(2-hydroxyethyl)-L- threose (12)

Compound **11** (462 mg, 0.957 mmol) and palladium-carbon (10%, 102 mg, 0.0957 mmol) in 4 mL of degassed dry ethanol was hydrogenated for 2.5 hours. The palladium-carbon was filtered through a celite pad, the volatiles were evaporated and the residue was purified by chromatography on a silica gel column (n-Hexane:EtOAc = 6:1) to afford **12** (315 mg, 0.803 mmol, 84%) as a colorless oil. It was not identified at this stage which compound represents which isomer (α or β). The mixture of **12a** and **12b** was used in the next step reaction). Data for **12a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.04–0.10 (m, 12H, $SiCH_3$), 0.87 (s, 9H, CH_3), 0.88 (s, 9H, CH_3), 2.55 (br, 1H, OH), 3.56–3.80 (m, 5H, (OCH_2, 2H), (CH_2OH, 2H), (C(3′)H, 1H)), 3.92 (dd, $J_1 = 9.4$ Hz, $J_2 = 3.4$ Hz, 1H, C(4′)H_a), 4.07–4.16 (m, 2H, C(4′)H_b, C(2′)H), 5.13 (s, 1H, C(1′)H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C −5.11 ($SiCH_3$), −4.76 ($SiCH_3$), −4.64 ($SiCH_3$), −4.50 ($SiCH_3$), 17.97 ($C(CH_3)_3$), 25.71 ($C(CH_3)_3$), 61.77 (CH_2OH), 70.53 (OCH_2), 71.66 (C-4′), 81.07 (C-2′), 85.27 (C-3′), 104.12 (C-1′); exact mass calcd. for $C_{18}H_{40}O_5Si_2Na_1$ $[M+Na]^+$ 415.231, found 415.229. Data for **12b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.05–0.08 (m, 12H, $SiCH_3$), 0.88 (s, 18H, CH_3), 2.25 (br, 1H, OH), 3.50–3.69 (m, 5H, (CH_2OH, 2H), (OCH_2, 2H), (C(3′)H, 1H)), 3.99–4.07 (m, 2H,

C(4′)H), 4.12–4.18 (m, 1H, C(2′)H), 5.11 (d, J = 11.5 Hz, 1H, C(1′)H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C −5.05 ($SiCH_3$), −4.93 ($SiCH_3$), −4.48 ($SiCH_3$), −4.43 ($SiCH_3$), 17.97 ($C(CH_3)_3$), 18.06 ($C(CH_3)_3$), 25.70 ($C(CH_3)_3$), 25.77 ($C(CH_3)_3$), 62.00 (CH_2OH), 68.85 (OCH_2), 71.54 (C-4′), 78.90 (C-2′), 83.67 (C-3′), 97.22 (C-1′); exact mass calcd. for $C_{18}H_{40}O_5Si_2Na_1$ $[M+Na]^+$ 415.231, found 415.233.

1,2-Di-*O*-*tert*-butyldimethylsilyl-3-*O*-(2-bromoethyl)-L-threose (13)

A solution of PPh_3 (0.393 g, 1.5 mmol) in dried CH_2Cl_2 (3 mL) was added dropwise to a suspension of N-bromosuccinimide (0.267 g, 1.5 mmol) in dried CH_2Cl_2 (4 mL) at −78°C under nitrogen in the darkness. Stirring was continued until the suspension was completely dissolved (approx. 10min). A solution of compound **12** (0.491 g, 1.25 mmol) in dried CH_2Cl_2 (3 mL) was dropwise added, the cooling bath was removed and stirring was continued for 1 hour. The reaction solution was poured into aqueous NH_4Cl solution; the organic layer was washed with water and brine, dried over Na_2SO_4, and the volatiles were evaporated in vacuo. The residue was purified by chromatography on a silica gel column (CH_2Cl_2: n-Hexane = 1:2 and 1:1) to afford **13** (358 mg, 0.787 mmol, 63%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.08–0.10 (m, 12H, $SiCH_3$), 0.89 (s, 18H, CH_3), 3.40 (t, J = 6.3 Hz, 2H, $BrCH_2$), 3.72–3.91 (m, 4H, (OCH_2, 2H), (C(3′)H, 1H), ($C(4')H_a$, 1H)), 4.04–4.14 (m, 2H, $C(4')H_b$, C(2′)H), 5.10–5.13(m, 1H, C(1′)H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C -5.18 ($SiCH_3$), −5.04 ($SiCH_3$), −4.89 ($SiCH_3$), −4.77 ($SiCH_3$), −4.59 ($SiCH_3$), −4.46 ($SiCH_3$), −4.41 ($SiCH_3$), −4.28 ($SiCH_3$), 17.86 ($C(CH_3)_3$), 17.99 ($C(CH_3)_3$), 18.07 ($C(CH_3)_3$), 25.65 ($C(CH_3)_3$), 25.69 ($C(CH_3)_3$), 25.72 ($C(CH_3)_3$), 25.80 ($C(CH_3)_3$), 30.01 ($BrCH_2$), 30.21 ($BrCH_2$), 68.74 (C-4′), 69.95 (C-4′), 70.29 (OCH_2), 70.32 (OCH_2), 78.92 (C-2′), 82.84 (C-2′), 83.72 (C-3′), 85.98 (C-3′), 97.23 (C-1′), 103.96 (C-1′); exact mass calcd. for $C_{18}H_{39}BrO_4Si_2Na_1$ $[M+Na]^+$ 477.147, found 477.148.

1,2-Di-*O*-*tert*-butyldimethylsilyl-3-*O*-(diethylphosphonoethyl)-L-threose (14)

A mixture of **13** (0.358 g, 0.786 mmol) and triethylphosphite (0.384 g, 2.31 mmol) was heated to 160°C under nitrogen and refluxed for 8 hours. The unreacted triethylphosphite was removed by vacuum distillation. The residue was purified by chromatography on a silica gel column (n-Hexane:EtOAc = 2:1 and 1:1) to afford **14** (352 mg, 0.686 mmol, 87%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.06–0.09 (m, 12H, $SiCH_3$), 0.88–0.89 (m, 18H, CH_3), 1.29 (t, J = 6.9 Hz, 6H, OCH_2CH_3), 2.03–2.14 (m, 2H, PCH_2), 3.64–3.85 (m, 3H, (OCH_2, 2H), (C(3′)H, 1H)), 3.99–4.11 (m, 7H, (OCH_2CH_3, 4H), (C(4′)H, 2H), (C(2′)H, 1H)), 5.09 (m, 1H, C(1′)H);

^{13}C NMR (75 MHz, $CDCl_3$) δ_C −5.21 ($SiCH_3$), −5.06 ($SiCH_3$), −4.94 ($SiCH_3$), −4.81($SiCH_3$), −4.72 ($SiCH_3$), −4.64 ($SiCH_3$), −4.48 ($SiCH_3$), −4.32 ($SiCH_3$), 16.36 (OCH_2CH_3), 16.44 (OCH_2CH_3), 17.84 ($C(CH_3)_3$), 17.97 ($C(CH_3)_3$), 18.05 ($C(CH_3)_3$), 25.66 ($C(CH_3)_3$), 25.70 ($C(CH_3)_3$), 25.77 ($C(CH_3)_3$), 26.30 ($C(CH_3)_3$), 26.44 ($C(CH_3)_3$), 28.15 (d, $J_{P,C}$ = 138.7 Hz, PCH_2), 28.29 (d, $J_{P,C}$ = 138.6 Hz, PCH_2), 61.53 (OCH_2), 61.61 (OCH_2), 61.69 (OCH_2), 61.78 (OCH_2), 63.90 (OCH_2CH_3), 64.29 (OCH_2CH_3), 68.81 (C-4′), 70.31 (C-4′), 78.86 (C-2′), 82.77 (C-3′), 83.44 (C-2′), 85.78 (C-3′), 97.21 (C-1′), 104.02 (C-1′); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ_P 28.19; exact mass calcd. for $C_{22}H_{49}O_7P_1Si_2Na_1$ $[M+Na]^+$ 535.265, found 535.265.

1,2-Di-*O*-benzoyl-3-*O*-(diethylphosphonoethyl)-L-threose (15)

Compound **14** (0.89 g, 1.735 mmol) was dissolved in a solution of trifluoroacetic acid/H_2O (2.8 mL, V/V = 3:1) at 0°C. The reaction mixture was allowed to stand for 3 hours at room temperature. Saturated $NaHCO_3$ (5 mL) was added at 0°C, followed by adding solid $NaHCO_3$ to neutralize the TFA. The reaction mixture was extracted with $CHCl_3$ (15 mL × 5), the organic layer was dried over Na_2SO_4, and the volatile was evaporated in vacuo. The residue was purified by chromatography on a silica gel column (CH_2Cl_2: MeOH = 19:1 and 9:1) to give 3-*O*-diethylphosphonoethyl-L-threose (0.43 g, 1.51 mmol, 87%) as a colorless oil. To the solution of 3-*O*-diethylphosphonoethyl-L-threose (0.43 g, 1.51 mmol) in dry pyridine (6 mL) was added dropwise BzCl (527 μL, 4.54 mmol) at 0°C. The reaction mixture was slowly warmed to room temperature and stirred overnight. The reaction mixture was concentrated and co-evaporated with 10 mL of toluene two times in vacuo. The residue was partitioned between water (10 mL) and EtOAc (50 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 (n-Hexane:EtOAc = 3:1) to give **15** (0.56 g, 1.14 mmol, 76%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.24–1.31 (m, 12H, CH_3), 2.07–2.23 (m, 4H, PCH_2), 3.75–3.90 (m, 3H, OCH_2), 3.92–4.16 (m, 11H, (OCH_2, 1H), (OCH_2CH_3, 8H), (C(3′)H, 2H)), 4.22–4.25 (m, 1H, C(4′)H), 4.36–4.53 (m, 3H, C(4′)H), 5.50 (t, J = 4.4 Hz, 1H, C(2′)H), 5.55 (s, 1H, C(2′)H), 6.54 (s, 1H, C(1′)H), 6.73 (d, J = 4.5 Hz, 1H, C(1′)H), 7.30–7.62 (m, 12H, Bz Ar-H), 7.88–8.08 (m, 8H, Bz Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 16.36 (CH_3), 16.44 (CH_3), 26.15 (d, $J_{P,C}$ = 139.6 Hz, PCH_2), 26.21 (d, $J_{P,C}$ = 139.5 Hz, PCH_2), 61.69 (d, $J_{P,C}$ = 11.5 Hz, OCH_2), 61.77 (OCH_2), 64.18 (OCH_2CH_3), 64.48 (OCH_2CH_3), 70.82 (C-4′), 73.48 (C-4′), 77.75 (C-2′), 80.29 (C-2′), 80.90 (C-3′), 82.19 (C-3′), 95.63 (C-1′), 100.18 (C-1′), 128.34 (aroma-C), 128.37 (aroma-C), 128.45 (aroma-C), 128.50 (aroma-C), 128.56 (aroma-C), 128.95 (aroma-C), 129.48 (aroma-C), 129.57 (aroma-C), 129.70 (aroma-C), 129.73 (aroma-C), 129.85 (aroma-C), 129.97 (aroma-C), 133.33 (aroma-C). 133.47 (aroma-C). 133.51

(aroma-C). 133.69 (aroma-C). 164.96 (OBz, CO), 165.09 (OBz, CO), 165.29 (OBz, CO), 165.34 (OBz, CO); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ_P 27.95, 27.97; exact mass calcd. for $C_{24}H_{30}O_9P_1$ $[M+H]^+$ 493.163, found 493.163.

1-(Adenin-9-yl)-2-*O*-benzoyl-3-*O*-(diethylphosphonoethyl)-L-threose (16)

$SnCl_4$ (95 μL, 0.812 mmol) was added dropwise to a solution of **15** (100 mg, 0.203 mmol) and N^6-benzoyladenine (97 mg, 0.406 mmol) in 4 mL of dry CH_3CN at room temperature under N_2. The reaction mixture was allowed to stir for 3 hours. Then the reaction was quenched with aqueous NH_4Cl and concentrated. The residue was partitioned between H_2O (10 mL) and $CHCl_3$ (50 mL × 3). 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 = 29:1, 19:1 and 9:1) to give **16** (86 mg, 0.168 mmol, 83%) as an amorphous solid. ^{1}H NMR (300 MHz, MeOH-d_4) δ_H 1.28–1.32 (m, 6H, CH_3), 2.11–2.19 (m, 2H, PCH_2), 3.88–3.94 (m, 2H, OCH_2), 4.04–4.12 (m, 4H, OCH_2CH_3), 4.45–4.46 (m, 3H, (C(4′)H, 2H), (C(3′)H, 1H)), 5.82 (s, 1H, C(2′)H), 6.44(s, 1H, C(1′)H), 7.52–7.67 (m, 3H, Ar H), 8.06–8.08 (m, 2H, Ar H), 8.37 (s, 1H, A C(2)H), 8.53 (s, 1H, A C(8)H); ^{13}C NMR (75 MHz, MeOH-d_4) δ_C 15.27 (CH_3), 15.35 (CH_3), 24.87 (d, $J_{P,C}$ = 140.0 Hz, PCH_2), 61.99 (OCH_2CH_3), 62.08 (OCH_2CH_3), 63.73 (d, $J_{P,C}$ = 3.3 Hz, OCH_2), 73.53 (C-4′), 80.48 (C-2′), 81.63 (C-3′), 88.62 (C-1′), 118.69 (A C(5)), 128.44 (aroma-C), 128.73 (aroma-C), 129.47 (aroma-C), 133.66 (aroma-C), 142.10 (A C(8)), 145.84 (A C(4)), 148.43 (A C(2)), 151.48 (A C(6)), 165.25 (OBz, CO); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ_P 27.47; exact mass calcd. for $C_{22}H_{29}N_5O_7P_1$ $[M+H]^+$ 506.180, found 506.180.

1-(Thymin-1-yl)-2-*O*-benzoyl-3-*O*-(diethylphosphonoethyl)-L-threose (17)

Thymine (192 mg, 1.523 mmol), ammonium sulfate (4.8 mg, 0.036 mmol) and 3 mL of HMDS were added to a dried flask. The mixture was refluxed overnight under N_2. HMDS was removed in vacuo. To the flask with the residue was added a solution of compound **15** (300 mg, 0.609 mmol) in 10 mL of dried CH_3CN, followed by dropwise adding $SnCl_4$ (214 μL, 1.827 mmol) at room temperature under N_2. The reaction mixture was allowed to stir for 4 hours. The reaction was quenched with saturated NH_4Cl and concentrated to a small volume. The residue was partitioned between H_2O (10 mL) and EtOAc (50 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 (n-Hexane:EtOAc = 1:3 and CH_2Cl_2: MeOH = 29:1) to afford **17** (286 mg, 0.576 mmol) as a colorless

amorphous solid in 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.30 (t, J = 6.9 Hz, 6H, CH_3), 1.94 (s, 3H, T CH_3), 2.05–2.16 (m, 2H, PCH_2), 3.85–3.98 (m, 2H, OCH_2), 4.07–4.17 (m, 6H, (OCH_2CH_3, 4H), (C(4′)H_a, 1H), (C(3′)H, 1H)), 4.33–4.36 (d, J = 10.7 Hz, 1H, C(4′)H_b), 5.35 (s, 1H, C(2′)H), 6.23 (s, 1H, C(1′)H), 7.43–7.62 (m, 4H, (Ar H, 3H), (T C(6)H, 1H)), 8.01 (d, J = 7.6 Hz, 2H, Ar H), 9.32 (br, 1H, T NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 12.50 (T CH_3), 16.38 (CH_3), 16.46 (CH_3), 26.03 (d, $J_{P,C}$ = 140.1 Hz, PCH_2), 61.80 (d, $J_{P,C}$ = 4.8 Hz, OCH_2), 61.95 (OCH_2), 63.81 (OCH_2), 73.08 (C-4′), 80.19 (C-2′), 81.43 (C-3′), 89.08 (C-1′), 110.84 (T C(5)), 128.56 (aroma-C), 128.67 (aroma-C), 129.87 (aroma-C), 133.79 (T C(6)), 136.16 (aroma-C), 150.37 (T C(2)), 163.89 (T C(4)), 165.19 (BzO, CO); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ_P 27.35; exact mass calcd. for $C_{22}H_{30}N_2O_9P_1$ $[M+H]^+$ 497.169, found 497.169.

1-(Adenin-9-yl)-3-*O*-(diethylphosphonoethyl)-L-threose (18)

A solution of **16** (142 mg, 0.281 mmol) in methanol saturated with ammonia (3 mL) was stirred at room temperature overnight. The mixture was concentrated, and the residue was purified by chromatography on a silica gel column (CH_2Cl_2: MeOH = 19:1 and 9:1) to afford **18** (97 mg, 0.241 mmol) as a white powder in 86% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.24–1.30 (m, 6H, CH_3), 1.95–2.08 (m, 2H, PCH_2), 3.65–3.81 (m, 2H, OCH_2), 4.00–4.15 (m, 5H, (OCH_2, 4H), (C(3′)H, 1H)), 4.24 (dd, J_1 = 9.7 Hz, J_2 = 3.1 Hz, 1H, C(4′)H_a), 4.30 (dd, J_1 = 9.7 Hz, J_2 = 4.9 Hz, 1H,C(4′)H_b), 4.64 (s, 1H, C(2′)H), 6.01 (d, J = 2.7 Hz, 1H, C(1′)H), 6.20 (br s, 2H, NH_2), 8.06 (s, 1H, A C(2)H), 8.27 (s, 1H, A C(8)H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 16.34 (OCH_2CH_3), 16.41 (OCH_2CH_3), 25.98 (d, $J_{P,C}$ = 139.6 Hz, PCH_2), 61.76 (d, $J_{P,C}$ = 13.1 Hz, OCH_2), 61.85 (OCH_2), 63.84 (OCH_2), 72.78 (C-4′), 77.44 (C-2′), 83.50 (C-3′), 91.12 (C-1′), 119.61 (A C(5)), 139.12 (A C(8)), 149.09 (A C(4)), 152.64 (A C(2)), 155.51 (A C(6)); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ_P 28.23; exact mass calcd. for $C_{15}H_{25}N_5O_6P_1$ $[M+H]^+$ 402.154, found 402.153.

1-(Thymin-1-yl)-3-*O*-(diethylphosphonoethyl)-L-threose (19)

A solution of **17** (153 mg, 0.309 mmol) in methanol saturated with ammonia (3 mL) was stirred at room temperature overnight. The mixture was concentrated, and the residue was purified by chromatography on a silica gel column (CH_2Cl_2: MeOH = 29:1 and 9:1) to afford **19** (107 mg, 0.272 mmol) as a white powder in 88% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.29 (t, J = 7.0 Hz, 6H, CH_3), 1.91 (s, 3H, T CH_3), 1.96–2.02 (m, 2H, PCH_2), 3.65–3.76 (m, 2H, OCH_2), 4.01–4.13 (m, 5H, (OCH_2CH_3, 4H), (C(4′)H_a, 1H)), 4.28–4.34 (m, 3H, (C(4′)H_b, 1H), (C(3′)H, 1H), (C(2′)H, 1H)), 5.42 (br s, 1H, OH), 5.80 (s, 1H, C(1′)H), 7.37 (s, 1H, T(C6)H), 10.36

(br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 12.43 (T CH_3), 16.39 (CH_3), 16.47 (CH_3), 26.03 (d, $J_{P,C}$ = 139.7 Hz, PCH_2), 61.80 (OCH_2CH_3), 61.88 (OCH_2CH_3), 63.29 (OCH_2), 74.11 (C-4′), 78.57 (C-2′), 82.74 (C-3′), 93.16 (C-1′), 109.50 (C(5)), 136.48 (C(6)), 150.99 (C(2)), 164.52 (C(4)); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ_P 27.60; exact mass calcd. for $C_{15}H_{25}N_2O_8P_1Na_1$ $[M+Na]^+$ 415.125, found 415.124.

1-(Adenin-9-yl)-2-deoxy-3-*O*-(diethylphosphonoethyl)-L-threose (20)

To a solution of PhOC(S)Cl (70 μL, 0.506 mmol) and DMAP (185 mg, 1.516 mmol) in dried MeCN (8 mL) was added compound **18** (135 mg, 0.337 mmol) at room temperature under N_2. The reaction mixture was stirred for 3 hours. The mixture was concentrated at room temperature, and the residue was purified by chromatography on a silica gel column (CH_2Cl_2: MeOH = 29:1 and 19:1) to give 1-(adenin-9-yl)-2-*O*-phenoxythionocarbonyl-3-*O*-(diethylphosphonoethyl)-L-threose as a white amorphous foam in 63% yield. To a solution of 1-(adenin-9-yl)-2-*O*-phenoxythionocarbonyl-3-*O*-(diethylphosphonoethyl)-L-threose in dry and degassed toluene (10 mL) was added AIBN (18 mg, 0.106 mmol) and tributyltin hydride (115 μL, 0.428 mmol) under N_2. The reaction mixture was refluxed for 8 hours and concentrated in vacuo. The residue was purified by chromatography on a silica gel column (CH_2Cl_2: MeOH = 19:1 and 9:1) to give compound **20** (75 mg, 0.194 mmol) as a colorless oil in 57% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.24–1.30 (m, 6H, CH_3), 1.95–2.08 (m, 2H, PCH_2), 2.51–2.67 (m, 2H, C(2′)H), 3.57–3.76 (m, 2H, OCH_2), 4.00–4.11 (m, 5H, (OCH_2, 4H), (C(3′)H, 1H)), 4.25–4.28 (m, 2H, C(4′)H), 6.06 (br s, 2H, A NH_2), 6.42 (dd, J_1 = 7.3 Hz, J_2 = 2.1 Hz, 1H, C(1′)H), 8.26 (s, 1H, A C(2)H), 8.32 (s, 1H, A C(8)H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 16.36 (OCH_2CH_3), 16.44 (OCH_2CH_3), 26.02 (d, $J_{P,C}$ = 139.8 Hz, PCH_2), 38.45 (C-2′), 61.72 (OCH_2), 61.81 (OCH_2), 63.49 (OCH_2), 73.94 (C-4′), 78.39 (C-3′), 83.57 (C-1′), 119.51 (A C(5)), 139.58 (A C(8)), 149.63 (A C(4)), 152.96 (A C(2)), 155.49 (A C(6)); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ_P 27.84; exact mass calcd. for $C_{15}H_{25}N_5O_5P_1$ $[M+H]^+$ 386.159, found 386.158.

1-(Thymin-1-yl)-2-deoxy-3-*O*-(diethylphosphonoethyl)-L-threose (21)

This compound was prepared as described for **20**, using **19** (131 mg, 0.334 mmol) as starting material. Column chromatographic purification (CH_2Cl_2: MeOH = 29:1) gave compound **21** (100 mg, 0.265 mmol) as a colorless oil in 79% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.30 (dd, J_1 = 7.0 Hz, J_2 = 1.6 Hz, 3H, CH_3), 1.32 (dd, J_1 = 7.0 Hz, J_2 = 1.6 Hz, 3H, CH_3), 1.92 (d, J = 0.9 Hz, 3H, T CH_3), 2.01–2.16 (m, 3H, (PCH_2, 2H), (C(2′)H_a,

1H)), 2.44–2.54 (m, 1H, C(2′)H_b), 3.62–3.74 (m, 2H, OCH_2), 3.82 (dd, J_1 = 10.2 Hz, J_2 = 3.5 Hz, 1H, C(4′)H_a), 4.06–4.18 (m, 5H, (C(4′)H_b, 1H), (OCH_2CH_3, 4H)), 4.27 (d, J = 9.3 Hz, 1H, C(3′)H), 6.20 (dd, J_1 = 7.8 Hz, J_2 = 2.4 Hz, 1H, C(1′)H), 7.50 (d, J = 1.1 Hz, 1H, T C(6)H), 9.4 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 12.54 (T CH_3), 16,38 (CH_3), 16.45 (CH_3), 26.08 (d, $J_{P,C}$ = 139.9 Hz, PCH_2), 38.18 (C-2′), 61.75 (OCH_2CH_3), 61.83 (OCH_2CH_3), 63.04 (OCH_2CH_2P), 73.80 (C-4′), 77.91 (C-3′), 85.02 (C-1′), 110.12 (T C(5)), 136.51 (T C(6)), 150.69 (T C(2)), 164.11 (T C(4)); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ_P 27.69; exact mass calcd. for $C_{15}H_{25}N_2O_7P_1Na_1$ $[M+Na]^+$ 399.129, found 399.127.

1-(Adenin-9-yl)-3-*O*-(phosphonoethyl)-L-threose Sodium Salt (1a)

To a solution of compound **18** (190 mg, 0.473 mmol) and Et_3N (665 μL, 4.73 mmol) in 20 mL of dry CH_2Cl_2 was added iodotrimethylsilane (515 μL, 3.787 mmol) at 0°C under nitrogen. The reaction mixture was continuously stirred for 4 hours at 0°C. The reaction was quenched with 0.5 M TEAB solution. The mixture was concentrated in vacuo, and the residue was purified by chromatography on a silica gel column (CH_2Cl_2: MeOH = 2:1 and $CHCl_3$: MeOH: H_2O = 5:4:1) to give crude **1a**. Purification by HPLC using reverse phase C_{18} column (isocratic mobile phase: 1% MeCN and 99% H_2O) and ion exchange with Dowex-Na^+ resin offered **1a** (140 mg, 0.359 mmol) as a colorless solid after lyophilization in 76% yield. ^{1}H NMR (500 MHz, D_2O) δ_H 1.67–1.90 (m, 2H, PCH_2), 3.67–3.78 (m, 2H, OCH_2), 4.22 (s, 1H, C(3′)H), 4.36 (d, J = 3.1 Hz, 2H, C(4′)H), 4.71 (s, 1H, C(2′)H), 6.03 (s, 1H, C(1′)H), 8.13 (s, 1H, C(2)H), 8.20 (s, 1H, C(8)H); ^{13}C NMR (125 MHz, D_2O) δ_C 28.40 (d, $J_{P,C}$ = 128 Hz, PCH_2), 65.25 (OCH_2), 72.79 (C-4′), 77.17 (C-2′), 82.38 (C-3′), 89.57 (C-1′), 118.08 (A C(5)), 139.84 (A C(8)), 148.83 (A, C(4)), 152.16 (A, C(2)), 154.93 (A, C(6)); ^{31}P NMR (202.5 MHz, D_2O) δ_P 19.04; exact mass calcd. for $C_{11}H_{15}N_5O_6P_1$ $[M-H]^-$ 344.076, found 344.075.

1-(Thymin-1-yl)-3-*O*-(phosphonoethyl)-L-threose Sodium Salt (1b)

This compound was prepared as described for **1a**, using **19** (234 mg, 0.596 mmol) as starting material and iodotrimethylsilane (649 μL, 4.77 mmol). Compound **1b** (158 mg, 0.415 mmol) was obtained as a colorless solid after lyophilization in 69% yield: ^{1}H NMR (500 MHz, D_2O) δ_H 1.72–1.88 (m, 2H, PCH_2), 1.90 (d, J = 1.0 Hz, 3H, T-CH_3), 3.58–3.70 (m, 2H, OCH_2), 4.13 (d, J = 4.0 Hz, 1H, C(3′)H), 4.25 (dd, J_1 = 10.8 Hz, J_2 = 4.0 Hz, 1H, C(4′)H_a), 4.40 (d, J = 10.8 Hz, 1H, C(4′)H_b), 4.41 (s, 1H, C(2′)H), 5.81 (s, 1H, C(1′)H), 7.56 (d, J = 1.0 Hz, 1H, T C(6)H); ^{13}C NMR (125 MHz, D_2O) δ_C 11.19 (T CH_3), 28.68 (d, $J_{P,C}$ = 128 Hz, PCH_2), 65.21 (OCH_2), 73.09 (C-4′), 77.15 (C-2′), 81.85 (C-3′), 91.31 (C-1′), 109,66 (T C(5)), 137.53

(T C(6)), 151.15 (T, C(2)), 166.37 (T C(4)); ^{31}P NMR (202.5 MHz, D_2O) δ_P 18.37; exact mass calcd. for $C_{11}H_{16}N_2O_8P_1$ [M-H]$^-$ 335.064, found 335.062.

1-(Adenin-9-yl)-2-deoxy-3-*O*-(phosphonoethyl)-L-threose Sodium Salt (1c)

This compound was prepared as described for **1a**, using **20** (55 mg, 0.142 mmol) as starting material and iodotrimethylsilane (155 μL, 1.138 mmol). Compound **1c** (40 mg, 0.107 mmol) was obtained as a colorless solid after lyophilization in 75% yield: ^{1}H NMR (500 MHz, D_2O) δ_H 1.75–1.92 (m, 2H, PCH_2), 2.62 (d, J = 15.2 Hz, 1H, C(2′)H_a), 2.70 (ddd, J_1 = 15.2 Hz, J_2 = 7.4 Hz, J_3 = 5.6 Hz, 1H, C(2′)H_b), 3.62–3.74 (m, 2H, OCH_2), 4.11 (dd, J_1 = 10.5 Hz, J_2 = 4.1 Hz, 1H, C(4′)H_a), 4.33 (d, J = 10.5 Hz, 1H, C(4′)H_b), 4.46 (t, J = 4.7 Hz, 1H, C(3′)H), 6.37 (dd, J_1 = 5.4 Hz, J_2 = 1.7 Hz, 1H, C(1′)H), 8.19 (s, 1H, C(2)H), 8.33 (s, 1H, C(8)H); ^{13}C NMR (125 MHz, D_2O) δ_C 28.24 (d, $J_{P,C}$ = 128 Hz, PCH_2), 36.81 (C-2′), 64.43 (OCH_2), 73.69 (C-4′), 77.32 (C-3′), 83.96 (C-1′), 118.24 (A C(5)), 140.14 (A C(8)), 147.94 (A, C(4)), 152.10 (A, C(2)), 155,08 (A, C(6)); ^{31}P NMR (202.5 MHz, D_2O) δ_P 19.70; exact mass calcd. for $C_{11}H_{15}N_5O_5P_1$ [M-H]$^-$ 328.081, found 328.082.

1-(Thymin-1-yl)-2-deoxy-3-*O*-(phosphonoethyl)-L-threose Sodium Salt (1d)

This compound was prepared as described for **1a**, using **21** (127 mg, 0.337 mmol) as starting material and iodotrimethylsilane (367 μL, 2.698 mmol). Compound **1d** (50 mg, 0.137 mmol) was obtained as a colorless solid after lyophilization in 41% yield: ^{1}H NMR (500 MHz, D_2O) δ_H 1.80–1.89 (m, 2H, PCH_2), 1.90 (d, J = 1.0 Hz, 3H, T-CH_3), 2.25 (d, J = 15.2 Hz, 1H, C(2′)H_a), 2.53 (ddd, J_1 = 15.1 Hz, J_2 = 7.6 Hz, J_3 = 5.5 Hz, 1H, C(2′)H_b), 3.63–3.75 (m, 2H, OCH_2), 3.97 (dd, J_1 = 10.5 Hz, J_2 = 3.6 Hz, 1H, C(4′)H_a), 4.36 (t, J = 8.8 Hz, 1H, C(3′)H), 4.40 (d, J = 10.5 Hz, 1H, C(4′)H_b), 6.12 (dd, J_1 = 7.6 Hz, J_2 = 1.9 Hz, 1H, C(1′)H), 7.68 (d, J = 1.1 Hz, T C(6)H); ^{13}C NMR (125 MHz, D_2O) δ_C 11.26 (T CH_3), 28.57 (d, $J_{P,C}$ = 128 Hz, PCH_2), 36.82 (C-2′), 64.41 (OCH_2), 73.81 (C-4′), 77.02 (C-3′), 85.69 (C-1′), 109.85 (T C(5)), 137.89 (T C(6)), 151.24 (T C(2)), 166.36 (T C(4)); ^{31}P NMR (202.5 MHz, D_2O) δ_P 19.00; exact mass calcd. for $C_{11}H_{16}N_2O_7P_1$ [M-H]$^-$ 319.069, found 319.067.

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