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Prolinol-based nucleoside phosphonic acids: new isosteric conformationally flexible nucleotide analogues

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ABSTRACT

trans-4-Hydroxy-L-proline has been used as a starting material for the synthesis of prolinol-based nucleotide analogues with an *N*-phosphonomethyl moiety attached to the prolinol ring nitrogen atom. The synthetic methodology based on the inversion of configuration at both 1- and 4-position led to all diastereoisomeric *O*-protected 4-mesyloxyprolinol-*N*-phosphonates. Alkylation of nucleobases using the synthons in the L-series afforded the nucleotide analogues corresponding to α-L- and β-L-nucleotide. The NMR-based conformational study of these compounds in aqueous solution performed at two different pH values, showing either *N*-fully protonated or deprotonated forms, revealed the occurrence of the same mostly populated conformer in both cases. All final L-prolinol-based nucleoside phosphonic acids were tested for cytotoxic and antiviral properties, but no significant activity was found.

1. Introduction

Nucleoside phosphonic acids (NPAs) represent a promising group of nucleotide analogues with potential antiviral and/or cytostatic properties. Thus, several acyclic nucleoside phosphonic acids based drugs (e.g., Cidofovir, Hepsera, Tenofovir) are in clinical use for treatment of CMV-induced retinitis, hepatitis B, and HIV (Fig. 1).[1,2] Recently Gilead Sciences, Inc. reported[3] highly promising preclinical studies with a PMEG prodrug, the compound GS-9219 (6-*N*-cyclopropyl-PMEDAP derivative[4]) against leukaemia and non-Hodgkin's lymphoma.

These findings suggest that the search for novel phosphonate nucleotide analogues is highly desirable. NPAs are metabolically stable due to the presence of a phosphonate P–C linkage instead of a P–O phosphoester making these compounds resistant towards phosphomonoesterases and nucleotidases. Moreover, NPAs do not require the first intracellular phosphorylation step, which is essential for the antiviral effect of nucleoside drugs.[2]

The idea of nucleosides or nucleotides with a pyrrolidine ring is not new.[5–8] Up to date, however, several types of aza-sugar nucleoside phosphonates have been reported. Harnden et al.[9] prepared a series of phosphonomethoxy derivatives **1** (Fig. 2) containing a pyrrolidine ring linked to the base via the heteroatom, which exerted weak antiviral properties. Isoxazolidine phosphonates **2** reported by Adams et al.,[10] bearing a phosphonomethyl moiety attached to the ring nitrogen atom, showed no anti-HIV1

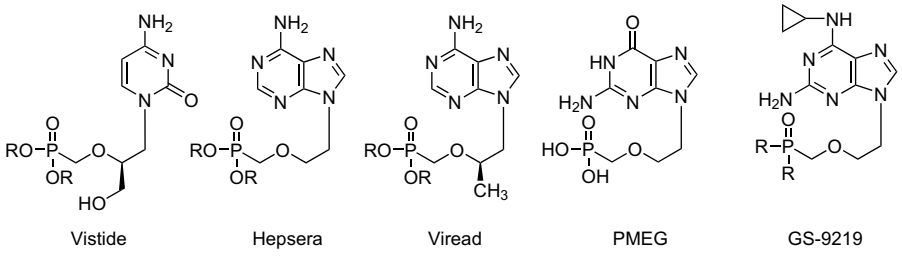

Figure 1. Structures of significant NPA-based antiviral and anticancer drugs.

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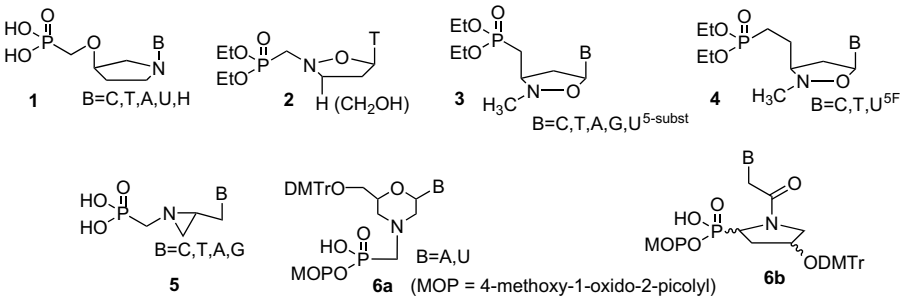


Figure 2. Nitrogen containing, sugar modified nucleoside phosphonates.

activity. In contrast, similar isoxazolidine nucleotide analogues (carbocyclic 2′-oxa-3′-azanucleoside phosphonates) **3** developed by Chiacchio et al. with a phosphonomethyl moiety joined to the 4′-carbon atom exhibited significant inhibition of reverse transcriptase comparable to AZT in efficiency, as well as low levels of cytotoxicity.[11] However, an attempt to obtain more potent inhibitors **4** by inserting a second methylene group into a 4′-carbon and phosphonate group linker (to form an isostere of natural 5′-phosphate) led to the complete loss of antiviral activity.[12] Recently, extending the former series brought compounds **3**, which gave accordingly good bioactivity results.[13] Sheikha et al.[14] synthesized a series of aziridine *N*-methylphosphonate nucleotides **5**, which were proposed as conformationally constrained analogues of well-known phosphonate antivirotics of PMPA type;[15] none of these compounds showed antiviral or antimicrobial activity. Chakhmakhcheva et al.[16] prepared morpholine-based phosphonates **6a** as monomers designed for modified oligonucleotide assembly. In the pyrrolidine series, all four diastereoisomers **6b** as monomers for solid-phase synthesis of phosphonate-based PNA were synthesized by Effimov and co-workers.[17,18]

Herein, we report the synthesis of nucleotide analogues related to α-L- and β-L-2′-deoxynucleoside 3′-phosphate, containing a prolinol moiety instead of the pentofuranosyl sugar residue, in which the 4′-oxygen atom is replaced by a methylene group and the pyrrolidine nitrogen atom is located in place of the 3′-sugar carbon atom. Looking at these compounds as aza-pentofuranosyl derivatives, we can also consider the pair of pyrrolidine nucleotides differing in the chirality on C4′ as α- and β-anomer. The presence of a nitrogen atom at the 3′-position leads to the loss of chirality at this centre and thus, the *N*-phosphonomethyl moiety could adopt cis or trans-orientation relative to any of both stereogenic centres. It is obvious that the 3′-nitrogen moiety as a tertiary amine will be protonated in a large extent of pH values due to the presence of the acidic phosphorus moiety. In this case the formed chiral protonated form may be stabilized via an intramolecular hydrogen bridge (Fig. 3).

2. Results and discussion

2.1. Chemistry

For the synthesis of all prolinol-based nucleoside phosphonates the commercially available *trans*-4-hydroxy-L-proline (**7a**) served as a convenient starting material (Scheme 1). The initial steps essentially follow methods previously described by Ceulemans et al.[19] Inversion of configuration at C(2) of **7a** afforded *cis*-4-hydroxy-D-proline **7b** in high yield. The epimerisation of **7b** with acetic anhydride (first described by Robinson and Greenstein,[20] total yield 42%, later improved by Baker et al.,[21] total yield 57%) was carried out as a one-pot reaction according to Verheijen et al.[22] (yield only 27%); a slightly modified method of final crystallization gave pure **7b** in 70% yield, which is close to the results of a detailed study published recently.[23] Both L- and D-hydroxyproline were protected on nitrogen with the benzyloxycarbonyl group providing carbamates **8a** and **8b**, and these compounds were then converted to their respective methyl esters **9a** and **9b** in quantitative yield by direct introduction of gaseous diazomethane into the ethanolic solution of **8a** or **8b** at low temperature. Reduction of methyl ester to alcohol proceeded smoothly by treatment with $NaBH_4$ in ethanol, giving 4-hydroxyprolinol derivatives **10a**[24] and **10b**. The use of $NaBH_4$/EtOH (yields around 90%) instead of $LiBH_4$/THF (reported yields 90–97%[19,24,25]) caused only a small decrease of yield of the reduction but lowered the cost. Removal of the *Z* protecting group by catalytic hydrogenolysis afforded the 4-hydroxyprolinols **11a** and **11b**. The *N*-phosphonomethyl moiety was introduced into the compounds via a Kabachnik–Fields reaction, following the general method described by Fields.[26] Prolinols **11a** and **11b** were treated with aqueous formaldehyde followed by adding the diisopropyl phosphonate. At first, we performed the reaction in different solvents (acetonitrile, methanol, isopropanol) but it demanded prolonged heating and the yields of these reactions were low and variable in most cases. Exclusion of the solvent (in fact its replacement with excess of diisopropyl *H*-phosphonate) led to an exothermic reaction providing significantly increased yields of phosphonates **12a** and **12b**. The primary hydroxyl of these phosphonates was protected with a dimethoxytrityl group to form **13a** and **13b**, and the key synthons **14a** and **14b** were prepared by the reaction with methanesulfonyl chloride in CH_2Cl_2–pyridine mixture at 0 °C.

Since we aspired to obtain a complete set of synthons suitable for the alkylation of nucleobases, it was necessary to also prepare the two remaining enantiomeric synthons **17a** and **17b**. Thus, we inverted the configuration at C4 of the pyrrolidine ring. Our initial effort to invert directly the OH at C4 of the intermediates **13a** and

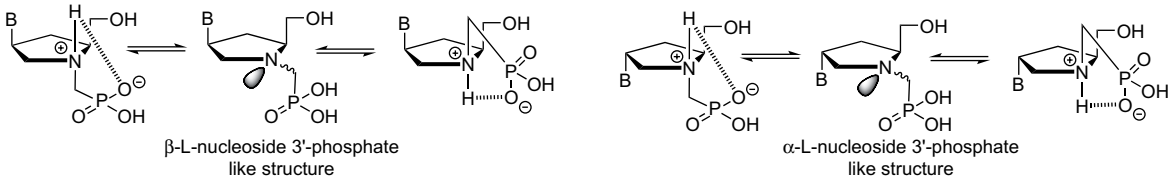
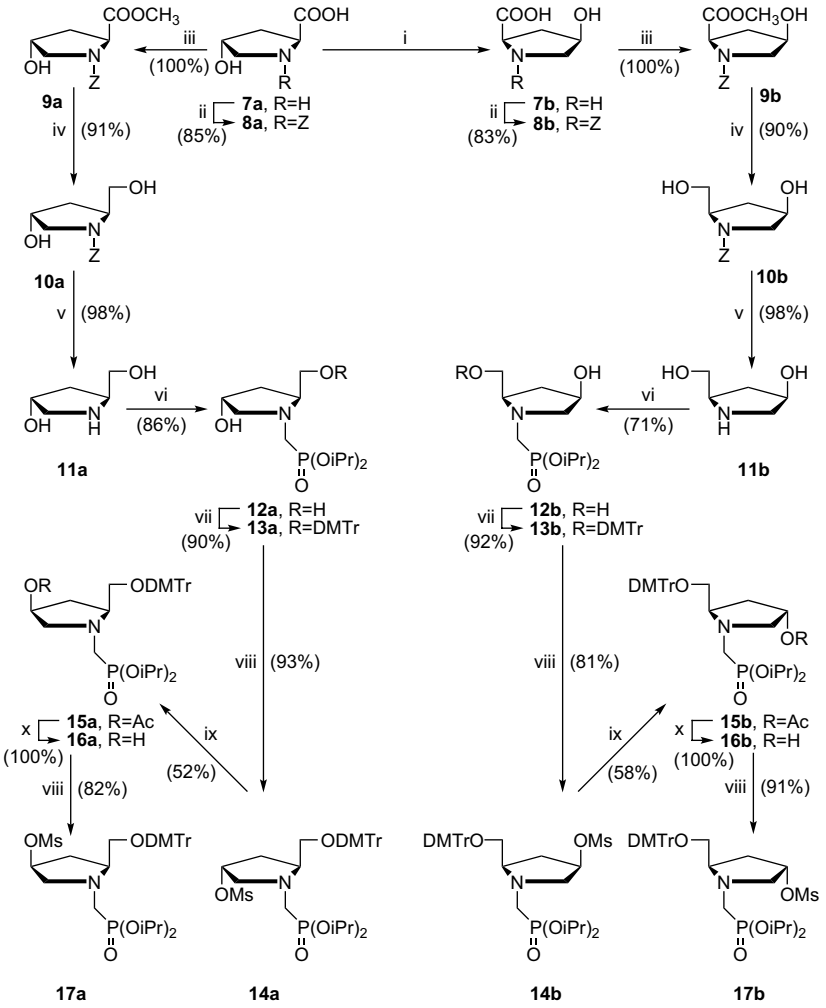


Figure 3. L-Prolinol-based nucleoside *N*-methylphosphonic acids.



Scheme 1. Synthetic route to prolinol-phosphonate synthons. Reagents and conditions: (i) (a) Ac_2O, AcOH, reflux; (b) HCl, reflux; (ii) BnOCOCl, $NaHCO_3$, H_2O–dioxane, rt; (iii) CH_2N_2, Et_2O, 0 °C; (iv) $NaBH_4$, EtOH, 0–20 °C; (v) H_2, Pd–C, MeOH–EtOAc, rt; (vi) $HP(O)(O^iPr)_2$, CH_2O aq, 60 °C; (vii) DMTrCl, Py, rt; (viii) MsCl, CH_2Cl_2, Py, 0 °C; (ix) NaOAc, DMF, 120 °C; (x) MeONa, MeOH, rt.

13b by Mitsunobu reaction was successful but the reaction mixture work-up was very time-consuming and tedious when larger quantities were required. Therefore, we changed the approach to simple nucleophilic substitution of a mesyl group in **14a** and **14b** by acetate ion followed by methanolysis of acetates **15a** and **15b**, which afforded enantiomeric alcohols **16a** and **16b**, respectively. Although this route is somewhat longer, it is more convenient and works with almost the same efficiency. Finally, mesylation of **16a** and **16** gave the desired synthons **17a** and **17b**.

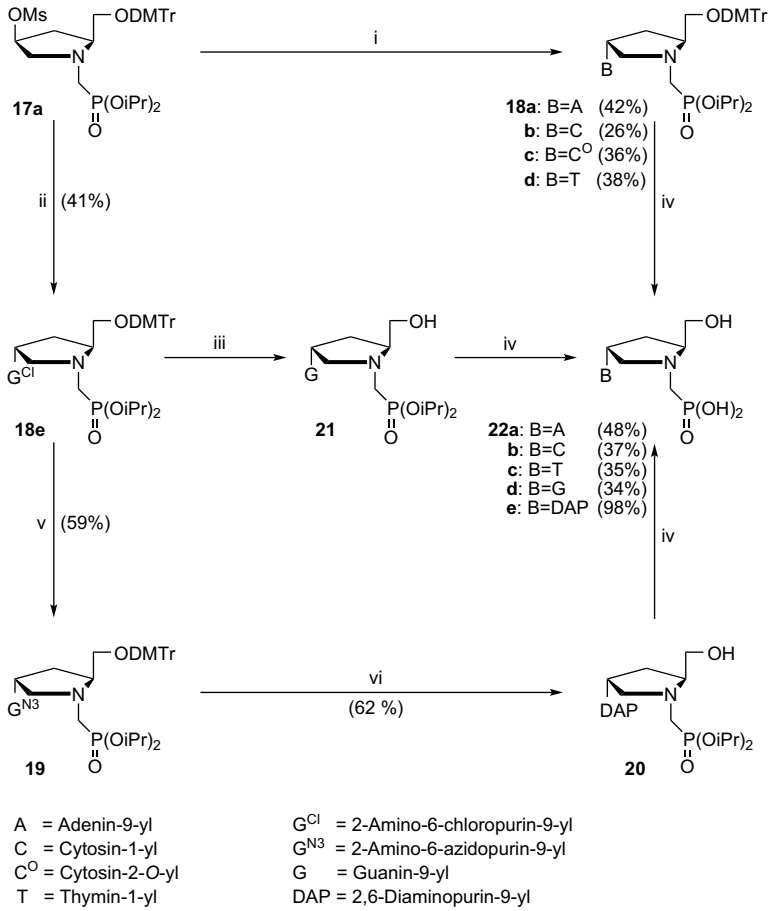
Protected nucleotide analogues were obtained by direct alkylation of nucleobases with mesylates (our previous attempts to use alcohols **13a** and **16a** for Mitsunobu reactions failed). In this article, only the preparation of the α-L- and β-L-series of nucleotides is described.

The alkylation of nucleobases was performed in DMF in the presence of Cs_2CO_3 at 100–120 °C (Schemes 2 and 3). In general, higher yields were usually achieved with higher temperature and shorter reaction time. In the case of cytosine, a mixture of *O*-alkylated and *N*-alkylated nucleobases was obtained using mesylate **14a** under the conditions described above; with mesylate **17a**, no *N*-alkylated product was isolated at all. This problem was successfully solved after changing the solvent and base from DMF–Cs_2CO_3 to DMSO–NaH.[27] Reaction of 2-amino-6-chloropurine with the mesylates **14a** and **17a** afforded intermediates **18e** and **23e**. The 6-chloro atom was substituted by an azido group on treatment with NaN_3 in DMF at 110 °C, giving the 6-azido derivatives **19** and **24**, which were hydrogenated to yield the 2,6-diaminopurine compounds **20** and **25**. Hydrolysis of the 6-chloropurine derivatives **18e** and **23e** with 80% formic acid furnished the respective guanine analogues **21** and **26**.

Cleavage of the phosphonate diesters and/or dimethoxytrityl group by bromotrimethylsilane in anhydrous acetonitrile finally afforded the free nucleotide analogues **22a**–**27e**, which were purified by reverse-phase chromatography, converted to the sodium salts via Dowex 50 (Na^+) and lyophilized from water.

2.2. NMR structural analysis

The NMR spectra of selected nucleosides **22a**, **22c**, **27a** and **27c** in buffered water solutions at pH 3.6, 6.6 and 11.6 showed only very small changes of chemical shifts and coupling constants with pH and the preferred *N*-protonated form. Significant changes in NMR spectra were observed in more alkaline solutions (pH ~12.5), obviously due to deprotonation at nitrogen atom (Fig. 3). The NMR data at pH 3.6 and 12.5 are shown in Table 1 (for numbering of atoms see Fig. 4).



Scheme 2. Synthetic route to purine α-L-prolinol nucleoside phosphonates. Reagents and conditions: (i) DMF or DMSO, Cs_2CO_3 or NaH, base, 120 °C; (ii) DMF, Cs_2CO_3, 2-amino-6-chloropurine, 110 °C; (iii) 80% HCOOH, 80 °C; (iv) $BrSiMe_3$, ACN, rt; (v) NaN_3, DMF, 110 °C; (vi) Pd–C, H_2, MeOH–HCl, rt.

The configurational assignment of the methylene protons of the pyrrolidine ring was determined from 2D-H,H-ROESY spectra using the observed NOE contacts with protons and substituents at positions 1′ and 4′ with known configuration. These NOE contacts in compounds **22c** and **27c** are shown with black arrows in Figure 4.

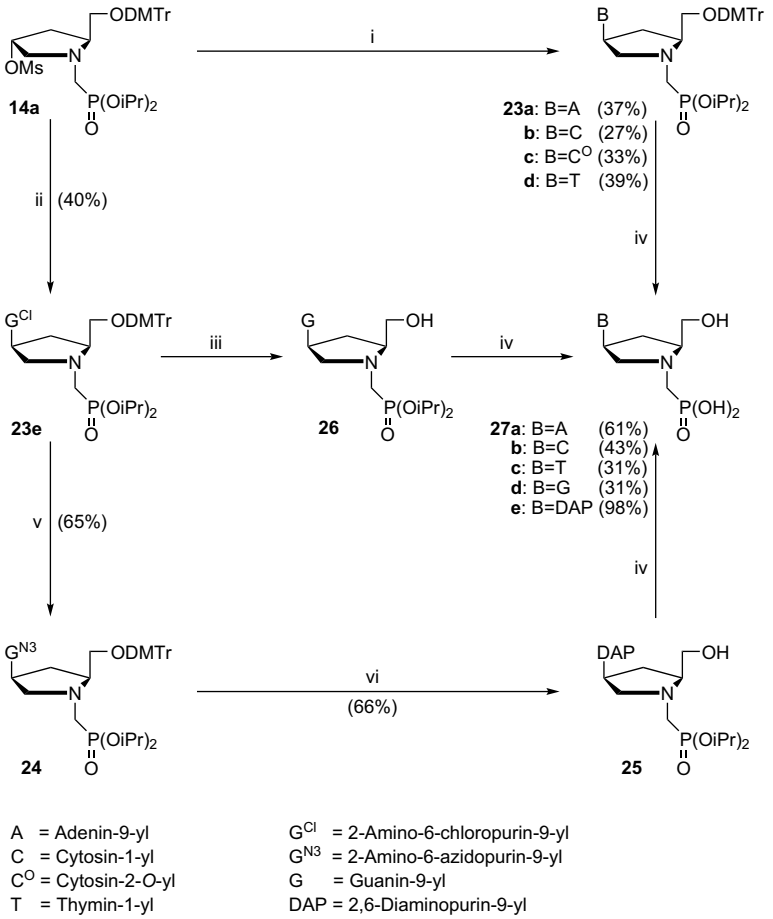
The preferred configuration at protonated nitrogen atom in compounds **22** and **27** was derived from NOE contacts of methylene hydrogens of $–CH_2–P(O)(OH)_2$ group. Their NOE contacts with hydrogen atoms H-2A′ and H-4′ (shown with red arrows for compounds **22c** and **27c** in Fig. 4) indicate that NH proton is cis-oriented to neighbouring CH_2OH group while $CH_2–P(O)(OH)_2$ group adopts trans-orientation to CH_2OH substituent (Fig. 5). Such preferred side of protonation was supported by the theoretical calculations (molecular mechanics, MM+). The search over conformational space defined by the pseudorotation pathway[28] of protonated pyrrolidine ring showed global energy minima for $_N$E type conformations with phase angle $P \sim 270$ using definition of torsion angles for proline as they are shown in Figure 4 and relation $\tau_i=\tau_m\cos(P+4\pi i/5)$ with maximum puckering amplitude τ_m. Calculation (energy minimization) was done for whole range of phase angles (P=0–360°) in 9° steps with τ_m=40°, endocyclic torsion angles constrained and free geometry optimization of substituents.

The comparison of vicinal proton coupling constants observed for *N*-protonated forms of compounds **22** and **27** (Table 1) with those calculated using generalized Karplus equation[29] and described for proline by Altona et.al.[30] shows a best semiquantitative fit for the conformations with phase angle *P* around 270°, similarly as the above described theoretical calculations. The detailed NMR conformation study of the different *N*-protonated and non-protonated prolinol type nucleosides will be a subject of our next paper.

The results obtained by NMR spectroscopy clearly show conformational differences between α-L- and β-L-prolinol nucleoside phosphonic acids **22** and **27**, respectively, in terms of cis and trans mutual position of nucleobase and *N*-phosphonomethyl moiety (Fig. 5). There is no doubt that both conformers **22** and **27** fit very well with the configuration of the corresponding 'natural' α-L- and β-L-nucleoside 3′-phosphates, respectively. However, a cis mutual position of the nucleobase and *N*-methylphosphonate moiety in the case of the α-L conformer **22** (Fig. 5, structure **II**) is the common structural feature with the β-D-nucleoside 5′-phosphates. Therefore, we suppose that compounds **22** could mimic in some cases the natural 5′-nucleotides. But only abilities of compounds **22** to pass the relevant biochemical/biological experiments can confirm plausibility of this hypothesis. Such a study is underway.

3. Biological activity

The cytostatic activity of analogues **22a**–**27e** was examined on L1210, L929 and HeLa S3 cell lines. The antiviral activity against DNA viruses was evaluated using infected E6SM, HeLa and Vero cell cultures. No significant activity was found.



Scheme 3. Synthetic route to purine β-L-prolinolnucleoside phosphonates Reagents and conditions: (i) DMF or DMSO, Cs_2CO_3 or NaH, base, 120 °C; (ii) DMF, Cs_2CO_3, 2-amino-6-chloropurine, 110 °C; (iii) 80% HCOOH, 80 °C; (iv) $BrSiMe_3$, ACN, rt; (v) NaN_3, DMF, 110 °C; (vi) Pd–C, H_2, MeOH–HCl, rt.

Table 1
The effect of pH on the NMR spectra of compounds **22a**, **22c**, **27a** and **27c** in D_2O

Compound	pH	Proton chemical shifts													
		H-1′	H-2′A	H-2′B	H-4′	H-4′aA	H-4′aB	H-5′A	H-5′B	CHaP	CHbP	H-2	H6	H-8	5-CH_3
22a	**3.60**	5.40	3.96	4.31	4.35	2.66	2.75	4.15	3.90	3.49	3.38	8.24	—	8.22	—
	12.66	4.97	***3.05***	3.86	3.18	2.31	2.34	***3.73***	3.68	2.98	2.61	8.28	—	8.12	—
22c	**3.60**	4.95	4.15	3.76	4.17	2.58	2.53	4.07	3.84	3.45	3.23	—	7.51	—	1.88
	12.47	5.02	***2.73***	3.60	3.09	2.04	2.10	∼***3.65***	∼3.65	2.92	2.54	—	7.52	—	1.87
27a	**3.60**	5.50	3.89	4.40	3.82	3.01	2.26	4.18	3.95	3.70	3.17	8.27	—	8.16	—
	12.65	4.97	***3.00***	3.84	2.74	2.65	1.84	***3.75***	3.47	3.00	2.40	8.13	—	8.64	—
27c	**3.60**	4.86	3.73	4.29	3.72	2.75	2.39	4.12	3.89	3.50	3.04	—	7.48	—	1.87
	12.45	4.98	***2.86***	3.47	2.65	2.48	1.61	***3.76***	3.55	2.96	2.30	—	7.97	—	1.89

Comp.	pH	Carbon chemical shifts and coupling constants *J*(C,P)													
		C-1′	C-2′	C-4′	C-4′a	C-5′	NCH_2P	C-2	C-4	C-5	C-6	C-8	5-CH_3	^{1}J(P,CH)	^{3}J(P,C4′)
22a	**3.60**	54.81	61.69	70.45	35.01	60.92	52.96	154.85	158.05	121.65	151.20	143.87	—	130.1	5.9
	12.66	54.89	62.30	67.75	36.23	64.86	54.98	154.80	158.03	121.22	151.54	143.41	—	143.3	11.8
22c	**3.60**	59.31	60.44	71.50	32.99	60.09	53.11	154.69	169.50	113.78	144.69	—	14.09	128.6	6.2
	12.47	55.43	62.20	68.08	35.49	65.01	54.94	163.11	179.16	114.28	141.41	—	15.51	142.3	11.2
27a	**3.60**	54.92	63.03	72.86	35.67	59.73	53.25	154.62	158.07	121.69	150.45	144.35	—	130.5	7.2
	12.65	55.29	62.77	69.04	37.48	63.38	55.03	154.62	157.93	121.00	151.25	144.33	—	146.5	14.4
27c	**3.60**	60.78	61.97	72.63	33.22	58.85	52.72	154.82	169.62	113.35	145.98	—	14.02	128.8	7.0
	12.45	55.78	62.45	69.16	37.72	63.42	55.15	162.90	179.21	113.92	142.30	—	15.68	145.0	13.9

Comp.	pH	Coupling constants *J*(H,H) and *J*(H,P)												
		1′,2′A	1′,2′B	2′A,2′B	1′,4′aA	1′,4′aB	4′aA, 4′aB	4′,4′aA	4′,4′aB	4′,5′A	4′,5′B	5′A,5′B	CHa,CHb	CHa,P	CHb,P
22a	**3.60**	6.3	7.8	12.4	5.1	9.4	14.7	8.7	7.4	3.3	3.6	13.2	14.4	12.9	11.1
	12.66	9.1	6.9	9.8	7.3	9.0	13.5	8.6	7.3	4.6	3.9	11.8	14.5	15.2	8.9
22c	**3.60**	8.4	7.2	12.3	5.9	9.8	14.4	8.6	7.9	3.3	3.5	13.4	14.4	13.0	11.2
	12.47	9.4	7.3	9.8	6.8	10.2	13.8	8.7	7.7	∼4.5	∼4.5	13.8	14.5	14.8	9.3
27a	**3.60**	8.1	1.6	13.2	9.8	4.6	14.8	8.6	10.8	3.3	3.6	13.6	14.5	13.7	10.8
	12.65	6.2	1.3	11.4	8.4	3.1	14.0	9.0	7.2	3.4	3.1	12.3	14.2	16.4	8.0
27c	**3.60**	9.4	1.9	13.2	9.9	6.2	14.3	7.8	11.9	3.3	2.7	13.6	14.3	13.7	10.7
	12.45	8.0	2.1	11.6	9.0	5.1	13.7	7.9	9.0	3.8	3.1	12.1	14.2	16.2	8.5

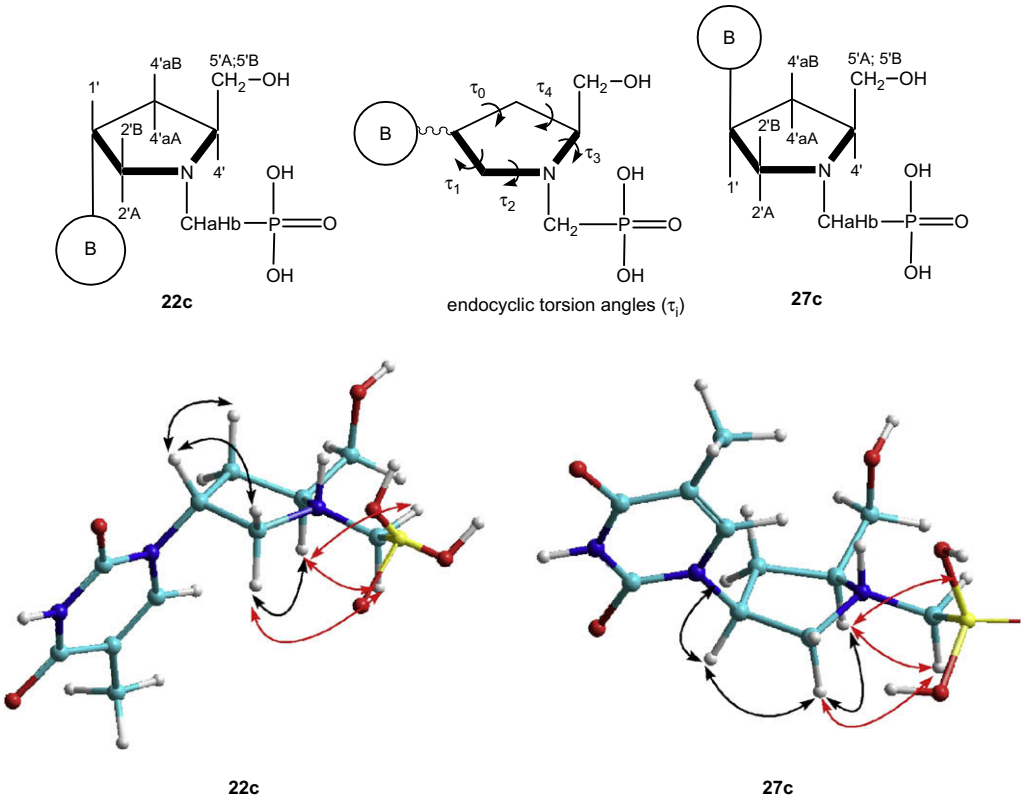


Figure 4. The numbering of hydrogen atoms, endocyclic torsion angles and the observed NOE contacts in compounds **22c** and **27c** (in D_2O, pH=3.6). The black arrows indicate NOEs used for stereochemical assignment of geminal hydrogens at C-2′ and C-4′; the red arrows show NOEs used for determination of the configuration at protonated nitrogen atom.

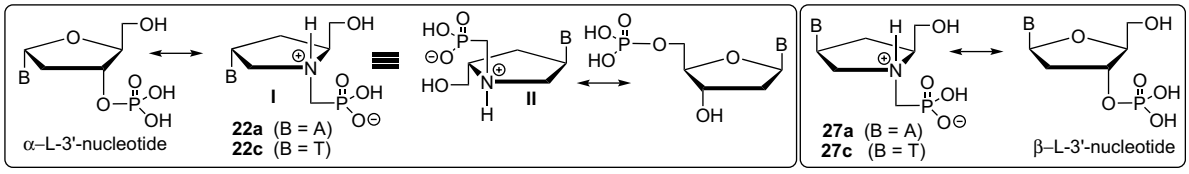


Figure 5.

4. Conclusion

We have synthesized novel isosteric 3′-nucleotide analogues, α-L- and β-L-prolinol nucleoside 3′-*N*-methylphosphonic acids lacking stereogenic centre in the 3′-position of the prolinol ring. Remarkable conformational differences between α-L- and β-L-prolinol nucleotides were found by NMR spectroscopic study. Both conformers **22** and **27** fit very well with the configuration of the corresponding 'natural' α and β-L-nucleoside 3′-phosphates, respectively. However, a cis mutual position of the nucleobase and *N*-methylphosphonate moiety in the case of the α-L conformer **22** suggests a structural similarity with the β-D-nucleoside 5′-phosphates. The α-D- and β-D-prolinol nucleotides (not reported here) having an identical conformation as their L-congeners fit the natural D-nucleotides, and therefore they are currently incorporated into modified oligonucleotides to study the influence of the conformational adaptability on the hybridization properties. Finally, the antiviral and cytostatic properties of the prepared prolinol nucleotides will be re-evaluated in the form of suitable prodrugs.

5. Experimental

5.1. General

The solvents were evaporated at 40 °C and 2 kPa, and the products were dried over phosphorus pentoxide at rt and 13 Pa. The course of the reactions was checked on TLC cards (Fluka, Merck) whereby the products were detected by UV monitoring, by ninhydrine spraying (dark blue colour of amines) and by spraying with 1% ethanolic solution of 4-(4-nitrobenzyl)pyridine followed by heating and treating with gaseous ammonia (blue colour of diesters of phosphonic acids). For flash column chromatography, silica gel 40–60 μm (Fluka) was used. The TLC and the preparative silica gel chromatography were carried out in the following solvent systems (v/v): chloroform–ethanol 9:1 (C1); chloroform–ethanol 19:1 (C2); ethyl acetate–acetone–ethanol–water 4:1:1:1 (H1); ethyl acetate–acetone–ethanol–water 6:1:1:0.5 (H3); 2-propanol–concd aqueous ammonia–water 7:1:2 (I); 50% EtOAc–toluene (T1), 20% ethyl acetate–toluene (T2). Analytical HPLC was performed on Nucleosil 100–5 C18 (4.6×150 mm; Macharey–Nagel) using a linear gradient of methanol in 0.1 M TEAA. Preparative reversed-phase chromatography was carried out on an octadecyl silica column (25×250 mm, 20 μm, IOCB Prague); compounds were eluted with a linear gradient of methanol in water at 15 ml/min. UV spectra and thermal characteristics were taken on a Cary Bio 100 (Varian) spectrophotometer. High resolution FAB mass spectra were recorded on a ZAB-EQ (VG Analytical) instrument with glycerol and thioglycerol as matrices. NMR spectra were measured on a Varian UNITY-500, Bruker AVANCE-500 and AVANCE-600 instruments (^{1}H at 500 or 600 MHz; ^{13}C at 125.7 or 150.9 MHz frequency) in DMSO-d_6 and/or D_2O at 27 °C. The chemical shifts were referenced either to solvent signal

(converted to δ scale using relations δ_H(DMSO)=2.50 and δ_C(DMSO)=39.7 ppm) or to DSS (in D_2O). The 2D-H,H-COSY spectra were used for the structural assignment of coupled protons and 2D-H,H-ROESY spectra for the configuration determination. Carbon-13 chemical shifts and coupling constants *J*(C,P) were obtained from broad band proton-decoupled spectra using APT pulse sequence. The 2D-correlated H,C-HSQC and H,C-HMBC spectra were used for structural assignment of carbon signals.

5.1.1. *cis-4-Hydroxy-D-proline (**7b**)*

A solution of *trans*-4-hydroxy-L-proline **7a**(Fluka, 100 g, 763 mmol) in acetic anhydride (500 mL) and acetic acid (1000 mL) was heated to reflux for 7 h. The solution was then concentrated in vacuo, the residue was diluted with 2 M aqueous HCl (1000 mL) and the mixture was heated under reflux for 4 h. Then activated charcoal (5 g) was added, the hot mixture was filtered immediately through a Celite layer and the cake was washed with hot water. The colourless solution was neutralized with triethylamine and evaporated to dryness. The crude product was refluxed in ethanol (2500 mL) and water was added carefully to the boiling mixture until the solid disappeared (but the solution remained still a little turbid). The solution was then left to stand overnight at −20 °C to afford white crystals, which were filtered off, washed with cold ethanol and dried in vacuo to yield 70 g (70%) of compound **7b**. $[\alpha]_{20}^{D}$ +57.2 (*c* 0.252H_2O, lit.[21] $[\alpha]_{22}^{D}$ +60.3 (*c* 2.0H_2O)).

5.1.2. *N-Benzyloxycarbonyl-trans-4-hydroxy-L-proline (**8a**)*

A solution of benzyl chloroformate (65 mL, 457 mmol, 1.2 equiv) in dioxane (150 mL) was added dropwise to the vigorously stirred solution of *trans*-4-hydroxy-L-proline **7a** (Fluka, 50 g, 381 mmol) and sodium hydrogen carbonate (84 g, 1.0 mol, 2.6 equiv) in water (1000 mL) at rt, and the reaction mixture was stirred overnight (TLC in I). The excess of benzyl chloroformate was extracted with diethyl ether (2×100 mL) and the aqueous layer was acidified with hydrochloric acid to pH 2. The product was extracted with ethyl acetate (3×150 mL), combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give a viscous colourless oil **8a** (86 g, 85%). HRMS (FAB) calcd for $C_{13}H_{16}NO_5$ $[M+H]^+$ 266.1029, found: 266.1025. The recorded ^1H and ^{13}C NMR spectra were in accordance with the literature data.[31,32]

5.1.3. *N-Benzyloxycarbonyl-cis-**4**-hydroxy-D-proline (**8b**)*

Using conditions and amounts described for compound **8a**, the title proline derivative **8b** was prepared from *cis*-4-hydroxy-D-proline **7b** as viscous oil (84 g, 83%). HRMS (FAB) calcd for $C_{13}H_{16}NO_5$ $[M+H]^+$ 266.1029, found: 266.1020. ^1H and ^{13}C NMR spectra recorded were in accordance with the literature data.[33]

5.1.4. *N-Benzyloxycarbonyl-trans-4-hydroxy-L-proline methyl ester (**9a**)*

Stirred solution of potassium hydroxide (28 g, 500 mmol) in an Et_2O–EtOH mixture (780 mL, 2:1) was treated with Diazald (21.4 g, 100 mmol) at 50 °C. The diazomethane generated was blown via a stream of argon into an ice-cooled flask containing **8a** (20.05 g, 75.6 mmol) in Et_2O (250 mL) at 0 °C until the reaction mixture turned yellow. The solution was concentrated and the product **9a** was obtained as colourless oil (22 g, 100%). HRMS (FAB) calcd for $C_{14}H_{18}NO_5$ $[M+H]^+$ 280.1185, found: 280.1189. The recorded ^1H and ^{13}C NMR spectra were in accordance with the literature data.[24,34]

5.1.5. *N-Benzyloxycarbonyl-cis-4-hydroxy-D-proline methyl ester (**9b**)*

Using the procedure outlined for **9a**, the title compound **9b** was prepared from **8b** (12.8 g, 48.7 mmol) as colourless oil (13.6 g, 100%). HRMS (FAB) calcd for $C_{14}H_{18}NO_5$ $[M+H]^+$ 280.1185, found: 280.1190. The recorded ^1H and ^{13}C NMR spectra were in accordance with lit.[35]

5.1.6. *N-Benzyloxycarbonyl-trans-4-hydroxy-L-prolinol (**10a**)*

Sodium borohydride (17.16 g, 453.5 mmol, 6 equiv) was added in one portion to a stirred solution of methyl ester **9a** (22 g, 75.6 mmol) in EtOH (600 mL) at 0 °C, and the turbid solution was stirred for 12 h at rt (TLC in C2). The solution was cooled to 0 °C and the excess of sodium borohydride was carefully quenched by adding dropwise AcOH (32 mL). The mixture was then evaporated in vacuo, the residue was dissolved in water (1000 mL), the product was extracted with EtOAc (3×100 mL), combined organic layer was dried over $MgSO_4$ and evaporated in vacuo to afford pale yellow thick oil (17.20 g, 91%). HRMS (FAB) calcd for $C_{13}H_{18}NO_4$ $[M+H]^+$ 252.1236, found: 252.1226. The recorded ^1H and ^{13}C NMR spectra were in accordance with the literature data.[24]

5.1.7. *N-Benzyloxycarbonyl-cis-4-hydroxy-D-prolinol (**10b**)*

Sodium borohydride (11.06 g, 292.2 mmol, 6 equiv) was added in one portion to a stirred solution of methyl ester **9b** (13.60 g, 48.7 mmol) in EtOH (600 mL) at 0 °C, and the turbid solution was stirred for 12 h at rt (TLC in C2). The solution was cooled to 0 °C and carefully quenched by adding dropwise AcOH (20 mL). The mixture was then evaporated in vacuo, the residue was dissolved in water (1000 mL), the product was extracted with EtOAc (3×100 mL), the organic layer was dried over $MgSO_4$ and evaporated in vacuo. Prolinol derivative **10b** was obtained as a pale yellow thick oil (11.01 g, 90%). HRMS (FAB) calcd for $C_{13}H_{18}NO_4$ $[M+H]^+$ 252.1236, found: 252.1246. ^1H NMR (DMSO-d_6): (a) two sets of signals belonging to two isomers around N–CO bond (ratio ca. 3:2) are observed only for some hydrogen atoms but nearly for all carbon atoms (b) heavy overlap does not allow to determine most of *J*(H,H)s 7.29–7.39 m, 5H (C_6H_5 (Z)); 5.16 d, 1H, *J*(OH,1)=4.7 (1-OH); 4.955 dd, 1H, *J*(OH,5A)=5.8, *J*(OH,5B)=5.0 (5-OH); 5.07 d, 1H and 5.04 d, 1H, *J*(*gem*)=12.7+5.10 d, 1H and 5.04 d, 1H, *J*(*gem*)=12.7 (CH_2(Z)); 4.195 m, 1H (H-1); 3.81 m, 1H (H-4); 3.58 m, 2H+3.55 m, 2H (H-5A, H-5B); 3.52 m, 1H (H-2A); 3.13 m, 1H+3.13 m, 1H (H-2B); 2.09 m, 1H+2.07 m, 1H (H-4aA); 1.89 m, 1H+1.84 m, 1H (H-4aB). ^{13}C NMR (DMSO-d_6): 154.57+154.42 (C=O); 137.27, 128.60 (2), 127.96 and 127.68 (2) (C_6H_5 (*Z*)); 69.02+68.26 (C-1); 65.90+65.03 (CH_2 (*Z*)); 61.86+62.52 (C-5); 58.88+58.15 (C-4); 55.43+55.88 (C-2); 35.89+36.66 (C-4a).

5.1.8. *trans-4-Hydroxy-L-prolinol (**11a**)*

To a solution of *N*-Z-hydroxyprolinol **10a** (17.19 g, 68 mmol) in deoxygenated MeOH–EtOAc mixture (2:1, 500 mL) was added 10% Pd on charcoal (0.2 g) under argon atmosphere, and the vigorously stirred reaction mixture was left to react under an atmosphere of hydrogen (10 psi) at rt for 12 h (TLC in C1). The catalyst was filtered off and the solution was passed through a column of Dowex 50 (H^+), which was then washed with MeOH. The product was liberated from Dowex with diluted aqueous ammonia (2.5%), the solution was evaporated, the residue was co-distilled with ethanol and dried in vacuo, giving **11a** as a pale yellow thick oil (7.87 g, 98%). HRMS (FAB) calcd for $C_5H_{12}NO_2$ $[M+H]^+$ 118.0868, found: 118.0865. ^1H NMR (DMSO-d_6): 4.18 m, 1H, *J*(1,2A)=4.7, *J*(1,2B)=2.7, *J*(1,4aA)=2.3, *J*(1,4aB)=5.6 (H-1); 3.32 m, 3H (H-4, H-5A, H-5B); 2.93 dd, 1H, *J*(2A,1)=4.7, *J*(2A,2B)=11.4 (H-2A); 2.67 dd, 1H, *J*(2B,1)=2.7, *J*(2B,2A)=11.4, *J*(2B,4aA)=1.3 (H-2B); 1.65 dddd, 1H, *J*(4aA,1)=2.3, *J*(4aA,4aB)=13.1, *J*(4aA,4)=6.8, *J*(4aA,2B)=1.3 (H-4aA); 1.51 ddd, 1H, *J*(4aB,1)=5.6, *J*(4aB,4aA)=13.1, *J*(4aB,4)=8.1 (H-4aB). ^{13}C NMR (DMSO-d_6): 70.84 (C-1); 63.66 (C-5); 58.89 (C-4); 54.45 (C-2); 37.76 (C-4a).

5.1.9. *cis-4-Hydroxy-D-prolinol (**11b**)*

Using the procedure outlined for **11a**, compound **11b** was prepared from **10b** (11.01 g, 43.8 mmol) as a pale yellow thick oil (5.03 g, 98%). HRMS (FAB) calcd for $C_5H_{12}NO_2$ $[M+H]^+$ 118.0868, found: 118.0872. ^1H NMR (DMSO-d_6): 4.16 m, 1H, *J*(1,2A)=5.4, *J*(1,2B)=3.6, *J*(1,4aA)=6.5, *J*(1,4aB)=4.2 (H-1); 3.41 dd, 1H,

J(5A,4)=6.3, *J*(5A,5B)=10.9 (H-5A); 3.39 dd, 1H, *J*(5B,4)=5.1, *J*(5B,5A)=10.9 (H-5B); 3.13 m, 1H, *J*(4,4aA)=8.2, *J*(4,4aB)=6.8, *J*(4,5A)=6.3, *J*(4,5B)=5.1 (H-4); 2.84 dd, 1H, *J*(2A,1)=5.4, *J*(2A,2B)=11.1 (H-2A); 2.71 ddd, 1H, *J*(2B,1)=3.6, *J*(2B,2A)=11.1, *J*(2B,4aB)=1.0 (H-2B); 1.98 ddd, 1H, *J*(4aA,1)=6.5, *J*(4aA,4aB)=13.2, *J*(4aA,4)=8.2 (H-4aA); 1.34 dddd, 1H, *J*(4aB,1)=4.2, *J*(4aB,4aA)=13.2, *J*(4aB,4)=6.8, *J*(4aB,2B)=1.0 (H-4aB). ^{13}C NMR (DMSO-d_6): 70.66 (C-1); 63.76 (C-5); 59.62 (C-4); 54.32 (C-2); 37.32 (C-4a).

5.1.10. Diisopropyl 2,3-dideoxy-3-aza-4a-carba-α-L-glycero-pentofuranos-3-yl-methylphosphonate (**12a**)

Aqueous formaldehyde (14.5 M solution, 7.9 mL, 114 mmol, 1.7 equiv) was added to a stirred solution of 4-hydroxyprolinol **11a** (7.87 g, 67 mmol) in diisopropyl phosphonate (15.7 mL, 94 mmol, 1.4 equiv), and the mixture was heated to 60 °C for 3 h (TLC in H1). The reaction mixture was evaporated, dissolved in water and the solution was passed through a column of Dowex 50 (H^+-form), which was then washed with a mixture of H_2O–MeOH (1:1, 1 L). The product was liberated from Dowex with diluted (approx. 2.5%) aqueous ammonia and evaporated in vacuo to obtain **12a** as a slightly brown thick oil (17.00 g, 86%). HRMS (FAB) calcd for $C_{12}H_{27}NO_5P$ $[M+H]^+$ 296.1627, found: 296.1616. ^{1}H NMR (DMSO-d_6): 4.72 br s, 1H and 4.44 br s, 1H (2×OH); 4.07 m, 1H, *J*(1,2A)=5.7, *J*(1,2B)=5.3, *J*(1,4aA)=4.3, *J*(1,4aB)=6.9 (H-1); 4.56 m, 2H, 1.237 d, 3H, *J*=6.2, 1.235 d, 6H, *J*=6.2 and 1.233 d, 3H, *J*=6.2 (P(O^{i}Pr)$_2$); 3.32 dd, 1H, *J*(5A,4)=5.0, *J*(5A,5B)=11.0 (H-5A); 3.28 dd, 1H, *J*(5B,4)=5.2, *J*(5B,5A)=11.0 (H-5B); 3.28 dd, 1H, *J*(2A,1)=5.7, *J*(2A,2B)=9.8, (H-2A); 3.27 dd, 1H, 1H, *J*(*gem*)=15.2, *J*(H,P)=16.3 and 2.70 dd, 1H, *J*(*gem*)=15.2, *J*(H,P)=5.5 (N–CH_2–P); 2.76 m, 1H, *J*(4,4aA)=7.6, *J*(4,4aB)=7.8, *J*(4,5A)=5.0, *J*(4,5B)=5.2 (H-4); 2.29 dd, 1H, *J*(2B,1)=5.3, *J*(2B,2A)=9.8 (H-2B); 1.63 ddd, 1H, *J*(4aA,1)=4.3, *J*(4aA,4aB)=12.8, *J*(4aA,4)=7.6 (H-4aA); 1.58 ddd, 1H, *J*(4aB,1)=6.9, *J*(4aB,4aA)=12.8, *J*(4aB,4)=7.8 (H-4aB). ^{13}C NMR (DMSO-d_6): 69.88 d, *J*(C,P)=6.8; 69.65 d, *J*(C,P)=6.8; 24.04 d, *J*(C,P)=4.9; 23.98 d, *J*(C,P)=4.9; 23.88 (2) d, *J*(C,P)=4.9 (P(O^{i}Pr)$_2$); 68.65 (C-1); 65.57 d, *J*(4,P)=16.1 (C-4); 64.49 (C-5); 64.31 d, *J*(C,P)=2.0 (C-2); 51.50 d, *J*(C,P)=164.1 (N–CH_2–P); 37.98 (C-4a).

5.1.11. Diisopropyl 2,3-dideoxy-3-aza-4a-carba-β-D-glycero-pentofuranos-3-ylmethylphosphonate (**12b**)

Using the procedure outlined for **12a**, phosphonate **12b** was prepared from **11b** (5.03 g, 42.8 mmol), aqueous formaldehyde (5.0 mL, 72.8 mmol) and diisopropyl phosphonate (10.0 mL, 60.0 mmol) as a slightly brown thick oil (9.01 g, 71%). HRMS (FAB) calcd for $C_{12}H_{27}NO_5P$ $[M+H]^+$ 296.1627, found: 296.1633. ^{1}H NMR (DMSO-d_6): 4.11 m, 1H, *J*(1,2A)=2.0, *J*(1,2B)=5.6, *J*(1,4aA)=6.8, *J*(1,4aB)=3.7 (H-1); 4.59 m, 2H, 1.246 d, 3H, *J*=6.2, 1.242 d, 3H, *J*=6.2, 1.238 d, 3H, *J*=6.2 and 1.235 d, 3H, *J*=6.2 (P(O^{i}Pr)$_2$); 3.42 dd, 1H, *J*(5A,4)=4.8, *J*(5A,5B)=10.8 (H-5A); 3.37 dd, 1H, *J*(5B,4)=5.2, *J*(5B,5A)=10.8 (H-5B); 3.26 dd, 1H, 1H, *J*(*gem*)=15.2, *J*(H,P)=16.0 and 2.61 dd, 1H, *J*(*gem*)=15.2, *J*(H,P)=5.8 (N–CH_2–P); 3.10 ddd, 1H, *J*(2A,1)=2.0, *J*(2A,2B)=10.0, *J*(2A,4aB)=1.0 (H-2A); 2.55 m, 1H, *J*(4,4aA)=8.0, *J*(4,4aB)=7.2, *J*(4,5A)=4.8, *J*(4,5B)=5.2 (H-4); 2.47 ddd, 1H, *J*(2B,1)=5.6, *J*(2B,2A)=10.0, *J*(2B,4aB)=0.7 (H-2B); 2.06 ddd, 1H, *J*(4aA,1)=6.8, *J*(4aA,4aB)=13.0, *J*(4aA,4)=7.2 (H-4aA); 1.34 br ddd, 1H, *J*(4aB,1)=3.7, *J*(4aB,4aA)=13.0, *J*(4aB,4)=7.2, *J*(4aB,2A)=1.0, *J*(4aB,2B)=0.7 (H-4aB). ^{13}C NMR (DMSO-d_6): 70.03 d, *J*(C,P)=6.8, 69.70 d, *J*(C,P)=6.7, 24.18 d, *J*(C,P)=3.6, 24.10 d, *J*(C,P)=3.5, 24.01 d, *J*(C,P)=4.8 and 23.99 d, *J*(C,P)=4.6 (P(O^{i}Pr)$_2$); 68.77 (C-1); 66.30 d, *J*(4,P)=15.8 (C-4); 64.62 d, *J*(C,P)=1.6 (C-2); 64.34 (C-5); 51.12 d, *J*(C,P)=163.2 (N-CH_2-P); 37.98 (C-4a).

5.1.12. Diisopropyl 2,3-dideoxy-5-O-dimethoxytrityl-3-aza-4a-carba-α-L-glycero-pentofuranos-3-ylmethylphosphonate (**13a**)

Phosphonate **12a** (16.98 g, 57.5 mmol) was co-evaporated repeatedly with pyridine to remove traces of water, dissolved in dry pyridine (300 mL) and treated with dimethoxytrityl chloride (29.22 g, 86.2 mmol, 1.5 equiv) at rt (TLC in C2). After 1 h, the reaction was quenched by adding mixture of methanol, water and triethylamine (3:1:1, 50 mL) and concentrated under reduced pressure. The residue was dissolved in chloroform and the solution was washed with water. The organic layer was dried over Na_2SO_4 and evaporated. Crude product was purified by flash chromatography on silica (elution with a linear gradient of EtOH in $CHCl_3$) and dried in vacuo to give **13a** as a pale yellow thick oil (30.52 g, 90%). HRMS (FAB) calcd for $C_{33}H_{43}NO_7P$ $[M-H]^-$ 596.2777, found: 596.2757. ^{1}H NMR ($CDCl_3$): 7.43 m, 2H, 7.33 m, 4H, 7.27 m, 2H, 7.20 m, 1H and 6.81 m, 4H (2×C_6H_4 and C_6H_5 (ODMTr)); 4.25 m, 1H, *J*(1,2A)=5.0, *J*(1,2B)=2.8, *J*(1,4aA)=2.3, *J*(1,4aB)=5.7 (H-1); 4.68 m, 2H, 1.307 d, 3H, *J*=6.1, 1.294 d, 3H, *J*=6.2, 1.287 d, 3H, *J*=6.1 and 1.25 d, 3H, *J*=6.2 (P(O^{i}Pr)$_2$); 3.78 s, 6H (2×OMe (ODMTr)); 3.56 dd, 1H, *J*(2A,1)=5.0, *J*(2A,2B)=11.1, *J*(2A,P)=2.4 (H-2A); 3.40 m, 1H, *J*(4,4aA)=6.5, *J*(4,4aB)=9.6, *J*(4,5A)=6.0, *J*(4,5B)=5.0, *J*(4,2B)=1.5 (H-4); 3.29 dd, 1H, 1H, *J*(*gem*)=15.6, *J*(H,P)=12.0 and 3.20 dd, 1H, *J*(*gem*)=15.6, *J*(H,P)=6.0 (N–CH_2–P); 3.08 dd, 1H, *J*(5A,4)=6.0, *J*(5A,5B)=9.2 (H-5A); 3.04 dd, 1H, *J*(5B,4)=5.0, *J*(5B,5A)=9.2 (H-5B); 2.77 m, 1H, *J*(2B,1)=2.8, *J*(2B,2A)=11.1, *J*(2B,4)=1.5, *J*(2B,4aA)=1.5 (H-2B); 1.95 m, 1H, *J*(4aA,1)=2.3, *J*(4aA,4aB)=13.2, *J*(4aA,4)=6.5, *J*(4aA,2B)=1.5 (H-4aA); 1.60 ddd, 1H, *J*(4aB,1)=5.7, *J*(4aB,4aA)=13.2, *J*(4aB,4)=9.6 (H-4aB). ^{13}C NMR ($CDCl_3$): 158.38 (2), 145.05, 136.28, 136.25, 130.07 (4), 128.22 (2), 127.69 (2), 126.63 and 113.02 (4) (2×C_6H_4 and C_6H_5 (ODMTr)); 86.24 (>C< (ODMTr)); 70.86 (C-1); 70.64 d, *J*(C,P)=6.3, 70.28 d, *J*(C,P)=6.3, 24.16 d, *J*(C,P)=3.8, 24.13 d, *J*(C,P)=3.8, 24.08 d, *J*(C,P)=3.8 and 24.00 d, *J*(C,P)=3.8 (P(O^{i}Pr)$_2$); 67.35 (C-5); 63.18 (C-2); 62.34 d, *J*(4,P)=11.3 (C-4); 55.15 (2×OMe (ODMTr)); 50.73 d, *J*(C,P)=148.4 (N–CH_2–P); 39.48 (C-4a).

5.1.13. Diisopropyl 2,3-dideoxy-5-O-dimethoxytrityl-3-aza-4a-carba-β-D-glycero-pentofuranos-3-ylmethylphosphonate (**13b**)

Using the procedure outlined for **13a**, compound **13b** was prepared from **12b** (8.73 g, 29.6 mmol) and dimethoxytrityl chloride (15.03 g, 44.4 mmol) as a pale yellow thick oil (16.24 g, 92%). HRMS (FAB) calcd for $C_{33}H_{45}NO_7P$ $[M+H]^+$ 598.2934, found: 598.2949. ^{1}H NMR ($CDCl_3$): 7.44 m, 2H, 7.33 m, 4H, 7.28 m, 2H, 7.20 m, 1H and 6.83 m, 4H (2×C_6H_4 and C_6H_5 (ODMTr); 4.16 m, 1H, *J*(1,2A)=1.5, *J*(1,2B)=3.7, *J*(1,4aA)=6.0, *J*(1,4aB)=3.0 (H-1); 4.70 m, 2H, 1.31 d, 6H, *J*=6.2, 1.28 d, 3H, *J*=6.2 and 1.26 d, 3H, *J*=6.2 (P(O^{i}Pr)$_2$); 3.782 s, 3H and 3.780 s, 3H (2×OMe (ODMTr)); 3.36 dd, 1H, *J*(2A,1)=1.5, *J*(2A,2B)=9.8 (H-2A); 3.36 dd, 1H, 1H, *J*(*gem*)=15.0, *J*(H,P)=16.5 and 2.73 dd, 1H, *J*(*gem*)=15.0, *J*(H,P)=6.0 (N–CH_2–P); 3.28 dd, 1H, *J*(5A,4)=3.8, *J*(5A,5B)=9.8 (H-5A); 3.08 dd, 1H, *J*(5B,4)=4.5, *J*(5B,5A)=9.8 (H-5B); 2.80 m, 1H, *J*(4,4aA)=10.0, *J*(4,4aB)=5.0, *J*(4,5A)=3.8, *J*(4,5B)=4.5 (H-4); 2.62 ddd, 1H, *J*(2B,1)=3.7, *J*(2B,2A)=9.8, *J*(2B,4aB)=2.0 (H-2B); 2.20 ddd, 1H, *J*(4aA,1)=6.0, *J*(4aA,4aB)=14.0, *J*(4aA,4)=10.0 (H-4aA); 1.60 m, 1H, *J*(4aB,1)=3.0, *J*(4aB,4aA)=14.0, *J*(4aB,4)=5.0, *J*(4aB,2B)=2.0 (H-4aB). ^{13}C NMR ($CDCl_3$): 158.42 (2), 144.70, 136.06, 135.93, 130.18 (2), 130.11 (2), 128.30 (2), 127.76 (2), 126.74 and 113.04 (4) (2×C_6H_4 and C_6H_5 (ODMTr)); 86.66 (>C< (ODMTr)); 70.59 (C-1); 70.54 d, *J*(C,P)=7.4, 70.02 d, *J*(C,P)=6.8, 24.04–24.20 4×d, *J*(C,P)=3.8 (OiPr$_2$); 65.50 (C-5); 63.47 (C-2); 63.15 d, *J*(4,P)=15.1 (C-4); 55.14 (2×OMe (ODMTr)); 50.03 d, *J*(C,P)=158.1 (N–CH_2–P); 37.95 (C-4a).

5.1.14. Diisopropyl 2,3-dideoxy-5-O-dimethoxytrityl-1-O-methanesulfonyl-3-aza-4a-carba-α-L-glycero-pentofuranos-3-ylmethylphosphonate (**14a**)

Dimethoxytrityl derivative **13a** (29.25 g, 49.0 mmol) was co-evaporated with toluene to remove traces of water, dissolved in dichloromethane (400 mL) with pyridine (39.6 mL, 489.5 mmol, 10 equiv) and cooled to 0 °C. Mesyl chloride (18.9 mL, 244.7 mmol, 5 equiv) was added to the stirred mixture in one portion. After 30 min (TLC in C2), the reaction was quenched by carefully adding water

dropwise to the mixture that is intensively stirred and cooled to 0 °C in an ice bath. The solution was diluted with chloroform and washed subsequently with water, 10% aqueous citric acid, saturated sodium hydrogen carbonate solution and finally with water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Product was isolated by flash chromatography on silica (elution with a linear gradient of EtOAc in toluene) and dried in vacuo, giving yellow thick oil **14a** (30.62 g, 93%). HRMS (FAB) calcd for $C_{34}H_{47}NO_9PS$ $[M+H]^+$ 676.2709, found: 676.2739. IR ν_{max}/cm^{-1} ($CHCl_3$): 1362, 1176, 906 (MsO); 1608, 1509, 1176, 1035, 831 (–ODMTr); 2983, 1465, 1176, 1012, 992 (–$CH_2PO(O^iPr)_2$). ^1H NMR ($CDCl_3$): 7.40 m, 2H, 7.29 m, 4H, 7.28 m, 2H, 7.22 m, 1H and 6.82 m, 4H (2×C_6H_4 and C_6H_5 (ODMTr)); 5.10 m, 1H, *J*(1,2A)=4.0, *J*(1,2B)=6.0, *J*(1,4aA)=3.0, *J*(1,4aB)=7.0 (H-1); 4.65 m, 2H, 1.29 d, 3H, *J*=6.2, 1.27 d, 3H, *J*=6.2, 1.26 d, 3H, *J*=6.2 and 1.20 d, 3H, *J*=6.2 (P(O^iPr)$_2$); 3.78 s, 6H (2×OMe (ODMTr)); 3.76 dd, 1H, *J*(2A,1)=4.0, *J*(2A,2B)∼11 (H-2A); 3.30 dd, 1H, 1H, *J*(*gem*)=15.2, *J*(H,P)=17.4 and 2.81 dd, 1H, *J*(*gem*)=15.2, *J*(H,P)=5.5 (N–CH_2–P); 3.18 dd, 1H, *J*(5A,4)=4.0, *J*(5A,5B)=9.0 (H-5A); 3.10 m, 1H, *J*(4,4aA)=6.4, *J*(4,4aB)=7.0, *J*(4,5A)=4.0, *J*(4,5B)=5.0 (H-4); 3.07 dd, 1H, *J*(5B,4)=5.0, *J*(5B,5A)=9.0 (H-5B); 2.99 s, 3H (OMs); 2.85 br dd, 1H, *J*(2B,1)=6.0, *J*(2B,2A)∼11 (H-2B); 2.22 m, 1H, *J*(4aA,1)=3.0, *J*(4aA,4aB)=14.0, *J*(4aA,4)=6.4 (H-4aA); 1.90 m, 1H, *J*(4aB,1)=7.0, *J*(4aB,4aA)=14.0, *J*(4aB,4)=7.0 (H-4aB). ^{13}C NMR ($CDCl_3$): 158.38 (2), 144.72, 135.88, 135.85, 129.94 (4), 128.02 (2), 127.74 (2), 126.70 and 113.03 (4) (2×C_6H_4 and C_6H_5 (ODMTr)); 86.32 (>C< (ODMTr)); 79.68 (C-1); 70.72 d, *J*(C,P)=6.3, 70.23 d, *J*(C,P)=6.3, 24.08 d, *J*(C,P)=3.8, 23.98 (2) d, *J*(C,P)=3.8 and 23.92 d, *J*(C,P)=3.8 (P(O^iPr)$_2$); 65.98 (C-5); 62.32 d, *J*(4,P)=16.4 (C-4); 60.61 (C-2); 55.10 (2×OMe (ODMTr)); 50.88 d, *J*(C,P)=166.0 (N–CH_2–P); 38.31 (OMs); 36.45 (C-4a). $[\alpha]_{20}^{D}$ −11.0 (*c* 0.250, $CHCl_3$).

5.1.15. Diisopropyl 2,3-dideoxy-5-O-dimethoxytrityl-1-O-methanesulfonyl-3-aza-4a-carba-β-D-glycero-pentofuranos-3-ylmethylphosphonate (**14b**)

Using the procedure outlined for **14a**, compound **14b** was prepared from **13b** (16.24 g, 27.2 mmol), pyridine (22.0 mL, 271.7 mmol) and mesyl chloride (10.5 mL, 135.8 mmol) as a yellow thick oil (14.95 g, 81%). HRMS (FAB) calcd for $C_{34}H_{46}NO_9NaPS$ $[M+Na]^+$ 698.2529, found: 698.2547. IR ν_{max}/cm^{-1} ($CHCl_3$): 1360, 1176, 910 (MsO); 1608, 1509, 1176, 1035, 830 (–ODMTr); 2984, 1250, 1176, 1011, 993 (–$CH_2PO(O^iPr)_2$). ^1H NMR ($CDCl_3$): 7.42 m, 2H, 7.31 m, 4H, 7.28 m, 2H, 7.21 m, 1H and 6.82 m, 4H (2×C_6H_4 and C_6H_5 (ODMTr); 5.12 m, 1H, *J*(1,2A)∼1.0, *J*(1,2B)=4.8, *J*(1,4aA)=7.1, *J*(1,4aB)=2.2 (H-1); 4.67 m, 2H, 1.29 d, 6H, *J*=6.2, 1.285 d, 3H, *J*=6.2, 1.27 d, 3H, *J*=6.2 and 1.22 d, 3H, *J*=6.2 (P(O^iPr)$_2$); 3.79 s, 6H (2×OMe (ODMTr)); 3.71 dd, 1H, *J*(2A,1)∼1.0, *J*(2A,2B)=11.8 (H-2A); 3.39 dd, 1H, 1H, *J*(*gem*)=15.3, *J*(H,P)=18.1 and 2.68 dd, 1H, *J*(*gem*)=15.3, *J*(H,P)=5.3 (N–CH_2–P); 3.26 dd, 1H, *J*(5A,4)=6.0, *J*(5A,5B)=9.6 (H-5A); 3.11 dd, 1H, *J*(5B,4)=8.6, *J*(5B,5A)=9.6 (H-5B); 2.94 s, 3H (OMs); 2.78 m, 1H, *J*(4,4aA)=8.6, *J*(4,4aB)=1.6, *J*(4,5A)=6.0, *J*(4,5B)=5.5 (H-4); 2.69 br dd, 1H, *J*(2B,1)=4.8, *J*(2B,2A)=11.8 (H-2B); 2.39 ddd, 1H, *J*(4aA,1)=7.1, *J*(4aA,4aB)=15.0, *J*(4aA,4)=8.6 (H-4aA); 1.86 m, 1H, *J*(4aB,1)=1.6, *J*(4aB,4aA)=15.0, *J*(4aB,4)=2.2 (H-4aB). ^{13}C NMR ($CDCl_3$): 158.45 (2), 144.86, 136.07, 136.02, 130.06 (4), 128.16 (2), 127.80 (2), 126.76 and 113.09 (4) (2×C_6H_4 and C_6H_5 (ODMTr)); 86.41 (>C< (ODMTr)); 79.93 (C-1); 70.96 d, *J*(C,P)=6.5, 70.20 d, *J*(C,P)=6.7, 24.19 d, *J*(C,P)=3.9, 24.08 d, *J*(C,P)=4.6, 24.06 d, *J*(C,P)=4.6 and 23.96 d, *J*(C,P)=4.8 (O^iPr)$_2$); 66.49 (C-5); 63.80 d, *J*(4,P)=17.1 (C-4); 60.77 (C-2); 55.20 (2×OMe (ODMTr)); 50.42 d, *J*(C,P)=162.1 (N–CH_2–P); 38.86 (OMs); 35.99 (C-4a). $[\alpha]_{20}^{D}$ +24.4 (*c* 0.176, $CHCl_3$).

5.1.16. Diisopropyl 2,3-dideoxy-5-O-dimethoxytrityl-1-O-acetyl-3-aza-4a-carba-β-L-glycero-pentofuranos-3-ylmethylphosphonate (**15a**)

Anhydrous sodium acetate (26.00 g, 316.5 mmol, 10 equiv) was suspended in a solution of mesylate **14a** (21.38 g, 31.6 mmol) in dry dimethylformamide (200 mL). The flask was equipped with a calcium dichloride tube and the stirred mixture was heated to 120 °C for 6 h (TLC in C2). The reaction mixture was then cooled, DMF was evaporated in vacuo, the residue was dissolved in ethyl acetate and inorganic salts were filtered off. The organic layer was washed with water, dried over Na_2SO_4 and evaporated in vacuo. The crude was purified by flash chromatography on silica (elution with a linear gradient of EtOAc in toluene) and dried in vacuo to afford a pale yellow thick oil (10.62 g, 52%). HRMS (FAB) calcd for $C_{35}H_{45}NO_8P$ $[M-H]^-$ 638.2883, found: 638.2904. ^1H NMR ($CDCl_3$): 7.42 m, 2H, 7.31 m, 4H, 7.28 m, 2H, 7.20 m, 1H and 6.82 m, 4H (2×C_6H_4 and C_6H_5 (ODMTr)); 5.12 m, 1H, *J*(1,2A)=1.5, *J*(1,2B)=5.3, *J*(1,4aA)=2.9, *J*(1,4aB)=7.3 (H-1); 4.68 m, 2H, 1.29 d, 6H, *J*=6.2, 1.27 d, 3H, *J*=6.2 and 1.24 d, 3H, *J*=6.2 (P(O^iPr)$_2$); 3.79 s, 6H (2×OMe (ODMTr)); 3.44 dd, 1H, *J*(2A,1)=1.5, *J*(2A,2B)=11.2, *J*(2A,4aB)=1.1 (H-2A); 3.38 dd, 1H, 1H, *J*(*gem*)=15.0, *J*(H,P)=17.6 and 2.69 dd, 1H, *J*(*gem*)=15.0, *J*(H,P)=5.6 (N–CH_2–P); 3.22 dd, 1H, *J*(5A,4)=5.8, *J*(5A,5B)=9.5 (H-5A); 3.08 dd, 1H, *J*(5B,4)=5.7, *J*(5B,5A)=9.5 (H-5B); 2.78 m, 1H, *J*(4,4aA)=8.3, *J*(4,4aB)=7.2, *J*(4,5A)=5.8, *J*(4,5B)=5.7 (H-4); 2.67 ddd, 1H, *J*(2B,1)=5.3, *J*(2B,2A)=11.2, *J*(2B,4)=1.6 (H-2B); 1.93 s, 3H (OAc); 2.35 ddd, 1H, *J*(4aA,1)=7.3, *J*(4aA,4aB)=14.3, *J*(4aA,4)=8.3 (H-4aA); 1.59 dddd, 1H, *J*(4aB,1)=2.9, *J*(4aB,4aA)=14.3, *J*(4aB,4)=7.2 *J*(4aB,2A)=1.1 (H-4aB). ^{13}C NMR ($CDCl_3$): 170.80 and 21.11 (OAc); 158.34 (2), 144.93, 136.16, 136.13, 130.02 (4), 128.14 (2), 127.72 (2), 126.66 and 112.99 (4) (2×C_6H_4 and C_6H_5 (ODMTr)); 86.18 (>C< (ODMTr)); 73.13 (C-1); 70.80 d, *J*(C,P)=6.8, 70.05 d, *J*(C,P)=6.9, 24.19 d, *J*(C,P)=3.8, 24.04 d, *J*(C,P)=3.6, 24.02 d, *J*(C,P)=4.9 and 23.89 d, *J*(C,P)=4.8 (P(O^iPr)$_2$); 66.49 (C-5); 64.06 d, *J*(4,P)=16.8 (C-4); 60.80 (C-2); 55.15 (2×OMe (ODMTr)); 50.57 d, *J*(C,P)=161.5 (N–CH_2–P); 35.70 (C-4a).

5.1.17. Diisopropyl 2,3-dideoxy-5-O-dimethoxytrityl-1-O-acetyl-3-aza-4a-carba-α-D-glycero-pentofuranos-3-ylmethylphosphonate (**15b**)

Using the procedure outlined for **15a**, compound **15b** was prepared from **14b** (7.82 g, 11.6 mmol) and NaOAc (9.49 g, 115.7 mmol) as a pale yellow thick oil (4.30 g, 58%). HRMS (FAB) calcd for $C_{35}H_{46}NO_8NaP$ $[M+Na]^+$ 662.2859, found: 662.2832. ^1H NMR ($CDCl_3$): 7.41 m, 2H, 7.30 m, 4H, 7.27 m, 2H, 7.20 m, 1H and 6.82 m, 4H (2×C_6H_4 and C_6H_5 (ODMTr)); 5.12 m, 1H, *J*(1,2A)=6.2, *J*(1,2B)=4.2, *J*(1,4aA)=2.8, *J*(1,4aB)=7.1 (H-1); 4.65 m, 2H, 1.280 d, 3H, *J*=6.1, 1.274 d, 3H, *J*=6.2, 1.242 d, 3H, *J*=6.2 and 1.198 d, 3H, *J*=6.2 (P(O^iPr)$_2$); 3.78 s, 6H (2×OMe (ODMTr)); 3.70 dd, 1H, *J*(2A,1)=6.2, *J*(2A,2B)=11.3 (H-2A); 3.30 dd, 1H, *J*(*gem*)=15.0, *J*(H,P)=17.9 and 2.77 dd, 1H, *J*(*gem*)=15.0, *J*(H,P)=5.6 (N–CH_2–P); 3.18 dd, 1H, *J*(5A,4)=4.8, *J*(5A,5B)=8.8 (H-5A); 3.03 dd, 1H, *J*(5B,4)=5.6, *J*(5B,5A)=8.8 (H-5B); 3.01 m, 1H, *J*(4,4aA)=6.5, *J*(4,4aB)=8.5, *J*(4,5A)=4.8, *J*(4,5B)=5.6, *J*(4,2B)<1.0 (H-4); 2.60 ddt, 1H, *J*(2B,1)=4.2, *J*(2B,2A)=11.3, *J*(2B,4)<1.0, *J*(2B,4aA)<1.0 (H-2B); 2.04 s, 3H (OAc); 1.98 br ddd, 1H, *J*(4aA,1)=2.8, *J*(4aA,4aB)=13.8, *J*(4aA,4)=6.5, *J*(4aA,2B)<1.0 (H-4aA); 1.82 m, 1H, *J*(4aB,1)=7.1, *J*(4aB,4aA)=13.8, *J*(4aB,4)=8.5 (H-4aB). ^{13}C NMR ($CDCl_3$): 170.56 and 21.13 (OAc); 158.41 (2), 144.90, 136.12 (2), 130.02 (4), 128.15 (2), 127.72 (2), 126.67 and 113.02 (4) (2×C_6H_4 and C_6H_5 (ODMTr)); 86.27 (>C< (ODMTr)); 73.13 (C-1); 70.59 d, *J*(C,P)=7.5, 70.08 d, *J*(C,P)=6.3, 24.14 d, *J*(C,P)=3.8, 24.03 d, *J*(C,P)=3.8, 24.01 d, *J*(C,P)=5.0 and 23.95 d, *J*(C,P)=5.0 (P(O^iPr)$_2$); 66.47 (C-5); 63.72 d, *J*(4,P)=17.6 (C-4); 60.89 (C-2); 55.14 (2×OMe (ODMTr)); 51.30 d, *J*(C,P)=164.8 (N–CH_2–P); 36.17 (C-4a).

5.1.18. Diisopropyl 2,3-dideoxy-5-O-dimethoxytrityl-3-aza-4a-carba-β-L-glycero-pentofuranos-3-ylmethylphosphonate (**16a**)

Sodium methoxide (2 M solution) in methanol (1 mL) was added to a solution of **15a** (10.62 g, 16.6 mmol) in anhydrous methanol (100 mL). After 30 min (TLC in C2), the reaction mixture was worked up by adding Dowex 50 (Et_3N^+-form), which was

then filtered off, and the solution was concentrated in vacuo, giving pale yellow thick oil (9.92 g, ca. 100%). HRMS (FAB) calcd for $C_{33}H_{45}NO_7P$ $[M+H]^+$ 598.2934, found: 598.2920. ^1H and ^{13}C NMR spectra were identical to those recorded for enantiomeric **13b**.

*5.1.19. Diisopropyl 2,3-dideoxy-5-O-dimethoxytrityl-3-aza-4a-carba-α-D-glycero-pentofuranos-3-ylmethylphosphonate (**16b**)*

Using the procedure outlined for **16a**, compound **16b** was prepared from **15b** (4.30 g, 6.72 mmol) as a pale yellow thick oil (4.02 g, ca. 100%). HRMS (FAB) calcd for $C_{33}H_{45}NO_7P$ $[M+H]^+$ 598.2934, found: 598.2940. ^1H and ^{13}C NMR spectra were identical to those recorded for enantiomeric **13a**.

*5.1.20. Diisopropyl 2,3-dideoxy-5-O-dimethoxytrityl-1-O-methanesulfonyl-3-aza-4a-carba-β-L-glycero-pentofuranos-3-ylmethylphosphonate (**17a**)*

Using the procedure outlined for **14a**, compound **17a** was prepared from **16a** (9.92 g, 16.6 mmol), pyridine (13.4 mL, 166 mmol) and mesyl chloride (6.42 mL, 83 mmol) as a yellow thick oil (9.22 g, 82%). HRMS (FAB) calcd for $C_{34}H_{47}NO_9PS$ $[M+H]^+$ 676.2709, found: 676.2701. IR, ^1H and ^{13}C NMR spectra were identical to those recorded for enantiomeric **14b**. $[\alpha]_{20}^{D}$ −25.3 (*c* 0.211, $CHCl_3$).

*5.1.21. Diisopropyl 2,3-dideoxy-5-O-dimethoxytrityl-1-O-methanesulfonyl-3-aza-4a-carba-α-D-glycero-pentofuranos-3-ylmethylphosphonate (**17b**)*

Using the procedure outlined for **14a**, compound **17b** was prepared from **16b** (4.02 g, 6.72 mmol), pyridine (5.44 mL, 67.2 mmol) and mesyl chloride (2.60 mL, 33.6 mmol) as a yellow thick oil (4.14 g, 91%). HRMS (FAB) calcd for $C_{34}H_{46}NO_9NaPS$ $[M+Na]^+$ 698.2529, found: 698.2516. IR, ^1H and ^{13}C NMR spectra were identical to those recorded for enantiomeric **14a**. $[\alpha]_{20}^{D}$ +12.8 (*c* 0.218, $CHCl_3$).

5.2. Alkylation of nucleobases (general procedure A)

To a suspension of nucleobase (1.5 equiv) in dry DMF (6 mL/mmol) was added anhydrous caesium carbonate (1.2 equiv), and the reaction mixture was vigorously stirred under anhydrous conditions at 120 °C for 20 min. Then solution of mesylate (1 equiv) in DMF (3 mL/mmol) was added and the reaction mixture was stirred at 110 °C. After the reaction was complete (TLC in C2), DMF was evaporated, the residue was dissolved in $CHCl_3$ and inorganic precipitate was filtered off. Solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica (elution with a linear gradient of EtOH in $CHCl_3$).

*5.2.1. Diisopropyl 1-(adenin-9-yl)-5-O-dimethoxytrityl-1,2,3-trideoxy-3-aza-4a-carba-α-L-glycero-pentofuranos-3-ylmethylphosphonate (**18a**)*

The general procedure A was followed using mesylate **17a** (1.60 g, 2.36 mmol), Cs_2CO_3 (0.923 g, 2.83 mmol) and adenine (0.479 g, 3.54 mmol). The reaction was complete after 3 h. White foam (0.709 g, 42%). HRMS (FAB) calcd for $C_{38}H_{48}N_6O_6P$ $[M+H]^+$ 715.3373, found: 715.3389. IR ν_{max}/cm^{-1} ($CHCl_3$): 1630, 1608, 1414 (adenine); 1608, 1509, 1178, 1035 (–ODMTr); 2984, 1467, 1251, 1178, 1009, 992 (–$CH_2PO(O^iPr)_2$). ^1H NMR (DMSO-d_6): 8.23 s, 1H (H-8); 8.12 s, 1H (H-2); 7.40 m, 2H, 7.32 m, 2H, 7.27 m, 4H, 7.23 m, 1H and 6.90 m, 4H (2×C_6H_4 and C_6H_5 (ODMTr)); 7.20 br s, 2H (NH_2); 4.95 m, 1H, *J*(1′,2′A)=6.7, *J*(1′,2′B)=8.0, *J*(1′,4′aA)=6.8, *J*(1′,4′aB)=8.8 (H-1′); 4.51 m, 2H, 1.20 d, 3H, *J*=6.1, 1.185 d, 3H, *J*=6.1, 1.17 d, 3H, *J*=6.1 and 1.12 d, 3H, *J*=6.1 ($P(O^iPr)_2$); 3.74 s, 6H (2×OMe (ODMTr)); 3.66 dd, 1H, *J*(2′A,1′)=6.7, *J*(2′A,2′B)=9.2, (H-2′A); 3.28 m, 1H, *J*(4′,4′aA)=8.8, *J*(4′,4′aB)=5.8, *J*(4′,5′A)=5.4, *J*(4′,5′B)=5.2 (H-4′); 3.26 dd, 1H, *J*(*gem*)=15.0, *J*(H,P)=16.4 and 2.83 dd, 1H, *J*(*gem*)=15.0, *J*(H,P)=6.1 (N–CH_2–P); 3.10 dd, 1H, *J*(5′A,4′)=5.4, *J*(5′A,5′B)=9.7 (H-5′A); 3.06 dd, 1H, *J*(5′B,4′)=5.2, *J*(5′B,5′A)=9.7 (H-5′B); 2.93 dd, 1H, *J*(2′B,1′)=8.0, *J*(2′B,2′A)=9.2 (H-2′B); 2.40 ddd, 1H, *J*(4′aA,1′)=6.8, *J*(4′aA,4′aB)=13.4, *J*(4′aA,4′)=8.8 (H-4′aA); 2.07 ddd, 1H, *J*(4′aB,1′)=8.8, *J*(4′aB,4′aA)=13.4, *J*(4′aB,4′)=5.8 (H-4′aB). ^{13}C NMR (DMSO-d_6): 158.28 (2), 145.17, 135.85, 135.82, 129.95 (4), 128.07 (2), 127.91 (2), 126.90 and 113.40 (4) (2×C_6H_4 and C_6H_5 (ODMTr)); 156.12 (C-4); 152.48 (C-2); 149.57 (C-6); 139.68 (C-8); 119.28 (C-5); 86.00 (>C< (ODMTr)); 70.12 d, *J*(C,P)=7.5, 69.70 d, *J*(C,P)=6.3, 24.08 d, *J*(C,P)=5.0, 24.00 (2) d, *J*(C,P)=5.0 and 23.88 d, *J*(C,P)=5.0 ($P(O^iPr)_2$); 66.09 (C-5′); 62.99 d, *J*(4′,P)=17.6 (C-4′); 59.62 (C-2′); 55.23 (2×OMe (ODMTr)); 52.15 (C-1′); 49.90 d, *J*(C,P)=174.6 (N–CH_2–P); 33.81 (C-4′a).

*5.2.2. Diisopropyl 1-(cytosin-1-yl)-5-O-dimethoxytrityl-1,2,3-trideoxy-3-aza-4a-carba-α-L-glycero-pentofuranos-3-ylmethylphosphonate (**18b**)*

The general procedure A was followed using mesylate **17a** (1.51 g, 2.23 mmol) and cytosine (0.371 g, 3.34 mmol). NaH (60% suspension in oil, 0.107 g, 2.67 mmol, 1.2 equiv) and DMSO were used instead of Cs_2CO_3–DMF. The reaction was complete after 3 h. White foam (0.400 g, 26%). HRMS (FAB) calcd for $C_{37}H_{48}N_4O_7P$ $[M+H]^+$ 691.3261, found: 691.3241. IR ν_{max}/cm^{-1} ($CHCl_3$): 1648, 1600, 1483 (cytosine); 1608, 1509, 1493, 1178, 1035 (–ODMTr); 2985, 1251, 1178, 1010, 991 (–$CH_2PO(O^iPr)_2$). ^1H NMR (DMSO-d_6): 7.64 d, 1H, *J*(6,5)=7.5 (H-6); 7.38 m, 2H, 7.31 m, 2H, 7.25 m, 4H, 7.23 m, 1H and 6.89 m, 4H (2×C_6H_4 and C_6H_5 (ODMTr)); 7.04 br s, 1H and 6.99 br s, 1H (NH_2); 5.68 d, 1H, *J*(5,6)=7.5 (H-5); 4.89 m, 1H, *J*(1′,2′A)=6.8, *J*(1′,2′B)=7.8, *J*(1′,4′aA)=6.5, *J*(1′,4′aB)=9.5 (H-1′); 4.49 m, 2H, 1.20 d, 3H, *J*=6.2, 1.18 d, 3H, *J*=6.2, 1.17 d, 3H, *J*=6.2 and 1.12 d, 3H, *J*=6.2 ($P(O^iPr)_2$); 3.74 s, 6H (2×OMe (ODMTr)); 3.39 dd, 1H, *J*(2′A,1′)=6.8, *J*(2′A,2′B)=9.0 (H-2′A); 3.16 dd, 1H, 1H, *J*(*gem*)=15.0, *J*(H,P)=16.0 and 2.76 dd, 1H, *J*(*gem*)=15.0, *J*(H,P)=6.8 (N–CH_2–P); 3.15 m, 1H, *J*(4′,4′aA)=9.5, *J*(4′,4′aB)=6.0, *J*(4′,5′A)=5.2, *J*(4′,5′B)=5.0 (H-4′); 3.03 dd, 1H, *J*(5′A,4′)=5.2, *J*(5′A,5′B)=9.8 (H-5′A); 3.01 dd, 1H, *J*(5′B,4′)=5.0, *J*(5′B,5′A)=9.8 (H-5′B); 2.58 dd, 1H, *J*(2′B,1′)=7.8, *J*(2′B,2′A)=9.0 (H-2′B); 1.96 ddd, 1H, *J*(4′aA,1′)=6.5, *J*(4′aA,4′aB)=13.0, *J*(4′aA,4′)=9.5 (H-4′aA); 1.86 ddd, 1H, *J*(4′aB,1′)=9.5, *J*(4′aB,4′aA)=13.0, *J*(4′aB,4′)=6.0 (H-4′aB). ^{13}C NMR (DMSO-d_6): 165.42 (C-4); 158.24 (2), 145.12, 135.80, 135.76, 129.89 (4), 128.03 (2), 127.85 (2), 126.86 and 113.36 (4) (2×C_6H_4 and C_6H_5 (ODMTr)); 155.84 (C-2); 142.99 (C-6); 93.98 (C-5); 85.94 (>C< (ODMTr)); 70.02 d, *J*(C,P)=6.5, 69.62 d, *J*(C,P)=6.2, 24.04 d, *J*(C,P)=5.0, 23.94 (2) d, *J*(C,P)=4.9 and 23.85 d, *J*(C,P)=4.3 ($P(O^iPr)_2$); 65.72 (C-5′); 63.07 d, *J*(4′,P)=15.6 (C-4′); 59.04 (C-2′); 55.20 (2×OMe (ODMTr)); 53.61 (C-1′); 49.62 d, *J*(C,P)=163.0 (N–CH_2–P); 33.42 (C-4′a).

*5.2.3. Diisopropyl 1-(cytosin-2-O-yl)-5-O-dimethoxytrityl-1,2,3-trideoxy-3-aza-4a-carba-α-L-glycero-pentofuranos-3-ylmethylphosphonate (**18c**)*

The general procedure A was followed using mesylate **17a** (1.59 g, 2.37 mmol), Cs_2CO_3 (0.922 g, 2.83 mmol) and cytosine (0.393 g, 3.54 mmol). The reaction was complete after 3 h. White foam (0.584 g, 36%). HRMS (FAB) calcd for $C_{37}H_{48}N_4O_7P$ $[M+H]^+$ 691.3261, found: 691.3291. IR ν_{max}/cm^{-1} ($CHCl_3$): 1616, 1587, 1566, 1412, 1301 (cytosine); 1509, 1178, 1035 (–ODMTr); 2983, 1251, 1178, 1013, 993(–$CH_2PO(O^iPr)_2$). ^1H NMR (DMSO-d_6): 7.84 d, 1H, *J*(6,5)=5.7 (H-6); 7.38 m, 2H, 7.31 m, 2H, 7.24 m, 4H, 7.22 m, 1H and 6.89 m, 4H (2×C_6H_4 and C_6H_5 (ODMTr)); 6.79 br s, 2H (NH_2); 6.06 d, 1H, *J*(6,5)=5.7 (H-6); 5.13 m, 1H, *J*(1′,2′A)=5.9, *J*(1′,2′B)=4.2, *J*(1′,4′aA)=3.1, *J*(1′,4′aB)=7.2 (H-1′); 4.48 m, 2H, 1.19 d, 3H, *J*=6.1, 1.17 d, 3H, *J*=6.2, 1.16 d, 3H, *J*=6.2 and 1.09 d, 3H, *J*=6.2 ($P(O^iPr)_2$); 3.73 s, 6H (2×OMe (ODMTr)); 3.63 dd, 1H, *J*(2′A,1′)=5.9, *J*(2′A,2′B)=11.0,

(H-2′A); 3.28 dd, 1H, 1H, *J*(*gem*)=15.0, *J*(H,P)=16.4 and 2.70 dd, 1H, *J*(*gem*)=15.0, *J*(H,P)=5.2 (N–CH_2–P); 3.03 m, 1H, *J*(4′,4′aA)=6.6, *J*(4′,4′aB)=8.2 (H-4′); 3.03 m, 1H (H-5′A); 2.97 m, 1H (H-5′B); 2.51 dd, 1H, *J*(2′B,1′)=4.2, *J*(2′B,2′A)=11.0 (H-2′B); 1.92 ddd, 1H, *J*(4′aA,1′)=3.1, *J*(4′aA,4′aB)=13.6, *J*(4′aA,4′)=6.6 (H-4′aA); 1.74 ddd, 1H, *J*(4′aB,1′)=7.2, *J*(4′aB,4′aA)=13.6, *J*(4′aB,4′)=8.2 (H-4′aB). ^{13}C NMR (DMSO-d_6): 166.56 (C-4); 164.50 (C-2); 158.25 (2), 145.17, 135.88, 135.85, 129.90 (4), 128.05 (2), 127.88 (2), 126.87 and 113.39 (4) (2×C_6H_4 and C_6H_5 (ODMTr)); 156.38 (C-6); 99.63 (C-5); 85.91 (>C< (ODMTr)); 73.93 (C-1′); 70.04 d, *J*(C,P)=7.5, 69.58 d, *J*(C,P)=6.3, 24.09 d, *J*(C,P)=3.8, 24.00 d, *J*(C,P)=3.8, 23.96 d, *J*(C,P)=5.0 and 23.83 d, *J*(C,P)=5.0 (P(O^{i}Pr)$_2$); 66.65 (C-5′); 63.52 d, *J*(4′,P)=17.6 (C-4′); 61.53 (C-2′); 55.23 (2×OMe (ODMTr)); 51.13 d, *J*(C,P)=163.4 (N–CH_2–P); 35.88 (C-4′a).

5.2.4. Diisopropyl 1-(thymin-1-yl)-5-O-dimethoxytrityl-1,2,3-trideoxy-3-aza-4a-carba-α-L-glycero-pentofuranos-3-ylmethylphosphonate (**18d**)

The general procedure A was followed using mesylate **17a** (1.31 g, 1.94 mmol), Cs_2CO_3 (0.757 g, 2.32 mmol) and thymine (0.366 g, 2.90 mmol). The reaction was complete after 2 h. White foam (0.515 g, 38%). HRMS (FAB) calcd for $C_{38}H_{47}N_3O_8P$ $[M-H]^-$ 704.3101, found: 704.3070. IR ν_{max}/cm^{-1} ($CHCl_3$): 1685, 1648, 1276 (thymine); 1509, 1178, 1154, 1035 (–ODMTr); 1251, 1178, 1142, 1010, 991 (–CH_2PO(O^{i}Pr)$_2$). ^{1}H NMR (DMSO-d_6): 11.23 s, 1H (NH); 7.585 q, 1H, *J*(6,Me)=1.2 (H-6); 7.38 m, 2H, 7.32 m, 2H, 7.25 m, 4H, 7.23 m, 1H and 6.89 m, 4H (2×C_6H_4 and C_6H_5 (ODMTr)); 4.87 m, 1H, *J*(1′,2′A)=7.2, *J*(1′,2′B)=7.8, *J*(1′,4′aA)=6.6, *J*(1′,4′aB)=9.5 (H-1′); 4.50 m, 2H, 1.202 d, 3H, *J*=6.2, 1.186 d, 3H, *J*=6.2, 1.179 d, 3H, *J*=6.2 and 1.129 d, 3H, *J*=6.2 (P(O^{i}Pr)$_2$); 3.73 s, 3H and 3.735 s, 3H (2×OMe (ODMTr)); 3.39 dd, 1H, *J*(2′A,1′)=7.2, *J*(2′A,2′B)=9.2 (H-2′A); 3.17 m, 1H (H-4′); 3.15 dd, 1H, 1H, *J*(*gem*)=15.2, *J*(H,P)=15.8 and 2.79 dd, 1H, *J*(*gem*)=15.2, *J*(H,P)=7.2 (N–CH_2–P); 3.04 m, 2H (H-5′A+H-5′B); 2.64 dd, 1H, *J*(2′B,1′)=7.8, *J*(2′B,2′A)=9.2 (H-2′B); 2.01 ddd, 1H, *J*(4′aA,1′)=6.6, *J*(4′aA,4′aB)=13.5, *J*(4′aA,4′)=8.6 (H-4′aA); 1.88 ddd, 1H, *J*(4′aB,1′)=9.5, *J*(4′aB,4′aA)=13.5, *J*(4′aB,4′)=5.8 (H-4′aB); 1.78 d, 3H, *J*(Me,6)=1.2 (5-Me). ^{13}C NMR (d$_6$DMSO): 163.58 (C-2); 158.12 (2), 144.85, 135.66 (2), 129.66 (4), 127.71 (4), 126.60 and 113.18 (4) (2×C_6H_4 and C_6H_5 (ODMTr)); 150.86 (C-4); 137.79 (C-6); 109.20 (C-5); 85.97 (>C< (ODMTr)); 69.78 d, *J*(C,P)=6.9, 69.47 d, *J*(C,P)=6.9, 23.76–23.55 4×d, *J*(C,P)=5.0 (P(O^{i}Pr)$_2$); 65.22 (C-5′); 62.73 d, *J*(4′,P)=15.6 (C-4′); 57.94 (C-2′); 55.02 (2×OMe (ODMTr)); 52.64 (C-1′); 49.26 d, *J*(C,P)=163.0 (N–CH_2–P); 32.79 (C-4′a), 11.95 (5-Me).

5.2.5. Diisopropyl 1-(2-amino-6-chloropurin-9-yl)-5-O-dimethoxytrityl-1,2,3-trideoxy-3-aza-4a-carba-α-L-glycero-pentofuranos-3-ylmethylphosphonate (**18e**)

The general procedure A was followed using mesylate **17a** (1.278 g, 1.89 mmol), Cs_2CO_3 (0.740 g, 2.28 mmol) and 2-amino-6-chloropurine (0.481 g, 2.84 mmol). The reaction was complete after 3 h. White foam (0.581 g, 41%). HRMS (FAB) calcd for $C_{38}H_{47}N_6O_6PCl$ $[M+H]^+$ 749.2983, found: 749.3002. IR ν_{max}/cm^{-1} ($CHCl_3$): 1609, 1566, 1456, 1406 (chloropurine); 1609, 1509, 1456, 1178, 1035 (–ODMTr); 2985, 1251, 1178, 1011, 993 (–CH_2PO(O^{i}Pr)$_2$). ^{1}H NMR (DMSO-d_6): 8.25 s, 1H (H-8); 7.41 m, 2H, 7.32 m, 2H, 7.26 m, 4H, 7.23 m, 1H and 6.90 m, 4H (2×C_6H_4 and C_6H_5 (ODMTr)); ~6.90 br s, 2H (NH_2); 4.83 m, 1H, *J*(1′,2′A)=6.6, *J*(1′,2′B)≤2.0, *J*(1′,4′aA)=8.5, *J*(1′,4′aB)=6.0 (H-1′); 4.50 m, 2H, 1.195 d, 3H, *J*=6.2, 1.18 d, 3H, *J*=6.1, 1.17 d, 3H, *J*=6.0 and 1.115 d, 3H, *J*=6.1 (P(O^{i}Pr)$_2$); 3.86 br d, 1H, *J*(2′A,1′)≤2.0, *J*(2′A,2′B)=9.4, (H-2′A); 3.74 s, 6H (2×OMe (ODMTr)); 3.26 m, 1H, *J*(4′,4′aA)=6.5, *J*(4′,4′aB)=8.6, *J*(4′,5′A)=5.5, *J*(4′,5′B)=5.0 (H-4′); 3.24 dd, 1H, 1H, *J*(*gem*)=15.2, *J*(H,P)=16.4 and 2.84 dd, 1H, *J*(*gem*)=15.2, *J*(H,P)=6.3 (N–CH_2–P); 3.09 dd, 1H, *J*(5′A,4′)=5.5, *J*(5′A,5′B)=9.7 (H-5′A); 3.04 dd, 1H, *J*(5′B,4′)=5.0, *J*(5′B,5′A)=9.7 (H-5′B); 2.86 dd, 1H, *J*(2′B,1′)=6.6, *J*(2′B,2′A)=9.4 (H-2′B); 2.36 ddd, 1H, *J*(4′aA,1′)=8.5, *J*(4′aA,4′aB)=13.6, *J*(4′aA,4′)=6.5 (H-4′aA); 2.04 ddd, 1H, *J*(4′aB,1′)=6.0, *J*(4′aB,4′aA)=13.6, *J*(4′aB,4′)=8.6 (H-4′aB). ^{13}C NMR (DMSO-d_6): 159.78 (C-2); 158.28 (2), 145.12, 135.80, 135.79, 129.95 (4), 128.07 (2), 127.90 (2), 126.91 and 113.40 (4) (2×C_6H_4 and C_6H_5 (ODMTr)); 154.13 (C-4); 149.58 (C-6); 141.74 (C-8); 123.75 (C-5); 86.01 (>C< (ODMTr)); 70.12 d, *J*(C,P)=6.3, 69.72 d, *J*(C,P)=7.5, 24.06 d, *J*(C,P)=3.8, 23.98 (2) d, *J*(C,P)=3.8 and 23.87 d, *J*(C,P)=5.0 (P(OiPr)$_2$); 66.02 (C-5′); 62.82 d, *J*(4′,P)=16.4 (C-4′); 59.33 (C-2′); 55.24 (2×OMe (ODMTr)); 51.99 (C-1′); 49.80 d, *J*(C,P)=162.2 (N–CH_2–P); 33.65 (C-4′a).

5.2.6. Diisopropyl 1-(2-amino-6-azidopurin-9-yl)-5-O-dimethoxytrityl-1,2,3-trideoxy-3-aza-4a-carba-α-L-glycero-pentofuranos-3-ylmethylphosphonate (**19**)

To a solution of **18e** (0.342 g, 0.46 mmol) in anhydrous DMF (10 mL) was added NaN_3 (0.297 g, 4.57 mmol, 10 equiv). The reaction mixture was stirred for 3 h at 110 °C (TLC in C1), after which DMF was evaporated, the residue was suspended in $CHCl_3$ and the precipitate removed by filtration. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography on silica (elution with a linear gradient of EtOH in $CHCl_3$) to yield **19** as a colourless glassy solid (0.205 g, 59%). HRMS (FAB) calcd for $C_{38}H_{47}N_9O_6P$ $[M+H]^+$ 756.3387, found: 756.3408. ^{1}H NMR (DMSO-d_6): 8.36 br s, 2H (NH_2); 8.30 s, 1H (H-8); 7.41 m, 2H, 7.33 m, 2H, 7.27 m, 4H, 7.24 m, 1H and 6.90 m, 4H (2×C_6H_4 and C_6H_5 (ODMTr)); 4.98 m, 1H, *J*(1′,2′A)=6.7, *J*(1′,2′B)=8.0, *J*(1′,4′aA)=8.8, *J*(1′,4′aB)=6.3 (H-1′); 4.51 m, 2H, 1.20 d, 3H, *J*=6.2, 1.19 d, 3H, *J*=6.2, 1.17 d, 3H, *J*=6.2 and 1.13 d, 3H, *J*=6.2 (P(O^{i}Pr)$_2$); 3.74 s, 6H (2×OMe (ODMTr)); 3.69 dd, 1H, *J*(2′A,1′)=6.7, *J*(2′A,2′B)=9.2 (H-2′A); 3.30 m, 1H, *J*(4′,4′aA)=6.5, *J*(4′,4′aB)=9.2, *J*(4′,5′A)=5.5, *J*(4′,5′B)=5.2 (H-4′); 3.26 dd, 1H, *J*(*gem*)=15.0, *J*(H,P)=16.0 and 2.86 dd, 1H, *J*(*gem*)=15.0, *J*(H,P)=6.2 (N–CH_2–P); 3.12 dd, 1H, *J*(5′A,4′)=5.5, *J*(5′A,5′B)=9.7 (H-5′A); 3.07 dd, 1H, *J*(5′B,4′)=5.2, *J*(5′B,5′A)=9.7 (H-5′B); 2.91 dd, 1H, *J*(2′B,1′)=8.0, *J*(2′B,2′A)=9.2 (H-2′B); 2.39 ddd, 1H, *J*(4′aA,1′)=8.8, *J*(4′aA,4′aB)=13.4, *J*(4′aA,4′)=6.5 (H-4′aA); 2.11 ddd, 1H, *J*(4′aB,1′)=6.3, *J*(4′aB,4′aA)=13.4, *J*(4′aB,4′)=9.2 (H-4′aB). ^{13}C NMR (DMSO-d_6): 158.28 (2), 145.12, 135.80, 135.79, 129.95 (4), 128.07 (2), 127.90 (2), 126.91 and 113.40 (4) (2×C_6H_4 and C_6H_5 (ODMTr)); 146.23 (C-2); 144.81 (C-4); 143.67 (C-6); 138.54 (C-8); 112.14 (C-5); 86.01 (>C< (ODMTr)); 70.09 d, *J*(C,P)=6.8, 69.70 d, *J*(C,P)=6.7, ~24.06 4×d, *J*(C,P)=3.8 (P(O^{i}Pr)$_2$); 66.04 (C-5′); 62.91 d, *J*(4′,P)=16.2 (C-4′); 59.84 (C-2′); 55.21 (2×OMe (ODMTr)); 52.34 (C-1′); 49.44 d, *J*(C,P)=149.1 (N–CH_2–P); 34.10 (C-4′a).

5.2.7. Diisopropyl 1-(2,6-diaminopurin-9-yl)-5-O-dimethoxytrityl-1,2,3-trideoxy-3-aza-4a-carba-α-L-glycero-pentofuranos-3-ylmethylphosphonate (**20**)

To a solution of **19** (0.205 g, 0.27 mmol) in MeOH (50 mL) and concd HCl (1 mL) was added 10% Pd on charcoal (0.1 g), and the vigorously stirred reaction mixture was left to react under an atmosphere of hydrogen at rt for 5 h (TLC in H1). The catalyst was filtered off and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography on silica (elution with a linear gradient of H1 in EtOAc) to afford the desired product **20** as a colourless glassy solid (0.072 g, 62%). HRMS (FAB) calcd for $C_{17}H_{31}N_7O_4P$ $[M+H]^+$ 428.2175, found: 428.2188. ^{1}H NMR (DMSO-d_6): 7.83 s, 1H (H-8); 6.62 br s, 2H and 5.73 br s, 2H (2×NH_2); 4.78 m, 1H, *J*(1′,2′A)=6.7, *J*(1′,2′B)=8.0, *J*(1′,4′aA)=7.0, *J*(1′,4′aB)=8.7 (H-1′); 4.59 m, 2H, 1.251 d, 3H, *J*=6.2, 1.247 d, 3H, *J*=6.2, 1.243 d, 3H, *J*=6.2 and 1.240 d, 3H, *J*=6.2 (P(O^{i}Pr)$_2$); 3.56 dd, 1H, *J*(2′A,1′) 6.7, *J*(2′A,2′B)=9.0 (H-2′A); 3.47 dd, 1H, *J*(5′A,4′)=5.2, *J*(5′A,5′B)=10.8 (H-5′A); 3.40 dd, 1H, *J*(5′B,4′)=5.3, *J*(5′B,5′A)=10.8 (H-5′B); 3.06 m, 1H, *J*(4′,4′aA)=8.7, *J*(4′,4′aB)=5.8, *J*(4′,5′A)=5.2, *J*(4′,5′B)=5.3 (H-4′); 3.29 t, 1H, *J*(*gem*)=15.3, *J*(H,P)=15.3 and 2.91 dd, 1H, *J*(*gem*)=15.3, *J*(H,P)=7.0 (N–CH_2–P); 2.86 dd, 1H, *J*(2′B,1′)=8.0, *J*(2′B,2′A)=9.0 (H-2′B); 2.23 ddd, 1H, *J*(4′aA,1′)=7.0,

J(4′aA,4′aB)=13.2, J(4′aA,4′)=8.7 (H-4′aA); 2.07 ddd, 1H, J(4′aB,1′)=8.7, J(4′aB,4′aA)=13.2, J(4′aB,4′)=5.8 (H-4′aB). ^{13}C NMR (DMSO-d_6): 160.21 (C-2); 156.24 (C-6); 151.84 (C-4); 135.70 (C-8); 113.53 (C-5); 70.01 d, J(C,P)=6.8, 69.79 d, J(C,P)=6.4, ~24.00 4×d, J(C,P)=3.9 (P(O^{i}Pr)$_2$); 64.76 d, J(4′,P)=14.2 (C-4′); 63.55 (C-5′); 59.85 (C-2′); 51.15 (C-1′); 49.26 d, J(C,P)=164.1 (N–CH$_2$–P); 33.81 (C-4′a).

5.2.8. Diisopropyl 1-(adenin-9-yl)-5-O-dimethoxytrityl-1,2,3-trideoxy-3-aza-4a-carba-β-L-glycero-pentofuranos-3-ylmethylphosphonate (**23a**)

The general procedure A was followed using mesylate **14a** (1.34 g, 1.98 mmol), Cs_2CO_3 (0.78 g, 2.38 mmol) and adenine (0.40 g, 2.98 mmol). The reaction was complete after 4 h. White foam (0.530 g, 37%). HRMS (FAB) calcd for $C_{38}H_{48}N_6O_6P$ $[M+H]^+$ 715.3373, found: 715.3365. IR ν_{max}/cm^{-1} ($CHCl_3$): 1630, 1608, 1301 (adenine); 1608, 1509, 1178, 1035 (–ODMTr); 2983, 1467, 1250, 1178, 1010, 991 (–CH$_2$PO(O^{i}Pr)$_2$). ^{1}H NMR (DMSO-d_6): 8.26 s, 1H (H-8); 8.12 s, 1H (H-2); 7.30 m, 2H, 7.26 m, 2H, 7.19 m, 1H, 7.17 m, 2H, 7.16 m, 2H and 6.83 m, 4H (2×C$_6$H$_4$ and C$_6$H$_5$ (ODMTr)); 7.22 br s, 2H (NH$_2$); 4.97 m, 1H, J(1′,2′A)~1.0, J(1′,2′B)=5.7, J(1′,4′aA)=8.4, J(1′,4′aB)=2.4 (H-1′); 4.56 m, 2H, 1.24 d, 3H, J=6.1, 1.20 d, 3H, J=6.1, 1.195 d, 3H, J=6.1 and 1.16 d, 3H, J=6.1 (P(O^{i}Pr)$_2$); 3.72 s, 6H (2×OMe (ODMTr)); 3.63 br d, 1H, J(2′A,1′)~1.0, J(2′A,2′B)=10.8 (H-2′A); 3.41 dd, 1H, J(*gem*)=14.8, J(H,P)=18.8 and 2.66 dd, 1H, J(*gem*)=14.8, J(H,P)=4.6 (N–CH$_2$–P); 3.03 d, 2H, J(5′A,4′)~J(5′B,4′)~5.2 (H-5′A+H-5′B); 2.84 dd, 1H, J(2′B,1′)=5.7, J(2′B,2′A)=10.8 (H-2′B); 2.81 m, 1H, J(4′,4′aA)=8.8, J(4′,4′aB)=7.0, J(4′,5′A)~J(4′,5′B)~5.2 (H-4′); 2.53 ddd, 1H, J(4′aA,1′)=8.4, J(4′aA,4′aB)=13.8, J(4′aA,4′)=8.8 (H-4′aA); 1.71 ddd, 1H, J(4′aB,1′)=2.4, J(4′aB,4′aA)=13.8, J(4′aB,4′)=7.0 (H-4′aB). ^{13}C NMR (DMSO-d_6): 158.28, 158.20, 144.97, 135.85, 135.77, 129.83 (2), 129.80 (2), 127.97 (2), 127.90 (2), 126.84 and 113.31 (4) (2×C$_6$H$_4$ and C$_6$H$_5$ (ODMTr)); 156.12 (C-4); 152.20 (C-2); 149.36 (C-6); 138.73 (C-8); 118.83 (C-5); 85.55 (>C< (ODMTr)); 70.06 d, J(C,P)=6.3, 69.88 d, J(C,P)=7.5, 24.05 d, J(C,P)=3.8, 24.02 (2) d, J(C,P)=3.8 and 23.94 d, J(C,P)=3.8 (P(O^{i}Pr)$_2$); 65.0 (C-5′); 64.10 d, J(4′,P)=18.9 (C-4′); 60.33 (C-2′); 55.21 (2×OMe (ODMTr)); 51.70 (C-1′); 49.92 d, J(C,P)=162.2 (N–CH$_2$–P); 35.56 (C-4′a).

5.2.9. Diisopropyl 1-(cytosin-1-yl)-5-O-dimethoxytrityl-1,2,3-trideoxy-3-aza-4a-carba-β-L-glycero-pentofuranos-3-ylmethylphosphonate (**23b**) and diisopropyl 1-(cytosin-2-O-yl)-5-O-dimethoxytrityl-1,2,3-trideoxy-3-aza-4a-carba-β-L-glycero-pentofuranos-3-ylmethylphosphonate (**23c**)

The general procedure A was followed using mesylate **14a** (1.41 g, 2.09 mmol), Cs_2CO_3 (0.82 g, 2.51 mmol) and cytosine (0.35 g, 3.13 mmol). The reaction was complete after 4 h. Purification by flash chromatography afforded *N*-alkylated **23b** (white foam, 0.388 g, 27%) and *O*-alkylated **23c** (white foam, 0.475 g, 33%). Compound **23b**: HRMS (FAB) calcd for $C_{37}H_{48}N_4O_7P$ $[M+H]^+$ 691.3261, found: 691.3259. IR ν_{max}/cm^{-1} ($CHCl_3$): 1650, 1599, 1482, 1295 (cytosine); 1608, 1509, 1178, 1035 (–ODMTr); 2985, 1251, 1011, 990 (–CH$_2$PO(O^{i}Pr)$_2$). ^{1}H NMR (DMSO-d_6): 7.99 d, 1H, J(6,5)=7.4 (H-6); 7.36 m, 2H, 7.30 m, 2H, 7.23 m, 2H, 7.22 m, 3H and 6.87 m, 4H (2×C$_6$H$_4$ and C$_6$H$_5$ (ODMTr)); 7.04 br s, 1H and 6.96 br s, 1H (NH); 5.62 d, 1H, J(5,6)=7.4 (H-5); 4.89 m, 1H, J(1′,2′A)~0, J(1′,2′B)=6.7, J(1′,4′aA)=8.8, J(1′,4′aB)=2.8 (H-1′); 4.56 m, 2H, 1.23 d, 3H, J=6.3, 1.22 d, 3H, J=6.3, 1.20 d, 3H, J=6.3 and 1.16 d, 3H, J=6.3 (P(O^{i}Pr)$_2$); 3.73 s, 6H (2×OMe (ODMTr)); 3.34 dd, 1H, J(2′A,1′)~0, J(2′A,2′B)=11.0 (H-2′A); 3.30 dd, 1H, 1H, J(*gem*)=14.9, J(H,P)=19.3 and 2.47 dd, 1H, J(*gem*)=14.8, J(H,P)=4.8 (N–CH$_2$–P); 3.09 dd, 1H, J(5′A,4′)=3.9, J(5′A,5′B)=10.2 (H-5′A); 2.95 dd, 1H, J(5′B,4′)=4.8, J(5′B,5′A)=10.2 (H-5′B); 2.63 m, 1H, J(4′,4′aA)=9.0, J(4′,4′aB)=3.9, J(4′,5′A)=3.9, J(4′,5′B)=4.8 (H-4′); 2.62 dd, 1H, J(2′B,1′)=6.7, J(2′B,2′A)=11.0 (H-2′B); 2.36 ddd, 1H, J(4′aA,1′)=8.8, J(4′aA,4′aB)=14.0, J(4′aA,4′)=9.0 (H-4′aA); 1.47 ddd, 1H, J(4′aB,1′)=2.8, J(4′aB,4′aA)=14.0, J(4′aB,4′)=7.8 (H-4′aB). ^{13}C NMR (DMSO-d_6): 165.49 (C-4); 158.25, 158.24, 145.10, 135.86, 135.79, 129.90 (2), 129.87 (2), 128.00 (2), 127.9 (2), 126.86, 113.35 (2) and 113.33 (2) (2×C$_6$H$_4$ and C$_6$H$_5$ (ODMTr)); 155.83 (C-2); 142.62 (C-6); 93.55 (C-5); 85.79 (>C< (ODMTr)); 70.04 d, J(C,P)=6.3, 69.82 d, J(C,P)=7.5, 24.06 d, J(C,P)=5.0, 24.01 d J(C,P)=5.0, 24.00 d, J(C,P)=5.0 and 23.90 d, J(C,P)=5.0 (P(O^{i}Pr)$_2$); 64.50 d, J(4′,P)=18.9 (C-4′); 63.73 (C-5′); 60.03 (C-2′); 55.22 (2×OMe (ODMTr)); 52.26 (C-1′); 49.50 d, J(C,P)=170.5 (N–CH$_2$–P); 35.43 (C-4′a). Compound **23c**: HRMS (FAB) calcd for $C_{37}H_{48}N_4O_7P$ $[M+H]^+$ 691.3261, found: 691.3270. IR ν_{max}/cm^{-1} ($CHCl_3$): 1633, 1615, 1303, 1589, 1565, 1413, 1374 (cytosine); 2838, 1509, 1178, 1071 (–ODMTr); 2982, 1465, 1386, 1374, 1250, 1012, 993 (–CH$_2$PO(O^{i}Pr)$_2$). ^{1}H NMR (DMSO-d_6): 7.81 d, 1H, J(6,5)=5.7 (H-6); 7.37 m, 2H, 7.30 m, 2H, 7.24 m, 4H, 7.22 m, 1H and 6.88 m, 4H (2×C$_6$H$_4$ and C$_6$H$_5$ (ODMTr)); 6.87 br s, 1H and 6.76 br s, 1H (NH$_2$); 6.04 d, 1H, J(5,6)=5.7 (H-5); 5.15 m, 1H, J(1′,2′A)=1.6, J(1′,2′B)=5.5, J(1′,4′aA)=7.7, J(1′,4′aB)=3.6 (H-1′); 4.48 m, 2H, 1.185 d, 3H, J=6.2, 1.15 d, 6H, J=6.2 and 1.105 d, 3H, J=6.2 (P(O^{i}Pr)$_2$); 3.73 s, 6H (2×OMe (ODMTr)); 3.35 dd, 1H, J(2′A,1′)=1.6, J(2′A,2′B)=11.2 (H-2′A); 3.33 dd, 1H, 1H, J(*gem*)=15.5 and 2.57 dd, 1H, J(*gem*)=15.5, J(H,P)=4.8 (N–CH$_2$–P); 3.09 dd, 1H, J(5′A,4′)=6.2, J(5′A,5′B)=9.6 (H-5′A); 3.04 dd, 1H, J(5′B,4′)=5.0, J(5′B,5′A)=9.6 (H-5′B); 2.72 m, 1H, J(4′,4′aA)=7.7, J(4′,4′aB)=8.2, J(4′,5′A)=6.2, J(4′,5′B)=5.0 (H-4′); 2.61 dd, 1H, J(2′B,1′)=5.5, J(2′B,2′A)=11.2 (H-2′B); 2.26 dt, 1H, J(4′aA,1′)=7.7, J(4′aA,4′aB)=13.8, J(4′aA,4′)=7.7 (H-4′aA); 1.46 ddd, 1H, J(4′aB,1′)=3.6, J(4′aB,4′aA)=13.8, J(4′aB,4′)=8.2 (H-4′aB). ^{13}C NMR (DMSO-d_6): 165.51 (C-4); 164.65 (C-2); 158.24 (2), 145.21, 135.88, 135.87, 129.88 (4), 128.03 (2), 127.87 (2), 126.85, 113.37 (2) and 113.36 (2) (2×C$_6$H$_4$ and C$_6$H$_5$ (ODMTr)); 156.30 (C-6); 99.45 (C-5); 85.92 (>C< (ODMTr)); 73.96 (C-1′); 70.16 d, J(C,P)=6.3, 69.54 d, J(C,P)=6.3, 24.08 d, J(C,P)=3.8, 24.00 d, J(C,P)=3.8, 23.94 d, J(C,P)=5.0 and 23.85 d, J(C,P)=5.0 (P(O^{i}Pr)$_2$); 66.96 (C-5′); 64.18 d, J(4′,P)=17.6 (C-4′); 61.81 (C-2′); 55.21 (2×OMe (ODMTr)); 50.62 d, J(C,P)=163.4 (N–CH$_2$–P); 35.81 (C-4′a).

5.2.10. Diisopropyl 1-(thymin-1-yl)-5-O-dimethoxytrityl-1,2,3-trideoxy-3-aza-4a-carba-β-L-glycero-pentofuranos-3-ylmethylphosphonate (**23d**)

The general procedure A was followed using mesylate **14a** (1.35 g, 2.00 mmol), Cs_2CO_3 (0.78 g, 2.40 mmol) and thymine (0.38 g, 3.00 mmol). The reaction was complete after 3 h. White foam (0.554 g, 39%). HRMS (FAB) calcd for $C_{38}H_{49}N_3O_8P$ $[M+H]^+$ 706.3257, found: 706.3269. IR ν_{max}/cm^{-1} ($CHCl_3$): 1697, 1680 (thymine); 1509, 1178, 1154, 1035 (–ODMTr); 1251, 1178, 1011, 991 (–CH$_2$PO(O^{i}Pr)$_2$). ^{1}H NMR (DMSO-d_6): 11.20 br s, 1H (NH); 7.76 q, 1H, J(6,Me)=1.2 (H-6); 7.35 m, 2H, 7.28 m, 2H, 7.24 m, 2H, 7.22 m, 4H, 6.87 m, 2H and 6.86 m, 2H (2×C$_6$H$_4$ and C$_6$H$_5$ (ODMTr)); 4.83 m, 1H, J(1′,2′A)≤1.0, J(1′,2′B)=6.6, J(1′,4′aA)=9.2, J(1′,4′aB)=3.0 (H-1′); 4.55 m, 2H, 1.22 d, 3H, J=6.1, 1.21 d, 3H, J=6.2, 1.19 d, 3H, J=6.2 and 1.14 d, 3H, J=6.2 (P(O^{i}Pr)$_2$); 3.72 s, 6H (2×OMe (ODMTr)); 3.36 dd, 1H, 1H, J(*gem*)=14.8, J(H,P)=10.0 and 2.52 dd, 1H, J(*gem*)=14.8, J(H,P)=5.0 (N–CH$_2$–P); 3.33 br d, 1H, J(2′A,1′)≤1.0, J(2′A,2′B)=11.2 (H-2′A); 3.05 d, 2H, J(5′A,4′)~J(5′B,4′)~4.8 (H-5′A+H-5′B); 2.70 m, 1H, J(4′,4′aA)=8.2, J(4′,4′aB)=7.5, J(4′,5′A)~J(4′,5′A)~4.8 (H-4′); 2.65 dd, 1H, J(2′B,1′)=6.6, J(2′B,2′A)=11.2 (H-2′B); 2.39 ddd, 1H, J(4′aA,1′)=9.2, J(4′aA,4′aB)=14.0, J(4′aA,4′)=8.2 (H-4′aA); 1.50 ddd, 1H, J(4′aB,1′)=3.0, J(4′aB,4′aA)=14.0, J(4′aB,4′)=7.5 (H-4′aB); 1.62 d, 3H, J(Me,6)=1.2 (5-Me). ^{13}C NMR (DMSO-d_6): 163.95 (C-2); 158.26, 158.22, 145.08, 135.76 (2), 129.90 (2), 129.87 (2), 128.00 (2), 127.89 (2), 126.89, 113.35 (2) and 113.32 (2×C$_6$H$_4$ and C$_6$H$_5$ (ODMTr)); 151.06 (C-4); 137.94 (C-6); 108.95 (C-5); 85.85 (>C< (ODMTr)); 70.06 d, J(C,P)=6.3, 69.84 d, J(C,P)=6.3, 24.02 d, 3H, J(C,P)=3.8, 23.96 d, 6H, J(C,P)=3.8, 23.92 d, 3H, J(C,P)=3.8 (P(O^{i}Pr)$_2$); 64.55 (C-5′); 64.39 d, J(4′,P)=17.6 (C-4′); 59.69 (C-2′); 55.20 (2×OMe (ODMTr)); 52.22 (C-1′); 49.83 d, J(C,P)=163.5 (N–CH$_2$–P); 35.19 (C-4′a); 12.57 (5-Me).

*5.2.11. Diisopropyl 1-(2-amino-6-chloropurin-9-yl)-5-O-dimethoxytrityl-1,2,3-trideoxy-3-aza-4a-carba-β-L-glycero-pentofuranos-3-ylmethylphosphonate (**23e**)*

The general procedure A was followed using mesylate **14a** (2.95 g, 4.37 mmol), Cs_2CO_3 (1.71 g, 5.24 mmol) and 2-amino-6-chloropurine (1.11 g, 6.55 mmol). The reaction was complete after 4 h. White foam (1.317 g, 40%). HRMS (FAB) calcd for $C_{38}H_{45}N_6O_6PCl$ $[M-H]^-$ 747.2827, found: 747.2843. IR ν_{max}/cm^{-1} ($CHCl_3$): 1609, 1566, 1509, 1455, 1405 (chloropurine); 1609, 1509, 1178, 1035 (–ODMTr); 2985, 1250, 1178, 1011, 991 (–$CH_2PO(O^iPr)_2$). ^1H NMR (DMSO-d_6): 8.25 s, 1H (H-8); 7.28 m, 2H, 7.25 m, 2H, 7.19 m, 1H, 7.16 m, 2H, 7.15 m, 2H and 6.82 m, 4H (2×C_6H_4 and C_6H_5 (ODMTr)); 6.90 br s, 2H (NH_2); 4.81 m, 1H, *J*(1′,2′A)~1.0, *J*(1′,2′B)=5.2, *J*(1′,4′aA)=8.0, *J*(1′,4′aB)~2.0 (H-1′); 4.56 m, 2H, 1.24 d, 3H, *J*=6.1, 1.21 d, 3H, *J*=6.0, 1.20 d, 3H, *J*=6.0 and 1.16 d, 3H, *J*=6.1 ($P(O^iPr)_2$); 3.72 s, 6H (2×OMe (ODMTr)); 3.62 br d, 1H, *J*(2′A,1′)~1.0, *J*(2′A,2′B)=10.7 (H-2′A); 3.40 dd, 1H, *J*(*gem*)=15.0, *J*(H,P)=18.8 and 2.66 dd, 1H, *J*(*gem*)=15.0, *J*(H,P)=4.5 (N–CH_2–P); 3.02 dd, 1H, *J*(5′A,4′)=5.2; *J*(5′A,5′B)=10.0 (H-5′A); 2.99 dd, 1H, *J*(5′B,4′)=4.7; *J*(5′B,5′A)=10.0 (H-5′B); 2.81 dd, 1H, *J*(2′B,1′)=5.2, *J*(2′B,2′A)=10.7 (H-2′B); 2.80 m, 1H, *J*(4′,4′aA)=9.0, *J*(4′,4′aB)=5.2, *J*(4′,5′A)=5.2, *J*(4′,5′B)=4.7 (H-4′); 2.47 ddd, 1H, *J*(4′aA,1′)=8.0, *J*(4′aA,4′aB)=14.0, *J*(4′aA,4′)=9.0 (H-4′aA); 1.70 ddd, 1H, *J*(4′aB,1′)~2.0, *J*(4′aB,4′aA)=14.0, *J*(4′aB,4′)=6.5 (H-4′aB). ^{13}C NMR (DMSO-d_6): 159.88 (C-2); 158.20, 158.19, 144.95, 135.82, 135.71, 129.83 (2), 129.80 (2), 127.93 (2), 127.88 (2), 126.83, 113.29 (2) and 113.27 (2) (2×C_6H_4 and C_6H_5 (ODMTr)); 153.90 (C-4); 149.40 (C-6); 140.90 (C-8); 123.54 (C-5); 85.81 (>C< (ODMTr)); 70.12 d, *J*(C,P)=6.3, 69.94 d, *J*(C,P)=6.3, 24.04 d, *J*(C,P)=5.0, 24.01 (2) d, *J*(C,P)=5.0 and 23.93 d, *J*(C,P)=5.0 ($P(O^iPr)_2$); 64.78 (C-5′); 63.84 d, *J*(4′,P)=18.9 (C-4′); 59.82 (C-2′); 55.20 (2×OMe (ODMTr)); 52.07 (C-1′); 49.73 d, *J*(C,P)=163.5 (N–CH_2–P); 35.14 (C-4′a).

*5.2.12. Diisopropyl 1-(2-amino-6-azidopurin-9-yl)-5-O-dimethoxytrityl-1,2,3-trideoxy-3-aza-4a-carba-β-L-glycero-pentofuranos-3-ylmethylphosphonate (**24**)*

Using the procedure outlined for **19**, compound **24** was prepared from **23e** (0.767 g, 1.02 mmol) and NaN_3 (0.666 g, 10.24 mmol) as a colourless glassy solid (0.503 g, 65%). HRMS (FAB) calcd for $C_{38}H_{45}N_9O_6P$ $[M-H]^-$ 754.3230, found: 754.3244. ^1H NMR (DMSO-d_6): 8.37 br s, 2H (NH_2); 8.28 s, 1H (H-8); 7.30 m, 2H, 7.24 m, 2H, 7.16 m, 5H and 6.80 m, 4H (2×C_6H_4 and C_6H_5 (ODMTr)); 4.97 m, 1H, *J*(1′,2′A)≤2.0, *J*(1′,2′B)=5.6, *J*(1′,4′aA)=8.2, *J*(1′,4′aB)~2.0 (H-1′); 4.57 m, 2H, 1.25 d, 3H, *J*=6.2, 1.21 d, 3H, *J*=6.2, 1.205 d, 3H, *J*=6.2 and 1.16 d, 3H, *J*=6.2 ($P(O^iPr)_2$); 3.79 s, 3H and 3.685 s, 3H (2×OMe (ODMTr)); 3.66 br d, 1H, *J*(2′A,1′)≤2.0, *J*(2′A,2′B)=11.0 (H-2′A); 3.44 dd, 1H, *J*(*gem*)=15.3, *J*(H,P)=18.8 and 2.69 dd, 1H, *J*(*gem*)=15.3, *J*(H,P)=4.5 (N–CH_2–P); 3.12 dd, 1H, *J*(5′A,4′)=5.4; *J*(5′A,5′B)=10.0 (H-5′A); 2.98 dd, 1H, *J*(5′B,4′)=5.2; *J*(5′B,5′A)=10.0 (H-5′B); 2.88 dd, 1H, *J*(2′B,1′)=5.6, *J*(2′B,2′A)=11.0 (H-2′B); 2.84 m, 1H, *J*(4′,4′aA)≤2.0, *J*(4′,4′aB)=7.0, *J*(4′,5′A)=5.4, *J*(4′,5′B)=5.2 (H-4′); 2.55 ddd, 1H, *J*(4′aA,1′)=8.2, *J*(4′aA,4′aB)=14.0, *J*(4′aA,4′)≤2.0 (H-4′aA); 1.66 ddd, 1H, *J*(4′aB,1′)~2.0, *J*(4′aB,4′aA)=14.0, *J*(4′aB,4′)=7.0 (H-4′aB). ^{13}C NMR (DMSO-d_6): 158.13 (2), 144.87, 135.69, 135.62, 129.74 (4), 127.82 (2), 127.79 (2), 126.69 and 113.19 (4) (2×C_6H_4 and C_6H_5 (ODMTr)); C-2 not observed; 146.16 (C-6); 143.66 (C-4); 138.02 (C-8); 111.68 (C-5); 85.86 (>C< (ODMTr)); 70.02 d, *J*(C,P)=6.8, 69.82 d, *J*(C,P)=6.8, 23.95–23.79 4×d, *J*(C,P)=4.0 ($P(O^iPr)_2$); 65.20 (C-5′); 63.78 d, *J*(4′,P)=17.6 (C-4′); 60.14 (C-2′); 52.37 (C-1′); 55.12 (2×OMe (ODMTr)); 49.79 d, *J*(C,P)=161.7 (N–CH_2–P); 35.68 (C-4′a).

*5.2.13. Diisopropyl 1-(2,6-diaminopurin-9-yl)-5-O-dimethoxytrityl-1,2,3-trideoxy-3-aza-4a-carba-β-L-glycero-pentofuranos-3-ylmethylphosphonate (**25**)*

Using the procedure outlined for **20**, compound **25** was prepared from **24** (0.503 g, 0.67 mmol) as a colourless glassy solid (0.188 g, 66%). HRMS (FAB) calcd for $C_{17}H_{31}N_7O_4P$ $[M+H]^+$ 428.2175, found: 428.2167. ^1H NMR (DMSO-d_6): 7.94 s, 1H (H-8); 6.62 br s, 2H (NH_2); 5.72 br s, 2H (NH_2); 4.77 m, 1H, *J*(1′,2′A)~1.0, *J*(1′,2′B)=5.8, *J*(1′,4′aA)=8.7, *J*(1′,4′aB)=2.6 (H-1′); 4.71 br s, 1H (5′-OH); 4.59 m, 2H, 1.26 d, 3H, *J*=6.0, 1.245 d, 3H, *J*=6.0, 1.24 d, 3H, *J*=6.0 and 1.21 d, 3H, *J*=6.0 ($P(O^iPr)_2$); 3.49 dd, 1H, *J*(5′A,4′)=4.8; *J*(5′A,5′B)=11.0 (H-5′A); 3.46 br d, 1H, *J*(2′A,1′)~1.0, *J*(2′A,2′B)=10.5; *J*(2′A,4′aB)≤2 (H-2′A); 3.44 dd, 1H, *J*(*gem*)=15.2, *J*(H,P)=17.7 and 2.66 dd, 1H, *J*(*gem*)=15.2, *J*(H,P)=5.3 (N–CH_2–P); 3.41 dd, 1H, *J*(5′B,4′)=4.8; *J*(5′B,5′A)=11.0 (H-5′B); 2.76 dd, 1H, *J*(2′B,1′)=5.8, *J*(2′B,2′A)=10.5 (H-2′B); 2.64 m, 1H, *J*(4′,4′aA)=8.7, *J*(4′,4′aB)=7.0, *J*(4′,5′A)=4.8, *J*(4′,5′B)=4.8 (H-4′); 2.48 ddd, 1H, *J*(4′aA,1′)=8.7, *J*(4′aA,4′aB)=14.0, *J*(4′aA,4′)=8.7 (H-4′aA); 1.68 ddd, 1H, *J*(4′aB,1′)=2.6, *J*(4′aB,2′A)≤2, *J*(4′aB,4′aA)=14.0, *J*(4′aB,4′)=7.0 (H-4′aB). ^{13}C NMR (DMSO-d_6): 160.29 (C-2); 156.19 (C-6); 151.57 (C-4); 135.44 (C-8); 113.08 (C-5); 70.12 d, *J*(C,P)=6.7, 69.85 d, *J*(C,P)=6.7, 24.06 d, *J*(C,P)=5.5, 24.03 d, *J*(C,P)=5.8, 23.93 (2) d, *J*(C,P)=4.9 ($P(O^iPr)_2$); 65.98 d, *J*(4′,P)=16.5 (C-4′); 63.35 (C-5′); 61.22 (C-2′); 50.76 (C-1′); 49.68 d, *J*(C,P)=164.1 (N–CH_2–P); 35.55 (C-4′a).

5.3. Phosphonate group dealkylation (general procedure B)

To a solution of protected nucleotide in anhydrous acetonitrile (10 mL/mmol) was added bromotrimethylsilane (8 equiv), and the reaction was allowed to proceed at rt for 48 h under exclusion of moisture (TLC in I). The reaction was then concentrated in vacuo, residue dissolved in small amount of water and the solution was passed through a column of Dowex 50 (H^+-form), which was then washed successively with MeOH, and a mixture of H_2O–MeOH (1:1). The product was liberated from Dowex with diluted (approx. 2.5%) aqueous ammonia, evaporated in vacuo and purified by reverse-phase chromatography. Finally, the nucleotide was passed through a column of Dowex 50 (Na^+-form) and the sodium salt obtained was lyophilized from water.

*5.3.1. 1-(Adenin-9-yl)-1,2,3-trideoxy-3-aza-4a-carba-α-L-glycero-pentofuranos-3-ylmethylphosphonic acid (**22a**)*

The general procedure B was followed using phosphonate **18a** (0.709 g, 0.99 mmol) and Me_3SiBr (1.05 mL, 7.96 mmol). White solid (0.177 g, 48%). HRMS (FAB) calcd for $C_{11}H_{18}N_6O_4P$ $[M+H]^+$ 329.1127, found: 329.1121. IR ν_{max}/cm^{-1} (KBr): 3435 (vs, br) (OH, H_2O, NH_2); 1641 (s), 1605 (m, sh), 1574 (w), 1416 (w), 1332 (w), 1303 (w), 975 (w), 647 (w), 798 (w), 728 (w) (adenine); 1067 (w, br), 903 (w, br), 545 (m, br), 465 (w, br) (PO_3^{2-}) ^1H NMR (D_2O): 8.24 s, 1H (H-8); 8.21 s, 1H (H-2); 5.31 m, 1H, *J*(1′,2′A)=7.6, *J*(1′,2′B)=7.3, *J*(1′,4′aA)=9.2, *J*(1′,4′aB)=5.8 (H-1′); 4.23 dd, 1H, *J*(2′A,1′)=7.6, *J*(2′A,2′B)=12.0 (H-2′A); 4.12 m, 1H, *J*(4′,4′aA)=7.3, *J*(4′,4′aB)=8.7, *J*(4′,5′A)=3.5, *J*(4′,5′B)=3.6 (H-4′); 4.07 dd, 1H, *J*(5′A,4′)=3.5, *J*(5′A,5′B)=12.8 (H-5′A); 3.84 dd, 1H, *J*(5′B,4′)=3.6, *J*(5′B,5′A)=12.8 (H-5′B); 3.78 dd, 1H, *J*(2′B,1′)=7.3, *J*(2′B,2′A)=12.0 (H-2′B); 3.34 dd, 1H, 1H, *J*(*gem*)=14.4, *J*(H,P)=13.2 and 3.17 dd, 1H, *J*(*gem*)=14.4, *J*(H,P)=10.5 (N–CH_2–P); 2.66 ddd, 1H, *J*(4′aA,1′)=9.2, *J*(4′aA,4′aB)=14.5, *J*(4′aA,4′)=7.3 (H-4′aA); 2.61 ddd, 1H, *J*(4′aB,1′)=5.8, *J*(4′aB,4′aA)=14.5, *J*(4′aB,4′)=8.7 (H-4′aB). ^{13}C NMR (D_2O): 156.12 (C-4); 153.03 (C-2); 149.48 (C-6); 141.55 (C-8); 119.48 (C-5); 67.82 d, *J*(4′,P)=7.0 (C-4′); 59.63 (C-2′); 59.42 (C-5′); 52.56 (C-1′); 51.63 d, *J*(C,P)=174.6 (N–CH_2–P); 33.03 (C-4′a).

*5.3.2. 1-(Cytosin-1-yl)-1,2,3-trideoxy-3-aza-4a-carba-α-L-glycero-pentofuranos-3-ylmethylphosphonic acid (**22b**)*

The general procedure B was followed using phosphonate **18b** (0.400 g, 0.58 mmol) and Me_3SiBr (0.61 mL, 4.63 mmol). White solid (0.075 g, 37%). HRMS (FAB) calcd for $C_{10}H_{18}N_4O_5P$ $[M+H]^+$ 305.1015, found: 305.1016. IR ν_{max}/cm^{-1} (KBr): 3431 (s, br), 3201 (w, br) (OH, H_2O, NH_2); 1647 (vs), 1608 (m, sh), 1577 (m, sh), 1528

(m), 1492 (m), 1406 (w), 1294 (w), 980 (w), 787 (w) (cytosine); 1063 (w, br), 903 (w, br), 886 (w, br), 549 (m), 475 (w, br) (PO_3^{2-}). ^{1}H NMR (D_2O): 7.64 d, 1H, *J*(6,5)=7.5 (H-6); 5.99 d, 1H, *J*(5,6)=7.5 (H-5); 4.90 m, 1H (H-1′); 4.00 m, 2H (H-4′+H-5′A); 3.78 m, 2H (H-2′A+H-2′B); 3.62 m, 1H (H-5′B); 3.25 dd, 1H, 1H, *J*(*gem*)=14.0, *J*(H,P)=12.8 and 3.05 dd, 1H, *J*(*gem*)=14.0, *J*(H,P)=10.7 (N–CH_2–P); 2.45 m, 2H (H-4′aA+H-4′aB). ^{13}C NMR (D_2O): 166.85 (C-4); 158.52 (C-2); 146.44 (C-6); 96.54 (C-5); 68.34 d, *J*(4′,P)=6.5 (C-4′); 59.23 (C-2′); 58.78 (C-5′); 58.04 (C-1′); 51.29 d, *J*(C,P)=128.5 (N–CH_2–P); 31.75 (C-4′a).

5.3.3. 1-(Thymin-1-yl)-1,2,3-trideoxy-3-aza-4a-carba-α-L-glycero-pentofuranos-3-ylmethylphosphonic acid (**22c**)

The general procedure B was followed using phosphonate **18d** (0.515 g, 0.73 mmol) and Me_3SiBr (0.77 mL, 5.84 mmol). White solid (0.094 g, 35%). HRMS (FAB) calcd for $C_{11}H_{18}N_3O_6NaP$ $[M+Na]^+$ 342.0831, found: 342.0841. IR ν_{max}/cm^{-1} (KBr): 3425 (s, br), 3260 (m, br, sh) (OH, H_2O, NH_2); 3062 (m), 1695 (vs, br), 1472 (m), 1438 (m), 1227 (m), 938 (m), 768 (w), 2973 (m), 1373 (w) (thymine); 1064 (s, br), 905 (m, br), 548 (m), 476 (w, br) (PO_3^{2-}). ^{1}H NMR (D_2O): 7.51 q, 1H, *J*(6,Me)=1.2 (H-6); 4.94 m, 1H, *J*(1′,2′A)=8.4, *J*(1′,2′B)=7.6, *J*(1′,4′aA)∼*J*(1′,4′aB)∼7.8 (H-1′); 4.09 dd, 1H, *J*(2′A,1′)=8.4, *J*(2′A,2′B)=12.1 (H-2′A); 4.06 m, 1H (H-4′); 4.02 m, 1H and 3.80 m, 1H (H-5′A+H-5′B); 3.65 dd, 1H, *J*(2′B,1′)=7.6, *J*(2′B,2′A)=12.1 (H-2′B); 3.32 dd, 1H, 1H, *J*(*gem*)=14.4, *J*(H,P)=12.6 and 3.09 dd, 1H, *J*(*gem*)=14.4, *J*(H,P)=10.6 (N–CH_2–P); 2.49 m, 2H (H-4′aA+H-4′aB); 1.87 d, 3H, *J*(Me,6)=1.2 (5-Me); ^{13}C NMR (D_2O): 167.30 (C-4); 152.60 (C-2); 142.33 (C-6); 111.66 (C-5); 68.88 d, *J*(4′,P)=6.9 (C-4′); 58.64 (C-5′); 58.10 (C-2′); 56.74 (C-1′); 51.52 d, *J*(C,P)=130.1 (N–CH_2–P); 31.02 (C-4′a); 11.96 (5-Me (Thy)).

5.3.4. 1-(Guanin-9-yl)-1,2,3-trideoxy-3-aza-4a-carba-α-L-glycero-pentofuranos-3-ylmethylphosphonic acid (**22d**)

A solution of **18e** (0.220 g, 0.29 mmol) in formic acid (80%, 15 mL) was heated at 90 °C for 6 h. The reaction mixture was then evaporated in vacuo, co-evaporated successively with ethanol and anhydrous acetonitrile and treated with bromotrimethylsilane (0.31 mL, 2.36 mmol) according to the general procedure. White solid (0.039 g, 34%). HRMS (FAB) calcd for $C_{11}H_{18}N_6O_5P$ $[M+H]^+$ 345.1076, found: 345.1065. IR ν_{max}/cm^{-1} (KBr): 3428 (vs, br), 3122 (m, br, sh), 2800 (m, br, sh) (OH, H_2O, NH_2); 1680 (s, br), 1634 (s, br), 1574 (m), 1535 (w), 1485 (w), 1393 (w, br), 1120 (m, br, sh), 1079 (m), 979 (w), 782 (w) (guanine); 1079 (m), 907 (w, br), 553 (w, br), 484 (w, br) (PO_3^{2-}). ^{1}H NMR (D_2O): 7.77 s, 1H (H-8); 5.22 m, 1H, *J*(1′,2′A)=7.6, *J*(1′,2′B)=3.9, *J*(1′,4′aA)=9.8, *J*(1′,4′aB)=4.3 (H-1′); 4.18 m, 1H, *J*(4′,4′aA)=4.9, *J*(4′,4′aB)=9.1, *J*(4′,5′A)=3.2, *J*(4′,5′B)=3.6 (H-4′); 4.12 dd, 1H, *J*(5′A,4′)=3.2, *J*(5′A,5′B)=13.3 (H-5′A); 4.00 dd, 1H, *J*(2′A,1′)=7.6, *J*(2′A,2′B)=12.3 (H-2′A); 3.88 dd, 1H, *J*(2′B,1′)=3.9, *J*(2′B,2′A)=12.3 (H-2′B); 3.81 dd, 1H, *J*(5′B,4′)=3.6, *J*(5′B,5′A)=13.3 (H-5′B); 3.26 m, 2H (N–CH_2–P); 2.72 ddd, 1H, *J*(4′aA,1′)=9.8, *J*(4′aA,4′aB)=14.9, *J*(4′aA,4′)=4.9 (H-4′aA); 2.45 ddd, 1H, *J*(4′aB,1′)=4.3, *J*(4′aB,4′aA)=14.9, *J*(4′aB,4′)=9.1 (H-4′aB). ^{13}C NMR (D_2O): 161.80 (C-6); 156.80 (C-2); 153.04 (C-4); 141.46 (C-8); 118.99 (C-5); 67.92 d, *J*(4′,P)=4.7 (C-4′); 62.53 d, *J*(2′,P)=4.2 (C-2′); 61.94 (C-5′); 55.31 (C-1′); 51.92 d, *J*(C,P)=130.4 (N–CH_2–P); 36.40 (C-4′a).

5.3.5. 1-(2,6-Diaminopurin-9-yl)-1,2,3-trideoxy-3-aza-4a-carba-α-L-glycero-pentofuranos-3-ylmethylphosphonic acid (**22e**)

The general procedure B was followed using phosphonate **20** (0.072 g, 0.17 mmol) and Me_3SiBr (0.18 mL, 1.35 mmol). White solid (0.064 g, 98%). HRMS (FAB) calcd for $C_{11}H_{19}N_7O_4P$ $[M+H]^+$ 344.1236, found: 344.1247. IR ν_{max}/cm^{-1} (KBr): 3424 (vs, br), 3205 (s, br) (OH, H_2O, NH_2); 1639 (s), 1627 (s), 1600 (s), 1513 (w), 1474 (m), 1408 (m), 1348 (w), 1282 (w), 1225 (w, br), 977 (w), 638 (w), 790 (w) (diaminopurine); 1064 (m), 907 (w, br), 549 (m), 470 (w, br) (PO_3^{2-}). ^{1}H NMR (D_2O): 7.86 s, 1H (H-8); 5.18 m, 1H, *J*(1′,2′A)=7.4, *J*(1′,2′B)=4.0, *J*(1′,4′aA)=9.6, *J*(1′,4′aB)=4.4 (H-1′); 4.13 m, 1H, *J*(4′,4′aA)=5.2, *J*(4′,4′aB)=8.8, *J*(4′,5′A)=3.1, *J*(4′,5′B)=3.5 (H-4′); 4.10 dd, 1H, *J*(5′A,4′)=3.1, *J*(5′A,5′B)=12.7 (H-5′A); 4.01 dd, 1H, *J*(2′A,1′)=7.4, *J*(2′A,2′B)=12.0 (H-2′A); 3.80 dd, 1H, *J*(5′B,4′)=3.5, *J*(5′B,5′A)=12.7 (H-5′B); 3.71 dd, 1H, *J*(2′B,1′)=4.0, *J*(2′B,2′A)=12.0 (H-2′B); 3.25 dd, 1H, *J*(*gem*)=14.2, *J*(H,P)=14.4 and 3.19 dd, 1H, *J*(*gem*)=14.2, *J*(H,P)=10.2 (N–CH_2–P); 2.68 ddd, 1H, *J*(4′aA,1′)=9.6, *J*(4′aA,4′aB)=14.6, *J*(4′aA,4′)=5.2 (H-4′aA); 2.44 ddd, 1H, *J*(4′aB,1′)=4.4, *J*(4′aB,4′aA)=14.6, *J*(4′aB,4′)=8.8 (H-4′aB). ^{13}C NMR (D_2O): 162.60 (C-2); 159.00 (C-6); 153.04 (C-4); 141.39 (C-8); 115.93 (C-5); 67.70 d, *J*(4′,P)=4.9 (C-4′); 62.58 d, *J*(2′,P)=4.4 (C-2′); 62.12 (C-5′); 54.85 (C-1′); 52.26 d, *J*(C,P)=131.4 (N–CH_2–P); 36.37 (C-4′a).

5.3.6. 1-(Adenin-9-yl)-1,2,3-trideoxy-3-aza-4a-carba-β-L-glycero-pentofuranos-3-ylmethylphosphonic acid (**27a**)

The general procedure B was followed using phosphonate **23a** (0.530 g, 0.74 mmol) and Me_3SiBr (0.78 mL, 5.93 mmol). White solid (0.169 g, 61%). HRMS (FAB) calcd for $C_{11}H_{18}N_6O_4P$ $[M+H]^+$ 329.1127, found: 329.1141. IR ν_{max}/cm^{-1} (KBr): 3427 (vs, br) (OH, H_2O, NH_2); 1642 (s), 1604 (m), 1574 (m), 1477 (w), 1416 (w), 1333 (w), 1302 (w), 978 (w), 648 (m), 798 (w), 728 (w) (adenine); 1062 (m, br), 903 (w, br), 542 (m), 467 (m, br) (PO_3^{2-}). ^{1}H NMR (D_2O): 8.25 s, 1H (H-2); 8.18 s, 1H (H-8); 5.43 m, 1H, *J*(1′,2′A)=1.6, *J*(1′,2′B)=8.0, *J*(1′,4′aA)=9.4, *J*(1′,4′aB)=4.6 (H-1′); 4.14 dd, 1H, *J*(5′A,4′)=3.2, *J*(5′A,5′B)=13.6 (H-5′A); 4.33 dd, 1H, *J*(2′A,1′)=1.6, *J*(2′A,2′B)=13.2 (H-2′A); 3.89 dd, 1H, *J*(5′B,4′)=3.3, *J*(5′B,5′A)=13.6 (H-5′B); 3.79 dd, 1H, *J*(2′B,1′)=8.0, *J*(2′B,2′A)=13.2 (H-2′B); 3.71 m, 1H, *J*(4′,4′aA)=8.8, *J*(4′,4′aB)=10.8, *J*(4′,5′A)=3.2, *J*(4′,5′B)=3.3 (H-4′); 3.45 dd, 1H, *J*(*gem*)=14.3, *J*(H,P)=13.3 and 3.01 dd, 1H, *J*(*gem*)=14.3, *J*(H,P)=10.3 (N–CH_2–P); 2.96 ddd, 1H, *J*(4′aA,1′)=9.4, *J*(4′aA,4′aB)=14.8, *J*(4′aA,4′)=8.8 (H-4′aA); 2.23 ddd, 1H, *J*(4′aB,1′)=4.6, *J*(4′aB,4′aA)=14.8, *J*(4′aB,4′)=10.8 (H-4′aB). ^{13}C NMR (D_2O): 156.06 (C-4); 152.78 (C-2); 148.48 (C-6); 142.07 (C-8); 119.51 (C-5); 70.40 d, *J*(4′,P)=7.3 (C-4′); 60.90 (C-2′); 57.85 (C-5′); 52.73 (C-1′); 51.74 d, *J*(C,P)=128.4 (N–CH_2–P); 33.67 (C-4′a).

5.3.7. 1-(Cytosin-1-yl)-1,2,3-trideoxy-3-aza-4a-carba-β-L-glycero-pentofuranos-3-ylmethylphosphonic acid (**27b**)

The general procedure B was followed using phosphonate **23b** (0.388 g, 0.56 mmol) and Me_3SiBr (0.59 mL, 4.49 mmol). White solid (0.084 g, 43%). HRMS (FAB) calcd for $C_{10}H_{18}N_4O_5P$ $[M+H]^+$ 305.1015, found: 305.1005. IR ν_{max}/cm^{-1} (KBr): 3431 (vs, br), 3205 (m, br, sh) (OH, H_2O, NH_2); 1635 (m, br), 1602 (m), 1558 (m), 1495 (w), 1409 (m), 1296 (w, br), 980 (w), 789 (w) (cytosine); 1068 (m, br), 909 (w, br), 548 (m, br), 465 (w, br) (PO_3^{2-}). ^{1}H NMR (D_2O): 8.35 d, 1H, *J*(6,5)=7.5 (H-6); 6.04 d, 1H, *J*(5,6)=7.5 (H-5); 4.88 m, 1H, *J*(1′,2′A)<1.0, *J*(1′,2′B)=6.9, *J*(1′,4′aA)=8.7, *J*(1′,4′aB)=4.5 (H-1′); 3.74 dd, 1H, *J*(5′A,5′B)=12.4, *J*(5′A,4′)=3.1 (H-5′A); 3.56 br d, 1H, *J*(2′A,1′)<1.0, *J*(2′A,2′B)=11.9 (H-2′A); 3.46 dd, 1H, *J*(5′B,5′A)=12.4, *J*(5′B,4′)=2.6 (H-5′B); 2.93 dd, 1H, *J*(*gem*)=14.1, *J*(H,P)=16.6 and 2.24 dd, 1H, *J*(*gem*)=14.1, *J*(H,P)=8.0 (N–CH_2–P); 2.75 dd, 1H, *J*(2′B,1′)=6.9, *J*(2′B,2′A)=11.9 (H-2′B); 2.56 m, 1H, *J*(4′,4′aA)=8.8, *J*(4′,4′aB)=7.8, *J*(4′,5′A)=3.1, *J*(4′,5′B)=2.6 (H-4′); 2.52 ddd, 1H, *J*(4′aA,1′)=8.7, *J*(4′aA,4′)=8.8, *J*(4′aA,4′aB)=13.6 (H-4′aA); 1.59 ddd, 1H, *J*(4′aB,1′)=4.5, *J*(4′aB,4′)=7.8, *J*(4′aB,4′aA)=13.6 (H-4′aB). ^{13}C NMR (D_2O): 168.59 (C-4); 161.30 (C-2); 147.81 (C-6); 98.52 (C-5); 57.03 (C-1′); 69.26 d, *J*(4′,P)=15.2 (C-4′); 63.08 (C-5′); 62.16 (C-2′); 54.96 d, *J*(C,P)=147.0 (N–CH_2–P); 37.56 (C-4′a).

5.3.8. 1-(Thymin-1-yl)-1,2,3-trideoxy-3-aza-4a-carba-β-L-glycero-pentofuranos-3-ylmethylphosphonic acid (**27c**)

The general procedure B was followed using phosphonate **23d** (0.554 g, 0.78 mmol) and Me_3SiBr (0.83 mL, 6.28 mmol). White solid

(0.089 g, 31%). HRMS (FAB) calcd for $C_{11}H_{19}N_3O_6P$ $[M+H]^+$ 320.1011, found: 320.0996. IR ν_{max}/cm^{-1} (KBr): 3426 (vs, br), 3260 (m, br, sh) (OH, H_2O, NH_2); 3056 (m), 1690 (vs, br), 1474 (w), 1438 (w), 1285 (m), 1226 (w), 978 (w), 767 (w), 1375 (w) (thymine); 1065 (m, br), 903 (w, br), 549 (m, br), 479 (w, br) (PO_3^{2-}). ^1H NMR (D_2O): 7.59 d, 1H, *J*(6,Me)=1.2 (H-6); 6.29 d, 1H, *J*(5,6)=6.0 (H-5); 4.85 m, 1H, *J*(1′,2′A)=2.1, *J*(1′,2′B)=9.0, *J*(1′,4′aA)=9.7, *J*(1′,4′aB)=5.8 (H-1′); 4.14 dd, 1H, *J*(2′A,1′)=2.1, *J*(2′A,2′B)=13.0 (H-2′A); 4.06 dd, 1H, *J*(5′A,4′)=3.3, *J*(5′A,5′B)=13.0 (H-5′A); 3.81 dd, 1H, *J*(5′B,4′)=2.8, *J*(5′B,5′A)=13.0 (H-5′B); 3.55 dd, 1H, *J*(2′B,1′)=9.0, *J*(2′B,2′A)=13.0 (H-2′B); 3.49 m, 1H, *J*(4′,4′aA)=7.7, *J*(4′,4′aB)=11.2, *J*(4′,5′A)=3.3, *J*(4′,5′B)=2.8 (H-4′); 3.34 dd, 1H, *J*(*gem*)=13.3, *J*(H,P)=14.7 and 2.83 dd, 1H, *J*(*gem*)=13.3, *J*(H,P)=10.0 (N–CH_2–P); 2.69 ddd, 1H, *J*(4′aA,1′)=9.7, *J*(4′aA,4′)=7.7, *J*(4′aA,4′aB)=14.2 (H-4′aA); 2.25 ddd, 1H, *J*(4′aB,1′)=5.8, *J*(4′aB,4′)=11.2, *J*(4′aB,4′aA)=14.2 (H-4′aB); 1.92 d, 3H, *J*(Me,6)=1.2 (5-Me). ^{13}C NMR (D_2O): 167.60 (C-4); 152.82 (C-2); 143.44 (C-6); 111.22 (C-5); 69.87 d, *J*(4′,P)=7.8 (C-4′); 59.92 (C-2′); 57.79 (C-1′); 57.54 (C-5′); 51.41 d, *J*(C,P)=129.4 (N–CH_2–P); 31.79 (C-4′a); 11.96 (5-Me).

5.3.9. 1-(Guanin-9-yl)-1,2,3-trideoxy-3-aza-4a-carba-β-L-glycero-pentofuranos-3-ylmethylphosphonic acid (**27d**)

Using the procedure outlined for **22d**, compound **27d** was prepared from **23e** (0.545 g, 0.73 mmol) and bromotrimethylsilane (0.77 mL, 5.82 mmol). White solid (0.086 g, 31%). HRMS (FAB) calcd for $C_{11}H_{18}N_6O_5P$ $[M+H]^+$ 345.1076, found: 345.1087. IR ν_{max}/cm^{-1} (KBr): 3386 (s, br), 3315 (s, br), 3114 (s, vbr) (OH, H_2O, NH_2); 1680 (s, br), 1696 (vs), 1654 (s), 1535 (w), 1609 (s), 1484 (m), 1398 (m), 1364 (m), 1538 (m), 1169 (s), 973 (m), 780 (m), 641 w (guanine); 1075 (s), 922 (m, br), 537 (m), 456 (w, br) (PO_3^{2-}) ^1H NMR (D_2O+NaOD): 8.21 s, 1H (H-8); 4.81 m, 1H, *J*(1′,2′A)∼2.0, *J*(1′,2′B)=6.8, *J*(1′,4′aA)=8.5, *J*(1′,4′aB)=4.0 (H-1′); 3.72 dd, 1H, *J*(5′A,4′)=3.7; *J*(5′A,5′B)=12.2 (H-5′A); 3.67 dd, 1H, *J*(2′A,1′)∼2.0, *J*(2′A,2′B)=11.2 (H-2′A); 3.52 dd, 1H, *J*(5′B,4′)=3.5; *J*(5′B,5′A)=12.2 (H-5′B); 2.985 dd, 1H, *J*(2′B,1′)=6.8, *J*(2′B,2′A)=11.2 (H-2′B); 2.92 dd, 1H, *J*(*gem*)=14.4, *J*(H,P)=15.7 and 2.39 dd, 1H, *J*(*gem*)=14.4, *J*(H,P)=8.4 (N–CH_2–P); 2.75 m, 1H, *J*(4′,4′aA)=8.5, *J*(4′,4′aB)=8.0, *J*(4′,5′A)=3.7, *J*(4′,5′B)=3.5 (H-4′); 2.60 dt, 1H, *J*(4′aA,4′aB)=13.7, *J*(4′aA,1′)=8.5, *J*(4′aA,4′)=8.5 (H-4′aA); 1.79 ddd, 1H, *J*(4′aB,1′)=4.0, *J*(4′aB,4′aA)=13.7, *J*(4′aB,4′)=8.0 (H-4′aB). ^{13}C NMR (D_2O+NaOD): 170.93 (C-6); 163.70 (C-2); 153.84 (C-4); 139.94 (C-8); 120.06 (C-5); 69.05 d, *J*(C,P)=13.6 (C-4′); 63.88 (C-5′); 63.17 (C-2′); 55.23 d, *J*(C,P)=145.8 (N–CH_2–P); 54.24 (C-1′); 37.87 (C-4′a).

5.3.10. 1-(2,6-Diaminopurin-9-yl)-1,2,3-trideoxy-3-aza-4a-carba-β-L-glycero-pentofuranos-3-ylmethylphosphonic acid (**27e**)

The general procedure B was followed using phosphonate **25** (0.188 g, 0.44 mmol) and Me_3SiBr (0.47 mL, 3.52 mmol). White solid (0.168 g, 98%). HRMS (FAB) calcd for $C_{11}H_{19}N_7O_4P$ $[M+H]^+$ 344.1236, found: 344.1230. IR ν_{max}/cm^{-1} (KBr): 3383 (s, br), 3334 (s, br), 3192 (s, br), 3110 (s, br, sh) (OH, H_2O, NH_2); 1641 (vs), 1608 (vs), 1600 (s), 1518 (w), 1475 (m), 1419 (m), 1334 (w), 1273 (w), 1179 (m, br), 972 (w), 638 (w), 790 (w) (diaminopurine); 1073 (m, br), 912 (w, br), 548 (m), 461 (w, br) (PO_3^{2-}). ^1H NMR (D_2O+NaOD): 8.36 s, 1H (H-8); 4.81 m, 1H, *J*(1′,2′A)≤2.0, *J*(1′,2′B)=6.5, *J*(1′,4′aA)=8.7, *J*(1′,4′aB)=3.2 (H-1′); 3.74 dd, 1H, *J*(5′A,4′)=3.7, *J*(5′A,5′B)=12.2 (H-5′A); 3.73 dd, 1H, *J*(2′A,1′)≤2.0, *J*(2′A,2′B)=11.0 (H-2′A); 3.49 dd, 1H, *J*(5′B,4′)=3.2, *J*(5′B,5′A)=12.2 (H-5′B); 2.98 dd, 1H, *J*(*gem*)=14.2, *J*(H,P)=16.2 and 2.37 dd, 1H, *J*(*gem*)=14.2, *J*(H,P)=8.2 (N–CH_2–P); 2.95 dd, 1H, *J*(2′B,1′)=6.5, *J*(2′B,2′A)=11.0 (H-2′B); 2.72 m, 1H, *J*(4′,4′aA)=8.7, *J*(4′,4′aB)=7.5, *J*(4′,5′A)=3.7, *J*(4′,5′B)=3.2 (H-4′); 2.59 dt, 1H, *J*(4′aA,1′)=8.7, *J*(4′aA,4′aB)=13.7, *J*(4′aA,4′)=8.7 (H-4′aA); 1.80 ddd, 1H, *J*(4′aB,1′)=3.2, *J*(4′aB,4′aA)=13.7, *J*(4′aB,4′)=7.5 (H-4′aB). ^{13}C NMR (D_2O+NaOD): 162.52 (C-2); 158.71 (C-6); 153.52 (C-4); 142.03 (C-8); 115.60 (C-5); 69.05 d, *J*(4′,P)=14.0 (C-4′); 63.60 (C-2′); 62.97 (C-5′); 55.11 d, *J*(C,P)=146.1 (N–CH_2–P); 54.56 (C-1′); 37.59 (C-4′a).

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