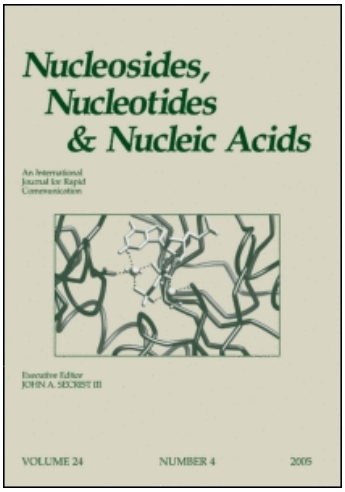


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

2'-*C*-ALKOXY AND 2'-*C*-ARYLOXY DERIVATIVES OF *N*-(2-PHOSPHONOMETHOXYETHYL)-PURINES AND -PYRIMIDINES: SYNTHESIS AND BIOLOGICAL ACTIVITY

Dominik Rejman[a]; Milena Masojídková[a]; Eric De Clercq[b]; Ivan Rosenberg[a]
[a] Institute of Organic Chemistry and Biochemistry, Academy of Science of the Czech Republic, Prague 6, Czech Republic [b] Rega Institute for Medical Research, Katholieke Universiteit Leuven, Leuven, Belgium

Online publication date: 31 July 2001

To cite this Article Rejman, Dominik , Masojídková, Milena , De Clercq, Eric and Rosenberg, Ivan(2001) '2'-*C*-ALKOXY AND 2'-*C*-ARYLOXY DERIVATIVES OF *N*-(2-PHOSPHONOMETHOXYETHYL)-PURINES AND -PYRIMIDINES: SYNTHESIS AND BIOLOGICAL ACTIVITY', Nucleosides, Nucleotides and Nucleic Acids, 20: 8, 1497 — 1522
To link to this Article: DOI: 10.1081/NCN-100105244
URL: http://dx.doi.org/10.1081/NCN-100105244

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 20(8), 1497–1522 (2001)

2′-*C*-ALKOXY AND 2′-*C*-ARYLOXY DERIVATIVES OF *N*-(2-PHOSPHONOMETHOXYETHYL)-PURINES AND -PYRIMIDINES: SYNTHESIS AND BIOLOGICAL ACTIVITY

Dominik Rejman,[1] Milena Masojídková,[1] Eric De Clercq,[2] and Ivan Rosenberg[1]

[1]Institute of Organic Chemistry and Biochemistry, Academy of Science of the Czech Republic, Flemingovo n. 2, 166 10 Prague 6, Czech Republic
[2]Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium

ABSTRACT

A series of novel, unusual type of acyclic phosphonate-based nucleotide analogues related to well-known antivirals (PMEA and HPMPA) was synthesized using easily available synthon. These compounds, which are distinguished for the presence of phosphonomethyl acetal linkage, form a group of derivatives that contribute to the understanding of structure-activity relationship within the area of acyclic nucleotide analogues.

The *N*-(2-phosphonomethoxyethyl)purines **1** (PME-derivatives) are known to strongly inhibit DNA viruses and retroviruses[1,2]. Modification of the side-chain of PME-derivatives strongly influences the selectivity in antiviral properties of the compounds. Thus, *N*-(3-hydroxy-2-phosphonomethoxypropyl)purines **2** act solely on DNA viruses[1], while *N*-(3-fluoro-2-phosphonomethoxypropyl)purines **3** and *N*-(2-phosphonomethoxypropyl)-purines **4** affect exclusively retroviruses[3,4]. The activity of compounds **4** corresponds to the fluoro derivatives **3** both in base specificity and requirement on a configuration[4].

In the frame of structure-activity study of acyclic nucleotide analogs, we report herein the synthesis of a novel group of compounds related to known

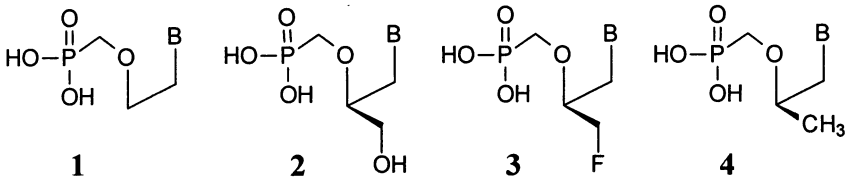


Figure 1. Inhibitors of replication of DNA viruses and retroviruses.

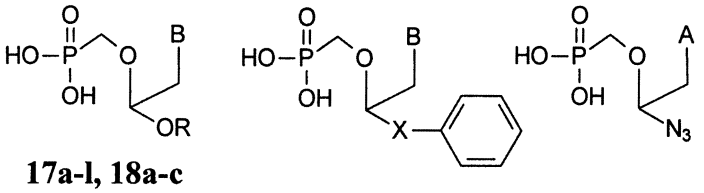


Figure 2. Prepared 2-*C*-substituted PME-derivatives.

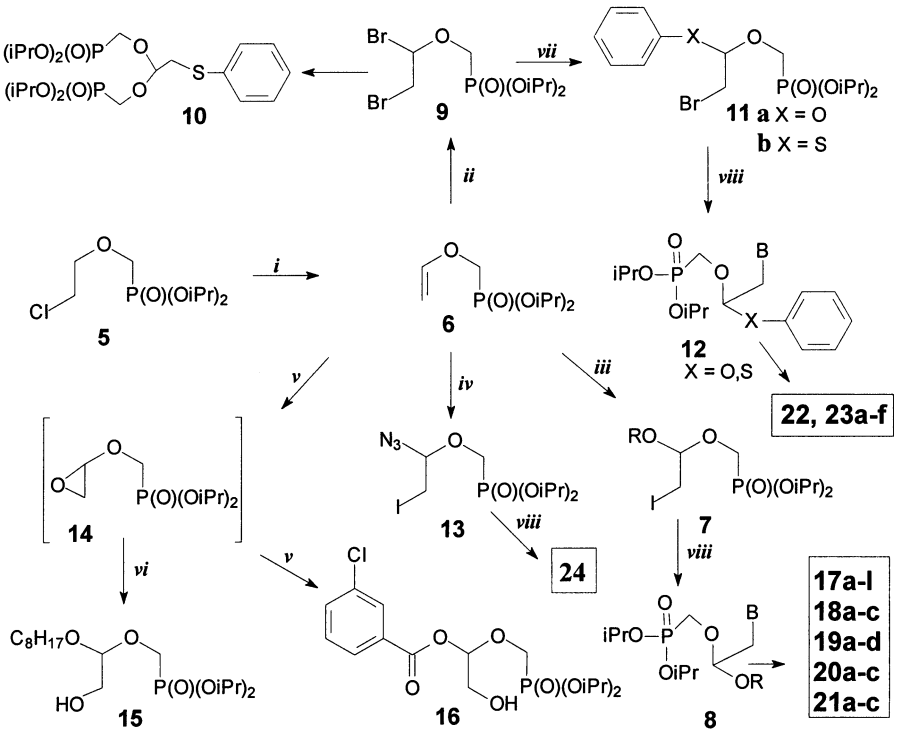
Table 1. Prepared 2-*C*-Substituted PME-Derivatives of Nucleobases (for structures see Figure 2)

Comp	B	R	Comp	B	R
17a	adenine	1-adamantanyl	**19c**	2,6-diaminopurine	2-fluoroethyl
17b	adenine	2-azidoethyl	**19d**	2,6-diaminopurine	2-hydroxyethyl
17c	adenine	benzyl			
17d	adenine	*tert*-butyl	**20a**	2-amino-6-bromopurine	allyl
17e	adenine	cyclohexyl	**20b**	2-amino-6-bromopurine	2-benzoyloxy-ethyl
17f	adenine	2-fluoroethyl	**20c**	2-amino-6-bromopurine	2-fluoroethyl
17g	adenine	8-hydroxy-3,6-dioxaoctyl			
17h	adenine	2-hydroxyethyl	**21a**	guanine	allyl
17i	adenine	methyl	**21b**	guanine	2-fluoroethyl
17j	adenine	*n*-octyl	**21c**	guanine	2-hydroxyethyl
17k	adenine	phosphonomethyl			
17l	adenine	2,2,2-trifluoroethyl	**22**	adenine	—
18a	cytosine	allyl	**23a**	adenine	—
18b	cytosine	2-fluoroethyl	**23b**	cytosine	—
18c	cytosine	methyl	**23c**	2,6-diaminopurine	—
			23d	guanine	—
19a	2,6-diamino-purine	2-azidoethyl	**23e**	thymine	—
19b	2,6-diamino-purine	2-benzoyloxyethyl	**23f**	uracil	—

antivirals **1-4**. In order to investigate the influence of a substituent in the 2-position of the side chain in PME-compounds on the antiviral activity, we elaborated the synthesis of racemic 2-*C*-alkoxy **17a-l**, **18a-c**, **19a-d**, **20a-c**, **21a-c**, 2-*C*-phenylthio **22**, 2-*C*-phenyloxy **23a-f**, and 2-*C*-azido **24** derivatives (Figure 1; for R and B see Table 1).

For the preparation of these compounds, the reaction of nucleobase with an appropriate phosphonate moiety-containing synthon **7, 11, 13** and **15** (Scheme 1) was used. A key, starting compound for the preparation of synthons, the diisopropyl vinyloxymethanephosphonate (**6**), was obtained in a high yield by β-elimination of hydrogen chloride from diisopropyl 2-chloroethoxymethanephosphonate (**5**) by treatment with potassium *tert*-butoxide. The compound **5** is easily accessible by Arbuzov reaction of the 2-chloroethylchloromethyl ether with *tris*-triisopropyl phosphite[5].

Thus, the reaction of vinyloxymethanephosphonate **6** with various hydroxy compounds R-OH (for **R** see Table 1) and *N*-iodosuccinimide (not *N*-bromosuccinimide) has led to the phosphonate synthons **7** and **13**; this type of electrophile-promoted addition of nucleophiles to a vinyl ether



i: *t*-BuOK/THF; *ii*: Br_2/CH_2Cl_2; *iii*: NIS/ROH/CH_2Cl_2; *iv*: IN_3/DMF; *v*: MCPBA/CH_2Cl_2; *vi*: $C_8H_{17}OH/CH_2Cl_2$; *vii*: C_6H_5OH or C_6H_5SH/diisopropylethylamin/CH_2Cl_2; *viii*: nucleobase/Cs_2CO_3/DMF

Scheme 1. Synthetic pathway for 2-*C*-substituted PME-derivatives of nucleobases.

moiety was already described[6]. Since the silica gel chromatography of several crude iodo derivatives **7** did not lead to their satisfactory purification, probably because of low stability, they were used for the further reaction step without chromatography.

Similarly, the preparation of synthons **11a**, **11b** containing phenoxy and phenylthio moiety starting from vinyloxymethanephosphonate **6** was elaborated. Reaction of this compound with bromine resulted in the disopropyl 1,2-dibromoethoxymethanephosphonate (**9**) in which the 1-bromo atom underwent nucleophilic displacement by phenoxy or phenylthio group.

We succeeded at the preparation of azido synthon **13**, although, in a very low yield in the reaction of iodoazide (generated *in situ* from sodium azide and iodochloride *7*) with vinyloxymethanephosphonate **6** in dimethylformamide. The reaction of the formed 1-azido-2-iodoethoxymethanephosphonate **13** with sodium salt of adenine at room temperature afforded, after deblocking procedure, the expected phosphonate **24**[8].

The alkylation of nucleobases (thymine, cytosine, adenine, 2,6-diaminopurine and 2-amino-6-chloropurine) by the appropriate phosphonate synthons **7, 11** and **13** in the presence of cesium carbonate was performed in DMF at elevated temperature.

Phenylthio derivative **22** was obtained in very low yield by alkylation of sodium salt of adenine with compound **11b** at room temperature. When performed at 100 °C and in the presence of cesium carbonate, the reaction afforded tetraisopropyl 2-phenylthio-1,1-bis(phosphonomethoxy)ethane (**10**) as the only major product (its formation is unclear).

All obtained diesters **8** and **12** were purified by silica gel chromatography and subjected, without characterization, to the transesterification procedure with bromotrimethylsilane. Thus, the free phosphonates **17a-g, 17i-l, 18a-c, 19a-c, 20a-c, 22**, and **23a-c,e,f** (Table 1) were prepared by this procedure directly whereas the phosphonates **17h** and **19d** were obtained after debenzoylation of the *O*-benzoyl derivative of compound **17h** and the *O*-benzoyl derivative **19b** under alkaline conditions. The guanine derivatives **21a-c** were prepared by hydrolysis of their 2-amino-6-bromopurine congeners **20a-c** in aqueous sodium hydroxide. The bromo compounds **20a-c** (confirmed by MS) were obtained unexpectedly during removal of the phosphonate diester moiety of the corresponding 2-amino-6-chloropurine derivatives by bromotrimethylsilane. To our knowledge, such exchange reaction of the 6-chloro atom for 6-bromo one in guanine derivatives has not been described so far in the literature.

We elaborated another approach for the preparation of phosphonate synthon(s) useful for subsequent reaction with nucleobases. Reaction of vinyloxymethanephosphonate **6** with the 3-chloroperoxybenzoic acid has led to epoxide **14** which underwent, in the presence of *n*-octanol, epoxide ring-opening to afforddiisopropyl 2-hydroxy-1-octyloxyethoxymethane-phosphonate (**15**) in a good yield. The absence of *n*-octanol in the reaction mixture has

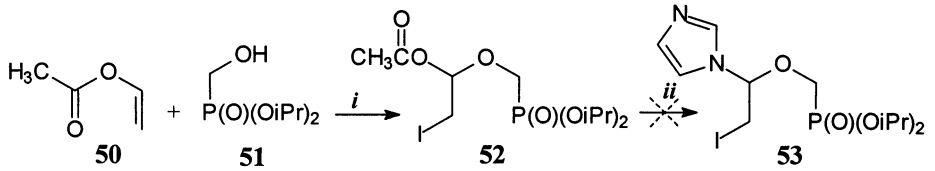
led to diisopropyl 1-(3-chlorobenzoyloxy)-2-hydroxyethoxymethanephosphonate (**16**). Mitsunobu alkylation of derivative **15** with 6-*N*-dibutylaminomethylenadenine gave a low yield of 6-*N*-dibutylaminomethylene-9-*N*-(2-(diisopropylphosphonomethoxy)-2-octyl-oxyethyl)adenine. MS FAB and UV spectroscopy data supported the proposed structure of this compound.

In order to elaborate general approach allowing for the preparation of "universal" phosphonate synthons containing *O,O*-, *O,N* and *O,S* mixed acetals with phosphonomethyl moiety (like compounds **7, 11** and **13**), we synthesized diisopropyl 1-acetoxy-2-iodomethanephosphonate (**52**) from vinylacetate (**50**) and diisopropyl hydroxymethanephosphonate (**51**)[9] in the presence of *N*-iodosuccinimide (Scheme 2) intended to replace the acetoxy group for hydroxy, amino or thiol function. Our attempt to prepare the compound **53** from 1-*N*-trimethylsilylimidazole as the nucleophile and compound **52** in the presence of trimethylsilyl triflate completely failed. A thorough study on the conditions of the reaction of compound **52** with the various *O*-, *S*- and *N*-nucleofiles and Lewis acid catalysts is underway.

Concerning the biological activity of prepared acyclic phosphonate nucleotides, we found neither cytostatic effects of compounds **17**–**23** using three cell lines (L929, L1210 and HeLa) nor anticancer activities of phosphonates **23a-f,** as evaluated also in three cell lines as well [NCI-H460 (Lung), MCF7 (Breast), and SF-268 (CNS)]. A thorough structure-activity study on the prepared nucleotides revealed only three compounds (**19c, 21b** and **22**) out of thirty-two to exhibit a marginal antiviral activity against DNA viruses and retroviruses (Table 2). In the light of these findings we can conclude that substitution of PME-derivatives of nucleobases at the 2-position of their side chain by alkoxy or phenoxy substituents does not lead, under currently used screening conditions, to antiviral/anticancer activities. Since there is no data on cellular uptake of novel nucleotides, some of them will be subjected to a detailed study aimed at this evaluation.

EXPERIMENTAL

Unless stated otherwise, the solutions were evaporated at 40 °C and 2 kPa. Purity of the products was checked by chromatographic methods



i: NIS/CH_2Cl_2; *ii*: *N*-trimethylsilylimidazole, $CF_3SO_3SiMe_3$,CH_3CN

Scheme 2. Preparation of "universal" synthon.

Table 2. Antiviral Properties of Prepared Compounds

	Antiviral Activity IC_{50} (μg/ml)[a]				Anti-HIV Activity[b] EC_{50} (μg/ml)[c]	
	TK^+ VZV (strains)		T K $^-$ V Z V (strains)			
Compound	OKA	YS	07/1	YS/R	HIV-1	HIV-2
19c	>50		>50		100	40.0 ± 0.0
21b	5.6	3.7	2.6	2.0	33.3 ± 23.1	7.67 ± 4.04
22	>50		> 50		53.3 ± 41.6	33.3 ± 11.5
ACV[d]	0.78	0.93	27	29	–	–
BVDU[e]	0.0031	0.0084	>50		–	–

[a]inhibitory concentration required to reduce virus plaque formation by 50%. Virus input was 20 plaque forming units (PFU); [b]performed in human T-lymphocyte (CEM cells); [c]50% effective concentration or concentration required to protect CEM cells against the cytopathogenicity of HIV by 50% [d]9-(2-hydroxyethoxymethyl)guanine; [e]5-(2-(*Z*)-bromovinyl)-2′-deoxyuridine.

(TLC, HPLC) and spectral methods (NMR, MS, UV). All the described reactions were monitored by TLC on Silufol UV 254 foils (Kavalier Glassworks, Votice, Czech Republic). The compounds were detected both by UV monitoring and by spraying with 1% ethanolic solution of 4-(4-nitrobenzyl)pyridine (PNBP) whereby, after short heating and exposing to ammonia vapours, the product (phosphonate diester) afforded intensively blue spot. Preparative column chromatography (diameter, 50 mm) was carried out on 40–60 μm silica gel (Fluka), the amount of adsorbent was 20–40 times the weight of the separated mixture. Elution was performed at the flow rate of 40 ml/min. Mass spectra were recorded on ZAB-EQ (VG Analytical) instrument, using FAB (ionization with Xe, accelerating voltage 8 kV). Glycerol and thioglycerol were used as matrices. NMR spectra were measured on Varian Unity 500 instrument (^{1}H at 500 MHz, ^{13}C at 125.7 MHz) in hexadeuteriodimethylsulfoxide (DMSO-d_6) or deuterized water and referenced to the solvent signal standard ($\delta_H = 2.5$, $\delta_C = 39.7$).

Diisopropyl 2-Chloroethoxymethanephosphonate (5)

Mild stream of hydrogen chloride was passed through a suspension of paraformaldehyde (112 g, 3.73 mol) in 2-chloroethanol (250 ml, 3.73 mol) at 0 °C until paraformaldehyde had dissolved (~4 h). After separation of aqueous layer, the crude 2-chloroethyl chloromethyl ether was dried over anhydrous $CaCl_2$ under stirring for 30 min, then filtered, and the solid portion was washed with dichloromethane. Filtrates were

combined and the dissolved hydrogen chloride was removed *in vacuo* at room temperature. The 2-chloroethyl chloromethyl ether was purified by distillation (b.p. 145–147 °C/760 torr) under argon atmosphere. Yield, 276.9 g (46%).

Triisopropyl phosphite (230 g, 1.1 mol) was added dropwise during 30 min under vigorous stirring to the 2-chloroethyl chloromethyl ether (117.66 g, 0.92 mol) at 120 °C. The mixture was then heated at 120 °C for additional 4 hours. The isopropylchloride evolving during reaction was continuously distilled off using a rectification head. The crude diisopropyl 2-chloroethoxymethanephosphonate (**5**) was purified by distillation at reduced pressure (b.p. 115 °C/0.15 torr). Yield, 207.4 g (80.2%).

Anal. calcd. for $C_9H_{20}ClO_4P$ (258.68): C, 41.79, H, 7.79. Found: C, 42.08, H, 8.27. MS (FAB): 259.1 (MH^+).^{1}H NMR (DMSO-d_6): 4.61 (2H, d sept, $J_{CH,CH_3} = 6.1$, $J_{P,OCH} = 7.8$, P-OCH), 3.80 (2H, d, $J_{P,CH} = 8.5$, P-CH_2), 3.78-3.72 (4H, m, O-CH_2 and CH_2Cl), 1.25 (6H, d, CH_3), 1.245 (6H, d, $J_{CH_3,CH} = 6.1$, CH_3).^{13}C NMR (DMSO-d_6): 70.44 (d, $J_{P,C} = 11.7$, O-C), 70.39 (d, $J_{P,C} = 6.8$, P-OC), 64.78 (d, $J_{P,C} = 165.0$, P-C), 43.36 (C-Cl), 24.01 (d, $J_{P,C} = 3.9$, CH_3), 23.89 (d, $J_{P,C} = 4.9$, CH_3).

Diisopropyl Vinyloxymethanephosphonate (6)

Potassium *tert*-butoxide (9 g, 80 mmol) was added under argon to a vigorously stirred solution of the diisopropyl 2-chloroethoxymethanephosphonate (**5**) (18.1 g, 70 mmol) in tetrahydrofuran (140 ml) at 0 °C. The ice bath was then removed and the mixture was stirred at room temperature for further 20 min. TLC on the silica gel plate performed in toluene-ethylacetate (1:1) revealed disappearance of the starting material and formation of a new product (R_f values of both compounds have very little difference) as detected on both PNBP and potassium permanganate spraying. The mixture was concentrated *in vacuo* and semi-solid residue was taken between ether and water. The ether layer was washed several times with water, dried over anhydrous sodium sulfate, filtered, and the solvent removed *in vacuo*. Distillation of the crude product at dimished pressure afforded 13.67 g (87.9%) of diisopropyl vinyloxymethanephosphonate (**6**) (60–65 °C, 0.02 torr).

Anal. calcd. for $C_9H_{19}O_4P.1/3H_2O$ (228.22): C, 47.36, H, 8.69. Found: C, 47.24, H, 8.74. MS (FAB): 331 (M^+ + thioglycerol).^{1}H NMR (DMSO-d_6): 6.53 (1H, dd, $J_{cis} = 6.6$, $J_{trans} = 14.2$, O-CH=), 4.62 (2H, d sept, J_{CH,CH_3}=6.1, $J_{P,OCH}$=7.8, P-OCH), 4.34 (1H, dd, J_g=2.2, J_{trans}=14.2, CH=), 4.07 (1H, dd, $J_g = 2.2$, $J_{cis} = 6.6$, CH=), 3.99 (2H, d, $J_{P,CH}$=9.0, P-CH_2), 1.26 (6H, d, CH_3), 1.24 (6H, d, $J_{CH_3,CH} = 6.1$, CH_3).^{13}C NMR (DMSO-d_6): 152.36 (d, $J_{P,C} = 12.7$, O-CH=), 88.34 (CH_2=), 70.71 (d, $J_{P,C} = 6.8$, P-OC), 62.26 (d, $J_{P,C} = 168.0$, P-C), 23.97 (d, CH_3), 23.85 (d, $J_{P,C} = 3.9$, CH_3).

General Procedures

Method A: Preparation of Synthons **7**

N-iodosuccinimide (1.24 g, 5.5 mmol) was added to a solution of diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol) and hydroxy derivative R-OH (for R, see **TABLE1**) (10 mmol) in dichloromethane at 0 °C under argon atmosphere. After 24 hours of stirring at room temperature, the reaction mixture was washed with saturated aqueous solution of sodium hydrogencarbonate. The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated. The crude products **7** and **13** were used without further purification and characterization for the subsequent reaction step.

Method B: Preparation of phosphonate diesters **8** and **12** (alkylation of nucleobases)

Crude synthons **7** and **11** ($\sim$ 5 mmol) (see ***Method A***), dried by codistillation with toluene (3 times) were treated in dimethylformamide (30 ml) under stirring at 110 °C with appropriate nucleobases (1 eq) in the presence of cesium carbonate (1 eq) for 10 hours. The course of the reaction was checked by TLC in ethyl acetate-acetone-ethanol-water (12:2:2:1) and detected using both UV absorption and spraying by PNBP. The solvents were removed *in vacuo* and the residue chromatographed on a silica gel column by a gradient elution of ethanol in chloroform (0- > 10%). The resulting compounds **8** and **12**, resp., were used for further reaction without characterization.

Deprotection of Phosphonate Diester 8 and 12

Method C: Preparation and Purification of Free Acyclic Nucleotides **17a-g, 17i-l, 18a-c, 19a-c, 20a-c, 22, 23a-c,e,f** and **24**

The phosphonate diesters **8** and **12** (***Method B***) in acetonitrile ($\sim$ 5 ml per mmol) were treated with bromotrimethylsilane ($\sim$ 3 equiv/mmol) at room temperature overnight. The course of the reaction was checked by TLC in isopropanol-conc. aqueous ammonia-water (7:1:2). The solution was evaporated and the solid residue dissolved in 0.1 M triethylammonium hydrogencarbonate in 50% aqueous methanol to hydrolyze ester trimethylsilyl groups. After 30 min of standing at room temperature the solvents were removed *in vacuo* and the crude free phosphonate was purified on a column of DEAE-Sephadex A25 (16 × 200 mm) using a gradient elution of triethylammonium hydrogencarbonate in water pH 7.5 (0—0.2 M, 2 × 1000 ml). Fractions containing the product were combined and evaporated. The residue was codistilled several times with methanol to destroy the excess of buffer, and the pure phosphonate was converted into the sodium

salt on Dowex 50 (Na^+ form) column. Adjustment of the compounds was performed by lyophilisation from their aqueous solutions.

Method D: Preparation and Purification of Free Acyclic Nucleotides **17h, 19d, 21a-c** and **23d**

The diisopropyl esters of compounds .**17h, 19b, 20a-c** and compound **12**. (X = O; B = 2-amino-6-chloropurin-9-yl) in acetonitrile (~5 ml per mmol) were treated with bromotrimethylsilane (3 equiv/mmol) at room temperature overnight. The solution was evaporated and the solid residue dissolved in aqueous 0.2 M-sodium hydroxide (50 ml per mmol) to remove the *O*-benzoyl group and to hydrolyze the 2-amino-6-halopurine derivatives to guanine ones. After standing at room temperature for 16 hr the alkaline solution was treated with Dowex 50 (triethylammonium form) (25 ml per mmol) to remove sodium ions, and after filtering off the resin, the clear solution was concentrated *in vacuo*. For purification step see ***Method C***.

Diisopropyl 2-bromo-1-phenylthioethoxymethanephosphonate (11b)

1 M solution of bromine (5.5 ml, 5.5 mmol of Br_2) in dichloromethane was added dropwise during 30 min to the solution of diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol) in dichloromethane (15 ml) at −78 °C under argon atmosphere. Solution of sodium thiophenolate in THF (0.55 M, 10 ml) (prepared from thiophenol and sodium hydride) was then added to the above mixture. The reaction was set aside at room temperature overnight. The reaction mixture was diluted by dichloromethane (50 ml), washed with saturated aqueous solution of sodium hydrogencarbonate, and organic layer was evaporated. Crude product was isolated on silica gel column by gradient elution of acetone (0–50%) in toluene. Yield, 0.841 g (40.9%) of compound **11b**.

MS: 382.3 (MH^+).^{1}H NMR (DMSO-d_6): 7.58-7.52 m, 2H a 7.42-7.35 m, 3H (arom H), 5.16 dd, 1H, J = 3.7 a 8.9 (O-C-H), 4.62 m, 2H (P-OCH), 4.13 dd, 1H, J = 10.0 a 13.7 a 3.91 dd, 1H, J = 8.6 a 13.7 (P-CH_2), 3.84 dd, 1H, J = 3.7 a 11.0 a 3.52 dd, 1H, J = 8.9 a 11.0 (CH_2-Br), 1.26 d, 6H a 1.24 d, 6H, J (CH_3, CH) = 6.1 (CH_3).^{13}C NMR: 88.10 d,J (P, C) = 15.6 (O-C-S), 70.76 d a 70.71 d, J (P, C) = 6.8 (P-OC), 62.14 d, J (P, C) = 166.0 (P-C), 34.62 (C-Br), 24.03 d a 24.00 d a 23.92 d a 23.89 d, J (P, C) = 3.9 (CH_3). Arom C: 134.17, 2C, 130.42, 129.39, 2C, 128.74.

Diisopropyl 2-hydroxy-1-octylethoxymethanephosphonate (15)

The 3-chloroperoxybenzoic acid (0.807 g, 5.5 mmol) was added to a solution of diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol)

and octanol (9 ml, 55 mmol) in dichloromethane (15 ml) at 0 °C under argon atmosphere, and the reaction mixture was kept at room temperature for 16 hours. The solution was washed with sodium hydrogencarbonate, organic layer dried with anhydrous sodium sulfate, and evaporated. Chromatography on a silica gel column in 0–50% of acetone in toluene afforded 0.95 g (51.6%) of compound **15**.

MS (FAB): 369.2 (MH^+). ^{1}H NMR (DMSO-d_6): 4.76 (1H, t, $J_{OH,\ CH_2} = 6.0$, OH), 4.60 (2H, m, P-PCH), 4.52 (1H, t, J = 5.4, O-CH-O), 3.77 (1H, dd, $J_{P,CH} = 9.0$, $J_g = 13.7$, P-CH_2), 3.72 (1H, dd, $J_{P,CH} = 9.5$, $J_g = 13.7$, P-CH_2), 3.70-3.58 (1H, m, O-CH_2), 3.44-3.31 (3H, m, O-CH_2), 1.50 (2H, m, C-CH_2) 1.35-1.20 (10H, m, C-CH_2), 1.22 (12H, d, $J_{CH_3,CH} = 6.1$, CH_3), 0.85 (3H, t, $J_{CH_3,CH_2} = 7.1$, CH_3). ^{13}C NMR: 103.40 (d, $J_{P,C} = 11.7$, O-C-O), 70.35 (d, P-OC), 70.34 (d, $J_{P,C} = 5.8$, P-OC), 66.62 (O-C), 61.39 (O-C), 59.09 (d, $J_{P,C} = 168.0$, P-C), 31.39 and 29.41 and 28.95 and 28.86 and 25.78 and 22.24 (C-C), 23.94 (d, CH_3) 23.85 (d, $J_{P,C} = 4.9$, CH_3), 14.09 (CH_3).

Diisopropyl 1-(3-chlorobenzoyloxy)-2-hydroxyethoxymethanephosphonate (16)

The 3-chloroperoxybenzoic acid (0.173 g, 1 mmol) was added under argon atmosphere to a solution of diisopropyl vinyloxymethanephosphonate (**6**) (0.22 ml, 1 mmol) in dichloromethane (5 ml) at 0 °C, and the reaction was kept aside at room temperature for 16 hrs. The solution was washed with sodium hydrogencarbonate, dried with anhydrous sodium sulfate, and evaporated. Chromatography on a silica gel column in 0–50% of acetone in toluene afforded 0.090 g (25%) of compound **16**.

^{1}H NMR (DMSO-d_6): 8.00 (1H, dd, J = 1.7,) 2.2 (1H, ddd, J = 1.0 and 1.7 and 7.8 and 7.77, arom H), 7.97 (1H, ddd, J = 1.0 and 2.2 and 8.0, arom H), 7.60 (1H, t, J = 7.9, arom H), 5.99 (1H, dd, $J_1 = 4.6$, $J_2 = 5.6$, O-CH-O),5.17 (1H, t, $J_{OH,\ CH_2} = 6.1$, H), 4.60 (2H, m, P-OCH), 4.01 (2H, d, $J_{P,CH} = 9.0$, P-CH_2), 3.65 (1H, ddd, $J_1 = 4.6$, $J_2 = 6.1$, $J_3 = 12.0$, O-CH_2), 3.58 (1H, dt, $J_1 = 5.9$, $J_2 = 5.9$, $J_3 = 12.0$, O-CH_2), 1.23 (3H, d, CH_3), 1.22 (6H, d, CH_3), 1.21 (3H, d, $J_{CH_3,CH} = 6.1$, CH_3). ^{13}C NMR: 99.52 (d, $J_{P,C} = 11.7$, O-C-O), 70.68 (d, P-OC), 70.66 (d, $J_{P,\ C} = 6.8$, P-OC), 63.13 (d, $J_{P,C} = 166.0$, P-C), 61.48 (O-C), 23.94 (d, CH_3), 23.92 (d, CH_3), 23.78 (2C, d, $J_{P,C} = 3.9$, CH_3), arom: 164.59 (C=O), 133.69 and 133.67 and 131.67 and 131.01 and 129.28 and 128.44.

9-*N*-(2-(1-adamantanyloxy)-2-phosphonomethoxyethyl)adenine (17a)

Synthon **8** (R=1-adamantanyl; B=adenine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), 1-adamantanol (0.91 g, 6 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol). Reaction performed according to ***Method B*** with adenine (0.68 g, 5 mmol) followed by deprotection and purification (***Method C***) afforded 318 mg (15%) of **17a**.

Anal. calcd. for $C_{18}H_{24}N_5O_5PNa_2 \cdot l2H_2O$ (503.41): C, 42.9, H, 5.6, N, 13.9, P, 6.2. Found: C, 43.0, H, 5.44, N, 13.52, P, 6.4. MS (FAB): 446.5 ((M^+)+Na).^{1}H NMR (D_2O): 8.22 and 8.18 ($2 \times 1H$, s, H-2 and H-8), 5.24 (1H, dd, $J_{2',1'a} = 3.4$, $J_{2',1'b} = 7.3$, H-2′), 4.45 (1H, dd, $J_{1'a,2'} = 3.4$, $J_{gem} = 14.2$, H-1′a), 4.28 (1H, dd, $J_{1'b,2'} = 7.3$, $J_{gem} = 14.2$, H-1′b), 3.80 (, 1H, dd $J_{P,Cha} = 9.5$, $J_{gem} = 12.7$, P-CHa), 3.68 (, 1H, dd $J_{P,CHb} = 10.0$, $J_{gem} = 12.7$, P-CHb), 2.10 (3H, m, C-CH adamantane), 1.56 (6H, m, C-CH adamantane), 1.46 (6H, m, C-CH adamantane).

9-*N*-(2-(2-azidoethoxy)-2-phosphonomethoxyethyl)adenine (17b)

Synthon **8** (R=2-azidoethyl; B=adenine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), 2-azidoethanol (1.3 g, 10 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol). Reaction performed according to ***Method B*** with adenine (1.35 g, 10 mmol) followed by deprotection and purification (***Method C***) afforded 707 mg (20%) of **17b**.

HR FAB calcd for $C_{10}H_{15}N_8O_5P$ 358.090304, found 381.080074 (M + Na).^{1}H NMR (D_2O): 8.17 and 8.16 ($2 \times 1H$, s, H-8, H-2), 5.06 (1H, dd, CH-2′, $J_{2'1'a} = 3.9$, $J_{2'1'b} = 5.4$), 4.47 (1H, dd, CH2-1′, $J_{1'a2'} = 3.9$, $J_g = 14.65$), 4.41 (1H, dd, CH_2-1′, $J_{1'b2'} = 5.6$, $J_g = 14.65$), 3.94 (1H, ddd, OCH_2, $J_1 = 3.7$, $J_2 = 5.6$, $J_3 = 11.0$), 3.67 (1H, ddd, OCH_2, $J_1 = 4.1$, $J_2 = 6.1$, $J_3 = 11.5$), 3.89 (1H, dd, P-CH_2, $J_{PCHa} = 9.3$, $J_g = 12.9$), 3.76 (1H, dd, P-CH_2, $J_{PCHb} = 10.0$, $J_g = 12.9$), 3.35 (2H, m, NCH_2),^{13}C NMR: 154.90 (C-6), 151.875 (C-2), 148.73 (C-4), 142.78 (C-8), 117.61 (C-5), 101.33 (C-2′, d, J = 11.7), 66.88 (OCH_2), 63.39 (PC, d, J = 157.2), 50.23 (NCH_2), 45.09 (C-1′).

9-*N*-(Benzyloxy-2-phosphonomethoxyethyl)adenine (17c)

Synthon **8** (R-benzyl; B-adenine) was prepared by ***Method A*** using *N*-iodosuccinimide (0.79 g, 3.5 mmol), benzoylalcohol (0.38 g, 3.5 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (0.75 ml, 3.4 mmol). Reaction performed according to ***Method B*** with adenine (0.47 g, 3.5 mmol) followed by deprotection and purification (***Method C***) afforded 300 mg (23%) of **17c**.

Anal. calcd. for $C_{15}H_{17}N_5O_5PNa \cdot 3H_2O$ (455.35): C, 39.6, H, 5.1, N, 15.4, P, 6.8. Found: C, 39.34, H, 5.15, N, 15.26, P, 6.76. MS (FAB): 379.3 (MH^+).^{1}H NMR (D_2O): 7.91 and 7.85 ($2 \times 1H$, s, H-2 a H-8), 7.08 (1H, t, arom H), 6.99 (2H, t, arom H), 6.81 (2H, d, arom H), 5.02 (1H, dd, $J_{2',1'a} = 3.2$, $J_{2',1'b} = 8.0$, H-2′), 4.71 (1H, d, O-CH_2 arom), 4.42 (1H, d, $J_{gem} = 12.2$, O-CH_2 arom), 4.27 (1H, dd, $J_{1'a,2'} = 3.2$, $J_g = 14.7$, H-1′a), 4.17 (1H, dd, $J_{1'b,2'} = 8.0$, J_g) = 14.7, H-1′b), 3.93 (1H, dd, $J_{P,CHa} = 9.5$, $J_g = 12.5$, P-CHa), 3.79 (1H, dd, $J_{P,CHb} = 10.0$, $J_g = 12.5$, P-CHb).

9-*N*-(2-tert-butyloxy-2-phosphonomethoxyethyl)adenine (17d)

Synthon **8** (R=*tert*-butyl; B=adenine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), *tert*-butanol (1.5 g, 20 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol). Reaction performed according to ***Method B*** with adenine (0.68 g, 5 mmol) followed by deprotection and purification (***Method C***) afforded 287 mg (16%) of **17d**.

Anal. calcd. for $C_{12}H_{19}N_5O_5PNa \cdot 3H_2O$ (421.32): C, 34.2, H, 6.0, N, 16.6, P 7.4. Found: C, 34.56, H, 5.89, N, 16.6,P, 7.27.^{1}H NMR (D_2O): 8.21 and 8.17 (2 × 1H, s, H-2 and H-8), 5.11 (1H, dd, $J_{2',1'a} = 3.7$, $J_{2',1'b} = 6.4$, H-2′), 4.45 (1H, dd, $J_{1'a,2'} = 3.7$, $J_{gem} = 14.7$, H-1′b), 4.28 (1H, dd, $J_{1'b,2'} = 6.4$, $J_{gem} = 14.7$, H-1′b), 3.79 (1H, dd, $J_{P,CHa} = 9.8$, $J_{gem} = 12.7$, P-CHa), 3.70 (1H, dd, $J_{P,CHb} = 10.2$, $J_{gem} = 12.7$, P-CHb).

9-*N*-(2-cyclohexyloxy-2-phosphonomethoxyethyl)adenine (17e)

Synthon **8** (R=cyclohexyl; B=adenine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), cyclohexanol (2.5 g, 25 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol). Reaction performed according to ***Method B*** with adenine (0.68 g, 5 mmol) followed by deprotection and purification (***Method C***) afforded 342 mg (18%) of **17e**.

Anal.calcd.for $C_{14}H_{21}N_5O_5PNa.\ 3H_2O$ (447.36): C, 37.6, H, 6.1, N, 15.7, P, 6.9. Found: C, 37.83, H, 5.97, N, 15.93, P, 6.86. MS (FAB): 372.1 (MH^+). 1 H NMR (D_2O): 8.18 and 8.16 (2 × 1H, s, H-2 a H-8), 5.08 (1H, dd, $J_{2',1'a} = 3.7$, $J_{2',1'b} = 6.1$, H-2′), 4.44 (1H, dd,$J_{1'a,2'} = 3.7$, $J_{gem} = 14.7$, H-1′a), 4.30 (1H, dd, $J_{1'b,2'} = 6.1$, $J_{gem} = 14.7$, H-1′b), 3.85 (1H, dd,$J_{P,CHa} = 9.3$, $J_{gem} = 12.7$, P-CHa), 3.67 (1H, dd, $J_{P,CHb} = 10.2$, $J_{gem} = 12.7$, P-CHb), 3.56 (1H, m, 1″-CH), 1.90 (1H, m, C-CH), 1.60 (1H, m, C-CH), 1.40 (1H, m, C-CH), 1.30 (2H, m, C-CH), 1.23 (, 1H, m C-CH), 1.05 (2H, m, C-CH), 0.82 (1H, m, C-CH).

9-*N*-(2-(2-fluoroethoxy)-2-phosphonomethoxyethyl)adenine (17f)

Synthon **8** (R=2-fluoroethyl, B=adenine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), 2-fluoroethanol (0.6 ml, 10 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol). Reaction performed according to ***Method B*** with adenine (0.68 g, 5 mmol) followed by deprotection and purification (***Method C***) afforded 114 mg (7%) of **17f**.

Anal. calcd. for $C_{10}H_{14}N_5O_5PFNa \cdot 4H_2O$ (429.27): C, 28.0, H, 5.2, N, 16.3, P, 7.2. Found: C, 28.03, H, 5.17, N, 16.27, P, 8.05.^{1}H NMR (D_2O): 8.22 and 8.21 (2 × 1H, s, H-2 and H-8), 5.07 (1H, dd, $J_{2',1'a} = 3.9$, $J_{2',1'b} = 5.4$, H-2′), 4.54 (1H, dddd, $J_{1''a,2''a} = 2.2$, $J_{1''a,2''b} = 6.1$, $J_{gem} = 11.0$, $J_{1''a,\ F} = 21.5$, H-1″a), 4.50 (1H, dd, $J_{1'a,2'} = 3.9$, $J_{gem} = 14.7$, H-1a), 4.44 (1H, dddd, $J_{1''b,\ 2''a} = 5.4$, $J_{1''b,2''b} = 2.2$, $J_{gem} = 11.0$, $J_{1''b,F} = 20.5$, H-1″b), 4.43 (1H, dd, $J_{1'b,}$

$_{2'} = 5.4$, $J_{gem} = 14.7$, H-1′b), 4.02 (1H, dddd, $J_{2''a,1''a} = 2.2$, $J_{2''a,1''b} = 5.4$, $J_{gem} = 12.5$, $J_{2''a,F} = 32.5$, H-2″a), 3.82 (1H, dddd, $J_{2''b,1''a} = 6.1$, $J_{2''b,1''b} = 2.2$, $J_{gem} = 12.5$, $J_{2''b,F} = 30.3$, H-2″b), 3.83 (1H, dd, $J_{P,CHa} = 9.5$, $J_{gem} = 12.7$, P-CHa), 3.67 (1H, dd, $J_{P,CHb} = 10.0$, $J_{gem} = 12.7$, P-CHb).

9-*N*-(2-(8-hydroxy-3,6-dioxaoctyloxy)-2-phosphonomethoxyethyl) adenine (17g)

Synthon **8** (R=8-dimethoxytrityloxy-3,6-dioxaoctyl; B=adenine) was prepared by ***Method A*** using *N*-iodosuccinimide (2.48 g, 11 mmol), 8-dimethoxytrityloxy-3,6-dioxaoctanol (8.8 g, 20 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (2.2 ml, 10 mmol). Reaction performed according to ***Method B*** with adenine (1.35 g, 10 mmol) followed by deprotection and purification (***Method C***) afforded 139 mg (3.3%) of **17g**.

Anal. calcd. for $C_{14}H_{23}N_5O_8PNa.2H_2O$ (479.37): C, 35.1, H, 5.7, N, 14.6. Found: C, 35.08, H, 5.72, N, 14.48. MS (FAB): 422.4 (MH^+). ^{1}H NMR (D_2O): 8.215 and 8.21 (2 × 1H s, H-2 and H-8), 5.05 (1H, dd, $J_{2',1'a} = 3.9$, $J_{2',1'b} = 5.6$, H-2′), 4.48 (1H, dd, $J_{1'a,\ 2'} = 3.9$, $J_{gem} = 14.7$, H-1′a), 4.42 (1H, dd, $J_{1'b,2'} = 5.6$, $J_{gem} = 14.7$, H-1′b), 3.93 (1H, m, OCH_2), 3.71 (1H, m, OCH_2), 3.87 (1H, dd, $J_{P,CHa} = 9.3$, $J_{gem} = 12.9$, P-CHa), 3.75 (1H, dd, $J_{P,CHb} = 9.8$, $J_{gem} = 12.9$, P-CHb), 3.69 (2H, m, (OCH_2), 3.57–3.40 (8H, m, (OCH_2).

9-*N*-(2-(2-hydroxyethoxy)-2-phosphonomethoxyethyl)adenine (17h)

Synthon **8** (R=2-benzoyloxyethyl; B=adenine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), 2-benzoyloxyethanol (1.7 g, 10 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol). Reaction performed according to ***Method B*** with adenine (0.68 g, 5 mmol) followed by deprotection and purification (***Method D***) afforded 160 mg (9%) of **17h**.

Anal. calcd. for $C_{10}H_{14}N_5O_6PNa_2{\cdot}3H_2O$ (431.26): C, 27.9, H, 4.7, N, 16.2, P 7.2. Found: C, 27.68, H, 4.3, N, 15.58, P, 7.8. MS (FAB): 334.1 (MH^+). ^{1}H NMR (D_2O): 8.21 and 8.20 (2 × 1H, s, H-2 and H-8), 5.04 (1H, t, J = 4.6, H-2′), 4.47 (1H, dd, $J_{1'a,2'} = 4.4$, $J_{gem} = 14.7$, H-1′a), 4.43 (1H, dd, $J_{1'b,\ 2'} = 4.9$, $J_{gem} = 14.7$, H-1′b), 3.87 (2H, m, O-CH_2), 3.84 (1H, dd, $J_{P,CHa} = 9.3$, $J_{gem} = 12.9$, P-CHa), 3.68 (1H, dd, $J_{P,CHb}) = 9.8$, $J_{gem} = 12.9$, P-CHb), 3.64 (2H, m, O-CH_2).

9-*N*-(2-methoxy-2-phosphonomethoxyethyl)adenine (17i)

Synthon **8** (R=methyl; B=adenine) was prepared by ***Method A*** using *N*-iodosuccinimide (0.52 g, 2.3 mmol), methanol (0.1 ml, 2.52 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (0.51 ml, 2.3 mmol). Reaction

performed according to ***Method B*** with adenine (0.31 g, 2.3 mmol) followed by deprotection and purification (***Method C***) afforded 340 mg (48%) of **17i**.

Anal. calcd. for $C_9H_{12}N_5O_5PNa_2{\cdot}3H_2O$ (401.22): C, 26.9, H, 4.5, N, 17.5, P, 7.7. Found: C, 27.24, H, 4.31, N, 17.40, P, 7.67. MS (FAB): 303.2 (M^+).^{1}H NMR (D_2O): 8.13 and 8.05 ($2 \times 1H$, s, H-2 and H-8), 4.95 (1H, dd, $J_{2',\,1'a} = 4.4$, $J_{2',\,1'b} = 4.9$, H-2′), 4.40 (1H, dd, $J_{1'a,\,2'} = 4.4$, $J_g = 14.6$, H - 1′a), 4.36 (1H, dd, $J_{1'b,\,2'}$4.9, $J_{gem} = 14.6$, H -1′b), 3.88 (1H, dd, $J_{P,\,CHa} = 9.5$, $J_{gem} = 12.5$, P - Cha), 3.73 (1H, dd, $J_{P,\,CHb} = 9.8$, $J_{gem} = 12.5$, P - Chb), 3.5 (3H, s, OCH_3).

9-*N*-(2-octyloxy-2-phosphonomethoxyethyl)adenine (17j)

Synthon **8** (R=*n*-octyl; B=adenine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), *n*-octanol (0.72 g, 5.5 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol). Reaction performed according to ***Method B*** with adenine (0.68 g, 5 mmol) followed by deprotection and purification (***Method C***) afforded 466 mg (23%) of **17j**.

HR FAB calcd. for $C_{16}H_{28}N_5O_5P$ 401.182807, found 402.190633 (M+H).^{1}H NMR (D_2O): 8.23 and 8.205 ($2 \times 1H$, s, H-8, H-2), 5.03 (1H, dd, CH-2′, $J_{2'1'a} = 3.4$, $J_{2'1'b} = 7.1$), 4.50 (1H, dd, CH_2-1′, $J_{1'a2'} = 3.4$, $J_g = 14.7$), 4.36 (1H, dd, CH_2-1′, $J_{1'b2'} = 7.1$, $J_g = 14.7$), 3.83 (1H, dd, P-CH_2, $J_{PCHa} = 9.1$, $J_g = 12.7$), 3.68 (1H, dd, P-CH_2, $J_{PCHb} = 9.8$, $J_g = 12.7$), 3.78 (1H, m, OCH_2), 3.43 (1H, m, OCH_2),1.18-1.32 (4H, m, CCH_2), 0.65-1.10 (11H, m, CCH_2).

9-*N*-(bis-2,2-(phosphonomethoxy)ethyl)adenine (17k)

Synthon **8** (R=diisopropylphosphonomethyl; B=adenine) was prepared by ***Method A*** using *N*-iodosuccinimide (0.79 g, 3.5 mmol), diisopropyl hydroxymethanephosphonate (**51**) (0.62 g, 3.16 mmol) and of diisopropyl vinyloxymethanephosphonate (**6**) (0.75 ml, 3.4 mmol). Reaction performed according to ***Method B*** with adenine (0.47 g, 3.5 mmol) followed by deprotection and purification (***Method C***) afforded 160 mg (23%) of **17k**.

Anal. calcd. for $C_9H_{13}N_5O_8P_2Na_2{\cdot}5/2H_2O$ (472.21): C, 21.3, H, 4.4, N, 13.8, P, 12.2. Found: C, 21.48, H, 4.25, N, 13.61, P, 11.67. MS (FAB): 383.2 (MH^+).^{1}H NMR (D_2O): 8.16 and 8.06 ($2 \times 1H$, s, H-2 a H-8), 5.02 (1H, t, $J_{2',\,1'} = 4.6$, H-2′), 4.41 (2H, d, $J_{1',2'} = 4.6$, H-1′), 3.86 (2H, dd, $J_{P,CHa} = 9.5$, $J_g = 12.9$, P-CHa), 3.71 (2H, dd, J_P, CHb = 9.8, $J_g = 12.9$, P-CHb).

9-*N*-(2-(2,2,2-trifluoroethoxy)-2-phosphonomethoxyethyl)adenine (17l)

Synthon **8** (R=2,2,2-trifluoroethyl; B=adenine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), 2,2,2-trifluoroethanol (0.55 g, 5.5 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml,

5 mmol). Reaction performed according to ***Method B*** with adenine (0.68 g, 5 mmol) followed by deprotection and purification (***Method C***) afforded 367 mg (20) of **17l**.

Anal. calcd. for $C_{10}H_{13}N_5O_5PF_3Na{\cdot}3H_2O$ (448.25): C, 26, H, 4.1, N, 15.7, P, 6.9. Found: C, 26.58, H, 3.98, N, 15.15, P, 7.13. MS (FAB): 372 (MH^+).^{1}H NMR (D_2O): 8.17 (2H, s, H-2 a H-8), 5.15 (dd, 1H, $J_{2',1'a} = 3.9$, $J_{2',1'b} = 4.6$, H-2′), 4.50 (dd, 1H, $J_{1'a,2'} = 3.9$, $J_{gem} = 14.9$, H-1′), 4.45 (dd, 1H, $J_{1'b,2'} = 4.6$, $J_{gem} = 14.9$, H-1′), 4.26 (dq, 1H, $J_{1''a,F} = 8.8$, $J_{gem} = 12.5$, H-1″), 4.12 (dq, 1H, $J_{1''b,F} = 8.8$, $J_{gem} = 12.5$, H-1″, 3.87 (dd, 1H, $J_{P,\ CHa} = 9.5$, $J_{gem} = 12.7$, P-CHa), 3.74 (dd, 1H, $J_{P,CHb} = 10.0$, $J_{gem} = 12.7$, P-CHb).

1-*N*-(2-allyloxy-2-phosphonomethoxyethyl)cytosine (18a)

Synthon **8** (R=allyl; B=cytosine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), allyl alcohol (0.58 g, 10 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol). Reaction performed according to ***Method B*** with cytosine (0.56 g, 5 mmol) followed by deprotection and purification (***Method C***) afforded 564 mg (37%) of **18a**. HR FAB calcd for $C_{10}H_{16}N_3O_6P$ 305.077673, found 350.049388 (M-H+2Na).^{1}H NMR (D_2O): 7.60 (1H, d, H-6), 5.99 (1H, d, H-5, $J_{56} = 7.3$), 5.86 (1H, ddt, 5′-H, $J_{5'4'} = 5.9$, $J_{5'6'a(trans)} = 17.1$, $J_{5'6'b(cis)} = 10.5$), 5.29 (1H, dq, 6′-H, $J_{6'4'} \sim J_g = 1.5$, $J_{6'a5'} = 17.1$), 5.22 (1H, dq, 6′-H, $J_{6'4'} \sim J_g = 1.5$, $J_{6'b5'} = 10.5$), 4.91 (1H, dd, CH-2′, $J_{2'1'a} = 4.4$, $J_{2'1'b} = 5.9$), 4.30 (1H, ddt, 4′-H, $J_{4'a6'} = 1.5$, $J_{4'a5'} = 5.6$, $J_g = 12.7$), 4.12 (1H, ddt, 4′-H, $J_{4'b6'} = 1.5$, $J_{4'b5'} = 6.3$, $J_g = 12.7$), 4.06 (1H, dd, CH_2-1′, $J_{1'a2'} = 4.4$, $J_g = 14.1$), 3.85 (1H, dd, CH_2-1′, $J_{1'b2'} = 6.1$, $J_g = 14.1$), 3.82 (1H, dd, P-CH_2, $J_{PCHa} = 9.5$, $J_g = 12.7$), 3.64 (1H, dd, P-CH_2, $J_{PCHb} = 10.0$, $J_g = 12.7$),^{13}C NMR: 166.21 (C-4), 158.00 (C-2), 147.67 (C-6), 133.05 (C-5′), 118.27 (C-6′), 100.80 (C-2′,d , J = 11.7), 95.26 (C-5), 69.60 (C-4′), 63.73 (P-C, d, J = 157.2), 51.315 (C-1′).

1-*N*-(2-(2-fluoroethoxy)-2-phosphonomethoxyethyl)cytosine (18b)

Synthon **8** (R=2-fluoroethyl; B=cytosine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), 2-fluoroethanol (0.6 ml, 10 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol). Reaction performed according to ***Method B*** with 2,6-diaminopurine (0.75 g, 5 mmol) followed by deprotection and purification (*Method C*) afforded 451 mg (29%) of **18b**.

HR FAB calcd. for $C_9H_{15}FN_3O_6P$ 311.068252, found 312.076077 (M+H).^{1}H NMR (D_2O): 7.66 (1H, d, H-6), 6.03 (1H, d, H-5, $J_{56} = 7.3$), 4.94 (1H, dd, CH-2′, $J_{2'1'a} = 4.6$, $J_{2'1'b} = 5.6$), 4.61 (1H, dddd, FCH_2, $J_{5'a4'a} = 2.7$, $J_{5'a4'b} = 5.7$, $J_{5'aF} = 47.6$, $J_g = 11$), 4.57 (1H, dddd, FCH_2, $J_{5'b4'a} = 4.9$, $J_{5'b4'a} = 2.7$, $J_{5'aF} = 47.4$, $J_g = 11$), 4.06 (1H, dd, CH_2-1′, $J_{1'a2'} = 4.6$, $J_g = 14.2$),

3.94 (1H, dd, CH_2-1′, $J_{1'b2'} = 5.6$, $J_g = 14.2$), 4.05 (1H, dddd, OCH_2, $J_{4'a5'a} = 2.7$, $J_{4'a5'b} = 4.9$, $J_{4'aF} = 32.8$, $J_g = 12.4$), 3.89 (1H, dddd, OCH_2, $J_{4'b5'a} = 2.7$, $J_{4'b5'b} = 5.7$, $J_{4'bF} = 30.5$, $J_g = 12.4$), 3.84 (1H, dd, P-CH_2, $J_{PCHa} = 9.5$, $J_g = 12.9$), 3.67 (1H, dd, P-CH_2, $J_{PCHb} = 10.0$, $J_g = 12.9$),^{13}C NMR: 164.95 (C-4), 156.35 (C-2), 148.07 (C-6), 101.48 (C-2′,d, J = 12.7), 83.21 (C-F, d, J = 164.1), 67.575 (O-C, d , J = 17.6), 63.31 (P-C, d, J = 158.2), 50.85 (C-1′).

1-*N*-(2-methoxy-2-phosphonomethoxyethyl)cytosine (18c)

Synthon **8** (R=methyl; B=cytosine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), methanol (0.81 ml, 20 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol). Reaction performed according to ***Method B*** with cytosine (0.56 g, 5 mmol) followed by deprotection and purification (***Method C***) afforded 741 mg (53%) of **18c**.

HR FAB calcd for $C_8H_{14}N_3O_6P$ 279.06203, found 302.051794 (M+Na).^{1}H NMR (D_2O): 7.63 (1H, d, H-6, $J_{56} = 7.3$), 6.01 (1H, d, H-5), 4.79 (1H, brt, CH-2′, $J_{2'1'a} = 4.9$, $J_{2'1'b} = 5.1$), 4.00 (1H, dd, CH_2-1′, $J_{1'a2'} = 4.9$, $J_g = 14.2$), 3.99 (1H, dd, CH_2-1′, $J_{1'b2'} = 5.1$, $J_g = 14.2$), 3.82 (1H, dd, P-CH_2, $J_{PCHa} = 9.5$, $J_g = 12.9$), 3.66 (1H, dd, P-CH_2, $J_{PCHb} = 10.0$, $J_g = 12.9$), 3.47 (3H, s, OCH_3),^{13}C NMR: 165.32 (C-4), 156.89 (C-2), 147.85 (C-6), 102.12 (C-2′,d, J = 11.7), 95.15 (C-5), 63.47 (P-C, d, J = 158.2), 54.98 (OCH_3).

2,6-diamino-9-*N*-(2-(2-azidoethoxy)-2-phosphonomethoxyethyl)purine (19a)

Synthon **8** (R=2-azidoethyl; B=2,6-diaminopurine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), 2-azidoethanol (1.3 g, 15 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (2.2 ml, 10 mmol). Reaction performed according to ***Method B*** with 2,6-diaminopurine (1.5 g, 10 mmol) followed by deprotection and purification (***Method C***) afforded 747 mg (20%) of **19a**.

HR FAB calcd for $C_{10}H_{16}N_9O_5P$ 373.101203, found 418.072918 (M-H+2Na).^{1}H NMR (D_2O): 7.885 (1H, s, H-8), 5.02 (1H, dd, CH-2′, $J_{2'1'a} = 3.7$, $J_{2'1'b} = 5.9$), 4.32 (1H, dd, CH_2-1′, $J_{1'a2'} = 3.7$, $J_g = 14.65$), 4.24 (1H, dd, CH_2-1′, $J_{1'b2'} = 5.9$, $J_g = 14.65$), 3.95 (1H, ddd, OCH_2, $J_1 = 3.7$, $J_2 = 5.6$, $J_3 = 11.0$), 3.65 (1H, ddd, OCH_2, $J_1 = 3.7$, $J_2 = 6.1$, $J_3 = 11.0$), 3.81 (1H, dd, P-CH_2, $J_{PCHa} = 9.3$, $J_g = 12.2$), 3.67 (1H, dd, P-CH_2, $J_{PCHb} = 10.0$, $J_g = 12.2$), 3.34 (2H, m, NCH_2),^{13}C NMR: 159.43 (C-2), 155.57 (C-6), 150.94 (C-4), 140.46 (C-8), 112.24 (C-5), 101.57 (C-2′,d, J = 11.7), 66.915 (OCH_2), 64.17 (PC, d, J = 155.3), 50.31 (NCH_2, d, J = 163.6), 44.87 (C-1′).

2,6-diamino-9-*N*-(2-(2-benzoyloxyethoxy)-2-phosphonomethoxyethyl)-purine (19b)

Synthon **8** (R=2-benzoyloxyethyl; B=2,6-diaminopurine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), 2-benzoyloxyethanol (1.7 g, 10 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol). Reaction performed according to ***Method B*** with 2,6-diaminopurine (0.75 g, 5 mmol) followed by deprotection and purification (***Method C***) afforded 178 mg (8%) of **19b**.

HR FAB calcd for $C_{17}H_{21}N_6O_7P$ 452.120935, found 475.110705 (M+Na).^{1}H NMR (D_2O): 7.79 (1H, s, H-8), 7.64 (3H, m, arom.), 7.44 (2H, t, arom.), 5.10 (1H, dd, CH-2′, $J_{2'1'a}=2.7$, $J_{2'1'b}=8.3$), 4.34–4.29 (2H, m, CH_2-1′), 4.23 (1H, m, 4′-O-CH_2), 4.13–4.06 (3H, m, 4′-O-CH_2), 3.81 (1H, dd, P-CH_2, $J_{PCHa}=9.5$, $J_g=12.0$), 3.69 (1H, dd, P-CH_2, $J_{PCHb}=10.0$, $J_g=12.0$),^{13}C NMR: 165.9 (arom.), 159.14 (C-2), 154.97 (C-6), 150.31 (C-4), 140.04 (C-8), 133.385 (arom.), 128.53 (arom.), 128.165 (arom.), 127.69 (arom.), 112.02 (C-5), 102.40 (C-2′,d, J = 11.7), 66.88 (O-C), 65.05 (O-C), 65.06 (P-C, d, J = 152.0), 44.97 (C-1′).

2,6-diamino-9-*N*-(2-(2-fluoroethoxy)-2-phosphonomethoxyethyl)purine (19c)

Synthon **8** (R=2-fluoroethyl; B=2,6-diaminopurine) was prepared by ***Method A*** using *N*-iodosuccinimide (2.25 g, 10 mmol), 2-fluoroethanol (1.1 ml, 18 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.98 ml, 9 mmol). Reaction performed according to ***Method B*** with 2,6-diaminopurine (1.35 g, 9 mmol) followed by deprotection and purification (***Method C***) afforded 338 mg (11%) of **19c**.

MS (FAB): 351.1 (MH^+).^{1}H NMR (D_2O): 7.91 (1H, s, H-8), 5.01 (1H, dd, CH-2′, $J_{2'1'a}=3.4$, $J_{2'1'b}=6.3$), 4.49 (1H, dddd, $J_{5'a4'a}=2.0$, $J_{5'a4'}b=6.1$, $J_{5'aF}=47.6$, $J_g=10.7$), 4.44 (1H, dddd, $J_{5'b4'a}=5.4$, $J_{5'b4'a}=2.0$, $J_{5'aF}=47.6$, $J_g=10.7$), 4.35 (1H, dd, CH_2-1′, $J_{1'a2'}=3.4$, $J_g=14.65$), 4.24 (1H, dd, CH_2-1′, $J_{1'b2'}=6.3$, $J_g=14.65$), 4.03 (1H, dddd, $J_{4'a5'a}=2.0$, $J_{4'a5'b}=5.6$, $J_{4'aF}=32.2$, $J_g=12.4$), 3.76 (1H, dddd, $J_{4'b5'a}=6.1$, $J_{4'b5'b}=2.0$, $J_{4'bF}=30.8$, $J_g=12.4$), 3.73 (1H, dd, P-CH_2, $J_{PCHa}=9.0$, $J_g=12.2$), 3.54 (1H, dd, P-CH_2, $J_{PCHb}=9.8$, $J_g=12.2$),^{13}C NMR: 159.76 (C-2), 155.83 (C-6), 151.145 (C-4), 140.67 (C-8), 112.32 (C-5), 101.71 (C-2′,d, J = 11.7), 83.14 (C-F, d, J = 163.6), 67.41 (O-C,d, J = 18.6), 65.59 (P-C, d, J = 151.4), 44.95 (C-1′).

2,6-diamino-9-*N*-(2-(2-hydroxyethoxy)-2-phosphonomethoxyethyl)purine (19d)

Synthon **8** (R=2-benzoyloxyethyl; B=2,6-diaminopurine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), 2-benzoyloxyethanol (1.7 g, 10 mmol) and diisopropyl vinyloxymethanephosphonate (**6**)

(1.1 ml, 5 mmol). Reaction performed according to ***Method B*** with 2,6-diaminopurine (0.75 g, 5 mmol) followed by deprotection and purification (***Method D***) afforded 87 mg (5%) of **19d**.

HR FAB calcd. for $C_{10}H_{17}N_6O_6P$ 348.094720, found 393.066435 (M-H+2Na).^{1}H NMR (D_2O): 7.93 (1H, s, H-8), 4.98 (1H, dd, CH-2′, $J_{2'1'a} = 3.9$, $J_{2'1'b} = 5.6$), 4.33 (1H, dd, CH_2-1′, $J_{1'a2'} = 3.9$, $J_g = 14.6$), 4.25 (1H, dd, CH_2-1′, $J_{1'b2'} = 5.6$, $J_g = 14.6$), 3.86 (1H, m, OCH_2), 3.74 (1H, dd, P-CH_2, $J_{PCHa} = 9.3$, $J_g = 12.4$), 3.62 (3H, m, OCH_2), 3.57 (1H, dd, P-CH_2, $J_{PCHa} = 9.6$, $J_g = 12.4$),^{13}C NMR: 159.71 (C-2), 155.82 (C-6), 151.06 (C-4), 140.76 (C-8), 112.32 (C-5), 101.59 (C-2′,d, J = 11.7), 69.30 (OCH_2), 64.96 (P-C, d, J = 151.4), 60.36 (OCH_2), 45.08 (C-1′).

2-amino-6-bromo-9-*N*-(2-allyloxy-2-phosphonomethoxyethyl)purine (20a)

Synthon **8** (R=allyl; B=2-amino-6-chloropurine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), allyl alcohol (0.58 g, 10 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol). Reaction performed according to ***Method B*** with 2-amino-6-chloropurine (0.75 g, 5 mmol) followed by deprotection and purification (***Method C***) afforded 389 mg (21%) of **20a**.

FAB 453 (M-H+2Na).^{1}H NMR (D_2O): 8.18 (1H, s, H-8), 5.68 (1H, brddt, 5′-CH, $J_{5'4'a} \sim J_{5'4'b} = 5.9$, $J_{5'6'a} = 17.2$, $J_{5'6'b} = 10.5$), 5.12 (1H, dq, 6′-CH_2, $J_{6'a4'} \sim J_g = 1.5$, $J_{6'a5'} = 17.2$), 5.07 (1H, dq, 6′-CH_2, $J_{6'b4'} \sim J_g = 1.5$, $J_{6'b5'} = 10.5$), 5.01 (1H, dd, CH-2′, $J_{2'1'a} = 3.9$, $J_{2'1'b} = 5.8$), 4.39 (1H, dd, CH_2-1′, $J_{1'a2'} = 3.9$, $J_g = 14.4$), 4.30 (1H, dd, CH_2-1′, $J_{1'b2'} = 5.8$, $J_g = 14.4$), 4.26 (1H, ddt, 4′-H, $J_{4'a6'} = 1.5$, $J_{4'a5'} = 5.5$, $J_g = 12.7$), 4.04 (1H, ddt, 4′-H, $J_{4'b6'} = 1.5$, $J_{4'b5'} = 6.3$, $J_g = 12.7$), 3.83 (1H, dd, P-CH_2, $J_{PCHa} = 9.4$, $J_g = 12.8$), 3.66 (1H, dd, P-CH_2, $J_{PCHb} = 9.8$, $J_g = 12.8$),^{13}C NMR: 159.04 (C-2), 152.14 (C-4), 144.95 (C-8), 142.12 (C-6), 132.84 (C-5′), 125.84 (C-5), 117.96 (C-6′), 100.65 (C-2′,d, J = 12.2), 69.52 (C-4′), 64.05 (P-C, d, J = 156.25), 45.31 (C-1′).

2-amino-6-bromo-9-*N*-(2-(2-benzoyloxyethoxy)-2-phosphonomethoxyethyl)purine (20b)

Synthon **8** (R=2-benzoyloxyethyl; B=2-amino-6-chloropurine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), 2-benzoyloxyethanol (1.7 g, 10 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol). Reaction performed according to ***Method B*** with 2-amino-6-chloropurine (0.85 g, 5 mmol) followed by deprotection and purification (***Method C***) afforded 147 mg (6%) of **20b**.

FAB 562.2 (M+2Na).^{1}H NMR (D_2O): 8.17 (1H, s, H-8), 7.88 (2H, d, arom.), 7.56 (1H, t, arom.), 7.49 (2H, t, arom.), 5.08 (1H, t, CH-2′, J = 5.3),

4.43 (1H, dd, CH_2-1′, $J_{1'a2'} = 5.0$, $J_g = 14.4$), 4.33 (1H, dd, CH_2-1′, $J_{1'a2'} = 5.5$, $J_g = 14.4$), 4.23 (2H, m, 4′-O-CH_2), 4.12 (2H, m, 4′-O-CH_2), 3.82 (1H, dd, P-CH_2, $J_{PCHa} = 9.3$, $J_g = 12.0$), 3.69 (1H, dd, P-CH_2, $J_{PCHb} = 10.0$, $J_g = 12.0$).

2-amino-6-bromo-9-*N*-(2-(2-fluoroethoxy)-2-phosphonomethoxyethyl)-purine (20c)

Synthon **8** (R=2-fluoroethyl; B=2-amino-6-chloropurine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), 2-fluoroethanol (0.6 ml, 10 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol). Reaction performed according to ***Method B*** with 2-amino-6-chloropurine (0.85 g, 5 mmol) followed by deprotection and purification (***Method C***) afforded 747 mg (40%) of **20c**.

^{1}H NMR (D_2O): 8.165 (1H, s, H-8), 5.05 (1H, dd, CH-2′. $J_{2'1'a} = 3.9$, $J_{2'1'b} = 5.4$), 4.54 (1H, dddd, F-CH_2, $J_{5'a4'a} = 2.2$, $J_{5'a4'b} = 5.9$, $J_{5'aF} = 47.9$, $J_g = 11.0$), 4.51 (1H, dddd, F-CH_2, $J_{5'b4'a} = 5.1$, $J_{5'b4'a} = 2.4$, $J_{5'aF} = 47.6$, $J_g = 11.0$), 4.40 (1H, dd, CH_2-1′, $J_{1'a2'} = 3.9$, $J_g = 14.65$), 4.33 (1H, dd, CH_2-1′, $J_{1'b2'} = 5.4$, $J_g = 14.65$), 4.04 (1H, dddd, 4′-O-CH_2, $J_{4'a5'a} = 2.2$, $J_{4'a5'b} = 5.1$, $J_{4'aF} = 32.7$, $J_g = 12.4$), 3.85 (1H, dddd, 4′-O-CH_2, $J_{4'b5'a} = 5.9$, $J_{4'b5'b} = 2.4$, $J_{4'bF} = 30.0$, $J_g = 12.4$), 3.86 (1H, dd, P-CH_2, $J_{PCHa} = 9.3$, $J_g = 12.9$), 3.71 (1H,dd, P-CH_2, $J_{PCHb} = 10.0$, $J_g = 12.9$),^{13}C NMR: 158.98 (C-2), 152.015 (C-4), 144.83 (C-8), 141.99 (C-6), 125.68 (C-5), 101.22 (C-2′, d, J = 11.7), 83.07 (C-F, d, J = 163.1), 67.39 (O-C, d, J = 18.6), 63.34 (P-C, d, J = 157.2), 44.975 (C-1′).

9-*N*-(2-allyloxy-2-phosphonomethoxyethyl)guanine (21a)

Synthon **8** (R=allyl; B=2-amino-6-chloropurine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), allyl alcohol (0.58 g, 15 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol). Reaction performed according to ***Method B*** with 2-amino-6-chloropurine (0.85 g, 5 mmol) followed by deprotection and purification (***Method D***) afforded 158 mg (9%) of **21a**.

HR FAB calcd. for $C_{11}H_{16}N_5O_6P$ 345.083821 found 368.073592 (M+Na).^{1}H NMR (D_2O): 7.87 (1H, s, H-8), 5.69 (1H, dddd, 5′-CH, $J_{5'4'a} = 5.5$, $J_{5'4'b} = 6.4$, $J_{5'6'a} = 17.2$, $J_{5'6'b} = 10.4$), 5.14 (1H, dq, 6′-CH_2, $J_{6'a4'} \sim J_g = 1.6$, $J_{6'a5'} = 17.2$), 5.09 (1H, ddt, 6′-CH_2, $J_{6'b4'} = 1.2$, $J_g = 1.6$, $J_{6'b5'} = 10.4$), 5.00 (1H, dd, CH-2′, $J_{2'1'a} = 3.5$, $J_{2'1'b} = 6.5$), 4.33 (1H, dd, CH_2-1′, $J_{1'a2'} = 3.5$, $J_g = 14.6$), 4.22 (1H, dd, CH_2-1′, $J_{1'b2'} = 6.5$, $J_g = 14.6$), 4.27 (1H, brddt, 4′-H, $J_{4'a6'} = 1.2$, $J_{4'a5'} = 5.5$, $J_g = 12.8$), 4.03 (1H, ddt, 4′-H, $J_{4'b6'} = 1.2$, $J_{4'b5'} = 6.4$, $J_g = 12.8$).^{13}C NMR: 158.75 (C-6), 153.45 (C-2), 151.64 (C-4), 140.54 (C-8), 132.94 (C-5′), 117.83 (C-6′), 115.41 (C-5), 100.98 (C-2′, d, J = 11.7), 69.56 (C-4′), 64.86 (P-C, d, J = 154.8), 45.31 (C-1′).

9-*N*-(2-(2-fluoroethoxy)-2-phosphonomethoxyethyl)guanine (21b)

Synthon **8** (R=2-fluoroethyl; B=2-amino-6-chloropurine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), 2-fluoroethanol (0.6 ml, 10 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol). Reaction performed according to ***Method B*** with 2-amino-6-chloropurine (0.85 g, 5 mmol) followed by deprotection and purification (***Method D***) afforded 405 mg (23%) of **21b**.

HR FAB calcd. for $C_{10}C_{15}FN_5O_6P$ 351.074400, found 374.064170 (M+Na).^{1}H NMR (D_2O): 7.86 (1H, s, H-8), 5.02 (1H, dd, CH-2′, $J_{2'1'a}=4.0$, $J_{2'1'b}=5.7$), 4.54 (1H, dddd, $J_{5'a4'a}=2.2$, $J_{5'a4'b}=6.0$, $J_{5'aF}=47.6$, $J_g=10.8$), 4.50 (1H, dddd, $J_{5'b4'b}=2.2$, $J_{5'b4'a}=5.4$, $J_{5'aF}=47.6$, $J_g=10.8$), 4.32 (1H, dd, CH_2-1′, $J_{1'a2'}=4.0$, $J_g=14.6$), 4.24 (1H, dd, CH_2-1′, $J_{1'b2'}=5.7$, $J_g=14.6$), 4.03 (1H, dddd, $J_{4'a5'a}=2.2$, $J_{4'a5'b}=5.4$, $J_{4'aF}=32.2$, $J_g=12.4$), 3.81 (1H, dddd, $J_{4'b5'a}=6.0$, $J_{4'b5'b}=2.2$, $J_{4'bF}=31.0$, $J_g=12.4$), 3.81 (1H, dd, P-CH_2, $J_{PCHa}=9.4$, $J_g=12.7$), 3.65 (1H, dd, CH_2-1′, $J_{PCHb}=9.8$, $J_g=12.7$),^{13}C NMR: 158.64 (C-6), 153.44 (C-2), 151.55 (C-4), 140.44 (C-8), 115.29 (C-5), 101.52 (C-2′, d, J = 11.2), 83.15 (C-5′, d, J = 163.6), 67.35 (C-4′, d, J = 18.6), 63.97 (P-C, d, J = 155.3), 44.93 (C-1′).

9-*N*-(2-(2-hydroxyethoxy)-2-phosphonomethoxyethyl)guanine (21c)

Synthon **8** (R=2-benzoyloxyethyl; B=2-amino-6-chloropurine) was prepared by ***Method A*** using *N*-iodosuccinimide (1.24 g, 5.5 mmol), 2-benzoyloxyethanol (1.7 g, 10 mmol) and diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol). Reaction performed according to ***Method B*** with 2-amino-6-chloropurine (0.85 g, 5 mmol) followed by deprotection and purification (***Method D***) afforded 35 mg (2%) of **21c**.

HR FAB calcd. for $C_{10}H_{16}N_5O_7P$ 349.078736, found 372.068506 (M+Na).^{1}H NMR (D_2O): 7.90 (1H, s, H-8), 4.99 (1H, dd, CH-2′, $J_{2'1'a}=3.8$, $J_{2'1'b}=6.2$), 4.34 (1H, dd, CH_2-1′, $J_{1'a2'}=3.8$, $J_g=14.6$), 4.24 (1H, dd, CH_2-1′, $J_{1'b2'}=6.2$, $J_g=14.6$), 3.86 (1H, m, OCH_2), 3.72 (1H, dd, P-CH_2, $J_{PCHa}=9.1$, $J_g=12.2$), 3.62 (3H, m, OCH_2), 3.55 (1H, dd, P-CH_2, $J_{PCHa}=9.6$, $J_g=12.2$).

9-*N*-(2-Phenylthio-2-phosphonomethoxyethyl)adenine (22) and tetraisopropyl 2-phenylthio-1,1-bis-(phosphonomethoxy)ethane (10)

(***i***): A mixture of diisopropyl 2-bromo-1-fenylthioethoxymethanephosphonate (**11b**) (2.045 mmol) and sodium salt of adenine (1.86 mmol), prepared by heating of adenine (0.25 g, 1.86 mmol) with sodium hydride (0.075 g, 1.86 mmol) in DMF at 80 °C for 30 minutes, was stirred at room temperature until diisopropyl 2-bromo-1-fenylthioethoxymethanphosphonate (**11b**)

disappeared. The course of the reaction was checked by TLC in ethylacetate-acetone-ethanol-water (12:2:2:1). Reaction mixture was concentrated *in vacuo* and oily residue chromatographed on a silica gel column in ethanol-chloroform mixture (0–10%). Obtained protected adenine nucleotide **12** (X = S; B = adenine) was treated with bromotrimethylsilane in acetonitrile at room temperature. The course of the transesterification reaction was checked by TLC in isopropanol-conc. aqueous ammonia-water (7:1:2). The reaction mixture was evaporated and bis(trimethylsilyl) ester groups were hydrolyzed inwater-methanol-triethylamine mixture (5:5:2). After 30 min of standing, the solution was concentrated *in vacuo*. The crude free phosphonate **22** was purified on DEAE-Sephadex A25 column (16 × 200 mm) by elution with linear gradient of triethylammonium hydrogencarbonate pH 7.5 (0–0.2 M, 2 × 1000 ml) in water. Fractions containing the product were collected and evaporated. Pure phosphonate was converted into the sodium salt on Dowex 50 (Na+). Yield 0.087 g (9%) of product **22**.

Anal. Calcd. for $C_{14}C_{15}N_5O_4PSNa.4H_2O$ (475.39): C, 35.4, H, 4.9, N, 14.7, P, 6.5. Found: C, 35.2, H, 4.52, N, 14.44, P, 6.7. MS (FAB): 382.3 (MH^+). ^{1}H NMR (D_2O): 8.15 and 8.07 (2 × 1H, s, H-2 a H-8), 7.05–6.90 (5H, m, arom H), 5.83 (1H, dd, $J_{2',1'a} = 9.3$, $J_{2',1'b} = 3.2$, H-2′), 3.96 (1H, dd, $J_{1'a,2'} = 9.3$, $J_g = 15.1$, H-1′a), 3.62 (1H, dd, $J_{1'b,\ 2'} = 3.2$, $J_g = 15.1$, H-1′b), 3.54 (1H, dd, $J_{P,CHa} = 9.5$, $J_g = 12.7$, P-CHa), 3.44 (1H, dd, $J_{P,CHb} = 9.3$, $J_g = 12.7$, P-CHb).

(ii): A mixture of diisopropyl 2-bromo-1-fenylthioethoxymethanephosphonate (**11b**) (0.59 g, 1.55 mmol), adenine (0.6 g, 4.44 mmol) and cesium carbonate (1.4 g, 4.44 mmol) in DMF was heated at 110 °C for 8 hours. Reaction mixture was concentrated *in vacuo* and the residue chromatographed on a silica gel column in ethanol-chloroform mixture (0–10%). Besides unchanged adenine, only the phosphonate **10** was isolated from the mixture in very low yield.

^{1}H NMR (DMSO-d_6): 7.37 (2H, d, arom H), 7.31 (2H, t, arom H) 7.20 (1H, t, arom H), 4.83 (1H, t, J = 5.4, O-CH-O), 4.60 (4H, m, P-OCH), 3.89 (2H, dd, $J_{P,CH} = 9.3$, $J_g = 13.7$, P-CH_2), 3.81 (2H, dd, $J_{P,CH} = 9.8$, $J_g = 13.7$, P-CH_2), 3.21 (2H, d, J = 5.4, S-CH_2), 1.26-1.23 (24 H, m, CH_3). ^{13}C NMR: 102.71 (t, $J_{P,\ C} = 12.7$, O-C-O), 70.54 (2C, d, P-OC), 70.52 (2C, d, $J_{P,C} = 6.8$, P-OC), 59.82 (2C, d, $J_{P,C} = 167.0$, P-C), 35.19 (S-C), 23.99 (2C, d, CH_3), 23.98 (2C, $J_{P\text{-}C} = 3.9$, CH_3), 23.91 (2C, d, CH_3), 23.88 (2C, d, $J_{P,C} = 4.9$, CH_3), arom C: 136.08, 129.27, 2C, 128.54, 2C, 126.14.

9-*N*-(2-phenyloxy-2-phosphonomethoxyethyl)adenine (23a)

Preparation of synthon **11a**: 1M solution of bromine in dichloromethane (30 ml, 30 mmol of Br_2) was added dropwise during 30 minutes to the solution of diisopropyl vinyloxymethanephosphonate (**6**) (6.9 g, 30 mmol) in dichloromethane (70 ml) at −78 °C under argon atmosphere. Then a solution of

phenol (3.4 g, 36 mmol) and *N*-ethyldiisopropylamine (6.7 ml, 39 mmol) in dichloromethane (30 ml) was added at low temperature, and the reaction mixture was set aside overnight at room temperature. Resulting clear solution was washed with saturated aqueous solution of sodium hydrogencarbonate. Organic layer was dried over sodium sulfate and concentrated *in vacuo*. The product was isolated on silica gel column in 0–50% of acetone in toluene. Yield 7.59 g, (64%) of diisopropyl 2-bromo-1-phenyloxyethoxymethanephosphonate (**11a**) which was used without characterization for further reaction.

Reaction of compound **11a** (2.33 g, 5.9 mmol) with adenine (0.8 g, 5.9 mmol) performed according to ***Method B*** followed by deprotection and purification (***Method C***) afforded 0.3 g (13.9%) of compound **23a**.

Anal. calcd. for $C_{14}C_{15}N_5O_5PNa.5/2H_2O$ (432.32): C, 37.3, H, 4.9, N, 15.6, P, 6.9. Found: C, 37.58, H, 4.75, N, 15.63, P, 6.57. MS (FAB): 365.297 (M^+).^{1}H NMR (D_2O): 8.12 s, 1H a 8.05 s, 1H (H-2 a H-8), 7.14 t, 2H a 6.93 t, 1H a 6.75 d, 2H (arom H), 5.70 dd, 1H, J (2′, 1′a) = 3.2, J (2′,1′b) = 6.3 (H-2′), 4.57 dd, 1H, J (1′a, 2′) = 3.2, J (gem) = 14.7 (H-1′a), 4.51 dd, 1H, J (1′b, 2′) = 6.3, J (gem) = 14.7 (H-1′b), 3.88 dd, 1H, J (P, CHa) = 9.3, J (gem) = 12.9 (P-CHa), 3.68 dd, 1H, J (P, CHb) = 10.0, J (gem) = 12.9 (P-CHb).

9- *N*-(2-phenyloxy-2-phosphonomethoxyethyl)cytosine (23b)

Alkylation with the diisopropyl 2-bromo-1-phenyloxyethoxymethanphosphonate (**11a**; for preparation see comp.**23a**) (1.78 g, 4.5 mmol), performed according to ***Method B*** with cytosine (0.5 g, 4.5) followed by deprotection and purification (***Method C***) afforded 0.523 g (34%) of product **23b**. HR FAB calcd for $C_{13}C_{15}N_2O_7P$ 341.077673, found 386.049388 (M-H+2Na).

^{1}H NMR (D_2O): 7.67 (1H, d, H-6, $J_{56} = 7.3$), 7.36 (2H, t, arom), 7.10 (1H, t, arom), 6.94 (2H, d, arom), 5.92 (1H, d, H5), 5.62 (1H, dd, CH-2′, $J_{2'1'a} = 3.7$, $J_{2'1'b} = 6.6$), 4.31 (1H, dd, CH_2-1′, $J_{1'a2'} = 3.7$, $J_g = 14.3$), 4.02 (1H, dd, CH_2-1′, $J_{1'b2'} = 6.6$, $J_g = 14.3$), 3.81 (1H, dd, P-CH_2, $J_{PCHa} = 9.3$, $J_g = 12.0$), 3.52 (1H, dd, CH_2-1′, $J_{PCHb} = 10$, $J_g = 12.0$).^{13}C NMR: 169.21 (C-4), 159.445 (arom), 153.72 (C-2), 150.60 (C-6), 132.62 (2C, arom), 125.68 (arom), 119.89 (2C, arom), 98.20 (C-5), 104.32 (C-2′, d, J = 12.4), 69.06 (P-C, d, J = 150.6), 54.72 (C-1′).

2,6-diamino-9-*N*-(2-phenyloxy-2-phosphonomethoxyethyl)purine (23c)

Reaction of diisopropyl 2-bromo-1-phenyloxyethoxymethanephosphonate (**11a**; for preparation see comp. **23a**) (2.27 g, 5.74 mmol) with 2,6-diaminopurine (0.9 g, 6 mmol) performed according to ***Method B*** followed by deprotection and purification (***Method C***) afforded 0.966 g (43.1%) of product **23c**.

HR FAB calcd for $C_{14}H_{17}N_6O_5P$ 380.099806, found 381.107631 (M+H).^{1}H NMR (D_2O): 7.86 (1H, s, H-8), 7.21 (2H, t, arom), 6.98 (1H, t, arom), 6.80 (2H, d, arom), 5.76 (1H, dd, CH-2′, $J_{2'1'a} = 2.9$ and $J_{2'1'b} = 7.0$), 4.50 (1H, dd, CH_2-1′, $J_{1'a2'} = 2.9$, $J_g = 14.6$), 4.39 (1H, dd, CH_2-1′, $J_{1'b2'} = 7.0$, $J_g = 14.6$), 3.86 (1H, dd, P-CH_2, $J_{PCHa} = 9.2$, $J_g = 12.1$), 3.61 (1H, dd, CH_2-1′, $J_{PCHb} = 9.6$, $J_g = 12.1$),^{13}C NMR: 162.49 (C-2), 158.81 (arom), 158.51 (C-6), 153.93 (C-4), 143.31 (C-8), 132.18 (2C, arom), 125.49 (arom), 119.65 (2C, arom), 115.22 (C-5), 104.17 (C-2′,d, J = 11.9), 68.61 (P-C, d, J = 151.6), 48.58 (C-1′).

9-*N*-(2-phenyloxy-2-phosphonomethoxyethyl)guanine (23d)

Reaction of diisopropyl 2-bromo-1-phenyloxyethoxymethanephosphonate (**11a**; for preparation see comp. **23a**) (1.86 g, 4.7 mmol) with 2-amino-6-chloropurine (0.8 g, 4.7 mmol) performed according to ***Method B*** followed by deprotection and purification (***Method D***) afforded 0.437 g (24.4%) of product **23d**.

HR FAB calcd for C14H16N5O6P 381.083821, found 382.091647 (M+H).^{1}H NMR (D_2O): 7.87 (1H, s, H-8), 7.26 (2H, t, arom), 7.03 (1H, t, arom), 6.88 (2H, d, arom), 5.76 (1H, dd, CH-2′, J = 3.5 and 6.4), 4.48 (1H, dd, CH_2-1′, $J_{1'a2'} = 3.5$, $J_g = 14.7$), 4.41 (1H, dd, CH_2-1′, $J_{1'b2'} = 6.4$, $J_g = 14.7$), 3.93 (1H, dd, P-CH_2, $J_{PCHa} = 9.4$, $J_g = 12.7$), 3.73 (1H, dd, CH_2-1′, $J_{PCHb} = 9.6$, $J_g = 12.7$),^{13}C NMR: 161.37 (C-6), 158.56 (arom), 156.20 (C-2), 154.40 (C-4), 143.22 (C-8), 132.26 (2C, arom), 125.73 (arom), 119.78 (2C, arom), 118.21 (C-5), 103.71 (C-2′,d, J = 12.4), 67.21 (P-C, d, J = 155.7), 48.48 (C-1′).

1-*N*-(2-phenyloxy-2-phosphonomethoxyethyl)thymine (23e)

Reaction of diisopropyl 2-bromo-1-phenyloxyethoxymethanephosphonate (**11a**; for preparation see comp. **23a**) (1.86 g, 4.7 mmol) with thymine (0.6 g, 4.7 mmol) performed according to ***Method B*** followed by deprotection and purification (***Method C***) afforded 0.23 g (13.7%) of product **23e**.

HR FAB calcd for $C_{14}H_{17}N_2O_7P$ 356.077339, found 379.067109 (M+Na).^{1}H NMR (D_2O): 7.55 (1H, d, H-6, $J_{56} = 7.9$), 7.38 (2H, t, arom), 7.12 (1H, t, arom), 6.98 (2H, d, arom), 5.68 (1H, dd, CH-2′, J = 4.0 and 6.2), 4.22 (1H, dd, CH_2-1′, $J_{1'a2'} = 4.0$, $J_g = 14.4$), 4.09 (1H, dd, CH_2-1′, $J_{1'b2'} = 6.2$, $J_g = 14.4$), 3.88 (1H, dd, P-CH_2, $J_{PCHa} = 9.4$, $J_g = 12.7$), 3.68 (1H, dd, CH_2-1′, $J_{PCHb} = 9.7$, $J_g = 12.7$). 1.83 (3H, d, CH_3),^{13}C NMR: 169.46 (C-4), 158.88 (arom), 154.98 (C-2), 149.37 (C-6), 132.55 (2C, arom), 125.81 (arom), 119.825 (2C, arom), 113.14 (C-5), 103.52 (C-2′,d, J = 12.8), 67.40 (P-C, d, J = 155.2), 52.99 (C-1′), 13.72 (CH_3).

1-*N*-(2-phenyloxy-2-phosphonomethoxyethyl)uracil (23f)

Alkylation with the diisopropyl 2-bromo-1-phenyloxyethoxymethanephosphonate (**11a**; for preparation see comp. **23a**) (1.86 g, 4.7 mmol), performed according to ***Method B*** with uracil (0.53 g, 4.7) followed by deprotection and purification (***Method C***), afforded 0.16 g (10%) of product **23f**.

HR FAB calcd for $C_{13}H_{15}N_2O_7P$ 342.061689, found 365.051459 (M+Na).^{1}H NMR (D_2O): 7.73 (1H, d, H-6, $J_{56} = 7.9$), 7.39 (2H, t, arom), 7.14 (1H, t, arom), 7.11 (2H, d, arom), 5.79 (1H, d, H5), 5.65 (1H, dd, CH-2′, J = 4.4 and 5.6), 4.23 (1H, dd, CH_2-1′, $J_{1'a2'} = 4.4$, $J_g = 14.6$), 4.14 (1H, dd, CH_2-1′, $J_{1'b2'} = 5.6$, $J_g = 14.6$), 3.89 (1H, dd, P-CH_2, $J_{PCHa} = 9.4$, $J_g = 12.6$), 3.66 (1H, dd, CH_2-1′, $J_{PCHb} = 9.8$, $J_g = 12.7$).^{13}C NMR: 169.295 (C-4), 158.86 (arom), 154.91 (C-2), 150.63 (C-6), 132.6 (2C, arom), 125.89 (arom), 119.90 (2C, arom), 104.04 (C-5), 103.48(C-2′,d, J = 12.8), 67.27 (P-C, d, J = 156.1), 52.95 (C-1′).

9-*N*-(2-azido-2-phosphonomethoxyethyl)adenine (24)

The chloroiodide (0.81 g, 5 mmol) was added under vigorous stirring to a suspension of sodium azide (0.4 g, 6 mmol) in dimethylformamide (5 ml) at 0 °C. After 30 min, the diisopropyl vinyloxymethanephosphonate (**6**) (1.1 ml, 5 mmol) was added, and the reaction mixture was kept at room temperature for 16 hrs. The resulting suspension was diluted with ether (50 ml), and this solution was subsequently washed with saturated aqueous solutions of sodium hydrogencarbonate and sodium thiosulfate. Ether layer was dried with sodium sulfate and evaporated. A crude diisopropyl 1-azido-2-iodoethoxymethanephosphonate (**13**) was purified on a silica gel column in 0–10% of ethanol in chloroform, and the obtained product was treated with sodium salt of adenine, prepared by heating of adenine (0.31 g, 2.27 mmol) and sodium hydride (0.092 g, 2.27 mmol) in DMF (20 ml) at 80 °C for 30 min. The reaction mixture was stirred at room temperature overnight, and the reaction course was checked by TLC in ethylacetate-acetone-ethanol-water (12:2:2:1). Reaction mixture was concentrated *in vacuo* and the residue chromatographed on a silica gel column in 0–10% of ethanol in chloroform. The product was deprotected according to ***Method C***. Yield 0.033 g (1.6%) of compound **24**.

Anal. calcd. for $C_8H_{10}N_8O_4PNa.4H_2O$ (408.24): C, 23.50, H, 4.40, N, 27.40. Found: C, 23.56, H, 4.43, N, 26.71. MS (FAB): 315.1 (MH^+).^{1}H NMR (D_2O): 8.25 and 8.23 (2 × 1H, s, H-2 a H-8), 5.20 (1H, t, $J_{2',1'} = 4.6$, H-2′), 4.55 (1H, dd, $J_{1'a,2'} = 4.6$, $J_g = 14.7$, H-1′a), 4.51 (1H, dd, $J_{1'b,2'} = 4.6$, $J_g = 14.7$, H-1′b), 3.91 (1H, dd, $J_{P,CHa} = 9.5$, $J_g = 12.7$, P-CHa), 3.70 (1H, dd, $J_{P,CHb} = 9.5$, $J_g = 12.7$, P-CHb).^{13}C NMR: 155.76 (C-6), 152.80 (C-2), 149.50 (C-4), 143.54 (C-8), 118.29 (C-5), 90.53 (d, $J_{P,C} = 12.7$, C-2′), 65.97 (d, $J_{P,C} = 155.3$, P-C), 46.58 (C-1′).

Diisopropyl 1-acetoxy-2-iodoethoxymethanephosphonate (52)

N-iodosuccinimide (0.496 g, 2.2 mmol) was added under argon atmosphere to a solution of vinylacetate (**50**) (0.172 g, 2 mmol) and diisopropyl hydroxymethanephosphonate [9] (**51**) (0.432 g, 2.2 mmol) in dichloromethane at 0 °C, and the reaction was set aside at room temperature for 16 hrs. The solution was washed with sodium hydrogencarbonate, organic layer dried with anhydrous sodium sulfate, and evaporated. Chromatography of the residue on a silica gel column in 0–50% of acetone in toluene afforded 0.117 g (14.3%) of compound 52.

MS (FAB): 409.5 (MH^+). ^{1}H NMR (DMSO-d_6): 5.71 (1H, t, J = 4.9, O-CH-O), 4.62 (2H, m, P-OCH), 3.97 (1H, dd, $J_1 = 9.3$, $J_2 = 13.7$, 3.89 (1H, dd, $J_1 = 9.0$, $J_2 = 13.7$, P-CH_2), 3.43 (2H, d, J = 4.9, CH_2-I), 2.08 (3H, s, CH_3), 1.26 (12 H, d, $J_{CH3,CH} = 6.1$, CH_3). ^{13}C NMR: 170.09 (C = O), 96.22 (d, $J_{P,C} = 12.7$, O-C-O), 70.77 (d, P-OC), 70.72 (d, $J_{P,C} = 5.9$, P-OC), 62.67 (d, $J_{P,C} = 166.0$, P-C), 24.01 (d, CH_3), 23.98 (d, CH_3), 23.90 (d, CH_3), 23.87 (d, $J_{P,C} = 3.9$, CH_3), 20.89 (CH_3), 4.96 (C-I).

ACKNOWLEDGMENTS

This work was supported by grant No. NL5441-3 of the Grant Agency of Ministry of Health Czech Republic, and by Gilead Science, CA, U.S.A.. The authors are indebted to Dr. Ivan Votruba and Dr. Jitka Kohoutová, both of this Institute, for the evaluation of cytostatic properties of prepared compounds and mass spectra measurements, respectively. Special thanks are given to the Department of Health & Human Services (NIH, NCI), MD, U.S.A. for anticancer assays of selected compounds, and to Dr. Zdeněk Točik of this Institute for valuable discussion and help at the preparation of the manuscript.

REFERENCES

1. De Clercq, E.; Baba, M.; Pauwels, R.; Balzarini, J.; Rosenberg, I.; Holý, A. Antiviral Res. **1987**, *8*, 261.
2. Balzarini, J.; Naesens, L.; Herdewijn, P.; Rosenberg, I.; Holý, A.; Pauwels, R.; Baba, M.; Johns, D.G.; De Clercq, E. Proc. Natl. Acad. Sci. U.S.A. **1989**, *86*, 332.
3. Balzarini, J.; Holý, A.; Jindřich, J.; Dvořáková, H.; Hao, Z.; Snoeck, R.; Herdewijn, P.; Johnson, D.G.; De Clercq, E. Proc. Natl. Acad. Sci. U.S.A. **1991**, *88*, 4961.
4. Balzarini, J.; Holý, A.; Jindřich, J.; Naesens, L.; Snoeck, R.; Schols, D.; De Clercq, E. Antimicrob. Agents Chemother. **1993**, *37*, 332.
5. Holý, A.; Rosenberg, I.; Dvořáková, H. Collect. Czech. Chem. Commun. **1989**, *54*, 2190.

6. Kim, U.K.; Luh, B.I.; Martin, J.C. Tetrahedron Lett. **1992**, *33*, 25.
7. Woerner, F.P.; Reimlinger, H. Chem. Ber. **1970**, *103*, 1908.
8. Rejman, D.; Rosenberg, I. Collect. Czech. Chem. Commun. (Special Issue) **1996**, *61*, S122.
9. Hammerschmidt, F.; Kaehlig, H.; Mueller, N. J. Chem. Soc. Perkin Trans. 1 **1991**, 365.

Received May 25, 2000
Accepted December 30, 2000