SYNTHESIS OF *N*-(3-FLUORO-2-PHOSPHONOMETHOXYPROPYL) (FPMP) DERIVATIVES OF HETEROCYCLIC BASES

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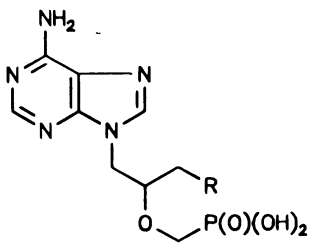
A new group of compounds has been prepared: *N*-(3-fluoro-2-phosphonomethoxypropyl) (FPMP) derivatives of purine and pyrimidine bases which exhibit a significant selective activity against a broad spectrum of retroviruses. Racemic *N*-(3-fluoro-2-phosphonomethoxypropyl) derivatives of adenine (*V*), guanine (*IX*), cytosine (*XIII*), 2,6-diaminopurine (*XXI*), 3-deazaadenine (*XVII*), xanthine (*X*) and hypoxanthine (*VI*) were prepared from the corresponding *N*-(3-fluoro-2-hydroxypropyl) derivatives after protection of amino group at the heterocyclic ring by selective benzoylation, reaction with diisopropyl *p*-toluenesulfonyloxymethylphosphonate (*II*), and subsequent removal of the protecting groups. Chiral FPMP derivatives were prepared by reaction of heterocyclic base with the corresponding chiral synthon (*XXX*, *XXXVII*) followed by deprotection. The required chiral synthons were obtained from enantiomeric 3-fluoro-1,2-propanediols by two methods. In the first, the primary hydroxyl group was tritylated, the obtained derivative was reacted with compound *II*, the trityl group was removed and the product was mesylated to give synthon *XXXVII*. The second pathway consisted in selective tosylation of the primary hydroxyl group and conversion of the secondary hydroxyl into the acetoxymethyl ether via the methoxymethyl ether; treatment of the acetoxy compound with bromotrimethylsilane and triisopropyl phosphite afforded the desired synthon *XXX*.

Within the framework of structure–activity studies in the series of nucleotide analogs[1], we investigated in our previous communications the role of the presence and absolute configuration of hydroxymethyl group in the series of significant antivirals, *N*-(3-hydroxy-2-phosphonomethoxypropyl) derivatives (HPMP-derivatives) of purine and pyrimidine bases. Compounds of this series, derived from adenine, 2,6-diaminopurine, guanine[2], 3-deazaadenine[3] and cytosine[2,4], exhibit a strong in vitro as well as in vivo inhibitory effect on DNA viruses[5]. It appeared that enantiospecificity of the biological effect depends on the character of the heterocyclic base and is probably connected with enantiospecificity of their cellular activation[6]. Replacement of the hydroxy group in adenine *Ia* with an alkoxy (*Ib*, refs[7-9]), azido or amino group (*Ic*, *Id*, ref.[10]), an atom of hydrogen[7], a phosphonomethoxy group[17] or a carbon chain of various types[7] led in all cases to a complete disappearance of in vitro activity against DNA viruses.

In the bioorganic chemistry, fluorine atom often proved to be a successful substitute for the essential hydroxyl group, particularly in cases where the presence of an electro-

negative atom is sufficient for an interaction with the target enzyme. In many regions of bioorganic chemistry, fluoro analogs of hydroxy derivatives are biologically active. Thus, e.g., from the region of sugars and nucleosides alone, we may mention 2-deoxy-2-fluoro-D-glucose[11], 2-deoxy-2-fluoro-β-D-arabinofuranosylpyrimidines (e.g., FIAU, FIAC, FMAU)[12,13] and other compounds. Naturally, the mentioned effect does not represent a rule, particularly if the hydroxyl group is essential for the path of an enzyme-catalyzed reaction or for the character of interaction with the target enzyme. In our recent communication we described the preparation of regioisomeric fluoro analogs of *N*-(2,3-dihydroxypropyl) derivatives of heterocyclic bases: the fluorohydroxypropyl-adenines obtained neither had any biological in vivo effect comparable with the parent dihydroxy derivative (DHPA) nor inhibited in vitro its target enzyme SAH-hydrolase[14]. On the other hand, 9-(4-fluoro-3-hydroxybutyl)guanine is described to possess a certain antiviral effect, comparable with the corresponding diol[15]. In the present communication we describe the synthesis of *N*-(3-fluoro-2-phoshonomethoxypropyl) derivatives of purine and pyrimidine bases which can be derived by replacement of the hydroxyl group in HPMP-derivatives with an atom of fluorine.

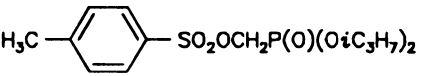


Ia, R = OH *Id*, R = NH_2
Ib, R = OAlkyl *Ie*, R = $OCH_2P(O)(OH)_2$
Ic, R = N_3 *If*, R = H

Racemic *N*-(3-fluoro-2-phosphonomethoxypropyl) derivatives of purine bases were prepared from the mentioned racemic *N*-(3-fluoro-2-hydroxypropyl) derivatives *III*, *VII*, *XI*, *XIV*: the phosphonomethyl group was introduced into the molecule by etherification of the free hydroxyl in a suitably protected acyclonucleoside with the corresponding phosphonate synthon[7,15].

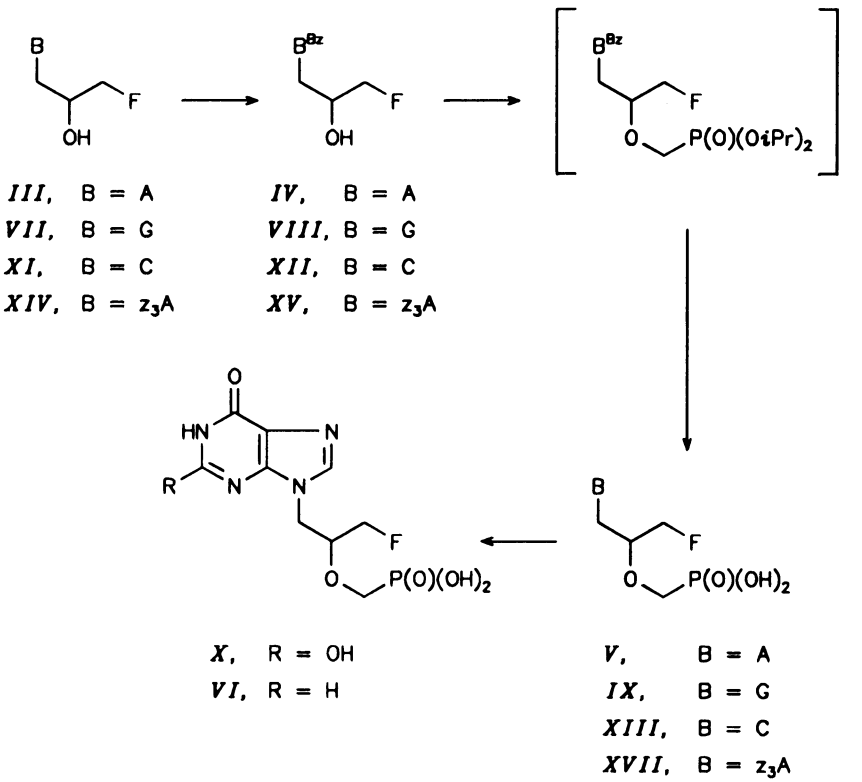
Amino groups of the heterocyclic bases were selectively protected by benzoylation[15] with benzoyl chloride after in situ protection of the hydroxy group as the trimethylsilyl ether[16]. The free hydroxyl was alkylated with diisopropyl *p*-toluenesulfonyloxymethylphosphonate (*II*, ref.[17]). With this ester, there was practically no alkylation of the heterocyclic base with the phosphonate alkyl which takes place with the ethyl and parti-

cularly the methyl esters. The phosphonic acid was easily liberated from the diisopropyl ester by bromotrimethylsilane in acetonitrile[18] under mild conditions.



II

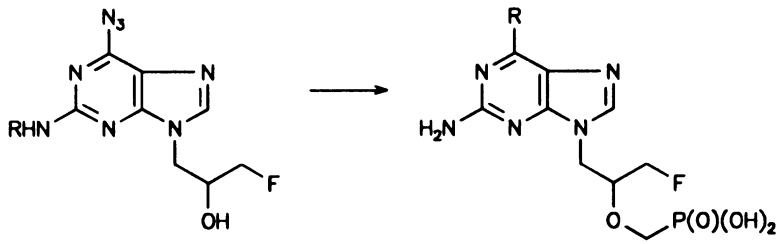
Using this reaction scheme (Scheme 1), we prepared racemic phosphonate derivatives of adenine (*V*), guanine (*IX*), cytosine (*XIII*) and 3-deazaadenine (*XVII*). The adenine derivative was deaminated to give hypoxanthine derivative *VI*, deamination of



A, adenin–9–yl; G, guanin–9–yl; C, cytosin–1–yl; z_3A, 3–deazaadenin–9–yl residue; B^{Bz}, *N*–benzoyl derivative of B

SCHEME 1

the guanine derivative afforded xanthine derivative *X*. Racemic phosphonate derivative of 2,6-diaminopurine *XXI* was similarly prepared by alkylation of azide *XVIII*, reduction of the azido group to amine and subsequent removal of the ester groups (Scheme 2).



XVIII, R = H
XIX, R = C_6H_5CO

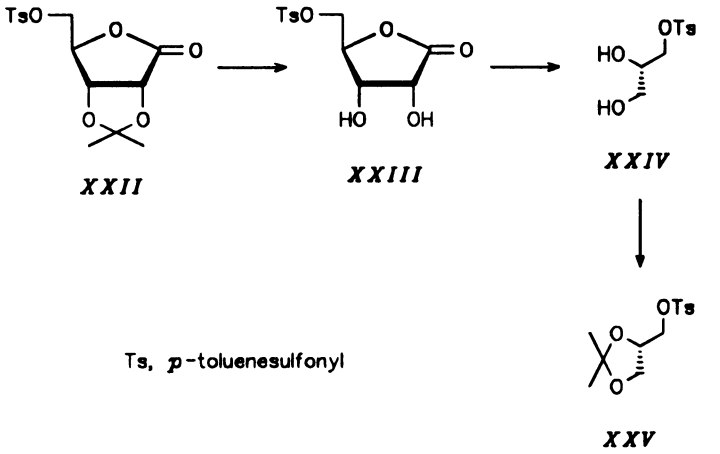
XX, R = N_3
XXI, R = NH_2

SCHEME 2

Since already during this study some of these racemic phosphonate derivatives showed significant antiviral activity[19] we set out to prepare their optical antipodes. For this purpose we made use of an alternative synthetic strategy based on utilization of a common chiral synthon bearing all the required structural functionalities of the side-chain together with a leaving group that would make such compound an alkylation reagent.

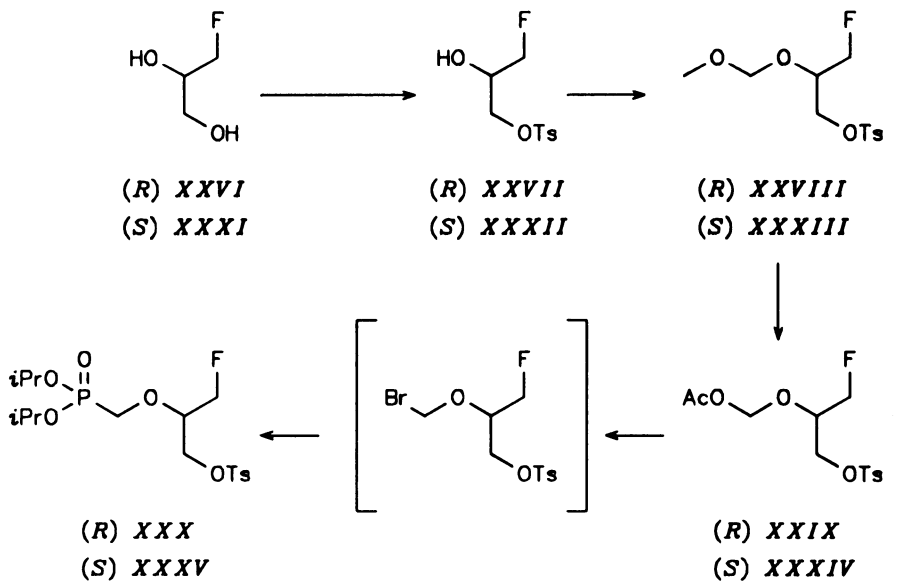
As starting compounds for the synthesis of chiral fluorinated synthons we chose 1-*O*-*p*-toluenesulfonyl-2,3-*O*-isopropylideneglycerols. The (*R*)-enantiomer was obtained by the standard procedure from D-mannitol[20]. (*S*)-1-*O*-Tosyl-2,3-*O*-isopropylideneglycerol (*XXV*) was prepared using a modification of the known procedure[21] starting from D-ribonolactone. Instead of protection of the hydroxyl groups in positions 2 and 3 in D-ribonolactone by conversion into benzylidene grouping which, after tosylation of the 5-hydroxyl, was in the original synthesis removed by hydrogenation, we made use of 5-*O*-tosyl derivative[22] of D-ribonolactone, protected by isopropylidene group (*XXII*) removable by a controlled acid hydrolysis (Scheme 3). Instead in an anhydrous medium, the diol grouping was cleaved in an aqueous solution which permitted the use of sodium periodate instead of the free periodic acid. (*S*)-1-*O*-Tosylglycerol (*XXIV*), obtained by cleavage of intermediate *XXIII* with sodium periodate and reduction with sodium borohydride, was subjected to acid-catalyzed reaction with 2,2-dimethoxypropane in acetone to give the desired derivative *XXV*. This modification makes possible an easy laboratory preparation of compound *XXV* on a larger scale.

Further procedure[23], identical for both enantiomers, consisted in substitution of the tosyl group with potassium fluoride and removal of the isopropylidene protecting group. The obtained enantiomeric 3-fluoropropane-1,2-diols (*XXVI*, *XXXI*) were selectively tosylated on the primary hydroxyl group; the secondary hydroxyl was then



SCHEME 3

converted into the methoxymethyl ether by reaction with dimethoxymethane catalyzed with phosphorus pentoxide (Scheme 4). The thus-prepared synthons *XXVIII* and *XXXIII* were reacted with acetic anhydride and boron trifluoride etherate to give the

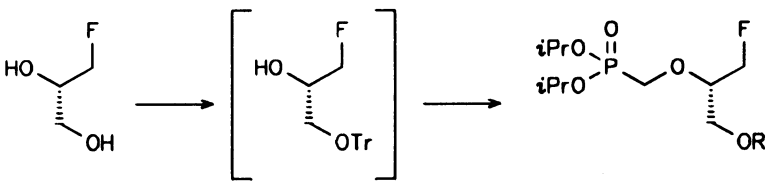


Ts, *p*-toluenesulfonyl; Ac, acetyl; *i*Pr, 2-propyl

SCHEME 4

corresponding acetoxymethyl derivatives which on successive treatment with bromotrimethylsilane and triisopropyl phosphite[24] afforded phosphonates *XXX* and *XXXV*.

An alternative method (Scheme 5) of preparation of FPMP-derivatives makes use of synthon *XXXVII* which has a mesyl instead of tosyl group. Its preparation consists in protection of the primary hydroxyl in compound *XXXI* with a trityl group, introduction of phosphonate group by reaction with tosyloxymethylphosphonate *II* and detritylation without isolation of the tritylated intermediate. Mesylation of the obtained derivative *XXXVI* finally afforded the desired chiral synthon *XXXVII*. Worth notice is the fact that under commonly used conditions the derivative *XXXVI* was not tosylated; the use of strong bases led apparently to a cyclic phosphonate.



XXXI ***XXXVI***, R = H
XXXVII, R = Ms

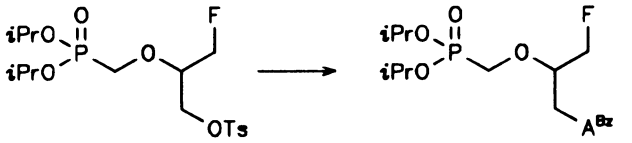
Tr, trityl; iPr, 2-propyl; Ms, methanesulfonyl

SCHEME 5

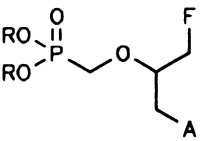
Optical antipodes of the adenine derivative *V* (compounds *XL* and *XLIII*) were obtained by condensation of N^6-benzoyladenine sodium salt with phosphonate synthons *XXX* and *XXXV*, deprotection by methanolysis and subsequent reaction with bromotrimethylsilane (Scheme 6).

The optically active derivatives of other purine bases were synthesized starting from 2-amino-6-chloropurine (*LIV*). Its sodium salt was condensed with synthon *XXX* or *XXXVII* to give intermediates *XLIV* and *IL* which on acid hydrolysis and deprotection of the phosphonate afforded the enantiomeric guanine derivatives *XLVI* and *LI*. Hydrogenolysis and removal of the protecting groups from the intermediates *XLIV* and *IL* gave 2-aminopurine derivatives *XLVIII* and *LIII*. 2,6-Diaminopurine compounds *LVII* and *LX* were prepared from the same intermediates by reaction with sodium azide, reduction of the azido group and deprotection (Scheme 7). The (*R*)-enantiomer of 3-deazaadenine derivative *LXIII* was obtained by reaction of synthon *XXX* directly with 3-deazaadenine. Instead of the sodium salt we used the free base *LXI* in the presence of cesium carbonate[25] (Scheme 8).

The FPMP-derivatives prepared were isolated mostly in their zwitterionic forms and were characterized by NMR and mass spectra.



(*R*) ***XXX*** (*R*) ***XXXVIII***
(*S*) ***XXXV*** (*S*) ***XLI***



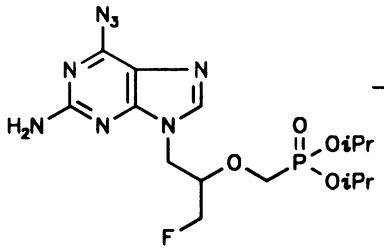
(*R*) ***XXXIX***, R = iPr
(*S*) ***XLII***, R = iPr
(*R*) ***XL***, R = H
(*S*) ***XLIII***, R = H

iPr, 2-propyl; Ts, *p*-toluenesulfonyl; A, adenin-9-yl;
A^{Bz}, N^6-benzoyladenin-9-yl

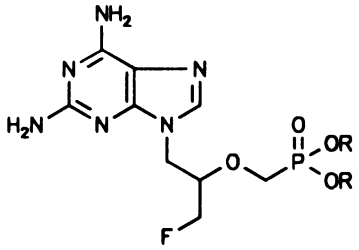
SCHEME 6

The antiviral activity of compounds prepared in this study was determined in the Rega Institute of the Catholic University in Leuven (Belgium) (Professor E. DeClercq); preliminary results have already been published[26]. The compounds are inactive or exhibit only marginal in vitro effect against herpes simplex viruses type 1 and 2 (HSV-1, HSV-2) and vaccinia virus (VV) (representatives of DNA viruses), against vesicular stomatitis virus (VSV), reovirus type 1, parainfluenza virus 3, poliovirus and sindbis virus (RNA viruses).

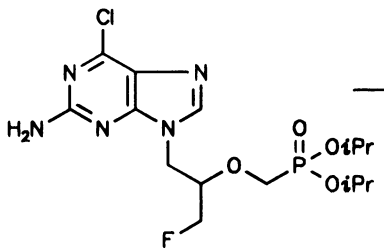
Already the racemic 9-(3-fluoro-2-phosphonomethoxypropyl) (FPMP) derivatives of purine bases (adenine, guanine and 2,6-diaminopurine) have been found to be significantly active against a broad spectrum of retroviruses. The mentioned properties place these compounds outside the group of *N*-(2-phosphonomethoxyethyl) (PME) derivatives (active against retroviruses and DNA viruses) as well as the group of HPMP derivatives (active against broad spectrum of DNA viruses). Compared with the PME



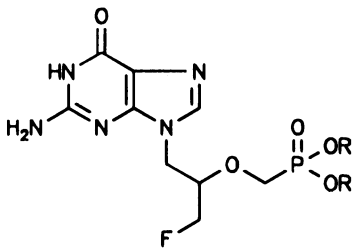
(*R*) *LV*
(*S*) *LVIII*



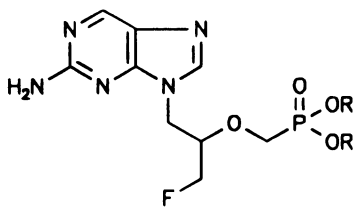
(*R*) *LVI*, R = *i*Pr
(*S*) *LIX*, R = *i*Pr
(*R*) *LVII*, R = H
(*S*) *LX*, R = H



(*R*) *XLIV*
(*S*) *IL*



(*R*) *XLV*, R = *i*Pr
(*S*) *L*, R = *i*Pr
(*R*) *XLVI*, R = H
(*S*) *LI*, R = H

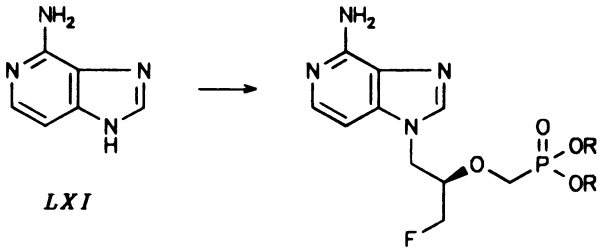


(*R*) *XLVII*, R = *i*Pr
(*S*) *LII*, R = *i*Pr
(*R*) *XLVIII*, R = H
(*S*) *LIII*, R = H

*i*Pr, 2-propyl

SCHEME 7

derivatives, the FPMP compounds are less toxic to the host cells. Similarly to the PME or HPMP derivatives, also FPMP compounds are phosphorylated in the cell to give diphosphates which terminate the DNA chain growth[19].



LXI

LXII, R = *i*Pr

LXIII, R = H

*i*Pr, 2-propyl

SCHEME 8

Studies of the individual enantiomers revealed that the (*S*)-enantiomer of the adenine derivative (FPMPA) is 30 – 50 times more effective inhibitor of HIV-1 and HIV-2 virus replication than is its (*R*)-antipode, whereas in the series of 2,6-diaminopurine (FPMPDAP) and guanine (FPMPG) both enantiomers have approximately the same inhibitory effect[27]. This fact may be connected with the enantiospecificity of phosphorylation which is apparently dependent on the character of the base as recently confirmed by a study of phosphorylation with adenylate kinase from L-1210 cells that takes place exclusively with the (*S*)-enantiomers of HPMPA and FPMPA[28]. However, we also cannot exclude a limiting influence of absolute configuration in the membrane transport of the compounds or different inhibitory effects of active metabolites in both series.

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. Solvents were evaporated on a rotatory evaporator at 40 °C/2 kPa, compounds were dried at 25 °C/6.5 Pa. Optical rotations were measured on a Perkin–Elmer 141 polarimeter at 25 °C. ^1H and ^{13}C NMR spectra (δ, ppm; *J*, Hz) were obtained with Varian XL-200 (200 MHz) or Varian XR-500 (500 MHz) instruments in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard, or in D_2O with sodium 3 (trimethylsilyl)-1-propanesulfonate (DSS) as internal standard. UV absorption spectra were measured on a Pye–Unicam 8800 UV-VIS spectrophotometer, the wavelength maxima are given in nm. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using the EI (electron energy 70 eV) and FAB (ionization with Xe, accelerating voltage 8 kV) techniques. Thin-layer chromatography was performed on Silufol UV_{254} foils, column chromatography on Silpearl silica gel (both Kavalier, The Czech Republic). Spots were detected in UV light (at 254 nm), compound of alkylating character were detected by spraying

with 2% solution of 4-(*p*-nitrobenzyl)pyridine in ethanol, heating and exposure to ammonia vapours. Further detection procedures were carbonization or treatment with aqueous $KMnO_4$. Solvent systems for TLC: S1 chloroform–methanol (10 : 1), S2 2-propanol–concentrated aqueous ammonia–water (7 : 1 : 2), S3 chloroform–methanol (20 : 1), S4 toluene–ethyl acetate (10 : 1), S5 chloroform–methanol (5 : 1). High performance liquid chromatography was performed on 250 × 4 mm or 250 × 17 mm columns packed with Separon SGXC18 (5 μm or 10 μm; Laboratorní přístroje, Praha, The Czech Republic). Paper electrophoresis was carried out on Whatman No. 3 MM paper at 20 V/cm (1 h) in 0.1 M triethylammonium hydrogen carbonate, pH 7.5 (TEAB). The electrophoretic mobilities given (E_{Up}) are referenced to uridine 3′-phosphate.

p-Nitrobenzylpyridine, bromotrimethylsilane, chlorotrimethylsilane, dimethoxymethane, methanesulfonyl chloride, dimethylformamide, acetonitrile, triisopropyl phosphite, sodium hydride and 10% palladium on carbon were Janssen (Belgium) products; 2-amino-6-chloropurine was purchased from Mack (Germany), adenine and cytosine from Fluka (Switzerland), and trityl chloride, 2,2-dimethoxypropane and diisopropylethylamine from Merck (Germany). Dimethylformamide and acetonitrile were dried by distillation from phosphorus pentoxide and stored over molecular sieves.

N-Benzoylation of *N*-(3-Fluoro-2-hydroxypropyl) Derivatives – General Procedure

Chlorotrimethylsilane (24 ml) was added to a suspension of *N*-(3-fluoro-2-hydroxypropyl) derivative (*III*, *VII*, *XI* or *XVIII*; 28.4 mmol) in pyridine (160 ml) and the formed solution was stirred at room temperature for 1 h. Benzoyl chloride (18.5 ml, 150 mmol) was then added and the mixture was stirred for another 2 h. The solution was cooled to 0 °C and ice-cold water (29 ml) was added dropwise, followed by concentrated aqueous ammonia solution (66 ml). After stirring for 30 min at 0 °C, the reaction mixture was concentrated and the dry residue was crystallized from water.

Using this method, compound *III* was converted into 7.5 g (84%) of N^6-benzoyl-9-(*RS*)-(3-fluoro-2-hydroxypropyl)adenine (*IV*), m.p. 196 – 197 °C, R_F 0.35 (S1). For $C_{15}H_{14}FN_5O_2$ (315.3) calculated: 57.14% C, 4.48% H, 6.03% F, 22.21% N; found: 57.42% C, 4.56% H, 6.04% F, 22.37% N. ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 4.20 – 4.65 m, 5 H (C-1′ + C-2′ + C-3′); 5.63 d, 1 H, J(OH,2′) = 5.0 (OH); 7.50 – 7.70 m, 3 H and 8.03 – 8.10, 2 H (arom.); 8.42 s, 1 H (H-8); 8.75 s, 1 H (H-2); 11.14 brs, 1 H (NH). ^{13}C NMR spectrum (hexadeuteriodimethyl sulfoxide): 45.91 d, ^3J(C,F) = 8.0 (C-1′); 67.5 d, ^2J(C,F) = 19.2 (C-2′); 85.05 d, ^1J(C,F) = 169.1 (C-3′).

Compound *VII* (4.7 g, 20.7 mmol) afforded 3.8 g (55%) of N^6-benzoyl-9-(*RS*)-(3-fluoro-2-hydroxypropyl)guanine (*VIII*), m.p. 178 °C (H_2O), R_F 0.20 (S1). For $C_{15}H_{14}FN_5O_3$ (331.3) calculated: 54.38% C, 4.26% H, 5.73% F, 21.14% N; found: 54.52% C, 4.07% H, 5.71% F, 21.29% N. ^{1}H NMR spectrum (200 MHz, hexadeuteriodimethyl sulfoxide): 4.08 – 4.30 m, 3 H (H-1′ + H-2′); 4.42 ddd, 2 H, J(3′,2′) = 4.0, J(3″,2′) = 5.0, J_g = 10.2, J(3′,F) = 47.0 (H-3′); 5.60 brs, 1 H (OH); 7.50 – 7.78 m, 3 H and 7.90 – 8.16, 3 H (arom. + H-8); 11.60 brs, 1 H (NH). ^{13}C NMR spectrum (hexadeuteriodimethyl sulfoxide): 45.73, ^3J(C,F) = 7.1, (C-1′); 67.54, ^2J(C,F) = 19.5 (C-2′); 85.04, ^1J(C,F) = 168.5 (C-3′).

Compound *XI* (5.9 g, 31.6 mmol) was converted into 10.0 g (95%) of N^4-benzoyl-1-(*RS*)-(3-fluoro-2-hydroxypropyl)cytosine (*XII*), m.p. 205 – 206 °C. For $C_{14}H_{14}FN_3O_3$ (291.3) calculated: 57.73% C, 4.84% H, 6.52% F, 14.43% N; found: 58.09% C, 4.63% H, 6.32% F, 14.09% N. ^{13}C NMR spectrum (hexadeuteriodimethyl sulfoxide): 52.28 d, ^3J(C,F) = 7.6 (C-1′); 66.63 d, ^2J(C,F) = 18.8 (C-2′); 85.27 d, ^1J(C,F) = 168.6 (C-3′); 95.76 (C-5); 128.63 and 132.87 and 133.50 (Ph); 151.61 (C-6); 155.55 (C-2); 163.31 (C-4); 167.61 (COPh).

The reaction of compound *XVIII* (2.5 g, 10 mmol) was performed in the same manner. The product was obtained by chromatography on silica gel and subsequent crystallization from ethanol–ether; yield of 6-azido-2-benzoylamino-9-(*RS*)-(3-fluoro-2-hydroxypropyl)purine (*XIX*) was 1.75 (49%). For $C_{15}H_{13}FN_8O_2$ (356.3) calculated: 50.56% C, 3.68% H, 5.33% F, 31.45% N; found: 50.42% C, 4.08% H, 5.32% F,

31.25% N. ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): (9 : 10 mixture of acyclic and cyclic forms of the azido derivative) 4.10 – 4.65 m (H-1' + H-2' + H-3'); 5.60 d, J = 5.0 + 5.64 d, J = 5.25 (9 : 10) (OH); 7.45 – 7.80 m + 7.90 – 8.15 m (arom.); 8.35 s and 8.57 s (10 : 9) (H-8); 11.05 s and 12.27 s (10 : 9) (NH).

9-(*RS*)-(3-Fluoro-2-phosphonomethoxypropyl)adenine (*V*)

Compound *IV* (7.2 g, 22.9 mmol) was codistilled with dimethylformamide (2 × 50 ml), dissolved in dimethylformamide (80 ml) and mixed with 60% dispersion of sodium hydride in oil (2.8 g, 70 mmol). The mixture was stirred at room temperature for 30 min, and a solution of compound *II* (9.1 g, 26 mmol) in dimethylformamide (20 ml) was then added. Stirring was continued for 16 h at room temperature and then 16 h at 80 °C. The reaction mixture was concentrated to a minimum volume, the residue codistilled with toluene (2 × 100 ml) and dissolved in 0.1 M methanolic sodium methoxide. After standing for 16 h at room temperature, the solution was neutralized with Dowex 50X8 (H^+ form), made alkaline with triethylamine, filtered and the solvent was evaporated to dryness. The residue was applied onto a column of the same ion exchanger (200 ml), washed with water and the intermediate was eluted with dilute (1 : 10) aqueous ammonia. The ammonia solution was evaporated to dryness, the residue codistilled with ethanol and dried in vacuo. The obtained diester was dissolved in acetonitrile (150 ml) and bromotrimethylsilane (15 ml) was added. After standing at room temperature for 3 days, the reaction mixture was concentrated and the residue codistilled with acetonitrile (50 ml). After addition of 0.4 M TEAB (100 ml), the solution was again concentrated and the dry residue applied onto a column of Dowex 50X8 (H^+ form; 250 ml). The column was washed with water and the product was eluted with dilute (1 : 10) aqueous ammonia. The obtained solution was evaporated to dryness, the residue applied onto a column of Dowex 1X2 (acetate form; 100 ml) and the product eluted with a gradient of acetic acid (0 – 0.5 mol l^{-1}; à 1 l). Yield 1.17 g (17%) of compound *V*, m.p. 265 °C, R_F 0.24 (S2). For $C_9H_{13}FN_5O_4P$ (305.2) calculated: 35.42% C, 4.29% H, 6.22% F, 22.95% N, 10.15% P; found: 35.69% C, 4.36% H, 6.25% F, 23.14% N, 9.81% P. ^{13}C NMR spectrum (D_2O + NaOD, dioxane): 43.12 d, ^3J(C,F) = 6.8 (C-1'); 68.37 d, ^1J(C,P) = 149.8 (C-P); 77.47 dd, ^2J(C,F) = 19.0, ^3J(C,P) = 11.0 (C-2'); 82.32 d, ^1J(C,F) = 167.3 (C-3'); 117.83 (C-5); 143.20 (C-8); 148.68 (C-4); 152.28 (C-1); 155.22 (C-6). HPLC: 0.05 M TEAB, 2% acetonitrile, k = 1.62. E_{Up} = 0.88.

9-(*RS*)-(3-Fluoro-2-phosphonomethoxypropyl)hypoxanthine (*VI*) and 9-(*RS*)-(3-Fluoro-2-phosphonomethoxypropyl)xanthine (*X*)

A solution of compound *V* (200 mg, 0.66 mmol) in a mixture of 80% acetic acid (80 ml) and isoamyl nitrite (2 ml) was set aside at room temperature overnight. The solution was concentrated, the residue codistilled with water and applied onto a column of Dowex 50X8 (H^+ form; 150 ml). The product was eluted with water (with retention). After evaporation of water, the product was dissolved in methanol and precipitated with ether; yield 50 mg (25%). HPLC: 0.05 M TEAB, k = 0.91.

In a similar manner, compound *IX* (200 mg, 0.62 mmol) was converted into compound *X* (185 mg; 92%), m.p. >300 °C. For $C_9H_{12}FN_4O_6P$ (322.2) calculated: 33.55% C, 3.75% H, 5.90% F, 17.39% N, 9.61% P; found: 33.52% C, 4.15% H, 6.00% F, 18.16% N, 9.44% P. HPLC: 0.05 M TEAB, k = 0.20.

9-(*RS*)-(3-Fluoro-2-phosphonomethoxypropyl)guanine (*IX*)

Compound *VIII* (6.6 g, 20 mmol) was codistilled with dimethylformamide (2 × 100 ml) at 40 °C/13 Pa. After addition of compound *II* (7.7 g, 21 mmol) in dimethylformamide (80 ml), the solution was cooled to −20 °C, sodium hydride (60% dispersion in oil, 1.44 g, 60 mmol) was added and the reaction mixture was stirred at −20 °C for 1 h, at 0 °C for 6 h and at room temperature for 12 h. Finally, the mixture was heated at 70 °C for 6 h and concentrated to a minimum volume. The residue was codistilled with toluene,

dissolved in 0.1 M methanolic sodium methoxide (250 ml) and warmed to 50 °C. The solution was neutralized with Dowex 50X8 (H^+ form), made alkaline with triethylamine, filtered and the solvent was evaporated. The dry residue was dissolved in water (200 ml), extracted with ether (2 × 100 ml), the aqueous phase was concentrated to a minimum volume and applied onto a column of Dowex 50X8 (H^+ form). The column was washed with water and the product eluted with dilute aqueous ammonia (1 : 10). The obtained solution was taken down, the residue was dried under diminished pressure, dissolved in acetonitrile (80 ml) and mixed with bromotrimethylsilane (12 ml). After standing at room temperature for 2 days, the solution was evaporated, the residue codistilled with acetonitrile and mixed with water (100 ml). After 30 min the mixture was made alkaline with triethylamine, concentrated, the residue was codistilled with water and deionized on a column of Dowex 50X8 (H^+ form; 100 ml). The ammonia solution of the product was taken down and an alkaline solution of the residue was applied onto a column of Dowex 1X2 (acetate form). The product was eluted with a gradient (0.05 – 0.5 mol l^{-1}) of acetic acid; yield 1.10 g (17%), m.p. >300 °C, R_F 0.08 (S2). For $C_9H_{13}FN_5O_5P$ (321.2) calculated: 33.65% C, 4.08% H, 5.91% F, 21.80% N, 9.64% P; found: 34.00% C, 4.35% H, 5.60% F, 21.87% N, 9.40% P. ^1H NMR spectrum (D_2O + NaOD): 3.70 – 4.95 m, 5 H (H-1′ + H-2′ + H-3′), 3.58 d, 2 H, J(H,P) = 9.2 (PCH_2); 7.86 s, 1 H (H-8). ^{13}C NMR spectrum (D_2O + NaOD): 42.22 d, ^3J(C,F) = 8.3 (C-1′); 67.96 d, ^1J(C,P) = 150.1 (PC); 77.52 dd, ^2J(C,F) = 19.0, ^3J(C,P) = 11.3 (C-2′); 82.05 d, ^1J(C,F) = 166.8 (C-3′); 117.07 (C-5); 138.82 (C-8); 151.14 (C-4); 160.76 (C-2); 168.00 (C-6).

1-(*RS*)-(3-Fluoro-2-phosphonomethoxypropyl)cytosine (*XIII*)

Compound *XII* (9.5 g, 28.5 mmol) was codistilled with dimethylformamide (2 × 100 ml), then dissolved in dimethylformamide (100 ml) and a 60% dispersion of sodium hydride in oil (3.75 g, 93.8 mmol) was added. The mixture was stirred at room temperature for 30 min and then mixed with a solution of compound *II* (11.6 g, 33 mmol) in dimethylformamide (25 ml). After heating at 80 °C for 11 h, the mixture was concentrated to a minimum volume, the residue was dried at 60 °C and 13 Pa and dissolved in 0.1 M methanolic sodium methoxide (300 ml). After standing at room temperature for 15 h, the solution was neutralized with Dowex 50X8 (H^+ form), made alkaline with triethylamine, the ion-exchanger was filtered off and washed with methanol (300 ml). The combined methanolic solutions were evaporated to dryness. The residue was mixed with water (500 ml) and the aqueous phase was extracted with ether (3 × 200 ml). The combined ethereal phases were extracted with water (2 × 100 ml), the combined aqueous phases were concentrated to 200 ml, filtered through Celite and applied onto a column of Dowex 50X8 (H^+ form; 300 ml). The column was washed with water and the product eluted with dilute ammonia (1 : 10). The eluate was evaporated to dryness, the residue codistilled with ethanol and dried over phosphorus pentoxide under diminished pressure. The residue (5.0 g) was then mixed with acetonitrile (150 ml) and bromotrimethylsilane (15.0 ml) and the mixture was stirred to homogeneity. After 16 h at room temperature, the reaction mixture was concentrated and codistilled with acetonitrile. Water (200 ml) was added, the mixture was made alkaline with triethylamine, the solvent was evaporated to dryness, the residue was codistilled with methanol and applied onto a column of Dowex 50X8 (H^+ form). The column was washed with water and the product was eluted with dilute ammonia. The eluate was taken down, the residue applied onto a column of Dowex 1X2 (acetate form) and the column was washed with water. The product was eluted with a gradient of acetic acid (0 – 0.25 mol l^{-1}) and purified by preparative HPLC on a reversed phase in water. Yield 1.1 g (14%), m.p. 219 °C. E_{Up} = 0.95. For $C_8H_{13}FN_3O_5P$ (281.2) calculated: 34.17% C, 4.66% H, 6.76% F, 14.94% N, 11.02% P; found: 34.35% C, 5.00% H, 6.70% F, 15.07% N, 11.44% P. ^{13}C NMR spectrum (D_2O + NaOD, dioxane): 49.42 d, ^3J(C,F) = 7.1 (C-1′); 67.79 d, ^1J(C,P) = 153.9 (PC); 78.04 dd, ^2J(C,F) = 18.5, ^3J(C,P) = 11.4 (C-2′); 82.78 d, ^1J(C,F) = 167.2 (C-3′); 95.70 (C-5); 147.97 (C-4); 158.36 (C-2); 166.53 (C-6).

9-(*RS*)-(3-Fluoro-2-phosphonomethoxypropyl)-3-deazaadenine (*XVII*)

Chlorotrimethylsilane (2.3 ml) was added to a suspension of compound *XIV* (0.73 g, 3 mmol) in pyridine (20 ml). After 1 h, benzoyl chloride (1.8 ml) was added and after further 2 h the mixture was decomposed at 0 °C by successive addition of water (2 ml) and concentrated aqueous ammonia (6 ml). After standing at 0 °C for 30 min, the mixture was taken down, the residue codistilled with ethanol (3 × 50 ml) and chromatographed on a column of silica gel (100 g) in chloroform, the product was eluted with chloroform–methanol (95 : 5). Evaporation of the solvents gave 0.2 g (20%) of compound *XV*, R_F 0.12 (chloroform–methanol 9 : 1). This product was mixed with a solution of tosyloxymethylphosphonate *II* (0.25 g) in dimethylformamide (2 ml), the mixture was cooled to −15 °C and 60% dispersion of sodium hydride in oil (75 mg) was added. After stirring at room temperature for 16 h under exclusion of air, the mixture was evaporated, the residue was codistilled with toluene (2 × 25 ml) and set aside with 0.1 M methanolic sodium methoxide (200 ml). The mixture was neutralized with Dowex 50X8 (H^+ form) and made alkaline with triethylamine, filtered, the ion exchanger was washed with methanol and the filtrate was concentrated. The residue was deionized on Dowex 50X8 (H^+ form; 50 ml). The column was first washed with 20% aqueous methanol and then with 2.5% aqueous ammonia. Evaporation, codistillation with ethanol (2 × 25 ml) and drying over phosphorus pentoxide afforded 150 mg of the oily product *XVI*. ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 8.05 s, 1 H (H-8); 7.68 d, 1 H (H-2); 6.89 d, 1 H (H-3); 6.41 brs, 2 H (NH_2); 4.43 dd, 1 H, $J(1',2')$ = 3.9, J_g = 14.6 (H-1'); 4.34 dd, 1 H, $J(1'',2')$ = 7.3 (H-1''); 4.05 dsext, 1 H, ΣJ = 41.4, $J(2',F)$ = 23.0 (H-2'); 4.64 ddd, 1 H, $J(3',2')$ = 3.3, J_g = 10.3, $J(3',F)$ = 47.4 (H-3'); 4.41 ddd, 1 H, $J(3'',2')$ = 3.9, J_g = 10.3, $J(3'',F)$ = 47.4 (H-3''); 3.89 dd, 1 H, $J(PCH)$ = 8.8, J_g = 14.2 (PCH_2); 3.77 dd, 1 H, $J(P,CH)$ = 9.3 (PCH_2); 4.52 and 4.47 2 × dq, 2 H, $J(CH,CH_3)$ = 5.9, $J(P,OCH)$ = 7.8 and 7.3 (OCH); 1.096, 1.184, 1.147 and 1.135 4 × d, 12 H, J = 5.9 (4 × CH_3).

A mixture of compound *XVI*, bromotrimethylsilane (0.6 ml) and acetonitrile (6 ml) was stirred in a stoppered flask for 24 h. The mixture was worked up as described for the preparation of compound *V*. The residue was deionized on Dowex 50X8 (H^+ form; 100 ml). The obtained crude residue was applied onto a column of Dowex 1X2 (acetate form) and the column was washed to drop of the UV absorption to the original value and then the product was eluted with 0.5 M acetic acid. The principal UV-absorbing fraction was concentrated, the residue codistilled with water and crystallized from 80% aqueous ethanol (addition of ether to turbidity). Yield 90 mg (41%) of compound *XVII*, m.p. >250 °C. HPLC: 1% acetonitrile in 0.05 M TEAB, k = 1.85. E_{Up} = 0.73. For $C_{10}H_{14}FN_4O_4P$. H_2O (322.2) calculated: 37.23% C, 5.00% H, 17.38% N, 9.62% P, 5.89% F; found: 36.96% C, 4.71% H, 17.18% N, 8.91% P, 6.10% F. ^{1}H NMR spectrum (D_2O + NaOD): 8.20 s, 1 H (H-8); 7.74 d, 1 H (H-2); 6.98 d, 1 H (H-3); 4.45 d, 2 H, $J(1',2')$ = 5.9 (H-1'); 4.06 dddd, 1 H, ΣJ = 42.5, $J(2',F)$ = 23.4 (H-2'); 4.59 ddd, 1 H, $J(3',2')$ = 3.9, J_g = 10.3, $J(3',F)$ = 47.4 (H-3'); 4.39 ddd, 1 H , $J(3'',2')$ = 3.4, $J(3'',F)$ = 46.4 (H-3''); 3.56 2 × d, 2 H, $J(P,CH)$ = 9.0 (PCH_2). UV spectrum ($\lambda_{max}(\varepsilon)$), pH 2: 263.0 (9 200); pH 13: 266.5 (9 500).

2-Amino-6-azido-9-(*RS*)-(3-fluoro-2-phosphonomethoxypropyl)purine (*XX*)

A dispersion of sodium hydride in oil (60%, 0.54 g, 13.5 mmol) was added at −15 °C to a mixture of compound *XIX* (1.6 g, 4.5 mmol), tosyloxymethylphosphonate *II* (1.9 g, 5.4 mmol) and dimethylformamide. After stirring at room temperature for 4 days in the dark, methanol (100 ml) was added and, after standing at room temperature for 16 h, the solution was neutralized with Dowex 50X8 (H^+ form), made alkaline with triethylamine, filtered and the solvent was evaporated. The residue was codistilled with toluene and applied onto a column of Dowex 50X8 (H^+ form; 200 ml). The column was washed with 20% methanol and the product was eluted with dilute aqueous ammonia (1 : 10). Evaporation of the solvent afforded diisopropyl ester of compound *XX* (1.8 g, 4.2 mmol) which was dried under diminished pressure. Acetonitrile (40 ml) and bromotrimethylsilane (4 ml) were added and the mixture was stirred at room temperature for 16 h. The volatile material was evaporated and the residue was codistilled with acetonitrile.

Water (50 ml) was added and the mixture was made alkaline with ammonia. After 30 min the mixture was concentrated, the residue codistilled with water, applied onto a column of Dowex 50X8 (H^+ form; 200 ml) and the product was eluted with water. Yield 700 mg (45%) of compound *XX*. For $C_9H_{12}FN_8O_4P$ (346.2) calculated: 31.22% C, 3.49% H, 5.49% F, 32.37% N, 8.95% P; found: 31.16% C, 3.53% H, 5.10% F, 32.35% N, 8.66% P. HPLC: 0.05 M TEAB, 15% acetonitrile, k = 0.70, E_{Up} 0.75.

2,6-Diamino-9-(*RS*)-(3-fluoro-2-phosphonomethoxypropyl)purine (*XXI*)

Compound *XX* (400 mg, 1.16 mmol) was hydrogenated in 80% acetic acid (50 ml) over 10% Pd/C (500 mg) at room temperature and atmospheric pressure for 40 h. The reaction mixture was filtered through Celite which was then washed with methanol, 80% acetic acid and water. The combined filtrates were concentrated, the residue was codistilled with water and crystallized from water–ethanol–ether. Yield 280 mg (75%), m.p. >300 °C, R_F 0.17 (S2). For $C_9H_{14}FN_6O_4P$ (320.2) calculated: 33.76% C, 4.41% H, 5.93% F, 26.24% N, 9.67% P; found: 34.02% C, 4.45% H, 6.10% F, 26.01% N, 9.38% P. HPLC: 0.05 M TEAB, 6% acetonitrile, k = 1.05. E_{Up} 0.73.

5-*O*-(*p*-Toluenesulfonyl)-D-ribonolactone (*XXIII*)

Concentrated hydrochloric acid (50 ml) was added to a solution of compound *XXII* (50 g, 146 mmol) in dioxane (500 ml) and the mixture was stirred for 12 h. Water (130 ml) was added and the mixture was neutralized by addition of solid sodium hydrogen carbonate. The lower aqueous layer was separated, extracted with ethyl acetate (500 ml), and the combined organic phases were dried over magnesium sulfate. After filtration, the solvents were evaporated and the dry residue was crystallized from a mixture of ethyl acetate (130 ml) and toluene (500 ml), the toluene being added to the boiling ethyl acetate solution. Yield 31.6 g (71%) of compound *XXIII*; m.p. 108 – 109 °C, R_F 0.15 (S4). For $C_{12}H_{14}SO_7$ (302.3) calculated: 47.67% C, 4.66% H, 10.60% S; found: 47.34% C, 4.49% H, 10.63% S. Mass spectrum, *m/e* (rel.%): 302 (M, 15), 238 (12), 173 (54), 155 (Ts, 50), 130 (20), 91 (100), 73 (35), 65 (28), 55 (23), 28 (25).

(*S*)-2,3-Dihydroxypropyl *p*-Toluenesulfonate (*XXIV*)

A solution of sodium periodate (22.8 g, 107 mmol) in water (165 ml) was added at 0 °C to a solution of compound *XXIII* (30.7 g, 102 mmol) in water (75 ml) and dioxane (75 ml). The mixture was stirred at room temperature for 20 min, cooled to 0 °C and after 20 min dioxane (150 ml) was added. The solution was filtered and the filtrate was treated with several portions of sodium borohydride (total 4.73 g, 125 mmol), the temperature of the mixture being kept under 20 °C. After stirring at room temperature for 30 min, the reaction mixture was poured into ethyl acetate (1.3 l), the organic layer was washed with 1 M HCl (saturated with sodium chloride) (2 × 150 ml) and a 1 : 1 mixture of saturated solutions of sodium chloride and sodium hydrogen carbonate (2 × 150 ml). The ethyl acetate solution was then dried over magnesium sulfate, filtered and the solvent was evaporated to give 20.1 g (80%) of compound *XXIV*, R_F 0.22 (S1). For $C_{10}H_{14}O_5S$ (246.1) calculated: 48.76% C, 5.73% H, 13.00% S; found: 48.86% C, 5.83% H, 12.94% S.

(*S*)-2,2-(Dimethyl-1,3-dioxolan-4-yl)methyl *p*-Toluenesulfonate (*XXV*)

2,2-Dimethoxypropane (20.2 ml, 164 mmol) and trifluoromethanesulfonic acid (10 μl, 0.1 mmol) were added at room temperature to a solution of compound *XXIV* (27.0 g, 110 mmol) in acetone (150 ml). After stirring at room temperature for 1 h, triethylamine (0.5 ml) was added and the reaction mixture was concentrated to a minimum volume. The residue was dissolved in toluene (500 ml), the solution was washed with water (3 × 250 ml) and dried over magnesium sulfate. Evaporation of toluene afforded

compound *XXV*; yield 28.3 g (90%), R_F 0.15 (S4). For $C_{13}H_{18}O_5S$ (286.1) calculated: 54.52% C, 6.34% H, 11.18% S; found: 54.80% C, 6.41% H, 11.04% S.

(*R*)- and (*S*)-1-Fluoro-3-*O*-*p*-toluenesulfonyl-2,3-propanediol (*XXVII*, *XXXII*)

A solution of *p*-toluenesulfonyl chloride (26.4 g, 138 mmol) in pyridine (30 ml) was added at −30 °C to a solution of compound *XXVI* (12.4 g, 132 mmol) in pyridine (30 ml). After standing at −30 °C for 48 h, the reaction mixture was poured into ethyl acetate (1 300 ml) and, with ice-cooling, washed successively with 1 M HCl to acid reaction of the aqueous phase, water, sodium hydrogen carbonate solution, and water. After drying over magnesium sulfate and filtration, the solvent was evaporated and the residue was chromatographed on silica gel (500 g) in toluene and then in toluene–ethyl acetate 50 : 1. Yield 21 g (64%) of compound *XXVII*, R_F 0.41 (S3). $[\alpha]_D$ −4.4° (*c* 0.95, methanol). For $C_{10}H_{13}FO_4S$ (248.3) calculated: 48.37% C, 5.27% H, 7.65% F, 12.91% S; found: 48.44% C, 5.41% H, 7.45% F, 12.77% S. ^{1}H NMR spectrum (500 MHz, hexadeuteriodimethyl sulfoxide): 2.42 s, 3 H (CH_3(Ts)); 3.90 m, 1 H, J(2,F) = 22.7 (H-2); 3.93 m and 4.00 dd, 2 H, J(1,2) = 3.7, J_g = 10.5 (H-1); 4.45 dm, 2 H, J(3,2) = 4.4, J(3′,2) = 4.9, J(3,F) = J(3′,F) = 47.1 (H-3); 5.58 d, 1 H, J = 5.4 (OH); 7.48 d and 7.80 d, 2 + 2 H, J = 8.3 (Ts).

Analogously, compound *XXXI* (12.4 g, 132 mmol) was converted into the (*S*)-enantiomer *XXXII* (21 g, 64%). R_F 0.41 (S3). For $C_{10}H_{13}FO_4S$ (248.3) calculated: 48.37% C, 5.27% H, 7.65% F, 12.91% S; found: 48.54% C, 5.31% H, 7.43% F, 12.80% S.

(*R*)- and (*S*)-1-Fluoro-2-methoxymethoxypropyl *p*-Toluenesulfonate (*XXVIII*, *XXXIII*)

Phosphorus pentoxide was added at room temperature to a stirred mixture of compound *XXVII* (11 g, 44.3 mmol), dimethoxyethane (11 ml) and dichloromethane (11 ml) until the starting compound disappeared (TLC in toluene–ethyl acetate 5 : 1). Celite (10 g) was added, the reaction mixture was filtered and the solid on filter was washed with chloroform and the filtrate was concentrated. Yield 11.9 g (93%) of compound *XXVIII*, R_F 0.19 (S4). $[\alpha]_D$ −17.6° (*c* 1.6, methanol). For $C_{12}H_{15}FO_5S$ (290.3) calculated: 49.65% C, 5.20% H, 6.54% F, 11.04% S; found: 49.85% C, 5.34% H, 6.40% F, 10.91% S. ^{1}H NMR spectrum (500 MHz, hexadeuteriodimethyl sulfoxide): 2.43 s, 3 H (CH_3(Ts)); 3.21 s, 3 H (OCH_3); 3.96 dm, 1 H, ΣJ = 39.0, J(2,F) = 20.5 (H-2); 4.07 bdd, 1 H, J(1,2) = 5.6, J_g = 10.5, J(1,F) = 0.5 (H-1); 4.15 ddd, 1 H, J(1′,2) = 3.9, J(1′,F) = 1.5 (H-1′); 4.42 ddd, 1 H, J(3,2) = 4.9, J_g = 10.0, J(3,F) = 47.0 (H-3); 4.46 ddd, 1 H, J(3′,2) = 3.9, J(3′,F) = 47.0 (H-3′); 4.587 s and 4.591 s, 1 + 1 H (OCH_2O); 7.49 d and 7.80 d, 4 H, J = 8.3 (Ts).

Under identical conditions compound *XXXII* (11 g, 44.4 mmol) was converted into the (*S*)-enantiomer *XXXIII* (11.9 g, 93%), R_F 0.19 (S4). For $C_{12}H_{15}FO_5S$ (290.3) calculated: 49.65% C, 5.20% H, 6.54% F, 11.04% S; found: 49.85% C, 5.34% H, 6.40% F, 10.91% S.

(*R*)- and (*S*)-2-Acetoxymethoxy-3-fluoropropyl *p*-Toluenesulfonate (*XXIX*, *XXXIV*)

A mixture of compound *XXXIII* (2.45 g), acetic anhydride (5 ml) and boron trifluoride etherate (1 ml) was stirred at 0 °C for 2 h and then poured into a mixture of sodium hydrogen carbonate (10 g), water (100 ml) and toluene (100 ml). After shaking, the aqueous layer was separated, the toluene one was washed with water (2 × 50 ml) and dried over magnesium sulfate. Evaporation of the toluene afforded the (*S*)-enantiomer *XXXIV* in practically quantitative yield, R_F 0.16 (S4). $[\alpha]_D$ −7.2° (*c* 1.0, methanol). For $C_{13}H_{17}FO_6S$ (320.1) calculated: 48.73% C, 5.35% H, 5.93% F, 10.00% S; found: 48.82% C, 5.51% H, 5.80% F, 9.95% S. ^{1}H NMR spectrum (500 MHz, hexadeuteriodimethyl sulfoxide): 2.01 s, 3 H (Ac); 2.43 s, 3 H (CH_3(Ts)); 4.01 ss, 1 H, J(1,2) = 6.1, J_g = 10.5 (H-1); 4.11 dm, 1 H, ΣJ = 39.0, J(2,F) = 20.5 (H-2); 4.16 ddd, 1 H, J(1′,2) = 3.6, J(1′,F) = 1.0 (H-1′); 4.41 ddd, 1 H, J(3,2) = 5.1, J_g = 10.25, J(3,F) = 47.1 (H-3); 4.47 ddd,

1 H, $J(3',2)$ = 3.7, $J(3',F)$ = 46.6 (H-3'); 5.18 d and 5.22 d, 2 H, J = 6.6 (OCH_2O); 7.50 d and 7.79 d, 2 + 2 H, J = 8.03 (Ts).

The (R)- derivative *XXIX* was obtained analogously by reaction of compound *XXVIII* in a quantitative yield.

(*R*)- and (*S*)-2-Diisopropylphosphonylmethoxy-3-fluoropropyl *p*-Toluenesulfonate (*XXX*, *XXXV*)

Compound *XXIX* (11.0 g, 34.4 mmol) was codistilled with toluene (3 × 10 ml), then mixed with toluene (20 ml) and bromotrimethylsilane (6.8 ml) and heated at 80 °C for 16 h. After evaporation of toluene and addition of triisopropyl phosphite (10 ml), the mixture was kept at 50 °C for 2 h, codistilled with toluene and chromatographed on silica gel (100 g); elution with toluene, toluene–ethyl acetate (5 : 1) and toluene–ethyl acetate (1 : 1). Yield 11.0 g (75%) of compound *XXX*, R_F 0.38 (S3). $[\alpha]_D$ −12.8° (*c* 0.8, chloroform). For $C_{17}H_{28}FO_7PS$ (426.4) calculated: 47.87% C, 6.61% H, 7.26% P; found: 48.13% C, 6.91% H, 7.35% P. Mass spectrum, *m/e* (rel.%): 427 (M + H, 55), 385 (M − *i*Pr, 17), 342 (M − 2 *i*Pr, 100), 259 (9), 171 (TsO, 36). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 1.20 d, 6 H (2 × CH_3); 1.26 d, 6 H (2 × CH_3); 2.43 s, 3 H (CH_3(Ts)); 3.8 – 4.8 m, 9 H (HCO, H_2CF), 7.3 – 7.8 m, 4 H (Ts).

Analogously, compound *XXXIV* (11.0 g, 34.4 mmol) was converted into (*S*)-2-diisopropylphosphonylmethoxy-3-fluoropropyl *p*-toluenesulfonate (*XXXV*) (11.3 g, 77%), R_F 0.38 (S3). $[\alpha]_D$ +12.5° (*c* 0.8, chloroform). For $C_{17}H_{28}FO_7PS$ (426.4) calculated: 47.87% C, 6.61% H, 7.26% P; found: 48.04% C, 6.97% H, 7.45% P. Mass spectrum, *m/e* (rel.%): 427 (M + H, 55), 385 (M − *i*Pr, 17), 342 (M − 2 *i*Pr, 100), 259 (9), 171 (TsO, 36). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 1.20 d, 6 H (2 × CH_3); 1.26 d, 6 H (2 × CH_3); 2.43 s, 3 H (CH_3(Ts)); 3.8 – 4.8 m, 9 H (HCO,H_2CF); 7.3 – 7.8 m, 4 H (Ts).

(*S*)-2-Diisopropylphosphonylmethoxy-3-fluoropropanol (*XXXVI*)

Trityl chloride (13.0 g, 46.8 mmol) was added to a solution of compound *XXXI* (4.00 g, 42.5 mmol) and diisopropylethylamine (10.9 ml, 63.8 mmol) in dichloromethane. After stirring for 6 h, the reaction mixture was diluted with toluene (500 ml), washed successively with water (250 ml), 5% solution of sodium hydrogen carbonate (250 ml), dried over magnesium sulfate and filtered. The solvent was evaporated and the residue dissolved in tetrahydrofuran (80 ml). Compound *II* (15.4 g, 44.0 mmol), followed by 60% suspension of sodium hydride in oil (1.68 g, 42 mmol), was added. After stirring for 24 h at room temperature, the reaction mixture was concentrated to a minimum volume and the residue was refluxed with 80% acetic acid (140 ml) for 15 min. The solvent was evaporated and the residue was column chromatographed on silica gel (300 g) in chloroform–methanol (100 :1); yield 5.6 g (48%) of compound *XXXVI*, R_F 0.13 (S3). $[\alpha]_D$ +5.7° (*c* 0.8, methanol). For $C_{10}H_{22}FO_5P$ (272.3) calculated: 44.11% C, 8.15% H, 6.98% F, 11.38% P; found: 44.20% C, 8.35% H, 7.00% F, 11.10% P. Mass spectrum, *m/e* (rel.%): 273 (M + 1, 90), 231 (19), 189 (100), 171 (8), 113 (17), 96 (6).

(*S*)-2-Diisopropylphosphonylmethoxy-3-fluoropropyl Methanesulfonate (*XXXVII*)

Methanesulfonyl chloride (2.2 ml, 28.1 mmol) was added dropwise at 0 °C to a stirred solution of compound *XXXVI* (5.1 g, 18.8 mmol) and diisopropylethylamine (9.6 ml, 56.2 mmol) in dichloromethane (20 ml). After standing at room temperature for 24 h, the mixture was diluted with ethyl acetate (500 ml), washed successively with water, 1 M HCl and 5% solution of sodium hydrogen carbonate. After drying and evaporation of the solvent, the residue was chromatographed on silica gel in chloroform–methanol (50 : 1). Yield 5.3 g (80%) of compound *XXXVII*, R_F 0.20 (S3). $[\alpha]_D$ +18.7° (*c* 0.1, methanol). For $C_{11}H_{24}FO_7PS$ (350.3) calculated: 37.71% C, 6.90% H, 5.42% F, 8.84% P, 9.15% S; found: 37.83% C, 6.94% H, 5.31% F, 8.91% P, 9.02% S. Mass spectrum, *m/e* (rel.%): 351 (M + 1, 65), 309 (13), 267 (100), 189 (5), 171 (10), 151 (11), 111 (7), 95 (8). ^{1}H NMR spectrum (200 MHz, hexadeuteriodimethyl sulfoxide): 1.25 m, 12 H

(4 × CH_3); 3.22 s, 3 H (SCH_3); 3.90 – 4.10 m, 1 H (H-2); 3.93 d, 2 H, J(H,P) = 9.2 (PCH_2); 4.20 – 4.80 m, 6 H (H-1 + H-3 + 2 × (CH_3)C**H**).

(*R*)- and (*S*)-N^6-Benzoyl-9-(2-diisopropylphosphonylmethoxy-3-fluoropropyl)adenine (*XXXVIII*, *XLI*)

Sodium hydride (60% suspension in oil, 1.125 g, 28.1 mmol) was added to a suspension of N^6-benzoyladenine (6.5 g, 26.9 mmol) in dimethylformamide (100 ml) and the stirred mixture was heated at 60 °C for 15 min. Compound *XXX* (10 g, 23.6 mmol) was added and the mixture was further stirred and heated at 80 °C for 6 h. After neutralization with acetic acid and evaporation of the dimethylformamide (40 °C, 100 Pa), the residue was extracted with chloroform, the chloroform extract was filtered through Celite and the filtrate was taken down. The sirupy residue was chromatographed on silica gel (500 g) in chloroform–methanol (50 : 1). Yield 3.7 g (32%) of compound *XXXVIII*. For $C_{22}H_{29}FN_5O_5P$ (493.5) calculated: 53.54% C, 5.92% H, 3.85% F, 14.19% N; found: 53.67% C, 5.99% H, 3.70% F, 13.95% N.

(*S*)-N^6-Benzoyl-9-(2-diisopropylphosphonylmethoxy-3-fluoropropyl)adenine (*XLI*) was obtained in an analogous way with the use of compound *XXXV*; yield 3.7 g (32%). For $C_{22}H_{29}FN_5O_5P$ (493.5) calculated: 53.54% C, 5.92% H, 3.85% F, 14.19% N; found: 53.71% C, 5.83% H, 3.71% F, 13.97% N.

(*R*)- and (*S*)-9-(2-Diisopropylphosphonylmethoxy-3-fluoropropyl)adenine (*XXXIX*, *XLII*)

Sodium hydride (50 mg, 2 mmol) was added to a solution of compound *XXXVIII* (2.1 g, 4.25 mmol) in methanol (20 ml). After standing at room temperature for 16 h, acetic acid (250 µl) was added, the mixture was concentrated to a minimum volume and the residue was chromatographed on a column of silica gel in chloroform–methanol (30 : 1). Yield 1.1 g (67%) of compound *XXXIX*, m.p. 72 – 74 °C (toluene), R_F 0.31 (S5). For $C_{15}H_{25}FN_5O_4P$ (389.4) calculated: 46.26% C, 6.47% H, 4.87% F, 17.98% N, 7.95% P; found: 47.16% C, 7.12% H, 4.81% F, 17.32% N, 7.46% P. Mass spectrum, *m/e* (rel%): 389 (M, 10), 374 (M – CH_3, 8), 288 (20), 209 (M – $CH_2P(O)(OiPr)_2$, 48), 195 ($OCH_2P(O)(OiPr)_2$, 100), 174 (12), 149 (AdeCH_2, 40), 135 (Ade, 60). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 1.08 – 1.20 m, 12 H (4 × CH_3); 3.7 – 4.7 m, 9 H (HCO, H_2CF); 7.19 bs, 2 H (NH_2); 8.09 s, 1 H (H-8); 8.15 s, 1 H (H-2).

Analogously, compound *XLI* (2.1 g, 4.25 mmol) was converted into (*S*)-9-(2-diisopropylphosphonylmethoxy-3-fluoropropyl)adenine (*XLII*) (1.1 g, 67%), m.p. 73 – 74 °C (toluene), R_F 0.31 (S5). $[\alpha]_D$ –60.9° (*c* 0.5, dimethylformamide). For $C_{15}H_{25}FN_5O_4P$ (389.4) calculated: 46.26% C, 6.47% H, 4.87% F, 17.98% N, 7.95% P; found: 47.26% C, 7.31% H, 4.90% F, 17.13% N, 7.26% P. Mass spectrum, *m/e* (rel.%): 389 (M, 10), 374 (M – CH_3, 8), 288 (20), 209 (M – $CH_2P(O)(OiPr)_2$, 48), 195 ($OCH_2P(O)(OiPr)_2$, 100), 174 (12), 149 (AdeCH_2, 40), 135 (Ade, 60). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 1.08 – 1.20 m, 12 H (4 × CH_3); 3.7 – 4.7 m, 9 H (HCO, H_2CF); 7.19 bs, 2 H (NH_2); 8.09 s, 1 H (H-8); 8.15 s, 1 H (H-2).

(*R*)- and (*S*)-9-(3-Fluoro-2-phosphonomethoxypropyl)adenine (*XL*, *XLIII*)

Bromotrimethylsilane (2.17 ml, 16.4 mmol) was added at room temperature to a solution of compound *XXXIX* (1.6 g, 4.1 mmol) in acetonitrile (8 ml), the mixture was stirred at room temperature for 24 h and concentrated to a minimum volume. The residue was codistilled with toluene (2 × 10 ml) and methanol (10 ml), and then mixed with 2% aqueous ammonia (10 ml). After standing at ambient temperature for 1 h, the solution was taken down, the dry residue was dissolved in a minimum amount of water and applied onto a column of Dowex 50X8 (H^+ form; 50 ml). The column was washed with water to negative bromide reaction and the product was eluted with 2% ammonia solution. The obtained solution was concentrated to a minimum volume and applied onto a column of Dowex 1X2 (acetate form; 50 ml). After washing the column with water to negative reaction to ammonia, the product was eluted with 1 M acetic acid. Evaporation of the solvent and codistillation with water afforded 1.14 g (91%) of product *XL*, m.p. 194 – 197 °C, R_F 0.24 (S2). $[\alpha]_D$ +18.68° (*c* 0.4, water). For $C_9H_{13}FN_5O_4P$ (305.2) calculated: 35.41% C, 4.29% H, 6.22% F,

22.94% N, 10.14% P; found: 36.65% C, 5.34% H, 5.77% F, 20.14% N, 9.79% P. ^{1}H NMR spectrum (500 MHz, hexadeuteriodimethyl sulfoxide): 3.63 dd, 1 H, J(H,P) = 9.8, J_g = 13.4 (PCH); 3.68 dd, 1 H, J(H',P) = 9.0 (PCH'); 4.06 dm, 1 H, ΣJ = 40.5, J(2',F) = 21.5 (H-2'); 4.29 dd, 1 H, J(1',2') = 6.3, J_g = 14.4 (H-1'); 4.36 ddd, 1 H, J(3',2') = 4.5, J_g = 10.25, J(3',F) = 47.1 (H-3'); 4.41 dd, 1 H, J(1'',2') = 4.5 (H-1''); 4.57 ddd, 1 H, J(3'',2') = 3.7, J(3'',F) = 47.4 (H-3''); 7.34 bs, 2 H (NH_2); 8.14 s and 8.15 s, 1 + 1 H (H-2 + H-8).

In an analogous manner, the (*S*)-enantiomer *XLIII* was obtained from compound *XLII* (1.6 g, 4.1 mmol); yield 1.1 g (90%), m.p. 194 – 197 °C, R_F 0.24 (S2). $[\alpha]_D$ −16.84° (*c* 0.38, water). For $C_9H_{13}FN_5O_4P$ (305.2) calculated: 35.41% C, 4.29% H, 6.22% F, 22.94% N, 10.14% P; found: 35.20% C, 4.43% H, 5.85% F, 22.73% N, 10.44% P. ^{1}H NMR spectrum (500 MHz, hexadeuteriodimethyl sulfoxide): 3.63 dd, 1 H, J(H,P) = 9.8, J_g = 13.4 (PCH); 3.68 dd, 1 H, J(H',P) = 9.0 (PCH'); 4.06 dm, 1 H, ΣJ = 41.0, J(2',F) = 21.5 (H-2'); 4.29 dd, 1 H, J(1',2') = 6.3, J_g = 14.7 (H-1'); 4.36 ddd, 1 H, J(3',2') = 4.9, J_g = 10.25, J(3',F) = 47.1 (H-3'); 4.42 dd, 1 H, J(1'',2') = 4.6 (H-1''); 4.57 ddd, 1 H, J(3'',2') = 3.7, J(3'',F) = 47.4 (H-3''); 7.34 bs, 2 H (NH_2); 8.15 s, 2 H (H-2 + H-8).

(*R*)- and (*S*)-2-Amino-6-chloro-9-(2-diisopropylphosphonylmethoxy-3-fluoropropyl)purine (*XLIV*, *IL*)

A mixture of 2-amino-6-chloropurine (1.75 g, 10.3 mmol), sodium hydride (60% suspension in oil, 376 mg, 9.4 mmol) and dimethylformamide (25 ml) was heated at 90 °C for 5 min, compound *XXX* (4.0 g, 9.4 mmol) was then added and the mixture was heated at 90 °C for 2 h under stirring. The dimethylformamide was evaporated (40 °C, 100 Pa), the residue was mixed with Celite (25 ml) and chloroform (150 ml) and the mixture was filtered through Celite. The filtrate was concentrated to a minimum volume and chromatographed on silica gel (150 g) in chloroform–methanol (50 : 1). Yield 2.8 g (68%) of compound *XLIV*, m.p. 133 – 134 °C (toluene), R_F 0.51 (S5). $[\alpha]_D$ +26.9° (*c* 0.8, dimethylformamide). For $C_{15}H_{24}ClFN_5O_5P$ (439.8) calculated: 40.96% C, 5.50% H, 8.06% Cl, 4.32% F, 15.92% N, 7.04% P; found: 41.10% C, 5.83% H, 8.48% Cl, 4.40% F, 15.96% N, 7.20% P. Mass spectrum, *m/e* (rel.%): 424 (M – CH_3, 75), 390 (26), 340 (100), 306 (25), 258 (10), 228 (19), 170 (34), 134 (17), 113 (12).

The (*S*)-enantiomer *IL* was obtained in an analogous manner from compound *XXXV* (3.84 g, 9.0 mmol); yield 2.1 g (53%), m.p. 136 °C (toluene), R_F 0.51 (S5). $[\alpha]_D$ −25.9° (*c* 0.8, dimethylformamide). For $C_{15}H_{24}ClFN_5O_5P$ (439.8) calculated: 40.96% C, 5.50% H, 8.06% Cl, 4.32% F, 15.92% N, 7.04% P; found: 41.48% C, 6.04% H, 8.28% Cl, 4.10% F, 15.91% N, 6.47% P. Mass spectrum, *m/e* (rel.%): 424 (M – CH_3, 100), 390 (58), 382 (25), 348 (9), 340 (98), 306 (30), 229 (20), 210 (15), 194 (17), 170 (38), 136 (18). ^{1}H NMR spectrum (200 MHz, hexadeuteriodimethyl sulfoxide): 1.15 m, 12 H (CH_3); 3.76 dd and 3.91 dd, 2 H, J(H,P) = 8.5, J_g = 14 (PCH_2); 4.00 – 4.54 m, 5 H (H-1' + H-2' + 2 × (CH_3)C**H**); 4.70 ddd, 2 H, J(3',2') = 3.5, J_g = 10.5, J(3',F) = 47.5 (H-3'); 6.88 s, 2 H (NH_2); 8.07 s, 1 H (H-8).

(*R*)- and (*S*)-9-(2-Diisopropylphosphonylmethoxy-3-fluoropropyl)guanine (*XLV*, *L*)

A mixture of compound *XLIV* (500 mg, 1.14 mmol) and 75% trifluoroacetic acid (5 ml) was allowed to stand at room temperature for 48 h. After the end of the reaction (TLC in S5), the mixture was concentrated in vacuo, the residue codistilled with water, neutralized with a mixture of concentrated aqueous ammonia and methanol (1 : 10, 15 ml) and the solvent was evaporated. The residue was chromatographed on silica gel (30 ml) in chloroform–methanol (20 : 1). Yield 440 mg (92%) of compound *XLV*, m.p. 85 °C, R_F 0.25 (S5). $[\alpha]_D$ +13.3° (*c* 0.4, dimethylformamide). For $C_{15}H_{25}FN_5O_6P$ (421.4) calculated: 42.75% C, 5.98% H, 4.50% F, 16.62% N, 7.35% P; found: 42.95% C, 5.92% H, 4.40% F, 17.16% N, 7.34% P. Mass spectrum, *m/e* (rel.%): 420 (M – H, 5), 406 (100), 364 (13), 322 (50), 304 (4), 262 (4), 226 (5), 210 (10), 151 (19).

Analogously, the (*S*)-enantiomer *L* was prepared from compound *IL* (412 mg, 0.94 mmol); yield 394 mg (99%), m.p. 84 – 87 °C, R_F 0.25 (S5). $[\alpha]_D$ −12.3° (*c* 0.45, dimethylformamide). For $C_{15}H_{25}FN_5O_6P$ (421.4) calculated: 42.75% C, 5.98% H, 4.50% F, 16.62% N, 7.35% P; found: 43.03% C, 5.82% H, 4.30% F, 17.01% N, 7.28% P. ^{1}H NMR spectrum (500 MHz, hexadeuteriodimethyl sulfoxide): 1.15 d and 1.181 d

and 1.121 d and 1.178 d, 4 × 3 H, $J(CH_3,CH)$ = 6.1 (4 × CH_3); 3.77 dd, 1 H , J(H,P) = 9.5, J_g = 13.7 (PCH); 3.88 dd, 1 H, J(H,P) = 9.3 (PCH); 4.06 dddd, 1 H, ΣJ = 41.3, J(2',F) = 22.2 (H-2'); 4.11 dd, 1 H, J(1',2') = 7.6, J_g = 14.6 (H-1'); 4.17 dd, 1 H , J(1",2') = 3.9, J_g = 14.1 (H-1"); 4.41 ddd, 1 H, J(3',2') = 4.4, J_g = 10.7, J(3',F) = 47.1 (H-3'); 4.49 dq and 4.52 dq, 2 × 1 H, $J(CH,CH_3)$ = 6.1, J(H,P) = 7.6 ($POCH_2$); 4.62 ddd, 1 H, J(3",2') = 3.2, J(3",F) = 47.4 (H-3"); 6.5 brs, 2 H (NH_2); 10.65 s, 1 H (NH).

(*R*)- and (*S*)-9-(3-Fluoro-2-phosphonomethoxypropyl)guanine (*XLVI*, *LI*)

A mixture of compound *XLV* (290 mg, 0.689 mmol), bromotrimethylsilane (364 mg, 2.75 mmol) and acetonitrile (3 ml) was stirred at room temperature for 24 h. The reaction mixture was then codistilled with toluene and mixed with dilute aqueous ammonia (5 : 1, 5 ml). The solution was concentrated, the residue codistilled with water and in aqueous solution applied onto a column of Dowex 50X8 (H^+ form; 20 ml). After washing the column with water to negative bromide reaction, the product was eluted with dilute ammonia and applied onto a column of Dowex 1X2 (acetate form; 20 ml). The column was washed with water and the compound was eluted with 1 M acetic acid. Evaporation of the solvent and codistillation with water afforded 210 mg (95%) of compound *XLVI*, m.p. 248 – 250 °C (water–acetone), R_F 0.08 (S2). $[\alpha]_D$ +2.53° (*c* 0.6, 2% aqueous ammonia). For $C_9H_{13}FN_5O_5P$ (321.2) calculated: 33.65% C, 4.07% H, 5.91% F, 21.80% N, 9.64% P; found: 33.83% C, 4.23% H, 5.90% F, 19.17% N, 9.86% P. Mass spectrum, *m/e* (rel.%): 322 (M + H, 50), 279 (10), 257 (8), 228 (10), 181 (28), 149 (100), 110 (100). ^{1}H NMR spectrum (500 MHz, D_2O + NaOD): 3.60 dd, + 3.55 dd, 2 H, J(H,P) = 9.0, J_g = 12.2 (PCH_2); 4.05 m, 1 H, ΣJ = 43.2, J(2',F) = 24.2, (H-2'); 4.29 dd, and 4.34 dd, 2 H, J(1',2') = 5.9, J_g = 14.6 (H-1'); 4.45 ddd, 1 H, J(3',2') = 3.7, J_g = 10.5, J(3',F) = 46.4 (H-3'); 4.67 ddd, 1 H, J(3",2') = 3.4, J(3",F) = 47.4 (H-3"); 7.87 s, 1 H (H-8).

In an analogous manner, compound *L* (290 mg, 0.69 mmol) was converted into the (*S*)-enantiomer *LI* (180 mg, 81%), R_F 0.08 (S2). $[\alpha]_D$ −2.5° (*c* 0.6, 2% aqueous ammonia). For $C_9H_{13}FN_5O_5P$ (321.2) calculated: 33.65% C, 4.07% H, 5.91% F, 21.80% N, 9.64% P; found: 33.83% C, 4.23% H, 5.90% F, 19.17% N, 9.86% P. ^{1}H NMR spectrum (500 MHz, D_2O + NaOD): 3.55 dd, 1 H, J(H,P) = 9.0, J_g = 12.2 (PCH); 3.59 dd, 1 H, J(H,P) = 9.0 (PCH); 4.05 dddd, 1 H, ΣJ = 4.5, J(2',F) = 24.4 (H-2'); 4.29 dd, 1 H, J(1',2') = 6.1, J_g = 14.6 (H-1'); 4.33, 1 H, J(1",2') = 5.9 (H-1"); 4.43 ddd, 1 H, J(3',2') = 3.7, J_g = 10.5, J(3',F) = 46.6 (H-3'); 4.67 ddd, 1 H, J(3",2') = 3.4, J(3",F) = 47.4 (H-3"); 7.84 s, 1 H (H-8).

(*R*)- and (*S*)-2-Amino-9-(2-diisopropylphosphonylmethoxy-3-fluoropropyl)purine (*XLVII*, *LII*)

Compound *XLIV* (500 mg, 1.14 mmol) was hydrogenated over 10% Pd/C (50 mg) in methanol (10 ml) at room temperature for 4 h. After the end of the reaction (followed by TLC in S5) the reaction mixture was neutralized with a mixture of concentrated aqueous ammonia and methanol (1 : 10, 10 ml), filtered, evaporated and chromatographed on silica gel (50 ml) in chloroform–methanol (50 : 1, 20 : 1); yield 200 mg (45%) of compound *XLVII*, m.p. 78 – 79 °C, R_F 0.37 (S5). $[\alpha]_D$ +30.2° (*c* 0.4, dimethylformamide). For $C_{15}H_{25}FN_5O_4P$ (389.4) calculated: 46.27% C, 6.47% H, 4.88% F, 17.99% N, 7.95% P; found: 44.71% C, 6.44% H, 4.30% F, 17.44% N, 8.14% P. Mass spectrum, *m/e* (rel.%): 406 (M + H, 5), 309 (100), 348 (6), 306 (207), 210 (33), 194 (7), 149 (5), 136 (10).

In an analogous manner, compound *IL* (470 mg, 1.07 mmol) was converted into the (*S*)-enantiomer *LII* (280 mg, 67%), R_F 0.37 (S5). For $C_{15}H_{25}FN_5O_4P$ (389.4) calculated: 46.27% C, 6.47% H, 4.88% F, 17.99% N, 7.95% P; found: 44.71% C, 6.44% H, 4.30% F, 17.44% N, 8.14% P. ^{1}H NMR spectrum (500 MHz, hexadeuteriodimethyl sulfoxide): 1.10 d and 1.147 d and 1.153 d and 1.20 d, 12 H, J = 6.1 (4 × CH_3); 3.77 dd, 1 H, J(H,P) = 9.8, J_g =13.7 (PCH); 3.90 dd, 1 H, J(H,P) = 9.3 (PCH); 4.12 dddd, 1 H, ΣJ = 41.8, J(2',F) = 22.6 (H-2'); 4.21 dd, J(1',2') = 7.6, J_g = 14.6 (H-1'); 4.28 dd, 1 H, J(1",2') = 4.1, J_g = 14.4 (H-1"); 4.45 ddd, 1 H, J(3',2') = 4.1, J_g = 10.7, J(3',F) = 46.4 (H-3'); 4.46 dq, 1H, $J(CH,CH_3)$ = 6.1,

J(H,P) = 7.6 (POCH); 4.50 dq, 1 H, J(CH,CH_3) = 6.1, J(H,P) = 7.6 (POCH); 4.69 ddd, 1 H, J(3″,2′) = 3.4, J_g = 10.5, J(3″,F) = 47.6 (H-3″); 6.50 brs, 2 H (NH_2); 8.01 s and 8.57 s, 1 + 1 H (H-6 + H-8).

(*R*)- and (*S*)-2-Amino-9-(3-fluoro-2-phosphonomethoxypropyl)purine (*XLVIII*, *LIII*)

Bromotrimethylsilane (280 μl, 2.1 mmol) was added to a solution of compound *XLVII* (80 mg, 0.21 mmol) in acetonitrile (1.6 ml). After stirring at room temperature for 24 h, the reaction mixture was codistilled with toluene, mixed with dilute aqueous ammonia (10 : 1, 5 ml) and concentrated under diminished pressure. The residue was dissolved in water and applied onto a column of Dowex 50X8 (H^+ form; 20 ml). The column was washed with water to negative bromide reaction and then the product was eluted with dilute ammonia and applied onto a column of Dowex 1X2 (acetate form; 20 ml). After washing the column with water, the product was eluted with 1 M acetic acid. Evaporation of the solvent and codistillation of the residue with water afforded 50 mg (80%) of compound *XLVIII*, m.p. 172 – 174 °C, R_F 0.24 (S2). $[\alpha]_D$ +6.94° (*c* 0.4, 2% aqueous ammonia). For $C_9H_{13}FN_5O_4P$ (305.2) calculated: 35.41% C, 4.29% H, 6.22% F, 22.94% N, 10.14% P; found: 34.95% C, 4.34% H, 5.98% F, 22.50% N, 9.73% P. Mass spectrum, *m/e* (rel.%): 306 (M + 1, 100), 289 (10), 277 (18), 257 (30), 241 (10), 232 (20), 226 (6), 215 (92). ^{1}H NMR spectrum (500 MHz, D_2O + NaOD): 3.55 dd and 3.61 dd, 2 H, J(H,P) = 9.0, J_g = 12.2 (PCH_2); 4.09 m, 1 H, J = 42.2, J(2′,F) = 23.7 (H-2′); 4.40 dd, 1 H, J(1′,2′) = 5.9, J_g = 15.0 (H-1′); 4.47 dd, 1 H, J(1″,2′) = 5.2 (H-1″); 4.49 ddd, 1 H , J(3′,2′) = 3.7, J_g = 10.5, J(3′,F) = 46.4 (H-3′); 4.67 ddd, 1 H, J(3″,2′) = 3.7, J(3″,F) = 47.4 (H-3″); 8.29 s, 1 H (H-8); 8.62 s, 1 H (H-6).

In an analogous manner, compound *LII* (230 mg, 0.59 mmol) was converted into the (*S*)-enantiomer *LIII* (100 mg, 55%), m.p. 173 °C, R_F 0.24 (S2). $[\alpha]_D$ −7.3° (*c* 0.4, 2% aqueous ammonia). For $C_9H_{13}FN_5O_4P$ (305.2) calculated: 35.41% C, 4.29% H, 6.22% F, 22.94% N, 10.14% P; found: 34.83% C, 4.44% H, 5.91% F, 22.72% N, 9.66% P. ^{1}H NMR spectrum (500 MHz, hexadeuteriodimethyl sulfoxide): 3.61 dd, 1 H, J(H,P) = 9.8, J_g = 13.2 (PCH); 3.67 dd, 1 H, J(H,P) = 9.3 (PCH); 4.05 dddd, 1 H, ΣJ = 40.5, J(2′,F) = 21.5 (H-2′); 4.18 dd, 1 H, J(1′,2′) = 6.8, J_g = 14.4 (H-1′); 4.30 dd, 1 H, J(1″,2′) = 4.1 (H-2′); 4.39 ddd, 1 H , J(3′,2′) = 4.4, J_g = 10.5, J(3′,F) = 46.9 (H-3′); 4.58 ddd, 1 H, J(3″,2′) = 3.7, J(3″,F) = 47.4 (H-3″); 6.60 bs, 2 H (NH_2); 8.09 s and 8.52 s, 1 + 1 H (H-6 + H-8).

(*R*)- and (*S*)-2-Amino-6-azido-9-(2-diisopropylphosphonylmethoxy-3-fluoropropyl)purine (*LV*, *LVIII*)

A mixture of compound *XLIV* (1.0 g, 2.27 mmol), sodium azide (2.0 g) and dimethylformamide (15 ml) was heated at 110 °C for 5 h. The dimethylformamide was evaporated, the residue was suspended in chloroform, mixed with silica gel (4 g) and the mixture was evaporated to dryness. The product was freed from salts on a small column of silica gel by elution with chloroform–methanol (10 : 1) and purified by chromatography on silica gel in chloroform–methanol (30 : 1). Yield 700 mg (69%) of compound *LV*, m.p. 146 – 148 °C, R_F 0.38 (S5). $[\alpha]_D$ +20.4° (*c* 0.4, dimethylformamide). For $C_{15}H_{24}FN_8O_5P$ (446.4) calculated: 40.35% C, 5.41% H, 4.25% F, 25.10% N, 6.93% P; found: 40.45% C, 5.56% H, 4.01% F, 25.23% N, 6.81% P. Mass spectrum, *m/e* (rel.%): 445 (M − H, 1), 431 (100), 405 (21), 390 (3), 319 (9), 225 (8), 210 (9), 150 (11).

Analogously, compound *LI* (1.00 g, 2.27 mmol) was converted into the (*S*)-enantiomer *LVIII*; yield 700 mg (69%), m.p. 151 – 152 °C (toluene), R_F 0.38 (S5). $[\alpha]_D$ −21.9° (*c* 0.4, dimethylformamide). For $C_{15}H_{24}FN_8O_5P$ (446.4) calculated: 40.35% C, 5.41% H, 4.25% F, 25.10% N, 6.93% P; found: 41.32% C, 6.06% H, 3.90% F, 25.10% N, 7.17% P. Mass spectrum, *m/e* (rel.%): 431 (M − CH_3, 100), 405 (60), 390 (8), 361 (12), 319 (27), 277 (9), 225 (21), 210 (38), 171 (11), 164 (14), 150 (32), 135 (10), 122 (9), 113 (12). ^{1}H NMR spectrum (200 MHz, hexadeuteriodimethyl sulfoxide): 1.11 m, 12 H (4 × CH_3); 3.77 dd and 3.90 dd, 2 H, J(H,P) = 8.5, J_g = 13 (PCH_2); 4.16 dm, 1 H, J(2′,F) = 23 (H-2′); 4.27 – 4.55 m, 4 H (H-1′ + 2 × (CH_3)C**H**); 4.71 ddd, 2 H, J(3′,2′) = 3.5, J_g = 11, J(3′,F) = 48 (H-3′); 8.12 s, 1 H (H-8); 8.20 s, 2 H (NH_2).

(*R*)- and (*S*)-2,6-Diamino-9-(2-diisopropylphosphonylmethoxy-3-fluoropropyl)purine (*LVI*, *LIX*)

Compound *LV* (300 mg, 0.67 mmol) was hydrogenated over 10% Pd/C (30 mg) in methanol (6 ml) at room temperature for 10 h. The reaction mixture was filtered, the filtrate concentrated and the residue chromatographed on silica gel (30 ml) in chloroform–methanol (40 : 1) to give 217 mg (80%) of compound *LVI*, R_F 0.24 (S5). For $C_{15}H_{26}FN_6O_4P$ (404.4) calculated: 44.55% C, 6.48% H, 4.70% F, 20.78% N, 7.66% P; found: 44.71% C, 6.69% H, 4.60% F, 20.57% N, 7.36% P. Mass spectrum, *m/e* (rel.%): 405 (M, 100), 363 (10), 321 (45), 239 (5), 225 (10), 210 (23), 165 (8), 150 (20).

Compound *LVIII* (430 mg, 0.96 mmol) was converted in an analogous manner into the (*S*)-enantiomer *LIX* (220 mg, 57%), R_F 0.11 (S2). For $C_{15}H_{26}FN_6O_4P$ (404.4) calculated: 44.55% C, 6.48% H, 4.70% F, 20.78% N, 7.66% P; found: 44.83% C, 6.37% H, 4.39% F, 20.77% N, 7.46% P. ^{1}H NMR spectrum (500 MHz, hexadeuteriodimethyl sulfoxide): 1.14 d and 1.18 d, 6 H (2 × CH_3), J = 6.1; 1.18 d and 1.21 d, 6 H (2 × CH_3), J = 6.3; 3.77 dd, 1 H, J(H,P) = 9.8, J_g = 13.7 (PCH); 3.88 dd, 1 H, J(H,P) = 9.8 (PCH); 4.08 dm, 1 H, J(2′,F) = 21.5 (H-2′); 4.10 dd, 1 H, J(1′,2′) = 6.3 (H-1′); 4.17 dd, 1 H, J(1″,2′) = 4.0, J_g = 14.9 (H-1″); 4.39 dd, 1 H, J(3′,2′) = 4.4, J_g = 10.5, J(3′,F) = 46.6 (H-3′); 4.49 dq, 1 H, J(CH,CH_3) = 6.1, J(H,P) = 7.6 (POCH); 4.53 dq, 1 H, J(CH,CH_3) = 6.3, J(H,P) = 7.8 (POCH); 4.65 dd, 1 H, J(3″,2′) = 3.2, J(3″,F) = 47.4 (H-3″); 6.78 bs and 5.77 bs, 2 × 2 H (2 × NH_2); 7.665 s, 1 H (H-8).

(*R*)- and (*S*)-2,6-Diamino-9-(3-fluoro-2-phosphonomethoxypropyl)purine (*LVII*, *LX*)

Bromotrimethylsilane (263 μl, 2.0 mmol) was added to a suspension of compound *LVI* (150 mg, 0.37 mmol) in acetonitrile (1.5 ml). After stirring at room temperature for 24 h, the reaction mixture was codistilled with toluene, dilute aqueous ammonia (10 : 1, 5 ml) was added and the solution was concentrated. The residue was codistilled with water and applied onto a column of Dowex 50X8 (H^+ form). The column was washed with water to negative reaction for bromides and the product was then eluted with dilute ammonia. The eluate was evaporated and an alkaline aqueous solution of the residue was applied onto a column of Dowex 1X2 (acetate form; 20 ml). After washing with water, the compound was eluted with 1 M acetic acid. Evaporation of the solvent and codistillation with water afforded 100 mg (80%) of compound *LVII*, m.p. 254 °C (decomp.), R_F 0.17 (S2). $[\alpha]_D$ +3.52° (*c* 0.4, 2% aqueous ammonia). For $C_9H_{14}FN_6O_4P$ (320.2) calculated: 33.76% C, 4.41% H, 5.93% F, 26.24% N, 9.67% P; found: 33.06% C, 4.51% H, 5.40% F, 28.26% N, 9.26% P. Mass spectrum, *m/e* (rel.%): 321 (M + 1, 53), 307 (83), 305 (37), 289 (36), 278 (42), 273 (43), 257 (100), 232 (70). ^{1}H NMR spectrum (500 MHz, D_2O + NaOD): 3.53 dd and 3.59 dd, 2 H, J(C,P) = 9.0, J_g = 12.2 (PCH_2); 4.03 m, 1 H, J = 43.0, J(2′,F) = 24.0 (H-2′); 4.29 dd, 1 H, J(1′,2′) = 6.1 J_g = 14.8 (H-1′); 4.34 dd, 1 H, J(1″,2′) = 5.4, J_g = 14.8 (H-1″); 4.46 ddd, 1 H, J(3′,2′) = 3.7, J_g = 10.5, J(3′,F) = 46.4 (H-3′); 4.66 ddd, 1 H, J(3″,2′) = 3.4, J(3″,F) = 47.4 (H-3″); 7.97 s, 1 H (H-8).

In an analogous manner, compound *LIX* (200 mg, 0.495 mmol) was converted into the (*S*)-enantiomer *LX* (116 mg, 73%), m.p. 267 – 268 °C. For $C_9H_{14}FN_6O_4P$ (320.2) calculated: 33.76% C, 4.41% H, 5.93% F, 26.24% N, 9.67% P; found: 33.06% C, 4.51% H, 5.40% F, 28.26% N, 9.26% P. ^{1}H NMR spectrum (500 MHz, D_2O + NaOD): 3.52 dd, 1 H, J(H,P) = 9.3, J_g = 12.2 (PCH); 3.57 dd, 1 H, J(H,P) = 9.3 (PCH); 4.02 dm, 1 H, ΣJ = 42.7, J(2′,F) = 23.9 (H-2′); 4.30 dd, 1 H, J(1′,2′) = 6.0, J_g = 14.6 (H-1′); 4.34 dd, 1 H, J(1″,2′) = 5.4 (H-1″); 4.45 ddd, 1 H, J(3′,2′) = 3.7, J_g = 10.5, J(3′,F) = 46.4 (H-3′); 4.65 ddd, 1 H, J(3″,2′) = 3.7, J(3″,F) = 47.4 (H-3″); 7.96 s, 1 H (H-8).

9-(*R*)-(3-Fluoro-2-phosphonomethoxypropyl)-3-deazaadenine (*LXIII*)

A mixture of 3-deazaadenine (*LXI*; 0.78 g, 5.8 mmol), dimethylformamide (25 ml), cesium carbonate (0.95 g, 2.9 mmol) and synthon *XXX* (3.0 g, 7.0 mmol) was heated at 100 °C for 10 h under stirring and exclusion of moisture until the starting base disappeared (TLC in chloroform–methanol 7 : 1). After evaporation of dimethylformamide and codistillation with toluene (3 × 50 ml), the residue was extracted with boiling

chloroform and subjected to preparative thin-layer chromatography in chloroform–methanol (8 : 2). Yield 1.7 g (87%) of compound *LXII* as an amorphous foam. ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 8.05 s, 1 H (H-8); 7.68 d, 1 H (H-2); 6.89 d, 1 H (H-3); 6.41 brs, 2 H (2 × NH_2); 4.43 dd, 1 H, J(1′,2′) = 3.9, J_g = 14.6 (H-1′); 4.34 dd, 1 H, J(1″,2′) = 7.3 (H-1″); 4.05 dsext, 1 H, ΣJ = 41.4, J(2′,F) = 23.0 (H-2′); 4.64 ddd, 1 H, J(3′,2′) = 3.3, J_g = 10.3, J(3′,F) = 47.4 (H-3′); 4.41 ddd, 1 H, J(3″,2′) = 3.9, J(3″,F) = 47.4 (H-3″); 3.89 dd, 1 H, J(P,CH) = 8.8, J_g = 14.2 (PCH_2); 3.77 dd, 1 H, J(P,CH) = 9.3 (PCH_2); 4.52 and 4.47 2 × dq, 2 H, J(CH,CH_3) = 5.9, J(P,OCH) = 7.8 and 7.3 (OCH); 1.096, 1.184, 1.147 and 1.135 4 × d, 12 H, J = 5.9 (4 × CH_3).

A mixture of the obtained compound *LXII*, acetonitrile (50 ml) and bromotrimethylsilane (5 ml) was stirred in a stoppered flask for 24 h at room temperature. The mixture was worked up as described for the preparation of compound *V* and deionized on a column of Dowex 50*X*8 (H^+ form; 100 ml). The crude material was then chromatographed on a column of Dowex 1X2 (acetate form; 100 ml). The product was eluted with 0.2 M acetic acid and crystallized from water–ethanol (1 : 4); yield 0.97 g (55%) of compound *LXIII*, m.p. >250 °C, k = 1.85 (1% acetonitrile in 0.05 M TEAB), E_{Up} = 0.75. For $C_{10}H_{14}FN_4O_4P$. H_2O (322.2) calculated: 37.23% C, 5.00% H, 5.89% F, 17.38% N, 9.62% P; found: 37.03% C, 4.81% H, 6.15% F, 17.25% N, 9.43% P. ^{1}H NMR spectrum (D_2O + NaOD): 8.20 s, 1 H (H-8); 7.74 d, 1 H, J(2,3) = 6.1 (H-2); 6.98 d, 1 H (H-3); 4.45 d, 2 H, J(1′,2′) = 5.9 (H-1′); 4.06 dddd, 1 H, ΣJ = 42.5, J(2′,F) = 23.4 (H-2′); 4.59 ddd, 1 H, J(3′,2′) = 3.9, J_g = 10.3, J(3′,F) = 47.4 (H-3′); 4.39 ddd, 1 H, J(3″,2′) = 3.4, J(3″,F) = 46.4 (H-3″); 3.56 2 × d, 2 H, J(P,CH) = 9.0 (PCH_2). UV spectrum (λ_{max} (ε)), pH 2: 262.5 (9 500); pH 13: 267.0 (10 000).

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