SYNTHESIS OF ACYCLIC NUCLEOSIDE AND NUCLEOTIDE ANALOGS DERIVED FROM 6-AMINO-7*H*-PURIN-8(9*H*)-ONE

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Reaction of 8-bromoadenine derivatives **2** with sodium acetate in acetic acid and cleavage of (*S*)-7-[(trityloxy)methyl]-7,8-dihydro[1,3]oxazolo[3,2-*e*]purin-4-amine (**12**) and diisopropyl (*S*)-{[(4-amino-8,9-dihydro-7*H*-[1,3]oxazino[3,2-*e*]purin-8-yl)oxy]methyl}phosphonate (**13a**) were used for the synthesis of the corresponding N^9-substituted derivatives of 6-amino-7*H*-purin-8(9*H*)-one **3a**–**3c** and **7**. Alkylation of 6-amino-7*H*-purin-8(9*H*)-one (**3a**) with diverse alkylation agents afforded the title N^9-monosubstituted **3b**, **3d** and **7a** and N^7,N^9-disubstituted acyclic nucleoside and nucleotide analogs **6b**, **6d** and **8a**.

Key words: Purines; Acyclic analogs; Nucleosides; Nucleotides; Alkylation; Anhydro derivatives; Phosphonates; Bromination.

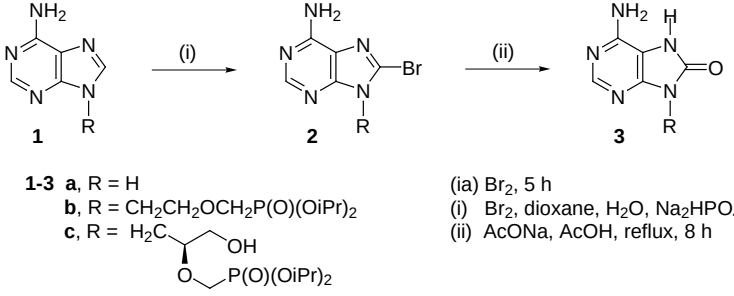
8-Substituted purine derivatives occupy a prominent place in nucleoside and nucleotide chemistry. The importance of these compounds as potential antiviral and anticancer agents is obvious. Of them, 8-hydroxy derivatives (*e.g.* 8-hydroxyguanosine[1]) and 8-amino derivatives (*e.g.* 8-aminoguanosine[1] or 8-amino-9-benzylguanine[2]) should be particularly mentioned.

Many biologically active acyclic nucleotide analogs have been prepared. Among others, two important groups of compounds of this type have been studied in detail owing to their antiviral properties *in vitro* and *in vivo*: *N*-[2-(phosphonomethoxy)ethyl] (PME) and (*S*)-*N*-[3-hydroxy-2-(phosphonomethoxy)propyl] (HPMP) derivatives of heterocyclic bases[3]. Exhaustive information was obtained on the influence of substituents in positions 6 and 2 of the purine ring[4]. However, the data on the effect of the substitution in position 8 on the antiviral and/or cytostatic activity in these series are rather scarce. Such compounds derived from 6-amino-7*H*-purin-8(9*H*)-one (**3a**) are now of special interest for us.

RESULTS AND DISCUSSION

There are two principal approaches for the preparation of 8-substituted purine acyclic nucleoside and nucleotide analogs: (i) modification of the corresponding acyclic nucleoside or nucleotide derivative in position 8 of the purine moiety or (ii) preparation of an 8-substituted purine base and its subsequent alkylation with a suitable reagent.

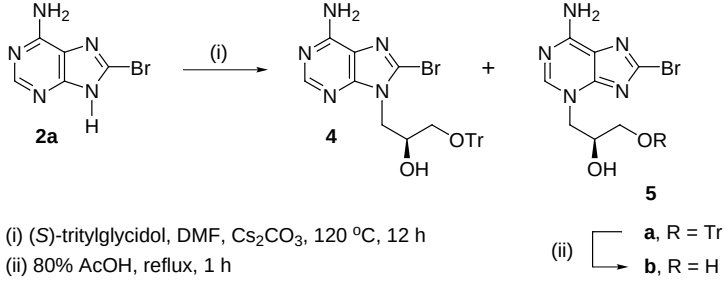
Bromination of purine derivatives is the first step in modification of bases in position 8. 8-Bromoadenine[5] (**2a**) was prepared by 5 h treatment of adenine (**1a**) with bromine (Scheme 1). Bromination of acyclic nucleotide analogs **1b** and **1c** with bromine in a mixture of dioxane and 10% aqueous solution of disodium hydrogenphosphate afforded the corresponding 8-bromopurine derivatives **2b** and **2c** in good yields[3g,6].



SCHEME 1

Synthesis of compounds containing oxo (hydroxy) group in position 8 of the purine moiety can be performed by the reaction of appropriate 8-bromo derivatives with sodium acetate in acetic acid under reflux[7]. Thus, 8-bromoadenine (**2a**) was converted to 6-amino-7*H*-purin-8(9*H*)-one in 94% yield (**3a**, Scheme 1) and, similarly, 8-bromo-9-{2-[(diisopropoxyphosphoryl)methoxy]ethyl}adenine (**2b**, PMEA derivative) and (*S*)-8-bromo-9-{2-[(diisopropoxyphosphoryl)methoxy]-3-hydroxypropyl}adenine (**2c**, (*S*)-HPMPA derivative) were converted to the corresponding 8-oxo derivatives **3b** and **3c**, respectively. In the case of HPMP derivative **3c**, diester is partly cleaved to monoester under reaction conditions as confirmed by electrophoresis and TLC. This is in accord with the described cleavage of phosphonate diesters with nucleophilic reagents. Therefore, the mixture was treated with TMSBr without any purification to afford phosphonate **9** (Scheme 3).

8-Bromoadenine (**2a**) gave, in the alkylation reaction with (*S*)-tritylglycidol in DMF in the presence of Cs_2CO_3, N^9-isomer **4** and N^3-isomer **5a** in yields of 48 and 20%, respectively (Scheme 2). The formation and a similar ratio of N^9- and N^3-isomers in 8-bromoadenine alkylation was recently reported[8]. Acid treatment of compound **5a** afforded (*S*)-8-bromo-3-(2,3-dihydroxypropyl)adenine (**5b**).



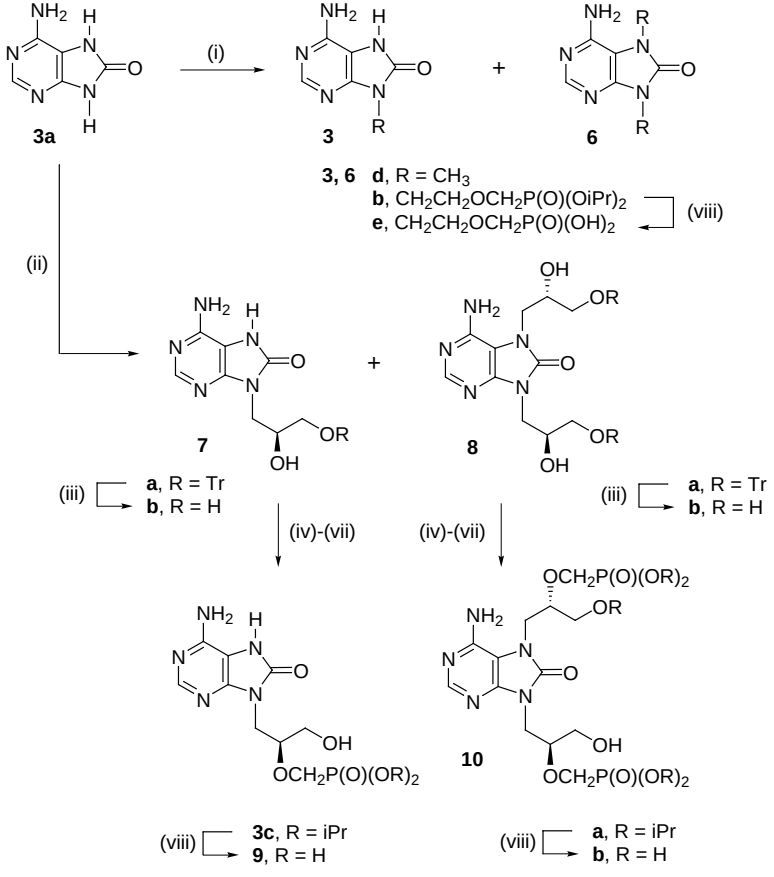
SCHEME 2

An alternative alkylation approach for the synthesis of 8-oxopurine derivatives is interesting because it offers a possibility to obtain diverse regiomers as the alkylation products. In order to obtain introductory information about the regiospecificity of this reaction, alkylation of compound **3a** was performed with diverse alkylation agents (Scheme 3): methyl tosylate, diisopropyl [(2-chloroethoxy)methyl]phosphonate (PME reagent) and (*S*)-tritylglycidol, in DMF and with sodium hydride or cesium carbonate as a base[7b]. In all cases the corresponding *N*^{9}-alkyl derivatives **3b**, **3d** and **7a** were obtained, accompanied by N^7,N^9-disubstituted derivatives **6b**, **6d** and **8a**. The PME derivative **3b** is identical with the authentic compound prepared by base modification of the corresponding acyclic nucleoside analog (Scheme 1). Monoalkyl derivative **7a** and dialkyl derivative **8a** were obtained in 33 and 22% yields, respectively, when 1.2 equivalent of the (*S*)-tritylglycidol was used, and in 15 and 52% yields, respectively, when 2.4 equivalents of the same reagent was used for alkylation. No formation of N^7-monosubstituted product was detected in any of these alkylations.

On acid treatment, the dialkyl derivative **8a** underwent detritylation to give compound **8b** (Scheme 3). *N*^{6}-[(Dimethylamino)methylidene] derivative of compound **8a** was prepared by the reaction with dimethylformamide dimethylacetal; it afforded, on treatment with diisopropyl [(tosyloxy)methyl]phosphonate[3d] and sodium hydride in THF, the bis(HPMP) derivative **10a**. Similarly, monoalkyl derivative **7b** and HPMP

derivative **3c** (identical with the authentic compound prepared by base modification, Scheme 1) were prepared from monosubstituted derivative **7a**.

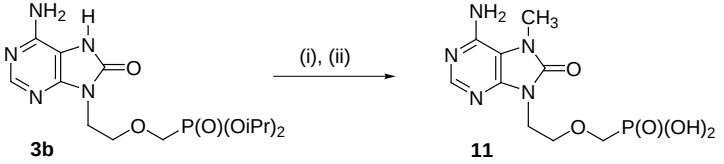
The alkylation of 6-amino-7*H*-purin-8(9*H*)-one (**3a**) with the used reagents gives a mixture of two products: N^9-monosubstituted derivatives and N^7,N^9-disubstituted derivatives bearing identical alkyl groups. The ratio of both products of the reaction depends on the excess of the alkylation reagent. The originally formed N^9-monosubstituted derivatives can be further substituted in the N^7 position to give N^7,N^9-disubstituted derivatives containing two different alkyl groups. Thus, compound **11** was prepared by



(ia) MeOTs, DMF, NaH; (ib) $ClCH_2CH_2OCH_2P(O)(OiPr)_2$, DMF, NaH; (ii) (*S*)-tritylglycidol, DMF, Cs_2CO_3; (iii) 80% AcOH, reflux, 1 h; (iv) $Me_2NCH(OMe)_2$, DMF; (v) $TsOCH_2P(O)(OiPr)_2$, THF, NaH; (vi) methanolic NH_3; (vii) 80% aq. AcOH; (viii) TMSBr, MeCN

SCHEME 3

methylation of compound **3b** with methyl tosylate and sodium hydride in DMF followed by standard transsilylation cleavage of the phosphonate diesters (Scheme 4).

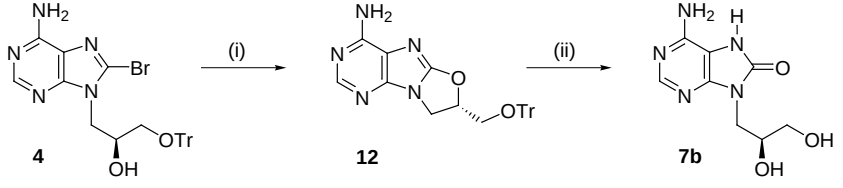


(i) MeOTs, DMF, NaH; (ii) TMSBr, MeCN

SCHEME 4

Generally, 8-hydroxypurine nucleosides are useful key intermediates of the purine cyclonucleoside synthesis[9]. On the other hand, purine cyclonucleosides and their acyclic analogs containing *O*-anhydro linkages are formed as intermediates in various transformations leading to the 8-hydroxy (8-oxo) purine derivatives[10].

In the previous study[6], we have reported on the preparation of some anhydro derivatives of acyclic nucleoside analogs either by oxidative cyclization of 9-(ω-hydroxyalkyl)adenine derivatives with lead(IV) acetate or by reaction of the corresponding 8-bromo derivatives with aqueous ammonia, sodium hydride, potassium *tert*-butoxide or 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU). As a simple model of such a cyclic intermediate we have prepared compound **12** by the intramolecular cyclization of bromo derivative **4** with sodium hydride in THF (Scheme 5). Acid treatment of cyclic derivative **12** (Dowex 50) gave compound **7b** in 66% yield, identical with the compound prepared by alkylation of 8-hydroxyadenine with (*S*)-tritylglycidol and subsequent detritylation (Scheme 3).

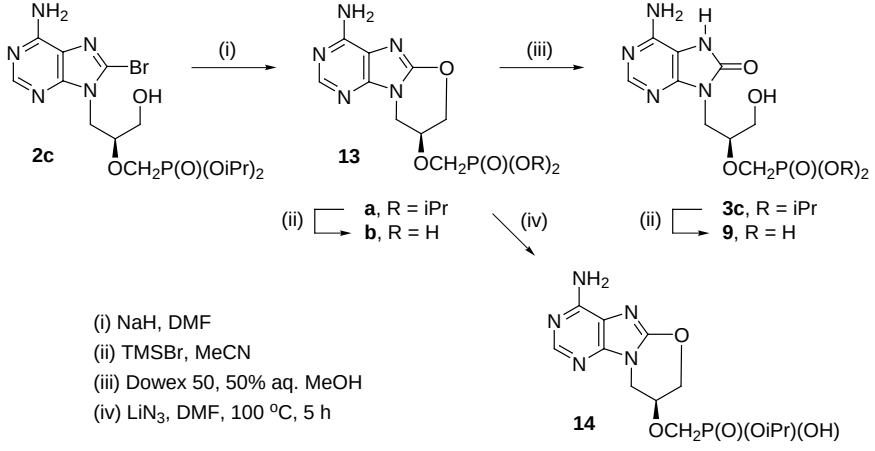


(i) THF, NaH; (ii) Dowex 50 (H^+), 50% aq. MeOH

SCHEME 5

Similarly, 8-bromo derivative **2c** gave on treatment with 2 equivalents of sodium hydride in DMF anhydro derivative **13a** in 50% yield (Scheme 6).

Acid treatment of compound **13a** afforded compound **3c** (identical with the authentic compounds prepared by the base modification in position 8 (Scheme 1) and by another independent synthesis (Scheme 3)). Also in this case, a partial cleavage of compound **3c** to the monoester was observed. Partial cleavage of diesters **13a** using lithium azide[11] gave monoester **14** in 73% yield.



SCHEME 6

Standard treatment with bromotrimethylsilane (TMSBr) in acetonitrile followed by hydrolysis was used for the ultimate cleavage of phosphonate diesters[3g]. Deionisation on Dowex 50 (H^+) followed by Dowex 1 (AcO^-) ion-exchange chromatography was used for isolation of the free phosphonates.

All new compounds were fully characterized by ^{1}H NMR (and ^{13}C NMR), MS and HR-MS or microanalysis. The structures of the compounds prepared by alkylation of starting compound **3a** were determined on the basis of proton-coupled ^{13}C NMR spectra. An example is given for a pair of N^9-[2-(phosphonomethoxy)ethyl] derivative **3b** and its N^7,N^9-bis[2-(phosphonomethoxy)ethyl] analog **6b**. The assignment of the carbon NMR signals of C-2 (^1J(C-2,H-2) = 200.2), C-6 (^3J(C-6,H-2) = 11.7) and C-5 (splitting by NH_2 protons to triplet, J = 4.9, the splitting disappears after D_2O addition) was confirmed for compound **3b** prepared by two independent procedures. The signal δ 147.81 of C-4 (^3J(C-4,H-2) = 12.7) was splitted to triplet of doublet by H-1′ protons. Similarly, the signal δ 152.17 of C-8 was splitted by H-1′ protons to triplet (J = 3.9). The N^7,N^9-disubstitution of compound **6b** was confirmed by the presence of other two coupling constants of C-5

(^3J(C-5,H-1″) = 3.9) and by splitting of the signal δ 152.47 of C-8 to quintet by H-1′ and H-1″ protons. Similar results were obtained for the other pairs of N^9-mono- and N^7,N^9-disubstituted analogs.

Similarly, the structure of N^3-substituted 8-bromoadenine derivative **5b** was determined by the presence of characteristic alkylation effects (upfield shift (–7 ppm) at C-2 and downfield shift (12 ppm) at C-8) and by the signal multiplicity in proton-coupled ^{13}C NMR spectrum: doublet δ 154.09 was assigned to C-6 (^3J(C-6,H-2) = 11.7), doublet of triplets δ 150.46 to C-4 (^3J(C-4,H-2) = 5.9, ^3J(C-4,H-1′) = 3.5), doublet of triplets δ 145.40 to C-2 (^1J(C-2,H-2) = 209.0, ^3J(C-2,H-1) = 5.9), singlet δ 139.42 to C-8 and singlet δ 121.67 to C-5.

The character of the purine bases and their substitution is unambiguously reflected in their UV spectra. They are additional evidence of the mono- or disubstitution of 6-amino-7*H*-purin-8(9*H*)-one (**3a**) and of the character of substituent in position 8 of the purine moiety[12]. Thus, it is easily possible to distinguish between (average values of λ_{max} and ε_{max} are given, respectively): the *O*,8-anhydro derivatives of adenine **13b** and **14** (pH 2, 263 nm, 14 000; pH 12, 263 nm, 14 000)[12a], the N^9-monosubstituted derivatives of 6-amino-7*H*-purin-8(9*H*)-one **3d**, **3e**, **7b** and **9** (pH 2, 280 nm, 10 000; pH 12, 280 nm, 10 000)[12b,12c] and their N^7,N^9-disubstituted analogs **6d**, **6e**, **8b** and **10b** (pH 2, 286 nm, 10 000; pH 12, 273 nm, 11 000)[12d]. For characterization of 6-amino-7*H*-purin-8(9*H*)-one derivatives, we have used also IR spectra which support the occurrence of the –N^7H–CO– form on C-8 of N^9-monosubstituted compounds **3**, **7** and **9** rather than tautomeric 8-OH function (typical C=O absorption bands in the 1 720–1 700 cm^{-1}). Also paper electrophoresis was used for corroboration of the structure of the free phosphonates.

In conclusion, different independent methods for preparation of acyclic nucleoside and nucleotide derivatives derived from 6-amino-7*H*-purin-8(9*H*)-one (**3a**) were used. These are: (i) modification of 8-bromoadenine in position 8 of the base, (ii) alkylation of 6-amino-7*H*-purin-8(9*H*)-one with diverse alkylation agents and (iii) ring opening of some *O*,8-anhydro derivatives under acid conditions. The first method is the most direct and convenient one, and good yields of products can be reached out. The second one, the base alkylation, is suitable for the synthesis of otherwise alkylated derivatives; in this case of N^7,N^9-disubstituted derivatives (**6**, **8** and **10**). The third method, ring opening, is also convenient for synthesis of 8-oxoadenine derivatives, though it contains one more reaction step compared with direct modification of 8-bromoadenine derivatives with sodium acetate in acetic acid. Some N^9-substituted analogs (**3b**, **3c** and **7b**) were prepared by

different independent ways. Biological activities of the final compounds will be examined.

EXPERIMENTAL

Unless otherwise stated, solvents were evaporated at 40 °C/2 kPa and compounds were dried at 2 kPa over P_2O_5. Melting points were determined on a Kofler block and are uncorrected. Analytical TLC was performed on Silufol UV 254 plates (Kavalier Votice, Czech Republic) in the systems chloroform–methanol (9 : 1) (S1), chloroform–methanol (85 : 15) (S2), chloroform–methanol (8 : 2) (S3), water–ethanol–acetone–ethyl acetate (1 : 1 : 1 : 4) (S4). Preparative TLC was carried out on 40 × 17 × 0.4 cm loose-layer plates of silica gel containing UV indicator (made in the Service Laboratory of the Institute). Paper electrophoresis was performed on a Whatman No. 3 MM paper at 40 V/cm for 1 h in 0.05 M triethylammonium hydrogencarbonate (TEAB) at pH 7.5; the electrophoretical mobilities are referenced to uridine 3′-phosphate. NMR spectra (δ, ppm; *J*, Hz) were measured on a Varian Unity 500 spectrometer (500 MHz for ^{1}H and 125.7 MHz for ^{13}C NMR) in hexadeuteriodimethyl sulfoxide (DMSO-d_6) referenced to the solvent signals (2.5 ppm for ^{1}H and 39.7 ppm for ^{13}C NMR), or in deuterium oxide containing sodium deuteroxide with sodium 3-(trimethylsilyl)propane-1-sulfonate as an internal standard for ^{1}H and dioxane as an external standard for ^{13}C NMR (δ(dioxane) 66.86 ppm). Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol matrix) or EI (electron energy 70 eV) techniques. UV absorption spectra were measured on a Beckman DU-65 spectrometr (λ, nm), CD spectra on a Jobin Yvon Mark V instrument and IR absorption spectra on an IFS 88 spectrometer ($CHCl_3$ or KBr method).

Starting Materials and Reagents

Bromo(trimethyl)silane and cesium carbonate were purchased from Fluka (Switzerland). Dimethylformamide was distilled from P_2O_5 and stored over molecular sieves (4Å). Acetonitrile was refluxed with CaH_2 and distilled over molecular sieves (4Å). Tetrahydrofuran was distilled before use from sodium metal.

Bromination of Purine Derivatives[6]. General Procedure

Bromine (0.5 ml, 19.4 mmol) was added to a suspension of compound **1b** or **1c** (7 mmol) in a mixture of dioxane (130 ml) and 10% aqueous solution of sodium hydrogenphosphate (90 ml) and the mixture was stirred at room temperature for 24 h. A concentrated solution of sodium hydrogensulfite was added until the mixture became colourless and the product was taken up in chloroform (6 × 30 ml). The chloroform extract was dried over anhydrous magnesium sulfate, filtered, the solvent was evaporated and the product was crystallized.

8-Bromo-9-{2-[(diisopropoxyphosphoryl)methoxy]ethyl}adenine (**2b**). White crystals, m.p. 132 °C (ethanol); yield 75%, R_F = 0.29 (S1). FAB MS, *m/z* (rel.%): 436/438 (100). ^{1}H NMR (500 MHz, DMSO-d_6): 1.08 (d, 6 H, $J(CH_3,CH)$ = 6.1, CH_3); 1.13 (d, 6 H, $J(CH_3,CH)$ = 6.1, CH_3); 3.75 (d, 2 H, $J(P,CH)$ = 8.3, PCH_2); 3.91 (t, 2 H, $J(2',1')$ = 5.3, H-2′); 4.31 (t, 2 H, $J(1',2')$ = 5.3, H-1′); 4.43 (m, 2 H, POCH); 7.38 (brs, 2 H, NH_2); 8.12 (s, 1 H, H-2). For $C_{14}H_{23}BrN_5O_4P$ (436.3) calculated: 38.55% C, 5.31% H, 18.32% Br, 16.05% N, 7.10% P; found: 38.42% C, 5.15% H, 18.53% Br, 15.76% N, 6.98% P.

(S)-8-Bromo-9-{2-[(diisopropoxyphosphoryl)methoxy]-3-hydroxypropyl}adenine (**2c**). White crystals, m.p. 139 °C (ethyl acetate); yield 64%, R_F = 0.32 (S1). FAB MS, *m/z* (rel.%): 466/468 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 1.01 (d, 3 H, J(CH_3,CH) = 6.1, CH_3); 1.06 (d, 3 H, J(CH_3,CH) = 6.1, CH_3); 1.11 (d, 3 H, J(CH_3,CH) = 6.1, CH_3); 1.16 (d, 3 H, J(CH_3,CH) = 6.1, CH_3); 3.55 (ddd, 1 H, J(3′b,2′) = 4.4, J(3′b,OH) = 5.8, J(gem) = 12.0, H-3′b); 3.59 (dd, 1 H, J(P,CHb) = 9.3, J(gem) = 13.9, PCHb); 3.61 (dt, 1 H, J(3′a,2′) = J(3′a,OH) = 5.0, J(gem) = 12.0, H-3′a); 3.82 (dd, 1 H, J(P,CHa) = 8.3, J(gem) = 13.9, PCHa); 3.99 (m, 1 H, H-2′); 4.21 (dd, 1 H, J(1′b,2′) = 4.2, J(gem) = 14.6, H-1′b); 4.27 (dd, 1 H, J(1′a,2′) = 8.5, J(gem) = 14.6, H-1′a); 4.34 (d sept, 1 H, J(CH,CH_3) = 6.1, J(P,OCH) = 7.6, POCH); 4.44 (d sept, 1 H, J(CH,CH_3) = 6.1, J(P,OCH) = 7.6, POCH); 4.97 (t, 1 H, J(OH,CH_2) = 5.6, OH); 7.40 (brs, 2 H, NH_2); 8.12 (s, 1 H, H-2). For $C_{15}H_{25}BrN_5O_5P$ (466.3) calculated: 38.64% C, 5.40% H, 17.14% Br, 15.02% N, 6.64% P; found: 38.64% C, 5.37% H, 17.35% Br, 14.91% N, 6.69% P.

8-Bromoadenine[5]

Bromine (30 ml) was added to adenine (**1a**; 10 g, 74 mmol) in a 250 ml flask, the flask was stoppered and set aside for 5 h. The excess of bromine was removed, the residue was suspended in water, alkalized with aqueous ammonia and finally neutralized with acetic acid. The precipitated solid was filtered off and washed with water. The crude solid was filtered off from a hot suspension in water and washed successively with water, acetone and ether to give 9.5 g (60%) of product **2a**. Yellowish powder, m.p. >250 °C; R_F = 0.30 (S2). FAB MS, *m/z* (rel.%): 213/215 (30) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 7.44 (brs, 2 H, NH_2); 8.10 (s, 1 H, H-2); 13.70 (br, 1 H, NH).

Alkylation of 8-Bromoadenine (**2a**)

A mixture of 8-bromoadenine (**2a**; 1 g, 4.7 mmol), DMF (30 ml), (*S*)-tritylglycidol (4.7 mmol), and cesium carbonate (0.25 mmol) was stirred at 120 °C for 12 h. The mixture was taken down *in vacuo*, codistilled with toluene (2 × 20 ml), the residue was taken up in chloroform (150 ml) and extracted with water (3 × 50 ml). The organic layer was dried with anhydrous magnesium sulfate, filtered, and taken down *in vacuo*. The residue afforded, by column chromatography on silica gel (chloroform–methanol) followed by crystallization, compounds **4** (1.2 g, 48%) and **5a** (0.5 g, 20%).

(S)-8-Bromo-9-[(2-hydroxy-3-(trityloxy)propyl]adenine (**4**): White crystals, m.p. 176 °C (ethyl acetate); R_F = 0.44 (S2). FAB MS, *m/z* (rel.%): 530/532 (15) [M + H], 243 (100) [trityl]. ^{1}H NMR (500 MHz, DMSO-d_6): 2.94 (dd, 1 H, J(3′b,2′) = 5.3, J(gem) = 9.5, H-3′b); 3.18 (dd, 1 H, J(3′a,2′) = 5.0, J(gem) = 9.5, H-3′a); 4.08 (dd, 1 H, J(1′b,2′) = 9.4, J(gem) = 15.1, H-1′b); 4.18 (m, 1 H, H-2′); 4.20 (dd, 1 H, J(1′a,2′) = 4.5, J(gem) = 15.1, H-1′a); 5.33 (d, 1 H, J(OH,2′) = 5.5, OH); 7.29 (brs, 2 H, NH_2); 7.24 (m, 3 H, arom.); 7.30–7.40 (m, 12 H, arom.); 8.10 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 48.33 (C-1′); 66.75 (C-3′); 68.02 (C-2′); 86.62 (C-Ph); 119.48 (C-5); 127.63 (C-8); 127.49 (3 C, arom.); 128.34 (6 C, arom.); 128.76 (6 C, arom.); 144.18 (3 C, arom.); 151.50 (C-4); 152.97 (C-2); 155.05 (C-6). For $C_{27}H_{24}BrN_5O_2$ (530.4) calculated: 61.14% C, 4.56% H, 15.06% Br, 13.20% N; found: 61.22% C, 4.65% H, 14.98% Br, 13.20% N.

(S)-8-Bromo-3-[(2-hydroxy-3-(trityloxy)propyl]adenine (**5a**). White crystals, m.p. 131 °C (ethyl acetate); R_F = 0.41 (S2). FAB MS spectrum and elemental analysis are identical with those of compound **4**. ^{1}H NMR (500 MHz, DMSO-d_6): 2.98 (dd, 1 H, J(3′b,2′) = 4.0, J(gem) = 10.5, H-3′b); 3.03 (dd, 1 H, J(3′a,2′) = 4.0, J(gem) = 10.5, H-3′a); 4.16 (m, 2 H) and 4.50 (m, 1 H,

H-1′a + H-1′b + H-2′); 5.45 (br, 1 H, OH); 7.26 (brt, 3 H, arom.); 7.34 (brt, 6 H, arom.); 7.41 (brd, 6 H, arom.); 7.40 (br, 1 H, NH_2) and 8.20 (br, 1 H, NH_2); 8.29 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 53.08 (C-1′); 66.01 (C-3′); 66.99 (C-2′); 86.21 (C-Ph); 120.33 (C-5); 127.25 (3 C, arom.); 128.12 and 128.48 (12 C, arom.); 137.50 (C-8); 143.83 (3 C, arom.); 145.48 (C-2); 149.61 (C-4); 153.68 (C-6).

(*S*)-8-Bromo-3-(2,3-dihydroxypropyl)adenine (**5b**)

Mixture of the trityl derivative **5a** (1.5 g, 2.8 mmol) in aqueous acetic acid (80%, 30 ml) was refluxed for 1 h, the solvent was evaporated *in vacuo*, the residue was codistilled with water (2 × 20 ml), dissolved in water (100 ml) and extracted with ether (3 × 50 ml). The aqueous phase was evaporated *in vacuo*, the residue was dissolved in methanolic ammonia (60 ml) and the mixture was heated to 50 °C for 1 h. It was then neutralized with hydrochloric acid, taken down and the residue was crystallized from water to give 0.42 g (52%) of compound **5b**. White crystals, m.p. 243–245 °C (water); R_F = 0.26 (S2). FAB MS, *m/z* (rel.%): 287/289 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 3.35 (ddd, 1 H, *J*(3′b,2′) = 6.0, *J*(3′b,OH) = 5.0, *J*(gem) = 11.2, H-3′b); 3.46 (dt, 1 H, *J*(3′a,2′) = *J*(3′a,OH) = 5.0, *J*(gem) = 11.2, H-3′a); 3.95 (m, 1 H, H-2′); 4.02 (dd, 1 H, *J*(1′b,2′) = 9.0, *J*(gem) = 13.4, H-1′b); 4.45 (dd, 1 H, *J*(1′a,2′) = 3.0, *J*(gem) = 13.4, H-1′a); 4.90 (t, 1 H, *J*(OH,3′) = 5.0, OH); 5.15 (d, 1 H, *J*(OH,2′) = 5.0, OH); 7.98 (brs, 1 H, NH) and 8.13 (brs, 1 H, NH); 8.18 (s, 1 H, H-2). For $C_8H_{10}BrN_5O_2$ (288.1) calculated: 33.35% C, 3.50% H, 27.73% Br, 24.31% N; found: 33.24% C, 3.66% H, 27.56% Br, 24.08% N.

Reaction of 8-Bromopurine Derivatives **2** with Sodium Acetate in Acetic Acid. General Procedure

A mixture of the corresponding 8-bromo derivative **2** (5 mmol), acetic acid (30 ml) and sodium acetate (40 mmol) was refluxed for 8 h, evaporated *in vacuo* and codistilled with water (3 × 30 ml). The residue was stirred with sodium methoxide (20 ml, 0.25 mol) at 50 °C for 2 h, neutralized with HCl and evaporated *in vacuo*. The residue was deionized on a Dowex 50 X 8 (H^+) column (150 ml, elution with water followed by 2.5% aqueous ammonia), the UV-absorbing ammonia eluate was collected and evaporated *in vacuo* and the residue was crystallized from water–ethanol. In the case of compound **3a**, the crude residue after deacetylation was neutralized with HCl, concentrated *in vacuo* and the precipitated solid was filtered off and washed with water, acetone and ether.

6-Amino-7H-purin-8(9H)-one (**3a**). Yellowish powder, m.p. >350 °C; yield 94%, R_F = 0.17 (S2). EI MS, *m/z* (rel.%): 151 (100) [M]. ^{1}H NMR (500 MHz, DMSO-d_6): 6.33 (brs, 2 H, NH_2); 7.94 (s, 1 H, H-2); 9.90 (brs, 1 H, NH); 11.24 (brs, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 104.54 (C-5); 146.59 (C-6); 148.20 (C-4); 151.11 (C-2); 152.97 (C-8). IR (KBr): 3 440 (NH_2); 3 251, 3 092, 2 990 (NH_2, NH); 1 711 (CO); 1 665, 1 644 (NH_2); 1 614, 1 600 (ring). Exact mass (FAB HRMS) found: 152.0592; calculated for $C_5H_6N_5O$ [M + H]: 152.0572.

6-Amino-9-[2-(diisopropoxyphosphorylmethoxy)ethyl]-7H-purin-8(9H)-one (**3b**). White crystals, m.p. 159 °C (ethanol); yield 65%, R_F = 0.43 (S1). FAB MS, *m/z* (rel.%): 374 (100) [M + H]. ^{1}H NMR (200 MHz, DMSO-d_6): 1.10 (d, 6 H, *J*(CH_3,CH) = 6.1, CH_3); 1.14 (d, 6 H, *J*(CH_3,CH) = 6.1, CH_3); 3.73 (d, 2 H, *J*(P,CH) = 8.3, PCH_2); 3.80 (t, 2 H, *J*(2′,1′) = 4.9, H-2′); 3.90 (t, 2 H, *J*(1′,2′) = 4.9, H-1′); 4.46 (m, 2 H, POCH); 6.40 (brs, 2 H, NH_2); 7.99 (s, 1 H, H-2); 10.05 (br, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 23.70 (d, 2 C, *J*(P,C) = 4.9, CH_3); 23.89 (d, 2 C,

J(P,C) = 3.9, CH_3); 38.70 (C-1′); 64.56 (d, *J*(P,C) = 163.1, PC); 69.00 (d, *J*(P,C) = 11.7, C-2′); 70.31 (d, 2 C, *J*(P,C) = 6.8, POC); 103.40 (C-5); 146.73 (C-6); 147.81 (C-4); 151.06 (C-2); 152.17 (C-8). Proton-coupled ^{13}C NMR of the purine part (125 MHz, DMSO-d_6): 103.395 (t, ^3J(C-5,NH_2) = 4.9 (2 ×), singlet after D_2O addition, C-5); 146.73 (d, *J*(C-6,H-2) = 11.7, C-6); 147.81 (ddd, ^3J(C-4,H-2) = 13.7, ^3J(C-4,H-1′) = 2.9 and 4.9, C-4); 151.06 (d, *J*(C-2,H-2) = 200.2, C-2); 152.17 (t, ^3J(C-8,H-1′) = 3.9 (2 ×), C-8). IR ($CHCl_3$): 3 487 (NH_2); 3 340, 3 292, 3 245, 3 199 (NH_2, NH); 1 718 (CO); 1 654 (NH_2); 1 623, 1 595, 1 497 (ring); 1 233 (PO); 1 002 (POC). For $C_{14}H_{24}N_5O_5P$ (373.4) calculated: 45.04% C, 6.48% H, 18.76% N, 8.30% P; found: 45.05% C, 6.45% H, 18.95% N, 8.26% P.

6-Amino-9-[2-(diisopropoxyphosphorylmethoxy)-3-hydroxypropyl]-7H-purin-8(9H)-one (**3c**). R_F = 0.60 (S2). FAB MS, *m/z* (rel.%): 404 (100) [M + H]. Exact mass (FAB HRMS) found: 404.1706; calculated for $C_{15}H_{27}N_5O_6P$ [M + H]: 404.1699. By TLC and electrophoresis a mixture of diisopropyl phosphonate (R_F = 0.60 (S2), E_{Up} = 0.07) and monoisopropyl phosphonate (R_F = 0.00 (S2), E_{Up} = 0.43) was detected. The mixture was directly treated with TMSBr under standard conditions, see compound **9**.

Alkylation of 6-Amino-7*H*-purin-8(9*H*)-one (**3a**) with Methyl Tosylate. General Procedure

A mixture of compound **3a** (0.5 g, 3.3 mmol), and sodium hydride (0.2 g of 60% dispersion, 5 mmol) in DMF (30 ml) was stirred at 110 °C for 1 h. Methyl tosylate (0.6 ml, 4 mmol) was added and the mixture was stirred at this temperature for another 4 h. The solvent was evaporated and preparative chromatography on a silica gel plate in chloroform–methanol (S2) followed by crystallization from ethanol afforded 0.30 g (55%) of compounds **3d** and 0.2 g (34%) of compound **6d**.

6-Amino-9-methyl-7H-purin-8(9H)-one[12b,12c] (**3d**). Yellowish crystals, m.p. 340 °C (ethanol); R_F = 0.37 (S1). FAB MS, *m/z* (rel.%): 166 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 3.21 (s, 3 H, CH_3); 6.44 (brs, 2 H, NH_2); 8.02 (s, 1 H, H-2); 9.65 (br, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 25.65 (CH_3); 103.52 (C-5); 146.69 (C-6); 147.97 (C-4); 151.15 (C-2); 152.51 (C-8). IR (KBr): 3 406 (NH_2); 3 265, 3 135 (NH_2, NH); 1 718, 1 669 (CO); 1 648 (NH_2); 1 605, 1 596, 1 509 (ring); 2 958, 1 376 (CH_3). Exact mass (FAB HRMS) found: 166.0732; calculated for $C_6H_8N_5O$ [M + H]: 166.0728. UV, λ_{max} (ε_{max}): (pH 2) 278 (10 700); (pH 12) 272 (13 900).

6-Amino-7,9-dimethyl-7H-purin-8(9H)-one[12d] (**6d**). Yellowish crystals, m.p. 275 °C (ethanol); R_F = 0.31 (S1). FAB MS, *m/z* (rel.%): 180 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 3.22 (s, 3 H, CH_3); 3.47 (s, 3 H, CH_3); 6.55 (brs, 2 H, NH_2); 8.01 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 26.08 (CH_3); 28.82 (CH_3); 105.34 (C-5); 147.30 and 147.45 (C-4 and C-6); 150.90 (C-2); 152.84 (C-8). IR ($CHCl_3$): 3 520 (NH_2); 1 713, 1 721 (CO); 1 639 (NH_2); 1 599, 1 592, 1 512 (ring); 1 389 (CH_3). For $C_7H_9N_5O$ (179.2) calculated: 46.92% C, 5.06% H, 39.09% N; found: 46.90% C, 5.03% H, 38,84% N. UV, λ_{max} (ε_{max}): (pH 2) 286 (10 600); (pH 12) 272 (12 400).

Alkylation of **3a** with Diisopropyl [(2-Chloroethoxy)methyl]phosphonate. General Procedure

A mixture of compound **3a** (1 g, 6.6 mmol) and sodium hydride (0.4 g of 60% dispersion, 10 mmol) in DMF (35 ml) was stirred at 110 °C for 1 h. Diisopropyl [(2-chloroethoxy)-methyl]phosphonate (2.5 ml, 9.7 mmol) was added and the mixture was stirred for another

18 h. The same workup as in the previous section afforded 0.72 g (29%) of compound **3b** and 0.80 g (20%) of compound **6b**.

6-Amino-9-[2-(diisopropoxyphosphorylmethoxy)ethyl]-7H-purin-8(9H)-one (**3b**). White crystals, m.p. 166–167 °C (ethanol); R_F = 0.43 (S1). FAB MS, ^{1}H NMR and ^{13}C NMR spectra are identical with the authentic compound.

6-Amino-7,9-bis[2-(diisopropoxyphosphorylmethoxy)ethyl]-7H-purin-8(9H)-one (**6b**). Oil, R_F = 0.40 (S1). FAB MS, *m/z* (rel.%): 596 (100) [M + H]. ^{1}H NMR (200 MHz, DMSO-d_6): 1.10 (d, 6 H, J(CH$_3$,CH) = 6.1, CH$_3$); 1.11 (d, 6 H, J(CH$_3$,CH) = 6.1, CH$_3$); 1.14 (d, 6 H, J(CH$_3$,CH) = 6.1, CH$_3$); 1.15 (d, 6 H, J(CH$_3$,CH) = 6.1, CH$_3$); 3.71 (t, 2 H, J(CH$_2$,CH$_2$) = 5.0, CH$_2$); 3.73 (d, 4 H, J(P,CH) = 8.3, PCH$_2$); 3.79 (t, 2 H, J(CH$_2$,CH$_2$) = 5.0, CH$_2$); 3.94 (t, 2 H, J(CH$_2$,CH$_2$) = 5.0, CH$_2$); 4.12 (t, 2 H, J(CH$_2$,CH$_2$) = 5.0, CH$_2$); 4.47 (m, 4 H, POCH); 6.46 (brs, 2 H, NH$_2$); 8.01 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 23.70 (d, 2 C, J(P,C) = 2.9, CH$_3$); 23.87 (d, 2 C, J(P,C) = 2.9, CH$_3$); 23.89 (d, 4 C, J(P,C) = 2.9, CH$_3$); 39.09 (C-1′); 41.20 (C-1″); 64.59 (d, J(P,C) = 164.1, PC); 64.93 (d, J(P,C) = 163.1, PC); 68.95 (d, J(P,C) = 11.7, C-2′); 70.30 (d, J(P,C) = 6.8, POC); 70.32 (d, J(P,C) = 6.8, POC); 71.40 (d, J(P,C) = 10.7, C-2″); 105.00 (C-5); 147.33 (C-6); 147.52 (C-4); 150.84 (C-2); 152.47 (C-8). Proton-coupled ^{13}C NMR of the purine part (125 MHz, DMSO-d_6): 105.00 (dd, ^3J(C-5,H-1″) = 3.9 and 4.9, C-5); 147.33 (d, ^3J(C-6,H-2) = 10.7, C-6); 147.52 (ddd, ^3J(C-4,H-2) = 11.7, ^3J(C-4,H-1′) = 3.9 and 4.9, C-4); 150.84 (d, J(C-2,H-2) = 201.2, C-2); 152.47 (pent, ^3J(C-8,H-1′) = ^3J(C-8,H-1″) = 3.9 (2 ×), C-8). IR ($CHCl_3$): 3 461, 3 352 (NH$_2$); 1 714 (CO); 1 639 (NH$_2$); 1 603, 1 590, 1 497 (ring); 1 244 (PO). Exact mass (FAB HRMS) found: 596.2515; calculated for $C_{23}H_{44}N_5O_9P_2$ [M + H]: 596.2614.

Alkylation of **3a** with (*S*)-Tritylglycidol. General Procedure

A mixture of compound **3a** (1.5 g, 9.9 mmol), (*S*)-tritylglycidol (4 g, 12.6 mmol) and cesium carbonate (0.26 g, 0.8 mmol) in dimethylformamide (60 ml) was stirred at 110 °C for 25 h. The hot suspension was filtered over Celite and evaporated. The same workup as in the previous section afforded 1.5 g (33%) of compound **7a** and 1.7 g (22%) of compound **8a**. In an experiment with double quantity of (*S*)-tritylglycidol (8 g, 25.2 mmol) and cesium carbonate (0.52 g, 1.6 mmol) 0.7 g (15%) of compound **7a** and 4.0 g (52%) of compound **8a** were isolated.

(S)-6-Amino-9-[2-hydroxy-3-(trityloxy)propyl]-7H-purin-8(9H)-one (**7a**). Yellowish crystals, m.p. 134–135 °C; R_F = 0.47 (S2). FAB MS, *m/z* (rel.%): 468 (10) [M + H]; 243 (100) [trityl]. ^{1}H NMR (500 MHz, DMSO-d_6): 2.89 (dd, 1 H, J(3′b,2′) = 5.1, J(gem) = 9.8, H-3′b); 3.02 (dd, 1 H, J(3′a,2′) = 5.6, J(gem) = 9.8, H-3′a); 3.75 (d, 2 H, J(1′,2′) = 6.6, H-1′); 4.16 (m, 1 H, H-2′); 5.26 (br, 1 H, OH); 6.41 (brs, 2 H, NH$_2$); 7.22 (t, 3 H, arom.) and 7.29 (t, 6 H, arom.) and 7.34 (d, 6 H, arom.); 7.99 (s, 1 H, H-2); 10.14 (brs, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 43.53 (C-1′); 66.64 (C-3′); 67.12 (C-2′); 86.10 (C-Ph); 103.44 (C-5); 127.06 (3 C, arom.); 127.91 (6 C, arom.); 128.38 (6 C, arom.); 143.91 (3 C, arom.); 146.65 (C-6); 147.86 (C-4); 150.88 (C-2); 152.33 (C-8). IR (KBr): 3 470, 3 370, 3 332, 3 295, 3 205 (OH, NH$_2$, NH); 1 712, 1 698 (CO); 1 651 (NH$_2$); 1 628, 1 595, 1 505 (ring). For $C_{27}H_{25}N_5O_3$ (467.52) calculated: 69.36% C, 5.39% H, 14.98% N; found: 69.20% C, 5.51% H, 14.56% N.

6-Amino-7,9-bis[(2S)-2-hydroxy-3-(trityloxy)propyl]-7H-purin-8(9H)-one (**8a**). Yellowish crystals, m.p. 99–101 °C; R_F = 0.87 (S2). FAB MS, *m/z* (rel.%): 784 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 2.88 (dd, 1 H, J(3′b,2′) = 5.4, J(gem) = 9.5, H-3′b); 2.98 (dd, 1 H, J(3″b,2″) = 5.6, J(gem) = 9.5, H-3″b); 3.03 (dd, 1 H, J(3′a,2′) = 5.4, J(gem) = 9.5, H-3′a); 3.05 (dd, 1 H, J(3″a,2″) =

5.1, *J*(gem) = 9.5, H-3″a); 3.73 (dd, 1 H, *J*(1″b,2″) = 8.8, *J*(gem) = 14.9, H-1″b); 3.77 (d, 2 H, *J*(1′,2′) = 6.6, H-1′); 3.88 (m, 1 H, H-2″); 4.01 (brdd, 1 H, *J*(1″a,2″) = 2.0, *J*(gem) = 14.9, H-1″a); 4.15 (m, 1 H, H-2′); 5.22 (d, 1 H, *J*(OH,2′) = 5.9, OH); 5.86 (d, 1 H, *J*(OH,2″) = 4.4, OH); 6.58 (brs, 2 H, NH_2); 7.20–7.36 (m, 24 H, arom.) and 7.41 (m, 6 H, arom.); 8.01 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 43.95 (C-1′); 45.81 (C-1″); 65.87 (C-3″); 66.70 (C-3′); 67.09 (C-2′); 68.84 (C-2″); 86.12 (2 C, C-Ph); 105.98 (C-5); 127.05 (3 C, arom.); 127.17 (3 C, arom.); 127.92 (6 C, arom.); 128.04 (6 C, arom.); 128.38 (6 C, arom.); 128.42 (6 C, arom.); 143.87 (3 C, arom.); 143.89 (3 C, arom.); 147.40 and 147.73 (C-4 and C-6); 150.57 (C-2); 152.77 (C-8). Exact mass (FAB HRMS) found: 784.3513; calculated for $C_{49}H_{46}N_5O_5$ [M + H]: 784.3499.

Preparation of Diisopropyl Phosphonates from Compounds **8a** and **7a**. General Procedure

A mixture of compound **8a** (1.2 mmol), DMF (20 ml) and dimethylformamide dimethylacetal (5 ml) was stirred in a stoppered flask overnight at room temperature. After evaporation *in vacuo*, the residue was codistilled with DMF (10 ml), dissolved in THF (20 ml) and trace of water and excess of solid carbon dioxide were gradually added. After 1 h, the solution was taken down, the residue was codistilled with ethanol (3 × 20 ml) and dried over phosphorus pentoxide. The residue, without further purification, was dissolved in THF (20 ml), the solution was cooled to 0 °C, sodium hydride (2.4 mmol) was added, followed after 0.5 h with diisopropyl [(tosyloxy)methyl]phosphonate[3d] (2.2 mmol). The mixture was stirred at 0 °C for 2 h and at room temperature for 2 days. The mixture was evaporated, the residue was heated in methanolic ammonia (40 ml) in an autoclave at 80 °C for 5 h, evaporated and the residue was refluxed with aqueous acetic acid (80%, 40 ml) for 0.5 h. The mixture was evaporated, codistilled with water (2 × 30 ml) and ethanol (2 × 30 ml). Column chromatography of the residue on silica gel afforded 0.42 g (54%) of oily product **10a**. The same workup with compound **7a** (2 equivalents, 1.1 g, 2.4 mmol), followed by crystallization from ethanol, gave 0.5 g (52%) of compound **3c**.

6-Amino-7,9-bis{(2S)-3-hydroxy-2-[(diisopropoxyphosphoryl)methoxy]propyl}-7H-purin-8(9H)-one (**10a**). Oil, R_F = 0.56 (S2). FAB MS, *m/z* (rel.%): 656 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 1.09 (d, 3 H, *J*(CH_3,CH) = 6.1, CH_3); 1.12 (d, 3 H, *J*(CH_3,CH) = 6.1, CH_3); 1.13 (d, 3 H, *J*(CH_3,CH) = 6.1, CH_3); 1.15 (d, 9 H, *J*(CH_3,CH) = 6.1, CH_3); 1.17 (d, 3 H, *J*(CH_3,CH) = 6.1, CH_3); 1.18 (d, 3 H, *J*(CH_3,CH) = 6.1, CH_3); 3.45–4.03 (m, 14 H, OCH, NCH_2, OCH_2 and PCH_2); 4.48 (m, 4 H, POCH); 4.81 (t, 1 H, *J*(OH,CH_2) = 5.6, OH); 5.04 (t, 1 H, *J*(OH, CH_2) = 5.2, OH); 6.43 (brs, 2 H, NH_2); 8.03 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 23.59 (d, 2 C, *J*(P,C) = 3.9, CH_3); 23.65 (d, 2 C, *J*(P,C) = 3.9, CH_3); 23.75 (d, 2 C, *J*(P,C) = 3.9, CH_3); 23.80 (d, 2 C, *J*(P,C) = 3.9, CH_3); 40.61 (C-1′); 43.08 (C-1″); 59.73 (C-3′); 60.96 (C-3″); 63.59 (d, *J*(P,C) = 165.0, PC); 63.72 (d, *J*(P,C) = 164.1, PC); 70.20 (d, *J*(P,C) = 5.9, POC); 70.27 (d, *J*(P,C) = 5.9, POC); 70.33 (d, *J*(P,C) = 5.9, POC); 70.35 (d, *J*(P,C) = 5.9, POC); 79.25 (d, *J*(P,C) = 11.7, C-2′); 80.59 (d, *J*(P,C) = 9.8, C-2″); 105.61 (C-5); 147.53 and 147.57 (C-4 and C-6); 150.64 (C-2); 152.84 (C-8). Exact mass (FAB HRMS) found: 656.2819; calculated for $C_{25}H_{48}N_5O_{11}P_2$ [M + H]: 656.2827.

6-Amino-9-[2-(diisopropoxyphosphorylmethoxy)-3-hydroxypropyl]-7H-purin-8(9H)-one (**3c**). R_F = 0.60 (S2). FAB MS and exact mass (FAB HRMS) are identical with the authentic compound.

Deprotection of the Trityl Derivatives **8a** and **7a**. General Procedure

A trityl derivative (1 mmol) in aqueous acetic acid (80%, 20 ml) was refluxed for 1 h, poured into water (100 ml) and extracted with ether (3 × 50 ml). The aqueous phase was evaporated *in vacuo* and the residue was dissolved in aqueous ammonia (10%, 50 ml). After standing overnight at ambient temperature, the solution was evaporated *in vacuo* and the resulting solid was crystallized from water–ethanol mixture.

6-Amino-7,9-bis[(S)-2,3-dihydroxypropyl]-7H-purin-8(9H)-one (**8b**). White crystals, m.p. 125–127 °C; yield 48%, R_F = 0.14 (S3). FAB MS, *m/z* (rel.%): 300 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 3.33 (dt, 1 H, *J*(3′b,2′) = *J*(3′b,OH) = 5.6, *J*(gem) = 11.2, H-3′b); 3.37 (dt, 1 H, *J*(3′a,2′) = *J*(3′a,OH) = 5.6, *J*(gem) = 11.2, H-3′a); 3.41 (brt, 2 H, *J*(3″,2″) = *J*(3″,OH) = 5.4, H-3″); 3.71 (m, 1 H, H-2″); 3.77 (dd, 1 H, *J*(1″b,2″) = 8.3, *J*(gem) = 14.4, H-1″b); 3.78 (d, 2 H, *J*(1′,2′) = 6.3, H-1′); 3.91 (br sext, 1 H, *J* = 5.9, H-2′); 4.03 (dd, 1 H, *J*(1″a,2″) = 2.9, *J*(gem) = 14.4, H-1″a); 4.66 (t, 1 H, *J*(OH,3′) = 5.8, OH); 4.86 (t, 1 H, *J*(OH,3″) = 5.8, OH); 4.88 (d, 1 H, *J*(OH,2′) = 5.4, OH); 5.64 (d, 1 H, *J*(OH,2″) = 4.4, OH); 6.62 (brs, 2 H, NH_2); 8.03 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 43.95 (C-1′); 45.22 (C-1″); 63.41 (C-3′); 64.10 (C-3″); 68.92 (C-2′); 70.33 (C-2″); 106.07 (C-5); 147.85 and 147.59 (C-4 and C-6); 150.54 (C-2); 153.21 (C-8). IR (KBr): 3 415, 3 325, 3 162 (OH, NH_2); 1 700, 1 688 (CO); 1 662 (NH_2); 1 615, 1 584, 1 504, 1 475, 1 443 (ring); 1 109, 1 097, 1 086, 1 050 (COH). For $C_{11}H_{17}N_5O_5$ (299.3) calculated: 44.15% C, 5.73% H, 23.40% N; found: 43.96% C, 5.59% H, 23.17% N. UV, λ_{max} (ε_{max}): (pH 2) 284 (9 600); (pH 12) 273 (11 600). CD, λ (Δε) (0.01 M HCl): 294 (0.52), 225 (–1.08), 204 (1.37).

(S)-6-Amino-9-(2,3-dihydroxypropyl)-7H-purin-8(9H)-one (**7b**). Yellowish crystals, m.p. 230–232 °C; yield 54%, R_F = 0.22 (S2). FAB MS, *m/z* (rel.%): 226 (100) [M + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 3.33 (dt, 1 H, *J*(3′b,2′) = *J*(3′b,OH) = 5.7, *J*(gem) = 11.2, H-3′b); 3.37 (ddd, 1 H, *J*(3′a,2′) = 5.0, *J*(3′a,OH) = 6.0, *J*(gem) = 11.2, H-3′a); 3.73 (d, 2 H, *J*(1′,2′) = 6.4, H-1′); 3.91 (m, 1 H, H-2′); 4.70 (t, 1 H, *J*(OH,3′) = 5.9, OH); 4.92 (d, 1 H, *J*(OH,2′) = 5.4, OH); 6.41 (brs, 2 H, NH_2); 8.01 (s, 1 H, H-2); 10.16 (brs, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 43.31 (C-1′); 64.22 (C-3′); 69.11 (C-2′); 103.55 (C-5); 146.81 (C-6); 148.22 (C-4); 151.08 (C-2); 152.76 (C-8). Exact mass (FAB HRMS) found: 226.1013; calculated for $C_8H_{12}N_5O_3$ [M + H]: 226.0940. UV, λ_{max} (ε_{max}): (pH 2) 280 (10 400); (pH 12) 280 (10 400). CD, λ (Δε) (0.01 M HCl): 283 (–0.20), 255 (0.06), 220 (–1.74), 200 (–1.38).

Methylation of Compound **3b**

A mixture of compound **3b** (0.25 g, 0.7 mmol) and sodium hydride (32 mg of 60% dispersion, 0.8 mmol) in DMF (6 ml) was stirred at 110 °C for 1 h. Methyl tosylate (0.12 ml, 0.75 mmol) was added and the mixture was stirred for another 2 h. The solvent was evaporated and the residue (R_F = 0.45 (S1)) was dried and converted without any purification to the free phosphonate **11**. See under Deprotection of Phosphonates (*vide infra*). Total yield 95 mg (45%).

(*S*)-7-[(Trityloxy)methyl]-7,8-dihydro[1,3]oxazolo[3,2-*e*]purin-4-amine (**12**)

A mixture of compound **4** (1 g, 2 mmol), THF (20 ml) and sodium hydride (2.4 mmol) was stirred at room temperature. After 5 min, a white solid precipitated which was filtered off and thoroughly washed with hot DMF (3 × 20 ml), acetone (3 × 20 ml) and ether. White powder, m.p. >260 °C; yield 0.73 g (81%), R_F = 0.33 (S1). FAB MS, *m/z* (rel.%): 450 (95) [M + H];

243 (100) [trityl]. ^{1}H NMR (500 MHz, DMSO-d_6): 3.18 (dd, 1 H, J(3′b,2′) = 3.7, J(gem) = 11.0, H-3′b); 3.56 (dd, 1 H, J(3′a,2′) = 2.4, J(gem) = 11.0, H-3′a); 4.02 (dd, 1 H, J(1′b,2′) = 4.6, J(gem) = 9.7, H-1′b); 4.36 (dd, 1 H, J(1′a,2′) = 8.5, J(gem) = 9.7, H-1′a); 5.63 (m, 1 H, H-2′); 6.80 (brs, 2 H, NH_2); 7.24 (m, 15 H, arom.); 8.02 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 42.81 (C-1′); 64.69 (C-3′); 86.07 (3 C, CPh); 87.13 (C-2′); 120.29 (C-5); 127.42 (3 C, arom.); 128.17 (6 C, arom.); 128.28 (6 C, arom.); 143.36 (3 C, arom.); 147.28 (C-4); 150.74 (C-2); 154.13 (C-6); 160.65 (C-8). For $C_{27}H_{23}N_5O_2$ (449.5) calculated: 72.14% C, 5.16% H, 15.58% N; found: 71.88% C, 5.28% H, 15. 37% N.

Diisopropyl (*S*)-{[(4-Amino-8,9-dihydro-7*H*-[1,3]oxazino[3,2-*e*]purin-8-yl)oxy]methyl}-phosphonate (**13a**)

A mixture of compound **2c** (0.6 g, 1.3 mmol), DMF (20 ml) and sodium hydride (2.6 mmol) was stirred at room temperature overnight. The mixture was neutralized with acetic acid, taken down *in vacuo*, the residue was codistilled with toluene (2 × 10 ml) and purified on a silica gel plate (see above) in chloroform–methanol (4 : 1). The product was crystallized from ethyl acetate giving white crystals, m.p. 195–197 °C; yield 65%, R_F = 0.44 (S3). FAB MS, *m/z* (rel.%): 386 (40) [M + H]; 302 (100) [M + H – 2 iPr]. ^{1}H NMR (500 MHz, DMSO-d_6): 1.10 (d, 3 H, J(CH_3,CH) = 6.1, CH_3); 1.115 (d, 3 H, J(CH_3,CH) = 6.1, CH_3); 1.15 (d, 3 H, J(CH_3,CH) = 6.1, CH_3); 1.17 (d, 3 H, J(CH_3,CH) = 6.1, CH_3); 3.94 (dd, 1 H, J(P,CHb) = 9.3, J(gem) = 13.9, PCHb); 3.97 (dd, 1 H, J(P,CHa) = 8.8, J(gem) = 13.9, PCHa); 4.13 (dd, 1 H, J(3′b,2′) = 3.4, J(gem) = 13.2, H-3′b); 4.27 (dt, 1 H, J(3′a,2′) = J(3′a,P) = 2.2, J(gem) = 13.2, H-3′a); 4.31 (m, 1 H, H-2′); 4.515 (brd, 1 H, J(1′b,2′) = 1.0, J(gem) = 12.2, H-1′b); 4.52 (d sept, 2 H, J(CH,CH_3) = 6.1, J(P,OCH) = 7.8, POCH); 4.68 (dt, 1 H, J(1′a,2′) = J(1′a,P) = 2.7, J(gem) = 12.2, H-1′a); 6.81 (brs, 2 H, NH_2); 8.02 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 23.66 (d, J(P,C) = 4.9, CH_3); 23.67 (d, J(P,C) = 4.9, CH_3); 23.87 (d, J(P,C) = 3.9, CH_3); 23.89 (d, J(P,C) = 3.9, CH_3); 43.09 (C-1′); 62.81 (d, J(P,C) = 165.1, PC); 67.87 (C-3′); 68.71 (d, J(P,C) = 12.7, C-2′); 70.51 (d, J(P,C) = 5.9, POC); 70.53 (d, J(P,C) = 5.9, POC); 114.89 (C-5); 148.75 (C-4); 150.55 (C-2); 150.80 (C-8); 153.89 (C-6). For $C_{15}H_{24}N_5O_5P$ (385.4) calculated: 46.75% C, 6.28% H, 18.17% N, 8.04% P; found: 46.65% C, 6.17% H, 17.99% N, 8.35% P. UV, λ_{max} (ε_{max}) (MeOH): 262 (15 600). CD, λ ($\Delta\varepsilon$) (MeOH): 268 (0.67), 242 (0.40), 213 (–5.80), 202 (4.27).

Cleavage of *O*,8-Anhydropurine Derivatives. General Procedure

A mixture of an *O*,8-anhydropurine derivative (1 mmol), Dowex 50 X 8 (H^+) (5 ml), methanol (10 ml) and water (10 ml) was refluxed for 2 h, then filtered while hot and the resin was washed with a mixture of 35% aqueous ammonia and water (1 : 10). The filtrate was evaporated and the residue crystallized to afford a 6-amino-7*H*-purin-8(9*H*)-one derivative.

(S)-6-Amino-9-(2,3-dihydroxypropyl)-7H-purin-8(9H)-one (**7b**). Yellowish crystals, m.p. 223 °C (ethanol); yield 66%. R_F (S3), FAB MS, ^{1}H NMR, ^{13}C NMR, UV and CD spectra are identical with those of the authentic compound prepared by alkylation of compound **3a** followed by deprotection of trityl group.

6-Amino-9-[2-(diisopropoxyphosphorylmethoxy)-3-hydroxypropyl]-7H-purin-8(9H)-one (**3c**). R_F = 0.60 (S2). FAB MS and exact mass (FAB HRMS) are identical with the authentic compound. TLC and paper electrophoresis of the reaction mixture indicated the presence of diisopropyl phosphonate (R_F = 0.60 (S2), E_{Up} = 0.07) and monoisopropyl phosphonate (R_F = 0.00 (S2), E_{Up} = 0.43). The mixture was directly treated with TMSBr under standard conditions, see compound **9**.

Deprotection of Phosphonates with TMSBr[3g]. General Procedure

A mixture of the phosphonate diester (1 mmol), TMSBr (1 ml) and acetonitrile (5 ml) was stirred overnight at ambient temperature, then evaporated and codistilled with acetonitrile (10 ml). The residue was dissolved in water and alkalized with aqueous ammonia. The mixture was evaporated *in vacuo* and the residue was deionized on a Dowex 50 X 8 (H^+) column (50 ml) under standard conditions. The product was purified on a Dowex 1 X 2 (acetate) column by elution with linear gradient of acetic acid (0–0.5 M, 1 liter each). The UV-absorbing fractions were evaporated *in vacuo* and the residue was crystallized from water.

6-Amino-9-[2-(phosphonomethoxy)ethyl]-7H-purin-8(9H)-one (**3e**). White crystals, m.p. 210–213 °C; yield 54%, E_{Up} = 0.88. FAB MS, *m/z* (rel.%): 290 (100) [M + H]. ^{1}H NMR (500 MHz, D_2O + NaOD): 3.49 (d, 2 H, *J*(P,CH) = 8.3, PCH_2); 3.86 (t, 2 H, *J*(2′,1′) = 5.6, H-2′); 4.05 (t, 2 H, *J*(1′,2′) = 5.6, H-1′); 7.97 (s, 1 H, H-2). For $C_8H_{12}N_5O_5P$ (289.2) calculated: 33.23% C, 4.18% H, 24.22% N, 10.71% P; found: 32.90% C, 4.34% H, 23.94% N, 10.57% P. UV, λ_{max} (ε_{max}): (pH 2) 281 (8 800); (pH 12) 281 (11 200).

6-Amino-7,9-bis[2-(phosphonomethoxy)ethyl]-7H-purin-8(9H)-one (**6e**). Oil; yield 75%, E_{Up} = 0.92. FAB MS, *m/z* (rel.%): 428 (100) [M + H]. ^{1}H NMR (500 MHz, D_2O + NaOD): 3.68 (d, 2 H, *J*(P,CH) = 8.7, PCH_2); 3.71 (d, 2 H, *J*(P,CH) = 8.9, PCH_2); 3.90 (t, 2 H, *J*(2″,1″) = 4.5, H-2″); 3.94 (t, 2 H, *J*(2′,1′) = 5.1, H-2′); 4.22 (t, 2 H, *J*(1′,2′) = 5.1, H-1′); 4.28 (t, 2 H, *J*(1″,2″) = 4.5, H-1″); 8.36 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): 39.67 (C-1′); 41.92 (C-1″); 66.21 (d, *J*(P,C) = 160.2, PC); 66.67 (d, *J*(P,C) = 159.2, PC); 68.67 (d, *J*(P,C) = 10.7, C-2′); 70.94 (d, *J*(P,C) = 8.8, C-2″); 105.28 (C-5); 144.55 (C-6); 147.54 (C-4); 147.66 (C-2); 152.55 (C-8). Proton-coupled ^{13}C NMR of the purine part (125 MHz, DMSO-d_6 + D_2O): 105.28 (t, ^{3}*J*(C-5,H-1″) = 3.9 (2 ×), C-5); 144.55 (d, ^{3}*J*(C-6,H-2) = 9.8, C-6); 147.54 (dt, ^{3}*J*(C-4,H-2) = 11.7, ^{3}*J*(C-4,H-1) = 3.9 (2 ×), C-4); 147.66 (d, *J*(C-2,H-2) = 208.0, C-2); 152.55 (pent, ^{3}*J*(C-8,H-1′) = ^{3}*J*(C-8,H-1″) = 3.9 (2 ×), C-8). IR (KBr): 3 384, 3 351, 3 203 (NH_2); 2 768, 2 650, 2 305 (POH); 1 731 (CO); 1 681 (NH_2); 1 630, 1 598, 1 513 (ring); 1 189 (PO); 996, 935 (POH). Exact mass (FAB HRMS) found: 428.0720; calculated for $C_{11}H_{20}N_5O_9P_2$ [M + H]: 428.0736. UV, λ_{max} (ε_{max}): (pH 2) 286 (9 700); (pH 7) 273 nm (11 000); (pH 12) 273 (11 600).

6-Amino-9-[3-hydroxy-2-(phosphonomethoxy)propyl]-7H-purin-8(9H)-one (**9**). White crystals, m.p. 230 °C; yield 69%, E_{Up} = 0.80. FAB MS, *m/z* (rel.%): 320 (100) [M + H]. ^{1}H NMR (500 MHz, D_2O + NaOD): 3.60 (dd, 1 H, *J*(P,CHb) = 9.6, *J*(gem) = 12.7, PCHb); 3.605 (dd, 1 H, *J*(3′b,2′) = 5.6, *J*(gem) = 12.6, H-3′b); 3.66 (dd, 1 H, *J*(P,CHa) = 8.9, *J*(gem) = 12.7, PCHa); 3.79 (dd, 1 H, *J*(3′a,2′) = 3.3, *J*(gem) = 12.6, H-3′a); 3.86 (m, 1 H, H-2′); 3.93 (dd, 1 H, *J*(1′b,2′) = 5.6, *J*(gem) = 14.7, H-1′b); 4.05 (dd, 1 H, *J*(1′a,2′) = 6.6, *J*(gem) = 14.7, H-1′a); 8.04 (s, 1 H, H-2). ^{13}C NMR (125 MHz, D_2O): 39.88 (C-1′); 60.40 (C-3′); 66.74 (d, *J*(P,C) = 153.3, PC); 79.02 (d, *J*(P,C) = 10.7, C-2′); 103.53 (C-5); 146.61 and 146.64 (C-4 and C-6); 150.54 (C-2); 151.57 (C-8). IR (KBr): 3 424, 3 345 (NH_2); 3 280, 3 160, 3 102, 3 055 (OH, NH_2, NH); 2 747 (POH); 1 701 (CO); 1 650 (NH_2); 1 603, 1 574, 1 512 (ring); 1 168 (PO); 1 069 (OH); 1 032 (POH). For $C_9H_{14}N_5O_6P$ (319.2) calculated: 33.85% C, 4.42% H, 21.94% N, 9.71% P; found: 33.58% C, 4.55% H, 21.89% N, 9.35% P. UV, λ_{max} (ε_{max}): (pH 2) 279 (10 800); (pH 7) 271 (11 600); (pH 12) 279 (12 800). CD, λ ($\Delta\varepsilon$) (0.01 M HCl): 231 (0.08), 211 (–1.42), 198 (–1.82).

6-Amino-7,9-bis[(S)-3-hydroxy-2-(phosphonomethoxy)propyl]-7H-purin-8(9H)-one (**10b**). Oil; yield 71%, E_{Up} = 1.20. FAB MS, *m/z* (rel.%): 488 (100) [M + H]. ^{1}H NMR (500 MHz, D_2O): 3.57 (dd, 1 H, *J* = 9.0 and 12.9, PCH); 3.63 (dd, 1 H, *J* = 9.0 and 12.9, PCH); 3.63 (dd, 1 H, *J* =

5.1 and 12.7, OCH); 3.67 (dd, 1 H, *J* = 9.5 and 12.9, PCH); 3.72 (dd, 1 H, *J* = 3.4 and 12.4, OCH_2); 3.77 (dd, 1 H, *J* = 9.8 and 12.9, PCH_2); 3.82 (dd, 1 H, *J* = 3.4 and 12.4, OCH_2); 3.81 (m, 1 H, OCH); 3.89 (m, 1 H, OCH); 3.95 (dd, 1 H, *J* = 3.9 and 12.7, OCH); 4.01 (dd, 1 H, *J* = 5.4 and 14.7, NCH); 4.12 (dd, 1 H, *J* = 7.1 and 14.7, NCH); 4.13 (dd, 1 H, *J* = 8.3 and 15.6, NCH); 4.19 (dd, 1 H, *J* = 3.6 and 15.6, NCH); 8.10 (s, 1 H, H-2). ^{13}C NMR (125 MHz, D_2O): 40.42 (C-1′); 43.79 (C-1″); 59.33 and 60.43 (C-3′ and C-3″); 64.30 (d, 2 C, *J*(P,C) = 156.6, PC); 79.13 (d, *J*(P,C) = 10.9) and 79.92 (d, *J*(P,C) = 10.9) (C-2′ and C-2″); 106.27 (C-5); 146.50 (C-4); 147.79 (C-6); 150.41 (C-2); 153.59 (C-8). Proton-coupled ^{13}C NMR of the purine part (125 MHz, D_2O): 106.27 (t, ^3J(C-5,H-1″) = 3.9 (2 ×), C-5); 146.50 (dt, ^3J(C-4,H-2) = 10.5, ^3J(C-4,H-1′) = 3.9 (2 ×), C-4); 147.79 (d, ^3J(C-6,H-2) = 10.7, C-6); 150.41 (d, *J*(C-2,H-2) = 204.1, C-2); 153.59 (pent, ^3J(C-8,H-1′) = ^3J(C-8,H-1″) = 3.9 (2 ×), C-8). Exact mass (FAB HRMS) found: 488.0845; calculated for $C_{13}H_{24}N_5O_{11}P_2$ [M + H]: 488.0947. UV, λ_{max} (ε_{max}): (pH 2) 285 (7 700); (pH 7) 272 (8 900); (pH 12) 272 (9 200). CD, λ (Δε) (H_2O): 260 (0.39), 231 (0.18), 221 (0.40), 208 (–5.3).

6-Amino-7-methyl-9-[2-(phosphonomethoxy)ethyl]-7H-purin-8(9H)-one (**11**). White crystals, m.p. 213–215 °C (H_2O); yield 45%, E_{Up} = 0.87. FAB MS, *m/z* (rel.%): 304 (100) [M + H]. ^{1}H NMR (500 MHz, D_2O + NaOD): 3.44 (d, 2 H, *J*(P,CH) = 8.3, PCH_2); 3.54 (s, 3 H, NCH_3); 3.83 (t, 2 H, *J*(2′,1′) = 5.4, H-2′); 4.06 (t, 2 H, *J*(1′,2′) = 5.4, H-1′); 8.00 (s, 1 H, H-2). ^{13}C NMR (125 MHz, D_2O + NaOD): 28.48 (CH_3); 39.98 (C-1′); 68.70 (d, *J*(P,C) = 149.7, PC); 68.90 (d, *J*(P,C) = 9.2, C-2′); 105.68 (C-5); 146.20 (C-6); 147.72 (C-4); 150.48 (C-2); 153.52 (C-8). Exact mass (FAB HRMS) found: 304.0846; calculated for $C_9H_{15}N_5O_5P$ [M + H]: 304.0811. UV, λ_{max} (ε_{max}): (pH 2) 280 (9 300); (pH 12) 273 (11 200).

(S)-{[(4-Amino-8,9-dihydro-7H-[1,3]oxazino[3,2-e]purin-8-yl)oxy]methyl}phosphonic acid (**13b**). White crystals, m.p. >360 °C (H_2O); yield 52%, E_{Up} = 0.84. FAB MS, *m/z* (rel.%): 302 (100) [M + H]. ^{1}H NMR (500 MHz, D_2O + NaOD): 3.62 (dd, 1 H, *J*(P,CHb) = 8.8, *J*(gem) = 12.6, PCHb); 3.66 (dd, 1 H, *J*(P,CHa) = 8.6, *J*(gem) = 12.6, PCHa); 4.18 (dd, 1 H, *J*(1′b,2′) = 3.7, *J*(gem) = 13.2, H-1′b); 4.43 (dt, 1 H, *J*(1′a,2′) = *J*(1′a,P) = 2.0, *J*(gem) = 13.2, H-1′a); 4.49 (m, 1 H, H-2′); 4.60 (dd, 1 H, *J*(3′b,2′) = 1.0, *J*(gem) = 12.0, H-3′b); 4.88 (dt, 1 H, *J*(3′a,2′) = *J*(3′a,P) = 1.5, *J*(gem) = 12.0, H-3′a); 8.04 (s, 1 H, H-2). ^{13}C NMR (125 MHz, D_2O): 43.03 (C-1′); 66.48 (d, *J*(P,C) = 149.4, PC); 67.58 (d, *J*(P,C) = 9.8, C-2′); 68.76 (C-3′); 114.17 (C-5); 147.97 (C-4); 150.20 (C-2); 152.17 (C-8); 152.78 (C-6). Exact mass (FAB HRMS) found: 302.0605; calculated for $C_9H_{13}N_5O_5P$ [M + H]: 302.0654. UV, λ_{max} (ε_{max}): (pH 2) 263 (14 100); (pH 12) 263 (14 600). CD, λ (Δε) (MeOH): 278 (1.42), 254 (–0.70), 214 (–3.82), 203 (1.64).

Isopropyl Hydrogen (*S*)-{[(4-Amino-8,9-dihydro-7*H*-[1,3]oxazino[3,2-*e*]purin-8-yl)oxy]methyl}phosphonate[11] (**14**)

Compound **13a** (0.4 g, 1 mmol) and lithium azide (0.4 g) in DMF (10 ml) were stirred at 100 °C for 5 h and the solvent was evaporated *in vacuo*. The residue afforded, on preparative TLC (S4) followed by crystallization from ethanol, product **14** (0.25 g, 73%). White crystals, m.p. >360 °C; R_F = 0.12 (S4). FAB MS, *m/z* (rel.%): 366 (100) [M + Na + H]. ^{1}H NMR (500 MHz, DMSO-d_6): 1.00 (d, 3 H, *J*(CH_3,CH) = 6.2, CH_3); 1.01 (d, 3 H, *J*(CH_3,CH) = 6.2, CH_3); 3.42 (dd, 1 H, *J*(P,CHb) = 9.4, *J*(gem) = 12.9, PCHb); 3.47 (dd, 1 H, *J*(P,CHa) = 8.0, *J*(gem) = 12.9, PCHa); 4.09 (dd, 1 H, *J*(1′b,2′) = 3.3, *J*(gem) = 12.7, H-1′b); 4.22 (dt, 1 H, *J*(1′a,2′) = *J*(1′a,P) = 1.0, *J*(gem) = 12.7, H-1′a); 4.25 (m, 1 H, POCH); 4.45 (m, 1 H, H-2′); 4.47 (brd, 1 H, *J*(3′b,1′) = 1.0, *J*(gem) = 11.7, H-3′b); 4.64 (dt, 1 H, *J*(3′a,1′) = *J*(3′a,P) = 2.5, *J*(gem) = 11.7, H-3′a); 6.75 (brs, 2 H, NH_2); 8.01 (s, 1 H, H-2). ^{13}C NMR: 24.70 (d, 2 C, *J*(P,C) = 2.9, CH_3); 43.23 (C-1′);

65.77 (d, *J*(P,C) = 152.35, PC); 65.80 (d, *J*(P,C) = 5.9, POC); 66.99 (d, *J*(P,C) = 7.8, C-2′); 68.27 (C-3′); 114.89 (C-5); 148.78 (C-4); 150.42 (C-2); 151.06 (C-8); 153.77 (C-6). For $C_{12}H_{17}N_5NaO_5P$ (365.3) calculated: 39.46% C, 4.69% H, 19.17% N, 8.48% P; found: 39.43% C, 4.97% H, 18.90% N, 8.51% P. UV, λ_{max} (ε_{max}): (pH 2) 263 (13 600); (pH 12) 263 (13 600). CD, λ (Δε) (0.01 M HCl): 268 (1.57), 243 (0.88), 212 (–7.12), 202 (2.34).

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