SYNTHESIS OF ACYCLIC NUCLEOTIDE ANALOGUES DERIVED FROM 2-(AMINOMETHYL)ADENINE AND 2-(AMINOMETHYL)HYPOXANTHINE

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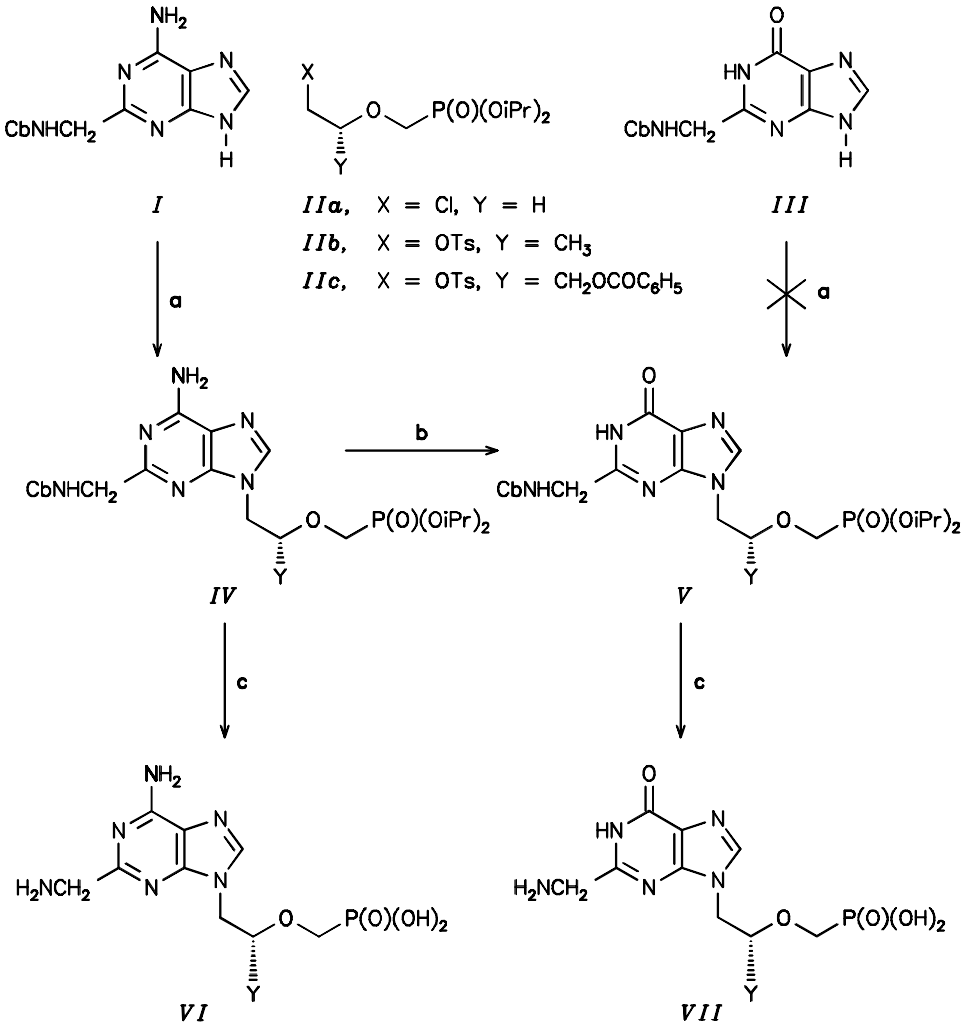
Synthesis of a series of 2-(aminomethyl)-9-(2-phosphonomethoxyalkyl)adenines *VI* and hypoxanthines *VII* is reported. The protected 2-(aminomethyl)adenine *I* was selectively alkylated with [bis(2-propoxy)phosphonylmethoxy]alkyl chlorides or tosylates *II* and the obtained 9-[bis(2-propoxy)-phosphonylmethoxy]alkyl-2-(benzyloxycarbonylaminomethyl)adenines *IV* were oxodeaminated to give the corresponding hypoxanthine derivatives *V*. The intermediates *IV* and *V* were completely deprotected by treatment with iodotrimethylsilane under formation of the title compounds *VI* and *VII*.

Phosphonomethoxyalkyl derivatives of pyrimidine and purine bases are potent antivirals[1]. The most promising of this group are the 2-phosphonomethoxyethyl (PME), (*R*)-2-phosphonomethoxypropyl (PMP) and (*S*)-3-hydroxy-2-phosphonomethoxypropyl (HPMP) derivatives. In our recent structure–activity relationship study of base-modified analogues of these compounds we have observed that the antiviral activity is connected with the presence of amino groups at the heterocyclic moiety. Thus, adenine, guanine, 2-aminopurine, 2,6-diaminopurine derivatives[2] and their aza and deaza analogues[3–6], as well as cytosine derivatives[2], exhibit potent antiviral effects while uracil, thymine, hypoxanthine, xanthine and other derivatives lacking the amino function are generally inactive[2].

The role of the amino group may consist just in its basicity or in the formation of hydrogen bonds with some (enzyme) counterparts. Several *N*(6)-monosubstituted and *N*(6)-disubstituted derivatives of adenine and 2,6-diaminopurine, however, possess some antiviral activity[7] as well. Therefore, we decided to investigate the synthesis and properties of acyclic nucleotide analogues bearing 2-aminomethyl function on the purine ring.

In general, (aminomethyl)purines are known[8–10] to be quite unstable due to their strongly basic benzyl-type amino group and are usually isolated as stable *N*-acyl derivatives[9,10]. Recently we have published[11] a facile synthesis of *N*-protected 2-(aminomethyl)purines; now we report on alkylation of these bases leading to acyclic nucleotide analogues (see Scheme 1).



In formulae *IV* – *VII*: **a**, Y = H; **b**, Y = CH_3; **c**, Y = CH_2OH

a) *II*, NaH, DMF; **b)** iAmONO, H_2SO_4, H_2O; **c)** TMSI, CH_3CN
Cb = $C_6H_5CH_2OCO$

SCHEME 1

Benzyloxycarbonyl-protected 2-(aminomethyl)adenine *I* (Cb = benzyloxycarbonyl) was alkylated using the following synthons: bis(2-propyl) 2-chloroethoxymethanephosphonate[3] (*IIa*), (*R*)-2-[bis(2-propoxy)phosphonylmethoxy]propyl tosylate[12] (*IIb*) and (*R*)-3-benzoyloxy-2-[bis(2-propoxy)phosphonylmethoxy]propyl tosylate[13] (*IIc*). Sodium salt of *I* was formed at room temperature by treatment with sodium hydride in dimethylformamide. After addition of the alkylating agent, the mixture was heated for 2 – 3 h at 100 °C until most of the starting material disappeared (TLC). Since slow decomposition of the product was observed after several hours of heating, the reaction was stopped before reaching complete conversion and the products were isolated by preparative TLC. After alkylation with the tosylate *IIc* the crude product was treated with methanolic ammonia prior to chromatography. The 9-substituted 2-(aminomethyl)-adenine derivatives *IV* were obtained in moderate yields and no substantial amount of other regioisomers was observed. Attempts to crystallize these products failed and the TLC-pure oily compounds were used in the further steps.

Attempted alkylation of the guanine analogue *III* by the same method was unsuccessful due to its low stability under the alkylation conditions. The 9-substituted 2-(aminomethyl)hypoxanthine derivatives *V* were, however, prepared in moderate yields by oxodeamination of *IV* using a mixture of 3-methylbutyl nitrite and dilute sulfuric acid. This procedure avoids formation of acetylated byproducts observed during usual oxodeamination with 3-methylbutyl nitrite in acetic acid and gives better yields than the use of sodium nitrite in sulfuric acid.

Treatment of the protected intermediates *IV* and *V* with iodotrimethylsilane[14] cleaved simultaneously both the Cb and the 2-propyl protecting groups, while analogous reaction with bromotrimethylsilane removed the 2-propyl functions only (a microscale experiment with MS detection). Pure 2-(aminomethyl)-9-(phosphonomethoxyalkyl)-adenines *VI* and hypoxanthines *VII* were obtained after ion exchange purification. These were hygroscopic but otherwise stable in the presence of air, representing thus the first example of stable *N*-unsubstituted aminomethylpurine derivatives. The stability could be explained by formation of zwitterionic structures.

Structure of the compounds was proved by ^{1}H and ^{13}C NMR spectra. The observed chemical shifts and interaction constants (see Experimental and Table I) are in good accord with the reported[15] values of 9-substituted adenine and hypoxanthine derivatives. The downfield shifts of C-2 (δ 165) and C-6 (δ 167) carbon signals of hypoxanthine derivatives *VII* in basic medium (NaOD) can be explained[16] by anion formation at N-1. This was also proved by ^{13}C NMR spectrum of derivative *VIIa* in D_2O which exhibited the expected shifts at 149.87 and 158.62, respectively.

The UV spectra of 9-substituted 2-(aminomethyl)adenines *VI* and 2-(aminomethyl)-hypoxanthines *VII* displayed maxima at 260 nm or 250 nm, respectively. The presence of the strongly basic amino group manifests itself in the electrophoretic mobility of the

TABLE I
^{13}C NMR spectra (δ, ppm) of compounds *IV* – *VII*[a]

Atom	*IVa*	*IVb*	*IVc*	*VIa*	*VIb*	*VIc*	*Va*	*Vb*	*Vc*	*VIIa*	*VIIb*	*VIIc*
C-2	155.80	155.92	155.87	154.98	154.98	155.00	155.32	155.30	155.67	165.24	165.21	162.18
C-4	149.96	150.54	150.48	149.33	149.61	149.48	148.64	148.92	148.80	150.20	150.60	150.31
C-5	117.35	117.36	117.43	116.75	116.73	116.42	122.43	122.12	122.34	121.15	120.87	121.07
C-6	156.48	156.44	156.48	159.30	155.92	160.15	156.60	156.16	156.68	167.66	167.67	165.96
C-8	141.70	141.80	141.59	142.57	143.10	142.92	140.57	140.86	140.85	140.88	141.36	141.41
NCH_2	45.96	46.64	46.48	44.00	46.68	45.67	42.85	46.93	42.96	46.39	46.89	44.91
C-1′	42.69	43.92	43.26	42.89	42.47	43.31	42.85	42.79	42.80	42.97	46.35	43.24
C-2′[b]	74.46	75.40	80.10	70.08	75.46	79.57	70.30	75.37	80.12	70.04	75.26	79.82
C-3′	–	16.91	60.17	–	15.99	60.16	–	16.88	60.21	–	15.95	60.25
CH_2P[c]	64.66	62.60	63.58	68.45	66.05	67.75	64.67	62.65	63.23	68.66	66.51	67.87

[a] Spectra of compounds *IV* and *V* contained additional signals of protecting groups carbon atoms: 23.8 (CH_3), 70.3 (CH), 65.6 (CH_2), 127 – 137 (four aromatic carbon signals), 157 – 160 (CO). [b] Doublet, ^3J(C,P) = 10. [c] Doublet, ^1J(C,P) = 165.

compounds *VI* and *VII* at slightly alkaline pH which is substantially lower compared to that of phosphonomethoxyalkyl derivatives of adenine and guanine.

The 2-(aminomethyl)-9-(phosphonomethoxyalkyl)purines *VI* and *VII* obtained by the above-described methods were tested[17] for their cytostatic (L-1210, P-388 mouse leukemia) and antiviral (selected RNA and DNA viruses and HIV-1, HIV-2) activity. None of these compounds showed any significant antiviral or cytostatic activity, nor did it exhibit any considerable cell toxicity.

EXPERIMENTAL

Unless otherwise stated, solvents were evaporated at 40 °C/2 kPa and compounds were dried at 60 °C/2 kPa over P_2O_5. Melting points were determined on a Kofler block and are uncorrected. TLC was performed on Silufol UV_{254} plates (Kavalier Votice, The Czech Republic) in a $CHCl_3$–CH_3OH (80 : 20) mixture. Preparative TLC was carried out on 40 × 17 × 0.4 cm plates of silica gel containing UV indicator. Paper electrophoresis was performed on a paper Whatman No. 3 MM at 40 V/cm for 1 h in 0.05 M triethylammonium hydrogen carbonate, pH 7.5. The electrophoretical mobilities (E_{Up}) are referenced to uridine 3′-phosphate. NMR spectra were measured on a Varian Unity 500 spectrometer (500 MHz for ^{1}H and 125.7 MHz for ^{13}C NMR) in hexadeuteriodimethyl sulfoxide 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 sulfonate (DSS) as internal standard for ^{1}H and dioxane as external standard for ^{13}C NMR (δ(dioxane) 66.86). Mass spectra were measured on a ZAB-EQ (VG Analytical) instrument using FAB technique (ionization by Xe, accelerating voltage 8 kV, glycerol matrix). UV absorption spectra were measured on a Beckman DU-65 spectrometer in aqueous HCl (0.01 M) solutions. CD spectra were recorded on Jobin Yvon Mark V spectrometer in aqueous HCl (0.01 M) solutions (c 1 . 10^{-3} mol/l). Dimethylformamide was distilled from P_2O_5 and stored over molecular sieves (4A). Acetonitrile was refluxed with CaH_2 and distilled. Iodotrimethylsilane was purchased from Aldrich (U.S.A.) and 3-methylbutyl nitrite from Janssen (Belgium). The starting 2-(aminomethyl)purines[11] *I* and *III* as well as the alkylation synthons[3,12,13] *II* were prepared according to previously reported methods.

Alkylation of Compound *I* – General Procedure

Method A: Sodium hydride (60% dispersion in mineral oil, 80 mg, 2 mmol) was added to a stirred solution of compound *I* (400 mg, 1.34 mmol) in DMF (20 ml) and stirring at room temperature was continued for 2 h. The alkylating agent *II* (2 mmol) was added and the mixture was stirred at 100 °C for 2 – 3 h. The solvent was evaporated, the residue was treated with water (50 ml) and extracted with ethyl acetate (3 × 50 ml). The combined organic layers were evaporated and the residue was chromatographed on a preparative layer of silica. The obtained chromatographically pure (TLC) yellowish oils were used in the further steps.

Method B: The procedure was identical with method *A* except that after evaporation of the extracts the residue was allowed to stand overnight with saturated methanolic ammonia (50 ml) and evaporated before the chromatography.

Bis(2-propyl) 2-(benzyloxycarbonylaminomethyl)-9-(2-phosphonomethoxyethyl)adenine (IVa), method *A*, yield 74%, R_F 0.60. FAB MS, *m/z* (rel.%): 521 (18) [M + H]. ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.13 d, 6 H, $J(CH_3,CH)$ = 6.1 (2 × CH_3); 1.17 d, 6 H, $J(CH_3,CH)$ = 6.1 (2 × CH_3); 3.78 d, 2 H, $J(P,CH_2)$ = 8.2 (PCH_2); 3.89 t, 2 H, $J(2',1')$ = 4.7 (H-2′); 4.24 d, 2 H, $J(CH_2,NH)$ = 5.8 (CH_2N); 4.31 t, 2 H, $J(1',2')$ = 4.7 (H-1′); 4.49 m, 2 H (POCH); 5.06 s, 2 H (CH_2Ph); 7.18 bs, 1 H

and 7.58 bs, 1 H (NH_2); 7.25 – 7.40 m, 5 H (arom. H); 7.55 bt, 1 H, *J*(NH,CH_2) = 5.8 (NHCb); 8.14 s, 1 H (H-8).

Bis(2-propyl) (R)-2-(benzyloxycarbonylaminomethyl)-9-(2-phosphonomethoxypropyl)adenine (IVb), method *A*, yield 56%, R_F 0.65. FAB MS *m/z* (rel.%): 535 (100) [M + H]. ^{1}H NMR spectrum ((CD_3)$_2$SO): 1.05 d, 3 H, *J*(3′,2′) = 6.3 (H-3′); 1.13 – 1.24 m, 12 H (4 × CH_3-iPr); 3.77 m, 2 H (PCH_2); 3.96 m, 1 H (H-2′); 4.12 dd, 1 H, *J*(1′b,2′) = 6.6, *J*(gem) = 14.4 (Hb-1′); 4.20 d, 2 H, *J*(CH_2,NH) = 5.9 (CH_2N); 4.22 dd, 1 H, *J*(1′a,2′) = 3.7, *J*(gem) = 14.4 (Ha-1′); 4.51 m, 2 H (2 × CH-iPr); 5.05 s, 2 H (CH_2Ph); 7.30 – 7.40 m, 5 H (arom. H); 7.19 bs, 2 H (NH_2); 7.42 t, 1 H, *J*(NH,CH_2) = 6.0 (NHCb); 8.01 s, 1 H (H-8).

Bis(2-propyl) (S)-2-(benzyloxycarbonylaminomethyl)-9-(3-hydroxy-2-phosphonomethoxypropyl)-adenine (IVc), method *B*, yield 42%, R_F 0.63. FAB MS, *m/z* (rel.%): 551 (100) [M + H]. ^{1}H NMR spectrum ((CD_3)$_2$SO): 1.155, 1.16, 1.24, 1.245 4 × d, 4 × 3 H, *J*(CH_3,CH) = 6.1 (CH_3-iPr); 3.42 m, 2 H (H-3′); 3.81 dd, 1 H, *J*(PCH) = 9.5, *J*(gem) = 13.7 (PC-Hb); 3.85 m, 1 H (H-2′); 3.88 dd, 1 H, *J*(P,CH) = 8.8, *J*(gem) = 13.7 (PC-Ha); 4.19 dd, 1 H, *J*(1′b,2′) = 6.8, *J*(gem) = 14.4 (Hb-1′); 4.20 d, 2 H, *J*(CH_2,NH) = 5.9 (CH_2N); 4.33 dd, 1 H, *J*(1′a,2′) = 3.6, *J*(gem) = 14.4 (Ha-1′); 4.47 and 4.51 2 × dsept, 2 × 1 H, *J*(CH,CH_3) = 6.1, *J*(P,OCH) = 7.8 (CH-iPr); 4.98 bs, 1 H (OH); 5.05 s, 2 H (CH_2Ph); 7.20 – 7.40 m, 5 H (arom. H); 7.25 bs, 2 H (NH_2); 7.44 t, 1 H, *J*(NH,CH_2) = 5.9 (NHCb); 8.02 s, 1 H (H-8).

Oxodeamination of Adenines *IV* to Hypoxanthines *V* – General Procedure

A mixture of the adenine derivative *IV* (1.33 mmol), water (50 ml), 98% sulfuric acid (1.5 ml) and 3-methylbutyl nitrite (3 g, 25.6 mmol) was stirred for 7 days at room temperature. The resulting yellow solution was neutralized with NaOH to pH 7 and extracted with ethyl acetate (4 × 100 ml). The combined organic layers were evaporated and the residue was chromatographed on a preparative layer of silica. The resulting (TLC pure) yellow oils were used in the further step.

Bis(2-propyl) 2-(benzyloxycarbonylaminomethyl)-9-(2-phosphonomethoxyethyl)hypoxanthine (Va), yield 47%, R_F 0.52. FAB MS, *m/z* (rel.%): 522 (100) [M + H]. ^{1}H NMR spectrum ((CD_3)$_2$SO): 1.14 and 1.18 2 × d, 2 × 6 H, *J*(CH_3,CH) = 6.1 (CH_3-iPr); 3.77 d, 2 H, *J*(P,CH) = 8.5 (PCH_2); 4.00 t, 2 H, *J*(2′,1′) = 5.1 (H-2′); 4.20 d, 2 H, *J*(CH_2,NH) = 6.1 (CH_2N); 4.26 t, 2 H, *J*(1′,2′) = 5.1 (H-1′); 4.50 dsept, 2 H, *J*(CH,CH_3) = 6.1, *J*(P,OCH) = 7.8 (CH-iPr); 5.06 s, 2 H (CH_2Ph); 7.10 – 7.40 m, 5 H (arom. H); 7.70 t, 1 H, *J*(NH,CH_2) = 6.0 (NHCb); 7.99 s, 1 H (H-8); 12.10 bs, 1 H (NH-1).

Bis(2-propyl) (R)-2-(benzyloxycarbonylaminomethyl)-9-(2-phosphonomethoxypropyl)hypoxanthine (Vb), yield 52%, R_F 0.59. FAB MS, *m/z* (rel.%): 536 (100) [M + H]. ^{1}H NMR spectrum ((CD_3)$_2$SO): 1.02 d, 3 H, *J*(3′,2′) = 6.3 (H-3′); 1.14, 1.17, 1.18 and 1.21 4 × d, 4 × 3 H, *J*(CH_3,CH) = 6.1 (CH_3-iPr); 3.72 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 13.7 (PC-Hb); 3.78 dd, 1 H, *J*(P,CH) = 9.3, *J*(gem) = 13.7 (PC-Ha); 3.93 m, 1 H (H-2′); 4.10 dd, 1 H, *J*(1′b,2′) = 6.3, *J*(gem) = 14.4 (Hb-1′); 4.19 d, 2 H, *J*(CH_2,NH) = 5.9 (CH_2N); 4.21 dd, 1 H, *J*(1′a, 2′) = 3.9, *J*(gem) = 14.4 (Ha-1′); 4.51 and 4.52 2 × dsept, 2 × 1 H, *J*(CH,CH_3) = 6.1, *J*(P,OCH) = 7.1 (CH-iPr); 5.06 s, 2 H (CH_2Ph); 7.10 – 7.40 m, 5 H (arom. H); 7.70 t, 1 H, *J*(NH,CH_2) = 5.9 (NHCb); 7.96 s, 1 H (H-8); 12.15 bs, 1 H (NH-1).

Bis(2-propyl) (S)-2-(benzyloxycarbonylaminomethyl)-9-(3-hydroxy-2-phosphonomethoxypropyl)-hypoxanthine (Vc), yield 46%, R_F 0.58. FAB MS, *m/z* (rel.%): 552 (100) [M + H]. ^{1}H NMR spectrum ((CD_3)$_2$SO): 1.16, 1.165, 1.23, 1.24 4 × d, 4 × 3 H, *J*(CH_3,CH) = 6.1 (CH_3-iPr); 3.45 m, 2 H (H-3′); 3.76 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 13.7 (PC-Hb); 3.85 m, 1 H (H-2′); 3.88 dd, 1 H, *J*(P,CH) = 8.8, *J*(gem) = 13.7 (PC-Ha); 4.15 dd, 1 H, *J*(1′b,2′) = 7.6, *J*(gem) = 14.4 (Hb-1′); 4.21 d, 2 H, *J*(CH_2,NH) = 6.0 (CH_2N); 4.30 dd, 1 H, *J*(1′a,2′) = 3.5, *J*(gem) = 14.4 (Ha-1′); 4.49 m, 2 H (CH-iPr); 5.00 bs, 1 H (OH); 5.06 s, 2 H (CH_2Ph); 7.10 – 7.40 m, 5 H (arom. H); 7.75 t, 1 H, *J*(NH,CH_2) = 6.0 (NHCb); 7.98 s, 1 H (H-8); 12.10 bs, 1 H (NH-1).

Deprotection of Intermediates *IV* and *V* – General Procedure

Iodotrimethylsilane (1.07 ml, 7.5 mmol) was added under argon to a stirred solution of protected intermediates *IV* or *V* (0.75 mmol) in acetonitrile (25 ml). The mixture was stirred overnight at room temperature, the solvent was evaporated in vacuo and the residue was codistilled with acetonitrile and toluene (2 × 20 ml each) to remove excess iodotrimethylsilane. Water (50 ml) and triethylamine (1 ml) were added and the mixture was washed with ether (3 × 50 ml). The aqueous layer was applied on a Dowex D1 X2 (200 – 400 mesh, acetate form) column (50 ml). The column was washed with water and the products were eluted with a gradient of acetic acid (0.01 – 0.1 mol/l). The resulting white solid was recrystallized from water–ethanol.

2-(Aminomethyl)-9-(2-phosphonomethoxyethyl)adenine (VIa), yield 57%, colourless needles, m.p. 264 – 266 °C (dec.), E_{Up} 0.56. For $C_9H_{15}N_6O_4P$ (302.2) calculated: 35.76% C, 5.00% H, 27.81% N, 10.25% P; found: 35.57% C, 4.95% H, 27.52% N, 10.26% P. FAB MS, *m/z* (rel.%): 303 (80) [M + H]. ^{1}H NMR spectrum (D_2O + NaOD): 3.52 d, 2 H, J(P, CH_2) = 8.8 (PCH_2); 3.96 t, 2 H, J(2′,1′) = 5.0 (H-2′); 4.02 s, 2 H (NCH_2); 4.41 t, 2 H, J(1′,2′) = 5.0 (H-1′); 8.21 s, 1 H (H-8). UV spectrum (0.01 M HCl): λ_{max} 262 nm (log ε 4.03).

(R)-2-(Aminomethyl)-9-(2-phosphonomethoxypropyl)adenine(VIb), yield 51%, hygroscopic colourless needles, m.p. 192 – 195 °C (dec.), E_{Up} 0.53. CD spectrum (0.01 M HCl): λ 274 nm (Δε 0.2). For $C_{10}H_{17}N_6O_4P$. 2 H_2O (352.3) calculated: 34.09% C, 6.01% H, 23.85% N, 8.85% P; found: 33.95% C, 5.79% H, 23.68% N, 8.85% P. FAB MS, *m/z* (rel.%): 317 (100) [M + H]. ^{1}H NMR spectrum (D_2O + NaOD): 1.14 d, 3 H, J(3′,2′) = 6.3 (H-3′); 3.54 dd, 1 H, J(P,CH) = 9.8, J(gem) = 12.2 (PC-Hb); 3.62 dd, 1 H, J(P,CH) = 9.5, J(gem) = 12.2 (PC-Ha); 3.98 m, 1 H (H-2′); 4.22 s, 2 H (NCH_2); 4.22 dd, 1 H, J(1′b,2′) = 5.6, J(gem) = 14.7 (Hb-1′); 4.45 dd, 1 H, J(1′a,2′) = 3.6, J(gem) = 14.7 (Ha-1′); 8.19 s, 1 H (H-8). UV spectrum (0.01 M HCl): λ_{max} 260 nm (log ε 4.06).

(S)-2-(Aminomethyl)-9-(3-hydroxy-2-phosphonomethoxypropyl)adenine (VIc), yield 68%, white powder, m.p. 210 – 213 °C (dec.), E_{Up} 0.49. CD spectrum (0.01 M HCl): λ 273 nm (Δε 0.26). For $C_{10}H_{17}N_6O_5P$. H_2O (350.3) calculated: 34.29% C, 5.46% H, 23.99% N, 8.84% P; found: 33.90% C, 5.31% H, 23.60% N, 8.47% P. FAB MS, *m/z* (rel.%): 333 (100) [M + H]. ^{1}H NMR spectrum (D_2O + NaOD): 3.48 dd, 1 H, J(3′b,2′) = 4.6, J(gem) = 12.4 (Hb-3′); 3.49 dd, 1 H, J(P,CH) = 9.0, J(gem) = 12.2 (PC-Hb); 3.54 dd, 1 H, J(P,CH) = 8.8, J(gem) = 12.2 (PC-Ha); 3.76 dd, 1 H, J(3′a,2′) = 3.7, J(gem) = 12.4 (Ha-3′); 3.83 s, 2 H (NCH_2); 3.86 m, 1 H (H-2′); 4.35 dd, 1 H, J(1′b,2′) = 6.3, J(gem) = 14.6 (Hb-1′); 4.42 dd, 1 H, J(1′a,2′) = 4.4, J(gem) = 14.6 (Ha-1′); 8.21 s, 1 H (H-8). UV spectrum (0.01 M HCl): λ_{max} 262 nm (log ε 4.06).

2-(Aminomethyl)-9-(2-phosphonomethoxyethyl)hypoxanthine (VIIa), yield 66%, colourless needles, m.p. >300 °C , E_{Up} 0.83. For $C_9H_{14}N_5O_5P$ (303.2) calculated: 35.65% C, 4.65% H, 23.10% N, 10.22% P; found: 35.35% C, 4.69% H, 22.96% N, 9.88% P. FAB MS, *m/z* (rel.%): 304 (54) [M + H]. ^{1}H NMR spectrum (D_2O + NaOD): 3.50 d, 2 H, J(P,CH_2) = 8.3 (PCH_2); 3.74 s, 2 H (NCH_2); 3.96 t, 2 H, J(2′,1′) = 5.1 (H-2′); 4.39 t, 2 H, J(1′,2′) = 5.1 (H-1′); 8.07 s, 1 H (H-8). UV spectrum (0.01 M HCl): λ_{max} 250 nm (log ε 3.95).

(R)-2-(Aminomethyl)-9-(2-phosphonomethoxypropyl)hypoxanthine (VIIb), yield 63%, white hygroscopic powder, m.p. 204 – 207 °C (dec.), E_{Up} 0.78. CD spectrum (0.01 M HCl): λ 266 nm (Δε 0.08), λ 248 nm (Δε –0.14), λ 223 nm (Δε 0.13). For $C_{10}H_{16}N_5O_5P$. 3 H_2O (371.3) calculated: 32.35% C, 5.97% H, 18.86% N, 8.34% P; found: 32.52% C, 5.80% H, 18.92% N, 8.16% P. FAB MS, *m/z* (rel.%): 318 (100) [M + H]. ^{1}H NMR spectrum (D_2O + NaOD): 1.12 d, 3 H, J(3′,2′) = 6.3 (H-3′); 3.46 dd, 1 H, J(P,CH) = 9.0, J(gem) = 12.4 (PC-Hb); 3.55 dd, 1 H, J(P,CH) = 8.3, J(gem) = 12.4 (PC-Ha); 3.74 s, 2 H (NCH_2); 4.01 m, 1 H (H-2′); 4.26 dd, 1 H, J(1′b,2′) = 5.6, J(gem) = 14.4 (Hb-1′); 4.35 dd, 1 H, J(1′a,2′) = 4.4, J(gem) = 14.4 (Ha-1′); 8.10 s, 1 H (H-8). UV spectrum (0.01 M HCl): λ_{max} 250 nm (log ε 4.00).

(S)-2-(Aminomethyl)-9-(3-hydroxy-2-phosphonomethoxypropyl)hypoxanthine (VIIc), yield 66%, colourless needles, m.p. 224 – 226 °C, E_{Up} 0.80. CD spectrum (0.01 M HCl): λ 269 nm (Δε 0.14), λ 248 nm (Δε –0.23), λ 223 (Δε 0.27). For $C_{10}H_{16}N_5O_6P$. 2.5 H_2O (378.3) calculated: 31.74% C, 5.59% H, 18.51% N, 8.19% P; found: 31.61% C, 5.18% H, 18.43% N, 8.78% P. FAB MS, *m/z* (rel.%): 334 (60) [M + H]. ^{1}H NMR spectrum (D_2O + NaOD): 3.47 dd, 1 H, *J*(3′b,2′) = 4.4, *J*(gem) = 12.4 (Hb-3′); 3.49 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 12.2 (PC-Hb); 3.57 dd, 1 H, *J*(P,CH) = 8.8, *J*(gem) = 12.2 (PC-Ha); 3.75 dd, 1 H, *J*(3′a,2′) = 3.4, *J*(gem) = 12.4 (Ha-3′); 3.86 s, 2 H (NCH_2); 3.88 m, 1 H (H-2′); 4.34 dd, 1 H, *J*(1′b,2′) = 6.1, *J*(gem) = 14.6 (Hb-1′); 4.41 dd, 1 H, *J*(1′a,2′) = 4.9, *J*(gem) = 14.6 (Ha-1′); 8.08 s, 1 H (H-8). UV spectrum (0.01 M HCl): λ_{max} 250 nm (log ε 3.94).

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