SYNTHESIS OF ENANTIOMERIC *N*-(2-PHOSPHONOMETHOXYPROPYL) DERIVATIVES OF PURINE AND PYRIMIDINE BASES. II. THE SYNTHON APPROACH*,**

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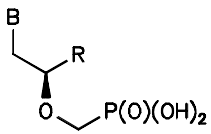
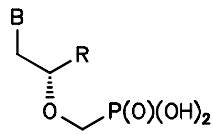
Another approach to (*R*)- and (*S*)-*N*-(2-phosphonomethoxypropyl) derivatives of purine and pyrimidine bases (PMP derivatives) *I* and *II* is described, consisting in alkylation of the heterocyclic base with (*R*)- and (*S*)-2-[bis(2-propyl)phosphonylmethoxy]propyl *p*-toluenesulfonates (*X* and *XVIII*) followed by transsilylation of the intermediary *N*-[2-bis(2-propyl)phosphonylmethoxypropyl] derivatives *XI* and *XIX*. The key intermediates *X* and *XVIII* were obtained from 1-benzyloxypropanols *VI* and *XIV* by two routes: (i) condensation with bis(2-propyl) *p*-toluenesulfonyloxymethylphosphonate (*XIII*), hydrogenolysis of the obtained 1-benzyloxy-2-bis(2-propyl)phosphonylmethoxypropanes *VIII* and *XVI* over Pd/C to 2-bis(2-propyl)phosphonylmethoxypropanols *IX* and *XVII* and tosylation of the latter or (ii) chloromethylation of compounds *VI* and *XIV* and subsequent reaction of the chloromethyl ethers *VII* and *XV* with tris(2-propyl) phosphite and further processing of the benzyl ethers *VIII* and *XVI* analogous to the enantiomeric propanols *IX* and *XVII*. This approach was used for the synthesis of derivatives of adenine (*Ia*, *IIa*), 2,6-diaminopurine (*Ib*, *IIb*) and 3-deazaadenine (*Ic*, *IIc*). Their guanine counterparts *Ie* and *IIe* were prepared by hydrolysis of 2-amino-6-chloropurine intermediates *XId* and *XIXd*. 6-Chloropurine was converted into diester *XIi* by reaction with tosylate *X*, which on reaction with thiourea and subsequent ester cleavage afforded the 6-thiopurine derivative *Ij*. Analogously, 2-amino-6-chloropurine derivative *XId* reacted with thiourea to give 9-(*R*)-(2-phosphonomethoxypropyl)-2-thioguanine (*If*), or with dimethylamine under formation of (2-phosphonomethoxypropyl)-2-amino-6-dimethylaminopurine (*Ig*). Hydrogenolysis of compound *XId* gave 9-(*R*)-(2-phosphonomethoxypropyl)-2-aminopurine (*Ik*). Hydrolytic deamination of adenine derivatives *Ia* and *IIa* led to enantiomeric (2-phosphonomethoxypropyl)hypoxanthines *Ih* and *IIh*.

Our preceding paper[3] described a synthetic approach to a novel class of acyclic nucleotide analogues with distinct antiretroviral activity, *N*-(2-phosphonomethoxypropyl) derivatives of purine and pyrimidine bases *I* and *II*. This route, consisting in the stepwise strategy, can be conveniently used for the preparation of larger quantities of com-

* This approach was reported in a preliminary form[1,2].
**Part I: ref.[3].

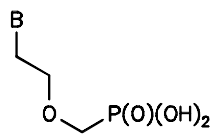
pounds where the advantage of stable crystalline intermediates, enantiomeric *N*-(2-hydroxypropyl) derivatives, can be suitably exploited. However, this advantage vanishes in those cases where the heterocyclic base is either not easily available or the alkylation by synthons used in the stepwise approach is not sufficiently regiospecific. In the acyclic nucleotide chemistry it is always preferable in such situations to employ a synthon bearing all features of the future side-chain which makes it possible to get the final intermediate in one step. We have used such approach already in the preparation of structurally related *N*-(2-phosphonomethoxyethyl) compounds[4] (PME derivatives, *V*) as well as of (3-hydroxy-2-phosphonomethoxypropyl) derivatives[5,6] (*III*, *IV*). This paper describes the synthesis of enantiomeric synthons applicable to the preparation of (*R*)-(*I*) and (*S*)-(2-phosphonomethoxypropyl) derivatives[7] (PMP-compounds, *II*) in two steps from the heterocyclic bases. These synthons are accessible from commercially available chiral materials – esters of D-(+)- and L-(–)-lactic acid. (The configuration of (*R*)-PMP-derivatives *I* corresponds generically to (*S*)-HPMP derivatives *III*).





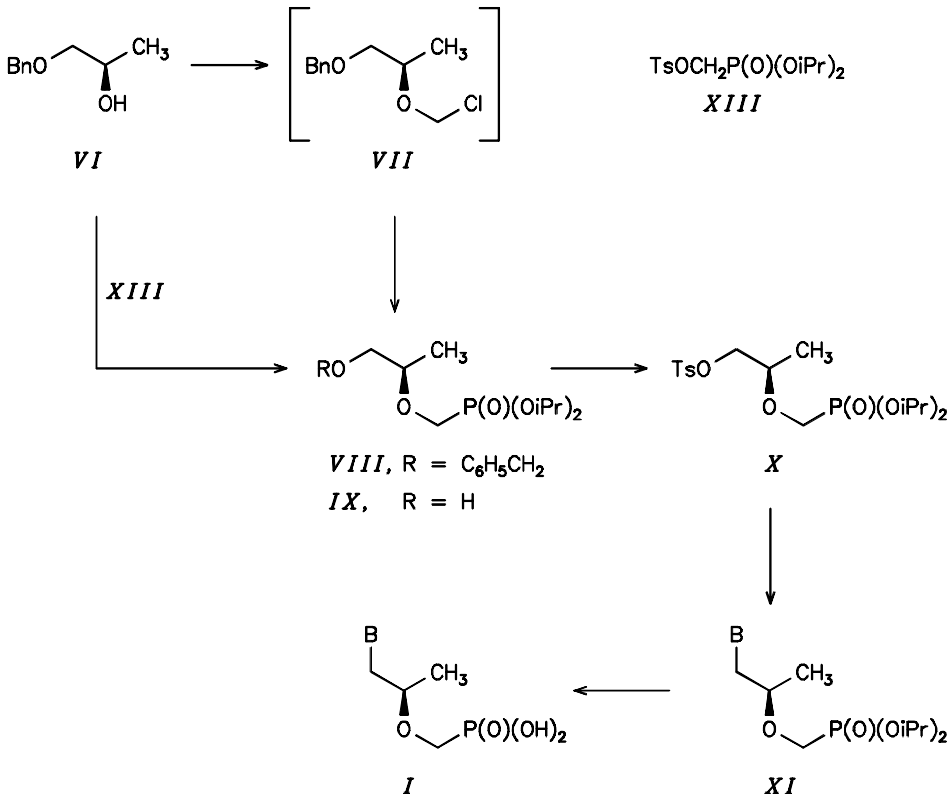
I, R = CH_3 (*R*) PMP series *II*, R = CH_3 (*S*) PMP series

III, R = CH_2OH (*S*) HPMP series *IV*, R = CH_2OH (*R*) HPMP series



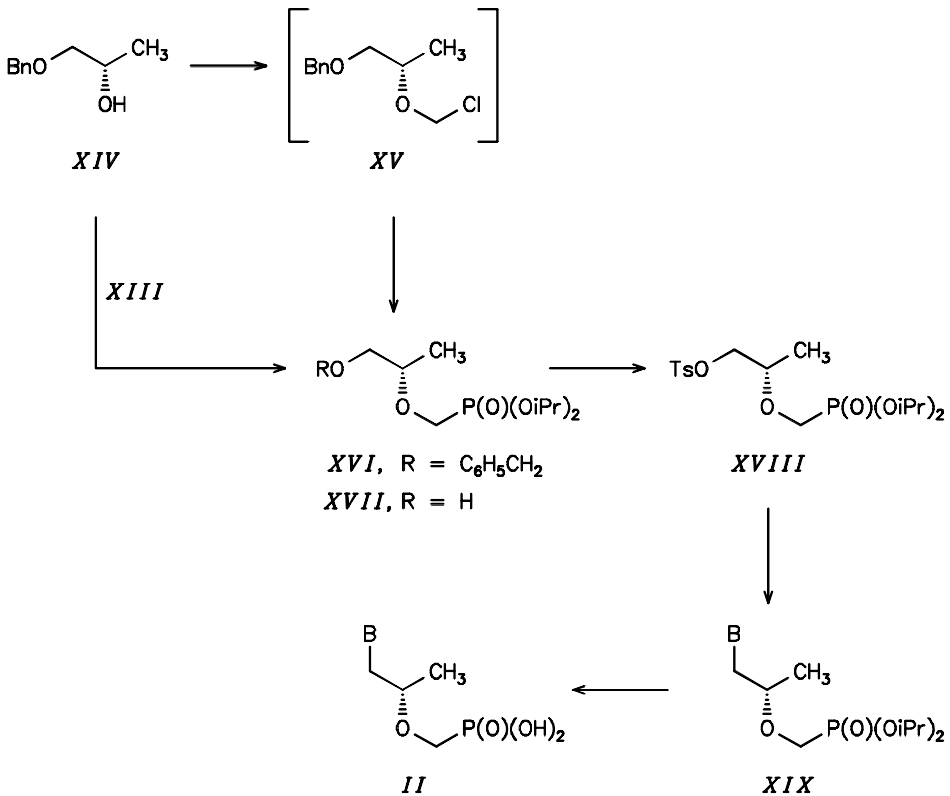
V, PME series

Starting material for the preparation of (*R*)-PMP derivatives (Scheme 1) was 1-benzyloxy-2-propanol (*VI*), easily available in large quantity from 2-methylpropyl L-(–)-lactate as described in the preceding paper[3]. Treatment of alcohol *VI* with paraformaldehyde and hydrogen chloride in the presence of calcium chloride gave the chloromethyl ether *VII* which was converted to the organophosphorus derivative *VIII* by Arbuzov reaction with tris(2-propyl) phosphite. The use of 2-propyl ester as a phosphate-protecting group is preferable over simple alkyl (methyl, ethyl) groups due to the alkylation potential of the latter in the reaction with heterocyclic bases. The product *VIII* was purified by chromatography on silica gel and characterized by mass and ^{1}H NMR spectra. Hydrogenolysis of this intermediate on a Pd/C catalyst afforded (*R*)-2-bis(2-propyl)phosphonylmethoxypropanol (*IX*) that was, in turn, converted into its



I, *XI*	B
a	adenin-9-yl
b	2,6-diaminopurin-9-yl
c	3-deazaadenin-9-yl
d	2-amino-6-chloropurin-9-yl
e	guanin-9-yl
f	6-thioguanin-9-yl
g	2-amino-6-dimethylaminopurin-9-yl
h	hypoxanthin-9-yl
i	6-chloropurin-9-yl
j	6-mercaptopurin-9-yl
k	2-aminopurin-9-yl
l	2-amino-6-azidopurin-9-yl

SCHEME 1



II, XIX	B
a	adenin-9-yl
b	2,6-diaminopurin-9-yl
d	2-amino-6-chloropurin-9-yl
e	guanin-9-yl
h	hypoxanthin-9-yl

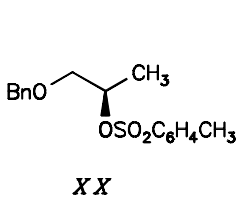
SCHEME 2

tosyl ester *X*. This product was finally purified by silica gel chromatography and characterized by mass and ^{1}H NMR spectra.

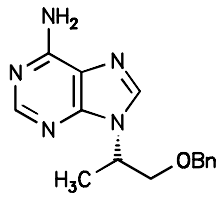
The same procedure was applied to (*S*)-1-benzyloxy-2-propanol (*XIV*) whose preparation from ethyl D-(+)-lactate was also described in the preceding paper[3]; this route led ultimately to the (*S*)-synthon *XVIII* (Scheme 2).

To avoid chloromethylation during the synthesis of the intermediate *VIII*, compound *VI* was *O*-alkylated with bis(2-propyl) *p*-toluenesulfonyloxymethylphosphonate[8] (*XIII*) in the presence of sodium hydride. While this reaction proceeded only sluggishly when performed in dimethylformamide (experiment not shown), it was quantitative in dry tetrahydrofuran. In the subsequent reaction steps, the phosphonyl derivative *VIII* gave the key synthon *X* of (*R*)-configuration.

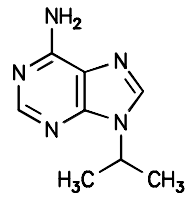
In addition to compound *VIII*, we have isolated a substantial amount (about 30%) of another product which – according to its mass and ^{1}H NMR spectra – was identified as (*R*)-1-benzyloxy-2-propyl *p*-toluenesulfonate (*XX*). On treatment with adenine under usual alkylation conditions, this tosylate gave (in an S_N2 reaction) (*S*)-9-(1-benzyloxy-2-propyl)adenine (*XXI*) as the main product. As minor product of this condensation we identified 9-(2-propyl)adenine (*XXII*). Thus, it can be deduced that the condensation of synthon *XIII* with alcohol *VI* in the presence of a slight excess of sodium hydride is accompanied by alkali-catalyzed transesterification of the bis(2-propyl)phosphonylmethyl tosylate (*XIII*) with alcohol *VI* (under formation of compound *XX*). The formation of 9-(2-propyl)adenine (*XXII*) can be due to a minor alkylation of the base with the phos-



XX



XXI



XXII

phonate ester residue; however, we have not yet observed this product in any alkylation that makes use of bis(2-propyl) esters of diverse phosphonates. We have not tried at this stage to minimize the above side reactions; it is plausible that a careful choice of the reaction time and temperature may affect the relative course of the substitution and reesterification reactions.

We have prepared authentic (*R*)-*XX* by tosylation of (*R*)-alcohol *VI* and used it in the condensation with adenine to produce compound *XXI* of the (presumably) (*S*)-configuration. The identical optical rotation values of the two products *XXI* witnessed that the configuration and the optical purity of the tosyl derivatives *XX* prepared by the above different routes were identical.

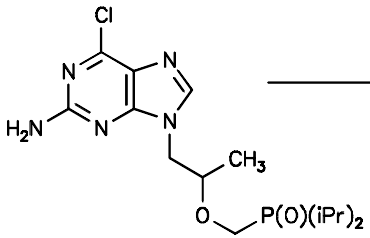
The use of synthons *X* and *XVIII* for the preparation of PMP-derivatives *I* and *II* followed the routine methodology: The heterocyclic base was transformed into its sodium salt by treatment with sodium hydride in dimethylformamide or pretreated with cesium carbonate in the same solvent. The reaction with synthons *X* and *XVIII* proceeded at elevated temperature and the diester intermediates *XI* and *XIX* were easily isolated by chromatography on silica. Their structure, including isomer assignment, was unequivocally proven by the ^{1}H NMR spectra. The structural assignment of the 3-deazaadenine derivatives was based on our previous UV spectral studies[9].

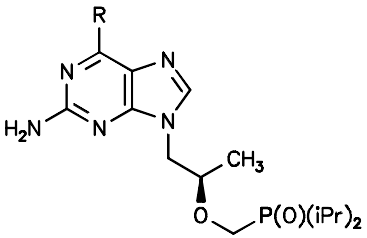
The ester groups in the diesters *XI* and *XIX* were cleaved by transsilylation with bromotrimethylsilane in acetonitrile, followed by hydrolysis. The PMP-derivatives were isolated by ion exchange chromatography. The adenine (*Ia*, *IIa*) and 2,6-diaminopurine (*Ib*, *IIb*) derivatives, prepared by this procedure in both the (*S*)- and (*R*)-series, were in all aspects identical with the products obtained by the stepwise procedure[3]. The preparation of 3-deazaadenine derivative *Ic* by this procedure proves its applicability to small-scale preparation.

Further applications involve syntheses of phosphonate-protected intermediates *XI* and *XIX* derived from heterocyclic bases bearing reactive grouping(s). Thus, 6-chloropurine and 2-amino-6-chloropurine were transformed into the respective pairs of enantiomeric diesters *XId*, *XIi* and *XIXd*, *XIXi*. The diesters *XId* and *XIXd* were transformed by treatment with DABCO (1,4-diazabicyclo[2.2.2]octane)[10] in alkaline aqueous solution into the enantiomeric guanine derivatives *XIe* and *XIXe* which were converted to the known[3] phosphonates (*R*)-PMPG (*Ie*) and (*S*)-PMPG (*IIe*). The reduction of compound *XId* over a Pd/C catalyst, followed by deprotection, afforded (*R*)-PMP derivative of 2-aminopurine (*Ik*) while its treatment with thiourea and subsequent removal of the ester group yielded (*R*)-9-(2-phosphonomethoxypropyl)-6-thioguanine (*If*). The reaction of *XId* with dimethylamine resulted in (*R*)-9-(2-phosphonomethoxypropyl)-2-amino-6-dimethylaminopurine (*Ig*), the parent structure of a series of N^6-substituted acyclic purine phosphonate derivatives some of which are very potent antiretrovirals[11] (Scheme 3). Finally, the compound *XId* was converted by reaction with lithium azide into the 2-amino-6-azido derivative *XIl* which on catalytic hydrogenation gave the antiviral 2,6-diaminopurine derivative[12] *Ib* (PMEDAP).

In accord with expectation, the 9-isomers *XId* and *XIXd*, formed on alkylation of 2-amino-6-chloropurine with the synthons *XX* and *XVIII*, were accompanied by minor side products which resisted our attempts to complete separation. The major components (about 70%) of these side-product mixtures were the N^7-isomers *XXIII* and *XXIV*. Formation of other regioisomers was negligible in the alkylation of 6-chloropurine.

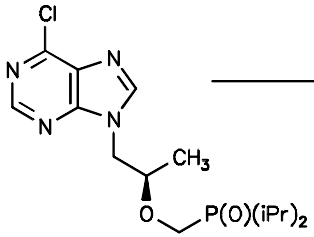
A similar reactivity profile of the 6-chloropurine derivative *XIi* is demonstrated by its conversion into bis(2-propyl) (*R*)-9-(2-phosphonomethoxypropyl)-6-mercaptopurine (*XIj*). While the above transformations made use of the preserved reactivity of the heterocyclic base in the protected intermediates *XI*, we have also transformed the adenine

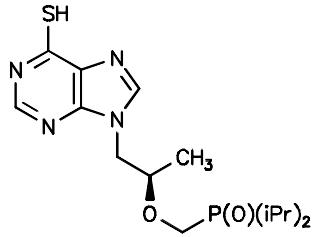




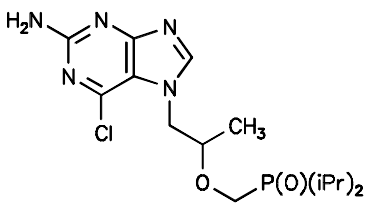
XId, (*R*)–series
XIXd, (*S*)–series

XIe, R = OH
XIf, R = SH
XIg, R = $N(CH_3)_2$
XIk, R = H
XIl, R = N_3
XIXe, R = OH





XIi ***XIj***



XXIII, (*R*)–series
XXIV, (*S*)–series

SCHEME 3

derivatives *Ia* and *IIa* (free phosphonic acids) into their hypoxanthine counterparts *Ih* and *IIh* by deamination with nitrous acid.

The synthon approach described in this paper was further applied to the preparation of additional base-modified PMP-compounds, e.g. aminomethylpurine derivatives[13], 8-aza-purine derivatives[14] or N^6-substituted adenine derivatives[11]. In combination with the stepwise approach described in our previous communication, it makes these interesting compounds of wide potential biological applicability practically available. For the sake of completeness it should be mentioned that other authors have applied another approach to the preparation of PMPG enantiomers (*Ie*, *IIe*). Their approach consists in the transformation of one of the hydroxymethyl groups of asymmetric 2-dialkoxyphosphonylglycerol derivatives into the methyl group via the mesylate and iodomethyl derivative[15]. Such an approach can hardly be competitive to the synthetic procedures described in our present communications.

EXPERIMENTAL

If not stated otherwise, the solutions were evaporated at 40 °C/2kPa and the compounds dried at 13 Pa over phosphorus pentoxide. Melting points were determined on a Kofler block and are uncorrected.

Thin-layer chromatography was carried out on silica plates Silufol UV254 (Kavalier Votice, Czech Republic) in the systems S1 chloroform, S2 chloroform–methanol (4 : 1). Column chromatography on silica gel (30 μm) was made with silica gel produced by the same company. Preparative TLC was performed on loose layers (45 × 16 × 0.3 cm) of silica with fluorescent indicator (30 μm), prepared in our Institute. Paper electrophoresis was performed on a Whatman No. 3 MM paper at 40 V/cm (1 h) in 0.05 M triethylammonium hydrogen carbonate, pH 7.5. Electrophoretic mobilities (E_{Up}) are referred to uridine 3′-phosphate.

Deionisation of the reaction mixtures was effected on columns of Dowex 50 X 8 (100–200 mesh, H^+ form); after application of the mixture, the column was washed with water (in the case of compounds *XI* and *XIX* with 20% aqueous methanol) to drop of UV absorption (254 nm) and pH to the original values. The compounds were then eluted with 2.5% ammonia in water (for *XI* and *XIX* in 20% methanol).

^{1}H NMR spectra were taken on a Varian UNITY-200 (200 MHz) and a Varian UNITY-500 (500 MHz) spectrometers in CD_3SOCD_3 with tetramethylsilane as internal standard or in D_2O with sodium 3-(trimethylsilyl)propanesulfonate (DSS) as internal standard.

Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer by EI (electron energy 70 eV) and FAB (ionisation Xe, accelerating voltage 8 kV) techniques.

Starting Materials and Reagents

Dimethylformamide, acetonitrile, tetrahydrofuran, 2-methylpropyl D-(+)-lactate, ethyl L-(–)-lactate, chlorotrimethylsilane, and Celite were obtained from Merck (Germany), cytosine, adenine, 6-chloropurine, *p*-toluenesulfonyl chloride, DABCO and cesium carbonate from Fluka (Switzerland), 2-aminoadenine from Tokyo Kasei Co. (Japan) and 2-amino-6-chloropurine from Mack (Germany), bromotrimethylsilane and 4-dimethylaminopyridine from Aldrich (Germany). Dimethylformamide and acetonitrile were dried by distillation from phosphorus pentoxide and stored over molecular sieves.

(*R*)-1-Benzyloxy-2-propanol (*VI*)

(*R*)-2-Tetrahydropyranyloxypropanol[3] (69.2 g, 0.43 mol) was added dropwise over 30 min to a stirred and ice-cooled suspension of sodium hydride (60% dispersion in oil; 17.2 g, 0.43 mol) in dimethylformamide (400 ml), placed in a 1 l round-bottom flask with dropping funnel and a calcium chloride protecting tube. The suspension was stirred for additional 1 h at 0 °C and benzyl bromide (51 ml, 0.43 mol) was added dropwise at 0 °C. The mixture was stirred for 4 h at 0 °C and left to stand for 48 h at ambient temperature. Methanolic ammonia (30% solution, 20 ml) was added and, after standing for 2 h, the solvent was taken down in vacuo. Ethyl acetate (500 ml) was added and the mixture was washed with water (4 × 100 ml). The organic phase was evaporated and the resulting oil was dissolved in 70% aqueous methanol (400 ml) and stirred under reflux with 50 ml Dowex 50 X 8 (H^+ form) for 4 h. The warm mixture was filtered, washed with methanol and the filtrate was evaporated in vacuo. The residual oil was taken up in ether (200 ml), washed with water (50 ml), dried and distilled in vacuo. Yield 60.8 g (85%) of (*R*)-1-benzyloxy-2-propanol (*VI*), b.p. 98–102 °C/Pa). $[\alpha]_D$ –13.0° (*c* 0.5, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$): 7.27–7.37 m, 5 H (arom. H); 4.55 s, 2 H (CH_2); 3.99 ddq, 1 H, *J*(1a,2) = 3.1, *J*(1b,2) = 8.1, *J*(2,3) = 6.4 (H-2); 3.46 dd, 1 H, *J*(1a,2) = 3.1, *J*(gem) = 10.5 (H-1a); 3.28 dd, 1 H, *J*(1b,2) = 8.1, *J*(gem) = 10.5 (H-1b); 1.14 d, 3 H, *J*(2,3) = 6.4 (H-3).

Bis(2-propyl) (*R*)-1-Benzyloxy-2-propyloxymethanephosphonate (*VIII*)

A solution of (*R*)-1-benzyloxy-2-propanol (*VI*) (83 g, 0.5 mol) in tetrahydrofuran (350 ml, freshly distilled from sodium hydride) was added dropwise under stirring and exclusion of moisture to a suspension of sodium hydride (13.2 g, 0.55 mol) (freshly washed with light petroleum from its dispersion in paraffin oil) in tetrahydrofuran (600 ml) and the reaction mixture was stirred for another 1 h at ambient temperature. The mixture was then cooled with ice and bis(2-propyl) *p*-toluenesulfonyloxymethanephosphonate (*XIII*) was added in one portion. The mixture was stirred for 3 h at 0 °C and 72 h at ambient temperature. The solvent was evaporated in vacuo, the residue diluted with ethyl acetate and extracted with water (3 × 100 ml). The organic layer was dried over magnesium sulfate, evaporated in vacuo and the residue was purified by chromatography on a silica gel column (1 l) in toluene to afford bis(2-propyl) (*R*)-1-benzyloxy-2-propyloxymethanephosphonate (*VIII*; 71 g, 41%). For $C_{17}H_{29}O_5P$ (344.4) calculated: 59.28% C, 8.49% H, 9.01% P; found: 59.14% C, 8.32% H, 9.13% P. Mass spectrum (*m/z*): 345.3 (M + 1).

Further elution with toluene gave (*R*)-1-benzyloxypropyl *p*-toluenesulfonate (*XX*) (48.2 g, 30%). For $C_{17}H_{20}O_4S$ (320.4) calculated: 63.73% C, 6.29% H, 10.01% S; found: 64.01% C, 6.35% H, 9.88% S. Mass spectrum (*m/z*): 321.1 (M + 1), 319.1 (M – 1). ^{1}H NMR spectrum was identical with that of an authentic material (vide infra).

(*R*)-2-[Bis(2-propyl)phosphonylmethoxy]propyl *p*-Toluenesulfonate (*X*)

A. Bis(2-propyl) (*R*)-1-benzyloxy-2-propyloxymethanephosphonate (*VIII*) (68.8 g, 0.2 mol) was hydrogenated in methanol (600 ml) over 10% Pd/C catalyst (2 g) in the presence of concentrated hydrochloric acid (2 ml) overnight. The mixture was filtered through Celite and evaporated in vacuo, the residue (compound *IX*) was codistilled with pyridine (3 × 100 ml) and redissolved in pyridine (300 ml). This solution was cooled to 0 °C, 4-dimethylaminopyridine (1 g) and *p*-toluenesulfonyl chloride (47 g, 0.25 mol) were added in one portion and the mixture was stirred for 3 h at 0 °C. After standing at ambient temperature for 48 h, the mixture was concentrated in vacuo to a half, ethyl acetate (1 l) was added and the mixture was extracted with water (3 × 200 ml). The organic layer was taken down in vacuo and the residue after codistillation with toluene (3 × 200 ml) was chromatographed on a silica gel column (700 ml). The product *X* was eluted with toluene–ethyl acetate (4 : 1).

Yield 65.5 g (95%). For $C_{17}H_{29}O_7PS$ (408.4) calculated: 49.99% C, 7.16% H, 7.58% P, 7.85% S; found: 50.37% C, 7.04% H, 7.90% P, 7.35% S. Mass spectrum: 409.3 (M + 1), 325.2 (409.3 – 2 × C_3H_7). $[\alpha]_D$ +1.4° (*c* 1, DMF). ^{1}H NMR spectrum ($CDCl_3$): 7.79 m, 2 H and 7.35 m, 2 H (arom.); 4.72 m, 2 H (POCH); 3.97 m, 2 H (H-1); 3.80 m, 1 H (H-2); 3.74 dd, 1 H, *J*(P,CHa) = 9.3, *J*(gem) = 13.4 (P-CHa); 3.70 dd, 1 H, *J*(P,CHb) = 9.0, *J*(gem) = 13.4 (P-CHb); 2.45 s, 3 H (CH_3 arom.); 1.33 d, 3 H, and 1.32 d, 3 H, and 1.31 d, 3 H, and 1.30 d, 3 H, *J* = 6.2 (4 × CH_3CH); 1.17 d, 3 H, *J*(2,3) = 6.4 (H-3).

B. Compound *VI* (33 g, 0.2 mol) was converted into the chloromethyl derivative *VII* which reacted further with tri(2-propyl) phosphite as described for compound *XVI* to give the crude phosphonic acid diester *VIII* (32 g). This was hydrogenated in methanol (300 ml) over 10% Pd/C catalyst (1 g) in the presence of concentrated hydrochloric acid (0.5 ml) overnight. The work-up and the subsequent reaction with *p*-toluenesulfonyl chloride were the same as described in method *A* and afforded (*R*)-2-[bis(2-propyl)phosphonylmethoxy]propyl *p*-toluenesulfonate (*X*) (24 g, 30%, related to compound *VI*).

(*S*)-1-Benzyloxy-2-propanol (*XIV*)

The synthesis was performed essentially as described for the (*R*)-enantiomer *VI*, starting from (*R*)-2-tetrahydropyranyloxypropanol[3] (42 g, 0.262 mol). (*S*)-1-Benzyloxypropanol (*XIV*) was obtained by distillation in vacuo (33 g, 76%, b.p. 100–105 °C/20 Pa), $[\alpha]_D$ +13.6° (*c* 0.5, $CHCl_3$).

Bis(2-propyl) (*S*)-1-Benzyloxy-2-propyloxymethanephosphonate (*XVI*)

Compound *XIV* (61 g, 0.37 mol) in 1,2-dichloroethane (200 ml) was stirred with paraformaldehyde (20 g) and calcium chloride (10 g) under simultaneous introduction of dry hydrogen chloride for 2 h at 0 °C. The mixture was taken down in vacuo and the residue of crude *XV* was codistilled with toluene (3 × 50 ml). Tris(2-propyl) phosphite (50 g) was added, the mixture was heated at 110 °C under stirring and the evolved volatile material was continuously removed by distillation through a column. After the exothermic reaction had subsided, the mixture was heated up to 150 °C and the volatiles were distilled off at 140 °C/1 kPa. The resulting material was filtered through a column (200 ml) of alumina which was then washed with benzene (0.5 l). The eluate was evaporated and the residue distilled in vacuo to yield bis(2-propyl) (*S*)-1-benzyloxy-2-propyloxymethanephosphonate (*XVI*) (44 g, 35%), b.p. 125–130 °C/13 Pa. For $C_{17}H_{29}O_5P$ (344.4) calculated: 59.28% C, 8.49% H, 9.01% P; found: 59.44% C, 8.28% H, 9.30% P. Mass spectrum (*m/z*): 345.1 (M + 1), 261.1 (M + 1 – 2 × C_3H_7).

(*S*)-2-[Bis(2-propyl)phosphonylmethoxy]propyl *p*-Toluenesulfonate (*XVIII*)

Compound *XVI* (44 g, 0.128 mol) in methanol (400 ml) was hydrogenated over 10% Pd/C (1.5 g) in the presence of concentrated hydrochloric acid (0.7 ml) at atmospheric pressure overnight. The catalyst was filtered off, the filtrate was made alkaline with triethylamine and evaporated in vacuo. A solution of the residue in ether (200 ml) was washed with water (2 × 20 ml), dried over magnesium sulfate and evaporated in vacuo to afford bis(2-propyl) (*S*)-1-hydroxy-2-propyloxymethanephosphonate (*XVII*) (24.4 g, 75%) as colourless oil. Mass spectrum (*m/z*): 255.2 (M + H). For $C_{10}H_{23}O_5P$ (254.3) calculated: 47.22% C, 9.12% H, 12.19% P; found: 47.60% C, 9.15% H, 11.90% P.

A stirred mixture of *VII*, obtained above (24.4 g, 96 mmol), 4-dimethylaminopyridine (1 g) and pyridine (200 ml) was treated dropwise at 0 °C with a solution of tosyl chloride (22 g, 0.115 mol) in pyridine (100 ml) and was left at 0 °C overnight. Water (10 ml) was added and the solvent evaporated in vacuo to about half of the original volume. Ethyl acetate (300 ml) was added, the mixture was washed successively (100 ml portions) with water, 1 M HCl (to acidic reaction), water, saturated

sodium hydrogen carbonate and water. The solution was finally dried with magnesium sulfate and evaporated in vacuo to afford crude product which was purified by chromatography on a column of silica gel (elution with chloroform). (*S*)-2-[Bis(2-propyl)phosphonylmethoxy]propyl *p*-toluenesulfonate (*XVIII*) (28 g, 72%) was obtained as a thick yellowish oil that was used for further preparations. Mass spectrum (*m/z*): 409.4 (M + H). For $C_{17}H_{29}O_7PS$ (408.4) calculated: 49.99% C, 7.16% H, 7.58% P, 7.85% S; found: 50.12% C, 7.30% H, 7.70% P, 8.03% S. $[\alpha]_D$ +0.5° (*c* 1, DMF). Its ^{1}H NMR spectrum was identical with that of compound *X*.

Bis(2-propyl) (*R*)-9-(2-Phosphonomethoxypropyl)adenine (*XIa*)

A mixture of adenine (2.7 g, 20 mmol) and cesium carbonate (3.3 g, 10 mmol) in dimethylformamide (50 ml) was stirred at 100 °C for 1 h; a solution of (*R*)-2-[(bis(2-propyl)phosphonylmethoxy]propyl *p*-toluenesulfonate (*X*) (9 g, 22 mmol) in dimethylformamide (20 ml) was added in one portion and the mixture was stirred at 110 °C under exclusion of moisture for 16 h. The mixture was evaporated in vacuo and the residue was extracted with boiling chloroform (3 × 100 ml), filtered and evaporated in vacuo. This crude material was purified by silica gel chromatography (200 ml) in chloroform–methanol (9 : 1) to give bis(2-propyl) (*R*)-9-(2-phosphonomethoxypropyl)adenine (*XIa*) which crystallized from ether. Yield 4.8 g (64%), m.p. 106 °C. For $C_{15}H_{26}N_5O_4P$ (371.5) calculated: 48.50% C, 7.06% H, 18.86% N, 8.36% P; found: 48.78% C, 7.22% H, 18.77% N, 8.23% P. $[\alpha]_D$ –2.38° (*c* 1, DMF). ^{1}H NMR spectrum ($(CD_3)_2SO$): 8.15 s, 1 H and 8.07 s, 1 H (H-2 and H-8); 7.29 br s, 2 H (NH_2); 4.49 d sept, 2 H, *J*(P,OCH) = 7.6, *J*(CH,CH_3) = 6.1 (POCH); 4.26 dd, 1 H, *J*(1′a,2′) = 3.7, *J*(gem) = 14.4 (H-1′a); 4.17 dd, 1 H, *J*(1′b,2′) = 6.6, *J*(gem) = 14.4 (H-1′b); 3.96 m, 1 H (H-2′); 3.79 dd, 1 H, *J*(P,CHa) = 9.3, *J*(gem) = 13.7 (P-CHa); 3.72 dd, 1 H, *J*(P,CHb) = 9.3, *J*(gem) = 13.7 (P-CHb); 1.19 d, 3 H, and 1.15 d, 3 H, and 1.115 d, 3 H, and 1.08 d, 3 H, *J* = 6.1 (4 × CH_3CH); 1.16 d, 3 H, *J*(3′,2′) = 6.3 (H-3′).

Bis(2-propyl) (*R*)-9-(2-Phosphonomethoxypropyl)-2,6-diaminopurine (*XIb*)

A mixture of 2,6-diaminopurine (8.25 g, 55 mmol), sodium hydride (60% dispersion in paraffin oil; 2.2 g, 55 mmol) and dimethylformamide (100 ml) was stirred for 1 h at 100 °C under exclusion of moisture and then compound *X* (21.6 g, 50 mmol) in dimethylformamide (50 ml) was added in one portion. After stirring at 100 °C for 16 h, the solvent was evaporated at 40 °C/13 Pa, the residue was codistilled with toluene (3 × 50 ml) and extracted with hot chloroform (3 × 200 ml). The extract was filtered through Celite and evaporated in vacuo. The residue was chromatographed on a silica gel column (200 ml) with chloroform–methanol gradient. Chloroform–methanol (4 : 1) eluted amorphous bis(2-propyl) ester *XIb* (12.0 g, 62%). M.p. 164 °C. $[\alpha]_D$ –12.4° (*c* 1, DMF). For $C_{15}H_{27}N_6O_4P$ (386.4) calculated: 46.63% C, 7.04% H, 21.75% N, 8.02% P; found: 46.80% C, 7.12% H, 22.02% N, 8.18% P. ^{1}H NMR spectrum ($(CD_3)_2SO$): 7.64 s, 1 H (H-8); 6.68 s, 2 H, and 5.77 s, 2 H (NH_2); 4.52 m, 2 H (POCH); 4.04 dd, 1 H, *J*(1′a,2′) = 3.7, *J*(gem) = 14.2 (H-1′a); 3.97 dd, 1 H, *J*(1′b,2′) = 6.6, *J*(gem) = 14.2 (H-1′b); 3.90 pent d, 1 H, *J*(2′,1′a) = 3.7, *J*(2′,3′) = 6.1, *J*(2′,1′b) = 6.6 (H-2′); 3.77 dd, 1 H, *J*(P,CHa) = 9.3, *J*(gem) = 13.7 (P-CHa); 3.68 dd, 1 H, *J*(P,CHb) = 9.5, *J*(gem) = 13.7 (P-CHb); 1.21 d, 3 H, and 1.19 d, 3 H, and 1.18 d, 3 H, and 1.15 d, 3 H, *J*(CH_3,CH) = 6.1 (4 × CH_3CH); 1.07 d, 3 H, *J*(3′,2′) = 6.1 (H-3′).

Bis(2-propyl) (*R*)-9-(2-Phosphonomethoxypropyl)-3-deazaadenine (*XIc*)

A mixture of 3-deazaadenine (1.45 g, 10.8 mmol), cesium carbonate (1.75 g, 5.4 mmol) and dimethylformamide (25 ml) was stirred at 100 °C for 1 h and a solution of (*R*)-2-[bis(2-propyl)phosphonylmethoxy]propyl *p*-toluenesulfonate (*X*) (3.67 g, 9 mmol) in dimethylformamide (10 ml) was

added in one portion. The mixture was then heated for 24 h at 110 °C under exclusion of moisture and taken down to dryness. The residue was extracted with boiling chloroform (300 ml total), filtered and the filtrate evaporated. The residue was chromatographed on a column of silica gel (300 ml) in chloroform. Crystallization from ethyl acetate–light petroleum gave bis(2-propyl) (*R*)-9-(2-phosphonomethoxypropyl)-3-deazaadenine (*XIc*) (1.07 g, 32%), m.p. 122 °C. For $C_{16}H_{27}N_4O_4P$ (370.5) calculated: 51.87% C, 7.35% H, 15.13% N, 8.38% P; found: 52.03% C, 7.69% H, 15.15% N, 8.59% P. UV spectrum (pH 2): λ_{max} 262 (ε 16 500). ^{1}H NMR spectrum ($(CD_3)_2SO$): 7.99 s, 1 H (H-8); 7.66 d, 1 H, *J*(2,3) = 5.9 (H-2); 6.85 d, 1 H, *J*(2,3) = 5.9 (H-3); 6.16 br s, 2 H (NH_2); 4.50 m, 2 H, *J*(P,OCH) = 7.3, *J*(CH,CH_3) = 6.1 (POCH); 4.29 dd, 1 H, *J*(1′a,2′) = 4.2, *J*(gem) = 14.6 (H-1′a); 4.16 dd, 1 H, *J*(1′b,2′) = 6.1, *J*(gem) = 14.6 (H-1′b); 3.90 m, 1 H (H-2′); 3.78 dd, 1 H, *J*(P,CHa) = 9.1, *J*(gem) = 13.9 (P-CHa); 3.67 dd, 1 H, *J*(P,CHb) = 9.5, *J*(gem) = 13.9 (P-CHb); 1.19 d, 3 H, and 1.16 d, 6 H, and 1.13 d, 3 H, and 1.07 d, 3 H, *J* = 6.1 (5 × CH_3).

Bis(2-propyl) (*R*)-9-(2-Phosphonomethoxypropyl)-2-amino-6-chloropurine (*XId*)

Sodium hydride (60% dispersion; 1.4 g, 35 mmol) was added to a stirred solution of 2-amino-6-chloropurine (5.94 g, 35 mmol) in dimethylformamide (60 ml) and, after stirring at ambient temperature for 1 h, (*R*)-2-[bis(2-propyl)phosphonylmethoxy]propyl *p*-toluenesulfonate (*X*) (12.2 g, 30 mmol) in dimethylformamide (20 ml) was added. The mixture was stirred at 80 °C for 10 h and evaporated in vacuo. The residue was extracted with boiling chloroform (300 ml), filtered and the filtrate was evaporated in vacuo. Column chromatography on silica gel (chloroform–methanol, 95 : 5) and crystallization from ethyl acetate (light petroleum added to turbidity) gave bis(2-propyl) (*R*)-9-(2-phosphonomethoxypropyl)-2-amino-6-chloropurine (*XId*) (10.7 g, 88%), m.p. 134–135 °C. $[\alpha]_D$ –24.3° (*c* 1, DMF), R_F 0.55 (S2). For $C_{15}H_{25}ClN_5O_4P$ (405.9) calculated: 44.38% C, 6.21% H, 8.74% Cl, 17.26% N, 7.65% P; found: 44.45% C, 6.35% H, 8.52% Cl, 16.88% N, 7.74% P. ^{1}H NMR spectrum ($(CD_3)_2SO$): 8.03 s, 1 H (H-8); 6.89 s, 2 H (NH_2); 4.50 m, 2 H, *J*(P,OCH) = 7.6 (POCH); 4.16 dd, 1 H, *J*(1′a,2′) = 4.4, *J*(gem) = 14.4 (H-1′a); 4.05 dd, 1 H, *J*(1′b,2′) = 7.3, *J*(gem) = 14.4 (H-1′b); 3.94 m, 1 H (H-2′); 3.79 dd, 1 H, *J*(P,CHa) = 9.0, *J*(gem) = 13.7 (P-CHa); 3.67 dd, 1 H, *J*(P,CHb) = 9.5, *J*(gem) = 13.7 (P-CHb); 1.19 d, 3 H, and 1.14 d, 6 H, *J* = 6.3, and 1.11 d, 3 H, *J* = 6.1, and 1.09 d, 3 H, *J* = 6.3 (5 × CH_3).

Further elution gave 1.15 g of crude compound *XXIV*, m.p. 139–140 °C (ethyl acetate–light petroleum), R_F 0.47 (S2). For $C_{15}H_{25}ClN_5O_4P$ (405.9) calculated: 44.38% C, 6.21% H, 8.74% Cl, 17.26% N, 7.65% P; found: 44.45% C, 6.37% H, 8.90% Cl, 17.17% N, 7.34% P. ^{1}H NMR spectrum ($(CD_3)_2SO$) (major component, about 70%): 8.24 s, 1 H (H-8); 6.61 s, 2 H (NH_2); 4.45 m, 2 H (POCH); 4.38 dd, 1 H, *J*(1′a,2′) = 3.2, *J*(gem) = 14.7 (H-1′a); 4.28 dd, 1 H, *J*(1′b,2′) = 9.2, *J*(gem) = 14.7 (H-1′b); 3.92 m, 1 H (H-2′); 3.75 dd, 1 H, *J*(P,CHa) = 9.0, *J*(gem) = 13.9 (P-CHa); 3.59 dd, 1 H, *J*(P,CHb) = 9.2, *J*(gem) = 13.9 (P-CHb); 1.17 d, 3 H, and 1.14 d, 6 H, and 1.11 d, 3 H, and 1.08 d, 3 H, *J*(CH_3,CH) = 6.1 (5 × CH_3).

Bis(2-propyl) (*R*)-9-(2-Phosphonomethoxypropyl)guanine (*XIe*)

A mixture of compound *XId* (2.02 g, 5 mmol), potassium carbonate (0.70 g), DABCO (0.65 g) and water (60 ml) was refluxed for 2 h, cooled, acidified by addition of Dowex 50 X 8 (H^+ form), made alkaline with triethylamine, filtered, and the resin was washed thoroughly with methanol. The filtrate was evaporated in vacuo to dryness and the residue was purified by preparative TLC on a silica gel plate (see above) in chloroform–methanol (85 : 15). The band of the product was eluted with methanol, evaporated and crystallized from ethanol (ether added to turbidity). Yield 1.35 g (70%), m.p. 208 °C, $[\alpha]_D$ –8.5° (*c* 1, DMF). For $C_{15}H_{26}N_5O_5P$ (387.4) calculated: 46.51% C, 6.77% H, 18.08% N, 8.00% P; found: 46.70% C, 6.92% H, 17.77% N, 7.68% P. ^{1}H NMR spectrum ($(CD_3)_2SO$): 10.58 brs, 1 H

(NH); 7.61 s, 1 H (H-8); 6.46 brs, 2 H (NH_2); 4.51 m, 2 H (POCH); 4.02 dd, 1 H, *J*(1′a,2′) = 3.7, *J*(gem) = 14.2 (H-1′a); 3.94 dd, 1 H, *J*(1′b,2′) = 6.8, *J*(gem) = 14.2 (H-1′b); 3.88 pent d, 1 H, *J*(2′,3′) = *J*(2′,1′b) = 6.4, *J*(2′,1′a) = 3.7 (H-2′); 3.76 dd, 1 H, *J*(P,CHa) = 9.0, *J*(gem) = 13.7 (P-CHa); 3.67 dd, 1 H, *J*(P,CHb) = 9.5, *J*(gem) = 13.7 (P-CHb); 1.21 d, 3 H, and 1.19 d, 3 H, and 1.18 d, 3 H, and 1.16 d, 3 H, and 1.07 d, 3 H, *J*(CH_3,CH) = 6.1 (5 × CH_3).

Bis(2-propyl) (*R*)-9-(2-Phosphonomethoxypropyl)-6-chloropurine (*XIi*)

Sodium hydride (60% dispersion in paraffin; 0.40 g, 10 mmol) was added to a solution of 6-chloropurine (1.55 g, 10 mmol) in dimethylformamide (25 ml) and the mixture was stirred for 1 h at ambient temperature. A solution of (*R*)-2-[bis(2-propyl)phosphonylmethoxy]propyl *p*-toluenesulfonate (*X*) (6.5 g, 16 mmol) in dimethylformamide (50 ml) was added and the mixture was stirred at 60 °C for 8 h. The solvent was then evaporated in vacuo and the residue was extracted with hot chloroform (250 ml total). The extract was then evaporated in vacuo and the residue chromatographed on a column (250 ml) of silica gel. The product was eluted with chloroform–methanol (95 : 5). Yield 2.35 g (60%) oily bis(2-propyl) (*R*)-9-(2-phosphonomethoxypropyl)-6-chloropurine (*XIi*), R_F 0.70 (S2), m.p. 148–150 °C (ethyl acetate–light petroleum), $[\alpha]_D$ –43.7° (*c* 0.5, 0.1 M HCl). For $C_{15}H_{24}ClN_4O_4P$ (390.9) calculated: 46.10% C, 6.19% H, 9.07% Cl, 14.34% N, 7.93% P; found: 46.33% C, 6.30% H, 9.15% Cl, 14.45% N, 8.12% P. Mass spectrum (*m/z*): 391 (M^+), 348 (M – C_3H_7), 306 (M – 2 × C_3H_7). ^{1}H NMR spectrum ($(CD_3)_2SO$): 8.77 s, 1 H, and 8.61 s, 1 H (H-2 and H-8); 4.49 m, 2 H, *J*(P,OCH) = 7.6 (POCH); 4.45 dd, 1 H, *J*(1′a,2′) = 3.6, *J*(gem) = 14.3 (H-1a′); 4.30 dd, 1 H, *J*(1′b,2′) = 7.00, *J*(gem) = 14.3 (H-1′b); 4.02 m, 1 H (H-2′); 3.82 dd, 1 H, *J*(P,CHa) = 9.2, *J*(gem) = 13.7 (P-CHa); 3.68 dd, 1 H, *J*(P,CHb) = 9.8, *J*(gem) = 13.7 (P-CHb); 1.33 d, 3 H, and 1.13 d, 3 H, *J* = 6.1, and 1.12 d, 6 H, *J* = 6.3 (CH_3); 1.05 d, 3 H, *J*(3′,2′) = 6.1 (H-3′).

Bis(2-propyl) (*S*)-9-(2-Phosphonomethoxypropyl)adenine (*XIXa*)

A mixture of adenine (1.62 g, 12 mmol) and cesium carbonate (2.1 g, 6.5 mmol) in dimethylformamide was stirred at 100 °C and a solution of (*S*)-2-[(bis(2-propyl)phosphonylmethoxy]propyl *p*-toluenesulfonate (*XVIII*) (4.1 g, 10 mmol) in dimethylformamide (10 ml) was added. The stirred mixture was heated at 110 °C with exclusion of moisture for 8 h and then evaporated in vacuo. The residue was triturated with boiling chloroform (3 × 50 ml), filtered and evaporated in vacuo. On purification by silica gel (150 ml) chromatography, this crude material afforded bis(2-propyl) (*S*)-9-(2-phosphonomethoxypropyl)adenine (*XIXa*) which crystallized from ether (1.7 g, 46%), m.p. 105 °C. For $C_{15}H_{26}N_5O_4P$ (371.5) calculated: 48.50% C, 7.06% H, 18.86% N, 8.36% P; found: 48.27% C, 7.15% H, 18.85% N, 8.44% P. $[\alpha]_D$ +5.5° (*c* 1, DMF). ^{1}H NMR spectrum was identical with that of compound *XIa*.

Bis(2-propyl) (*S*)-9-(2-Phosphonomethoxypropyl)-2-amino-6-chloropurine (*XIXd*)

Sodium hydride (60% dispersion; 1.4 g, 35 mmol) was added to a stirred solution of 2-amino-6-chloropurine (5.94 g, 35 mmol) in dimethylformamide (60 ml) and, after stirring at ambient temperature for 1 h, (*S*)-2-[bis(2-propyl)phosphonylmethoxy]propyl *p*-toluenesulfonate (*X*) (12.2 g, 30 mmol) in dimethylformamide (20 ml) was added. The mixture was stirred at 80 °C for 10 h and evaporated in vacuo. The mixture was worked up as described for compound *XId* to give bis(2-propyl) (*R*)-9-(2-phosphonomethoxypropyl)-2-amino-6-chloropurine (*XIXd*) as a thick oil, R_F 0.55 (S2). Crystallization from ethyl acetate (petroleum ether to turbidity) afforded 7.5 g (53%) of product *XIXd*, m.p. 132 °C. $[\alpha]_D$ +21.4° (*c* 1, DMF). For $C_{15}H_{25}ClN_5O_4P$ (405.9) calculated: 44.38% C, 6.21% H, 8.74% Cl,

17.26% N, 7.65% P; found: 44.28% C, 6.30% H, 8.80% Cl, 17.34% N, 7.80% P. ^{1}H NMR spectrum was identical with that of the (*R*)-isomer.

Further elution of the column gave 1.10 g of crude compound *XXV*, m.p. 146 °C (ethyl acetate–light petroleum). $[\alpha]_D$ +44.1° (*c* 1, DMF). For $C_{15}H_{25}ClN_5O_4P$ (405.9) calculated: 44.38% C, 6.21% H, 8.74% Cl, 17.26% N, 7.65% P; found: 44.52% C, 6.17% H, 8.55% Cl, 17.30% N, 7.76% P. ^{1}H NMR spectrum was essentially identical with that of compound *XXIV* (vide supra).

Bis(2-propyl) (*S*)-9-(2-Phosphonomethoxypropyl)guanine (*XIXe*)

A mixture of compound *XIXd* (2.02 g, 5 mmol), potassium carbonate (0.70 g), DABCO (0.65 g) and water (60 ml) was refluxed for 2 h, cooled, and worked up as described for compound *XIe*. The crude product was purified by preparative TLC on a silica gel plate (see above) in chloroform–methanol (85 : 15). The zone of the product was eluted with methanol, evaporated and crystallized from ethanol (ether added to turbidity). Yield of *XIXe* 1.20 g (62%), m.p. 201 °C, $[\alpha]_D$ +9.7° (*c* 1, DMF). For $C_{15}H_{26}N_5O_5P$ (387.4) calculated: 46.51% C, 6.77% H, 18.08% N, 8.00% P; found: 46.77% C, 7.01% H, 18.12% N, 8.34% P. ^{1}H NMR spectrum was identical with that of compound *XIe* (vide supra).

(*R*)-9-(2-Phosphonomethoxypropyl)adenine (*Ia*)

Compound *XIa* (1.8 g, 4.9 mmol) was treated with bromotrimethylsilane (3 ml) in acetonitrile (30 ml) overnight and evaporated in vacuo. This material was redissolved in water (50 ml), made alkaline with aqueous ammonia and evaporated in vacuo. The residue was desalted on a Dowex 50 column as described above and the ammonia eluate was evaporated in vacuo. The residue was desalted and purified by chromatography on a Dowex 1 X 2 column (100 ml). The column was washed with water until the UV absorption dropped and then with 1 M acetic acid. The UV-absorbing eluate was evaporated in vacuo, the residue was codistilled with water (3 × 50 ml) and dissolved in boiling water. Ethanol (three volumes) was added and the mixture crystallized overnight in a refrigerator. Yield 80% of (*R*)-9-(2-phosphonomethoxypropyl)adenine (*Ia*), m.p. 279 °C, $[\alpha]_D$ +21° (*c* 1, 0.1 M HCl). For $C_9H_{14}N_5O_4P$ (287.3) calculated: 37.62% C, 4.91% H, 24.38% N, 10.80% P; found: 37.35% C, 5.06% H, 24.48% N, 11.04% P.

(*R*)-9-(2-Phosphonomethoxypropyl)-2,6-diaminopurine (*Ib*)

A. Compound *XIb* (12.5 g, 32.3 mmol) was treated with bromotrimethylsilane (20 ml) in acetonitrile (150 ml) overnight. After evaporation in vacuo, the residue was codistilled with acetonitrile (100 ml) and treated with water (300 ml). Concentrated aqueous ammonia was added to dissolution and the solution was taken down. The residue was codistilled with water (100 ml), then dissolved in boiling water (200 ml), and the solution was adjusted to pH 3.5 with concentrated hydrochloric acid. The mixture was left aside overnight at ambient temperature and the crystalline material was filtered, washed with water, ethanol and ether, and dried in vacuo. Yield 7.7 g (79%) of compound *Ib*, m.p. 284–285 °C. For $C_9H_{15}N_6O_4P$ (302.3) calculated: 35.75% C, 5.00% H, 27.80% N, 10.27% P; found: 35.53% C, 5.22% H, 28.08% N, 10.14% P. $[\alpha]_D$ –25.5° (*c* 0.5, 0.1 M HCl).

B. A mixture of (*R*)-9-(2-phosphonomethoxypropyl)-2-amino-6-azidopurine (*Il*) (0.30 g, 0.9 mmol), 50% aqueous methanol (200 ml) and concentrated hydrochloric acid (0.5 ml) was hydrogenated over 10% Pd/C (0.5 g) overnight at room temperature. The mixture was filtered, washed with water, the filtrate was made alkaline with ammonia and the solvent was evaporated in vacuo. The residue was deionized on a column of Dowex 50 X 8 (50 ml) and the ammonia eluate was evaporated to dryness. The residue in water (adjusted to pH 9) was applied onto a column of Dowex 1 X 2 (acetate form). The salts were washed out with water and the product was then eluted with 1 M acetic acid. The

product-containing fractions were pooled, evaporated to dryness and codistilled with water (3 × 20 ml). The residue was crystallized from water (ethanol added to turbidity) to afford (*R*)-9-(2-phosphonomethoxypropyl)-2,6-diaminopurine (*Ib*) (120 mg, 45%) identical (HPLC and NMR) with an authentic sample, m.p. 286 °C.

(*R*)-9-(2-Phosphonomethoxypropyl)-3-deazaadenine (*Ic*)

Compound *XIc* (1.0 g, 2.7 mmol) was treated with acetonitrile (25 ml) and bromotrimethylsilane (2.5 ml) overnight and the mixture was then worked up as described for compound *Ia*. Deionization and chromatography on Dowex 1 X 2 gave (*R*)-9-(2-phosphonomethoxypropyl)-3-deazaadenine (*Ic*), not melting up to 300 °C, in 78% yield. For $C_{10}H_{15}N_4O_4P$ (286.3) calculated: 41.95% C, 5.28% H, 19.57% N, 10.84% P; found: 42.03% C, 5.63% H, 19.75% N, 11.09% P. UV spectrum (pH 2): λ_{max} 262 (ε 16 500). E_{Up} 0.68 (pH 7.5). ^{1}H NMR spectrum (D_2O + NaOD): 8.25 s, 1 H (H-8); 7.39 d, 1 H, *J*(2,3) = 6.8 (H-2); 6.91 d, 1 H, *J*(2,3) = 6.8 (H-3); 4.41 dd, 1 H, *J*(1′a,2′) = 2.4, *J*(gem) = 14.4 (H-1′a); 4.13 dd, 1 H, *J*(1′b,2′) = 5.1, *J*(gem) = 14.4 (H-1′b); 4.03 m, 1 H (H-2′); 3.72 dd, 1 H, *J*(P,CHa) = 9.5, *J*(gem) = 12.2 (P-CHa); 3.64 dd, 1 H, *J*(P,CHb) = 9.8, *J*(gem) = 12.2 (P-CHb); 0.89 d, 3 H, *J*(3′,2′) = 6.1 (H-3′).

(*R*)-9-(2-Phosphonomethoxypropyl)guanine (*Ie*)

A mixture of compound *XIe* (0.97 g, 2.5 mmol), acetonitrile (25 ml) and bromotrimethylsilane (2 ml) was left overnight at room temperature, evaporated and treated with water (50 ml). The solution was made alkaline with aqueous ammonia and the mixture was evaporated. The residue was deionized on a column of Dowex 50 X 8 (H^+ form, 50 ml) and the residue was applied in a slightly alkaline solution on a column (25 ml) of Dowex 1 X 2 (acetate form). The column was washed with water till the UV absorption dropped. The resin was suspended in 1 M acetic acid (150 ml), filtered and washed with boiling 0.5 M acetic acid (500 ml). The filtrates were combined and the solvent was evaporated. The residue was codistilled with water (3 × 50 ml) and then dissolved in boiling water. Ethanol (4 volumes) was added to the hot solution. On standing overnight in a refrigerator, the mixture afforded compound *Ie* (72% yield), identical with the authentic sample[3]. M.p. 286 °C, $[\alpha]_D$ –26.8° (*c* 1, 0.1 M HCl).

(*R*)-9-(2-Phosphonomethoxypropyl)-2-amino-6-thiopurine (*If*)

A solution of bis(2-propyl) (*R*)-9-(2-phosphonomethoxypropyl)-2-amino-6-chloropurine (*XId*) (2.5 g, 6.2 mmol) and thiourea (2.0 g) in absolute ethanol (100 ml) was stirred and refluxed for 1 h, made alkaline with triethylamine and evaporated. The residue was extracted with chloroform (2 × 100 ml), filtered and the filtrate was evaporated to dryness in vacuo. The remaining compound *XIf* (R_F 0.40, S2) was dried over phosphorus pentoxide overnight and treated with acetonitrile (30 ml) and bromotrimethylsilane (3 ml). After standing overnight at room temperature, the mixture was evaporated to dryness and the residue was dissolved in water (50 ml). After standing for 30 min, it was made alkaline with aqueous ammonia, the solvent was evaporated in vacuo and the residue was deionized on Dowex 50 (vide supra). The ammonia eluate was taken down in vacuo and applied on a column of Dowex 1 X 2 (acetate form, 150 ml) which was washed first with water and then with 1 M acetic acid (500 ml each); these eluates were discarded. The resin was stirred with 2 M formic acid (500 ml), filtered and washed with boiling water (1 l total). The filtrate was evaporated to dryness, the residue was codistilled with water (3 × 50 ml) and crystallized from water (equal volume of ethanol was added after dissolution). Yield 1.0 g (50%) of (*R*)-9-(2-phosphonomethoxypropyl)-2-amino-6-thiopurine (*If*), m.p. 188 °C (decomp.). For $C_9H_{14}N_5O_4PS$ (319.3) calculated: 33.85% C, 4.42% H,

21.94% N, 9.72% P, 10.04% S; found: 33.83% C, 4.69% H, 22.15% N, 9.99% P, 10.30% S. ^{1}H NMR spectrum (D_2O + NaOD): 8.05 s, 1 H (H-8); 4.20 dd, 1 H, *J*(1′a,2′) = 4.3, *J*(gem) = 14.6 (H-1′a); 4.09 dd, 1 H, *J*(1′b,2′) = 5.8, *J*(gem) = 14.6 (H-1′b); 3.98 m, 1 H (H-2′); 3.57 dd, 1 H, *J*(P,CHa) = 9.5, *J*(gem) = 12.2 (P-CHa); 3.46 dd, 1 H, *J*(P,CHb) = 9.5, *J*(gem) = 12.2 (P-CHb); 1.12 d, 3 H, *J*(3′,2′) = 6.1 (H-3′).

(*R*)-9-(2-Phosphonomethoxypropyl)-2-amino-6-dimethylaminopurine (*Ig*)

A mixture of bis(2-propyl) (*R*)-9-(2-phosphonomethoxypropyl)-2-amino-6-chloropurine (*XId*) (0.50 g) and 20% dimethylamine in methanol (70 ml) was heated to 110 °C for 20 h in a pressure vessel and the solution was evaporated in vacuo. The residue in 50% aqueous methanol (20 ml) was applied onto a column (50 ml) of Dowex 50 X 8 (H^+ form) in 20% aqueous methanol and the column was washed with the same eluent until the UV absorption dropped to the original value. The column was then washed with 2.5% ammonia solution in 20% aqueous methanol and the UV-absorbing eluate was taken to dryness. The residue was codistilled twice with ethanol (25 ml each) and dried over phosphorus pentoxide at 13 Pa. The resulting product *XIg* was treated with acetonitrile (30 ml) and bromotrimethylsilane (3 ml) overnight at room temperature and the solution was evaporated in vacuo. Water (50 ml) was added, the mixture was made alkaline by addition of concentrated aqueous ammonia and the solution was evaporated. Further work-up and purification was performed essentially as described for compound *Ia*. Yield 0.40 g (95%) of (*R*)-9-(2-phosphonomethoxypropyl)-2-amino-6-dimethylaminopurine (*Ig*), m.p. 154–156 °C, $[\alpha]_D$ –10.6° (*c* 0.5, 0.1 M HCl). For $C_{11}H_{19}N_6O_4P$ (330.3) calculated: 40.00% C, 5.80% H, 25,44% N, 9.38% P; found: 39.54% C, 5.75% H, 24.78% N, 8.92% P. ^{1}H NMR spectrum (D_2O + NaOD): 7.79 s, 1 H (H-8); 4.16 dd, 1 H, *J*(1′a, 2′) = 3.7, *J*(gem) = 14.6 (H-1′a); 4.06 dd, 1 H, *J*(1′b,2′) = 6.4, *J*(gem) = 14.6 (H-1′b); 3.91 m, 1 H (H-2′); 3.65 dd, 1 H, *J*(P,CHa) = 9.3, *J*(gem) = 12.9 (P-CHa); 3.47 dd, 1 H, *J*(P,CHb) = 9.5, *J*(gem) = 12.9 (P-CHb); 3.27 s, 6 H (NCH_3); 1.165 d, 3 H, *J*(3′,2′) = 6.3 (H-3′).

(*R*)-9-(2-Phosphonomethoxypropyl)hypoxanthine (*Ih*)

Concentrated hydrochloric acid (2 ml) was added to an ice-cold solution of (*R*)-9-(2-phosphonomethoxypropyl)adenine (*Ia*) (400 mg, 1.4 mmol) and sodium nitrite (1.4 g, 20 mmol) in water (40 ml). The mixture was stirred in an argon atmosphere at 0 °C for 3 h and then overnight at ambient temperature. The mixture was applied onto a column of Dowex 50 X 8 (H^+ form, 100 ml) and the column was eluted with water. The fraction of the product was evaporated in vacuo, the residue was codistilled with ethanol (2 × 50 ml) and the crystalline residue was filtered with ether. Yield 250 mg (62%) of (*R*)-9-(2-phosphonomethoxypropyl)hypoxanthine (*Ih*), m.p. 192 °C. $[\alpha]_D$ –23.6° (*c* 1, 0.1 M HCl). UV spectrum (pH 2): λ_{max} 251 nm. For $C_9H_{13}N_4O_5P$ (288.3) calculated: 37.50% C, 4.54% H, 19.44% N, 10.77% P; found: 37.35% C, 4.55% H, 19.22% N, 10.86% P.

(*R*)-9-(2-Phosphonomethoxypropyl)-6-mercaptopurine (*Ij*)

Compound *XIi* (2.2 g, 7.1 mmol) was treated with thiourea (2 g) in boiling ethanol (100 ml) for 1 h, the solution was made alkaline with triethylamine, taken down to dryness and the residue was extracted with chloroform (200 ml). The extract was evaporated in vacuo and the remaining compound *XIj* (R_F 0.63, S2) was dried in vacuo. Acetonitrile (40 ml) and bromotrimethylsilane (4 ml) were added, and the mixture was stirred till dissolution. The solution was left to stand overnight at room temperature, the solvent was evaporated in vacuo and the dry residue was dissolved in water (100 ml). Concentrated aqueous ammonia was added and the alkaline solution was then evaporated in vacuo. The residue in water (20 ml) (made alkaline with ammonia) was applied onto a column of Sephadex A-25

(150 ml) equilibrated with 0.05 M triethylammonium hydrogen carbonate (pH 7.5). The column was washed with the same buffer until the absorption of the eluate dropped to the original value, and then with linear gradient of triethylammonium hydrogen carbonate (pH 7.5) (0.02 M–0.2 M, 1 l each). The main UV-absorbing fraction was taken down to dryness. The residue was codistilled with methanol (5 × 50 ml) in vacuo, dissolved in water (10 ml) and applied on a column of Dowex 1 X 2 (acetate form, 50 ml). The column was washed with water and the ion exchanger was stirred with 10% aqueous formic acid (200 ml) for 15 min. The suspension was filtered and the resin was washed repeatedly with boiling water (total, 1 l). Upon concentration in vacuo and recrystallization from water, the filtrate afforded (*R*)-9-(2-phosphonomethoxypropyl)-6-mercaptopurine (*Ij*) (0.90 g, 49%), m.p. 156–158 °C, $[\alpha]_D$ –1.7° (*c* 0.5, 0.1 M HCl). For $C_9H_{13}N_4O_4PS$ (304.3) calculated: 35.52% C, 4.31% H, 18.42% N, 10.19% P, 10.50% S; found: 35.34% C, 4.70% H, 18.26% N, 10.76% P, 10.64 %S. ^{1}H NMR spectrum (D_2O + NaOD): 8.72 s, 1 H, and 8.35 s, 1 H (H-2 and H-8); 4.52 dd, 1 H, *J*(1′a,2′) = 2.0, *J*(gem) = 14.4 (H-1′a); 4.31 dd, 1 H, *J*(1′b,2′) = 6.8, *J*(gem) = 14.4 (H-1′b); 4.02 m, 1 H (H-2′); 3.79 dd, 1 H, *J*(P,CHa) = 9.5, *J*(gem) = 12.2 (P-CHa); 3.57 dd, 1 H, *J*(P,CHb) = 9.5, *J*(gem) = 12.2 (P-CHb); 1.25 d, 3 H, *J*(3′,2′) = 5.4 (H-3′).

(*R*)-9-(2-Phosphonomethoxypropyl)-2-aminopurine (*Ik*)

A solution of compound *XId* (2.5 g, 6.2 mmol) in methanol (200 ml) and concentrated hydrochloric acid (0.5 ml) was hydrogenated over 10% Pd/°C catalyst (1 g) at room temperature overnight. The catalyst was filtered off and the filtrate was made alkaline with triethylamine. After evaporation in vacuo, the residue was deionized on Dowex 50 X 8 (H^+ form) (100 ml) (elution with 20% aqueous methanol followed by 2.5% ammonia in the same solvent mixture). The ammonia eluate was evaporated and the remaining compound *XIk* was dried in vacuo over phosphorus pentoxide. Acetonitrile (25 ml) and bromotrimethylsilane (2.5 ml) were added and the solution was left aside overnight at room temperature. The mixture was evaporated to dryness and the residue was taken up in water (25 ml). After 30 min, the solution was made alkaline with ammonia and evaporated. Desalting on a Dowex 50 column and subsequent chromatography on Dowex 1 X 2 (acetate form, 150 ml) with linear gradient of acetic acid (0.75 l of water, 0.75 l of 0.5 M acetic acid) gave the product which was isolated from the pooled fractions by crystallization from aqueous ethanol (1 : 1). Yield 0.62 g (35%) of (*R*)-9-(2-phosphonomethoxypropyl)-2-aminopurine (*Ik*), m.p. 156 °C. For $C_9H_{14}N_5O_4P$ (287.3) calculated: 37.62% C, 4.91% H, 24.38% N, 10.80% P; found: 37.82% C, 5.05% H, 24.65% N, 11.06% P. ^{1}H NMR spectrum (D_2O + NaOD): 8.46 s, 1 H (H-6); 8.15 s, 1 H (H-8); 4.25 dd, 1 H, *J*(1′a,2′) = 3.5, *J*(gem) = 14.6 (H-1′a); 4.10 dd, 1 H, *J*(1′b,2′) = 6.3, *J*(gem) = 14.6 (H-1′b); 3.94 m, 1 H (H-2′); 3.70 dd, 1 H, *J*(P,CHa) = 9.3, *J*(gem) = 12.2 (P-CHa); 3.52 dd, 1 H, *J*(P,CHb) = 9.5, *J*(gem) = 12.2 (P-CHb); 1.18 d, 3 H, *J*(3′,2′) = 6.3 (H-3′).

(*R*)-9-(2-Phosphonomethoxypropyl)-2-amino-6-azidopurine (*Il*)

A solution of bis(2-propyl) (*R*)-9-(2-phosphonomethoxypropyl)-2-amino-6-chloropurine (*XId*) (2.5 g, 6.2 mmol) and lithium azide (1.0 g, 20 mmol) in dimethylformamide (40 ml) was stirred for 4 h at 100 °C under exclusion of moisture. The mixture was filtered through Celite which was then washed with dimethylformamide (20 ml), and the filtrate was evaporated in vacuo. The remaining compound *XIl* (R_F 0.30, S2) was dried over phosphorus pentoxide overnight and treated with acetonitrile (20 ml) and bromotrimethylsilane (2 ml). After standing overnight at room temperature, the mixture was evaporated to dryness and taken up in water (50 ml). After standing for 30 min, it was made alkaline with aqueous ammonia, evaporated in vacuo and the residue was applied on a Dowex 50 column (H^+ form, 100 ml). Washing with water eluted the UV-absorbing peak of the product. Evaporation of the solvent in vacuo and crystallization from water (equal volume of ethanol added after dissolution) gave 0.95 g

(47%) of (*R*)-9-(2-phosphonomethoxypropyl)-2-amino-6-azidopurine (*Il*), not melting up to 300 °C. For $C_9H_{13}N_8O_4P$ (328.3) calculated: 32.92% C, 3.99% H, 34.14% N, 9.45% P; found: 33.03% C, 4.29% H, 33.75% N, 9.59% P. ^{1}H NMR spectrum (D_2O + NaOD): Isomer *A*: 8.24 s, 1 H (H-8); 4.41 dd, 1 H, *J*(1′a,2′) = 4.3, *J*(gem) = 14.6 (H-1′a); 4.30 dd, 1 H, *J*(1′b,2′) = 5.2, *J*(gem) = 14.6 (H-1′b); 4.04 m, 1 H (H-2′); 3.57 dd, 1 H, *J*(P,CHa) = 9.1, *J*(gem) = 12.5 (P-CHa); 3.485 dd, 1 H, *J*(P,CHb) = 9.1, *J*(gem) = 12.5 (P-CHb); 1.17 d, 3 H, *J*(3′, 2′) = 6.1 (H-3′). Isomer *B*: 7.55 s, 1 H (H-8); 4.04 d, 2 H, *J*(1′,2′) = 5.2 (H-1′); 3.95 m, 1 H (H-2′); 3.57 dd, 1 H, *J*(P,CHa) = 9.1, *J*(gem) = 12.5 (P-CHa); 3.48 dd, 1 H, *J*(P,CHb) = 9.1, *J*(gem) = 12.5 (P-CHb); 1.15 d, 3 H, *J*(3′,2′) = 6.1 (H-3′).

(*S*)-9-(2-Phosphonomethoxypropyl)adenine (*IIa*)

Compound *XIXa* (1.4 g, 3.9 mmol) in acetonitrile (25 ml) was treated with bromotrimethylsilane (2.5 ml) overnight at room temperature. The mixture was taken down in vacuo and the product was desalted and purified by chromatography on a Dowex 1 X 2 column (100 ml) as described for compound *Ia*. Yield 0.85 g (77%) of compound *IIa*; m.p. 276–278 °C, $[\alpha]_D$ +28.3° (*c* 1, 0.1 M HCl). For $C_9H_{14}N_5O_4P$ (287.3) calculated: 37.62% C, 4.91% H, 24.38% N, 10.80% P; found: 37.78% C, 5.13% H, 24.15% N, 10.62% P. For ^{1}H NMR spectrum, see ref[3].

(*S*)-9-(2-Phosphonomethoxypropyl)-2,6-diaminopurine (*IIb*)

A mixture of tosylate *XVIII* (5.7 g, 14 mmol), 2,6-diaminopurine (1.5 g, 10 mmol), cesium carbonate (1.8 g, 5.4 mmol) and dimethylformamide (40 ml) was stirred at 110 °C for 6 h. The solvent was evaporated in vacuo, the residue was codistilled with toluene (2 × 25 ml) and extracted with boiling chloroform (2 × 100 ml). The residue after evaporation of the chloroform extract was chromatographed on a silica gel column (150 ml). Product *XIXb* was eluted with chloroform–methanol (9 : 1). The ester *XIXb* (2.1 g, 54%) was treated with bromotrimethylsilane (2.5 ml) in acetonitrile (25 ml) overnight, evaporated in vacuo and the residue was dissolved in water (100 ml), made alkaline with concentrated aqueous ammonia and evaporated in vacuo. After deionisation on a Dowex 50 X 8 column (100 ml) under standard conditions, the remaining ammonium salt was dissolved in boiling water (100 ml) and acidified with concentrated hydrochloric acid to pH 3–4. After standing overnight in a refrigerator, the crystalline product was collected and washed with cold water, ethanol and ether to afford (*S*)-(2-phosphonomethoxypropyl)-2,6-diaminopurine (*IIb*). Yield 1.2 g (74% related to *XIXb*) of compound *IIb*, identical with an authentic material[3]. M.p. 276–278 °C. $[\alpha]_D$ +29.0° (*c* 0.5, 0.1 M HCl). For $C_9H_{15}N_6O_4P$ (302.3) calculated: 35.75% C, 5.00% H, 27.80% N, 10.27% P; found: 35.70% C, 5.12% H, 28.11% N, 10.02% P. E_{Up} 0.70; ^{1}H NMR spectrum is identical with that of (*R*)-enantiomer *Ib*.

(*S*)-9-(2-Phosphonomethoxypropyl)guanine (*IIe*)

A mixture of compound *XIXe* (0.97 g, 2.5 mmol), acetonitrile (25 ml) and bromotrimethylsilane (2 ml) was left overnight at room temperature, evaporated and treated with water (50 ml). The reaction mixture was worked up as described for the (*R*)-enantiomer *Ie*. Compound *IIe*, which was obtained in 68% yield, was identical with an authentic preparation[3]. M.p. 287 °C, $[\alpha]_D$ +27.2° (*c* 1, 0.1 M HCl).

(*S*)-9-(2-Phosphonomethoxypropyl)hypoxanthine (*IIh*)

Concentrated hydrochloric acid (2 ml) was added to an ice-cooled solution of (*S*)-9-(2-phosphonomethoxypropyl)adenine (*IIa*) (400 mg, 1.4 mmol) and sodium nitrite (1.4 g, 20 mmol) in water (40 ml). Further work-up was the same as described for compound *Ih*. Yield 66% of (*S*)-9-(2-phosphonomethoxypropyl) hypoxanthine (*IIh*), m.p. 194 °C, $[\alpha]_D$ +23.7° (*c* 1, 0.1 M HCl). UV spectrum (pH 2): λ_{max}

251 nm. For $C_9H_{13}N_4O_5P$ (288.3) calculated: 37.50% C, 4.54% H, 19.44% N, 10.77% P; found: 37.80% C, 4.65% H, 19.56% N, 10.55% P. ^{1}H NMR spectrum (D_2O + NaOD): 8.21 s, 1 H and 8.16 s, 1 H (H-2 and H-8); 4.42 dd, 1 H, *J*(1′a,2′) = 3.7, *J*(gem) = 13.6 (H-1′a); 4.25 dd, 1 H, *J*(1′b,2′) = 6.3, *J*(gem) = 13.6 (H-1′b); 4.01 m, 1 H (H-2′); 3.71 dd, 1 H, *J*(P,CHa) = 9.3, *J*(gem) = 13.2 (P-CHa); 3.54 dd, 1 H, *J*(P,CHb) = 9.8, *J*(gem) = 13.2 (P-CHb); 1.20 d, 3 H, *J*(3′,2′) = 6.3 (H-3′).

(*R*)-1-Benzyloxy-2-propyl *p*-Toluenesulfonate (*XX*)

A solution of (*R*)-1-benzyloxypropanol (*V*; 33.2 g, 0.2 mol) in pyridine (50 ml) was added dropwise under stirring and cooling with ice over 30 min to a solution of *p*-toluenesulfonyl chloride (41.9 g, 0.22 mol) and 4-dimethylaminopyridine (1 g) in pyridine (300 ml). The reaction mixture was stirred at 0 °C for additional 3 h and left overnight at ambient temperature. Water (10 ml) was added and the mixture was concentrated to a half in vacuo. Ethyl acetate (300 ml) was added to the residue and the mixture was washed with water (3 × 200 ml). The organic layer was evaporated and the residue was codistilled with toluene (5 × 100 ml) to remove pyridine. The chromatographically homogeneous product (R_F 0.65, S1) was dissolved in light petroleum (150 ml) and the solution was stirred at 0 °C for 1 h. The crystals were suction-filtered, washed with cold light petroleum and dried in vacuo. Yield 17.4 g, m.p. 31 °C. For $C_{17}H_{20}O_4S$ (320.4) calculated: 63.73% C, 6.29% H, 10.01% S; found: 63.82% C, 6.38% H, 10.14% S. Mass spectrum (*m/z*): 321.1 (M + 1), 319.1 (M – 1). ^{1}H NMR spectrum ($CDCl_3$): 7.78 m, 2 H and 7.19–7.32 m, 7 H (arom. H); 4.73 m, 1 H (H-2); 4.43 d, 1 H and 4.39 d, 1 H, *J*(gem) = 12.0 (CH_2 arom.); 3.50 dd, 1 H, *J*(1a,2) = 5.9, *J*(gem) = 10.6 (H-1a); 3.43 dd, 1 H, *J*(1b,2) = 4.4, *J*(gem) = 10.6 (H-1b); 2.40 s, 3 H (CH_3 arom.); 1.30 d, 3 H, *J*(3,2) = 6.6 (H-3).

(*S*)-9-(1-Benzyloxy-2-propyl)adenine (*XXI*)

A. A mixture of adenine (13.5 g, 0.1 mol), cesium carbonate (16.5 g, 50 mmol) and dimethylformamide (200 ml) was stirred at 100 °C for 30 min. A solution of compound *XX* (40.0 g, 125 mmol) in dimethylformamide (50 ml) was added in one portion. The resulting solution was heated at 110 °C for 16 h and the solvent was evaporated in vacuo. The mixture was extracted with boiling chloroform (600 ml total) and filtered through Celite. The extract was evaporated in vacuo and the residue was chromatographed on a column of silica gel (300 ml) in a chloroform–methanol gradient. The product was obtained by crystallization of the relevant fraction from ethyl acetate–light petroleum. Yield 4.5 g (16%) of the compound *XXI*, m.p. 154–155 °C. $[\alpha]_D$ +11.7° (*c* 1, DMF). For $C_{15}H_{17}N_5O$ (283.3) calculated: 63.59% C, 6.05% H, 24.72% N; found: 63.70% C, 6.14% H, 24.83% N. ^{1}H NMR spectrum ($(CD_3)_2SO$): 8.20 s, 1 H and 8.11 s, 1 H (H-2 and H-8); 7.28–7.20 m, 3 H (arom.); 7.20 br s, 2 H (NH_2); 7.15–7.12 m, 2 H (H arom.); 4.83 m, 1 H (H-2′); 4.47 d, 1 H and 4.41 d, 1 H, *J*(gem) = 12.2 (CH_2 arom.); 3.90 dd, 1 H, *J*(1′a,2′) = 7.7, *J*(gem) = 10.0 (H-1′a); 3.73 dd, 1 H, *J*(1′b,2′) 4.6, *J*(gem) = 10.0 (H-1′b); 1.52 d, 3 H, *J*(3′,2′) = 7.0 (H-3′).

Further elution gave 1.0 g (6%) of 9-(2-propyl)adenine (*XXII*), m.p. 131 °C. For $C_8H_{11}N_5$ (177.2) calculated: 54.21% C, 6.26% H, 39.53% N; found: 54.44% C, 6.35% H, 39.72% N. Mass spectrum (*m/z*): 178.1 (M + 1), 136.0 (Ade + 1). ^{1}H NMR spectrum ($(CH_3)_2SO$): 8.09 s, 1 H and 7.98 s, 1 H (H-2 and H-8); 7.20 br s, 2 H (NH_2); 4.58 sept, 1 H, *J*(1′,2′) = 6.8 (H-2′); 1.54 d, 6 H, *J* = 6.8 (H-1′ and H-3′).

B. A mixture of adenine (13.5 g, 0.1 mol) and cesium carbonate (16.5 g, 50 mmol) in dimethylformamide (200 ml) was stirred at 100 °C for 30 min and tosylate *XX* (prepared by tosylation of (*R*)-1-benzyloxy-2-propanol (*V*)) (35 g, 0.11 mol) was added. The clear solution was heated at 100 °C under exclusion of moisture for 16 h. The solvent was evaporated to dryness in vacuo, the residue was extracted with boiling chloroform (total, 600 ml) and the insoluble portion (adenine and inorganic salts) was discarded. The chloroform was evaporated in vacuo and the residue was purified on a

silica gel (300 ml) column. The product-containing fractions were crystallized from ethyl acetate to give compound *XXI*, chromatographically homogeneous (R_F 0.55, S2) and identical with the preparation obtained by method *A*. Yield 11.0 g (39%), needles, m.p. 154 °C, $[\alpha]_D$ +13.1° (*c* 1, DMF). For $C_{15}H_{17}N_5O$ (283.3) calculated: 63.59% C, 6.05% H, 24.72% N; found: 63.34% C, 6.01% H, 24.56% N. ^{1}H NMR spectrum ($(CD_3)_2SO$): 8.23 s, 1 H and 8.19 s, 1 H (H-2 and H-8); 7.38 s, 2 H (NH_2); 7.26–7.18 m, 3 H and 7.15–7.17 m, 2 H (H arom.); 4.86 m, 1 H (H-2′); 4.46 d, 1 H, and 4.39 d, 1 H, *J*(gem) = 12.2 (CH_2 arom.); 3.90 dd, 1 H, *J*(1′a,2′) = 7.6, *J*(gem) = 10.0 (H-1′a); 3.72 dd, 1 H, *J*(1′b,2′) = 4.6, *J*(gem) = 10.0 (H-1′b); 1.52 d, 3 H, *J*(3′,2′) = 7.1 (H-3′).

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