SYNTHESIS OF ENANTIOMERIC *N*-(2-PHOSPHONOMETHOXYPROPYL) DERIVATIVES OF PURINE AND PYRIMIDINE BASES. I. THE STEPWISE APPROACH*

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The (*R*)- and (*S*)-*N*-(2-phosphonomethoxypropyl) derivatives of purine and pyrimidine bases (PMP derivatives) exhibit very high activity against retroviruses. This paper describes the synthesis of enantiomeric 9-(2-phosphonomethoxypropyl)adenines (*I* and *XXVII*), 9-(2-phosphonomethoxypropyl)-2,6-diaminopurines (*II* and *XXXI*), 9-(2-phosphonomethoxypropyl)guanines (*III* and *XXIX*) and 1-(*R*)-(2-phosphonomethoxypropyl)cytosine (*XIX*) by alkylation of *N*-protected *N*-(2-hydroxypropyl) derivatives of the corresponding bases with bis(2-propyl) *p*-toluenesulfonyloxymethylphosphonate (*X*), followed by stepwise *N*- and *O*-deprotection of the intermediates. The key intermediates, *N*-(2-hydroxypropyl) derivatives *IX* and *XXV*, were obtained by alkylation of the appropriate heterocyclic base with (*R*)- or (*S*)-2-(2-tetrahydropyranyloxy)propyl *p*-toluenesulfonate (*VII* or *XXIII*) and acid hydrolysis of the resulting *N*-[2-(2-tetrahydropyranyloxy)propyl] derivatives *VIII* and *XXII*. The chiral synthons were prepared by tosylation of (*R*)- or (*S*)-2-(2-tetrahydropyranyloxy)propanol (*VI* or *XXI*) available by reduction of enantiomeric alkyl 2-*O*-tetrahydropyranyllactates *V* and *XXI* with sodium bis(2-methoxyethoxy)aluminum hydride. This approach was used for the synthesis of cytosine, adenine and 2,6-diaminopurine derivatives, while compounds derived from guanine were prepared by hydrolysis of 2-amino-6-chloropurine intermediates. Cytosine derivative *IXe* was also synthesized by alkylation of 4-methoxy-2-pyrimidone followed by ammonolysis of the intermediate *IXf*.

In the course of our systematic structure–activity studies on acyclic phosphonate analogs of nucleotides containing a phosphonomethylether functional group, we discovered recently a significant antiviral activity of a new group of compounds, *N*-(2-phosphonomethoxypropyl) derivatives of heterocyclic bases, the so-called PMP-derivatives of adenine (*I*), 2,6-diaminopurine (*II*) and guanine[3,4] (*III*). This discovery is important from the following two viewpoints: In *N*-(2-phosphonomethoxyethyl) derivatives (PME-derivatives[5–8]) substitution with an alkyl, cycloalkyl or arylalkyl group in position β to the heterocyclic base led so far to loss of activity[9,10]

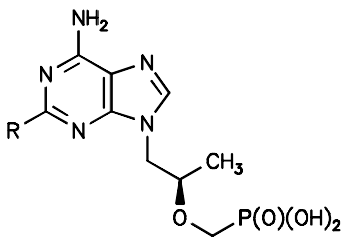
* This approach was reported previously in a preliminary form[1,2].

(except for the (*S*)-hydroxymethyl[5,10] and (*S*)-fluoromethyl[11] derivatives). The biological effect of these compounds concerns retroviruses (the group involving HIV, causing AIDS) and is thus different from the parent PME-derivatives which are active both against retroviruses and DNA viruses. The second interesting feature is the finding[11] that for those derivatives of heterocyclic bases, where the biological effect of the acyclic phosphonates is limited to only one enantiomer, its absolute configuration in the PMP-derivatives (in this case *R*) corresponds to that of the active enantiomer of their hydroxymethyl analogs[5,8] as well as fluoromethyl analogs (*S*-enantiomers)[11,*], although the specificity of their biological effect is principally different.

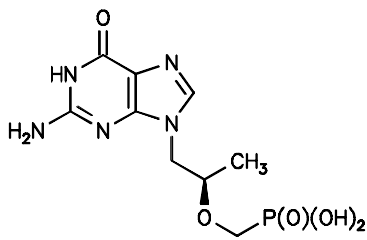
The first findings of the interesting biological properties of these compounds gave impetus to extensive studies of their optimal preparation, stress being put particularly on the enantiomeric purity of the products, general applicability to various heterocyclic systems and accessibility and enantiomeric purity of the starting chiral material. The only optimal type of starting chiral material, accessible in both enantiomeric forms, is lactic acid or its esters.

The first synthetic variant, described in this paper, is the stepwise approach that consists in introduction of the phosphonomethyl group into a heterocyclic base derivative with preformed side chain bearing one hydroxyl functionality. We made use of our previous experience with the synthesis of *N*-(3-hydroxy-2-phosphonomethoxypropyl) derivatives[12].

The first phase of the synthesis was focused on the preparation of *N*-(2-hydroxypropyl) derivatives of heterocyclic bases. We rejected the apparently simplest chiral methyloxiranes as synthons because of their unsuitable physical properties and limited



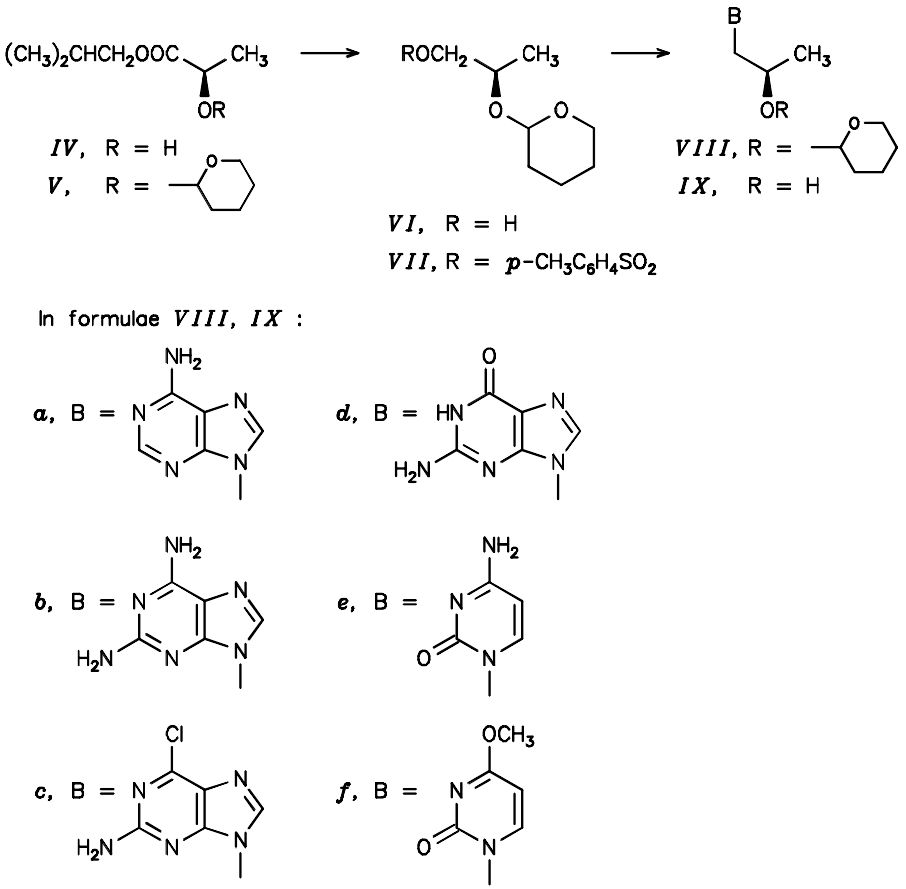
I, R = H (PMPA)
II, R = NH_2 (PMPDAP)



III (PMPG)

* The formal difference in the designation is due to different preferences of the methyl, hydroxymethyl and fluoromethyl groups in the Cahn–Ingold–Prelog notation.

accessibility[13]; as the key synthon we have chosen the tosyl derivative of 1,2-propanediol, protected on the secondary hydroxyl. The commercially accessible 2-methylpropyl ester of D-(–)-lactic acid (*IV*) was converted into the tetrahydropyranyl derivative *V* which was reduced with sodium bis(2-methoxyethoxy)lithium aluminum hydride to give (*R*)-2-(2-tetrahydropyranyloxy)propanol (*VI*) in high yield. Tosylation of *VI* under usual conditions afforded the tosyl derivative *VII*. This compound was used for alkylation of heterocyclic bases; according to our former experience, in most cases we alkylated the unprotected heterocyclic base in the presence of half equivalent of cesium carbonate. Under such conditions the alkylation reactions proceeded rapidly and with high regiospecificity. In this way, we alkylated adenine, 2,6-diaminopurine and cytosine to obtain the respective 2-*O*-tetrahydropyranyl derivatives *VIIIa*, *VIIIb* and *VIIIe* (Scheme 1).



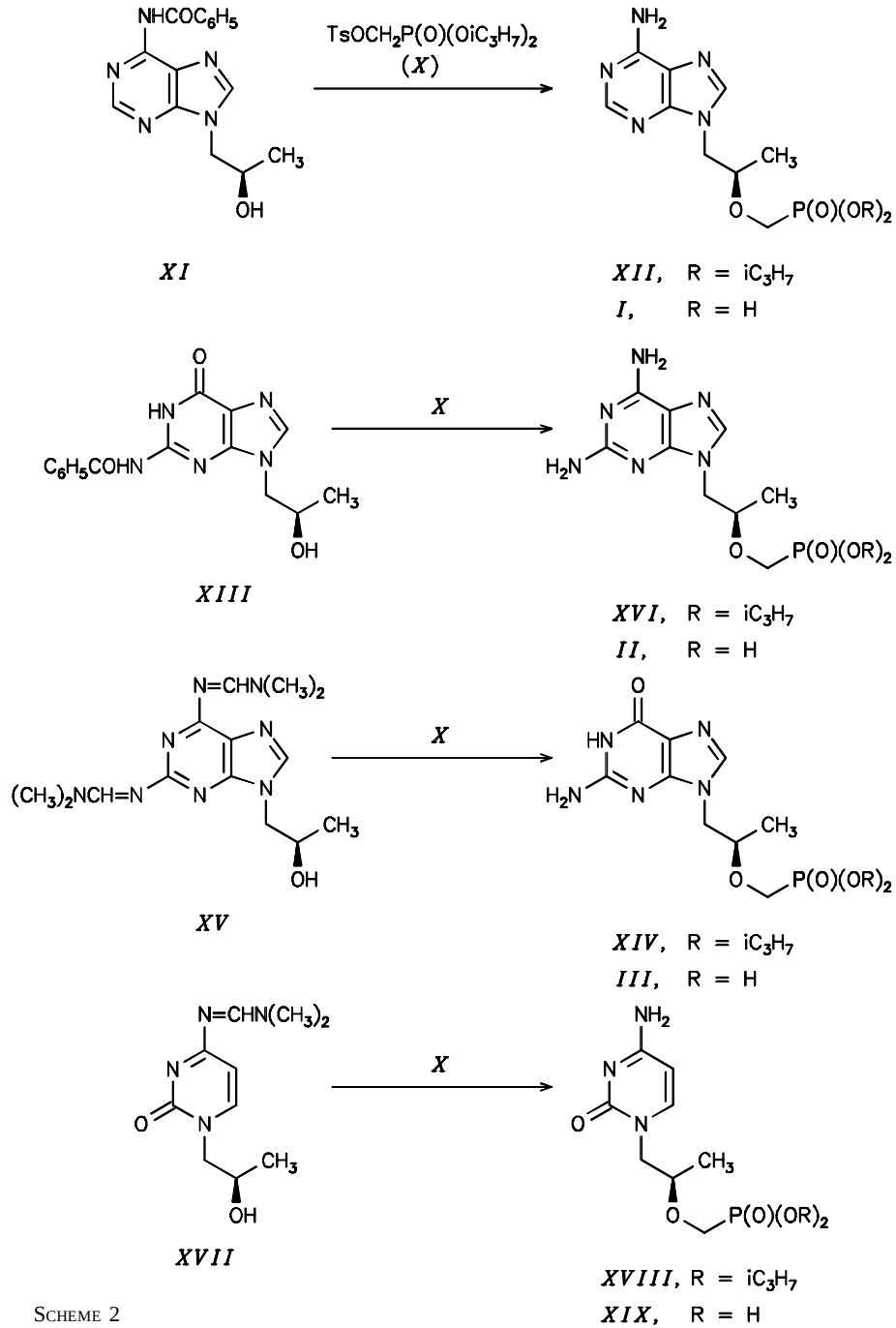
SCHEME 1

As a second alternative for the preparation of the cytosine derivative *VIIIe* we checked also the ammonolysis of the 4-methoxy-2-pyrimidone derivative *VIIIf* prepared by alkylation of 4-methoxy-2-pyrimidone under standard conditions. We have found, however, that the regiospecificity of alkylation of cytosine with the synthon *VII* is sufficiently high, so that this indirect alternative offers no particular advantage. Acid hydrolysis with a mineral acid afforded the *N*-(2-hydroxypropyl) derivatives *IXa*, *IXb* and *IXe* in high purity. In addition to these compounds, we synthesized the guanine derivative *IXd* by alkylation of 2-amino-6-chloropurine with the synthon *VII*. The reaction gave predominantly the 9-isomer *VIIIc* (we did not isolate pure 7-isomer), which on acid hydrolysis of the C–Cl bond afforded, with simultaneous removal of the tetrahydropyranyl group, (*R*)-9-(2-hydroxypropyl)guanine (*IXd*). The structure of the obtained compounds followed unequivocally from their ^{1}H NMR spectra.

Prior to the condensation with synthon[12] *X*, the amino groups of the heterocyclic bases should be protected. Therefore, we converted adenine and guanine into the *N*-benzoyl derivatives *XI* and *XIII*, cytosine and 2,4-diaminopurine into amidines *XV*. These derivatives were condensed with tosyl derivative *X* in the presence of an excess (3 equivalents) of sodium hydride, and the protecting groups were then removed by methanolysis. Deionization of the crude mixtures afforded bis(2-propyl) esters of (*R*)-PMP-derivatives *XII*, *XIV*, *XVI* and *XVIII*, which were finally subjected to transsilylation with bromotrimethylsilane and subsequent hydrolysis. The obtained compounds *I–III* and *XIX* were isolated by ion-exchange chromatography and crystallized in their zwitterionic form (Scheme 2).

The same procedures were used in the preparation of (*S*)-PMP-derivatives, where the starting compound was ethyl L-(+)-lactate (*XX*). Pyranylation, followed by reduction of the tetrahydropyranyl derivative *XXI*, and subsequent tosylation of the protected diol *XXII* afforded the (*S*)-synthon *XXIII*. Alkylation of bases with this synthon led to tetrahydropyranyl derivatives *XXIV* which were cleaved with acid to give the desired (*S*)-(2-hydroxypropyl) derivatives *XXV* (Scheme 3). In this series, the described method was used for the preparation of derivatives of adenine (*XXVa*) and 2,6-diaminopurine (*XXVb*); the guanine derivative *XXVd* was obtained again via the 2-amino-6-chloropurine intermediate *XXIVc* (vide supra).

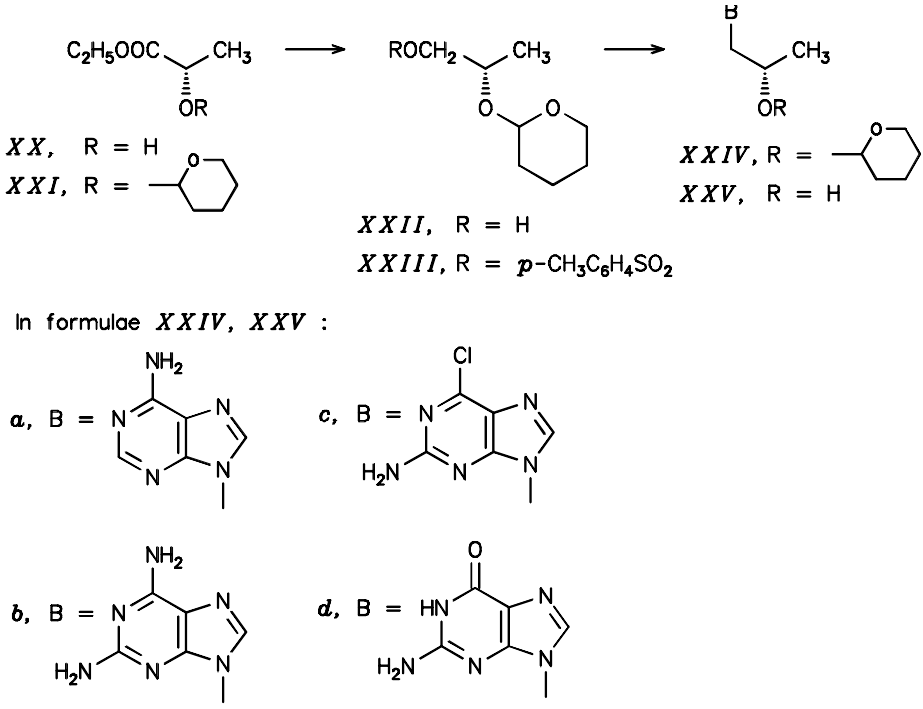
In the further step we made use of the same strategy: conversion of the adenine and guanine derivatives into the *N*-benzoyl derivatives *XXVI* and *XXVIII* which were condensed with the reagent *X* in the presence of sodium hydride. For 2,6-diaminopurine we have chosen the amidine protection method (*N*-benzoyl derivatives of this base are very stable toward methanolysis): this led to compound *XXX* as the starting compound for the condensation. After condensation with compound *X* and removal of the protecting groups, the crude diesters were deionized on a cation-exchanger and finally their ester functionalities were hydrolyzed after transsilylation with bromotrimethylsilane. Also in


NHCOC6H5
TsOCH2P(O)(OiC3H7)2
(X)
NH2
CH3
OH
O
P(O)(OR)2
XI
XII, R = iC3H7
I, R = H
HN
C6H5COHN
X
H2N
XIII
XVI, R = iC3H7
II, R = H
N=CHN(CH3)2
(CH3)2NCH=N
XV
XIV, R = iC3H7
III, R = H
XVII
XVIII, R = iC3H7
XIX, R = H

SCHEME 2

this case the final (*S*)-PMP-derivatives *XXVII*, *XXIX* and *XXXI* were obtained in the zwitterion form (Scheme 4).

In addition to sufficient characterization of the 2-hydroxypropyl and *N*-benzoyl derivatives in both enantiomeric series, the structure of the phosphonates of the PMP-series was confirmed by ^{1}H NMR spectra of their salts. The spectra proved the presence of all the three characteristic groupings in the molecule (heterocyclic base, methyl and phosphonomethyl groups). Their electrophoretical mobility in a weakly alkaline medium corresponds to dissociation to the second degree and their UV spectra are compatible with the corresponding chromophore. Their homogeneity was checked by HPLC; the chromatographic parameters were identical for both enantiomers and were in accord with those of compounds prepared by other methods[2,14]. The absolute values of $[\alpha]_D$ were identical within the experimental error for both enantiomers. The optical purity was limited by that of the starting esters of D-(+)- and L-(–)-lactic acid*.



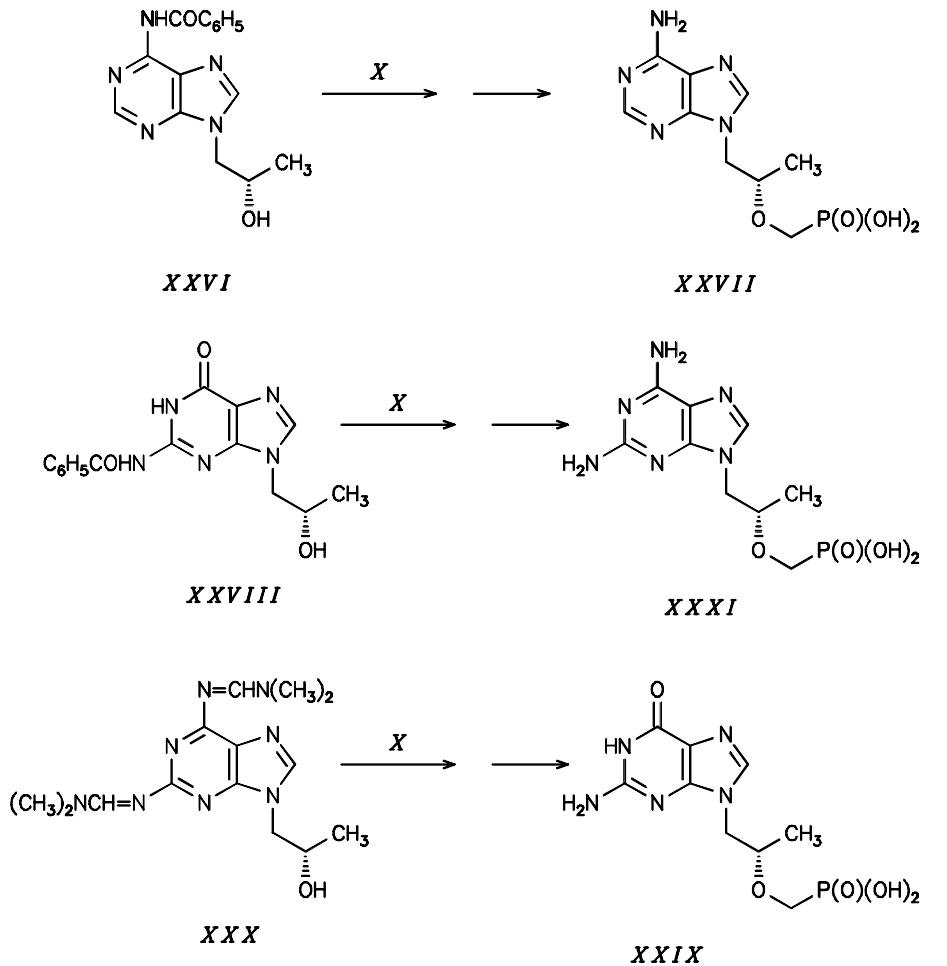
SCHEME 3

* The value of $[\alpha]_D$ (–11.06° (neat)) for ethyl L-(–)-lactate is identical with the published[15] value (–11.3°) whereas the value for isobutyl D-(+)-lactate (+17.25°) is significantly higher than the published[15] one (+15.2°).

EXPERIMENTAL

If not stated otherwise, the solutions were evaporated at 40 °C/2 kPa and the compounds were 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 Silufol UV_{254} plates (Kavalier, Votice, Czech Republic) in the systems S1 chloroform, S2 chloroform–methanol (4 : 1) and S3 chloroform–methanol (95 : 5). Preparative TLC was performed on loose layers (40 × 17 × 0.4 cm) of silica gel with fluorescent indicator (Kavalier, Votice, Czech Republic). Column chromatography on silica gel (30 μm) was carried out with material of the same origin. Paper electrophoresis was performed on 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.



SCHEME 4

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 until the UV absorption at 254 nm dropped to the original value. The compounds were then eluted with 2.5% aqueous ammonia.

^{1}H NMR spectra were measured on Varian UNITY-200 (200 MHz) and Varian UNITY-500 (500 MHz) spectrometers in $(CD_3)_2SO$ 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 the EI (electron energy 70 eV) and FAB (ionization Xe, accelerating voltage 8 kV) techniques.

Starting Materials and Reagents

Sodium bis(2-methoxyethoxy)aluminum hydride (70% solution in toluene, Synhydride) was purchased from Spolana, Neratovice (Czech Republic), dimethylformamide, acetonitrile, 2-methylpropyl D-(+)-lactate, ethyl L-(–)-lactate, 3,4-dihydropyran, chlorotrimethylsilane, benzoyl chloride and Celite were obtained from Merck (Germany), cytosine, adenine 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 were purchased from Aldrich (Germany). Dimethylformamide and acetonitrile were dried by distillation from phosphorus pentoxide and stored over molecular sieves. Hydrogen chloride in dimethylformamide was prepared by introduction of dry HCl into dimethylformamide under ice-cooling, followed by dissolution of the obtained crystalline product by addition of dimethylformamide.

(*R*)-2-(2-Tetrahydropyranyloxy)propanol (*VI*)

To a mixture of 2-methylpropyl D-(+)-lactate (*IV*, 100 ml, 0.66 mol) and 3,4-dihydropyran (70 ml) was added 6 M solution of HCl in dimethylformamide (4 ml). After standing overnight at ambient temperature (calcium chloride tube), silver carbonate (20 g) was added and the suspension was stirred at room temperature for 3 h. The mixture was filtered, the solid washed with ether and the filtrate concentrated in vacuo. Distillation in vacuo afforded 120 g (79%) of 2-tetrahydropyranyl derivative *VI*, b.p. 85–90 °C/13 Pa.

This product was dissolved in ether (170 ml) and the solution was added dropwise during 1 h to a stirred and gently refluxing solution of sodium bis(2-methoxyethoxy)aluminum hydride (70% toluene solution, 227 g) in ether (700 ml) under exclusion of moisture. After stirring for 2 h, the mixture was decomposed by successive addition of ethyl acetate (100 ml) and water (115 ml). The suspension was filtered through a layer of Celite, the solid was washed with dioxane (200 ml) and the filtrate was concentrated in vacuo. The residue was dissolved in ether (300 ml), dried over magnesium sulfate, filtered, evaporated and distilled in vacuo. Yield 79.3 g (95%) of alcohol *VI*, b.p. 82–83 °C/13 Pa. For $C_8H_{16}O_3$ (160.2) calculated: 59.98% C, 10.07% H; found: 60.04% C, 10.17% H.

(*R*)-2-(2-Tetrahydropyranyloxy)propyl *p*-Toluenesulfonate (*VII*)

A solution of *p*-toluenesulfonyl chloride (107.5 g, 0.56 mol) in pyridine (300 ml) was added during 30 min to a stirred and ice-cooled solution of alcohol *VI* (80.1 g, 0.5 mol) and 4-dimethylaminopyridine (2 g) in pyridine (750 ml). The mixture was stirred at 0 °C for 3 h under exclusion of moisture and then set aside at 0 °C overnight. Water (20 ml) was added and, after standing for 1 h, the mixture was concentrated in vacuo at 30 °C to a half. After addition of ethyl acetate (2 l), the mixture was extracted with water (3 × 300 ml) and the organic phase was evaporated in vacuo. The residue was codistilled with toluene (4 × 250 ml) until the pyridine was completely removed and the remaining

oil was chromatographed on a column of silica gel in chloroform. Yield 144 g (92%) of colourless oily tosylate *VII*, R_F 0.60 (S1). For $C_{15}H_{22}O_5S$ (314.4) calculated: 57.30% C, 7.05% H, 10.20% S; found: 57.22% C, 7.30% H, 10.01% S.

(*S*)-2-(2-Tetrahydropyranyloxy)propanol (*XXII*)

To a mixture of ethyl L-(–)-lactate (*XX*, 50 g, 0.42 mol) and 3,4-dihydropyran (70 ml) was addded 6 M solution of hydrogen chloride in dimethylformamide and the mixture was allowed to stand under exclusion of moisture at room temperature overnight. The further work-up was executed as described for compound *VI*. Distillation in vacuo afforded 85.5 g (100%) of colourless oily product *XXI*, b.p. 101–105 °C/2 kPa.

This product was dissolved in ether (200 ml) and the solution was added dropwise during 30 min under exclusion of moisture to a stirred solution of Synhydride (200 g) in ether (500 ml) (reflux condenser). After stirring for 2 h, the mixture was decomposed by successive addition of ethyl acetate (70 ml) and water (100 ml). Further work-up was the same as described for compound *VI*. Yield 69.2 g (96%) of compound *XXII*, b.p. 85–87 °C/13 Pa. For $C_8H_{16}O_3$ (160.2) calculated: 59.98% C, 10.07% H; found: 59.80% C, 10.14% H.

(*S*)-2-(2-Tetrahydropyranyloxy)propyl *p*-Toluenesulfonate (*XXIII*)

A solution of *p*-toluenesulfonyl chloride (91 g, 0.477 mol) in pyridine (300 ml) was added during 30 min under stirring and ice-cooling to a solution od compound *XXII* (67.3 g, 0.42 mol) and 4-dimethylaminopyridine (2 g) in pyridine (600 ml). The mixture was stirred for 3 h at 0 °C under exclusion of moisture and then set aside at 0 °C overnight. Further work-up was the same as described for compound *VII*; yield 122 g (93%) of compound *XXIII* as a thick oil, R_F 0.60 (S1). For $C_{15}H_{22}O_5S$ (314.4) calculated: 57.30% C, 7.05% H, 10.20% S; found: 57.15% C, 7.22% H, 10.52% S.

(*R*)-9-[2-(2-Tetrahydropyranyloxy)propyl]adenine (*VIIIa*)

A solution of tosyl derivative *VII* (31.4 g, 0.1 mol) in dimethylformamide (100 ml) was added dropwise during 20 min to a stirred suspension of adenine (13.5 g, 0.1 mol) and cesium carbonate (16.4 g, 0.05 mol) in dimethylformamide (300 ml), pre-heated to 100 °C. The mixture was heated at 100 °C for 16 h under exclusion of moisture. The solvent was evaporated in vacuo and the residue was extracted with hot chloroform (1 l total). The extract was filtered through Celite. The filtrate was concentrated in vacuo and the residue was crystallized from ethanol (ether added to turbidity) to give compound *VIIIa* (7.3 g). Another portion (4.9 g) of the product was obtained from the mother liquors by chromatography on silica gel (300 ml) and subsequent crystallization from ethanol. Total yield 12.2 g (44%) of *VIIIa*, m.p. 171–172 °C, R_F 0.55 (S2). For $C_{13}H_{19}N_5O_2$ (277.3) calculated: 56.30% C, 6.91% H, 25.26% N; found: 56.57% C, 6.71% H, 25.41% N. ^{1}H NMR spectrum (200 MHz): 8.14 s, 1 H and 8.04 s, 1 H (H-2 and H-8); 7.20 br s, 2 H (NH_2); 4.23 dd, 1 H, J(1′a,2′) = 3.2, J(gem) = 13.7 (H-1′a); 4.11 dd, 1 H, J(1′b,2′) = 7.1, J(gem) = 13.7 (H-1′b); 4.06, m, 1 H (H-2′); 1.12 d, 3 H, J(3′,2′) = 6.1 (H-3′); tetrahydropyranyl: 4.28 dd, 1 H, J = 2.9 and 4.4 (H-2″); 3.72 ddd, 1 H, J = 3.9, 7.8 and 11.2 and 3.34 ddd, 1 H, J = 4.9, 5.1 and 11.2 (H-6″); 1.20–1.65 m, 6 H (2 × H-3″, 2 × H-4″, 2 × H-5″).

(*R*)-9-(2-Hydroxypropyl)adenine (*IXa*)

A solution of tetrahydropyranyl derivative *VIIIa* (7.0 g, 25.2 mmol) in 0.25 M sulfuric acid (150 ml) was set aside at room temperature overnight and then neutralized with saturated barium hydroxide solution. The suspension was heated to 80 °C, filtered through Celite and the solid was washed with

boiling water (1 l). Evaporation of the filtrate in vacuo and crystallization of the residue from ethanol (ether added to turbidity) afforded 4.1 g (85%) of compound *IXa*, m.p. 202 °C, R_F 0.40 (S2). For $C_8H_{11}N_5O$ (193.2) calculated: 49.73% C, 5.74% H, 36.25% N; found: 49.59% C, 5.54% H, 36.29% N. $[\alpha]_D$ –40.8° (*c* 0.5, 0.1 M HCl). ^{1}H NMR spectrum (200 MHz): 8.14 and 8.05 2 × s, 2 × 1 H (H-2 and H-8); 7.23 br s, 2 H (NH_2); 5.05 d, 1 H, *J*(OH,CH) = 4.2 (OH); 3.97–4.13 m, 3 H (H-1′ and H-2′); 1.06 d, 3 H, *J*(3′,2′) = 5.6 (H-3′).

(*R*)-9-(2-Hydroxypropyl)-2,6-diaminopurine (*IXb*)

(*R*)-2-(2-Tetrahydropyranyloxy)propyl *p*-toluenesulfonate (*VII*) (32.8 g, 0.104 mol) was added to a suspension of 2,6-diaminopurine (15 g, 0.1 mol) and cesium carbonate (16.4 g, 0.05 mol) in dimethylformamide (250 ml), pre-heated to 100 °C, and the mixture was stirred at 100 °C for 20 h. After evaporation at 50 °C/13 Pa, the residue was extracted with boiling chloroform (3 × 300 ml). The extract was filtered, the filtrate concentrated in vacuo and chromatographed on a column of silica gel (500 ml). The product was eluted with chloroform–methanol (95 : 5) and crystallized from ethyl acetate (ether added to turbidity). Yield of (*R*)-9-[2-(2-tetrahydropyranyloxy)propyl]-2,6-diaminopurine (*VIIIb*) was 14.2 g (49%), m.p. 150–152 °C, R_F 0.30 (S2). For $C_{13}H_{20}N_6O_2$ (292.3) calculated: 53.41% C, 6.90% H, 28.76% N; found: 53.27% C, 7.02% H, 28.77% N.

A solution of compound *VIIIb* (11.7 g, 0.04 mol) in 0.25 M sulfuric acid (400 ml) was set aside at room temperature overnight, neutralized with ammonia, concentrated in vacuo, applied onto a column of Dowex 50 X 8 (250 ml, H^+ form) and the column was washed with water until the UV absorption dropped to the original value. Then the column was eluted with dilute (1 : 10) aqueous ammonia and the UV-absorbing eluate was concentrated in vacuo. Crystallization of the residue from ethanol afforded 9-(*R*)-(2-hydroxypropyl)-2,6-diaminopurine (*IXb*) (6.5 g, 78%), m.p. 192 °C, R_F 0.22 (S2). $[\alpha]_D$ –40.7° (*c* 0.5, 0.1 M HCl). For $C_8H_{12}N_6O$ (208.2) calculated: 46.15% C, 5.81% H, 40.37% N; found: 45.97% C, 5.72% H, 40.56% N. ^{1}H NMR spectrum (200 MHz): 7.62 s, 1 H (H-8); 6.65 and 5.77, 2 × br s, 2 × 2 H (NH_2); 5.05 br, 1 H (OH); 3.90 dd, 1 H, *J*(1′a,2′) = 3.9, *J*(gem) = 13.7 (H-1′a); 3.80 dd, 1 H, *J*(1′b,2′) = 7.6, *J*(gem) = 13.7 (H-1′b); 3.95 m, 1 H (H-2′); 1.04 d, 3 H, *J*(3′,2′) = 6.1 (H-3′).

(*R*)-9-[2-(2-Tetrahydropyranyloxy)propyl]-2-amino-6-chloropurine (*VIIIc*)

A solution of (*R*)-2-(2-tetrahydropyranyloxy)propyl *p*-toluenesulfonate (*VII*) (42.0 g, 0.134 mol) in dimethylformamide (100 ml) was added dropwise during 30 min to a suspension of 2-amino-6-chloropurine (18.6 g, 0.11 mol) and cesium carbonate (17.9 g, 0.055 mol) in dimethylformamide (350 ml), which had been pre-heated to 100 °C for 30 min. The mixture was heated at 100 °C for 6 h under stirring and exlusion of moisture. After evaporation at 50 °C/13 Pa, the residue was extracted with boiling chloroform (3 × 300 ml). The extract was filtered through Celite, the solvent was evaporated in vacuo and chromatographed on a column (500 ml) of silica gel in chloroform. The UV-absorbing product fractions were combined, taken down in vacuo and the residue was dried in vacuo. (*R*)-9-[2-(2-Tetrahydropyranyloxy)propyl]-2-amino-6-chloropurine (*VIIIc*) was obtained as an amorphous foam (10.7 g, 31%), R_F 0.64 (S2). For $C_{13}H_{18}ClN_5O_2$ (311.8) calculated: 50.08% C, 5.82% H, 11.37% Cl, 22.47% N; found: 49.92% C, 6.08% H, 11.44% Cl, 22.54% N. ^{1}H NMR spectrum (200 MHz): 8.06 s, 1 H (H-8); 4.01 dd, 1 H, *J*(1′a,2′) = 7.3, *J*(gem) = 14.2 (H-1′a); 3.94 dd, 1 H, *J*(1′b,2′) = 5.4, *J*(gem) = 14.2 (H-1′b); 3.42 m, 1 H (H-2′); 1.06 d, 3 H, *J*(3′,2′) = 5.4 (H-3′); tetrahydropyranyl: 5.07 dd, 1 H, *J* = 2.9, and 8.3 (H-2″); 4.02 m and 3.80 m, 2 H (H-6″); 1.30–1.90 m, 6 H (other CH_2).

(*R*)-9-(2-Hydroxypropyl)guanine (*IXd*)

A solution of compound *VIIIc* (10 g, 0.032 mol) in 1 M hydrochloric acid (200 ml) was refluxed with stirring for 1 h. After cooling, the mixture was made alkaline with ammonia and evaporated in vacuo to dryness. Crystallization of the residue from water (a little charcoal added) afforded (*R*)-9-(2-hydroxypropyl)guanine (*IXd*) (6.0 g, 91%), m.p. 255 °C. $[\alpha]_D$ –35.7° (*c* 0.5, 0.1 M HCl), R_F 0.13 (S2). For $C_8H_{11}N_5O_2$ (209.2) calculated: 45.92% C, 5.30% H, 33.48% N; found: 46.02% C, 5.25% H, 33.41% N. ^{1}H NMR spectrum (200 MHz): 10.80 br, 1 H (NH); 7.61 s, 1 H (H-8); 6.74 br s, 2 H, (2-NH_2); 5.05 br, 1 H (OH); 3.93 m, 1 H (H-2′); 3.89 dd, 1 H, *J*(1′a,2′) = 3.7, *J*(gem) = 13.4 (H-1′a); 3.78 dd, 1 H, *J*(1′b,2′) = 7.8, *J*(gem) = 13.4 (H-1′b); 1.03 d, 3 H, *J*(3′,2′) = 6.1 (H-3′).

(*R*)-1-[2-(2-Tetrahydropyranyloxy)propyl]cytosine (*VIIIe*)

A mixture of cytosine (8.5 g, 76 mmol), cesium carbonate (13 g, 40 mmol), *p*-toluenesulfonate *VII* (24 g, 76 mmol) and dimethylformamide (300 ml) was heated at 100 °C under stirring and exclusion of moisture, filtered while hot through Celite, and the solvent was evaporated in vacuo. The residue was chromatographed on a column of silica gel (300 ml) in chloroform. The product was eluted with chloroform–methanol (95 : 5). The product fractions were combined, concentrated in vacuo and the residue was crystallized from ethyl acetate (with ether added to turbidity). Yield 4.6 g (18 mmol, 24%) of (*R*)-1-[2-(2-tetrahydropyranyloxy)propyl]cytosine (*VIIIe*), m.p. 259–260 °C. For $C_{12}H_{19}N_3O_3$ (253.3) calculated: 56.89% C, 7.57% H, 16.59% N; found: 55.80% C, 7.72% H, 16.85% N. ^{1}H NMR spectrum (200 MHz) (mixture of diastereomers, 3 : 1), major isomer: 7.52 d, 1 H, *J*(5,6) = 7.3 (H-6); 6.98 br s, 2 H (NH_2); 5.73 d, 1 H, *J*(5,6) = 7.3 (H-5); 3.72–4.01 m, 3 H (H-1′ and H-2′); 1.13 d, 3 H, *J* = 6.1 (H-3′); tetrahydropyranyl: 4.36 br t, 1 H, *J* = 3.2 (H-2″); 3.26–3.54 m, 2 H (H-6″); 1.20–1.70 m, 6 H (additional CH_2 groups).

(*R*)-1-(2-Hydroxypropyl)cytosine (*IXe*)

Procedure A. A solution of compound *VIIIe* (4.0 g, 16 mmol) in 0.25 M sulfuric acid (50 ml) was set aside overnight at room temperature. The mixture was neutralized with saturated barium hydroxide solution, heated to 80 °C and filtered through Celite. The precipitate was washed with boiling water (500 ml) and the filtrate was evaporated in vacuo to dryness. The residue was codistilled with ethanol (200 ml) and crystallized from ethanol (ether added) to give 2.5 g (94%) of (*R*)-1-(2-hydroxypropyl)cytosine (*IXe*), m.p. 246 °C, R_F 0.17 (S2), $[\alpha]_D$ –107.0° (*c* 0.5, 0.1 M HCl). For $C_7H_{11}N_3O_2$ (169.2) calculated: 49.69% C, 6.55% H, 24.84% N; found: 49.48% C, 6.70% H, 24.70% N. ^{1}H NMR spectrum (500 MHz): 7.45 d, 1 H, *J*(5,6) = 7.3 (H-6); 7.04 and 6.98 2 × br s, 2 × 1 H (NH_2); 5.61 d, 1 H, *J*(5,6) = 7.3 (H-5); 4.88 br, 1 H (OH); 3.82 m, 1 H (H-2′); 3.73 dd, 1 H, *J*(1′a,2′) = 3.9, *J*(gem) = 13.2 (H-1′a); 3.31 dd, 1 H, *J*(1′b,2′) = 8.0, *J*(gem) = 13.2 (H-1′b); 1.08 d, 3 H, *J*(3′,2′) = 6.3 (H-3′).

Procedure B. 4-Methoxy-2-pyrimidone (12.6 g, 0.1 mol) was added at 0 °C to a stirred suspension of sodium hydride (4.0 g of 60% dispersion in paraffin, 0.1 mol) in dimethylformamide (300 ml) and the mixture was stirred at 0 °C for 1 h (calcium chloride tube). To the resulting solution *p*-toluenesulfonate *VII* (31.4 g, 0.1 mol) in dimethylformamide (100 ml) was added and the stirred mixture was heated at 80 °C for 8 h under exclusion of moisture. After evaporation in vacuo, the residue was extracted with boiling chloroform (3 × 200 ml), the extract was filtered through Celite and the solvent was evaporated in vacuo. The residue was chromatographed on a column of silica gel (300 ml). The product fractions were combined, taken down in vacuo and dried in vacuo. Yield 16.9 g (63%) of (*R*)-1-[2-(2-tetrahydropyranyloxy)propyl]-4-methoxy-2-pyrimidone (*VIIIf*) as an amorphous foam. This product was heated with methanolic ammonia (500 ml, saturated at 0 °C) at 110 °C for 8 h in an autoclave. The suspension was then evaporated in vacuo and the remaining compound *VIIIe* was

heated with 0.25 M sulfuric acid (300 ml) at 70 °C for 5 h. The mixture was neutralized with ammonia, filtered through Celite and the filtrate was concentrated in vacuo. The obtained solution was deionized on a column of Dowex 50 X 8 (250 ml; H^+ form) and the UV-absorbing ammonia eluate was taken down in vacuo. Crystallization from ethanol afforded 7.8 g (73%) of (*R*)-1-(2-hydroxypropyl)cytosine (*IXe*), identical with the product obtained according to procedure *A*.

(*S*)-9-[2-(2-Tetrahydropyranyloxy)propyl]adenine (*XXIVa*)

A solution of (*S*)-2-(2-tetrahydropyranyloxy)propyl *p*-toluenesulfonate (*XXIII*) (31.4 g, 0.1 mol) in dimethylformamide (200 ml) was added dropwise during 30 min to a stirred mixture of adenine (13.5 g, 0.1 mol), cesium carbonate (16.4 g, 0.05 mol) and dimethylformamide (400 ml) that had been preheated to 100 °C. The mixture was heated at 100 °C for 6 h under stirring and exclusion of moisture. The solvent was evaporated in vacuo and the residue was extracted with boiling chloroform (3 × 300 ml). The extract was filtered through Celite and the filtrate was taken down in vacuo. Crystallization of the residue from ethanol afforded (*S*)-9-[2-(2-tetrahydropyranyloxy)propyl]adenine (*XXIVa*) (13.2 g, 48%), m.p. 172 °C, R_F 0.55 (S2). For $C_{13}H_{19}N_5O_2$ (277.3) calculated: 56.30% C, 6.91% H, 25.26% N; found: 56.46% C, 6.82% H, 25.57% N. ^{1}H NMR spectrum (200 MHz): 8.14 and 8.04 2 × s, 2 × 1 H (H-2 and H-8); 7.20 br s, 2 H (NH_2); 4.23 dd, 1 H, *J*(1′a,2′) = 3.2, *J*(gem) = 13.7 (H-1′a); 4.11 dd, 1 H, *J*(gem) = 13.7, *J*(1′b,2′) = 7.1 (H-1′b); 4.06 m, 1 H (H-2′); 1.12 d, 3 H, *J*(3′,2′) = 6.1 (H-3′); tetrahydropyranyl: 4.28 dd, 1 H, *J* = 2.9 and 4.4 (H-2″); 3.72 ddd, 1 H, *J* = 3.9, 7.8, 11.2 and 3.34 ddd, 1 H, *J* = 4.9, 5.1 and 11.2 (H-6″); 1.20–1.65 m, 6 H (additional CH_2).

(*S*)-9-(2-Hydroxypropyl)adenine (*XXVa*)

A solution of compound *XXIVa* (13 g, 0.047 mol) in 0.25 M sulfuric acid (300 ml) was set aside at ambient temperature overnight. The mixture was neutralized with saturated barium hydroxide solution, heated to 80 °C and filtered through Celite. The precipitate was washed with boiling water (500 ml) and the filtrate was taken down in vacuo. The dry residue was crystallized from ethanol to give 7.7 g (85%) of compound *XXVa*, m.p. 202 °C, R_F 0.40 (S2). For $C_8H_{11}N_5O$ (193.2) calculated: 49.73% C, 5.74% H, 36.25% N; found: 49.59% C, 5.54% H, 36.29% N. $[\alpha]_D$ +41.0° (*c* 0.5, 0.1 M HCl). ^{1}H NMR spectrum (200 MHz): 8.14 and 8.05 2 × s, 2 × 1 H (H-2 and H-8); 7.23 br s, 2 H (NH_2); 5.05 brd, 1 H, *J*(OH,CH) = 4.2 (OH); 3.97–4.13 m, 3 H (H-1′ and H-2′); 1.06 d, 3 H, *J*(3′,2′) = 5.6 (H-3′).

(*S*)-9-(2-Hydroxypropyl)-2,6-diaminopurine (*XXVb*)

A mixture of 2,6-diaminopurine (5 g, 33 mmol), cesium carbonate (5.1 g, 16.5 mmol), *p*-toluenesulfonate *XXIII* (13.5 g, 0.43 mol) and dimethylformamide (100 ml) was heated at 100 °C for 16 h and worked up as described for compound *XXIVa*. The product-containing fraction on evaporation gave *XXIVb* (5.6 g, 19.1 mmol, 58%) which was dissolved in 0.25 M sulfuric acid (100 ml) and left to stand overnight at ambient temperature. The solution was neutralized with saturated solution of barium hydroxide, heated to 80 °C, filtered through Celite and the precipitate was washed with boiling water (500 ml). The filtrate was taken down in vacuo and the residue crystallized from ethanol. Yield 3.65 g (53% related to the base) of compound *XXVb*, m.p. 191–192 °C, R_F 0.22 (S2). $[\alpha]_D$ +41.2° (*c* 0.5, 0.1 M HCl). For $C_8H_{12}N_6O$ (208.2) calculated: 46.15% C, 5.81% H, 40.37% N; found: 46.08% C, 5.74% H, 40.18% N. Its ^{1}H NMR spectrum was identical with that of the (*R*)-enantiomer *IXb*.

(*S*)-9-[2-(2-Tetrahydropyranyloxy)propyl]-2-amino-6-chloropurine (*XXIVc*)

A mixture of 6-amino-2-chloropurine (18.6 g, 0.11 mol), cesium carbonate (17.9 g, 0.055 mol) and dimethylformamide (350 ml) was heated at 100 °C. A solution of compound *XXIII* (42.1 g, 0.134 mol) in dimethylformamide (100 ml) was added and the mixture was heated at 100 °C for 6 h under stirring and exclusion of moisture. After evaporation at 40 °C/13 Pa, the residue was extracted with boiling chloroform (3 × 300 ml), filtered and the solvent was evaporated in vacuo. Column chromatography of the residue on silica gel (300 ml) in chloroform afforded 10.65 g (31%) of the 9-isomer *XXIVc* as an amorphous foam, R_F 0.64 (S2). For $C_{13}H_{18}ClN_5O_2$ (311.8) calculated: 50.08% C, 5.82% H, 11.37% Cl, 22.47% N; found: 50.32% C, 5.88% H, 11.51% Cl, 22.32% N. ^{1}H NMR spectrum (200 MHz): 8.06 s, 1 H (H-8); 4.01 dd, 1 H, *J*(1′a,2′) = 7.3, *J*(gem) = 14.2 (H-1′a); 3.94 dd, 1 H, *J*(1′b,2′) = 5.4, *J*(gem) = 14.2 (H-1′b); 3.42 m, 1 H (H-2′); 1.06 d, 3 H, *J*(3′,2′) = 5.4 (3′-H); tetrahydropyranyl: 5.17 dd and 4.63 dd, total 1 H (ratio 7 : 1), *J* = 2.9 and 8.3, or 2.4 and 6.3 (H-2″); 4.02 m and 3.80 m, total 2 H (H-6″); 1.30–1.90 m, 6 H (other CH_2 groups).

Further elution and precipitation with ether from ethyl acetate gave 5.7 g (17%) of an amorphous product which, according to its NMR spectrum, was a mixture of isomers (R_F 0.48 (S3)) with the 7-isomer probably predominating.

(*S*)-9-(2-Hydroxypropyl)guanine (*XXVd*)

Compound *XXIVc* (10.4 g, 33.3 mmol) was refluxed for 1 h with a mixture of 2 M hydrochloric acid (100 ml) and dioxane (100 ml). After cooling, the mixture was neutralized with ammonia and taken down. Crystallization from water afforded 5.7 g (77%) of (*S*)-9-(2-hydroxypropyl)guanine (*XXVd*), m.p. 256 °C, R_F 0.13 (S2). $[\alpha]_D$ +36.2° (*c* 0.5, 0.1 M HCl). For $C_8H_{11}N_5O_2$ (209.2) calculated: 45.92% C, 5.30% H, 33.48% N; found: 45.88% C, 5.25% H, 33.41% N. The ^{1}H NMR spectrum (200 MHz) was identical with that of the (*R*)-enantiomer *IXd*.

(*R*)-9-(2-Hydroxypropyl)-N^6-benzoyladenine (*XI*)

Chlorotrimethylsilane (26 ml) was added to a suspension of (*R*)-9-(2-hydroxypropyl)adenine (*IXa*) (5.8 g, 30 mmol) in pyridine (160 ml) and the mixture was stirred at room temperature for 1 h. Benzoyl chloride (20 ml) was added and stirring was continued for another 2 h at room temperature. After cooling with ice, ice-cold water (30 ml) was added during 15 min, followed by concentrated aqueous ammonia (70 ml). The mixture was concentrated in vacuo and the residue was codistilled with ethanol (3 × 150 ml) and crystallized from boiling water. Recrystallization from ethanol afforded 7.8 g (87%) of (*R*)-9-(2-hydroxypropyl)-N^6-benzoyladenine (*XI*), m.p. 227 °C, R_F 0.45 (S2). $[\alpha]_D$ –21.7° (*c* 0.5, DMF). For $C_{15}H_{15}N_5O_2$ (297.3) calculated: 60.59% C, 5.09% H, 23.56% N; found: 60.73% C, 5.28% H, 23.47% N. ^{1}H NMR spectrum (200 MHz): 8.73 and 8.42, 2 × s, 2 × 1 H (H-2 and H-8); 7.30–8.10 m, 6 H (arom. H and NH); 4.05–4.30 m, 3 H (H-1′ and H-2′); 1.11 d, 3 H, *J*(3′,2′) = 5.6 (H-3′).

(*S*)-9-(2-Hydroxypropyl)-N^6-benzoyladenine (*XXVI*)

The benzoyl derivative *XXVI* was prepared analogously as compound *XI* from (*S*)-9-(2-hydroxypropyl)adenine (*XXVa*) (6.8 g, 35 mmol); yield 4.4 g (43%), m.p. 230 °C. The combined mother liquors were evaporated and the residue was stirred with ethanol (150 ml) for 30 min, and filtered. The ethanolic extract was evaporated in vacuo and the residue was extracted with chloroform (2 × 150 ml). After evaporation of the solvent, the residue was chromatographed on a column of silica gel (200 ml). The product was eluted with chloroform–ethanol (9 : 1). The product fractions were combined, the solvent evaporated in vacuo and the residue was crystallized from ethyl acetate (light petroleum

added to turbidity) to give further crop (3.0 g) of the same product; total yield 7.4 of compound *XXVI*, m.p. 230 °C, R_F 0.45 (S2). $[\alpha]_D$ +25.2° (*c* 0.5, 0.1 M HCl). For $C_{15}H_{15}N_5O_2$ (297.3) calculated: 60.59% C, 5.09% H, 23.56% N; found: 60.63% C, 5.16% H, 23.30% N. The ^{1}H NMR spectrum was identical with that of the (*R*)-isomer.

(*R*)-9-(2-Hydroxypropyl)-N^2-benzoylguanine (*XIII*)

The benzoyl derivative *XIII* was prepared analogously as the compound *XI* from (*R*)-9-(2-hydroxypropyl)guanine (*IXd*) (2.5 g, 12 mmol). After evaporation of pyridine, the residue was stirred with a mixture of water (200 ml) and ethyl acetate (200 ml). The mixture was filtered, the crystalline product was washed with water, ethyl acetate, ether, and dried in vacuo. Yield 2.4 g (57%), m.p. 276 °C, R_F 0.33 (S2). $[\alpha]_D$ –28.4° (*c* 0.5, DMF). For $C_{15}H_{15}N_5O_3$. 2 H_2O (349.4) calculated: 51.56% C, 5.49% H, 20.05% N; found: 51.28% C, 5.62% H, 20.24% N. ^{1}H NMR spectrum (500 MHz): 12.30 and 11.90 2 × br, 2 × 1 H (NH); 8.05 m, 2 H and 7.50–7.70 m, 3 H (arom. H); 7.95 s, 1 H (H-8); 5.05 d, 1 H, *J*(2′,OH) = 4.9 (2′-OH); 4.05 dd, 1 H, *J*(1′a,2′) = 3.4, *J*(gem) = 12.5 (H-1′a); 4.01 br m, 1 H (H-2′); 3.96 dd, 1 H, *J*(1′b,2′) = 7.1, *J*(gem) = 12.5 (H-1′b); 1.09 dd, 3 H, *J*(3′,2′) = 6.1 (H-3′).

(*S*)-9-(2-Hydroxypropyl)-N^2-benzoylguanine (*XXVIII*)

The reaction with (*R*)-9-(2-hydroxypropyl)guanine (*IXd*) (5.0 g, 24 mmol) was executed as described for compound *XI*. After evaporation of pyridine, the residue was stirred with a mixture of water (200 ml) and ethyl acetate (200 ml). The mixture was filtered, the crystalline product was washed with water, ethyl acetate, ether, and dried in vacuo. Yield of the chromatographically pure (*S*)-9-(2-hydroxypropyl)-N^2-benzoylguanine (*XXVIII*) was 3.4 g (40%), R_F 0.33 (S2), m.p. 278 °C. $[\alpha]_D$ +28.1° (*c* 0.5, DMF). For $C_{15}H_{15}N_5O_3$. 2 H_2O (349.4) calculated: 51.56% C, 5.49% H, 20.05% N; found: 51.48% C, 5.41% H, 20.05% N. The ^{1}H NMR spectrum was identical with that of compound *IXd*.

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

A mixture of (*R*)-9-(2-hydroxypropyl)-N^6-benzoyladenine (*XI*) (3.0 g, 10 mmol) and bis(isopropyl) *p*-toluenesulfonyloxymethylphosphonate (*X*) (4.2 g, 12 mmol) was codistilled with dimethylformamide (2 × 25 ml) at 40 °C/13 Pa. The residue was again dissolved in dimethylformamide (50 ml) by gentle warming, cooled with ice, and sodium hydride (60% dispersion, 1.2 g, 30 mmol) was added. The mixture was stirred under exclusion of moisture at room temperature for 48 h, 0.1 M methanolic sodium methoxide was added (150 ml) and the mixture was set aside under exclusion of moisture at room temperature overnight. After neutralization by addition of Dowex 50 X 8 (H^+ form), the mixture was made alkaline with triethylamine, filtered and the ion exchanger was washed with methanol (200 ml). The filtrate was evaporated in vacuo, the residue was dissolved in water (200 ml) and extracted with ether (2 × 100 ml). The aqueous phase was concentrated in vacuo to about 100 ml and this solution was applied onto a column of Dowex 50 X 8 (250 ml). The column was washed with 20% aqueous methanol till the UV absorption of the eluate dropped to the original value. The crude product *XII* was then eluted with dilute (1 : 10) aqueous ammonia and the UV-absorbing eluate was taken down in vacuo. The residue was codistilled with ethanol (2 × 50 ml) and dried at 13 Pa over phosphorus pentoxide. Yield of crude bis(isopropyl) ester *XII* was 3.0 g; R_F 0.55 (S2).

This residue was dissolved in a mixture of acetonitrile (50 ml) and bromotrimethylsilane (5 ml). The mixture was set aside under exclusion of moisture at room temperature overnight and the reaction was monitored by paper electrophoresis of a hydrolyzed sample. The mixture was taken down in vacuo and water (100 ml) was added. After 30 min the mixture was made alkaline with ammonia and again taken down in vacuo. The residue was deionized on a column of Dowex 50 as described above

and the ammonia eluate of the product was evaporated to dryness. The residue was again dissolved in water (50 ml) by adjusting the pH to 9–10, and this solution was applied onto a column of Dowex 1 X 2 (250 ml, acetate form), pre-equilibrated with 0.02 M acetic acid. The column was washed with the same eluent until the UV absorption dropped and then with linear gradient of 0.02–1 M acetic acid (1 l each). The product was eluted at concentration 1 M and the product fraction was taken down in vacuo. The residue was codistilled with water (3 × 50 ml) and then dissolved in a minimum amount of boiling water, three parts of ethanol were added and the mixture was left to crystallize. Yield of (*R*)-9-(2-phosphonomethoxypropyl)adenine (*I*) was 1.35 g (47%), m.p. 279 °C, $[\alpha]_D$ –21.2° (*c* 0.5, 0.1 M HCl). For $C_9H_{14}N_5O_4P$. H_2O (305.3) calculated: 35.40% C, 5.29% H, 22.94% N, 10.17% P; found: 35.28% C, 5.37% H, 23.03% N, 10.17% P. E_{Up} 0.80. ^{1}H NMR spectrum (200 MHz, D_2O + NaOD): 8.25 s, 1 H (H-2); 8.09 s, 1 H (H-8); 4.35 dd, 1 H, *J*(1′a,2′) = 4.4, *J*(gem) = 14.4 (H-1′a); 4.22 dd, 1 H, *J*(1′b,2′) = 5.1, *J*(gem) = 14.4 (H-1′b); 3.97 m, 1 H (H-2′); 3.57 dd, 1 H, *J*(P,CHa) = 9.5, *J*(gem) = 12.4 (P-CHa); 3.46 dd, 1 H, *J*(P,CHb) = 9.3, *J*(gem) = 12.4 (P-CHb); 1.11 d, 3 H, *J*(3′,2′) = 6.3 (H-3′).

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

The title compound was prepared in the same manner as described for compound *I* from 3.57 g (12 mmol) of compound *XXVI*, yield 1.9 g (56%), m.p. 276–278 °C, $[\alpha]_D$ +21.2° (*c* 0.5, 0.1 M HCl). For $C_9H_{14}N_5O_4P$. H_2O (305.3) calculated: 35.40% C, 5.29% H, 22.94% N, 10.17% P; found: 35.33% C, 5.56% H, 23.14% N, 10.00% P. Electrophoretic mobility and ^{1}H NMR spectrum were identical with those of the (*R*)-isomer *I*.

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

(*R*)-9-(2-Hydroxypropyl)-2,6-diaminopurine (*IXb*) (2.1 g, 10 mmol) was dissolved in a warm mixture of dimethylformamide (40 ml) and dimethylformamide dimethyl acetal (25 ml). After standing at ambient temperature overnight under exclusion of moisture, the mixture was taken down at 40 °C/13 Pa. The residue was codistilled with dimethylformamide (2 × 20 ml) and then mixed with 50% aqueous pyridine (50 ml) and finely crushed dry ice (about 20 g). After 30 min the mixture was evaporated at 40 °C/13 Pa and the residue was codistilled with pyridine (4 × 25 ml). Bis(isopropyl) *p*-toluenesulfonyloxymethylphosphonate (*X*) (4.2 g, 12 mmol) was added, the mixture was codistilled with dimethylformamide (2 × 25 ml) and the residue was dissolved in dimethylformamide (40 ml) and cooled to –10 °C. Sodium hydride (60% dispersion, 1.2 g, 30 mmol) was added and the mixture was stirred under exclusion of moisture at room temperature for 48 h. After decomposition with acetic acid (1.8 ml, 30 mmol), the solvent was evaporated in vacuo and the residue was dissolved in dilute (1 : 1) aqueous ammonia (100 ml). The solution was set aside at room temperature overnight, evaporated in vacuo and the residue was deionized on a column of Dowex 50 as described for compound *I*. After cleavage with bromotrimethylsilane, the mixture was again deionized on the same ion-exchanger. The obtained ammonium salt was dissolved in hot water (50 ml) and under stirring acidified with 1 M hydrochloric acid to pH 3.5. The crystalline product was collected, washed successively with water, ethanol, ether, and dried in vacuo. Yield 1.4 g (46%) of (*R*)-9-(2-phosphonomethoxypropyl)-2,6-diaminopurine (*II*), m.p. 287 °C. $[\alpha]_D$ –26.1° (*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: 35.93% C, 5.02% H, 27.59% N, 10.28% P. ^{1}H NMR spectrum (500 MHz, D_2O + NaOD): 7.94 s, 1 H (H-8); 4.17 dd, 1 H, *J*(1′a,2′) = 4.4, *J*(gem) = 14.6 (H-1′a); 4.09 dd, 1 H, *J*(1′b,2′) = 5.4, *J*(gem) = 14.6 (H-1′b); 3.93 m, 1 H (H-2′); 3.54 dd, 1 H, *J*(P,CHa) = 9.3, *J*(gem) = 12.2 (P-CHa); 3.45 dd, 1 H, *J*(P,CHb) = 9.3, *J*(gem) = 12.2 (P-CHb); 1.12 d, 3 H *J*(3′,2′) = 6.3 (H-3′). E_{Up} 0.70.

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

The title compound was prepared in 33% yield from (*S*)-9-(2-hydroxypropyl)-2,6-diaminopurine (*IXb*) (2.1 g, 10 mmol) in the same manner as its (*R*)-enantiomer *II*. M.p. 275–278 °C, E_{Up} 0.70. $[\alpha]_D$ +28.5° (*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: 35.56% C, 5.08% H, 27.99% N, 10.18% P. The ^{1}H NMR spectrum was identical with that of its (*R*)-enantiomer.

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

The reaction was performed with (*R*)-9-(2-hydroxypropyl)-N^2-benzoylguanine (*XIII*) (2.5 g, 7 mmol) and bis(2-propyl) *p*-toluenesulfonyloxymethylphosphonate (*X*; 2.9 g, 8.4 mmol) in dimethylformamide (30 ml). After standing for 24 h at room temperature, methanol (100 ml) was added and the mixture was set aside at room temperature overnight under exclusion of moisture. The mixture was neutralized with Dowex 50 X 8 (H^+ form) and filtered. The filtrate was worked up as described for compound *I*. Chromatography on Dowex 1 X 2 and subsequent crystallization from water gave 0.90 g (43%) of (*R*)-9-(2-phosphonomethoxypropyl)guanine (*III*), m.p. 286 °C. $[\alpha]_D$ –26.1° (*c* 0.5, 0.1 M HCl). For $C_9H_{14}N_5O_5P$ (303.3) calculated: 35.64% C, 4.65% H, 23.10% N, 10.23% P; found: 35.35% C, 4.58% H, 23.24% N, 10.40% P. ^{1}H NMR spectrum (500 MHz, D_2O + NaOD): 7.90 s, 1 H (H-8); 4.21 dd, 1 H, *J*(1′a,2′) = 4.6, *J*(gem) = 14.5 (H-1′a); 4.15 dd, 1 H, *J*(1′b,2′) = 5.5, *J*(gem) = 14.5 (H-1′b); 3.99 m, 1 H (H-2′); 3.56 dd, 1 H, *J*(P,CHa) = 9.3, *J*(gem) = 12.4 (P-CHa); 3.48 dd, 1 H, *J*(P,CHb) = 9.2, *J*(gem) = 12.4 (P-CHb); 1.14 d, 3 H, *J*(3′,2′) = 6.2 (H-3′).

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

The reaction of compound *XXVIII* (1.57 g, 5 mmol) with bis(isopropyl) *p*-toluenesulfonyloxymethylphosphonate (*X*) (2.1 g, 6 mmol) was performed as described for the preparation of the (*R*)-enantiomer *III*. Compound *XXIX* was obtained as the free acid by crystallization from water in 43% yield (0.65 g), m.p. 287 °C. $[\alpha]_D$ +26.3° (*c* 0.5, 0.1 M HCl). For $C_9H_{14}N_5O_5P$ (303.3) calculated: 35.64% C, 4.65% H, 23.10% N, 10.23% P; found: 35.72% C, 4.54% H, 23.06% N, 10.29% P. The ^{1}H NMR spectrum was identical with that of the (*R*)-enantiomer *III*.

(*R*)-1-(2-Phosphonomethoxypropyl)cytosine (*XIX*)

A mixture of (*R*)-1-(2-hydroxypropyl)cytosine (*IXe*) (1.7 g, 10 mmol), dimethylformamide (40 ml) and dimethylformamide dimethyl acetal (15 ml) was stirred overnight and then evaporated at 40 °C/13 Pa. The work-up with aqueous pyridine and dry ice was carried out as described for compound *II*. The obtained compound *XVII* was mixed with *p*-toluenesulfonyloxyphosphonate (*X*; 4.2 g, 12 mmol), the mixture was dried by codistillation with dimethylformamide and the reaction with sodium hydride was carried out as described for compound *II*. After addition of 0.1 M methanolic sodium methoxide (100 ml), the mixture was allowed to stand overnight at room temperature, then neutralized with Dowex 50 X 8 (H^+ form), and filtered. The ion exchanger on the filter was washed with methanol (200 ml), the filtrate was concentrated and the residue was deionized under standard conditions. The obtained compound *XVIII* was treated with bromotrimethylsilane as described for compound *I*. After deionization, the product was chromatographed on Dowex 1 X 2 (vide supra) in a linear gradient of acetic acid (1 l of water and 1 l of 0.3 M acetic acid). The product fraction was taken down in vacuo, the residue was codistilled with water (3 × 50 ml) and crystallized from aqueous ethanol to give 0.90 g (19%) of (*R*)-1-(2-phosphonomethoxypropyl)cytosine, m.p. 261 °C, E_{Up} 0.70. $[\alpha]_D$ –108.1° (*c* 0.5, 0.1 M HCl). For $C_8H_{14}N_3O_5P$ (263.3) calculated: 36.50% C, 5.36% H, 15.97% N, 11.79% P; found: 36.43% C, 5.39% H, 16.05% N, 11.82% P. ^{1}H NMR spectrum (500 MHz,

D_2O, NaOD): 7.66 d, 1 H, *J*(5,6) = 7.3 (H-6); 6.00 d, 1 H, *J*(5,6) = 7.3 (H-5); 3.98 dd, 1 H, *J*(1′a,2′) = 3.4, *J*(gem) = 14.2 (H-1′a); 3.84 m, 1 H (H-2′); 3.73 dd, 1 H, *J*(1′b,2′) = 7.6, *J*(gem) = 14.2 (H-1′b); 3.68 dd, 1 H, *J*(P,CHa) = 9.5, *J*(gem) = 13.2 (P-CHa); 3.50 dd, 1 H, *J*(P,CHb) = 9.5, *J*(gem) = 13.2 (P-CHb); 1.21 d, 3 H, *J*(3′,2′) = 6.1 (H-3′).

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