SYNTHESIS OF SOME 2′-*C*-ALKYL DERIVATIVES OF 9-(2-PHOSPHONOMETHOXYETHYL)ADENINE AND RELATED COMPOUNDS

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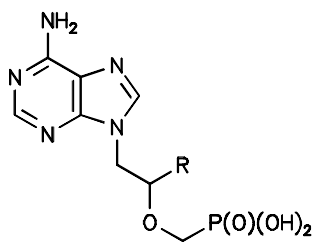
To study the effect of β-substitution in 2′-alkyl derivatives of 9-(2-phosphonomethoxyethyl)adenine (*Ia*) on the antiviral activity or group specificity, these derivatives were synthesized. 9-(2-Hydroxyalkyl)adenines *VIII* were prepared by alkylation of adenine with suitably substituted oxiranes *XIII* or 2-hydroxyalkyl *p*-toluenesulfonates *IV* and *VI*. After protection of the adenine amino group by benzoylation (compounds *IX*) or amidine formation (compounds *X*), the intermediates were alkylated with diisopropyl *p*-toluenesulfonyloxymethanephosphonate (*XI*) in the presence of sodium hydride. After deprotection, the obtained phosphonate diesters *XII* were converted into phosphonic acids *I* by transsilylation and hydrolysis. This synthetic scheme was used for the preparation of ethyl (*Ie*), propyl (*If*), 2-propyl (*Ig*), 2-methylpropyl (*Ih*), cyclopropyl (*Ii*), cyclohexyl (*Ij*), benzyl (*Ik*) and phenyl (*Il*) derivatives. The 2′-trifluoromethyl derivative *XXIIa* was prepared analogously from 9-(2-hydroxy-3,3,3-trifluoropropyl)adenine (*XXa*), obtained by alkylation of adenine sodium salt with 2-hydroxy-3,3,3-trifluoropropyl bromide. 2′-Trimethylsilyl derivative *XIXa* was obtained by alkylation of adenine with 2-diisopropylphosphonomethoxy-3-(4-toluenesulfonyloxy)propyltrimethylsilane (*XVII*) followed by transsilylation and hydrolysis of diester *XVIIIa*. 2,6-Diaminopurine derivatives *XVIIId* and *XXIIb* were obtained analogously. 9-(3-Phosphonomethoxybutyl)adenine (*XXVIII*) and 9-(2-methyl-2-phosphonomethoxypropyl)adenine (*XXXV*) were prepared from the corresponding hydroxy derivatives *XXVIb* and *XXXII*, respectively, by the same reaction pathway as derivatives *I*.

Acyclic phosphonate analogs of nucleotides, particularly phosphonomethyl ethers of some *N*-(hydroxyalkyl) derivatives of heterocyclic bases (*I*), attract recently much attention owing to their significant antiviral effect and unusual parameters such as e.g. unfrequent application regimen in vivo. We studied this group of compounds in detail from the viewpoint of structure–biological activity relationships, investigating independently the variation of all the three typical structural elements of their molecule: the heterocyclic base, the side chain attached to it, and the phosphorus-containing moiety (the phosphonate functionality) and its neighbourhood. We succeeded in defining the principal characteristics of the heterocyclic base that are indispensable for the antiviral activity in this group of compounds, as well as in specifying the relatively narrow structural margin defining the conditions necessary for the biological effect of these

molecules[1–3]. This relationship reflects several partial structure-dependent steps: membrane transport into the cell, transformation into the active metabolite and interaction with the target object (enzyme or an enzyme system). We have proven that a very specific protein can operate in the membrane transport[4], the activation by phosphorylation is catalyzed by action of various nucleotide kinases depending on the character of the base, which may or may not discriminate between the absolute configuration of the substrate[5,6], and that also the metabolism of the compounds and the targets of their antiviral effect may be different[3] (DNA polymerases, reverse transcriptases, ribonucleotide reductases) or yet unrecognized. Therefore, in attempts to evaluate the relationships between the chemical structure and the resulting effect in a biological system, the variety of parameters examined should be as low as possible.

Such opportunity is given by comparison of the effect of structural parameters on the antiviral activity and its specificity in a simple series of N^9-(2-phosphonomethoxyethyl) derivatives of adenine bearing a substituent at the position 2 of the side chain, as depicted by the general formula *I*. According to the information gathered in the course of our investigation, the unsubstituted compound of this series (PMEA, *Ia*) is active against a selected group of DNA viruses (herpes viruses, vaccinia) and retroviruses (HIV, MSV, SIV, Visna virus, hepatitis B virus etc., see refs[1–3,7–9]). Introduction of a hydroxymethylene functionality into the compound of (*S*)-configuration ((*S*)-HPMPA, *Ib*) results in a high, enantiospecific, and entirely group-specific effect aimed against DNA viruses (no resistent genus has been found so far), whereas replacement of the hydroxyl in these compounds by fluorine atom (*Ic*) (or by substitution of the parent structure with the fluoromethyl functionality) leads, under preservation of enantiospecificity, to a high and group-specific antiretroviral effect, without interference with DNA viruses[5,10]. Introduction of an aminomethyl or alkoxymethyl group into the said position quenches the antiviral effect completely[11,12]. We have recently found[6] that intro-



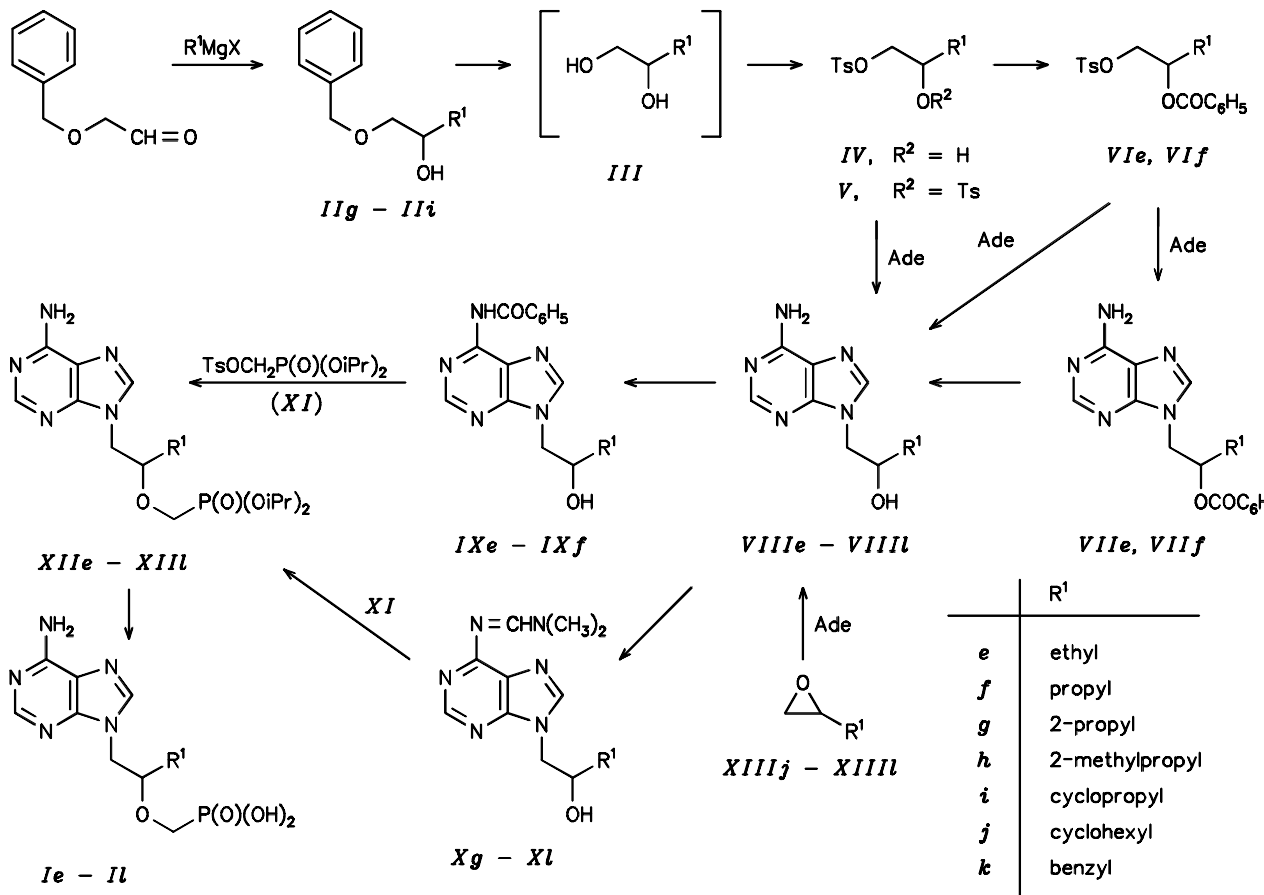
Ia, R = H
Ib, R = CH_2OH
Ic, R = CH_2F
Id, R = CH_3

duction of methyl group into position β of the parent structure *Ia* (the so-called PMP-derivatives and related compounds with modified base) induces a group-specific antiretroviral effect, similar to that found for compound *Ic* but substantially stronger. Also in this case, absolute enantioselectivity was observed for the adenine derivative *Id*: the biological effect is connected with the same series as (*S*)-HPMPA or (*S*)-FPMPA (the change of the designation from (*S*) to (*R*) for the PMP compounds is only formal).

The present study aims at the syntheses of alkyl derivatives of the type *I* bearing an alkyl group in position β of the side chain, in other words analogs of PMP-derivatives (*Id*). We synthesized systematically adenine derivatives substituted in position N^9 but, to eliminate at least in part the effect of the base, in some selected cases we extended our studies also to 2,6-diaminopurine derivatives (in all series hitherto studied, this base enhanced markedly the activity).

Acyclic phosphonates can be prepared by two principal methods: introduction of the phosphonomethyl ether functionality into the molecule of N^9-(2-hydroxyalkyl)adenine or alkylation of adenine with a synthon already containing the structure of the side chain together with the phosphonomethyl group. The latter method is of advantage if a series of derivatives with various bases has to be synthesized[10,13]. We made use of both the ways although, for practical reasons, the former was the method of choice.

The alkyl group in position β in compounds *I* was chosen so as to represent the steric, the hydrophobic and the electronegative effects. The desired N^9-(2-hydroxyalkyl)adenines were obtained by alkylation of adenine with tosylates of alkane-1,2-diols *IV* and *VI* or oxiranes *XIII* (Scheme 1). Some of the diols *III* were commercially available, most of them we prepared by reaction of the corresponding alkylmagnesium halides with benzyloxyacetaldehyde and subsequent hydrogenolysis. Alkane-1,2-diols were first converted into esters of *p*-toluenesulfonic acid *IV* under the usual conditions. The ditosyl derivatives *V*, arising as side products, were separated by chromatography on silica gel. Tosyl derivatives *IV* were then employed in the alkylation of adenine, either directly or after benzoylation with benzoyl cyanide[14] which afforded benzoyl derivatives *VI*. The alkylation of adenine with compounds *VI* was performed by reaction with sodium salt of adenine in dimethylformamide, the unprotected tosyl derivatives reacted with adenine in the presence of equimolecular amount of cesium carbonate in the same solvent. In the reaction with the benzoylated synthons *VI*, chromatography on silica gel gave first the benzoates *VII* from which the 9-(2-hydroxyalkyl)adenines *VIII* were obtained by methanolysis. Alkylation of adenine with unprotected synthon *IV* also gave compounds *VIII* which in some cases were obtained in sufficient purity directly by crystallization of the crude product. The third method of preparing 9-(2-hydroxyalkyl)adenines *VIII* consisted in alkylation of adenine with oxiranes *XIII* in the presence of catalytic amount of cesium carbonate. This method proved to be useful already earlier in alkylations of adenine as well as other purine and pyrimidine bases[15].



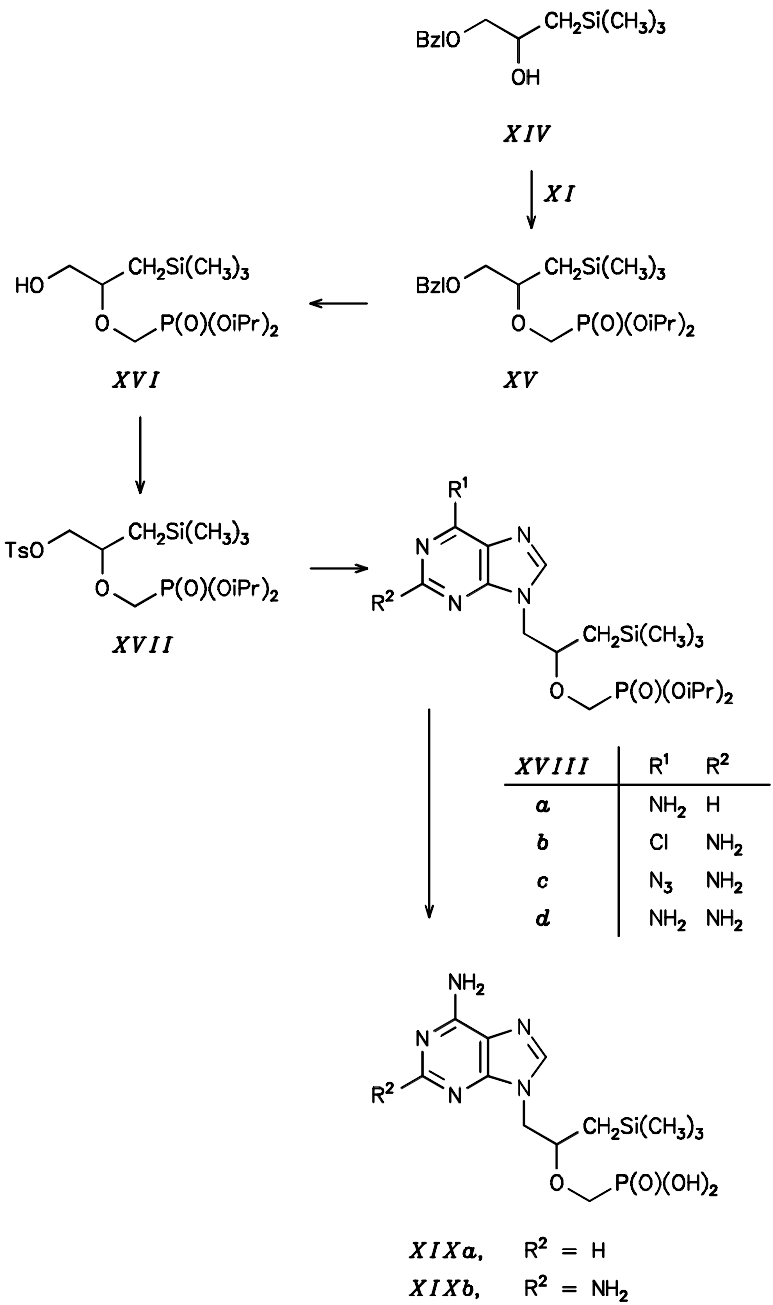
	R1
e	ethyl
f	propyl
g	2-propyl
h	2-methylpropyl
i	cyclopropyl
j	cyclohexyl
k	benzyl
l	phenyl

SCHEME 1

Condensation of these compounds with the phosphoroorganic synthon *XI* necessarily required a protection of the adenine amino group; this was realized by *N*-selective benzoylation[16] which afforded *N*-benzoyl derivatives *IX* isolated by chromatography and identified by NMR spectroscopy. Alternatively, both the amino groups of compounds *VIII* were protected by conversion into *N*-dimethylaminomethylene derivatives *X* with dimethylformamide dimethyl acetal[17]. The thus-protected derivatives *IX* or *X* were condensed with tosylate *XI* in the presence of excess sodium hydride in dimethylformamide[15] and the reaction mixture was then methanolyzed or ammonolyzed. The ester functionalities of phosphonates *XII* were removed by reaction with bromotrimethylsilane and subsequent hydrolysis. The resulting phosphonic acids *I* were isolated by ion exchange chromatography and their structure was confirmed by the usual spectroscopic methods, including the ^{1}H NMR spectra of the zwitterionic forms or their sodium salts.

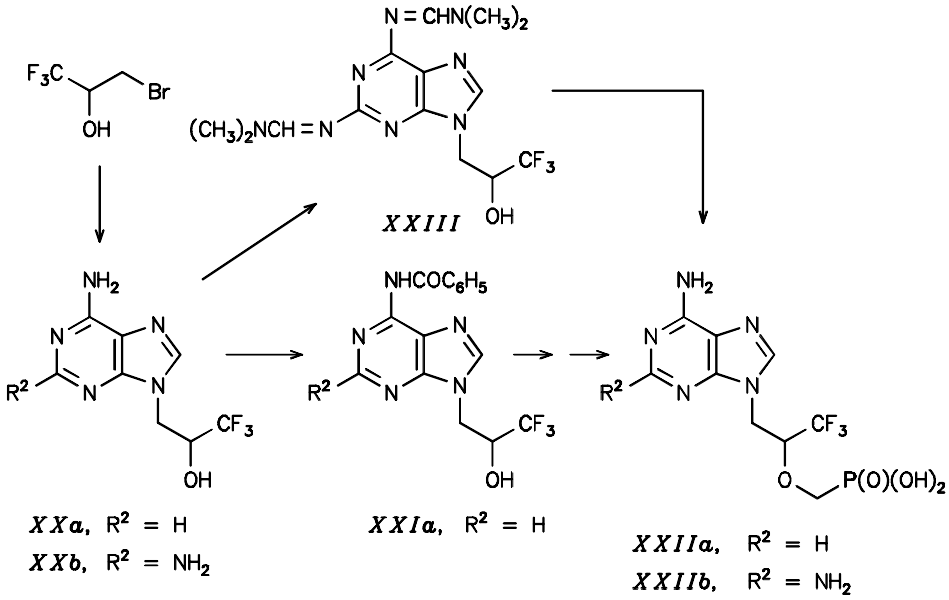
β-Trimethylsilylmethyl derivatives, representing compounds with a bulky hydrophobic substituent, were synthesized by alkylation of the heterocyclic base with a preformed phosphoroorganic synthon. Similarly as compounds *II*, also the starting protected diol *XIV* was prepared by Grignard rection of trimethylsilylmethylmagnesium chloride with benzyloxyacetaldehyde. Condensation of compound *XIV* with tosylate *XI* in the presence of sodium hydride and subsequent hydrogenolysis of the intermediate *XV* gave phosphonate *XVI* which upon tosylation under standard conditions was converted into the key synthon *XVII*. Alkylation of adenine with this compound in the presence of cesium carbonate afforded the expected diester *XVIIIa* which was converted into the desired substituted phosphonate *XIXa*. In the attempted preparation of the analogous derivative *XIXb* by alkylation of 2,6-diaminopurine the yields were low and we therefore chose an alternative way, analogous to that used with fluoromethyl derivative *Ic* (ref.[10]), starting from 2-amino-6-chloropurine as the alkylation substrate. In this case the reaction with synthon *XVII* gave satisfactory results; interestingly, the reaction afforded mainly the N^9-isomer whereas most alkylations of this base lead to significant amounts (up to 30%) of the N^7-regioisomer. Although the thus-obtained intermediate *XVIIIb* reacted smoothly with sodium azide to give the expected substitution on the base, the reaction was accompanied with partial cleavage of the ester functionality. Therefore, the mixture was only deionized and converted by hydrogenolysis into 2,6-diaminopurine derivatives which on transsilylation and hydrolysis gave the phosphonate *XIXb* as the final product of this reaction sequence (Scheme 2).

The outstanding properties of fluoromethyl derivative *Ic* (ref.[5]) prompted us to include also the trifluoromethyl group in the studied series of alkyl derivatives of the parent structure *Ia*. The trifluoromethyl group may manifest itself as an analog of the carboxyl functionality or of the methyl group (e.g. cytostatic and antiviral 2′-deoxy-5′-trifluoromethyluridine behaves as a thymidine analog). Also in this case we tried to prepare adenine as well as 2,6-diaminopurine (*XXIII*) derivatives (Scheme 3). The key alkylation reagent was 1-bromo-3,3,3-trifluoro-2-propanol prepared by reduction of


BzlO
CH2Si(CH3)3
OH
XIV
XI
HO
O
P(O)(OiPr)2
XVI
XV
TsO
XVII
R1
R2
N
XVIII
a NH2 H
b Cl NH2
c N3 NH2
d NH2 NH2
P(O)(OH)2
XIXa, R2 = H
XIXb, R2 = NH2

SCHEME 2

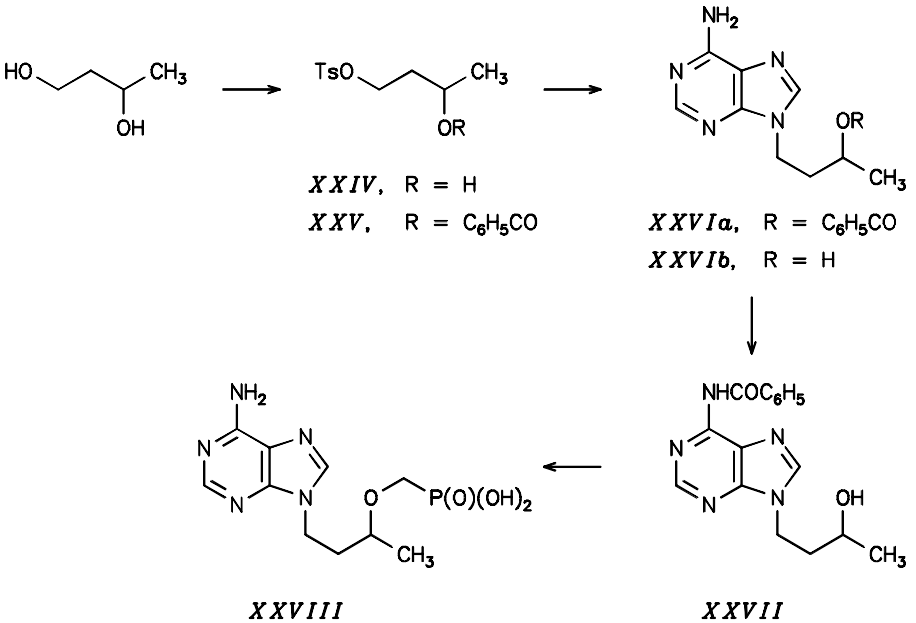
bromotrifluoroacetone[18]. This halogeno derivative smoothly alkylated sodium salt of adenine or 2,6-diaminopurine to give 9-(2-hydroxy-3,3,3-trifluoromethyl) derivatives *XX*. The adenine derivative was selectively *N*-benzoylated to compound *XXI* which was then condensed with tosyl derivative *XI*. The crude product was subjected to methanolysis and transsilylation of the ester functionalities to yield the desired β-trifluoromethyl derivative *XXIIa*. In the case of compound *XXb*, instead of *N*-benzoylation, we protected the amino groups with *N*-dimethylaminomethylene groups that are easier removable than the *N*-benzoyl functionalities. Upon condensation of the thus-obtained compound *XXIII* with tosyl derivative *XI*, ammonolysis and transsilylation, we isolated the β-trifluoromethyl derivative *XXIIb* by ion exchange chromatography.



SCHEME 3

We also prepared several other compounds relevant to the present study: first of all the linear homolog of the PMP-derivative *Id* in which the typical grouping of the PMP-series is one CH_2 group shifted farther from the heterocyclic nucleus (Scheme 4). Its synthesis started from butane-1,3-diol which was first tosylated on the primary hydroxyl and the remaining hydroxyl functionality in the formed ester *XXIV* was protected by benzoylation. Alkylation of sodium salt of adenine with the obtained synthon *XXV* afforded 4′-*O*-benzoyl derivative *XXVIa* which on methanolysis gave 9-(3-hydroxybutyl)adenine (*XXVIb*). Compound *XXVIb* was converted into the *N*-benzoyl derivative *XXVII* used finally in condensation with synthon *XI* in the presence of so-

dium hydride. The further reaction sequence involved standard operations: methanolysis, transsilylation, hydrolysis and finally isolation of the phosphonate *XXVIII* by ion-exchange chromatography.

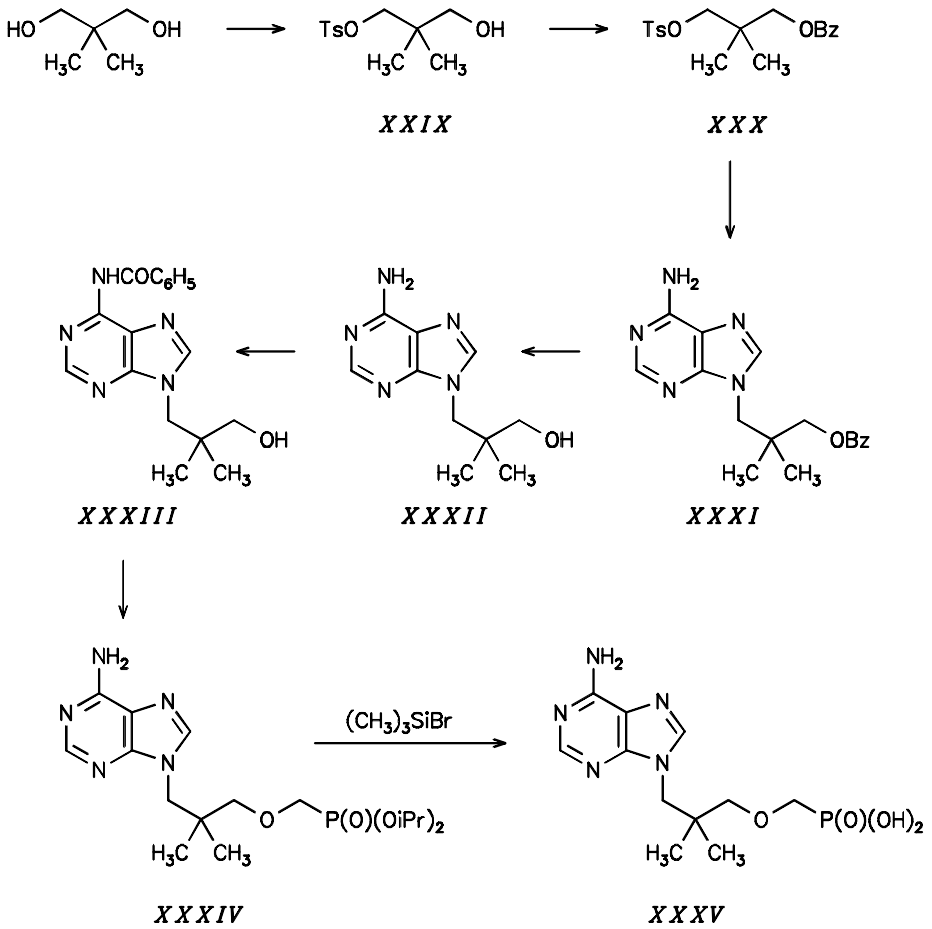


SCHEME 4

Related to compound *XXVIII* is the β,β-dimethyl derivative *XXXV* which was synthesized by a very similar method, simpler in that it started from a symmetrical 2,2-dimethylpropane-1,3-diol. Monotosylation to compound *XXIX*, its subsequent protection by benzoylation to compound *XXX*, alkylation of sodium salt of adenine with this derivative, isolation of the *O*-benzoylated intermediate *XXXI* and further analogous steps depicted in Scheme 5 finally afforded compound *XXXV*. Its identity, as well as the identity of most of the described compounds (intermediates and the final phosphonic acids) has been verified by physicochemical methods, particularly by the NMR spectroscopy.

Detailed results of biological studies will be reported elsewhere. Preliminary antiviral assays[19,20] afforded negative results. It seems thus that for retention of the antiviral activity the character (bulk) of the β-alkyl group in the side chain is extraordinarily strictly defined: the methyl group can be replaced by a hydroxymethyl or fluoromethyl group but no more by ethyl or even cyclopropyl group. Also, the characteristic grouping of the PMP-derivatives *Id* cannot be transferred by one carbon unit farther away

from the base. Equally striking is the complete inactivity of β-trifluoromethyl derivative *XXII*. Of course, the reason for all these negative responses may be primarily connected with the transport of these compounds through the cell membrane.



XXIX *XXX* *XXXI* *XXXII* *XXXIII* *XXXIV* *XXXV*

SCHEME 5

EXPERIMENTAL

Unless stated otherwise, solutions were evaporated at 40 °C/2 kPa and compounds were dried at 13 Pa over phosphorus pentoxide. Melting points were determined on a Kofler block and are uncorrected. Thin-layer chromatography was performed on Silufol UV_{254} sheets in the solvent systems: S1 benzene, S2 benzene–ethyl acetate (97 : 3), S3 benzene–ethyl acetate (95 : 5), S4 benzene–ethyl acetate (9 : 1), S5 toluene–ethyl acetate (1 : 1), S6 chloroform–methanol (97 : 3), S7 chloroform–methanol (9 : 1) S8 chloroform–methanol (4 : 1), S9 chloroform–ethanol (7 : 3). Preparative thin-layer chromatography

was carried out on 40 × 17 × 0.4 cm plates of silica gel containing a UV indicator (Kavalier, Votice, The Czech Republic). Paper chromatography was performed on a paper Whatman No. 1 in system S10 2-propanol–concentrated aqueous ammonia–water (7 : 1 : 2), paper electrophoresis on a paper Whatman No. 3 MM at 40 V/cm for 1 h in 0.05 M triethylammonium hydrogen carbonate pH 7.5. The electrophoretical mobilities are referenced to uridine 3′-phosphate. Reversed-phase liquid chromatography was carried out on Separon SGX columns (150 × 3.3 mm) in 0.05 M triethylammonium hydrogen carbonate pH 7.5, containing acetonitrile: H1 4%, H2 5%, H3 6%, H4 8%, H5 10%, H6 12%. ^{1}H NMR spectra were measured on a spectrometer Varian UNITY-200 (at 200 MHz) or Varian UNITY-500 (at 500 MHz) in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. The free phosphonic acids were measured in deuterium oxide containing sodium deuteroxide with sodium 3-(trimethylsilyl)-1-propanesulfonate (DSS) as internal standard. UV absorption spectra were measured on a Beckmann DU-65 spectrometer; the wavelengths of extrema are given in nm. Mass spectra were taken on a ZAB-EQ spectrometer (VG Analytical) using EI (electron energy 70 eV) and FAB (ionization by Xe, accelerating voltage 8 kV) techniques.

Starting Compounds and Reagents

2-Bromopropane and 1-bromo-2-methylpropane were prepared by reaction of the corresponding alcohols with phosphorus tribromide and were distilled immediately before use. Vinylcyclohexane, styrene oxide, trifluoroacetone, 2,2-dimethyl-1,3-propanediol, chloromethyltrimethylsilane and allylbenzene were purchased from Aldrich, cyclopropyl bromide, butane-1,2-diol and pentane-1,2-diol from Janssen. Adenine was a Fluka product, 2,6-diaminopurine was obtained from Tokyo Kasei (Japan) and 2-amino-6-chloropurine from Mack (Germany).

Deionization of Mixtures on Dowex 50

A solution of the mixture was applied onto a column of Dowex 50 X 8 (H^+ form) and the column was washed with water until the acid reaction disappeared and the UV absorption (254 nm) of the eluate dropped to the original value. The column was then washed with 2.5% aqueous ammonia and the UV-absorbing eluate was collected and evaporated in vacuo.

9-(2-Phosphonomethoxybutyl)adenine (*Ie*)

A mixture of compound *IXe* (1.56 g, 5 mmol) and tosyl derivative *XI* (2.1 g, 6 mmol) was codistilled with dimethylformamide (2 × 25 ml) at 40 °C/13 Pa. The residue was dissolved in dimethylformamide (25 ml), cooled to 0 °C and 60% sodium hydride dispersion (0.60 g, 15 mmol) was added. The mixture was then stirred at room temperature for 4 days (according to TLC in S7 the reaction was quantitative). Upon addition of methanol (50 ml) the mixture was set aside at room temperature overnight, neutralized with Dowex 50 X 8 (H^+ form) and made alkaline with triethylamine. The mixture was filtered, the ion exchanger washed with methanol (100 ml) and the filtrate evaporated to dryness in vacuo. The residue was deionized on a column of Dowex 50 X 8 (H^+ form); elution with 20% aqueous methanol and then with dilute (1 : 10) ammonia. The UV-absorbing fraction of the ammonia eluate was taken down in vacuo and the residue dried in vacuo overnight. Acetonitrile (25 ml) and bromotrimethylsilane (2.5 ml) were added and the solution was set aside at room temperature overnight under exclusion of moisture. After evaporation in vacuo, the residue was mixed with water (50 ml), made alkaline with ammonia and allowed to stand at room temperature for 1 h. The solvent was again evaporated, the residue was deionized on a column of Dowex 50 X 8 (H^+ form, 100 ml) (vide supra) and the material obtained from UV-absorbing fractions of the ammonia eluate was chromatographed on a column of Dowex 1 X 2 (acetate form, 100 ml) in a linear gradient of acetic acid (0 – 0.5

mol/l, à 1 l). The product was eluted with 0.3 – 0.4 M acetic acid. The main UV-absorbing part of the product was evaporated in vacuo and the residue was codistilled (3 × 50 ml) with water. Crystallization from 70% aqueous ethanol with addition of ether afforded 0.90 g (56.5%) of compound *Ie*, m.p. 252 °C, R_F 0.35 (S10), E_{Up} = 0.80, HPLC (H3): k = 2.84. For $C_{10}H_{16}N_5O_4P$. H_2O (319.3) calculated: 37.60% C, 5.68% H, 21.94% N, 9.72% P; found: 37.86% C, 5.71% H, 22.22% N, 9.87% P. ^{1}H NMR spectrum: 8.30 s, 1 H (H-2); 8.10 s, 1 H (H-8); 4.39 dd, 1 H, J(1a′,2′) = 4.2, J(gem) = 14.6 (H-1a′); 4.27 dd, 1 H, J(1b′,2′) = 5.6, J(gem) = 14.6 (H-1b′); 3.73 m, 1 H, ΣJ = 22.0 (H-2′); 1.44 m, 2 H (H-3′); 3.58 dd, 1 H, J(P,CH) = 9.5, J(gem) = 12.2 (P-CH_a); 3.50 dd, 1 H, J(P,CH) = 9.3, J(gem) = 12.2 (P-CH_b); 0.96 t, 3 H, J(4′,3′) = 6.5 (CH_3).

9-(2-Phosphonomethoxypentyl)adenine (*If*)

A mixture of compound *IXf* (1.62 g, 5 mmol) and tosylate *XI* (2.1 g, 6 mmol) was codistilled with dimethylformamide (2 × 25 ml) at 40 °C/13 Pa. The residue was dissolved in dimethylformamide (30 ml), cooled to 0 °C and 60% sodium hydride dispersion (0.60 g, 15 mmol) was added. The mixture was then stirred at room temperature for 4 days. Upon addition of methanol (50 ml) the mixture was set aside at room temperature overnight, neutralized with Dowex 50 X 8 (H^+ form) and made alkaline with triethylamine. The mixture was filtered, the ion exchanger washed with methanol (100 ml) and the filtrate evaporated to dryness in vacuo. The residue was deionized on a column of Dowex 50 X 8 (H^+ form), elution with 20% aqueous methanol, and then with dilute (1 : 10) ammonia. The UV-absorbing fraction of the ammonia eluate was taken down in vacuo and the residue dried in vacuo overnight. Acetonitrile (40 ml) and bromotrimethylsilane (4 ml) were added and the solution was set aside at room temperature overnight under exclusion of moisture. After evaporation in vacuo, the residue was mixed with water (50 ml), made alkaline with ammonia and allowed to stand at room temperature for 1 h. The solvent was again evaporated in vacuo, the residue was deionized on a column of Dowex 50 X 8 (H^+ form, 150 ml) (vide supra) and the material obtained from UV-absorbing fractions of the ammonia eluate was chromatographed on a column of Dowex 1 X 2 (acetate form, 100 ml) in a linear gradient of acetic acid (0 – 0.5 mol/l, à 1 l). The product was eluted with 0.2 – 0.3 M acetic acid. The main UV-absorbing part of the product was evaporated in vacuo and the residue was codistilled (3 × 50 ml) with water. Crystallization from ethanol with addition of ether afforded 0.80 g (48%) of compound *If*, m.p. 269 °C, R_F 0.42 (S10), E_{Up} = 0.80, HPLC (H3): k = 3.69. For $C_{11}H_{18}N_5O_4P.H_2O$ (333.3) calculated: 39.63% C, 6.05% H, 21.02% N, 9.31% P; found: 39.95% C, 5.74% H, 20.68% N, 9.09% P. ^{1}H NMR spectrum: 8.35 s, 1 H (H-2); 8.18 s, 1 H (H-8); 4.43 dd, 1 H, J(1a′,2′) = 4.0, J(gem) = 14.8, (H-1a′); 4.30 dd, 1 H, J(1b′,2′) = 5.0, J(gem) = 14.8 (H-1b′); 3.81 brpent, 1 H, ΣJ = 20.1 (H-2′); 1.28 – 1.44 m, 4 H (H-3′ and H-4′); 3.58 dd, 1 H, J(P,CH) = 9.3, J(gem) = 12.2 (P-CH_a); 3.52 dd, 1 H, J(P,CH) = 9.3, J(gem) = 12.2 (P-CH_b); 0.85 brt, 3 H, J(5′,4′) = 7.1 (CH_3).

General Method for Preparation of Compounds *Ig – Il*

A mixture of hydroxy derivative *VIIIg*, *VIIIh*, *VIIIi*, *VIIIj*, *VIIIk* or *VIIIl* (10 mmol), dimethylformamide (50 ml) and *N,N*- dimethylformamide dimethyl acetal (10 ml, 75 mmol) was allowed to stand at 20 °C for 24 h in a stoppered flask. After evaporation of the reaction mixture and codistillation with dimethylformamide (3 × 50 ml), the residue was stirred with solid carbon dioxide and pyridine–water (1 : 1, 100 ml) for 30 min. The mixture was then evaporated, codistilled with pyridine (3 × 50 ml) and with dimethylformamide (3 × 50 ml) and the crude dimethylaminomethylene derivative *X* was used without purification in the next reaction step.

Sodium hydride (1.2 g, 30 mmol, 60% dispersion) was added at –20 °C to a stirred mixture of crude dimethylaminomethylene derivative *X* and bis(2-propyl) *p*-toluenesulfonyloxymethanephospho-

nate (*XI*) (4.2 g, 12 mmol). The mixture was then allowed to warm to room temperature and was stirred under exclusion of moisture until the starting compound disappeared (24 h, TLC in S8). The reaction mixture was neutralized with acetic acid and the condensation product was deblocked by standing with ammonia–water–methanol (100 ml, 1 : 1 : 1) overnight. The mixture was taken down and deionized on Dowex 50 X 8 (H^+ form, 100 ml). The crude bis(2-propyl) ester *XII* was dried over phosphorus pentoxide and then used directly in the deprotection step.

The material from the preceding step was dissolved in acetonitrile (80 ml), bromotrimethylsilane (8 ml) was added and the mixture was set aside in a stoppered flask at 20 °C for 24 h. After evaporation, the residue was codistilled with acetonitrile (3 × 50 ml), mixed with water (50 ml) and adjusted to pH 8 with triethylamine. The mixture was allowed to stand for 1 h, then evaporated in vacuo and the residue was deionized on Dowex 50 X 8 (H^+ form, 100 ml). The obtained crude product was purified by chromatography on a column of Dowex 1 X 2 (acetate form, 100 ml). The product was eluted with a linear gradient of acetic acid (0 – 0.5 mol/l, 1 l each). Crystallization from 80% ethanol afforded the pure phosphonate.

9-(3-Methyl-2-phosphonomethoxybutyl)adenine (Ig), yield 1.51 g (48%), m.p. >250 °C, k = 2.5 (H1), E_{Up} = 0.70. For $C_{11}H_{18}N_5O_4P$ (315.3) calculated: 41.91% C, 5.75% H, 22.20% N, 9.83% P; found: 41.77% C, 5.54% H, 22.29% N, 9.62% P. ^{1}H NMR spectrum: 8.30 s and 8.11 s, 2 H (H-2, H-8); 4.35 dd, 1 H, J(1a′,2′) = 3.2, J(gem) = 14.6 (H-1a′); 4.22 dd, 1 H, J(1b′,2′) = 7.3, J(gem) = 14.6 (H-1b′); 3.48 td, 1 H, J(2′,1a′) = 3.2, J(2′, 1b′) = 7.3, J(2′,3′) = 7.1 (H-2′); 3.54 dd and 3.32 dd, 2 H, J(P,CH) = 10.0 and 9.5, J(gem) = 12.4 (PCH_2); 1.80 br oct, 1 H, ΣJ = 48 (H-3′); 1.01 d, 3 H and 0.97 d, 3 H, J(CH_3,CH) = 6.8 (CH_3). UV spectrum (pH 2): λ_{max} 260.5 nm (ε_{max} 15 900); (pH 7): λ_{max} 261.0 nm (ε_{max} 14 700); (pH 13): λ_{max} 261.0 (ε_{max} 13 900). Mass spectrum, *m*/*z*: 316.1 (M + H).

9-(4-Methyl-2-phosphonomethoxypentyl)adenine (Ih), yield 0.42 g (12%), m.p. 242 – 243 °C, k = 3.3 (H5), E_{Up} = 0.71. For $C_{12}H_{20}N_5O_4P$. 2 H_2O (365.3) calculated: 39.45% C, 7.17% H, 19.16% N, 8.49% P; found: 39.71% C, 6.69% H, 18.81% N, 7.76% P. ^{1}H NMR spectrum: 8.38 s and 8.18 s, 2 H (H-2, H-8); 4.46 dd, 1 H, J(1a′,2′) = 3.0, J(gem) = 14.2 (H-1a′); 4.30 dd, 1 H, J(1b′,2′) = 4.0, J(gem) = 14.2 (H-1b′); 3.88 m, 1 H (H-2′); 3.59 d, 2 H, J(P,CH) = 10.8 (PCH_2); 1.29 br pent, 1 H, J(3a′,2′) = 8.2, J(3a′,4′) = 5.1, J(gem) = 12.0 (H-3a′); 1.11 brpent, 1 H, J(3b′,2′) = 5.9, J(3b′,4′) = 7.4, J(gem) = 12.0, (H-3b′); 1.72 m, 1 H (H-4′); 0.85 and 0.83 2 × d, 2 × 3 H, J(CH_3,CH) = 6.1 and 6.3 (CH_3). UV spectrum (pH 2): λ_{max} 260.5 nm (ε_{max} 14 200); (pH 7): λ_{max} 262.5 nm (ε_{max} 14 400); (pH 13): λ_{max} 262.5 (ε_{max} 14 400). Mass spectrum, *m*/*z*: 330.2 (M + H).

9-(2-Cyclopropyl-2-phosphonomethoxyethyl)adenine (Ii), yield 1.70 g (51%), m.p. 241 – 242 °C, k = 4.9 (H2), E_{Up} = 0.77. For $C_{11}H_{16}N_5O_4P$. H_2O (331.2) calculated: 39.88% C, 4.87% H, 21.13% N, 9.36% P; found: 39.71% C, 4.86% H, 21.11% N, 9.40% P. ^{1}H NMR spectrum: 8.33 s and 8.18 s, 2 H (H-2, H-8); 4.47 dd, 1 H, J(1a′,2′) = 4.9, J(gem) = 14.4 (H-1a′); 4.43 dd, 1 H, J(1b′,2′) = 5.4, J(gem) = 14.4 (H-1b′); 3.09 dt, 1 H, ΣJ = 19.3 (H-2′); 3.77 dd and 3.52 dd, 2 H, J(P,CH) = 9.0 and 9.8, J(gem) = 12.2 (PCH_2); 0.62 m, 1 H and 0.56 m, 1 H and 0.42 m, 1 H and 0.27 m, 1 H and 0.12 m, 1 H (cyclopropyl). UV spectrum (pH 2): λ_{max} 259.0 nm (ε_{max} 13 000); (pH 7): λ_{max} 261.0 nm (ε_{max} 14 100); (pH 13): λ_{max} 261.0 (ε_{max} 12 900). Mass spectrum, *m*/*z*: 314.1 (M + H).

9-(2-Cyclohexyl-2-phosphonomethoxyethyl)adenine (Ij), yield 0.31 g (8%), m.p. >250 °C, k = 6.3 (H6), E_{Up} = 0.73. For $C_{14}H_{22}N_5O_4P$. 2 H_2O (391.4) calculated: 42.96% C, 5.67% H, 17.89% N, 7.92% P; found: 43.37% C, 5.79% H, 17.97% N, 7.82% P. ^{1}H NMR spectrum: 8.39 and 8.16 2 × s, 2 H (H-2, H-8); 4.41 dd, 1 H, J(1a′,2′) = 3.4, J(gem) = 14.6 (H-1a′); 4.29 dd, 1 H, J(1b′,2′) = 6.4, J(gem) = 14.6 (H-1b′); 3.49 td, 1 H, J(2′,1a′) = 3.4, J(2′,1b′) = 6.4, J(2′,3′) = 6.6 (H-2′); 3.54, dd, 1 H and 3.39 dd, 1 H, J(P,CH) = 9.5 and 9.3, J(gem) = 12.2 (PCH_2); 1.59 – 1.86 m, 5 H and 1.36 m, 1 H and 1.03 – 1.15 m, 5 H (cyclohexyl). UV spectrum (pH 2): λ_{max} 260.0 nm (ε_{max} 14 500); (pH 7): λ_{max} 261.0 nm (ε_{max} 13 400); (pH 13): λ_{max} 261.0 (ε_{max} 13 100). Mass spectrum, *m*/*z*: 356.1 (M + H).

9-(3-Phenyl-2-phosphonomethoxypropyl)adenine (Ik), yield 0.59 g (16%), m.p. >250 °C, k = 3.1 (H6), E_{Up} = 0.63. For $C_{15}H_{18}N_5O_4P$ (363.3) calculated: 49.59% C, 4.99% H, 19.27% N, 8.53% P; found: 49.12% C, 4.88% H, 18.99% N, 9.06% P. ^{1}H NMR spectrum: 8.195 s, 1 H and 8.03 s, 1 H (H-2, H-8); 7.15 m and 7.03 m, 5 H (arom.); 4.29 d, 2 H, J(1′,2′) = 5.4 (H-1′); 4.23 m, 1 H, ΣJ = 23.7 (H-2′); 3.02 dd, 1 H, J(3a′,2′) = 4.9, J(gem) = 14.4 (H-3a′); 2.67 dd, 1 H, J(3b′,2′) = 8.0, J(gem) = 14.4 (H-3b′); 3.70 dd, 1 H and 3.59, dd, 1 H, J(P,CH) = 9.3 and 9.5, J(gem) = 12.2 (PCH_2). UV spectrum (pH 2): λ_{max} 256.0 nm (ε_{max} 11 400); (pH 7): λ_{max} 262.0 nm (ε_{max} 11 200); (pH 13): λ_{max} 262.0 (ε_{max} 11 000). Mass spectrum, m/z: 364.2 (M + H).

9-(2-Phenyl-2-phosphonomethoxyethyl)adenine (Il), yield 2.10 g (60%), m.p. >250 °C, k = 2.8 (H3), E_{Up} = 0.77. For $C_{14}H_{16}N_5O_4P$ (349.3) calculated: 48.14% C, 4.62% H, 20.04% N, 8.88% P; found: 47.37% C, 4.62% H, 19.12% N, 8.22% P. ^{1}H NMR spectrum: 8.03 s, 1 H and 7.90 s, 1 H (H-2, H-8); 7.23 m and 7.10 m, 5 H (arom.); 4.53 dd, 1 H, J(1a′,2′) = 5.1, J(gem) = 14.2 (H-1a′); 4.48 dd, 1 H, J(1b′,2′) = 5.6, J(gem) = 14.2 (H-1b′); 4.87 brt, 1 H, J = 5.6 (H-2′); 3.46 dd, 1 H and 3.34 dd, 1 H, J(P,CH) = 9.0 and 9.8, J(gem) = 12.2 (PCH_2). UV spectrum (pH 2): λ_{max} 259.0 nm (ε_{max} 13 700); (pH 7): λ_{max} 260.0 nm (ε_{max} 14 100); (pH 13): λ_{max} 261.0 (ε_{max} 13 300). Mass spectrum, m/z: 250.0 (M + H).

Preparation of Compounds *II* (General Procedure)

A solution of the alkyl halogenide (0.25 mol) in ether (200 ml) was added dropwise to a stirred mixture of magnesium (6.1 g, 0.25 mol), ether (150 ml) and a trace of iodine to maintain reflux. The reaction mixture was then refluxed for one hour, benzyloxyacetaldehyde (32.3 g, 0.215 mol) in ether (150 ml) was added within 30 min and the reflux was continued for two more hours. The mixture was left to stand overnight, cooled with ice, and ammonium chloride (200 ml, saturated solution) was added dropwise. After stirring for 30 min, the mixture was filtered through a layer of Celite and extracted with ether. The aqueous layer was washed with ether (3 × 100 ml), the combined ethereal extracts were dried over magnesium sulfate, filtered and the solvent was evaporated. The crude products were chromatographed on silica gel (400 g).

1-Benzyloxy-3-methylbutan-2-ol (IIg). Reaction with isopropyl bromide and subsequent chromatography in benzene–ethyl acetate (97 : 3) afforded 24.4 g (63%) of compound *IIg*, R_F 0.26 (S3). ^{1}H NMR spectrum: 7.33 brs, 5 H (arom.); 4.53 d, 1 H, J(CH,OH) = 5.0 (OH); 4.48 s, 2 H ($PhCH_2O$); 3.35 m, 3 H (OCH_2,OCH); 1.68 septd, 1 H, J(CH,CH) = 4.4, J(CH,CH_3) = 6.8 (CCH); 0.85 d and 0.82 d, 6 H, J = 6.8 (CH_3).

1-Benzyloxy-4-methylpentan-2-ol (IIh). Reaction with isobutyl bromide and subsequent chromatography in chloroform afforded 35.4 g (79%) of compound *IIh*, R_F 0.4 (S2). ^{1}H NMR spectrum: 7.33 brs, 5 H (arom.); 4.49 dd, 1 H and 4.46 dd, 1 H, J(gem) = 12.2 ($PhCH_2O$); 3.32 dd, 1 H, J = 6.1, J(gem) = 9.5 (OCH_a); 3.27 dd, 1 H, J = 5.1, J(gem) = 9.5 (OCH_b); 3.67 m, 1 H, ΣJ = 24.2 (OCH); 1.25 dd, 1 H, J = 5.1, 8.8, J(gem) = 13.7 (CCH_a); 1.20 dd, 1 H, J = 4.4, 8.6, J(gem) = 13.7 (CCH_b); 1.76 m, 1 H, ΣJ = 54 (CCH); 0.88 and 0.85 2 × d, 6 H, J = 6.8, 6.6 (CH_3).

1-Benzyloxy-2-cyclopropylethan-2-ol (IIi). Reaction with cyclopropyl bromide and subsequent chromatography in system S2 afforded 27.0 g (70%) of compound *IIi*, R_F 0.27 (S2). ^{1}H NMR spectrum: 7.30 – 7.40 m, 5 H (arom.); 4.60 d, 1 H, J(CH,OH) = 4.9 (OH); 4.51 s, 2 H ($PhCH_2O$); 3.44 dd, 1 H, J = 4.9, J(gem) = 9.8 (OCH_a); 3.40 dd, 1 H, J = 6.8, J(gem) = 9.8 (OCH_b); 3.14 tt, 1 H, ΣJ = 23.0 (OCH); 0.79 – 0.85 m, 1 H, 0.30 – 0.38 m, 2 H and 0.19 m, 2 H (cyclopropyl).

Preparation of 2-Hydroxyalkyl *p*-Toluenesulfonates *IVg – IVi* (General Procedure)

Compounds *IIg – IIi* (0.11 mol) were hydrogenated over 10% Pd/C (2.1 g) in methanol (300 ml) and hydrochloric acid (2 ml) at room temperature for 4 h. The reaction mixture was filtered through a

layer of Celite which was then washed with methanol (200 ml). The filtrate was neutralized with pyridine, evaporated and the residue was codistilled with pyridine (3 × 50 ml). The obtained compound *III* was used directly in the tosylation step.

A solution of *p*-toluenesulfonyl chloride (25.2 g, 0.13 mol) in pyridine (70 ml) was added dropwise at 0 °C to a stirred solution of the 1,2-diol (0.11 mol) and 4-dimethylaminopyridine (0.1 g) in pyridine (70 ml) under exclusion of moisture. The reaction mixture was left to stand at 0 °C for 24 h and methanol (5 ml) was added. The mixture was stirred for 30 min, evaporated and partitioned between ethyl acetate and water. The organic phase was washed successively with 1 M HCl, water, sodium hydrogen carbonate solution, and water. The extract was dried over magnesium sulfate, filtered, the solvent was evaporated and the residue was chromatographed on silica gel.

2-Hydroxy-3-methylbutyl p-toluenesulfonate (IVg) *and 3-methyl-1,2-butanediyl bis(p-toluenesulfonate)* (Vg). The products were eluted with benzene–ethyl acetate (95 : 5 and then 90 : 10). Yield of the monotosylate *IVg* was 10.3 g (36%), R_F 0.26 (S2). For $C_{12}H_{18}O_4S$ (258.2) calculated: 55.80% C, 7.02% H, 12.39% S; found: 55.86% C, 6.94% H, 12.30% S. ^{1}H NMR spectrum: 7.79 d and 7.48 d, 4 H, J = 8.3 (arom.); 5.0 br, 1 H (OH); 3.34 td, 1 H, ΣJ = 16.0, (H-2); 3.92 dd, 1 H, J(1a,2) = 4.1, J(gem) = 9.8 (H-1a); 3.84 dd, 1 H, J(1b,2) = 6.3, J(gem) = 9.8 (H-1b); 2.42 s, 3 H ($TsCH_3$); 1.59 septd, 1 H, ΣJ = 46.4 (H-3); 0.76 d, 3 H, $J(CH_3,CH)$ = 6.8 (CH_3).

Ditosylate *Vg* was obtained in 29% yield (13.1 g), R_F 0.84 (S2). For $C_{19}H_{24}O_6S_2$ (412.4) calculated: 55.33% C, 5.87% H, 15.52% S; found: 55.71% C, 5.86% H, 15.64% S. ^{1}H NMR spectrum: 7.71 d and 7.46 d, 4 H, J = 8.3 (arom.); 7.69 d and 7.41 d, 4 H, J = 8.3 (arom.); 4.48 ddd, 1 H, ΣJ = 14.6 (H-2); 4.08 dd, 1 H, J(1a,2) = 4.6, J(gem) = 11.5 (H-1a); 4.02 dd, 1 H, J(1b,2) = 3.2, J(gem) = 11.5 (H-1b); 2.42 s, 3 H and 2.40 s, 3 H ($TsCH_3$); 1.89 oct, 1 H, ΣJ = 47.6 (H-3); 0.73 d, 3 H and 0.72 d, 3 H, $J(CH_3,CH)$ = 6.8 (CH_3).

2-Hydroxy-4-methylpentyl p-toluenesulfonate (IVh) *and 4-methyl-1,2-pentanediyl bis(p-toluenesulfonate)* (Vh). The products were eluted with chloroform–ethanol (98 : 2), yield of the monotosylate *IVh* was 10.0 g (34%), R_F 0.42 (S2). For $C_{13}H_{20}O_4S$ (272.3) calculated: 57.34% C, 7.40% H, 11.75% S; found: 58.08% C, 7.54% H, 11.64% S. ^{1}H NMR spectrum: 7.79 d and 7.48 d, 4 H, J = 8.3 (arom.); 4.95 brs, 1 H (OH); 3.63 brsext, 1 H, ΣJ = 23.0 (H-2); 3.84 dd, 1 H, J(1a,2) = 4.4, J(gem) = 9.8 (H-1a); 3.79 dd, 1 H, J(1b,2) = 5.9, J(gem) = 9.8 (H-1b); 2.42 s, 3 H ($TsCH_3$); 1.19 ddd, 1 H, J(3a,2) = 9.8, J(3a,4) = 5.4, J(gem) = 13.2, (H-3a); 1.05 ddd, 1 H, J(3b,2) = 3.9, J(3b,4) = 8.8, J(gem) = 13.2 (H-3b); 1.64 m, 1 H, ΣJ = 55.0 (H-4); 0.82 and 0.78 2 × d, 2 × 3 H, $J(CH_3,CH)$ = 6.8 (CH_3). Mass spectrum, *m/z*: 273 (M + H).

Ditosylate *Vh* was obtained in 26% yield (12.3 g), R_F 0.80 (S2). For $C_{20}H_{26}O_6S_2$ (426.4) calculated: 56.33% C, 6.15% H, 15.01% S; found: 55.87% C, 6.08% H, 15.21% S. ^{1}H NMR spectrum: 7.79 d and 7.68 d, 4 H, J = 8.3 (arom.); 7.48 d and 7.32 d, 4 H, J = 8.3 (arom.); 4.66 ddd, 1 H, ΣJ = 21.0 (H-2); 4.06 dd, 1 H, J(1a,2) = 3.9, J(gem) = 11.2 (H-1a); 4.03 dd, 1 H, J(1b,2) = 3.4, J(gem) = 11.2 (H-1b); 2.425 s, 3 H and 2.41 s, 3 H ($TsCH_3$); 1.45 ddd, 1 H, J(3a,2) = 8.8, J(3a,4) = 5.4, J(gem) = 13.6 (H-3a); 1.28 ddd, 1 H, J(3b,2) = 4.9, J(3b,4) = 8.3, J(gem) = 13.6 (H-3b); 1.37 m, 1 H, ΣJ = 54.5 (H-4); 0.74 d, 3 H and 0.63 d, 3 H, $J(CH_3,CH)$ = 6.8 (CH_3). Mass spectrum, *m/z*: 426 (M + H).

2-Cyclopropyl-2-hydroxyethyl p-toluenesulfonate (IVi). The product was eluted with benzene–ethyl acetate (95 : 5 and then 9 : 1), yield 15.9 g (57%), R_F 0.19 (S2). For $C_{12}H_{15}O_4S$ (255.2) calculated: 56.47% C, 5.92% H, 12.53% S; found: 56.43% C, 6.49% H, 11.72% S. ^{1}H NMR spectrum: 7.82 d and 7.50 d, 4 H, J = 8.3 (arom.); 4.27 dd, 1 H, J(1a,2) = 4.3, J(gem) = 11.0 (H-1a); 4.20 dd, 1 H, J(1b,2) = 5.8, J(gem) = 11.0 (H-1b); 3.65 ddd, 1 H, ΣJ = 19.8 (H-2); 2.425 s, 3 H (CH_3); 1.01 – 1.19 m, 1 H; 0.50 – 0.65 m, 2 H; 0.30 – 0.45 m, 2 H (cyclopropyl).

2-*O*-Benzoyloxybutyl *p*-Toluenesulfonate (*VIe*) and 2-*O*-Benzoyloxypentyl *p*-Toluenesulfonate (*VIf*)

A solution of tosyl chloride (50 g, 0.26 mol) in pyridine (150 ml) was added dropwise with stirring and ice-cooling to a solution of butane-1,2-diol (27 g, 0.3 mol) and 4-dimethylaminopyridine (1 g) in pyridine (250 ml). The mixture was stirred in ice for 3 h and then set aside at 0 °C for 48 h. Methanol (50 ml) was added and, after standing for 1 h, the mixture was diluted with ethyl acetate (1 l), washed with water (3 × 200 ml) and the solvent was evaporated in vacuo. The residue was codistilled with toluene (3 × 100 ml) and dried at 40 °C/13 Pa. The obtained crystalline tosylate *IVe* (62 g, 0.25 mol) was dissolved in dichloromethane (400 ml) and benzoyl cyanide (36 g, 0.275 mol) with triethylamine (5 ml) were added under ice-cooling. The mixture was allowed to stand under exclusion of moisture at room temperature overnight, methanol (10 ml) was added and the supernatant was evaporated in vacuo. The residue was dissolved in ether (150 ml), the same amount of light petroleum was added, the solution was decanted from the deposited impurities and the solvent was evaporated in vacuo. Crystallization of the residue from cyclohexane afforded 42 g (48%) of compound *IVe*, m.p. 63 °C, R_F 0.40 (S1), 0.62 (S4). For $C_{18}H_{20}O_5S$ (348.4) calculated: 62.05% C, 5.79% H, 9.20% S; found: 61.89% C, 5.78% H, 9.21% S.

Similarly, pentane-1,2-diol (0.3 mol) was converted into the tosyl derivative *VIf* (55 g, 61%), R_F 0.40 (S1). For $C_{19}H_{22}O_5S$ (362.4) calculated: 62.96% C, 6.12% H, 8.85% S; found: 62.88% C, 5.95% H, 9.14% S.

9-(2-Hydroxybutyl)adenine (*VIIIe*)

Sodium hydride (2.0 g, 50 mmol, 60% dispersion in paraffin) was added to a suspension of adenine (6.8 g, 50 mmol) in dimethylformamide (300 ml) and the stirred mixture was heated at 80 °C. Tosyl derivative *VIe* (18.0 g, 52 mmol) was added and the mixture was heated at 100 °C for 16 h under exclusion of moisture. After evaporation of the solvent at 40 °C/13 Pa, the residue was extracted with boiling chloroform (3 × 100 ml). The filtrate was taken down in vacuo and the residue chromatographed on a column of silica gel (300 ml) in chloroform. The obtained benzoyl derivative *VIIe* was dissolved in 0.1 M methanolic sodium methoxide (150 ml) and allowed to stand at room temperature overnight under exclusion of moisture. The mixture was neutralized by addition of Dowex 50 X 8 (H^+ form), made alkaline with triethylamine, filtered and the ion exchanger washed with methanol (100 ml). The filtrate was taken down in vacuo and the dry residue was codistilled with ethanol and crystallized from ethanol with addition of the same amount of ether. Yield 3.5 g (34%) of compound *VIIIe*, m.p. 195 °C. For $C_9H_{13}N_5O$ (207.2) calculated: 52.16% C, 6.31% H, 33.80% N; found: 52.40% C, 6.39% H, 33.74% N. ^{1}H NMR spectrum: 8.14 s, 1 H (H-2); 8.05 s, 1 H (H-8); 7.23 brs, 2 H (NH_2); 5.03 d, 1 H, J(2′,OH) = 5.03 (OH); 4.15 dd, 1 H, J(1a′,2′) = 4.0, J(gem) = 13.7 (H-1a′); 4.00 dd, 1 H, J(1b′,2′) = 7.5, J(gem) = 13.7 (H-1b′); 3.74 d, 1 H, ΣJ = 28.5 (H-2′); 1.34 m, 2 H (H-3′); 0.90 t, 3 H, J = 7.3 (CH_3).

9-(2-Hydroxypentyl)adenine (*VIIIf*)

Sodium hydride (1.6 g, 40 mmol, 60% dispersion in paraffin) was added to a suspension of adenine (5.4 g, 40 mmol) in dimethylformamide (250 ml) and the stirred mixture was heated at 80 °C. Tosyl derivative *VIf* (16.3 g, 45 mmol) was added and the mixture was heated at 100 °C for 20 h under exclusion of moisture. After evaporation of the solvent at 40 °C/13 Pa, the residue was extracted with boiling chloroform (3 × 100 ml). The filtrate was taken down in vacuo and the residue chromatographed on a column of silica gel (300 ml) in chloroform to give the 2-*O*-benzoyl derivative of compound *VIIf* (9.0 g, 69%) as an amorphous foam. This product was debenzoylated as described for the preparation of compound *VIIIe*. Yield 3.8 g (62%) of compound *VIIIf*, m.p. 189 °C. For $C_{10}H_{15}N_5O$

(221.3) calculated: 54.28% C, 6.83% H, 31.66% N; found: 54.17% C, 6.62% H, 31.86% N. ^{1}H NMR spectrum: 8.14 s, 1 H (H-2); 8.05 s, 1 H (H-8); 7.23 brs, 2 H (NH_2); 4.14 dd, 1 H, J(1a′,2′) = 3.9, J(gem) = 13.4 (H-1a′); 3.99 dd, 1 H, J(1b′,2′) = 7.8, J(gem) = 13.4 (H-1b′); 3.84 d, 1 H (H-2′); 1.23 – 1.46 m, 4 H (H-3′ and H-4′); 0.84 brt, 3 H, J = 6.8 (CH_3).

General Method for Preparation of Compounds *VIIIg – VIIIi*

A mixture of adenine (1.35 g, 10 mmol), cesium carbonate (3.25 g, 10 mmol), tosylate *IVg*, *IVh* or *IVi* (10 mmol) and dimethylformamide (25 ml) was heated at 120 °C for 16 h under stirring and exclusion of moisture. The reaction course was followed by TLC (S8). After concentration in vacuo, the residue was codistilled with toluene (3 × 50 ml) and chromatographed or crystallized.

9-(2-Hydroxy-3-methylbutyl)adenine (VIIIg). Isolated by chromatography on silica gel (80 g) in chloroform. The product was eluted with chloroform–methanol (95 : 5). Yield 0.8 g (36%), R_F 0.31 (S8), m.p. 183 – 184 °C. For $C_{10}H_{15}N_5O$ (221.2) calculated: 54.29% C, 6.83% H, 31.64% N; found: 53.11% C, 6.62% H, 30.87% N. ^{1}H NMR spectrum: 8.14 s, 1 H (H-2); 8.06 s, 1 H (H-8); 7.21 brs, 2 H (NH_2); 4.98 d, 1 H, J(OH,CH) = 5.6 (OH); 4.21 dd, 1 H, J(1a′,2′) = 3.0, J(gem) = 13.9 (H-1a′); 3.98 dd, 1 H, J(1b′,2′) = 8.5, J(gem) = 13.9 (H-1b′); 3.60 m, 1 H (H-2′); 1.59 broct, 1 H (H-3′); 0.93 d, 3 H and 0.92 d, 3 H (CH_3). UV spectrum (pH 2): λ_{max} 261.0 nm (ε_{max} 14 600); (pH 7): λ_{max} 261.0 nm (ε_{max} 14 900); (pH 13): λ_{max} 261.0 (ε_{max} 14 800).

9-(2-Hydroxy-4-methylpentyl)adenine (VIIIh). Isolated by crystallization from methanol; yield 0.92 g (40%), R_F 0.5 (S8), m.p. 183 – 185 °C. For $C_{11}H_{17}N_5O$ (235.2) calculated: 56.16% C, 7.28% H, 29.76% N; found: 55.34% C, 6.94% H, 29.84% N. ^{1}H NMR spectrum: 8.13 s, 1 H (H-2); 8.04 s, 1 H (H-8); 7.17 brs, 2 H (NH_2); 4.97 d, 1 H, J(OH,CH) = 5.6 (OH); 4.13 dd, 1 H, J(1a′,2′) = 3.4, J(gem) = 13.2 (H-1a′); 3.97 dd, 1 H, J(1b′,2′) = 7.3, J(gem) = 13.2 (H-1b′); 3.88 m, 1 H (H-2′); 1.27 ddd, 1 H, J(3a′,2′) = 8.3, J(3a′,4′) = 5.4, J(gem) = 13.7 (H-3a′); 1.23 ddd, 1 H, J(3b′,2′) = 4.1, J(3b′,4′) = 8.8, J(gem) = 13.7 (H-3b′); 1.77 m, 1 H (H-4′); 0.88 d, 3 H and 0.82 d, 3 H, J(CH_3,CH) = 6.8 and 6.35 (CH_3).

9-(2-Cyclopropyl-2-hydroxyethyl)adenine (VIIIi). Isolated by chromatography on silica gel (100 g) in chloroform. Elution with chloroform–ethanol (75 : 25) afforded 0.7 g (33%) of compound *VIIIi*, R_F 0.55 (S8), m.p. 204 – 205 °C. For $C_{10}H_{13}N_5O$ (219.2) calculated: 54.79% C, 5.98% H, 31.93% N; found: 54.60% C, 5.91% H, 31.45% N. ^{1}H NMR spectrum: 8.13 s, 1 H and 8.07 s, 1 H (H-2, H-8); 7.21 brs, 2 H (NH_2); 5.09 d, 1 H, J(OH,CH) = 5.1 (OH); 4.23 dd, 1 H, J(1a′,2′) = 4.4, J(gem) = 13.7 (H-1a′); 4.20 dd, 1 H, J(1b′,2′) = 7.8, J(gem) = 13.7 (H-1b′); 3.29 tt, 1 H, ΣJ = 24.7 (H-2′); 0.80 qt, 1 H; 0.29 – 0.37 m, 2 H; 0.22 – 0.26 m, 1 H; 0.04 – 0.08 m, 1 H (cyclopropyl). UV spectrum (pH 2): λ_{max} 259.0 nm (ε_{max} 12 200); (pH 7): λ_{max} 261.0 nm (ε_{max} 12 700); (pH 13): λ_{max} 261.0 (ε_{max} 12 600).

General Method for Preparation of Compounds *VIIIj – VIIIl* by Alkylation of Adenine with Oxiranes

A mixture of adenine (1.35 g, 10 mmol), cesium carbonate (0.25 g, (0.7 mmol), the appropriate oxirane (12 mmol); (phenyloxirane 1.4 g, cyclohexyloxirane 1.5 g, benzyloxirane 1.6 g) and dimethylformamide (25 ml) was heated at 120 °C for 8 h under stirring and exclusion of moisture. After the end of the reaction (TLC in S8) the mixture was concentrated in vacuo and the residue codistilled with toluene (3 × 50 ml).

9-(2-Cyclohexyl-2-hydroxyethyl)adenine (VIIIj) was prepared from cyclohexyloxirane (1.5 g). Crystallization from methanol yielded 1.58 g (61%) of compound *VIIIj*, R_F 0.54 (S8), m.p. 219 – 221 °C. For $C_{13}H_{19}N_5O$ (261.3) calculated: 59.76% C, 7.33% H, 26.79% N; found: 59.56% C, 7.29% H, 26.43% N. ^{1}H NMR spectrum: 8.13 s, 1 H (H-2); 8.06 s, 1 H (H-8); 7.18 brs, 2 H (NH_2); 4.94 d, 1 H,

J(OH,CH) = 5.9 (OH); 4.22 dd, 1 H, *J*(1a′,2′) = 3.4, *J*(gem) = 13.7 (H-1a′); 3.99 dd, 1 H, *J*(1b′,2′) = 8.5, *J*(gem) = 13.7 (H-1b′); 3.58 m, 1 H, Σ*J* = 22.8 (H-2′); 1.55 – 1.90 m, 5 H and 1.00 – 1.40 m, 6 H (cyclohexyl). UV spectrum (methanol) (pH 2): λ_{max} 261.0 nm (ε_{max} 14 800); (pH 7): λ_{max} 261.5 nm (ε_{max} 15 000); (pH 13): λ_{max} 262.5 (ε_{max} 15 900).

9-(2-Hydroxy-3-phenylpropyl)adenine (VIIIk) was prepared from benzyloxirane (1.6 g). Crystallization from ethanol with addition of ether afforded 2.4 g (74%) of compound *VIIIk*, R_F 0.60 (S8), m.p. 136 – 138 °C. For $C_{14}H_{15}N_5O$. H_2O (287.3) calculated: 58.53% C, 5.96% H, 24.37% N; found: 57.90% C, 5.76% H, 23.98% N. ^{1}H NMR spectrum: 8.13 s, 1 H (H-2); 8.07 s, 1 H (H-8); 7.19 brs, 2 H (NH_2); 7.10 – 7.35 m, 5 H (arom.); 5.01 br, 1 H (OH); 4.21 dd, 1 H, *J*(1a′,2′) = 2.1, *J*(gem) = 12.3 (H-1a′); 4.03 dd, 1 H *J*(1b′,2′) = 8.0, *J*(gem) = 12.3 (H-1b′); 4.11 m, 1 H (H-2′); 2.78 dd, 1 H, *J*(3a′,2′) = 4.3, *J*(gem) = 13.4 (H-3a′); 2.66 dd, 1 H, *J*(3b′,2′) = 6.6, *J*(gem) = 13.4 (H-3b′). UV spectrum (pH 2): λ_{max} 261.0 nm (ε_{max} 12 600); (pH 7): λ_{max} 262.0 nm (ε_{max} 14 700); (pH 13): λ_{max} 262.0 (ε_{max} 11 800).

9-(2-Hydroxy-2-phenylethyl)adenine (VIIIl) was prepared from phenyloxirane (1.4 g). Crystallization from methanol with addition of water gave 1.78 g (70%) of compound *VIIIl*, R_F 0.58 (S9), m.p. 226 – 227 °C. For $C_{13}H_{13}N_5O$ (255.2) calculated: 61.17% C, 5.13% H, 27.43% N; found: 60.84% C, 5.20% H, 27.37% N. ^{1}H NMR spectrum: 8.16 s, 1 H (H-2); 8.00 s, 1 H (H-8); 7.19 brs, 2 H (NH_2); 7.20 – 7.40 m, 5 H (arom.); 5.81 d, 1 H, *J*(OH,CH) = 4.6 (OH); 5.00 dt, 1 H, Σ*J* = 17.0 (H-2′); 4.31 dd, 1 H, *J*(1a′,2′) = 4.6, *J*(gem) = 13.9 (H-1a′); 4.23 dd, 1 H, *J*(1b′,2′) = 7.8, *J*(gem) = 13.9 (H-1b′). UV spectrum (pH 2): λ_{max} 259.0 nm (ε_{max} 12 200); (pH 7): λ_{max} 261.0 nm (ε_{max} 13 300); (pH 13): λ_{max} 262.0 (ε_{max} 12 700).

9-(2-Hydroxybutyl)-N^6-benzoyladenine (*IXe*)

Compound *VIIIe* (2.7 g, 12 mmol) was codistilled with pyridine (2 × 25 ml) in vacuo and suspended in pyridine (60 ml). Chlorotrimethylsilane (10 ml) was added and the suspension was stirred under exclusion of moisture at room temperature for 1 h. After addition of benzoyl chloride (8 ml), the mixture was stirred for another hour, cooled with ice and water (12 ml), followed by concentrated aqueous ammonia (30 ml) was added dropwise under ice-cooling. After 30 min at 0 °C the mixture was taken down in vacuo, the residue was codistilled with water in vacuo (3 × 100 ml), mixed with chloroform (500 ml) and filtered. The filtrate was evaporated and the residue chromatographed on a column of silica gel (200 ml). Crystallization from ethanol (light petroleum added) afforded 2.30 g (61.5%) of compound *IXe*, m.p. 169 °C, R_F 0.27 (S7). For $C_{16}H_{17}N_5O_2$ (311.4) calculated: 61.72% C, 5.50% H, 22.50% N; found: 61.57% C, 5.36% H, 22.31% N.

9-(2-Hydroxypentyl)-N^6-benzoyladenine (*IXf*)

The title compound was prepared from compound *VIIIf* (2.7 g, 12 mmol) in the same manner as described for benzoyladenine *IXe*; yield 1.80 g (46%) of *IXf*, m.p. 205 °C, R_F 0.30 (S7). For $C_{17}H_{19}N_5O_2$ (325.4) calculated: 62.74% C, 5.89% H, 21.53% N; found: 62.57% C, 5.69% H, 21.34% N. H^1 NMR spectrum: 11.13 s, 1 H (NH); 8.73 s, 1 H (H-2); 8.39 s, 1 H (H-8); 8.05 m, 2 H and 7.62 m, 1 H and 7.56, m, 2 H (arom.); 5.05 d, 1 H, *J*(2′,OH) = 5.6 (OH); 4.28 dd, 1 H, *J*(1a′,2′) = 3.7, *J*(gem) = 13.9, (H-1a′); 4.12 dd, 1 H, *J*(1b′,2′) = 8.0, *J*(gem) = 13.9 (H-1b′); 3.89 m, 1 H, Σ*J* = 29.3 (H-2′); 1.30 – 1.50 m, 4 H (H-3′ and H-4′); 0.89 brt, 3 H, *J*(5′,4′) = 6.8 (CH_3).

Cyclohexyloxirane (*XIIIj*)

An ice-cooled mixture of vinylcyclohexane (25 g, 0.227 mol), dichloromethane (115 ml), sodium hydrogen phosphate (91 g), water (110 ml) and peracetic acid[21] (130 ml) was stirred for 2 h. The

aqueous phase was diluted with water (50 ml), the organic one was separated and stirred with saturated solution of sodium hydrogen carbonate for 30 min, washed with water to neutrality and dried over magnesium sulfate. The solvent was evaporated and the residue distilled to give 10.0 g (35%) of compound *XIIIj*, b.p. 55 °C/2 kPa (reported[22] b.p. 63 – 65 °C/2 kPa). Purity (GLC) 98%. The product was used without further purification in the preparation of compound *VIIIj*.

Benzyloxirane (*XIIIk*) (see ref.[23])

Allylbenzene (2.7 ml, 0.02 mol) and *m*-chloroperbenzoic acid (4.7 g, content 70 – 75%, i.e. 0.02 mol) were added into cold chloroform (30 ml) and the mixture was stirred to homogeneity. After standing in a refrigerator for 6 days, the deposited *m*-chlorobenzoic acid was filtered off, washed with chloroform and the filtrate was washed with saturated sodium hydrogen carbonate solution (2 × 50 ml) and water (2 × 50 ml). The chloroform solution was dried over magnesium sulfate, the solvent was evaporated and the residue distilled to give 1.7 g (63%) of compound *XIIIk*, b.p. 90 – 95 °C/2 kPa (reported[24] b.p. 97 – 98 °C/ 2.4 kPa). The product was used without further purification in the preparation of compound *VIIIk*.

3-Benzyloxy-2-hydroxypropyltrimethylsilane (*XIV*)

To a mixture of magnesium (1.7 g, 70.0 mmol), chloromethyltrimethylsilane (0.5 ml, 3.6 mmol) and anhydrous tetrahydrofuran (5 ml) was added 1,2-dibromoethane (0.05 ml) at 60 °C. As soon as the mixture began to boil spontaneously, it was rapidly cooled in an ice bath and chlorotrimethylsilane (9.5 ml, 68.1 mmol) was added under stirring in the course of 30 min. After further 15 min of vigorous stirring, a solution of 2-benzyloxyacetaldehyde (6.7 g, 40.1 mmol) in tetrahydrofuran (10 ml) was adedd during 15 min. After stirring for 30 min at 0 °C, the reaction mixture was decomposed by addition of saturated ammonium chloride solution (50 ml). The suspension was mixed with ether (100 ml) and filtered through Celite which was then washed with ether (2 × 20 ml). The ethereal layer of the filtrate was dried over magnesium sulfate, filtered and taken down. Distillation of the residue afforded pure (GLC) product *XIV* (7.6 g, 80%) b.p. 120 °C/13 Pa, R_F 0.40 (S5). For $C_{13}H_{22}O_2Si$ (238.4) calculated: 65.49% C, 9.30% H; found: 65.05% C, 9.41% H.

3-Benzyloxy-2-diisopropylphosphonomethoxypropyltrimethylsilane (*XV*)

Sodium hydride (60% suspension in mineral oil, 1.1 g, 27.7 mmol) was added at –20 °C to a solution of 3-benzyloxy-2-hydroxypropyltrimethylsilane (*XIV*) (6.0 g, 25.2 mmol) and synthon *XI* (9.3 g, 27.7 mmol) in dimethylformamide (20 ml) and the mixture was vigorously stirred at room temperature for 15 h. The homogeneous solution was concentrated and the residue was extracted with hot toluene. Column chromatography on silica gel (100 g) in toluene–ethyl acetate (4 : 1) afforded compound *XV* (3.3 g, 31%), R_F 0.50 (S5). Mass spectrum, *m*/*z*: 417.3 (M + H). For $C_{20}H_{37}O_5PSi$ (416.6) calculated: 57.67% C, 8.95% H, 7.43% P; found: 57.59% C, 9.01% H, 7.23% P.

2-Diisopropylphosphonomethoxy-3-(*p*-toluenesulfonyloxy)propyltrimethylsilane (*XVII*)

Compound *XV* (3.0 g, 7.2 mmol) was hydrogenated in methanol (150 ml) over 10% Pd/C (300 mg) at 1.1 Pa and 20 °C for 2 h. The suspension was filtered through Celite, the catalyst was washed with methanol (2 × 50 ml) and the combined filtrates were taken down. The remaining hydroxy derivative *XVI* (R_F 0.15 (S5)) was codistilled with pyridine, dissolved in pyridine (20 ml) and mixed with tosyl chloride (2.0 g, 10.5 mmol). After standing at room temperature for 15 h, the mixture was decomposed with water (5 ml) and concentrated in vacuo. The residue was dissolved in chloroform (30 ml)

and applied onto a column of silica gel (50 g). Elution with chloroform gave 3.35 g (97%) of homogeneous product *XVII*, R_F 0.40 (S5). Mass spectrum, *m*/*z*: 481.0 (M + H). ^{1}H NMR spectrum: 7.80 d, 2 H and 7.49 d, 2 H (arom.); 4.55 2 × dsept, 2 H, *J*(P,OCH) = 7.8, *J*(CH,CH_3) = 6.1 (POCH); 4.06 dd, 1 H, *J* = 3.0, *J*(gem) = 11.0 (OCH_b); 3.90 dd, 1 H, *J* = 5.1, *J*(gem) = 11.0 (OCH_a); 3.69 brtdd, 1 H, Σ*J* = 22.5 (OCH); 3.65 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 13.4 (PCH_b); 3.61 dd, 1 H, *J*(P,CH) = 10.0, *J*(gem) = 13.4 (PCH_a); 2.42 s, 3 H (CH_3); 1.22 d, 6 H, *J* = 6.1 (2 × CH_3); 1.21 d, 3 H and 1.20 d, 3 H (2 × CH_3); 0.88 dd, *J* = 7.6, *J*(gem) = 14.65 ($SiCH_b$); 0.67 dd, *J* = 6.8, *J*(gem) = 14.65 ($SiCH_a$); 0.04 s, 9 H ($Si(CH_3)_3$).

9-(2-Phosphonomethoxy-3-trimethylsilylpropyl)adenine (*XIXa*)

A suspension of adenine sulfate (0.55 g, 3 mmol), cesium carbonate (2.9 g, 9 mmol) and tosyl derivative *XVII* (1.5 g, 3 mmol) in dimethylformamide (30 ml) was heated at 120 °C for 4 h. The reaction mixture was concentrated in vacuo, the residue extracted with hot chloroform and the solution applied onto a column of silica gel (50 g). Elution with chloroform–ethanol (18 : 1) afforded diester *XVIIIa* (0.9 g, 68%). Mass spectrum, *m*/*z*: 444 (M + H).

The obtained product was treated with bromotrimethylsilane as described above. The final purification of the free phosphonate *XIXa* was performed by chromatography on Dowex 1 X 8 (acetate form, 100 ml), elution with a gradient of acetic acid (0 – 1 mol/l, 2 × 1 l). After evaporation of the acetic acid, the product was freeze-dried from the aqueous solution to give homogeneous (electrophoresis and HPLC) compound *XIXa* (0.4 g, 55 %), m.p. 276 °C. Mass spectrum, *m*/*z*: 481.0 (M + H). ^{1}H NMR spectrum: 8.28 s, 1 H and 8.14 s, 1 H (H-2, H-8); 4.37 dd, 1 H, *J* = 3.4, *J*(gem) = 14.65 (NCH_b); 4.21 dd, 1 H, *J* = 5.9, *J*(gem) = 14.65 (NCH_a); 3.95 dddd, 1 H, Σ*J* = 23.4 (OCH); 3.70 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 12.7 (PCH_b); 3.55 dd, 1 H, *J*(P,CH) = 10.3, *J*(gem) = 12.7 (PCH_a); 0.87 dd, 1 H, *J* = 7.3, *J*(gem) = 14.9 ($SiCH_b$); 0.71 dd, 1 H, *J* = 6.6, *J*(gem) = 14.9 ($SiCH_a$); 0.03 s, 9 H (3 × CH_3).

9-(2-Phosphonomethoxy-3-trimethylsilylpropyl)-2,6-diaminopurine (*XIXb*)

A suspension of 2-amino-6-chloropurine (0.66 g, 3.9 mmol), cesium carbonate (2.6 g, 8 mmol), tosyl derivative *XVII* (1.9 g, 3.9 mmol) and dimethylformamide (39 ml) was heated at 130 °C for 3 h. The reaction mixture was worked up as described for the adenine derivative *XIXa* and afforded 9-(2-diisopropylphosphonomethoxy-3-trimethylsilylpropyl)-2-amino-6-chloropurine (*XVIIIb*) (1.3 g, 66%). Mass spectrum, *m*/*z*: 496.0 (M + H). This intermediate (0.82 g, 1.7 mmol) was heated with sodium azide (0.6 g, 8.6 mmol) in dimethylformamide (10 ml) at 120 °C for 2 h to give a mixture of 9-(2-diisopropylphosphonomethoxy-3-trimethylsilylpropyl)- 2-amino-6-azidopurine (*XVIIIc*) and the corresponding monoisopropyl ester. Both compounds were isolated by chromatography on C_{18} silica gel, combined and hydrogenated in aqueous methanol (1 : 1, 100 ml) on 10% Pd/C (120 mg). After filtering off the catalyst, its washing with aqueous methanol and evaporating the combined filtrates, the mixture was dried and treated with bromotrimethylsilane (vide supra). The compound *XIXb* was isolated by ion exchange chromatography as described for compound *XIXa*. Freeze-drying afforded 180 mg (28%) of *XIXb*, m.p. >280 °C. Mass spectrum, *m*/*z*: 481.0 (M + H). ^{1}H NMR spectrum: 8.08 s, 1 H (H-8); 4.23 dd, 1 H, *J* = 3.9, *J*(gem) = 14.65 (NCH_b); 4.10 dd, 1 H, *J* = 6.1, *J*(gem) = 14.65 (NCH_a); 3.89 m, 1 H, Σ*J* = 23.7 (OCH); 3.60 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 12.2 (PCH_b); 3.43 dd, 1 H, *J*(P,CH) = 10.0, *J*(gem) = 12.2 (PCH_a); 0.97 dd, 1 H, *J* = 6.1, *J*(gem) = 14.9 ($SiCH_b$); 0.70 dd, 1 H, *J* = 7.6, *J*(gem) = 14.9 ($SiCH_b$); 0.04 s, 9 H ($Si(CH_3)_3$).

9-(3,3,3-Trifluoro-2-hydroxypropyl)adenine (*XXa*)

Sodium hydride (60% dispersion in paraffin, 800 mg, 20 mmol) was added to a suspension of adenine (2.7 g, 20 mmol) in dimethylformamide (140 ml). After stirring under exclusion of moisture at 100 °C for 1 h, 1-bromo-3,3,3-trifluoropropan-2-ol (5.0 g, 25.9 mmol) was added and the obtained solution was stirred at 80 °C for 24 h. Acetic acid (0.60 ml, 10 mmol) was added and the mixture was taken down at 40 °C/13 Pa. The residue was dissolved in water (25 ml) and deionized on a column of Dowex 50 X 8 (H^+ form, 150 ml). After evaporation of the solvent, the residue was dissolved in water (20 ml) and applied onto a column of C_{18} silica gel (130 ml, 30 mesh). The column was washed with water (3 ml/min, 30 ml fractions, monitoring by HPLC in H4, k = 0.51, product 2.84). The product fractions were combined, evaporated and the residue was crystallized from water to give 1.70 g (35%) of compound *XXa*, m.p. 209 °C. For $C_8H_8F_3N_5O$ (247.2) calculated: 38.87% C, 3.26% H, 23.06% F, 28.34% N; found: 38.57% C, 3.18% H, 22.79% F, 28.70% N. ^{1}H NMR spectrum: 8.17 s, 1 H (H-2); 8.14 s, 1 H (H-8); 7.31 brs, 2 H (NH_2); 6.78 d, 1 H, J(2′,OH) = 6.6 (OH); 4.51 m, 1 H, J(2′,F) = 21.5, ΣJ = 40.3 (H-2′); 4.45 dd, 1 H, J(1a′,2′) = 3.4, J(gem) = 14.2 (H-1a′); 4.30 dd, 1 H, J(1b′,2′) = 8.8, J(gem) = 14.2 (H-1b′).

9-(3,3,3-Trifluoro-2-hydroxypropyl)-2,6-diaminopurine (*XXb*)

A mixture of 2,6-diaminopurine (6 g, 40 mmol) and sodium hydride (60% dispersion, 1.60 g, 40 mmol) in dimethylformamide (250 ml) was stirred at 100 °C for 1 h. After cooling to 60 °C, 1-bromo-3,3,3-trifluoropropan-2-ol (10 g, 52 mmol) was added and the mixture was stirred at 60 °C for 15 h under exclusion of moisture (calcium chloride tube). The solvent was evaporated at 40 °C/13 Pa, the residue was mixed with water (200 ml) and extracted with ether (2 × 50 ml). The aqueous phase was deionized on a column of Dowex 50 X 8 (H^+ form, 200 ml). The residue after evaporation was dissolved in methanol (200 ml) and adsorbed on silica gel (50 ml). This material was applied onto a column of silica gel (200 ml) in chloroform. After washing the column with chloroform to remove impurities, the product was eluted with chloroform–methanol (4 : 1). The product fractions were concentrated and the product crystallized from ethanol (ether added to turbidity). Yield 6.3 g (60%) of compound *XXb*, m.p. 191 °C. For $C_8H_9F_3N_9O$ (266.2) calculated: 36.64% C, 3.46% H, 21.74% F, 32.06% N; found: 36.91% C, 3.80% H, 21.70% F, 31.85% N. ^{1}H NMR spectrum: 7.71 s, 1 H (H-8); 6.76 m, 3 H (NH_2 + OH); 5.89 brs, 2 H (NH_2); 4.46 m, 1 H (H-2′); 4.25 dd, 1 H, J(1a′,2′) = 3.2, J(gem) = 13.9 (H-1a′); 4.11 dd, 1 H, J(1b′,2′) = 9.3, J(gem) = 13.9 (H-1b′).

9-(3,3,3-Trifluoro-2-hydroxypropyl)-N^6-benzoyladenine (*XXI*)

Chlorotrimethylsilane (4.5 ml) was added to a suspension of compound *XXa* (1.24 g, 5 mmol) in pyridine (30 ml). After stirring for 1 h, benzoyl chloride (3.5 ml) was added and the mixture was then stirred for 2 h. The mixture was cooled with ice and water (6 ml) and concentrated aqueous ammonia (14.5 ml) were successively added dropwise. After stirring in an ice bath for 30 min, the solvent was evaporated at 40 °C/2 kPa and the residue was codistilled with ethanol (3 × 25 ml). Chloroform (100 ml) was added and, after stirring for 15 min, the precipitated product was collected, washed with chloroform (50 ml) and crystallized from 50% aqueous ethanol, yield 0.75 g (43%) of compound *XXI*, m.p. 215 °C. The filtrate was taken down in vacuo, combined with the chloroform residue and the mixture was purified by chromatography on silica gel (200 ml). Elution with chloroform–methanol (9 : 1) and crystallization from 50% aqueous methanol gave further 0.35 g of compound *XXI*, the total yield being thus 63%. For $C_{15}H_{12}F_3N_5O_2$ (351.3) calculated: 51.28% C, 3.44% H, 16.23% F, 19.94% N; found: 51.37% C, 3.55% H, 16.22% F, 19.89% N. R_F 0.23 (S7). ^{1}H NMR spectrum: 11.20 s, 1 H (NH); 8.78 s, 1 H (H-2); 8.48 s, 1 H (H-8); 8.05 m, 2 H and 7.65 m, 1 H and

7.55 m, 2 H (arom.); 6.84 d, 1 H, J = 6.8 (OH); 4.58 dd, 1 H, J(1a′,2′) = 3.2, J(gem) = 14.6 (H-1a′); 4.45 dd, 1 H, J(1b′,2′) = 8.8, J(gem) = 14.6 (H-1b′); 4.60 m, 1 H (H-2′).

9-(2-Phosphonomethoxy-3,3,3-trifluoropropyl)adenine (*XXIIa*)

A mixture of compound *XXI* (0.70 g, 2 mmol) and tosyl derivative *XI* (1.05 g, 3 mmol) was codistilled with dimethylformamide (2 × 20 ml) at 40 °C/13 Pa. The residue was mixed with dimethylformamide (15 ml) and sodium hydride (60% dispersion, 0.25 g, 6.2 mmol) was added. The mixture was stirred at room temperature for 3 days, mixed with methanol (30 ml) and set aside at room temperature overnight. The solution was neutralized by addition of Dowex 50 X 8 (H^+ form), made alkaline with triethylamine, filtered and the ion exchanger was washed with ethanol (200 ml). The filtrate was taken down in vacuo, dissolved in 50% aqueous methanol (25 ml) and applied onto a column of the same ion exchanger (100 ml, in 20% methanol). After washing with 20% aqueous methanol to drop of UV absorption, the product was eluted with 2.5% ammonia in 20% aqueous methanol. The UV-absorbing fraction was concentrated in vacuo and the residue codistilled with ethanol (3 × 25 ml) and dried in vacuo over phosphorus pentoxide overnight. The residue was allowed to stand with acetonitrile (30 ml) and bromotrimethylsilane (3 ml) at room temperature overnight. After evaporation of the solvent, water (20 ml) was added, the mixture was made alkaline with concentrated aqueous ammonia and again evaporated in vacuo. The residue was deionized on a column of Dowex 50 X 8 (H^+ form) and the ammonia UV-absorbing eluate was evaporated to dryness in vacuo. The residue was dissolved in water (20 ml), the solution adjusted to pH 9 with ammonia and applied onto a column of Dowex 1 X 2 (acetate form, 100 ml). After washing the column with water to drop of UV absorption of the eluate, the product was eluted with a linear gradient of acetic acid (water (1 l), 1 M acetic acid (1 l)). The product fraction was evaporated in vacuo, the residue was codistilled with water (3 × 25 ml) and crystallized from 80% aqueous ethanol (ether added to turbidity). Yield 0.40 g of compound *XXIIIa* (58.5%), m.p. 276 °C, E_{Up} = 0.80. For $C_9H_{11}F_3N_5O_4P$ (341.3) calculated: 31.67% C, 3.25% H, 16.70% F, 20.53% N, 9.10% P; found: 31.48% C, 3.08% H, 16.40% F, 20.62% N, 9.02% P. ^{1}H NMR spectrum: 8.40 s, 1 H (H-2); 8.20 s, 1 H (H-8); 4.68 dd, 1 H, J(1a′,2′) = 4.2, J(gem) = 15.2 (H-1a′); 4.59 dd, 1 H, J(1b′,2′) = 5.9, J(gem) = 15.2 (H-1b′); 4.42 m, 1 H, ΣJ = 29.6, J(2′,F) = 19.5 (H-2′); 3.79 dd, 1 H, J(P,CH) = 9.2, J(gem) = 11.9 (PCH_a); 3.56 dd, 1 H, J(P,CH) = 9.5, J(gem) = 11.9 (PCH_b). HPLC (H3): k = 2.53.

9-(2-Phosphonomethoxy-3,3,3-trifluoropropyl)-2,6-diaminopurine (*XXIIb*)

A mixture of compound *XXb* (4.0 g, 15 mmol), dimethylformamide (70 ml) and dimethylformamide dimethyl acetal (30 ml) was stirred to homogeneity and the solution was set aside at room temperature for two days. The solvent was evaporated at 40 °C/13 Pa and the residue was mixed with 50% pyridine (30 ml) with addition of dry ice to render the pH neutral. After 30 min the mixture was evaporated at 40 °C/13 Pa and the residue codistilled with pyridine (3 × 20 ml) and dimethylformamide (2 × 20 ml) under the same conditions. The obtained compound *XXIII* was mixed with the tosyl derivative *XI* (6.3 g, 18 mmol), the mixture was again codistilled with dimethylformamide (2 × 20 ml) and dissolved in dimethylformamide (60 ml). Sodium hydride (60% suspension, 1.08 g, 45 mmol) was added to this solution at −10 °C and the mixture was stirred at room temperature for 2 days under exclusion of moisture. After addition of methanol (50%, 100 ml) and standing overnight, the deposited precipitate was filtered off, the filtrate was evaporated in vacuo, dissolved in water (100 ml), acidified by addition of Dowex 50 X 8 (H^+ form) and the suspension was applied onto a column of the same ion exchanger (150 ml). The column was washed with water to drop of UV absorption of the eluate and the product was eluted with dilute (1 : 10) aqueous ammonia. The main UV-absorbing fraction was evaporated in vacuo and the residue was codistilled with ethanol

and dried in vacuo. This residue was mixed with acetonitrile (40 ml) and bromotrimethylsilane (4 ml) and the solution was allowed to stand at room temperature overnight under exclusion of moisture. The solvent was evaporated in vacuo, the residue was mixed with water (100 ml) and the solution was made alkaline with aqueous ammonia. After standing at room temperature for 1 h, the mixture was concentrated in vacuo and the residue in water (20 ml) was deionized on a column of Dowex 50 X 8 (H^+ form, 150 ml). The ammonia UV-absorbing eluate was evaporated in vacuo and the residue applied onto a column of Dowex 1 X 2 (acetate form, 150 ml). The column was washed with water to remove salts and then with a linear gradient of acetic acid (0 – 0.3 mol/l, à 1 l). The product was eluted at 0.2 – 0.3 mol/l. The product fraction was concentrated in vacuo, the residue was codistilled with water (3 × 50 ml) and crystallized from water to give 1.80 g (33.5%) of compound *XXIIb*, m.p. 208 °C, E_{Up} = 0.67, k = 0.83 (H1). For $C_9H_{12}F_3N_6O_4P$ (356.3) calculated: 30.34% C, 3.40% H, 16.00% F, 23.60% N, 8.71% P; found: 30.51% C, 3.32% H, 16.10% F, 23.44% N, 9.07% P. ^{1}H NMR spectrum: 8.03 s, 1 H (H-8); 4.31 – 4.56 m, 3 H (NCH_2 + OCH); 3.77 dd, 1 H, J(P,CH) = 9.5, J(gem) = 11.9 (PCH_a); 3.55 dd, 1 H, J(P,CH) = 9.5, J(gem) = 11.9 (PCH_b).

3-*O*-Benzoyloxybutyl *p*-Toluenesulfonate (*XXV*)

The title compound was prepared from butane-1,3-diol (0.3 mol) as described for the tosyl derivatives *VIe* and *VIf* (isolation by column chromatography on silica gel (200 ml) in benzene). The product was crystallized from ether–light petroleum; yield 71 g (68%), m.p. 64 – 66 °C, R_F 0.62 (S4). For $C_{18}H_{20}O_5S$ (348.4) calculated: 62.05% C, 5.79% H, 9.20% S; found: 62.00% C, 5.66% H, 8.97% S.

9-(3-Hydroxybutyl)adenine (*XXVIb*)

A mixture of adenine (4.05 g, 30 mmol), sodium hydride (60% dispersion, 1.2 g, 30 mmol) and dimethylformamide (200 ml) was stirred at 100 °C for 1 h. Compound *XXV* (11.5 g, 33 mmol) was added and the mixture was stirred at 100 °C for 24 h. After evaporation of the solvent at 40 °C/13 Pa, the residue was extracted with boiling chloroform (3 × 100 ml). The extract was filtered, the solvent evaporated and the residue chromatographed on a column of silica gel (200 ml). The combined product-containing fractions were concentrated and the residue was crystallized from ethyl acetate–light petroleum to give 4.1 g (43%) of benzoyl derivative *XXVIa*, R_F 0.45 (S7), m.p. 154 °C. For $C_{16}H_{17}N_5O_2$ (311.4) calculated: 61.72% C, 5.50% H, 22.50% N; found: 61.53% C, 5.47% H, 22.79% N. This product was stirred with 0.1 M methanolic sodium methoxide (150 ml) at room temperature overnight, the mixture was neutralized by addition of Dowex 50 X 8 (H^+ form), made alkaline with triethylamine and filtered. The ion exchanger was washed with methanol (100 ml), the filtrate was taken down in vacuo and the dry residue was crystallized from ethanol–ether. Yield 1.9 g (75%) of compound *XXVIb*, m.p. 169 °C. For $C_9H_{13}N_5O$ (311.4) calculated: 52.16% C, 6.32% H, 33.80% N; found: 51.96% C, 6.34% H, 34.07% N. ^{1}H NMR spectrum: 8.16 s, 1 H (H-2); 8.13 s, 1 H (H-8); 7.29 brs, 2 H (NH_2); 4.77 d, 1 H, J(3′,OH) = 4.9 (OH); 4.21 m, 2 H (H-1′); 3.57 m, 1 H, (H-3′); 1.68 – 1.98 m, 2 H (H-2′); 1.06 t, 3 H, J = 6.1 (CH_3). After exchange: 4.25 ddd, 1 H, J(1a′,2a′) = 6.1, J(1a′,2b′) = 7.8, J(gem) = 14.0 (H-1a′); 4.17 dt, 1 H, J(1a′,2a′) = J(1b′,2b′) = 7.3, J(gem) = 13.7 (H-1b′); 3.55 d, 1 H, ΣJ = 31.2 (H-3′); 1.68 – 1.98 m, 2 H (H-2′); 1.05 t, 3 H, J = 6.1 (CH_3).

9-(3-Hydroxybutyl)-N^6-benzoyladenine (*XXVII*)

Compound *XXVIb* (2.1 g, 10 mmol) was codistilled with pyridine (2 × 25 ml) and suspended in pyridine (60 ml). Chlorotrimethylsilane (8 ml) was added and the suspension was stirred at room temperature for 1 h under exclusion of moisture. Benzoyl chloride (6 ml) was added, the mixture was stirred for another hour and then cooled with ice and decomposed by successive addition of water

(10 ml) and concentrated aqueous ammonia (25 ml). After 30 min at 0 °C, the mixture was concentrated in vacuo and the residue was codistilled with water in vacuo (3 × 100 ml). The residue was stirred with chloroform (500 ml), filtered and the filtrate was evaporated. Chromatography of the residue on a column of silica gel (200 ml) followed by crystallization from ethanol (with addition of light petroleum to turbidity) afforded 1.68 g (54%) of compound *XXVII*, m.p. 169 °C, R_F 0.27 (S7). For $C_{16}H_{17}N_5O_2$ (311.4) calculated: 61.72% C, 5.50% H, 22.50% N; found: 61.57% C, 5.36% H, 22.31% N.

9-(3-Phosphonomethoxybutyl)adenine (*XXVIII*)

A mixture of compound *XXVII* (1.56 g, 5 mmol) and tosyl derivative *XI* (2.1 g, 6 mmol) was codistilled with dimethylformamide (2 × 25 ml) at 40 °C/13 Pa. The residue was dissolved in dimethylformamide (30 ml), cooled to 0 °C and mixed with sodium hydride (60% dispersion, 0.60 g, 15 mmol). The mixture was stirred at ambient temperature for 4 days and then mixed with methanol (50 ml). After standing at room temperature overnight, the mixture was neutralized with Dowex 50 X 8 (H^+ form), made alkaline with triethylamine, filtered and the ion exchanger was washed with methanol (100 ml). The further workup was the same as described for compound *Ie*. Yield 0.60 g (38%) of compound *XXVIII*, m.p. 229 °C, E_{Up} 0.70. For $C_{10}H_{16}N_5O_4P \cdot H_2O$ (319.3) calculated: 37.60% C, 5.68% H, 21.94% N, 9.72% P; found: 37.98% C, 6.02% H, 21.79% N, 10.06% P. ^{1}H NMR spectrum: 8.16 s, 1 H (H-2); 8.08 s, 1 H (H-8); 4.35 dt, 1 H and 4.32 dt, 1 H, J(1′,2′) = 7.6 and 6.8, J(gem) = 14.2 (H-1′); 3.59 dd, 1 H, J(P,CH) = 9.5, J(gem) = 12.2 (PCH_a); 3.50 sext 1 H, J(3′,4′) = 6.1, J(2′,3′) = 6.5 (H-3′); 3.38 dd, 1 H, J(P,CH) = 9.8, J(gem) = 12.2 (PCH_b); 2.02 brq 2 H, J = 7.0 (H-2′); 1.19 brt, 3 H, J = 6.1(CH_3).

1-*O*-Benzoyloxy-2,2-dimethyl-3-propyl *p*-Toluenesulfonate (*XXX*)

Tosyl chloride (45.2 g, 0.237 mol), followed by 4-dimethylaminopyridine (1 g), was added at 0 °C to a solution of 2,2-dimethylpropane-1,3-diol (26 g, 0.25 mol) in pyridine (300 ml). The mixture was stirred at 0 °C for 2 h and then set aside for 3 days at 0 °C. Water (20 ml) was added and, after 30 min, the mixture was diluted with ethyl acetate (1 l) and washed with water (3 × 200 ml). The organic phase was dried, the solvent evaporated and the residue chromatographed on a column of silica gel (300 ml) in benzene. Yield 42 g (67%) of chromatographically pure (S7) tosyl derivative *XXIX* which was used directly in the next step.

The product obtained above was dissolved in dichloromethane (200 ml) and benzoyl cyanide (23 g, 0.175 mol) and triethylamine (10 ml) were added. After standing at room temperature for 30 min, the solvent was evaporated in vacuo and the residue crystallized from ethyl acetate (with addition of light petroleum to turbidity). Yield 38 g (65%) of compound *XXX*, m.p. 92 °C, R_F 0.53 (S8). For $C_{19}H_{22}O_5S$ (362.4) calculated: 62.97% C, 6.12% H, 8.85% S; found: 63.07% C, 6.18% H, 8.71% S. ^{1}H NMR spectrum: 7.62 – 7.84 m, 5 H and 7.45 – 7.55 m, 2 H and 7.31 d, 2 H, J = 8.0 (arom); 3.96 s, 2 H ($TsOCH_2$); 3.90 s, 2 H ($BzOCH_2$); 2.23 s, 3 H ($TsCH_3$), 0.95 s, 6 H (2 × CH_3).

9-(2,2-Dimethyl-3-benzoyloxypropyl)adenine (*XXXI*)

Sodium hydride (60% dispersion in paraffin, 2 g, 50 mmol) was added to a suspension of adenine (6.8 g, 50 mmol) in dimethylformamide (300 ml) and the mixture was stirred at 80 °C for 1 h under exclusion of moisture. Compound *XXX* (18.1 g, 50 mmol) was added and the mixture was heated at 100 °C for 18 h. The solvent was evaporated at 40 °C/13 Pa and the residue was extracted with boiling chloroform (3 × 100 ml). The filtered extract was taken down and the residue was crystallized from methanol to give 9.0 g (55%) of compound *XXXI*, m.p. 161 °C. For $C_{17}H_{19}N_5O_2$ (325.4)

calculated: 62.74% C, 5.89% H, 21.53% N; found: 62.55% C, 5.93% H, 21.37% N. ^{1}H NMR spectrum: 8.12 s, 1 H (H-2); 8.06 s, 1 H (H-8); 7.89 m, 2 H and 7.64 m, 1 H and 7.51, m, 2 H (arom.); 7.22 brs, 2 H (NH_2); 4.20 s, 2 H (H-1′); 4.06 s, 2 H, (H-3′); 1.03 s, 6 H (CH_3).

9-(2,2-Dimethyl-3-hydroxypropyl)adenine (*XXXII*)

A solution of compound *XXXI* (8.7 g, 26.7 mmol) in 0.1 M methanolic sodium methoxide (200 ml) was set aside at ambient temperature overnight. The mixture was neutralized with Dowex 50 X 8 (H^+ form) and made alkaline with triethylamine. The ion exchanger was filtered off and washed with methanol (200 ml), the filtrate was evaporated in vacuo and the dry residue was crystallized from ethanol (ether added to turbidity). Yield 4.4 g (74%) of compound *XXXII*, m.p. 240 °C. For $C_{10}H_{15}N_5O$ (221.3) calculated: 54.30% C, 6.83% H, 31.66% N; found: 54.14% C, 6.79% H, 31.30% N. ^{1}H NMR spectrum: 8.15 s, 1 H (H-2); 8.04 s, 1 H (H-8); 7.30 brs, 2 H (NH_2); 5.11 t, 1 H, J(OH,CH_2) = 5.9 (OH); 4.00 s, 2 H (H-1′); 3.08 d, 2 H, J(CH_2,OH) = 5.9 (H-3′); 0.91 s, 6H (CH_3).

9-(2,2-Dimethyl-3-hydroxypropyl)-N^6-benzoyladenine (*XXXIII*)

Chlorotrimethylsilane (12 ml) was added to a suspension of compound *XXXII* (3.3 g, 15 mmol) in pyridine (70 ml) and the mixture was stirred at room temperature for 1 h with exclusion of moisture. Benzoyl chloride (9 ml) was added, stirring was continued for another hour, the mixture was cooled with ice and decomposed by successive dropwise addition of water (15 ml) and concentrated aqueous ammonia (30 ml). After being kept at 0 °C for 30 min, the solvent was evaporated in vacuo and the residue codistilled with water in vacuo (3 × 100 ml). The residue was stirred with chloroform (500 ml), the mixture was filtered and the filtrate was taken down. Chromatography of the residue on a column of silica gel (200 ml) and crystallization from ethanol (light petroleum added to turbidity) afforded 3.3 g (68%) of compound *XXXIII*, m.p. 181 °C, R_F 0.36 (S7). For $C_{17}H_{19}N_5O_2$ (325.4) calculated: 62.74% C, 5.89% H, 21.53% N; found: 62.52% C, 5.88% H, 21.87% N. ^{1}H NMR spectrum: 11.15 brs, 1 H (NH); 8.74 s, 1 H (H-2); 8.38 s, 1 H (H-8); 8.05 m, 2 H and 7.64 m, 1 H and 7.55 m, 2 H (arom); 4.99 t, 1 H, J(OH,CH_2) = 5.4 (OH); 4.16 s, 2 H (H-1′); 3.18 d, 2 H, J(CH_2,OH) = 5.4 (H-3′); 0.95 s, 6 H (CH_3).

9-(2,2-Dimethyl-3-phosphonomethoxypropyl)adenine (*XXXV*)

A mixture of compound *XXXIII* (1.65 g, 5 mmol) and tosyl derivative *XI* (2.1 g, 6 mmol) was codistilled with dimethylformamide (2 × 25 ml) at 40 °C/13 Pa and then dissolved in dimethylformamide (30 ml). Sodium hydride (60% dispersion, 0.60 g, 15 mmol) was added at 0 °C and the mixture was stirred under exclusion of moisture at ambient temperature overnight. After addition of methanol (100 ml) and standing at room temperature overnight, the mixture was neutralized with Dowex 50 X 8 (H^+ form) and made alkaline with triethylamine. The ion exchanger was filtered off and washed with methanol (200 ml). The filtrate was taken down and the residue partitioned between water (150 ml) and ether (2 × 100 ml). The aqueous phase was evaporated and the residue deionized on a column of Dowex 50 X 8 (H^+ form, 100 ml). The ammonia eluate of compound *XXXIV* was evaporated, the residue dried in vacuo overnight and mixed with acetonitrile (20 ml) and bromotrimethylsilane (2 ml). After standing overnight at room temperature, the mixture was evaporated, mixed with water (100 ml), made alkaline with ammonia and taken down in vacuo. The residue was again deionized under the same conditions on Dowex 50 X 8 (100 ml), the ammonia eluate was taken down in vacuo and the residue was column-chromatographed on Sephadex A-25 (HCO_3^- form, 100 ml). The column was washed with 0.02 M triethylammonium hydrogen carbonate pH 7.5 and then by linear gradient of 0 – 0.4 mol/l (à 1 l) of the same buffer. The product fraction (0.30 mol/l)

was evaporated in vacuo, the residue was codistilled with methanol in vacuo (3 × 25 ml), dissolved in water and applied onto a column of Dowex 1 X 2 (acetate form, 25 ml). After washing the column with water, the product was eluted with 1 M acetic acid. The solvent was evaporated in vacuo, the residue codistilled with water (3 × 50 ml) and crystallized from 70% aqueous ethanol (ether added to turbidity) to give 0.70 g (42%) of compound *XXXV*, m.p. 268 °C. For $C_{11}H_{16}N_5O_5P \cdot H_2O$ (331.3) calculated: 39.87% C, 5.48% H, 21.14% N, 9.37% P; found: 39.46% C, 5.71% H, 21.07% N, 9.34% P. ^{1}H NMR spectrum: 8.12 s, 1 H (H-2); 8.06 s, 1 H (H-8); 4.10 s, 2 H (H-1′); 3.62 d, 2 H, *J*(P,CH) = 8.5 (PCH_2); 3.24 s, 2 H (H-3′); 0.87 s, 6 H (CH_3).

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