CARBOCYCLIC PHOSPHONATE-BASED NUCLEOTIDE ANALOGS RELATED TO PMEA II. RACEMIC *cis*-CONFIGURED DERIVATIVES

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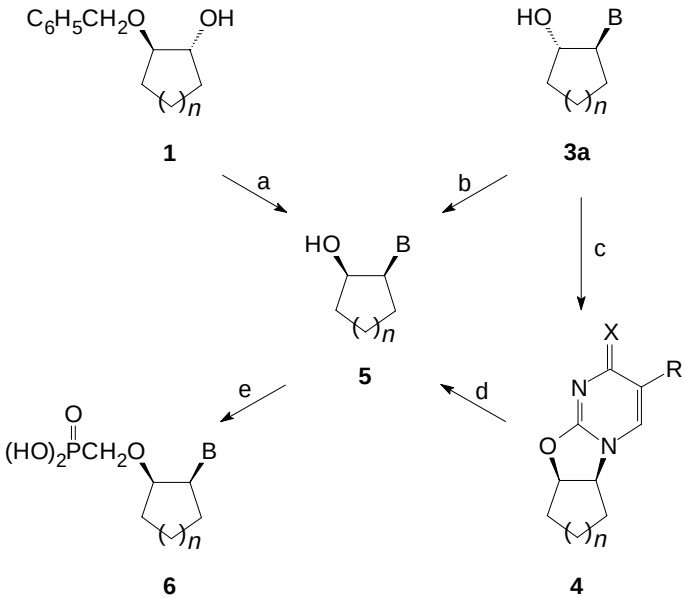
Racemic *N*-(*cis*-2-phosphonomethoxycycloalkyl) derivatives of heterocyclic bases, a novel type of nucleotide analogs related to 9-(2-phosphonomethoxyethyl)adenine (PMEA), are reported. The synthesis of adenine- (**6a**, **6b**), uracil- (**6c**) and cytosine- (**6d**) containing carbocyclic phosphonates is based on the reaction of *cis*-2-hydroxycycloalkyl derivatives of protected nucleobases with diisopropyl tosyloxymethanephosphonate. The starting purine-containing nucleoside analogs **5a–5f** were prepared by the Mitsunobu reaction of protected nucleobases with *trans*-2-benzyloxycycloalkanols, whereas pyrimidine-containing nucleoside analogs **5g–5k** were obtained by configurational inversion at C-2′ of the corresponding 1-(*trans*-2-hydroxycycloalkyl)pyrimidines via ring opening of their 2,2′-anhydro derivatives.

Key words: Carbocyclic analogs; Antivirals; Nucleoside phosphonates.

In our previous paper[1] we described the preparation of racemic *trans*-configured *N*-(2-phosphonomethoxycycloalkyl) derivatives of nucleobases as one type of conformationally restricted compounds related to *N*-(2-phosphonomethoxyethyl) derivatives of nucleobases (PME-compounds). Another type of such compounds are *cis*-configured *N*-(2-phosphonomethoxycycloalkyl) derivatives **6a–6d**, described in this communication. The importance of these compounds (*trans* as well as *cis* isomers) from the viewpoint of systematic study of antiviral effect of nucleotide phosphonate analogs has already been explained in our preceding communication[1].

Pyrimidine *cis*-2-hydroxycycloalkyl derivatives **5g–5k** were obtained from the corresponding *trans*-2-hydroxycycloalkylpyrimidines **3c** and **3e–3h** by inversion of configuration at the carbon atom bearing the hydroxy group. This was accomplished by closing and subsequent opening the ring in 2,2′-anhydro derivatives **4b** and **4d–4f** (for the cytosine derivative **5k** the 2,2′-anhydro derivative **4g** was not isolated). The 2,2′-anhydro derivatives were in turn prepared from the corresponding 2′-*O*-mesyl derivatives of *trans*-2-hydroxycycloalkylpyrimidines by intramolecular substitution with the oxygen atom of the 2-oxo group in the base on treatment with DBU in acetonitrile (Scheme 1). In the mesylation of pyrimidine *trans*-2-hydroxycyclopentyl derivatives **3b** and **3e** in



1	*n*
a	1
b	2
c	3

3	B	*n*
a	A	1
b	T	1
c	T	2
d	T	3
e	U	1
f	U	2
g	U	3
h	C	2

4	R	X	*n*
a	Me	O	1
b	Me	O	2
c	Me	O	3
d	H	O	1
e	H	O	2
f	H	O	3
g	H	NH_2	2

5	B	*n*
a	A	1
b	A	2
c	A	3
d	G	1
e	G	2
f	G	3
g	T	2
h	U	1
i	U	2
j	U	3
k	C	2

6	B	*n*
a	A	1
b	A	2
c	U	2
d	C	2

a) (i) protected nucleobase B (**2a**-**2c**), Ph_3P, DIPAD, THF; (ii) concentrated aqueous ammonia; (iii) H_2/Pd. b) (i) *N,N*-dibutylformamide dimethyl acetal; (ii) 4-nitrobenzoic acid, Ph_3P, DIPAD, THF; (iii) concentrated aqueous ammonia. c) mesyl chloride, pyridine (DBU). d) NaOH, pyridine, water; e) (i) *N,N*-dimethylformamide dimethylacetal; (ii) $TsOCH_2P(O)(OiPr)_2$, DMF, NaH; (iii) concentrated aqueous ammonia; (iv) bromotrimethylsilane.

SCHEME 1

pyridine, the mesylates have not been detected at all, the mesyl group being instantaneously removed under formation of the 2,2′-anhydro derivatives **4a** and **4d**. To obtain the desired *cis*-2-hydroxycycloalkylpyrimidines, the ring in the 2,2′-anhydro derivatives **4b** and **4d–4g** was opened by reaction with 0.02 M aqueous solution of sodium hydroxide at 100 °C. However, no *cis*-2-hydroxycyclopentylthymine has been obtained from compound **4a** under these conditions.

Purine *cis*-2-hydroxycycloalkyl derivatives **5a–5f** were prepared by the Mitsunobu reaction[2–4] that makes use of activation of a hydroxy group by formation of alkoxytriphenylphosphonium salt which as a strong leaving group undergoes nucleophilic substitution with a suitably protected nucleobase, resulting in configurational inversion at the corresponding carbon atom. We started from racemic *trans*-2-benzyloxycyclopentanol (**1a**), *trans*-2-benzyloxycyclohexanol[5] (**1b**) and *trans*-2-benzyloxycycloheptanol (**1c**). The compounds **1a** and **1c** were prepared by reaction of cyclopentene and cycloheptene oxide with benzyl alcohol in the presence of boron trifluoride etherate (in the case of cyclopentene epoxide we isolated, in addition to the desired compound **1a**, a product identified by ^{1}H NMR spectrum as a mixture of *trans*-2-(*trans*-2-benzyloxycyclopentyloxy)cyclopentanols). The obtained partially protected diols **1a–1c** reacted with 6-chloropurine, 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanine[6] or *N*-(dibutylaminomethylene) derivatives of adenine and 6-*O*-benzylguanine (**2a** and **2b**, respectively) in tetrahydrofuran in the presence of triphenylphosphine and diisopropyl azodicarboxylate (DIPAD). This procedure afforded the *cis* derivatives in the adenine (**5a–5c**) and guanine (**5d–5f**) series; an analogous treatment with 4-*N*-(dibutylaminomethylene)cytosine (**2c**) and 3-*N*-benzoylthymine[7] was not successful. Alternatively, we prepared 9-(*cis*-2-hydroxycyclopentyl)adenine (**5a**) by configurational inversion at the hydroxyl-bearing carbon atom in *N*-protected 9-(*trans*-2-hydroxycyclopentyl)adenine[1] (**3a**) using the Mitsunobu reaction in the presence of 4-nitrobenzoic acid[8]. The above-mentioned dibutylaminomethylene derivatives od adenine, 6-*O*-benzylguanine and cytosine (**2a–2c**) were obtained in quantitative yields by sonication of free nucleobases with *N*,*N*-dibutylformamide dineopentyl acetal[9] in dimethylformamide at room temperature. The thus-protected bases are much better soluble in organic solvents than other derivatives such as dimethylaminomethylene or *N*-benzoyl derivatives.

The obtained protected *cis* derivatives **5a–5f** were fully deprotected: the amidine group was removed by heating in methanolic ammonia in an autoclave, the diphenylcarbamoyl group by treatment with sodium methoxide in methanol, and the *O*-benzyl group by catalytic hydrogenation on palladium. The free purine (**5a, 5b**) and pyrimidine (**5i, 5k**) *cis*-hydroxycycloalkyl derivatives were further converted into the corresponding *O*-phosphonomethyl ethers **6a**, **6b** and **6c**, **6d**, respectively. The *O*-phosphonomethyl group was attached by reaction of an alkoxide generated from the secondary hydroxyl of the *N*,*N*-dimethylaminomethylene derivatives of compounds **5a** and **5b**, of the uracil derivative **5i**, and of the *N*-benzoyl derivative of compound **5k** with diisopropyl

tosyloxymethanephosphonate[1]. The *N*-protecting groups were removed by treatment with aqueous ammonia, the phosphonate ester groups were cleaved off with bromotrimethylsilane in acetonitrile and the free *cis*-2-phosphonomethoxycycloalkyl derivatives of adenine **6a** and **6b**, uracil **6c** and cytosine **6d** were obtained by ion exchanger chromatography.

The structure of the compounds was verified by ^{1}H NMR and J-modulated ^{13}C NMR spectra ("attached proton test pulse sequence"). The observed coupling constants J(H-1′, H-2′) of the carbocycles (4.2–4.6 Hz for five-membered, 2.4–3.4 Hz for six-membered, and 2.7–3.0 Hz for seven-membered rings), as well as the chemical shifts of individual carbon atoms (Table I) correspond to the *cis* configuration of 1,2-disubstituted cycloalkanols[10]. The ^{1}H NMR spectra of 2,2′-anhydro derivatives are characterized by downfield shift of the H-1′ and H-2′ signals (about 0.8 ppm) and by change in the coupling constant J(1′,2′) (6.8 and 9.0, respectively). The signals of the heterocyclic base protons are influenced only negligibly (about 0.2 ppm downfield shift); however, the ^{13}C NMR spectra exhibit marked downfield shifts (about 8 ppm) of the C-2 and C-4 carbon signals (Table I). These shifts, together with the observed downfield shift of the C-2′ signal (about 15 ppm; Table II), indicate a 2,2′-anhydro bond[10]. Chemical shifts (C-2′, C-P, ^{31}P) and coupling constants (^1J(P-C,P), ^3J(P,C-2′)) of the phosphonomethoxycycloalkyl derivatives are given in Table III.

The antiviral activity of all the nucleoside and nucleotide analogs prepared in this study was determined on virus-infected host cells in cell cultures in the laboratory of Prof. E. De Clercq, Catholic University, Leuven (Belgium). The effect on the following herpetic viruses was systematically studied: herpes simplex virus type 1 and 2 (HSV-1, HSV-2) and vaccinia virus (VV) as representatives of DNA viruses, vesicular stomatitis virus (VSV), in many cases also reovirus type 1, parainfluenzavirus 3, poliovirus and sindbisvirus as representatives of RNA viruses, and finally human immunodeficiency virus type 1 and 2 (HIV 1, HIV 2) and Moloney sarcoma virus (MSV) as retroviruses. None of the studied compounds approached the activity of the parent compound, 9-(2-phosphonomethoxyethyl)adenine (PMEA).

EXPERIMENTAL

Unless stated otherwise, solvents were evaporated at 40 °C and 2 kPa. The products were dried over phosphorus pentoxide at 50–70 °C and 13 Pa. Their purity was checked by chromatographic methods (TLC, HPLC, GLC), paper electrophoresis (for ionic compounds), spectral methods (NMR, MS, IR, quantitative UV determination) and elemental analysis.

All the described reactions were monitored by TLC (R_F values are given in the text) on Silufol UV 254 foils (Kavalier, Votice). Detection by (i) UV irradiation at 254 nm (aromatic chromophores); (ii) heating (mesyl and tosyl derivatives); (iii) spraying with 0.4% ethanolic solution of 4-(4-nitrobenzyl)pyridine, followed by heating at 150 °C for 10 min and exposure to ammonia vapours (blue coloration: mono- and diesters of phosphonic acids; pink coloration: tosyl and acyl groups; red-violet coloration 2-amino-6-chloropurine derivatives).

Preparative flash chromatography was carried out on 20–40 μm spherical silica gel (Tessek, Czech Republic); the amount of adsorbent was 20–40 times the weight of the separated mixture. Reversed-

phase preparative chromatography was carried out on spherical octadecylsilica gel (20–40 μm, Tessek, Czech Republic). Elution was performed with water or a linear gradient of methanol in water. For chromatographic solvent systems the concentrations are given in vol.%. Desalting of aqueous and aqueous-alcoholic solutions was carried out on a column of a cation exchanger (Dowex 50W X 2, 200–400 mesh, H^+ form). After washing the column with water (aqueous ethanol) to loss of absorption, the product was eluted with 2.8% ammonia in water (aqueous ethanol). Chromatography on anion exchanger Dowex 1 X 2 (acetate form) was executed using a linear concentration gradient of acetic acid in water (0–2 mol l^{-1}), chromatography on DEAE-Sephadex A-25 was carried out with a linear concentration gradient of triethylammonium hydrogen carbonate in water (0–0.3 mol l^{-1}).

TABLE I
Chemical shifts of carbon atoms in heterocyclic bases of compounds **4a–4f**, **5a–5k** and **6a–6d**

Compound	δ, ppm				
	C-2	C-4	C-5	C-6	C-8 (CH_3)
4a	160.37	171.84	116.51	133.15	(13.86)
4b	160.28	176.87	116.55	133.02	(13.86)
4c	159.51	171.81	116.38	132.82	(13.87)
4d	160.76	161.34	108.48	137.59	–
4e	160.62	171.42	108.48	137.52	–
4f	159.88	171.38	108.34	137.30	–
5a	152.26	150.06	118.75	156.06	140.52
5b	152.22	149.30	118.68	156.12	139.96
5c	152.84	148.34	117.90	157.22	141.87
5d	153.53	151.57	116.37	157.16	137.11
5e	154.54	150.12	112.16	159.66	136.55
5f	154.48	149.98	112.48	155.80	136.78
5g	151.28	163.98	107.15	139.62	(12.39)
5h	151.72	163.57	99.64	144.23	–
5i	151.35	163.46	99.88	143.84	–
5j	151.09	163.51	100.17	144.14	–
5k	155.93	165.36	92.28	144.16	–
6a	153.20	150.24	119.01	156.39	143.39
6b	152.97	149.46	118.91	156.33	143.52
6c	153.66	167.68	101.62	147.24	–
6d	160.04	167.40	96.71	147.50	–

HPLC analyses were performed on a reversed phase (C18) Separon SGX-RPS 10 μm (Laboratorni pristroje, Prague); isocratic elution with 0.1 M triethylammonium acetate or gradient of methanol in 0.1 M triethylammonium acetate. Electrophoreses were carried out on Whatman No. 3 MM or Whatman No. 1 paper in 0.1 M triethylammonium hydrogen carbonate (pH 7.5) at 20 V cm^{-1}. The electrophoretic mobilities (E_{Up}) relate to uridine 5′-phosphate.

Mass spectra (*m/z*) were taken on a ZAB-EQ (VG Analytical) instrument, using EI (electron energy 70 eV), FAB (ionization with Xe, accelerating voltage 8 kV) or SIMS (ionization with Cs^+, accelerating voltage 35 kV) techniques. Glycerol and thioglycerol were used as matrices. ^{1}H NMR spectra were measured on a Varian Unity 500 spectrometer (^{1}H at 500 MHz, ^{13}C at 125.7 MHz) in deuterated dimethyl sulfoxide with tetramethylsilane as internal standard. The free phosphonic acids were

TABLE II
Chemical shifts of carbon atoms in carbocycles of compounds **4a–4f**, **5a–5k** and **6a–6d**

Compound	δ, ppm						
	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	C-7′
4a	63.15	84.79	32.52	22.03	33.38	–	–
4b	56.41	77.73	25.32	18.59	18.47	25.39	–
4c	61.02	81.75	29.86	22.93	28.95	24.37	29.65
4d	63.03	85.11	32.69	22.02	33.32	–	–
4e	56.29	78.06	25.33	18.61	18.40	25.48	–
4f	60.93	82.03	29.84	22.92	28.99	24.41	29.61
5a	58.00	70.55	27.53	19.90	32.72	–	–
5b	56.23	66.24	32.40	18.81	25.69	25.16	–
5c	59.72	69.57	33.11	20.71	26.78	24.60	27.73
5d	57.79	70.45	27.43	19.81	32.68	–	–
5e	56.71	65.47	32.18	18.63	25.16	24.96	–
5f	59.65	69.01	33.07	20.60	26.67	24.62	27.55
5g	56.34	66.15	32.82	18.89	25.43	24.39	–
5h	58.57	69.63	26.05	20.06	32.79	–	–
5i	56.52	66.04	32.78	18.88	25.41	24.35	–
5j	58.87	68.84	33.85	20.50	26.56	25.24	27.21
5k	56.58	65.97	32.99	18.95	25.61	24.71	–
6a	58.46	82.73	29.48	20.57	30.16	–	–
6b	57.66	78.21	28.36	19.66	27.60	25.80	–
6c	58.24	78.65	28.33	19.54	26.06	25.85	–
6d	59.42	79.51	29.46	20.39	26.91	26.91	–

measured in deuterium oxide containing sodium deuteroxide, internal standard sodium 3-(trimethylsilyl)-1-propanesulfonate. The ^{13}C NMR spectra were referenced to the solvent signal ($\delta((CD_3)_2SO)$ = 39.7), for aqueous solutions dioxane was used as external standard (δ(dioxane) = 66.86). ^{31}P NMR spectra were measured on a Varian Unity 200 spectrometer at 81 MHz in deuterium oxide with H_3PO_4 as external standard.

The UV spectra (λ_{max}, nm) were measured in 0.01 M hydrochloric acid (pH 2) or in 0.01 M NaOH (pH 12) on a Pye Unicam SP 8000 or Beckmann DU65 spectrophotometer.

trans-2-Benzyloxycyclopentanol (**1a**)

Boron trifluoride etherate (0.62 ml, 5 mmol) was added at room temperature under argon to a mixture of cyclopentene oxide (8.4 g, 100 mmol) and benzyl alcohol (12.4 ml, 120 mmol). The reaction was strongly exothermic and the mixture was immediately cooled to room temperature in an ice bath. After 5 min the mixture did not contain any starting epoxide (reversed-phase HPLC, linear gradient 50–100% of methanol in water). The crude product was purified by preparative chromatography on octadecylsilica gel. Yield 6.15 g (32%) of *trans*-2-benzyloxycyclopentanol (**1a**). For $C_{12}H_{16}O_2 . 1/6 H_2O$ (195.3) calculated: 73.82% C, 8.43% H; found: 73.79% C, 8.44% C. ^1H NMR spectrum ($(CD_3)_2SO$): 1.36–1.70 m, 4 H and 1.70–1.92 m, 2 H (CCH_2); 3.68 m, 1 H and 4.00 m, 1 H (OCH); 4.48 s, 2 H (CH_2, benzyl); 4.69 d, 1 H, *J*(OH,CH) = 4.0 (OH); 7.32 m, 5 H (arom. H).

trans-2-Benzyloxycycloheptanol (**1c**)

The title compound was prepared from cycloheptene oxide (11.2 g, 100 mmol) as described above for compound **1a**. Yield 9.03 g (41%) of *trans*-2-benzyloxycycloheptanol (**1c**). For $C_{14}H_{20}O_2 . 1/6 H_2O$ (223.3) calculated: 75.30% C, 9.18% H; found: 75.11% C, 9.14% H. ^1H NMR spectrum ($(CD_3)_2SO$): 1.30–1.85 m, 10 H (CCH_2); 3.33 m, 1 H and 3.64 m, 1 H (OCH); 4.55 d, 1 H, *J*(OH, CH) = 4.3 (OH); 4.50 d, 1 H and 4.57 d, 1 H, *J*(gem) = 12.0 (CH_2, benzyl); 7.20–7.40 m, 5 H (arom. H).

6-*N*-(Dibutylaminomethylene)adenine (**2a**)

A suspension of adenine (2.7 g, 20 mmol) and dibutylformamide dineopentyl acetal (8.8 ml, 24 mmol) in dimethylformamide (40 ml) was sonicated at room temperature until the solid dissolved (2 h). The mixture was concentrated in vacuo and the oily residue was sonicated in methanol–ether (1 : 9, 50 ml) until all the oily material was converted into a white precipitate. This was collected, washed with

TABLE III
Selected chemical shifts and coupling constants for phosphonomethoxycycloalkyl derivatives **6**

Compound	δ, ppm; *J*, Hz				
	C-2′	^3J(P,C-2′)	C-P	^1J(P-C,P)	^{31}P
6a	82.73	10.7	68.20	152.6	13.61
6b	78.21	12.2	67.83	152.6	13.68
6c	78.65	13.7	65.71	158.7	16.06
6d	79.51	12.7	67.46	157.2	15.44

ether and dried. Yield 5.38 g (98%) of compound **2a**, m.p. 175–176 °C. UV spectrum: 333 (pH 2), 314 (pH 12). For $C_{14}H_{22}N_6$ (274.4) calculated: 61.29% C, 8.08% H, 30.63% N; found: 61.13% C, 8.10% H, 30.61% N. Mass spectrum (FAB): 275.6 ($M^+ + H$). ^{1}H NMR spectrum ($(CD_3)_2SO$): 0.91 t, 3 H and 0.92 t, 3 H, $J(CH_3,CH_2)$ = 7.3 (CH_3); 1.31 m, 4 H and 1.59 m, 4 H (CCH_2); 3.43 t, 2 H, $J(CH_2,CH_2)$ = 7.2 and 3.59 t, 2 H, $J(CH_2,CH_2)$ = 7.5 (NCH_2); 8.28 brs, 1 H (H-8); 8.41 s, 1 H (H-2); 8.90 s, 1 H (CH=N); 12.94 brs, 1 H (NH).

6-*O*-Benzyl-2-*N*-(dibutylaminomethylene)guanine (**2b**)

Compound **2b** was prepared from 6-*O*-benzylguanine (4.83 g, 20 mmol) as described for derivative **2a**. Yield 7.31 g (96%), m.p. 141–143 °C. UV spectrum: 271, 232 (pH 2), 294, 248 (pH 12). For $C_{21}H_{28}N_6O$ (380.5) calculated: 66.29% C, 7.41% H, 22.09% N; found: 66.10% C, 7.41% H, 21.85% N. Mass spectrum (FAB): 381.6 ($M^+ + H$). ^{1}H NMR spectrum ($(CD_3)_2SO$): 0.90 t, 3 H and 0.91 t, 3 H, $J(CH_3,CH_2)$ = 7.3 (CH_3); 1.29 m, 4 H and 1.54 m, 4 H (CCH_2); 3.34 t, 2 H, $J(CH_2,CH_2)$ = 7.1 and 3.44 t, 2 H, $J(CH_2, CH_2)$ = 7.6 (NCH_2); 8.07 brs, 1 H (H-8); 8.61 s, 1 H (CH=N); 12.80 brs, 1 H (NH).

4-*N*-(Dibutylaminomethylene)cytosine (**2c**)

Compound **2c** was prepared from cytosine (2.22 g, 20 mmol) in the same manner as described for the derivative **2a**; yield 4.91 g (98%), m.p. 179–181 °C. UV spectrum: 328, 260 (pH 2), 315, 267 (pH 12). For $C_{13}H_{22}N_4O$ (250.3) calculated: 62.37% C, 8.86% H, 22.38% N; found: 62.41% C, 8.95% H, 22.44% N. Mass spectrum (FAB): 251.5 ($M^+ + H$). ^{1}H NMR spectrum ($(CD_3)_2SO$): 0.90 t, 6 H, $J(CH_3,CH_2)$ = 7.3 (CH_3); 1.27 m, 4 H and 1.54 m, 4 H (CCH_2); 3.40 t, 2 H, $J(CH_2,CH_2)$ = 7.2 and 3.46 t, 2 H, $J(CH_2,CH_2)$ = 7.4 (NCH_2); 5.80 d, 1 H, J(5,6) = 6.8 (H-5); 7.51 brd, 1 H, J(6,5) = 6.8 (H-6); 8.58, s, 1 H (CH=N); 10.87 brs, 1 H (NH).

2,2′-Anhydro-1-(*cis*-2-hydroxycyclopentyl)thymine (**4a**)

A mixture of 1-(*trans*-2-hydroxycyclopentyl)thymine[1] (**3b**; 0.21 g, 1 mmol), mesyl chloride (0.5 ml, 6 mmol) and pyridine (5 ml) was stirred at room temperature for 4 h. Water (10 ml) was added and the mixture was set aside for 12 h. After evaporation of the solvent, the product was isolated by chromatography on silica gel in a gradient of methanol in ethyl acetate (0–20%). Yield 0.18 g (94%) of compound **4a**, m.p. 189 °C. Mass spectrum (FAB): 193 ($M^+ + H$), 127 (thymine + H^+). ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.40 m, 1 H, and 1.68–1.82 m, 3 H ($(CH_2)_2$); 1.78 d, 3 H, J(6, CH_3) = 1.0 (CH_3); 2.00 m, 2 H (CH_2); 4.86 brt, 1 H, J = 6.4 and 6.8 (OCH); 5.36 dd, 1 H, J = 5.9 and 6.8 (NCH); 7.65 brq, 1 H, J = 1.0 (H-6).

2,2′-Anhydro-1-(*cis*-2-hydroxycyclohexyl)thymine (**4b**)

A solution of 1-(*trans*-2-hydroxycyclohexyl)thymine[1] (**3c**; 0.23 g, 1 mmol) and mesyl chloride (0.5 ml, 6 mmol) in pyridine (5 ml) was stirred at room temperature for 4 h. After addition of water (10 ml) the reaction mixture deposited the *O*-mesyl derivative (0.15 g). This compound was stirred with DBU (0.082 ml, 0.55 mmol) in acetonitrile (5 ml) for 12 h and the product was isolated by chromatography on silica gel as described for compound **4a**. Yield 0.09 g (44% related to the *trans* derivative) of compound **4b**, m.p. 227 °C. Mass spectrum (FAB): 207 ($M^+ + H$), 127 (thymine + H^+). ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.30–1.50 m, 4 H, and 1.63 m, 1 H, and 1.86 m, 2 H, and 1.96 m, 1 H ($(CH_2)_4$); 1.79 d, 3 H, J(6,CH_3) = 1.2 (CH_3); 4.46 td, 1 H, J = 5.9, 6.6 and 6.6 (OCH); 4.96 dt, 1 H, J = 4.9, 4.9 and 6.8 (NCH); 7.71 brq, 1 H, J = 1.2 (H-6).

2,2′-Anhydro-1-(*cis*-2-hydroxycycloheptyl)thymine (**4c**)

1-(*trans*-2-Hydroxycycloheptyl)thymine[1] (**3d**; 0.12 g, 0.5 mmol) was treated with mesyl chloride (0.25 ml, 3 mmol) in pyridine (2.5 ml) as described for the preparation of **4b**. Freeze-drying from water afforded 0.08 g (73%) of compound **4c**. For $C_{12}H_{16}N_2O_2$ (220.3) calculated: 65.43% C, 7.32% H, 12.72% N; found: 65.18% C, 7.36% H, 12.60% N. ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.30–1.75 m, 6 H ($(CH_2)_3$); 1.78 d, 3 H, J(6,CH_3) = 1.0 (CH_3); 1.80–2.10 m, 4 H ($(CH_2)_2$); 4.62 m, 1 H (OCH); 5.14 m, 1 H (NCH); 7.68 brq, 1 H, J = 1.0 (H-6).

2,2′-Anhydro-1-(*cis*-2-hydroxycyclopentyl)uracil (**4d**)

Compound **4d** was prepared from 1-(*trans*-2-hydroxycyclopentyl)uracil[1] (**3e**; 0.13 g, 0.65 mmol) as described for the thymine derivative **4a**. Chromatography on octadecylsilica gel gave 0.10 g (86%) of compound **4d**, m.p. 203 °C. Mass spectrum (FAB): 179 (M^+ + H), 113 (uracil + H^+). ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.43 m, 1 H, 1.70–1.83 m, 4 H, and 2.00 m, 1 H ($(CH_2)_3$); 4.87 brt, 1 H, J = 6.4 and 6.8 (OCH); 5.38 dd, 1 H, J = 5.9 and 6.8 (NCH); 5.81 d, 1 H, J(5,6) = 7.3 (H-5); 7.75 d, 1 H, J(6,5) = 7.3 (H-6).

2,2′-Anhydro-1-(*cis*-2-hydroxycyclohexyl)uracil (**4e**)

Compound **4e** was prepared from 1-(*trans*-2-hydroxycyclohexyl)uracil[1] (**3f**; 0.21 g, 1 mmol) as described for the preparation of compound **4b**. Yield 0.17 g (90%) of product **4e**, m.p. 233 °C. Mass spectrum (FAB): 193 (M^+ + H), 113 (uracil + H^+). ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.30–1.50 m, 4 H, 1.60 m, 1 H, 1.88 m, 2 H, and 1.98 m, 1 H ($(CH_2)_4$); 4.48 td, 1 H, J = 5.9, 6.8 and 6.8 (OCH); 4.99 dt, 1 H, J = 4.6, 4.6 and 7.0 (NCH); 5.82 d, 1 H, J(5,6) = 7.3 (H-5); 7.80 d, 1 H, J(6,5) = 7.3 (H-6).

2,2′-Anhydro-1-(*cis*-2-hydroxycycloheptyl)uracil (**4f**)

Compound **4f** was prepared from 1-(*trans*-2-hydroxycycloheptyl)uracil[1] (**3g**; 0.67 g, 3 mmol) as described for the preparation of compound **4b**. Yield 0.57 g (92%) of product **4f**, m.p. 214 °C. For $C_{11}H_{14}N_2O_2$ (206.2) calculated: 64.06% C, 6.84% H, 13.58% N; found: 64.18% C, 6.92% H, 13.77% N. Mass spectrum (FAB): 207 (M^+ + H). ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.35–1.65 m, 6 H, and 1.90–2.05 m, 4 H ($(CH_2)_5$); 4.62 td, 1 H, J = 3.9, 9.0 and 9.0 (OCH); 5.16 td, 1 H, J = 3.9, 9.0 and 9.0 (NCH); 5.81 d, 1 H, J(5,6) = 7.3 (H-5); 7.77 d, 1 H, J(6,5) = 7.3 (H-6).

9-(*cis*-2-Hydroxycyclopentyl)adenine (**5a**)

Method A. A mixture of 6-chloropurine (0.77 g, 5 mmol), *trans*-2-benzyloxycyclopentanol (**1a**; 0.96 g, 5 mmol) and triphenylphosphine (3.93 g, 15 mmol) was dried by codistillation with toluene and dissolved in anhydrous THF (30 ml). Diisopropyl azodicarboxylate (2.95 ml, 15 mmol) was added with stirring at –70 °C. The reaction mixture was stirred at room temperature for 3 days, stripped of the solvent and the residue was chromatographed on silica gel (0–20% ethyl acetate in toluene). The obtained intermediate was heated at 100 °C for 8 h with methanolic ammonia (50 ml, saturated at –10 °C) in an autoclave. After evaporation of the solvent, the product was hydrogenated for 16 h over palladium (200 mg, 10% Pd/C) in a mixture of acetic acid (200 ml) and 1 M aqueous HCl (10 ml) at room temperature. The crude product **5a** was deionized and then chromatographed on Dowex 50W X 2. Crystallization from water afforded 0.28 g (26%) of product **5a**, m.p. 225 °C.

Method B. 9-(*trans*-2-Hydroxycyclopentyl)adenine (**3a**; 2.33 g, 10 mmol) was treated with dibutylformamide dimethyl acetal (5.5 ml, 15 mmol) in DMF (10 ml) to give the dibutylaminomethylene derivative as described for the preparation of 6-*N*-(dibutylaminomethylene)adenine (**2a**). The obtained

protected nucleoside derivative was mixed with triphenylphosphine (10.5 g, 40 mmol) and 4-nitrobenzoic acid (6.68 g, 40 mmol) in tetrahydrofuran (80 ml). Diisopropyl azodicarboxylate (7.9 ml, 40 mmol) was added at 10 °C to the stirred mixture under argon and the mixture was allowed to stand at room temperature for 2 days. The obtained solution was diluted with 28% aqueous ammonia (500 ml), saturated at 0 °C with gaseous ammonia, and the resulting suspension was stirred for 4 days at room temperature. After concentration, the solution was extracted with ether and the aqueous layer desalted on Dowex 50W X 2 (H^+ form). Crystallization from water gave 0.36 g (15%) of *cis* derivative **5a**, identical with the compound obtained according to method *A*. UV spectrum: 261 (pH 2), 262 (pH 12). For $C_{10}H_{13}N_5O$ (219.3) calculated: 54.78% C, 5.98% H, 31.94% N; found: 54.41% C, 6.01% H, 31.05% N. Mass spectrum (FAB): 220 ($M^+ + H$). ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.59–1.75 m, 2 H, 1.85–2.00 m, 2 H, 2.07 m, 1 H, and 2.24 m, 1 H ($(CH_2)_3$); 4.15 m, 1 H (OCH); 4.68 ddd, 1 H, J = 4.6, 7.8 and 11.5 (NCH); 4.97 brs, 1 H (OH); 7.22 brs, 2 H (NH_2); 8.14 s, 1 H and 8.16 s, 1 H (H-2, H-8).

9-(*cis*-2-Hydroxycyclohexyl)adenine (**5b**)

Compound **5b** was prepared from 6-*N*-(dibutylaminomethylene)adenine (**2a**; 1.37 g, 5 mmol) and *trans*-2-benzyloxycyclohexanol[5] (**1b**; 1.03 g, 5 mmol) as described for the preparation of derivative **5a** (method *A*). After stirring for 48 h, the mixture was concentrated, the residue mixed with methanol–water–triethylamine mixture (5 : 5 : 1; 50 ml) and heated at 80 °C for 4 h. The mixture was deionized and the obtained *O*-benzyl derivative of compound **5b** was chromatographed on octadecylsilica gel (methanol in water, 0–50%). Hydrogenolysis on palladium (200 mg, 10% Pd/C) under conditions described for **5a** (method *A*), deionization, and crystallization from water afforded 0.35 g (30%) of product **5b**, m.p. 234 °C. UV spectrum: 261 (pH 2), 262 (pH 12). For $C_{11}H_{15}N_5O$ (233.3) calculated: 56.64% C, 6.48% H, 30.02% N; found: 56.25% C, 6.64% H, 29.72% N. Mass spectrum (FAB): 234 ($M^+ + H$). ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.39–1.49 m, 2 H, 1.57–1.72 m, 3 H; 1.75–1.84 m, 2 H, and 2.25 m, 1 H ($(CH_2)_4$); 3.97 m, 1 H (OCH); 4.45 ddd, 1 H, J = 3.4, 2.7 and 12.9 (NCH); 5.02 d, 1 H, J(OH,CH) = 4.6 (OH); 7.20 brs, 2 H (NH_2); 8.12 s, 1 H and 8.13 s, 1 H (H-2, H-8).

9-(*cis*-2-Hydroxycycloheptyl)adenine (**5c**)

Compound **5c** was prepared from 6-*N*-(dibutylaminomethylene)adenine (**2a**; 0.27 g, 1 mmol) and *trans*-2-benzyloxycycloheptanol (**1c**; 0.22 g, 1 mmol) as described for the preparation of derivative **5a** (method *A*). After 48 h, the triphenylphosphine oxide was removed on Dowex 50W X 2 (H^+ form) by elution with ethanol–water mixture (75 : 25, v/v) and the fully protected product was liberated by addition of 2.8% solution of ammonia in the same mixture. After evaporation, the residue was heated with methanolic ammonia (saturated at –10 °C) at 110 °C for 8 h in an autoclave. Hydrogenolysis on palladium (200 mg, 10% Pd/C) under conditions described for the preparation of compound **5a** (method *A*) and crystallization from acetone–diethyl ether afforded 80 mg (32%) of product **5c**, m.p. 263 °C. UV spectrum: 261 (pH 2), 262 (pH 12). For $C_{12}H_{17}N_5O$ (247.3) calculated: 58.28% C, 6.93% H, 28.32% N; found: 58.25% C, 6.94% H, 28.23% N. Mass spectrum (FAB): 248 ($M^+ + H$). ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.10–1.80 m, 9 H, and 2.40 m, 1 H ($(CH_2)_5$); 3.97 m, 1 H (OCH); 4.59 ddd, 1 H, J = 1.5, 2.7 and 11.5 (NCH); 5.10 brs, 1 H (OH); 8.30 brs, 2 H (NH_2); 8.31 s, 1 H and 8.33 s, 1 H (H-2, H-8).

9-(*cis*-2-Hydroxycyclopentyl)guanine (**5d**)

Compound **5d** was prepared from 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanine[6] (1.94 g, 5 mmol) and *trans*-2-benzyloxycyclopentanol (**1a**; 0.96 g, 5 mmol) as described for the adenine derivative **5a**.

After 4 days, the reaction mixture was concentrated and the residue allowed to stand with 2 M methanolic sodium methoxide (50 ml) at room temperature for 12 h. Deionization with Dowex 50W X 2 (H^+ form), chromatography on silica gel in chloroform–ethanol (95 : 5) and crystallization from the same solvent mixture gave 0.60 g (38%) of 9-(*cis*-2-benzyloxycyclopentyl)guanine which was debenzylated on palladium (1 g, 10% Pd/C) under conditions described for compound **5a** (method *A*). Crystallization from water gave 0.27 g (90%) of compound **5d**, m.p. >335 °C (decomp.). UV spectrum: 254 (pH 2), 267 (pH 12). For $C_{10}H_{13}N_5O_2$ (235.3) calculated: 51.06% C, 5.57% H, 29.77% N; found: 50.96% C, 5.42% H, 29.75% N. Mass spectrum (FAB): 236 (M^+ + H), 152 (guanine + H^+). ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.40–2.30 m, 6 H ($(CH_2)_3$); 4.07 m, 1 H, (OCH); 4.40 m, 1 H (NCH); 4.94 brs, 1 H (OH); 6.41 brs, 2 H, (NH_2); 7.72 s, 1 H (H-8); 10.59 brs, 1 H (NH).

9-(*cis*-2-Hydroxycyclohexyl)guanine (**5e**)

Compound **5e** was prepared from 6-*O*-benzyl-2-*N*-(dibutylaminomethylene)guanine (**2b**; 1.91 g, 5 mmol) and *trans*-2-benzyloxycyclohexanol[5] (**1b**; 1.03 g, 5 mmol) as described for the adenine derivative **5a** (method *A*). After hydrogenation, the crude product was purified by reversed-phase chromatography. Yield 0.35 g (28%) of compound **5e**, m.p. >310 °C (decomp.). UV spectrum: 254 (pH 2), 267 (pH 12). For $C_{11}H_{15}N_5O_2$ (249.3) calculated: 53.00% C, 6.07% H, 28.10% N; found: 52.81% C, 5.93% H, 27.83% N. Mass spectrum (FAB): 250 (M^+ + H). ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.34–1.70 m, 5 H, 1.80 m, 2 H, and 2.16 m, 1 H ($(CH_2)_4$); 3.90 brs, 1 H (OCH); 4.26 ddd, 1 H, J = 2.5, 3.5 and 12.5 (NCH); 5.08 brs, 1 H (OH); 6.88 brs, 2 H (NH_2); 8.36 s, 1 H (H-8); 11.13 brs, 1 H (NH).

9-(*cis*-2-Hydroxycycloheptyl)guanine (**5f**)

Compound **5f** was prepared from 6-*O*-benzyl-2-*N*-(dibutylaminomethylene)guanine (**2b**; 0.38 g, 1 mmol) and *trans*-2-benzyloxycycloheptanol (**1c**; 1.03 g, 5 mmol) as described for the adenine derivative **5a** (method *A*). Hydrogenolysis on palladium (48 h, method *A*), chromatography on octadecylsilica gel (methanol in 0.1 M triethylammonium acetate, pH 7.1; gradient 0–50%), and desalting on the same carrier (gradient of methanol 0–50%) afforded 0.23 g (85%) of compound **5f**, m.p. >310 °C (decomp.) UV spectrum: 254 (pH 2), 267 (pH 12). For $C_{12}H_{17}N_5O_2$ (263.3) calculated: 54.74% C, 6.51% H, 26.60% N; found: 54.41% C, 6.36% H, 26.49% N. Mass spectrum (FAB): 264 (M^+ + H), 152 (guanine + H^+). ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.40–1.80 m, 9 H, and 2.28 m, 1 H ($(CH_2)_5$); 3.95 m, 1 H (OCH); 4.35 dt, 1 H, J = 3.0, 3.0 and 11.5 (NCH); 5.40 brs, 1 H (OH); 6.87 brs, 2 H (NH_2); 8.26 s, 1 H (H-8); 11.18 brs, 1 H (NH).

1-(*cis*-2-Hydroxycyclohexyl)thymine (**5g**)

Anhydro derivative **4b** (0.10 g, 0.5 mmol) was heated with 0.2 M aqueous sodium hydroxide (10 ml) at 60 °C for 1 h. Deionization on Dowex 50W X 2 (H^+ form; elution with 50% aqueous methanol), followed by freeze-drying, afforded the product **5g** in quantitative yield. For $C_{11}H_{16}N_2O_3$ (224.3) calculated: 58.91% C, 7.19% H, 12.49% N; found: 58.97% C, 7.25% H, 12.37% N. Mass spectrum (FAB): 225 (M^+ + H), 127 (thymine + H^+). ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.30–1.58 m, 5 H, and 1.75 m, 2 H, and 2.03 m, 1 H ($(CH_2)_4$); 1.76 d, 3 H, J(6,CH_3) = 1.0 (CH_3); 3.82 m, 1 H (OCH); 4.27 ddd, 1 H, J = 2.4, 3.5 and 12.9 (NCH); 4.92 d, 1 H, J(OH,CH) = 4.6 (OH); 7.48 brq, 1 H, J = 1.0 (H-6); 11.17 brs, 1 H (NH).

1-(*cis*-2-Hydroxycyclopentyl)uracil (**5h**)

Compound **5h** was prepared in quantitative yield from the anhydro derivative **4d** (0.18 g, 1 mmol) by the same procedure as compound **5g**; m.p. 177 °C. UV spectrum: 267 (pH 2), 268 (pH 12). For $C_9H_{12}N_2O_3$ (196.2) calculated: 55.09% C, 6.16% H, 14.28% N; found: 54.94% C, 6.17% H, 14.14% N. Mass spectrum (FAB): 197 (M^+ + H), 113 (uracil + H^+). ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.48–1.62 m, 2 H, 1.74–1.84 m, 2 H, and 1.84–1.96 m, 2 H ($(CH_2)_3$); 4.02 m, 1 H, *J* = 2.1, 4.2, 4.6 and 5.6 (OCH); 4.50 ddd, 1 H, *J* = 4.6, 7.6 and 11.2 (NCH); 4.94 d, 1 H, *J*(OH,CH) = 4.2 (OH); 5.47 d, 1 H, *J*(5,6) = 8.0 (H-5); 7.60 d, 1 H, *J*(6,5) = 8.0 (H-6); 11.71 brs, 1 H (NH).

1-(*cis*-2-Hydroxycyclohexyl)uracil (**5i**)

Compound **5i** was prepared in quantitative yield from the anhydro derivative **4e** (0.17 g, 0.9 mmol) by the same procedure as described for compound **5g**; m.p. 248 °C. UV spectrum: 267 (pH 2), 268 (pH 12). For $C_{10}H_{14}N_2O_3$ (210.23) calculated: 57.13% C, 6.71% H, 13.32% N; found: 57.33% C, 6.78% H, 13.25% N. Mass spectrum (FAB): 211 (M^+ + H), 113 (uracil + H^+). ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.30–1.60 m, 5 H, 1.70–1.80 m, 2 H, and 1.97 m, 1 H ($(CH_2)_4$); 3.83 m, 1 H (OCH); 4.28 ddd, 1 H, *J* = 2.4, 3.4 and 13.2 (NCH); 4.94 d, 1 H, *J*(OH,CH) = 4.6 (OH); 5.48 d, 1 H, *J*(5, 6) = 8.0 (H-5); 7.60 d, 1 H, *J*(6,5) = 8.0 (H-6); 11.18 brs, 1 H (NH).

1-(*cis*-2-Hydroxycycloheptyl)uracil (**5j**)

Compound **5j** was prepared in quantitative yield from the anhydro derivative **4f** (0.41 g, 2 mmol) by the same procedure as described for compound **5g**; m.p. 221 °C. UV spectrum: 267 (pH 2), 268 (pH 12). For $C_{11}H_{16}N_2O_3$ (224.3) calculated: 58.91% C, 7.19% H, 12.49% N; found: 58.82% C, 7.09% H, 12.40% N. Mass spectrum (FAB): 225 (M^+ + H), 113 (uracil + H^+). ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.32–1.78 m, 9 H, and 2.02–2.11 m, 1 H ($(CH_2)_5$); 3.85 m, 1 H (OCH); 4.37 dt, 1 H, *J* = 2.5, 2.5 and 11.5 (NCH); 4.98 d, 1 H, *J*(OH,CH) = 5.1 (OH); 5.49 d, 1 H, *J*(5,6) = 8.0 (H-5); 7.52 d, 1 H, *J*(6,5) = 8.0 (H-6); 11.14 brs, 1 H (NH).

1-(*cis*-2-Hydroxycyclohexyl)cytosine (**5k**)

A solution of 1-(*trans*-2-hydroxycyclohexyl)cytosine[1] (**3h**; 1.04 g, 5 mmol) and mesyl chloride (1.2 ml, 15 mmol) in pyridine (25 ml) was set aside at room temperature for 24 h. The mixture was diluted with 1 M aqueous sodium hydroxide (100 ml) and heated at 100 °C for 3 h. Desalting on Dowex 50W X 2 (H^+ form) afforded 0.8 g (77%) of compound **5k**, m.p. 278 °C. UV spectrum: 286 (pH 2), 275 (pH 12). For $C_{10}H_{15}N_3O_2$ (209.3) calculated: 57.40% C, 7.23% H, 20.08% N; found: 57.64% C, 7.38% H, 19.89% N. Mass spectrum (FAB): 210 (M^+ + H), 112 (uracil + H^+). ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.35 m, 3 H, 1.40–1.60 m, 2 H, 1.73 m, 2 H, and 1.95 m, 1 H ($(CH_2)_4$); 3.80 m, 1 H (OCH); 4.37 ddd, 1 H, *J* = 2.4, 4.4 and 13.4 (NCH); 4.81 d, 1 H, *J*(OH,CH) = 4.6 (OH); 5.61 d, 1 H, *J*(5,6) = 7.3 (C-5); 6.84 brs, 1 H and 6.95 brs, 1 H (NH_2); 7.53 d, 1 H, *J*(6,5) = 7.3 (C-6).

9-(*cis*-2-Phosphonomethoxycyclopentyl)adenine (**6a**)

Nucleoside derivative **5a** (0.11 g, 0.5 mmol) was converted into the title compound as described for the *trans* isomer[1]. Freeze-drying afforded 0.12 g (67%) of sodium salt of compound **6a**. UV spectrum: 261 (pH 2), 262 (pH 12). Mass spectrum (FAB): 358 (M^+ + H). ^{1}H NMR spectrum (D_2O, NaOD): 1.80 m, 1 H, 2.05 m, 3 H, and 2.28 m, 2 H ($(CH_2)_3$); 3.04 dd, 1 H, *J*(P,CH) = 8.5, *J*(gem) = 12.7 and 3.27 dd, 1 H, *J*(P,CH) = 9.3, *J*(gem) = 12.7 (PCH_2); 4.17 brq, 1 H, *J* = 4.2 (OCH); 4.80 dt, 1 H, *J* = 4.2, 4.2 and 8.0 (NCH); 8.16 s, 1 H and 8.39 s, 1 H (H-2, H-8).

9-(*cis*-2-Phosphonomethoxycyclohexyl)adenine (**6b**)

Nucleoside derivative **5b** (0.12 g, 0.5 mmol) was converted into the title compound as described for the *trans* isomer[1]. Freeze-drying afforded 0.14 g (75%) of sodium salt of compound **6b**. UV spectrum: 261 (pH 2), 262 (pH 12). Mass spectrum (FAB): 372 (M^+ + H). ^{1}H NMR spectrum (D_2O, NaOD): 1.55 m, 3 H, 1.68 m, 1 H, 1.82 m, 1 H, 1.92 m, 1 H, and 2.30 m, 2 H (($CH_2)_4$); 3.06 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 12.2 and 3.44 dd, 1 H, *J*(P,CH) = 9.8, *J*(gem) = 12.2 (PCH_2); 3.77 brs, 1 H (OCH); 4.48 ddd, 1 H, *J* = 2.7, 3.8 and 12.9 (NCH); 8.13 s, 1 H and 8.56 s, 1 H (H-2, H-8).

1-(*cis*-2-Phosphonomethoxycyclohexyl)uracil (**6c**)

Compound **6c** was prepared from compound **5i** (0.21 g, 1 mmol) as described for the *trans* derivative[1]. Freeze-drying afforded 0.12 g (39%) of sodium salt of compound **6c**. UV spectrum: 268 (pH 2), 268 (pH 12). Mass spectrum (FAB): 305 (M^+ + H), 327 (M + Na). ^{1}H NMR spectrum (D_2O): 1.42–1.63 m, 5 H, 1.90 m, 1 H, and 2.07–2.20 m, 2 H (($CH_2)_4$); 3.32 dd, 1 H, *J*(P,CH) = 9.8, *J*(gem) = 12.9 and 3.67 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 12.9 (PCH_2); 3.71 brs, 1 H (OCH); 4.52 ddd, 1 H, *J* = 2.7, 3.9 and 13.2 (NCH); 5.82 d, 1 H, *J*(5,6) = 8.2 (H-5); 7.99 d, 1 H, *J*(6,5) = 8.2 (H-6).

1-(*cis*-2-Phosphonomethoxycyclohexyl)cytosine (**6d**)

Nucleoside derivative **5k** (0.48 g, 2 mmol) was converted into the title compound as described for the *trans* derivative[1]. Freeze-drying afforded 0.21 g (35%) of compound **6d**. Mass spectrum (FAB): 304 (M^+ + H). ^{1}H NMR spectrum (D_2O, NaOD): 1.35–1.65 m, 5 H, and 1.80–2.23 m, 3 H (($CH_2)_4$); 3.24 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 12.5 and 3.58 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 12.5 (PCH_2); 3.66 m, 1 H (OCH); 4.53 ddd, 1 H, *J* = 2.4, 3.4 and 13.1 (NCH); 6.01 d, 1 H, *J*(5,6) = 7.6 (H-5); 7.96 d, 1 H, *J*(6,5) = 7.6 (H-6).

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