# CARBOCYCLIC PHOSPHONATE-BASED NUCLEOTIDE ANALOGS RELATED TO PMEA. I. RACEMIC *trans*-CONFIGURED DERIVATIVES

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Racemic *trans*-*N*-(2-phosphonomethoxycycloalkyl) derivatives of heterocyclic bases, a novel type of nucleotide analogs related to 9-(2-phosphonomethoxyethyl)adenine (PMEA), are reported. The synthesis of fully protected adenine- (**5**), hypoxanthine- (**7**), guanine- (**11**), thymine- (**13**), uracil- (**16**) and cytosine-containing (**18**) carbocyclic nucleotide analogs is based on the reaction of *trans*-2-hydroxycycloalkyl derivatives of *N*-protected nucleobases (**2**, **10**, **12**, **14**, **17**) with diisopropyl tosyloxymethanephosphonate. Deprotection of these compounds afforded the title nucleotide analogs. The starting "nucleoside" derivatives have been prepared via nucleophilic oxirane ring opening of cycloalkene oxides with various protected or free nucleobases.
**Key words:** Carbocyclic analogs; Antivirals; Nucleoside phosphonates.

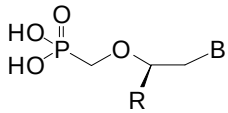
In the recent years, many biologically effective nucleotide analogs with a phosphonate group, resistant to dephosphorylating enzymes, have been prepared[1–5]. To the most studied compounds of this type belong two groups of acyclic nucleotide analogs containing the phosphonomethyl ether group: *N*-(2-phosphonomethoxyethyl) (PME, **1a**) and (*S*)-*N*-(2-phosphonomethoxy-3-hydroxypropyl) (HPMP, **1b**) derivatives of heterocyclic bases (adenine, guanine, 2,6-diaminopurine and cytosine). These act specifically against DNA viruses (herpesviruses, adenoviruses, poxviruses); the PME compounds are also effective against retroviruses (MSV, HIV) and exhibit a cytostatic effect in L-1210 mice leukemia cells (for a review see refs[1–4]).

Within the framework of structure–activity studies of the mentioned compounds, including many possible structural modifications[4,5], we studied previously the "fixed" PME and (*S*)-HPMP structures **1a** and **1b** (B = adenine), the so-called 5-(9-adeninyl)-pentofuranosyl phosphonates[6–8] **1c**, in which the C-2′ atom and the carbon atom of the methylenephosphonate grouping are part of a five-membered oxygen heterocyclic ring. In the present communication we describe the synthesis of a novel type of conformationally fixed nucleotide analogs derived from PME derivatives in which the atoms C-1′ and C-2′ of the parent aliphatic chain are part of a five-, six- or seven-membered carbocyclic ring. One of the objectives of this study was to investigate the effect of fixation of the originally acyclic skeleton in the PME derivatives on their biological

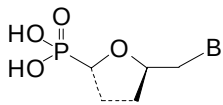
activity. The closure of a cycloalkane ring between the C-1′ and C-2′ atoms in a PME derivative gives rise to enantiomeric carbocyclic phosphonate nucleotides of *cis* or *trans* configuration (the preparation of *cis* derivatives and their biological activity are the subject of another study[5]). Both these isomers represent certain "limit" structures, concerning the mutual position of the phosphonomethoxyl moiety and the heterocyclic base. With increasing cycloalkane ring in the molecule of the *cis* or *trans* isomer the number of rotamers arising by rotation about the (C-1′)–(C-2′) bond will increase and some of them might interact advantageously with the target enzymes[6]. In such an interaction, substantial role might be played by the steric hindrance due to the cycloalkane ring as well as by the existence of enantiomeric forms.

We prepared therefore a series of racemic *trans*-*N*-(2-phosphonomethoxycycloalkyl) derivatives of nucleobases containing cyclopentane, cyclohexane or cycloheptane ring. The derivatives **5a**–**5c**, **11a**–**11c**, **13a**–**13c**, **16a**–**16c** and **18a**–**18c** were prepared from the corresponding *trans*-2-hydroxycycloalkyl derivatives of nucleobases **2a**–**2c**, **10a**–**10c**, **12a**–**12c**, **14a**, **14b** and **17a**–**17c** by nucleophilic substitution of the tosyl group in the diester of tosyloxymethanephosphonic acid with the alkoxide generated from the hydroxyl of the protected nucleoside. The *N*-protecting groups (dimethylaminomethylene for the adenine and guanine derivatives and benzoyl for the cytosine compounds) were removed with concentrated aqueous ammonia, the phosphonate ester groups and the 6-*O*-benzyl group of the guanine derivatives were split off by treatment with bromotrimethylsilane in acetonitrile. Ion-exchange chromatography afforded *trans*-2-phosphonomethoxycycloalkyl derivatives of adenine (**5a**–**5c**), guanine (**11a**–**11c**) and cytosine (**18a**–**18c**). The hypoxanthine phosphonates **7a**–**7c** were prepared by deamination of the free adenine phosphonates **5a**–**5c** on treatment with excess of isoamyl nitrite in 80% acetic acid. For comparative biological studies we isolated the diisopropyl ester of *trans*-2-phosphonomethoxycyclopentyl and -cyclohexyl adenine derivatives **3a** and **3b** which on partial alkaline hydrolysis were converted into the corresponding monoesters **4a** and **4b**, respectively.

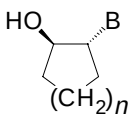
The key racemic *trans*-2-hydroxycycloalkyl derivatives of protected nucleobases **2a**–**2c**, **10a**–**10c**, **12a**–**12c**, **14a**, **14b** and **17a**–**17c** were prepared by nucleophilic opening of the oxirane ring in cycloalkene oxides with nucleobases[7]. Since the reaction of cyclohexene oxide with sodium salts of nucleobases, in situ generated by sodium hydride, did not give satisfactory yields, we prepared the 2-hydroxycyclopentyl and 2-hydroxycyclohexyl derivatives of adenine (**2a**, **2b**), 2-amino-6-chloropurine (**8a**, **8b**), and also of 4-ethoxy-2-pyrimidone (**14a**, **14b**) using potassium carbonate. However, this method failed in the reaction of the mentioned nucleobases with cycloheptene oxide: we did not detect any product. Therefore, we made use of cesium carbonate and to enhance the dissociation of the cesium salt of the nucleobase we performed the reaction in the presence of Kryptofix 2.2.2., which for cesium is more suitable than 18-crown-6. In this manner we prepared all the racemic *trans*-2-hydroxycycloheptyl derivatives **2c**, **10c**,

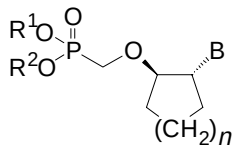


**1a,** R = H
**1b,** R = $CH_2OH$



**1c**





| | B | *n* |
|---|---|---|
| **2a** | A | 1 |
| **2b** | A | 2 |
| **2c** | A | 3 |
| **6a** | Hx | 1 |
| **6b** | Hx | 2 |
| **6c** | Hx | 3 |
| **8a** | $G^{Cl}$ | 1 |
| **8b** | $G^{Cl}$ | 2 |
| **9a** | G | 1 |
| **9b** | G | 2 |
| **9c** | G | 3 |
| **10a** | $G^{Bn}$ | 1 |
| **10b** | $G^{Bn}$ | 2 |
| **10c** | $G^{Bn}$ | 3 |
| **12a** | T | 1 |
| **12b** | T | 2 |
| **12c** | T | 3 |
| **14a** | $U^{Et}$ | 1 |
| **14b** | $U^{Et}$ | 2 |
| **15a** | U | 1 |
| **15b** | U | 2 |
| **15c** | U | 3 |
| **17a** | C | 1 |
| **17b** | C | 2 |
| **17c** | C | 3 |
| **17d** | 2-O-C | 2 |

| | B | $R^1$ | $R^2$ | *n* |
|---|---|---|---|---|
| **3a** | A | iPr | iPr | 1 |
| **3b** | A | iPr | iPr | 2 |
| **4a** | A | iPr | H | 1 |
| **4b** | A | iPr | H | 2 |
| **5a** | A | H | H | 1 |
| **5b** | A | H | H | 2 |
| **5c** | A | H | H | 3 |
| **7a** | Hx | H | H | 1 |
| **7b** | Hx | H | H | 2 |
| **7c** | Hx | H | H | 3 |
| **11a** | G | H | H | 1 |
| **11b** | G | H | H | 2 |
| **11c** | G | H | H | 3 |
| **13a** | T | H | H | 1 |
| **13b** | T | H | H | 2 |
| **13c** | T | H | H | 3 |
| **16a** | U | H | H | 1 |
| **16b** | U | H | H | 2 |
| **16c** | U | H | H | 3 |
| **18a** | C | H | H | 1 |
| **18b** | C | H | H | 2 |
| **18c** | C | H | H | 3 |

B = nucleobase
Hx = hypoxanthin-9-yl
$G^{Cl}$ = 2-amino-6-chloropurin-9-yl
$G^{Bn}$ = 6-*O*-benzylguanin-9-yl
$U^{Et}$ = 4-ethoxy-2-pyrimidon-1-yl
2-O-C = cytosin-2-*O*-yl

SCHEME 1

**12c**, **15c** and **17c**. The uracil 2-hydroxycycloheptyl derivative **15c** was isolated in low yield directly in reaction of cycloheptene oxide with 4-ethoxy-2-pyrimidone (the ethyl group was removed under the reaction conditions); in derivatives **14a** and **14b** the ethyl group was removed by treatment with bromotrimethylsilane under formation of free uracil derivatives **15a** and **15b**. We applied the cesium carbonate–Kryptofix 2.2.2. mixture also in the mentioned reactions of cyclopentene and cyclohexene oxide with nucleobases.

We also checked the preparation of the 2-hydroxycycloalkyl derivatives by the procedure employing DBU (ref.[8]) as deprotonation agent for the reaction of the nucleobase with cycloalkene oxides. Although the method afforded yields comparable with those obtained with cesium carbonate, the reaction mixtures contained numerous side-products (as found by HPLC) that made the isolation difficult. In the reaction of cytosine with cyclohexene oxide we isolated the *O*-substituted derivative **17d** in addition to the desired product **17b**.

For opening of the oxirane ring by nucleobases we also applied a method analogous to the silyl modification of the Hilbert–Jones nucleosidation reaction[9]. In this way, the silylated thymine was treated with cycloalkene oxides in dichloromethane in the presence of a Lewis acid to give thymine *trans*-2-hydroxycycloalkyl derivatives **12a**–**12c**. For cyclopentane the catalyst of choice was tin tetrachloride whereas for cyclohexene and cycloheptene oxide the best results were achieved with boron trifluoride etherate. On the other hand, the use of trimethylsilyl triflate or performing the reaction in acetonitrile as solvent or without solvent appeared as completely unsuitable. The yields depended on the magnitude of the cycloalkane ring that determined the reactivity of the oxirane ring (yield of compound **12b** amounted to 95% whereas products **12a** and **12c** were isolated in only 15% yield). Attempted preparation of adenine *trans*-2-hydroxycyclohexyl derivative **2b** by reaction of silylated 6-*N*-benzoyladenine or 6-*N*-(*N*,*N*-dibutylaminomethylene)adenine with cyclohexene oxide completely failed; treatment of the latter adenine derivative resulted only in loss of the amidine protecting group.

The structure of the above-mentioned compounds was verified by their NMR spectra. Using $^1$H NMR decoupling experiments we found that the coupling constants of carbocyclic ring protons, $J$(H-1′,H-2′), amounted to 5.5–7.5 Hz for the five-membered and 9.5–10.5 Hz for the six- and seven-membered rings. This corresponds to *trans*-configuration, and diaxial position, of protons H-1′ and H-2′. Also the chemical shifts of the carbon atoms C-1′ and C-2′ (Table I and II) correspond to values for *trans*-1,2-disubstituted cycloalkanes[11], being shifted downfield for about 5 ppm compared with the *cis*-isomers[10].

The chemical shifts of carbon atoms of the heterocyclic bases (Tables III and IV) were determined by measurement of J-modulated $^{13}$C NMR spectra (“attached proton test pulse sequence”). The downfield shifts of carbon atoms C-2 and C-4 (8–10 ppm)

found for thymidine derivatives **13a**–**13c** in alkaline medium of NaOD (Table V) can be explained by presence of the nucleobase as its 3-$N^{(-)}$ anion.

The antiviral effects of the nucleoside and nucleotide analogs prepared in this study were investigated in the laboratory of Professor E. De Clerq, Catholic University, Leuven (Belgium) and compared with those of PMEA. The effect was studied on virus-infected host cells in a cell culture, the compound being present in the medium for the whole cultivation period starting from the moment of virus infection. The cytopathic

TABLE I
Chemical shifts of carbon atoms in the carbocyclic ring of purine derivatives

| Compound | δ, ppm | | | | | | |
|---|---|---|---|---|---|---|---|
| | C-1′ | C-2′ | C-3′ | C-4′ | C-5′ | C-6′ | C-7′ |
| **2a** | 63.07 | 75.22 | 28.99 | 20.06 | 32.22 | – | – |
| **2b** | 61.01 | 70.12 | 35.23 | 24.24 | 24.99 | 31.41 | – |
| **2c** | 63.79 | 72.97 | 34.59 | 21.59 | 27.11 | 24.48 | 31.06 |
| **4a** | 60.59 | 85.54 | 29.63 | 21.17 | 30.07 | – | – |
| **4b** | 60.32 | 82.08 | 32.58 | 24.47 | 25.52 | 30.84 | – |
| **5a** | 62.17 | 87.04 | 30.26 | 21.71 | 31.02 | – | – |
| **5b** | 61.05 | 81.84 | 33.01 | 24.82 | 25.62 | 31.95 | – |
| **5c** | 63.92 | 85.49 | 32.27 | 22.91 | 28.61 | 25.77 | 30.89 |
| **6a** | 63.10 | 75.56 | 29.36 | 20.00 | 32.18 | – | – |
| **6b** | 63.17 | 70.51 | 34.67 | 24.07 | 24.74 | 30.96 | – |
| **6c** | 63.94 | 73.24 | 34.55 | 21.49 | 26.97 | 24.38 | 31.15 |
| **7a** | 62.49 | 87.61 | 30.40 | 21.80 | 31.12 | – | – |
| **7b** | 61.68 | 82.73 | 32.16 | 24.49 | 25.40 | 31.22 | – |
| **7c** | 63.87 | 85.54 | 32.44 | 22.85 | 28.48 | 25.52 | 30.65 |
| **8a** | 62.73 | 74.92 | 28.73 | 19.82 | 31.96 | – | – |
| **8b** | 60.73 | 70.09 | 35.09 | 24.14 | 24.94 | 31.10 | – |
| **9a** | 62.30 | 75.28 | 29.50 | 20.15 | 32.33 | – | – |
| **9b** | 59.97 | 70.24 | 35.33 | 24.17 | 25.01 | 31.85 | – |
| **9c** | 62.80 | 73.23 | 34.67 | 21.59 | 27.14 | 24.44 | 31.37 |
| **11a** | 61.45 | 87.62 | 30.44 | 21.90 | 31.19 | – | – |
| **11b** | 59.68 | 82.53 | 33.03 | 24.67 | 25.45 | 31.50 | – |
| **11c** | 62.43 | 85.87 | 32.40 | 22.84 | 28.32 | 25.17 | 30.36 |

effect of the virus was evaluated against a control, at the moment when the cytopathic changes in the control reached 100%. Systematically was studied the effect on herpetic viruses herpes simplex type 1 and 2 (HSV-1, HSV-2) and vaccinia virus (VV) as representatives of DNA viruses, on vesicular stomatitis virus (VSV) and in many cases also on reovirus type 1, parainfluenzavirus 3, poliovirus and sindbisvirus as representatives of RNA viruses, and finally retroviruses such as human immunodeficiency virus type 1

TABLE II
Chemical shifts of carbon atoms in the carbocyclic ring of pyrimidine derivatives

| Compound | δ, ppm | | | | | | |
|---|---|---|---|---|---|---|---|
| | C-1′ | C-2′ | C-3′ | C-4′ | C-5′ | C-6′ | C-7′ |
| **12a** | 63.50 | 73.75 | 27.52 | 19.55 | 31.84 | – | – |
| **12b** | 60.28 | 68.97 | 35.14 | 24.07 | 25.05 | 30.10 | – |
| **12c** | 63.77 | 71.90 | 34.46 | 19.04 | 26.76 | 24.55 | 29.93 |
| **13a** | 64.14 | 86.92 | 29.89 | 22.10 | 30.79 | – | – |
| **13a**[a] | 63.73 | 87.54 | 30.93 | 22.31 | 31.17 | – | – |
| **13b**[a] | 60.66 | 81.98 | 32.34 | 25.04 | 25.99 | 27.88 | – |
| **13c** | 64.00 | 85.28 | 30.88 | 22.12 | 28.29 | 26.02 | 30.03 |
| **13c**[a] | 63.70 | 85.95 | 32.24 | 22.56 | 28.73 | 26.32 | 30.96 |
| **14a** | 66.18 | 73.97 | 28.06 | 19.93 | 32.25 | – | – |
| **14b** | –[b] | 69.09 | 35.31 | 24.13 | 25.08 | 30.64 | – |
| **15a** | 64.10 | 73.87 | 27.58 | 19.63 | 31.89 | – | – |
| **15b** | 60.55 | 69.01 | 35.15 | 24.02 | 25.02 | 30.09 | – |
| **15c** | 62.30 | 71.97 | 34.59 | 21.30 | 26.84 | 24.65 | 29.95 |
| **16a** | 64.44 | 86.76 | 29.86 | 22.10 | 30.70 | – | – |
| **16b** | 60.96 | 81.48 | 31.35 | 24.71 | 25.71 | 31.49 | – |
| **16c** | –[b] | 85.56 | 31.51 | 22.77 | 28.91 | 26.58 | 30.62 |
| **17a** | 65.40 | 74.18 | 28.41 | 20.15 | 32.52 | – | – |
| **17b** | 61.22 | 69.29 | 35.53 | 24.28 | 25.21 | 31.02 | – |
| **17c** | 72.09 | 78.59 | 34.81 | 21.37 | 27.20 | 25.04 | 30.74 |
| **18a** | 65.77 | 86.34 | 29.50 | 21.80 | 30.34 | – | – |
| **18b**[a] | 62.10 | 81.05 | 32.21 | 24.84 | 25.80 | 31.83 | – |
| **18c**[a] | 64.37 | 85.20 | 31.44 | 22.26 | 28.37 | 26.13 | 30.30 |

[a] Measured after addition of a greater amount of NaOD (3-*N*-deprotonated form). [b] Very broad signal, exact value of chemical shift not determined.

and 2 (HIV 1, HIV 2) and Moloney sarcoma virus (MSV). Neither of the tested compounds was active against the mentioned DNA viruses and retroviruses.

The assumed mechanism of the antiviral effect of these compounds (inhibition of DNA polymerase or reverse transcriptase by diphosphoryl derivatives of phosphonate nucleotides, analogous to nucleoside triphosphates) depends on many factors such as cellular uptake, phosphorylation to give a triphosphate analog, and inhibition of the pertinent enzyme. As the first in succession, the cellular uptake has a specific position.

TABLE III
Chemical shifts of carbon atoms of the heterocyclic base in purine derivatives

| Compound | δ, ppm | | | | |
|---|---|---|---|---|---|
| | C-2 | C-4 | C-5 | C-6 | C-8 |
| **2a** | 152.29 | 149.83 | 119.51 | 156.23 | 140.23 |
| **2b** | 152.03 | 149.86 | 119.34 | 156.10 | 140.44 |
| **2c** | 152.05 | 149.56 | 119.34 | 156.09 | 140.55 |
| **4a** | 151.36 | 149.39 | 119.28 | 155.45 | 140.38 |
| **4b** | 152.97 | 150.08 | 119.57 | 155.70 | 142.71 |
| **5a** | 153.04 | 149.71 | 119.52 | 156.14 | 141.74 |
| **5b** | 153.40 | 150.14 | 119.87 | 156.68 | 142.81 |
| **5c** | 153.56 | 150.04 | 118.30 | 156.89 | 141.60 |
| **6a** | 145.23 | 148.63 | 124.59 | 156.86 | 140.00 |
| **6b** | 148.07 | 147.77 | 118.15 | 154.35 | 141.30 |
| **6c** | 144.94 | 148.38 | 124.29 | 156.96 | 139.78 |
| **7a** | 146.52 | 149.90 | 124.64 | 159.64 | 141.83 |
| **7b** | 147.97 | 149.57 | 120.98 | 157.89 | 140.99 |
| **7c** | 147.82 | 149.87 | 124.59 | 161.27 | 140.00 |
| **8a** | 159.68 | 154.45 | 123.96 | 149.49 | 142.40 |
| **8b** | 159.63 | 154.56 | 123.86 | 149.24 | 142.60 |
| **9a** | 153.91 | 151.64 | 116.99 | 157.41 | 136.40 |
| **9b** | 153.26 | 151.54 | 116.81 | 157.12 | 136.46 |
| **9c** | 153.29 | 151.28 | 116.76 | 157.25 | 136.75 |
| **11a** | 154.67 | 152.63 | 117.12 | 160.02 | 132.09 |
| **11b** | 154.57 | 152.74 | 116.95 | 159.95 | 142.61 |
| **11c** | 154.65 | 152.46 | 117.03 | 160.12 | 139.68 |

Recent studies with radioactive PMEA have shown that the transport of this compound across the plasma membrane is a highly selective process[12]. Consequently, even so-called "similar compounds" may not penetrate the cell and without radioactive tracing a study of cellular uptake is practically impossible. Further biochemical studies on the synthesized compounds will be published elsewhere.

TABLE IV
Chemical shifts of carbon atoms of the heterocyclic base in pyrimidine derivatives

| Compound | δ, ppm | | | | | |
|---|---|---|---|---|---|---|
| | C-2 | C-4 | C-5 | C-6 | $CH_2$ | $CH_3$ |
| **12a** | 151.47 | 164.03 | 109.02 | 138.72 | – | 12.23 |
| **12b** | 151.58 | 164.02 | 108.53 | 138.56 | – | 12.28 |
| **12c** | 151.28 | 164.10 | 108.31 | 139.54 | – | 12.23 |
| **13a** | 153.55 | 167.67 | 112.57 | 141.23 | – | 12.81 |
| **13a**[a] | 161.51 | 177.61 | 112.69 | 139.77 | – | 13.97 |
| **13b**[a] | 161.99 | 177.54 | 112.40 | 139.56 | – | 14.04 |
| **13c** | 153.71 | 167.73 | 112.23 | 142.00 | – | 12.56 |
| **13c**[a] | 161.60 | 177.55 | 112.41 | 140.32 | – | 13.99 |
| **14a** | 155.88 | 170.24 | 94.51 | 147.06 | 62.18 | 14.27 |
| **14b** | 155.99 | 169.95 | 94.15 | –[b] | 62.05 | 14.32 |
| **15a** | 151.51 | 163.53 | 101.40 | 143.29 | – | – |
| **15b** | 151.62 | 163.48 | 100.99 | 142.91 | – | – |
| **15c** | 151.39 | 163.66 | 100.82 | 144.15 | – | – |
| **16a** | 153.48 | 167.41 | 103.29 | 145.65 | – | – |
| **16b** | 154.02 | 167.42 | 103.21 | 145.07 | – | – |
| **16c** | 154.26 | 168.17 | 103.51 | –[b] | – | – |
| **17a** | 156.36 | 165.49 | 93.64 | 143.76 | – | – |
| **17b** | 156.51 | 165.30 | 93.40 | 143.23 | – | – |
| **17c** | 156.40 | 165.30 | 93.00 | 144.40 | – | – |
| **18a** | 151.28 | 160.85 | 96.21 | 148.04 | – | – |
| **18b**[a] | 159.99 | 166.84 | 97.22 | 144.83 | – | – |
| **18c**[a] | 158.16 | 165.80 | 96.85 | 146.38 | – | – |

[a] Measured after addition of a greater amount of NaOD (3-*N*-deprotonated form). [b] Very broad signal, exact value of chemical shift not determined.

## EXPERIMENTAL

Unless stated otherwise, the 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. The yields of the products are related to the starting nucleobase.

TABLE V
Selected chemical shifts and coupling constants of phosphonomethoxycycloalkyl derivatives

| Compound | δ, ppm; *J*, Hz | | | | |
|---|---|---|---|---|---|
| | C-2′ | $^{3}J$(P,C-2′) | P-C | $^{1}J$(P-C,P) | $^{31}$P |
| **4a**[a] | 85.54 | 11.75 | 64.22 | 162.3 | – |
| **4b**[a] | 82.08 | 12.7 | 64.29 | 159.2 | – |
| **5a** | 87.04 | 12.2 | 67.42 | 154.9 | 14.55 |
| **5b** | 81.84 | 9.9 | 68.22 | 150.3 | 13.02 |
| **5c** | 85.49 | 10.7 | 68.74 | 151.1 | 14.17 |
| **7a** | 87.61 | 12.2 | 66.81 | 157.2 | 16.38 |
| **7b** | 82.73 | 10.7 | 65.23 | 157.2 | 17.56 |
| **7c** | 85.54 | 10.7 | 68.47 | 151.1 | 14.30 |
| **11a** | 87.62 | 11.5 | 66.99 | 155.6 | 16.23 |
| **11b** | 82.53 | 12.2 | 66.20 | 157.2 | 14.41 |
| **11c** | 85.87 | 11.4 | 67.12 | 154.9 | 15.67 |
| **13a** | 86.92 | 12.2 | 66.71 | 157.2 | 16.16 |
| **13a**[b] | 87.54 | 12.2 | 68.74 | 151.1 | 14.13 |
| **13b**[b] | 81.98 | 11.45 | 68.56 | 151.1 | 14.38 |
| **13c** | 85.28 | 9.0 | 66.11 | 157.2 | 16.59 |
| **13c**[b] | 85.95 | 10.7 | 68.89 | 151.1 | 14.42 |
| **16a** | 86.76 | 12.2 | 67.24 | 154.9 | 15.96 |
| **16b** | 81.48 | 11.4 | 66.46 | 156.4 | 16.34 |
| **16c** | 85.56 | 9.9 | 68.19 | 156.3 | 16.32 |
| **18a** | 86.34 | 11.4 | 66.43 | 157.2 | 16.76 |
| **18b** | 81.05 | 10.7 | 68.48 | 150.3 | 14.41 |
| **18c** | 85.20 | 9.2 | 66.17 | 157.2 | 16.93 |

[a] In $(CD_3)_2SO$. Further signals **4a**: 23.96 d, $^{3}J$(P,C) = 3.0 ($CH_3$); 69.20 d, $^{2}J$(P,C) = 5.3 (POC). **4b**: 23.91 d, $^{3}J$(P,C) = 3.1 ($CH_3$); 24.08 d, $^{3}J$(P,C) = 3.9 ($CH_3$); 70.01 d, $^{2}J$(P,C) = 4.9 (POC). [b] Measured after addition of a greater amount of NaOD.

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 (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- or diesters of phosphonic acids; pink coloration: tosyl or acyl groups; red-violet coloration 2-amino-6-chloropurine derivatives).

Preparative column chromatography (PLC) was carried out on 20–40 μm spherical silica gel (Tessek, Prague); the amount of adsorbent was 20–40 times the weight of the separated mixture. Elution was performed at 0.5 MPa overpressure. TLC was carried out with the following solvent systems: toluene–ethyl acetate 4 : 1 (T1), 1 : 1 (T2); chloroform–ethanol 19 : 1 (C1), 9 : 1 (C2), 4 : 1 (C3); ethyl acetate–acetone–ethanol–water 4 : 1 : 1 : 1 (H1), 6 : 1 : 1 : 1 (H2), 12 : 2 : 2 : 1 (H3); for phosphonates 2-propanol–ammonia–water 7 : 1 : 2 (I).

Preparative chromatography on reversed phase was carried out on a spherical octadecylsilica gel 20–40 μm (Tessek, Prague). Compounds were eluted with a linear gradient of methanol in water.

Desalting of aqueous and aqueous-alcoholic solutions was performed on a column of a cation-exchanging resin (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-exchanging resin 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 $l^{-1}$).

HPLC analyses were performed on a reversed phase (C18) Separon SGX-RPS 7 μm (Laboratorni pristroje, Prague); isocratic elution with 0.1 M triethylammonium acetate or gradient of methanol in 0.1 M triethylammonium acetate.

Electrophoreses were performed on Whatman No. 3 MM or Whatman No. 1 paper in 0.1 M triethylammonium hydrogen carbonate (pH 7.5) at 20 V/cm. The electrophoretic mobilities ($E_{Up}$) relate to uridine 5′-phosphate.

The UV spectra ($\lambda_{max}$, nm) were measured in 0.01 M hydrochloric acid on a Beckmann DU65 spectrophotometer.

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 (ioinization with $Cs^+$, accelerating voltage 35 kV) techniques. Glycerol and thioglycerol were used as matrices.

Proton NMR spectra were measured on a Varian Unity 500 spectrometer ($^1H$ at 500 MHz, $^{13}C$ at 125.7 MHz) in deuterated dimethyl sulfoxide with tetramethylsilane as internal standard. The free phosphonic acids were measured in deuterium oxide containing sodium deuteride, 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 ($\delta$(dioxane) = 66.86). Phosphorus-31 NMR spectra were measured on a Varian Unity 200 spectrophotometer ($^{31}P$ at 81 MHz) in deuterium oxide with $H_3PO_4$ as external standard.

Preparation of (±)-*trans*-2-Hydroxycycloalkyl Derivatives **2a**, **2b**, **8a**, **8b**, **14a** and **14b**

*Method A.* A stirred mixture of cyclohexene oxide or cyclopentene oxide (1.1 equiv.), the nucleobase (1 equiv.), finely ground potassium carbonate (2 equiv.), Kryptofix 2.2.2. (0.1 equiv.) and DMF (10 ml per mmol of the nucleobase) was heated (calcium chloride tube) for 8–16 h at 120–125 °C and the reaction was monitored by TLC (in the system H3 all products were faster than the starting nucleobase). After evaporation of the solvent in vacuo, the residue was chromatographed on a column of

silica gel (10 g per mmol of the starting nucleobase), elution with a stepwise gradient of ethanol in chloroform (4–6%, depending on the nucleobase).

Preparation of (±)-*trans*-2-Hydroxycycloalkyl Derivatives **2c**, **10a**–**10c** and **17a**–**17c**

Method *B*. The same procedure as described for *A* but cesium carbonate was used instead of potassium carbonate.

*9-(trans-2-Hydroxycyclopentyl)adenine* (**2a**). Prepared by method *A* from adenine (30 mmol). Crystallization from acetone afforded 3.30 g (50%) of product **2a**, m.p. 198 °C. 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: 54.42% C, 5.88% H, 31.92% N. MS (FAB): 220 (M + $H^+$), 136 (adenine + $H^+$). $^1$H NMR spectrum: 1.50–2.15 m, 6 H ($CCH_2$); 4.46 qd, 1 H, *J* = 4.9, 7.3, 7.3, 7.3 (OCH); 4.49 q, 1 H, *J* = 7.3 (NCH); 5.21 d, 1 H, *J*(OH,CH) = 4.9 (OH); 7.24 br s, 2 H, ($NH_2$); 8.14 s, 1 H and 8.17 s, 1 H (H-2, H-8).

*9-(trans-2-Hydroxycyclohexyl)adenine* (**2b**). Prepared by method *A* from adenine (30 mmol). Recrystallization of the crude product from ethyl acetate afforded 4.50 g (75%) of compound **2b**, m.p. 299 °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: 56.72% C, 6.51% H, 29.87% N. MS (FAB): 234 (M + $H^+$), 136 (adenine + $H^+$). $^1$H NMR spectrum: 1.20–1.50 m, 3 H, and 1.60–2.20 m, 5 H ($CCH_2$); 4.00 br td, 1 H, *J*(a,e) = 4.6, *J*(a,a) = 10.0 and 10.0 (OCH); 4.09 td, 1 H, *J*(a,e) = 4.3, *J*(a,a) = 10.0 and 10.3 (NCH); 4.85 br s, 1 H (OH); 7.12 br s, 2 H ($NH_2$); 8.10 s, 1 H and 8.13 s, 1 H (H-2, H-8).

*9-(trans-2-Hydroxycycloheptyl)adenine* (**2c**). Prepared by method *B* from adenine (3 mmol). Crystallization from ethyl acetate–diethyl ether afforded 0.27 g of the product (36%), m.p. 254 °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: 58.35% C, 6.93% H, 28.48% N. MS (FAB): 248 (M + $H^+$), 136 (adenine + $H^+$). $^1$H NMR spectrum: 1.40–2.20 m, 10 H ($CCH_2$); 4.13 m, 1 H (OCH); 4.24 td, 1 H, *J* = 2.8, 9.5, 9.5 (NCH); 4.83 d, 1 H, *J*(OH,CH) = 4.9 (OH); 7.16 br s, 2 H ($NH_2$); 8.12 s, 1 H and 8.14 s, 1 H (H-2, H-8).

*9-[trans-2-(Diisopropylphosphonomethoxy)cyclopentyl]adenine* (**3a**). A mixture of nucleoside **2a** (2.19 g, 10 mmol), dimethylformamide dimethyl acetal (4 ml, 30 mmol) and DMF (25 ml) was stirred for 72 h at room temperature. The excess acetal was destroyed by addition of water (10 ml) and the solvent was evaporated. The residue was dried by codistillation with DMF (3 × 20 ml). The obtained 6-*N*-(*N*,*N*-dimethylaminomethylene) derivative of compound **2a** was used without purification in the next step. A solution of the protected derivative of compound **2a** (2.74 g, 10 mmol) and diisopropyl tosyloxymethanephosphonate (4.2 g, 12 mmol) in DMF (50 ml) was cooled in a dry ice bath, sodium hydride (1.2 g of 60% suspension in mineral oil, 30 mmol) was added and the reaction mixture was vigorously stirred, first 2 h at –78 °C and then 24 h at room temperature. The excess sodium hydride was destroyed with acetic acid (1.2 ml, 20 mmol) and the reaction mixture was diluted with 28% aqueous ammonia (500 ml). After standing for 24 h, the homogeneous solution was taken down and deionized on cation exchanger Dowex 50W X 2 ($H^+$ form). The crude diisopropyl phosphonate was purified by chromatography on silica gel in a gradient of ethanol in chloroform (up to 12% of ethanol). Yield of the diisopropyl ester **3a** 2.00 g (50%), m.p. 104 °C. UV spectrum: 261 (pH 2), 262 (pH 12). For $C_{17}H_{28}N_5O_4P$ (397.4) calculated: 51.38% C, 7.10% H, 17.62% N 7.79% P; found: 51.32% C, 7.11% H, 17.42% N 7.94% P. MS (FAB): 398 (M + $H^+$), 136 (adenine + $H^+$). $^1$H NMR spectrum: 1.07 d, 3 H, *J*(CH,$CH_3$) = 6.1 ($CH_3$); 1.08 d, 3 H, *J*(CH,$CH_3$) = 6.1 ($CH_3$); 1.11 d, 3 H, *J*(CH,$CH_3$) = 6.1 ($CH_3$); 1.15 d, 3 H, *J*(CH,$CH_3$) = 6.1 ($CH_3$); 1.66–1.93 m, 3 H, and 2.05–2.24 m, 3 H ($CCH_2$); 3.67 dd, 1 H, *J*(P,CH) = 9.0, *J*(gem) = 13.7 and 3.71 dd, 1 H, *J*(P,CH) = 9.0, *J*(gem) = 13.7 ($PCH_2$); 4.42 qd, 1 H, *J* = 6.1, *J*(P,H) = 1.5 (OCH); 4.47 dsept, 1 H, *J*(CH,$CH_3$) = 6.1, *J*(P,OCH) = 7.8 (POCH); 4.48 dsept, 1 H, *J*(CH,$CH_3$) = 6.1, *J*(P,OCH) = 7.8 (POCH); 4.73 td, 1 H, *J* = 6.1, 8.8, 8.8 (NCH); 7.23 br s, 2 H ($NH_2$); 8.13 s, 1 H and 8.23 s, 1 H (H-2, H-8). $^{31}$P NMR spectrum: 19.98 s (P).

*9-[trans-2-(Diisopropylphosphonomethoxy)cyclohexyl]adenine* (**3b**). Diisopropyl phosphonate **3b** was prepared from compound **2b** (2.33 g, 10 mmol) as described for the cyclopentane derivative **3a**. Yield 2.30 g (56%) of diisopropyl ester **3b**, m.p. 123 °C. UV spectrum: 261 (pH 2), 262 (pH 12). For $C_{18}H_{30}N_5O_4P$ (411.4) calculated: 52.55% C, 7.35% H, 17.02% N, 7.53% P; found: 52.44% C, 7.40% H, 17.03% N, 7.76% P. MS (FAB): 412 (M + $H^+$), 136 (adenine + $H^+$). $^1$H NMR spectrum: 0.91 d, 3 H, *J*(CH,$CH_3$) = 6.1 ($CH_3$); 0.99 d, 3 H, *J*(CH,$CH_3$) = 6.1 ($CH_3$); 1.01 d, 3 H, *J*(CH,$CH_3$) = 6.1 ($CH_3$); 1.08 d, 3 H, *J*(CH,$CH_3$) = 6.1 ($CH_3$); 1.20 m, 1 H, 1.36 m, 2 H, 1.77 m, 1 H, 1.90 m, 1 H, 2.05 m, 1 H, and 2.35 m, 1 H ($CCH_2$); 3.32 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 13.7 and 3.68 dd, 1 H, *J*(P,CH) = 9.3, *J*(gem) = 13.7 ($PCH_2$); 4.06 td, 1 H, *J*(a,e) = 4.4, *J*(a,a) = 10.5 and 10.7 (OCH); 4.19 dsept, 1 H, *J*(CH,$CH_3$) = 6.1, *J*(P,OCH) = 7.6 (POCH); 4.28 dsept, 1 H, *J*(CH,$CH_3$) = 6.1, *J*(P,OCH) = 7.6 (POCH); 4.29 m, 1 H (NCH); 7.15 br s, 2 H ($NH_2$); 8.10 s, 1 H and 8.19 s, 1 H (H-2, H-8). $^{31}$P NMR spectrum: 19.59 s (P).

*9-[trans-2-(Isopropylphosphonomethoxy)cyclopentyl]adenine* (**4a**). A solution of diester **3a** (0.4g, 1 mmol) in aqueous 2 M sodium hydroxide (10 ml) was heated at 80 °C until it disappeared (6 h) (TLC, H3). Deionization on Dowex 50W X 2 ($H^+$ form) and drying afforded 0.35 g (98%) of amorphous monoester **4a**. UV spectrum: 261 (pH 2), 262 (pH 12). For $C_{14}H_{22}N_5O_4P$ (355.3) calculated: 47.32% C, 6.24% H, 19.71% N; found: 46.98% C, 6.08% H, 19.52% N. MS (FAB): 356 (M + $H^+$), 314 (M + $H^+$ – $C_3H_7$). $^1$H NMR spectrum: 1.05 d, 3 H, *J*(CH,$CH_3$) = 6.1 ($CH_3$); 1.07 d, 3 H, *J*(CH,$CH_3$) = 6.1 ($CH_3$); 1.66–1.72 m, 1 H, 1.75–1.82 m, 1 H, 1.84–1.92 m, 1 H, 2.06 m, 1 H, 2.16 m, 1 H, and 2.22 m, 1 H ($CCH_2$); 3.56 d, 2 H, *J*(P,CH) = 9.3 ($PCH_2$); 4.36 dsept, 1 H, *J*(CH,$CH_3$) = 6.1, *J*(P,OCH) = 8.1 (POCH); 4.42 dt, 1 H, *J* = 5.9, 5.9 and 6.8 (OCH); 4.75 td, 1 H, *J* = 5.9, 8.5 and 8.5 (NCH); 7.52 br s, 2 H ($NH_2$); 8.16 s, 1 H and 8.29 s, 1 H (H-2, H-8).

*9-[trans-2-(Isopropylphosphonomethoxy)cyclohexyl]adenine* (**4b**). The title compound was prepared from diester **3b** (0.41 g, 1 mmol) in the same manner as the cyclopentane derivative **4a**. Yield of amorphous product **4b** was 0.36 g (97%). UV spectrum: 261 (pH 2), 262 (pH 12). For $C_{15}H_{24}N_5O_4P$ (369.4) calculated: 48.78% C, 6.55% H, 18.96% N; found: 48.42% C, 6.44% H, 18.92% N. MS (FAB): 370 (M + $H^+$), 328 (M + $H^+$ – $C_3H_7$). $^1$H NMR spectrum: 0.83 d, 3 H, *J*(CH,$CH_3$) = 6.1 ($CH_3$); 0.87 d, 3 H, *J*(CH,$CH_3$) = 6.1 ($CH_3$); 1.36 m, 1 H, 1.45 m, 2 H, 1.88 m, 2 H, 2.04 m, 1 H, 2.12 m, 1 H, and 2.43 m, 1 H ($CCH_2$); 3.26 dd, 1 H, *J*(P,CH) = 9.0, *J*(gem) = 13.4 and 3.61 dd, 1 H, *J*(P,CH) = 9.8, *J*(gem) = 13.4 ($PCH_2$); 3.92–4.00 m, 2 H (OCH, POCH); 4.44 ddd, 1 H, *J* = 4.4, 10.3 and 12.4 (NCH); 8.33 s, 1 H and 8.42 s, 1 H (H-2, H-8).

*9-(trans-2-Phosphonomethoxycyclopentyl)adenine* (**5a**). A solution of diester **4a** (2 g, 5 mmol) and trimethylsilyl bromide (4 ml, 30 mmol) in anhydrous acetonitrile (50 ml) was set aside at room temperature for 5 days, then the solvent was evaporated, the residue was dissolved in water and made alkaline with ammonia to pH 8–9. Chromatography on Dowex 1 X 2 (acetate form) and subsequent crystallization from water afforded 1.17 g (75%) of phosphonate **5a**, m.p. 230 °C. UV spectrum: 261 (pH 2), 262 (pH 12). For $C_{11}H_{16}N_5O_4P$ (313.3) calculated: 42.18% C, 5.15% H, 22.36% N, 9.89% P; found: 41.99% C, 6.93% H, 22.11% N, 9.84% P. MS (FAB): 358 (M + 2 Na), 336 (M + Na), 314 (M + $H^+$), 136 (adenine + $H^+$). $^1$H NMR spectrum: 1.80–2.05 m, 4 H, and 2.12–2.48 m, 2 H ($CCH_2$); 3.55 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 12.7 and 3.63 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 12.7 ($PCH_2$); 4.40 br q, 1 H, *J* = 5.9 (OCH); 4.75 td, 1 H, *J* = 6.1, 7.6 and 7.6 (NCH); 8.06 s, 1 H and 8.19 s, 1 H (H-2, H-8).

*9-(trans-2-Phosphonomethoxycyclohexyl)adenine* (**5b**). Compound **5b** was prepared from diester **3b** (2.05 g, 5 mmol) in the same manner as described for the cyclopentane derivative **5a**. Yield of the product **5b** was 1.38 g (82%), m.p. 309 °C. UV spectrum: 261 (pH 2), 262 (pH 12). For $C_{12}H_{18}N_5O_4P$ (327.3) calculated: 44.04% C, 5.54% H, 21.40% N, 9.46% P; found: 44.16% C, 5.59% H, 21.63% N, 9.87% P. MS (FAB): 372 (M + 2 Na), 350 (M + Na), 328 (M + $H^+$), 136 (adenine + $H^+$). $^1$H NMR spectrum: 1.35–1.50 m, 3 H, 1.79–1.90 m, 3 H, 1.99 m, 1 H and 2.45 m, 1 H ($CCH_2$); 3.08 dd,

1 H, *J*(P,CH) = 8.5, *J*(gem) = 12.5 and 3.28 dd, 1 H, *J*(P,CH) = 10.0, *J*(gem) = 12.5 ($PCH_2$); 3.96 td, 1 H, *J*(a,e) = 4.4, *J*(a,a) = 10.3 and 10.3 (OCH); 4.30 td, 1 H, *J*(a,e) = 4.4, *J*(a,a) = 10.3 and 10.5 (NCH); 8.16 s, 1 H and 8.28 s, 1 H (H-2, H-8).

*9-(trans-2-Phosphonomethoxycycloheptyl)adenine* (**5c**). Diisopropyl ester of compound **5c** was prepared from compound **2c** (0.25 g, 1 mmol) as described for the cyclopentane derivative **3a**. After deionization, the crude diester was further purified by reversed-phase chromatography, elution with a linear gradient of methanol in water (50–75% v/v). The ester groups were removed with bromotrimethylsilane as described for compound **5a**. The free phosphonate **5c** was purified by reversed-phase chromatography, linear gradient of methanol in water (0–50% v/v). Lyophilization of the aqueous solution afforded 0.20 g (59%) of phosphonate **5c**. UV spectrum: 261 (pH 2), 262 (pH 12). For $C_{13}H_{20}N_5O_4P$ (341.2) calculated: 45.75% C, 5.91% H, 20.52% N, 9.08% P; found: 45.55% C, 5.85% H, 20.16% N, 9.28% P. MS (FAB): 364 (M + Na), 342 (M + $H^+$), 136 (adenine + $H^+$). $^1$H NMR spectrum: 1.60 m, 2 H, 1.65–1.90 m, 6 H, and 2.10 m, 2 H ($CCH_2$); 3.02 dd, 1 H, *J*(P,CH) = 8.6, *J*(gem) = 12.2 and 3.26 dd, 1 H, *J*(P,CH) = 10.3, *J*(gem) = 12.2 ($PCH_2$); 4.00 ddd, 1 H, *J* = 3.6, 7.6 and 9.3 (OCH); 4.50 td, 1 H, *J* = 3.0, 9.5 and 9.8 (NCH); 8.22 s, 1 H and 8.30 s, 1 H (H-2, H-8).

*9-(trans-2-Hydroxycyclopentyl)hypoxanthine* (**6a**). A solution of nucleoside **2a** (0.44 g, 2 mmol) and isoamyl nitrite (2 ml, 15 mmol) in 80% aqueous acetic acid (50 ml) was allowed to stand at room temperature for 6 days. After removal of the volatile part in vacuo and several codistillations of the residue with water, the crude product was purified by reversed-phase chromatography, elution with linear gradient of methanol in water (0–50% v/v). Yield 0.40 g (91%) of compound **6a**, m.p. >260 °C (decomp). UV spectrum: 251 (pH 2), 255 (pH 12). For $C_{10}H_{12}N_4O_2$ (220.2) calculated: 54.54% C, 5.49% H, 25.44% N; found: 53.67% C, 5.43% H, 25.23% N. MS (FAB): 243 (M + Na), 221 (M + $H^+$), 137 (hypoxanthine + $H^+$). $^1$H NMR spectrum: 1.56 m, 1 H, 1.80 m, 2 H, 2.00 m, 2 H and 2.17 m, 1 H ($CCH_2$); 4.41 qd, 1 H, *J* = 4.9, 7.1, 7.1 and 7.1 (OCH); 4.48 dt, 1 H, *J* = 7.1, 7.3 and 8.8 (NCH); 5.16 d, 1 H, *J*(OH,CH) = 5.0; 8.02 s, 1 H and 8.14 s, 1 H (H-2, H-8); 12.27 br s; 1 H (NH).

*9-(trans-2-Hydroxycyclohexyl)hypoxanthine* (**6b**). Compound **6b** was prepared from derivative **2b** (0.47g, 2 mmol) by the same procedure as described for the cyclopentane derivative **6a**. The product crystallized from the reaction mixture. Yield 0.43 g (92%), m.p. >246 °C (decomp.). UV spectrum: 250 (pH 2), 255 (pH 12). For $C_{11}H_{14}N_4O_2$ (234.3) calculated: 56.40% C, 6.02% H, 23.92% N; found: 44.21% C, 5.09% H, 23.33% N. MS (FAB): 257 (M + Na), 235 (M + $H^+$), 137 (hypoxanthine + $H^+$). $^1$H NMR spectrum: 1.34 m, 3 H, 1.75 m, 2 H, and 2.01 m, 3 H ($CCH_2$); 3.94 td, 1 H, *J* = 4.9, 9.8 and 10.1 (OCH); 4.25 td, 1 H, *J* = 7.0, 9.8 and 9.8 (NCH); 8.20 br s, 1 H (OH); 8.29, 1 H and 9.26 s, 1 H (H-2, H-8); 13.05 br s, 1 H (NH).

*9-(trans-2-Hydroxycycloheptyl)hypoxanthine* (**6c**). Compound **6c** was prepared from derivative **2c** (0.125 g, 0.5 mmol) and isoamyl nitrite (1 ml, 7.5 mmol) in 80% acetic acid (20 ml) in the same manner as described for the cyclopentane derivative **6a**. Yield 0.11 g (89%), m.p. >285 °C (decomp.). UV spectrum: 251 (pH 2), 255 (pH 12). For $C_{12}H_{16}N_4O_2$ (248.3) calculated: 58.05% C, 6.50% H, 22.57% N; found: 55.80% C, 6.52% H, 21.26% N. MS (FAB): 249 (M + $H^+$), 137 (hypoxanthine + $H^+$). $^1$H NMR spectrum: 1.50–1.90 m, 9 H, and 1.99 m, 1 H ($CCH_2$); 4.05 m, 1 H (OCH); 4.22 ddd, 1 H, *J* = 3.2, 9.3 and 10.5 (NCH); 4.85 d, 1 H, *J*(OH,CH) = 5.1 (OH); 7.99 s, 1 H and 8.10 s, 1 H (H-2, H-8); 12.20 br s; 1 H (NH).

*9-(trans-2-Phosphonomethoxycyclopentyl)hypoxanthine* (**7a**). Compound **7a** was prepared from derivative **5a** (0.31 g, 1 mmol) and isoamyl nitrite (2 ml, 15 mmol) in 80% acetic acid (50 ml) in the same manner as described for the cyclopentane derivative **6a**. Yield 0.30 g (96%) (lyophilizate). UV spectrum: 251 (pH 2), 256 (pH 12). For $C_{11}H_{15}N_4O_5P$ (314.2) calculated: 42.04% C, 4.81% H, 17.83% N, 9.86% P; found: 42.02% C, 4.88% H, 17.72% N, 9.66% P. MS (FAB): 315 (M + $H^+$). $^1$H NMR spectrum: 1.87 m, 1 H, 1.95 m, 2 H, 2.04 m, 1 H, 2.25 m, 1 H, and 2.40 m, 1 H ($CCH_2$); 3.56 dd,

1 H, *J*(P,CH) = 9.5, *J*(gem) = 13.0 and 3.60 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 13.0 ($PCH_2$); 4.42 dt, 1 H, *J* = 5.6, 5.6 and 7.1 (OCH); 4.84 m, 1 H (NCH); 8.18 s, 1 H and 8.25 s, 1 H (H-2, H-8).

*9-(trans-2-Phosphonomethoxycyclohexyl)hypoxanthine* (**7b**). Compound **7b** was prepared from derivative **5b** (0.33 g, 1 mmol) and isoamyl nitrite (2 ml, 15 mmol) in 80% acetic acid (50 ml) in the same way as described for the cyclopentane derivative **6a**. Yield 0.31 g (95%) of lyophilizate **7b**. UV spectrum: 251 (pH 2), 256 (pH 12). For $C_{12}H_{17}N_4O_5P$ (328.3) calculated: 43.91% C, 5.22% H, 17.07% N, 9.44% P; found: 43.72% C, 5.48% H, 17.02% N, 9.28% P. MS (FAB): 351 (M + Na), 329 ($M + H^+$), 137 (hypoxanthine + $H^+$). $^1$H NMR spectrum: 1.42 m, 3 H, 1.90 m, 2 H, 2.05 m, 1 H, 2.20 m, 1 H, and 2.40 m, 1 H ($CCH_2$); 3.30 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 13.4 and 3.77 dd, 1 H, *J*(P,CH) = 9.0, *J*(gem) = 13.4 ($PCH_2$); 3.94 td, 1 H, *J* = 4.4, 10.3 and 10.3 (OCH); 4.52 ddd, 1 H, *J* = 4.4, 10.3 and 12.4 (NCH); 8.25 s, 1 H and 8.77 s, 1 H (H-2, H-8).

*9-(trans-2-Phosphonomethoxycycloheptyl)hypoxanthine* (**7c**). Compound **7c** was prepared from derivative **5c** (0.1 g, 0.3 mmol) and isoamyl nitrite (1 ml, 7.5 mmol) in 80% acetic acid (10 ml) in the same way as described for the cyclopentane derivative **6a**. Yield 0.1 g (97%) of lyophilizate **7c**. UV spectrum: 251 (pH 2), 256 (pH 12). For $C_{13}H_{19}N_4O_5P$ (342.3) calculated: 45.62% C, 5.59% H, 16.37% N, 9.05% P; found: 45.33% C, 5.47% H, 16.12% N, 8.91% P. MS (FAB): 343 ($M + H^+$), 137 (hypoxanthine + $H^+$). $^1$H NMR spectrum: 1.50–1.90 m, 8 H, and 2.10 m, 2 H ($CCH_2$); 3.09 dd, 1 H, *J*(P,CH) = 8.8, *J*(gem) = 12.2 and 3.33 dd, 1 H, *J*(P,CH) = 10.3, *J*(gem) = 12.2 ($PCH_2$); 4.00 ddd, 1 H, *J* = 3.4, 7.8 and 9.3 (OCH); 4.52 td, 1 H, *J* = 3.4, 9.5 and 9.7 (NCH); 8.15 s, 1 H and 8.26 s, 1 H (H-2, H-8).

*2-Amino-6-chloro-9-(trans-2-hydroxycyclopentyl)purine* (**8a**). Prepared by method *A* from 2-amino-6-chloropurine (30 mmol). Crystallization from acetone–light petroleum afforded 0.37 g (5%), m.p. 198 °C. For $C_{10}H_{12}ClN_5O$ (253.7) calculated: 47.34% C, 4.77% H, 27.61% N; found: 47.59% C, 4.80% H, 27.33% N. MS (FAB): 254 ($M + H^+$), 170 (2-amino-6-chloropurine + $H^+$). $^1$H NMR spectrum: 1.45–2.20 m, 6 H ($CCH_2$); 4.43 qd, 1 H, *J* = 4.6, 7.3, 7.3, 7.3 (OCH); 4.49 q, 1 H, *J* = 7.3 (NCH); 5.17 d, 1 H, *J*(OH,CH) = 4.6 (OH); 6.87 br s, 2 H ($NH_2$); 8.20 s, 1 H, (H-8).

*2-Amino-6-chloro-9-(trans-2-hydroxycyclohexyl)purine* (**8b**). Prepared by method *A* from 2-amino-6-chloropurine (30 mmol). Crystallization from acetone–light petroleum afforded 2.33 g (29%), m.p. 242 °C. For $C_{11}H_{14}ClN_5O$ (267.7) calculated: 49.35% C, 5.27% H, 26.16% N; found: 49.61% C, 5.28% H, 25.91% N. MS (FAB): 268 ($M + H^+$), 170 (2-amino-6-chloropurine + $H^+$). $^1$H NMR spectrum: 1.20–1.40 m, 3 H, and 1.65–2.10 m, 5 H ($CCH_2$); 3.95 tt, 1 H, *J*(OH,CH) = *J*(a,e) = 4.9, *J*(a,a) = 9.8 and 10.0 (OCH); 4.01 td, 1 H, *J*(a,e) = 5.2, *J*(a,a) = 10.0 and 10.1 (NCH); 4.93 d, 1 H, *J*(OH,CH) = 4.9 (OH); 6.83 br s, 2 H ($NH_2$); 8.19 s, 1 H (H-8).

*9-(trans-2-Hydroxycyclopentyl)guanine* (**9a**). A mixture of the 2-amino-6-chloropurine derivative **8a** (0.25 g, 1 mmol) and 80% formic acid was heated at 110 °C for 2 h. After evaporation, the remaining formic acid was removed by codistillation with water (3 × 20 ml) and the 2-*N*-formyl derivative was decomposed by standing with 28% aqueous ammonia (20 ml) for 12 h. The crystalline product was filtered, washed with a small amount of water and dried in vacuo (50 °C, 13.5 Pa, 6 h). Yield 0.23 g (97%) of compound **9a**, m.p. >295 °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: 50.79% C, 5.46% H, 29.10% N. MS (FAB): 236 ($M + H^+$), 152 (guanine + $H^+$). $^1$H NMR spectrum: 1.53 m, 1 H, 1.73 m, 2 H, 1.85 m, 1 H, 1.96 m, 1 H, and 2.08 m, 1 H ($CCH_2$); 4.28 br q, 1 H, *J* = 8.0 (OCH); 4.33 br q, 1 H, *J* = 7.1 (NCH); 6.90 br s, 3 H ($NH_2$, OH); 7.73 s, 1 H (H-8); 8.44 br s, 1 H (NH).

*9-(trans-2-Hydroxycyclohexyl)guanine* (**9b**). Compound **9b** was prepared from 2-amino-6-chloropurine derivative **8b** (0.27 g, 1 mmol) in the same manner as the cyclopentane derivative **9a**. Yield 0.24 g (96%) of crystalline product **9b**, m.p. >305 °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: 52.99% C, 5.85% H, 27.95% N. MS (FAB): 250 ($M + H^+$), 152 (guanine + $H^+$). $^1$H NMR spectrum: 1.20–1.40 m, 3 H,

1.70 m, 2 H, 1.85 m, 2 H, and 1.95 m, 1 H ($CCH_2$); 3.88 m, 2 H (OCH, NCH); 4.86 d, 1 H, *J*(OH,CH) = 5.0 (OH); 6.38 br s, 2 H ($NH_2$); 7.73 s, 1 H (H-8); 10.55 br s, 1 H (NH).

*9-(trans-2-Hydroxycycloheptyl)guanine* (**9c**). A solution of 6-*O*-benzyl derivative **10c** (0.35 g, 1 mmol) and bromotrimethylsilane (0.8 ml, 6 mmol) in acetonitrile (10 ml) was allowed to stand at room temperature for 12 h. The crystalline product was recrystallized from acetone to give 0.26 g (98%) of compound **9c**, m.p. >300 °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: 54.58% C, 6.83% H, 26.25% N. MS (FAB): 264 ($M + H^+$). $^1$H NMR spectrum: 1.45–2.00 m, 10 H ($CCH_2$); 4.01 m, 1 H (OCH); 4.06 td, 1 H, *J* = 3.4, 9.5 and 9.5 (NCH); 4.82 br s, 1 H (OH); 6.42 br s, 2 H ($NH_2$); 7.76 s, 1 H (H-8); 10.65 br s, 1 H (NH).

*6-O-Benzyl-9-(trans-2-hydroxycyclopentyl)guanine* (**10a**). Prepared by method *B* from 6-*O*-benzylguanine (20 mmol). Crystallization from chloroform–diethyl ether afforded 2.6 g (40%) of **10a**, m.p. 192 °C. For $C_{17}H_{19}N_5O_2$ (325.4) calculated: 62.76% C, 5.89% H, 21.52% N; found: 62.60% C, 5.88% H, 21.23% N. MS (FAB): 326 ($M + H^+$), 152 (guanine + $H^+$). $^1$H NMR spectrum: 1.55 m, 1 H, 1.78 m, 2 H, 1.92 m, 2 H, and 2.10 m, 1 H ($CCH_2$); 4.40 qd, 1 H, *J* = 4.9, 7.1, 7.1 and 7.1 (OCH); 4.36 q, 1 H, *J* = 8.0 (NCH); 5.15 d, 1 H, *J*(OH,CH) = 4.9 (OH); 5.49 s, 2 H ($PhCH_2O$); 6.42 br s, 2 H, ($NH_2$); 7.30–7.42 m, 3 H (arom.); 7.50 m, 2 H (arom.); 7.92 s, 1 H (H-8).

*6-O-Benzyl-9-(trans-2-hydroxycyclohexyl)guanine* (**10b**). Prepared by method *B* from 6-*O*-benzylguanine (3 mmol). Crystallization from chloroform–diethyl ether afforded 0.55 g (54%) of **10b**, m.p. 249 °C. For $C_{18}H_{21}N_5O_2$ (339.4) calculated: 63.70% C, 6.24% H, 20.63% N; found: 63.64% C, 6.14% H, 20.41% N. MS (FAB): 340 ($M + H^+$), 152 (guanine + $H^+$). $^1$H NMR spectrum: 1.20–1.40 m, 3 H, 1.72 m, 2 H, 1.88 m, 2 H, and 1.95 m, 1 H ($CCH_2$); 3.95 br tt, 1 H, *J* = 4.4, 5.0, 10.3 and 10.5 (OCH); 3.98 td, 1 H, *J* = 4.6, 10.0 and 11.0 (NCH); 4.84 d, 1 H, *J*(OH,CH) = 5.1 (OH); 5.49 s, 2 H ($PhCH_2O$); 6.37 br s, 2 H ($NH_2$); 7.30–7.42 m, 3 H (arom.); 7.50 m, 2 H (arom.); 7.91 s, 1 H (H-8).

*6-O-Benzyl-9-(trans-2-hydroxycycloheptyl)guanine* (**10c**). Prepared by method *B* from 6-*O*-benzylguanine (10 mmol). Crystallization from chloroform–diethyl ether afforded 0.97 g (27%) of **10c**, m.p. 230 °C. For $C_{19}H_{23}N_5O_2$ (253.4) calculated: 64.57% C, 5.56% H, 19.82% N; found: 64.56% C, 6.56% H, 19.81% N. MS (FAB): 354 ($M + H^+$), 264 ($M + H^+ - Bn$), 152 (guanine + $H^+$).

*9-(trans-2-Phosphonomethoxycyclopentyl)guanine* (**11a**). Nucleoside **10a** (1.63 g, 5 mmol) was converted into the *N*-2-(*N*,*N*-dimethylaminomethylene) derivative of compound **10a** as described for the preparation of compound **3a**. Chromatography of the crude product on silica gel (gradient of ethanol in chloroform 0–4% v/v) afforded 1.1 g (58%) of *N*-protected derivative of compound **10a**. This product was further phosphonylated and processed as described for compound **3a**. The obtained crude diester of compound **11a** was deprotected by treatment with bromotrimethylsilane as described for compound **3a**. The final product was purified by reversed-phase chromatography (DEAE-Sephadex A-25) and converted into the sodium salt on Dowex 50 X 2 ($Na^+$ form). Freeze-drying afforded 0.11 g (10%) of sodium phosphonate **11a**. UV spectrum: 255 (pH 2), 270 (pH 12). MS (FAB): 374 ($M + 2\ Na^+$). $^1$H NMR spectrum: 1.80–1.95 m, 4 H, 2.35 m, 1 H, and 2.38 m, 1 H ($CCH_2$); 3.59 d, 2 H, *J*(P,CH) = 9.3 ($PCH_2$); 4.34 dt, 1 H, *J* = 5.4, 5.4 and 7.1 (OCH); 4.64 td, 1 H, *J* = 5.4, 7.6 and 7.6 (NCH); 7.91 s, 1 H (H-8).

*9-(trans-2-Phosphonomethoxycyclohexyl)guanine* (**11b**). Nucleoside **10b** (1.4 g, 4.1 mmol) was converted into the phosphonate **11b** as described for compound **11a**. Freeze-drying afforded 0.24 g (21%) of sodium salt of phosphonate **11b**. UV spectrum: 255 (pH 2), 270 (pH 12). MS (FAB): 344 ($M + H^+$). $^1$H NMR spectrum: 1.42 m, 3 H, 1.70–2.10 m, 4 H and 2.50 m, 1 H ($CCH_2$); 3.29 dd, 1 H, *J*(P,CH) = 9.3, *J*(gem) = 12.0 and 3.50 dd, 1 H, *J*(P,CH) = 9.0, *J*(gem) = 12.0 ($PCH_2$); 3.95 td, 1 H, *J* = 4.4, 10.0 and 10.2 (OCH); 4.21 ddd, 1 H, *J* = 4.1, 10.2 and 12.3 (NCH); 7.99 s, 1 H (H-8).

*9-(trans-2-Phosphonomethoxycycloheptyl)guanine* (**11c**). Nucleoside **10c** (0.35 g, 1 mmol) was converted into compound **11c** as described for compound **11a**. Freeze-drying afforded 0.13 g (32%)

of sodium salt of phosphonate **11c**. UV spectrum: 255 (pH 2), 270 (pH 12). MS (FAB): 402 (M + 2 $Na^+$). $^1$H NMR spectrum: 1.50–1.70 m, 4 H, 1.75–1.90 m, 4 H, 1.95 m, 1 H, and 2.10 m, 1 H ($CCH_2$); 3.23 dd, 1 H, *J*(P,CH) = 9.3, *J*(gem) = 12.7 and 3.49 dd, 1 H, *J*(P,CH) = 10.0, *J*(gem) = 12.7 ($PCH_2$); 3.94 ddd, 1 H, *J* = 3.4, 8.1 and 9.3 (OCH); 4.35 td, 1 H, *J* = 3.4, 9.5 and 9.8 (NCH); 7.97 s, 1 H (H-8).

*1-(trans-2-Hydroxycyclopentyl)thymine* (**12a**). A mixture of thymine (12.6 g, 100 mmol), ammonium sulfate (0.5 g) and hexamethyldisilazane (50 ml) was refluxed under exclusion of moisture for 3 h. After evaporation of hexamethyldisilazane, the product was distilled under diminished pressure (b.p. 135 °C at 1.8 kPa) and stored under argon. Yield of 2,4-bis-*O*-trimethylsilylthymine was 22 g (86%). To a mixture of the silylated thymine (0.94 g, 5 mmol), cyclopentene oxide (0.46 g, 5.5 mmol) and dichloroethane (10 ml), cooled to 0 °C, was added tin tetrachloride (0.6 ml, 5 mmol). The mixture was set aside for three weeks at room temperature, the reaction being monitored by reversed-phase HPLC. The mixture was taken down and the residue decomposed by boiling with triethylamine–methanol–water mixture (50 ml, 1 : 5 : 5) for 30 min. The deposited solid was removed by centrifugation and the product was separated by preparative medium-pressure chromatography on octadecyl silica gel (linear gradient of methanol in water, 0–80%). In addition to the starting thymine (0.38 g; 61%), the reaction afforded 0.13 g (13%) of product **12a**, m.p. 199 °C. UV spectrum: 273 (pH 2), 271 (pH 12). For $C_{10}H_{14}N_2O_3$ (210.2) calculated: 57.13% C, 6.71% H, 13.32% N; found: 56.98% C, 6.62% H, 13.19% N. MS (FAB): 211 (M + $H^+$), 127 (thymine + $H^+$). $^1$H NMR spectrum: 1.47 m, 2 H, and 1.66 m, 2 H ($CCH_2$); 1.78 d, 3 H, *J*(6,$CH_3$) = 1.0 ($CH_3$); 1.90 m, 2 H ($CCH_2$); 4.15 qd, 1 H, *J* = 5.1, 7.8, 7.8 and 7.8 (OCH); 4.40 td, 1 H, *J* = 8.1, 9.3 and 9.3 (NCH); 5.01 d, 1 H, *J*(OH,CH) = 5.1 (OH); 7.53 br q, 1 H, *J* = 1.0 (H-6); 11.18 br s, 1 H (NH).

*1-(trans-2-Hydroxycyclohexyl)thymine* (**12b**). Boron trifluoride etherate (1.23 ml, 10 mmol) was added to a mixture of the silylated thymine (1.88 g, 10 mmol), cyclohexene oxide (1.08 g, 11 mmol) and dichloroethane (20 ml), cooled to –40 °C. After standing at room temperature for 24 h, the solvent was evaporated and the residue decomposed by boiling (30 min) with triethylamine–methanol–water (50 ml, 1 : 5 : 5). The deposited solid was removed by centrifugation and the product was purified by crystallization from water. Yield 0.4 g (18%) of product **12b**, m.p. 287 °C. UV spectrum: 273 (pH 2), 271 (pH 12). For $C_{11}H_{16}N_2O_3$ (224.3) calculated: 58.91% C, 7.19% H, 12.49% N; found: 58.77% C, 7.01% H, 12.38% N. MS (FAB): 225 (M + $H^+$), 127 (thymine + $H^+$). $^1$H NMR spectrum: 1.25 m, 3 H, 1.59 m, 1 H, and 1.66 m, 3 H ($CCH_2$); 1.77 d, 3 H, *J*(6,$CH_3$) = 1.0 ($CH_3$); 1.94 m, 1 H ($CCH_2$); 3.65 m, 1 H (OCH); 4.06 m, 1 H (NCH); 4.84 d, 1 H, *J*(OH,CH) = 5.4 (OH); 7.56 br s, 1 H (H-6); 11.09 br s, 1 H (NH).

*1-(trans-2-Hydroxycycloheptyl)thymine* (**12c**). Compound **12c** was prepared from silylated thymine (1.88 g, 10 mmol) and cycloheptene oxide (1.23 g, 11 mmol) in the same manner as described for the cyclohexane derivative **12b**. The product was isolated by preparative medium-pressure chromatography on octadecyl silica gel (linear gradient of methanol in water 0–75%) and purified by crystallization from water. Yield 0.35 g (15%) of product **12c**, m.p. 203 °C. UV spectrum: 273 (pH 2), 271 (pH 12). For $C_{12}H_{18}N_2O_3$ (238.3) calculated: 60.49% C, 7.61% H, 11.76% N; found: 60.27% C, 7.58% H, 11.68% N. MS (FAB): 239 (M + $H^+$), 127 (thymine + $H^+$). $^1$H NMR spectrum: 1.40–1.85 m, 10 H ($CCH_2$); 1.76 d, 3 H, *J*(6,$CH_3$) = 1.0 ($CH_3$); 3.77 m, 1 H (OCH); 4.09 m, 1 H (NCH); 4.78 d, 1 H, *J*(OH,CH) = 5.1 (OH); 7.53 br s, 1 H, (H-6); 11.04 br s, 1 H (NH).

*1-(trans-2-Phosphonomethoxycyclopentyl)thymine* (**13a**). The phosphonylation of nucleoside **12a** (0.21 g, 1 mmol) was performed as described for compound **3a**. After disappearence of the starting thymine derivative **12a** (4 h), the excess sodium hydride was destroyed with acetic acid (5 ml). The mixture was concentrated and the residue was codistilled with DMF. The ester groups were removed by heating (40 °C, 1 h) with bromotrimethylsilane (0.5 ml, 3.7 mmol) in anhydrous acetonitrile (10 ml). The crude product was chromatographed, first on DEAE-Sephadex A-25 and then on octadecyl silica gel. Freeze-drying afforded 0.23 g (76%) of phosphonate **13a**. UV spectrum: 274 (pH 2), 274 (pH 12).

MS (FAB): 305 (M + H$^+$). $^1$H NMR spectrum: 1.60–1.90 m, 4 H ($CCH_2$); 1.89 d, 3 H, $J$(6,$CH_3$) = 1.0 ($CH_3$); 2.15 m, 2 H ($CCH_2$); 3.40 d, 2 H, $J$(P,CH) = 9.5 ($PCH_2$); 4.11 m, 1 H (OCH); 4.65 m, 1 H (NCH); 7.39 br s, 1 H (H-6).

*1-(trans-2-Phosphonomethoxycyclohexyl)thymine* (**13b**). Phosphonylation of nucleoside **12b** (0.022 g, 0.1 mmol) was performed as described for compound **3a** and the further processing was executed as given for phosphonate **13a**. Freeze-drying afforded 0.02 g (63%) of product **13b**. UV spectrum: 273 (pH 2), 273 (pH 12). MS (FAB): 319 (M + H$^+$). $^1$H NMR spectrum: 1.20 m, 3 H, 1.58 m, 1 H, and 1.80 m, 3 H ($CCH_2$); 1.89 br s, 3 H ($CH_3$); 2.34 m, 1 H ($CCH_2$); 3.27 dd, 1 H, $J$(P,CH) = 8.3, $J$(gem) = 12.2 and 3.45 dd, 1 H, $J$(P,CH) = 9.3, $J$(gem) = 12.2 ($PCH_2$); 3.58 br m, 1 H (OCH); 4.41 br m, 1 H (NCH); 7.54 br s, 1 H (H-6).

*1-(trans-2-Phosphonomethoxycycloheptyl)thymine* (**13c**). Nucleoside **12c** (0.14 g, 0.5 mmol) was phosphonylated as described for compound **3a** and the further processing was as described for the phosphonate **13a**. The crude product was purified by chromatography on octadecyl silica gel. Freeze-drying afforded 0.13 g (80%) of product **13c**. UV spectrum: 273 (pH 2), 273 (pH 12). MS (FAB): 333 (M + H$^+$). $^1$H NMR spectrum: 1.40–2.00 m, 10 H ($CCH_2$); 1.88 br s, 3 H ($CH_3$); 3.23 dd, 1 H, $J$(P,CH) = 10.0, $J$(gem) = 12.2 and 3.37 dd, 1 H, $J$(P,CH) = 9.6, $J$(gem) = 12.2 ($PCH_2$); 3.65 m, 1 H (OCH); 4.50 m, 1 H (NCH); 7.47 br s, 1 H (H-6).

*4-Ethoxy-1-(trans-2-hydroxycyclopentyl)-2-pyrimidone* (**14a**). Prepared by method *A* from 4-ethoxy-2-pyrimidone (30 mmol). Crystallization from ethyl acetate–light petroleum afforded 1.55 g (23%) of product, m.p. 110 °C. MS (FAB): 225 (M + H$^+$). $^1$H NMR spectrum: 1.27 t, 3 H, $J$($CH_2$,$CH_3$) = 7.0 ($CH_3$); 1.40–2.10 m, 6 H ($CCH_2$); 4.24 qd, 1 H, $J$ = 5.2, 7.3, 7.3, 7.3 (OCH); 4.26 q, 2 H, $J$($CH_2$,$CH_3$) = 7.0 ($CH_2$); 4.45 dt, 1 H, $J$ = 7.3, 8.5, 8.5 (NCH); 5.02 d, 1 H, $J$(OH,CH) = 5.2 (OH); 5.95 d, 1 H, $J$(5,6) = 7.3 (H-5); 7.95 d, 1 H, $J$(6,5) = 7.3 (H-6).

*4-Ethoxy-1-(trans-2-hydroxycyclohexyl)-2-pyrimidone* (**14b**). Prepared by method *A* from 4-ethoxy-2-pyrimidone (30 mmol). Crystallization from ethyl acetate–light petroleum afforded 3.83 g (54%) of the product, m.p. 193 °C. MS (FAB): 239 (M + H$^+$). $^1$H NMR spectrum: 1.27 t, 3 H, $J$($CH_2$,$CH_3$) = 7.0 ($CH_3$); 1.20–1.40 m, 3 H, and 1.50–2.05 m, 5 H ($CCH_2$); 3.75 m, 1 H (OCH); 4.20 m, 1 H (NCH); 4.26 q, 2 H, $J$($CH_2$,$CH_3$) = 7.0 ($CH_2$); 4.81 d, 1 H, $J$(OH,CH) = 5.5 (OH); 5.93 d, 1 H, $J$(5,6) = 7.3 (H-5); 7.96 d, 1 H, $J$(6,5) = 7.3 (H-6).

*1-(trans-2-Hydroxycyclopentyl)uracil* (**15a**). A mixture of 4-ethoxy derivative **14a** (0.67 g, 3 mmol), bromotrimethylsilane (2.4 ml, 18 mmol) and anhydrous acetonitrile (30 ml) was stirred at room temperature until the formed precipitate dissolved (3 days). Evaporation of the solvent in vacuo and subsequent crystallization from water afforded 0.46 g (78%) of compound **15a**, m.p. 211 °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: 54.87% C, 6.11% H, 14.27% N. MS (FAB): 197 (M + H$^+$). $^1$H NMR spectrum: 1.47 m, 1 H, 1.65 m, 3 H, and 1.90 m, 2 H ($CCH_2$); 4.14 br q, 1 H, $J$ = 7.6 (OCH); 4.39 td, 1 H, $J$ = 7.8, 9.0 and 9.0 (NCH); 5.05 br s, 1 H (OH); 5.57 d, 1 H, $J$(5,6) = 8.1 (H-5); 7.65 d, 1 H, $J$(6,5) = 8.1 (H-6); 11.16 br s, 1 H (NH).

*1-(trans-2-Hydroxycyclohexyl)uracil* (**15b**). Compound **15b** was prepared from compound **14b** (0.71 g, 3 mmol) as described for the cyclopentane derivative **15a**. Yield 0.47 g (75%) of product **15b**, m.p. 217 °C. UV spectrum: 267 (pH 2), 268 (pH 12). For $C_{10}H_{14}N_2O_3$ (210.2) calculated: 57.13% C, 6.71% H, 13.32% N; found: 56.89% C, 6.71% H, 13.28% N. MS (FAB): 211 (M + H$^+$). $^1$H NMR spectrum: 1.25 m, 3 H, 1.60 m, 4 H, and 1.94 m, 1 H ($CCH_2$); 3.64 m, 1 H (OCH); 4.06 m, 1 H (NCH); 4.89 d, 1 H, $J$(OH,CH) = 5.4 (OH); 5.54 d, 1 H, $J$(5,6) = 7.8 (H-5); 7.75 d, 1 H, $J$(6,5) = 7.8 (H-6); 11.12 br s, 1 H (NH).

*1-(trans-2-Hydroxycycloheptyl)uracil* (**15c**). Gaseous nitrogen oxide was introduced for 15 min into a solution of cytosine derivative **17c** (0.67 g, 3 mmol) in glacial acetic acid (30 ml) at room temperature. After evaporation, the remaining nitrogen acids were removed on a Dowex 1 X 2 column

(acetate form). The product **15c** was obtained in quantitative yield. 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: 58.77% C, 7.03% H, 12.35% N. MS (FAB): 225 (M + $H^+$). $^1$H NMR spectrum: 1.44 m, 3 H, 1.57 m, 4 H, and 1.76 m, 3 H ($CCH_2$); 3.77 m, 1 H (OCH); 4.08 m, 1 H (NCH); 4.80 br s, 1 H (OH); 5.50 dd, 1 H, *J*(5,NH) = 2.1, *J*(5,6) = 7.9 (H-5); 7.63 d, 1 H, *J*(6,5) = 7.9 (H-6); 11.07 br s, 1 H (NH).

*1-(trans-2-Phosphonomethoxycyclopentyl)uracil* (**16a**). As described for compound **3a**, 4-ethoxy-2-pyrimidone derivative **14a** (0.67 g, 3 mmol) was converted into the phosphonate diester of compound **14a** which was not isolated but directly deblocked to give the phosphonate **16a**. This was purified by chromatography on octadecyl silica gel and converted into the sodium salt on Dowex 50 W X 2 ($Na^+$ form). Freeze-drying afforded 0.25 g (25%) of sodium salt of **16a**. UV spectrum: 268 (pH 2), 268 (pH 12). MS (FAB): 335 (M + $H^+$). $^1$H NMR spectrum: 1.70–1.85 m, 4 H, 2.05 m, 1 H, and 2.15 m, 1 H ($CCH_2$); 3.49 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 12.7 and 3.53 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 12.7 ($PCH_2$); 4.14 dt, 1 H, *J* = 5.6, 6.1 and 6.1 (OCH); 4.68 td, 1 H, *J* = 6.1, 7.6 and 7.6 (NCH); 5.85 d, 1 H, *J*(5,6) = 8.0 (H-5); 7.67 d, 1 H, *J*(6,5) = 8.0 (H-6).

*1-(trans-2-Phosphonomethoxycyclohexyl)uracil* (**16b**). The compound **16b** was prepared from the 4-ethoxy-2-pyrimidone derivative **14b** (0.71 g, 3 mmol) as described for the cyclopentane derivative **16a**. Freeze-drying afforded 0.33 g (32%) of sodium salt of **16b**. UV spectrum: 268 (pH 2), 268 (pH 12). MS (FAB): 349 (M + $H^+$). $^1$H NMR spectrum: 1.28–1.44 m, 3 H, 1.66 m, 1 H, 1.80 m, 2 H, 1.92 m, 1 H, and 2.36 m, 1 H ($CCH_2$); 3.44 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 12.9 and 3.67 dd, 1 H, *J*(P,CH) = 9.6, *J*(gem) = 12.9 ($PCH_2$); 3.68 m, 1 H (OCH); 4.38 m, 1 H (NCH); 5.92 d, 1 H, *J*(5,6) = 8.0 (H-5); 7.83 d, 1 H, *J*(6,5) = 8.0 (H-6).

*1-(trans-2-Phosphonomethoxycycloheptyl)uracil* (**16c**). Compound **16c** was prepared from the cytosine derivative **18c** (0.1 g, 0.3 mmol) by heating with 2 M NaOH (3 ml) at 100 °C for 3 days. The reaction mixture was desalted on Dowex 50W X 2 ($H^+$ form) and the free acid was converted into the sodium salt on Dowex 50W X 2 ($Na^+$ form). Freeze-drying afforded 86 mg (78 %) of sodium salt of **16c**. UV spectrum: 267 (pH 2), 267 (pH 12). MS (FAB): 363 (M + $H^+$), 341 (M – Na), 316 (M – 2 Na). $^1$H NMR spectrum: 1.40–2.00 m, 10 H ($CCH_2$); 3.34 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 12.9 and 3.59 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 12.9 ($PCH_2$); 3.74 m, 1 H (OCH); 4.36 m, 1 H (NCH); 5.85 d, 1 H, *J*(5,6) = 8.0 (H-5); 7.72 d, 1 H, *J*(6,5) = 8.0 (H-6);

*1-(trans-2-Hydroxycyclopentyl)cytosine* (**17a**). Prepared by method *B* from cytosine (1.11 g, 10 mmol); reaction time 62 h. The crude product, which was obtained by desalting of the reaction mixture on Dowex 50W X 2 ($H^+$ form), was decolorized on Dowex 1 X 2 (acetate form; elution with water) a purified by chromatography on octadecyl silica gel. Yield 0.4 g (21%) of compound **17a**, m.p. 233 °C. UV spectrum: 286 (pH 2), 275 (pH 12). For $C_9H_{13}N_3O_2$ (195.2) calculated: 55.37% C, 6.71% H, 21.52% N; found: 55.29% C, 6.95% H, 21.36% N. MS (FAB): 196 (M + $H^+$), 112 (cytosine + $H^+$). $^1$H NMR spectrum: 1.43–1.51 m, 1 H, 1.53–1.62 m, 1 H, 1.63–1.70 m, 2 H, and 1.85 – 1.97 m, 2 H ($CCH_2$); 4.14 qd, 1 H, *J* = 5.1, 7.1, 7.1, 7.3 (OCH); 4.38 td, 1 H, *J* = 7.3, 8.8, 9.0 (NCH); 4.96 d, 1 H, *J*(OH,CH) = 5.1 (OH); 7.02 br s, 2 H ($NH_2$); 5.68 d, 1 H, *J*(5,6) = 7.3 (H-5); 7.55 d, 1 H, *J*(6,5) = 7.3 (H-6).

*1-(trans-2-Hydroxycyclohexyl)cytosine* (**17b**). Prepared by method *B* from cytosine (1.11 g, 10 mmol) The reaction mixture was worked up as described for the cyclopentane derivative **17a**. Yield 1.35 g (62%) of compound **17b**, m.p. 274 °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: 57.36% C, 7.25% H, 20.01% N. MS (FAB): 210 (M + $H^+$), 112 (cytosine + $H^+$). $^1$H NMR spectrum: 1.25 m, 3 H, 1.40 m, 1 H, 1.65 m, 3 H, and 1.95 m, 1 H ($CCH_2$); 3.62 m, 1 H (OCH); 4.15 m, 1 H (NCH); 4.75 br s, 1 H (OH); 6.98 br s, 2 H ($NH_2$); 5.66 d, 1 H, *J*(5,6) = 7.3 (H-5); 7.57 d, 1 H, *J*(6,5) = 7.3 (H-6).

*1-(trans-2-Hydroxycycloheptyl)cytosine* (**17c**). Prepared by method *B* from cytosine (1.11 g, 10 mmol); reaction time 5 days. The reaction mixture was worked up as described for the cyclopentane deriva-

tive **17a**. Yield 0.54 g (24%) of compound **17c**, m.p. 263 °C. UV spectrum: 286 (pH 2), 275 (pH 12). For $C_{11}H_{17}N_3O_2$ (223.3) calculated: 59.17% C, 7.67% H, 18.82% N; found: 58.80% C, 7.94% H, 18.49% N. MS (FAB): 224 (M + $H^+$), 112 (cytosine + $H^+$). $^1$H NMR spectrum: 1.30–1.80 m, 10 H ($CCH_2$); 3.81 m, 1 H (OCH); 4.10 m, 1 H (NCH); 4.37 d, 1 H, *J*(OH,CH) = 5.1 (OH); 5.61 d, 1 H, *J*(5,6) = 7.3 (H-5); 6.90 br s, 2 H ($NH_2$); 7.54 d, 1 H, *J*(6,5) = 7.3 (H-6).

*2-O-(trans-2-Hydroxycyclohexyl)cytosine* (**17d**). A mixture of cytosine (1.11 g, 10 mmol), cyclohexene oxide (1.25 ml, 12.5 mmol), DBU (1.55 g, 10.2 mmol) and DMF (25 ml) was heated at 110 °C for 48 h. Desalting on Dowex 50W X 2 ($H^+$ form) and subsequent chromatography on silica gel (gradient of ethanol in chloroform 10–25%) afforded *N*-1 derivative **17b** (1.17 g, 56%) and *O* derivative **17d.** Crystallization from chloroform–ethanol (95 : 5) gave 0.42 g (20%) of compound **17d**, m.p. 146 °C. UV spectrum: 231, 261 (pH 2), 273 (pH 12). MS (FAB): 210 (M + $H^+$), 112 (uracil + $H^+$). $^1$H NMR spectrum: 1.18–1.32 m, 4 H, 1.59 m, 2 H, 1.84 m, 1 H, and 1.96 m, 1 H ($CCH_2$); 3.48 sept (tt), 1 H, $\Sigma J$ = 25.4 (*J* ≈ 4.2, 4.2, 8.5 a 8.5) (H-2); 4.69 td, 1 H, $\Sigma J$ = 21.7 (*J* ≈ 4.5, 8.6 and 8.6) (H-1); 4.85 d, 1 H, *J*(OH,CH) = 4.6 (OH); 6.03 d, 1 H, *J*(5,6) = 5.9 (C-5); 6.75 br s, 2 H ($NH_2$); 7.82 d, 1 H, *J*(6,5) = 5.9 (C-6).

*1-(trans-2-Phosphonomethoxycyclopentyl)cytosine* (**18a**). Nucleoside **17a** (0.32 g, 1.6 mmol) was converted into the 4-*N*-benzoyl derivative (0.44 g; 90%) by treatment with benzoic anhydride in boiling ethanol[13]. This product was phosphonylated as described for compound **3a**. The excess sodium hydride was decomposed with acetic acid, the mixture was taken down, the residue was heated with 0.1 M sodium methoxide (15 ml) at 50 °C for 4 h and then set aside at room temperature for 12 h. After deionization of the phosphonate diester on Dowex 50W X 2 ($H^+$ form), the ester groups were removed by treatment with bromotrimethylsilane (1.2 ml, 10 mmol) in DMF (15 ml) for 24 h at room temperature. The obtained crude phosphonate was purified by chromatography on Dowex 1 X 2 (acetate form), elution with linear gradient of acetic acid in water (0–2 mol $l^{-1}$). Freeze-drying afforded 0.37 g (88%) of product **18a** as the inner salt. UV spectrum: 287 (pH 2), 277 (pH 12). For $C_{10}H_{16}N_3O_5P$ (289.2) calculated: 41.53% C, 5.58% H, 14.53% N, 10.71% P; found: 40.60% C, 5.57% H, 14.00% N, 10.83% P. MS (FAB): 290 (M + $H^+$), 112 (cytosine + $H^+$). $^1$H NMR spectrum: 1.70–1.90 m, 4 H, 2.15 m, 1 H, and 2.23 m, 1 H ($CCH_2$); 3.57 dd, 1 H, *J*(P,CH) = 9.3, *J*(gem) = 13.2 and 3.64 dd, 1 H, *J*(P,CH) = 9.3, *J*(gem) = 13.2 ($PCH_2$); 4.26 br q, 1 H, *J* = 6.3 (OCH); 4.70 td, 1 H, *J* = 6.3, 8.8 and 8.8 (NCH); 6.19 d, 1 H, *J*(5,6) = 7.8 (H-5); 7.89 d, 1 H, *J*(6,5) = 7.8 (H-6).

*1-(trans-2-Phosphonomethoxycyclohexyl)cytosine* (**18b**). Nucleoside **17b** (0.42 g, 2 mmol) was converted into the 4-*N*-benzoyl derivative (0.58 g; 93%), phosphonylated, and the product was further processed as described for the cyclopentane derivative **18a**. Yield 0.49 g (91%) of product **18b** as the inner salt. UV spectrum: 287 (pH 2), 277 (pH 12). For $C_{11}H_{18}N_3O_5P$ (303.3) calculated: 43.57% C, 5.98% H, 13.86% N, 10.21% P; found: 43.09% C, 5.98% H, 13.87% N, 10.44% P. MS (FAB): 304 (M + $H^+$), 112 (cytosine + $H^+$). $^1$H NMR spectrum: 1.30–1.40 m, 3 H, 1.56 m, 1 H, 1.75–1.90 m, 3 H, and 2.40 m, 1 H ($CCH_2$); 3.33 dd, 1 H, *J*(P,CH) = 8.5, *J*(gem) = 12.6 and 3.44 dd, 1 H, *J*(P,CH) = 10.2, *J*(gem) = 12.6 ($PCH_2$); 3.69 m, 1 H (OCH); 4.39 m, 1 H (NCH); 6.08 d, 1 H, *J*(5,6) = 7.3 (H-5); 7.78 d, 1 H, *J*(6,5) = 7.3 (H-6).

*1-(trans-2-Phosphonomethoxycycloheptyl)cytosine* (**18c**). Nucleoside **17c** (0.45 g, 2 mmol) was converted into the 4-*N*-benzoyl derivative (0.56 g; 85%), phosphonylated, and the product was further processed as described for the cyclopentane derivative **18a**. Yield 0.33 g (62%) of product **18c** as the inner salt. UV spectrum: 287 (pH 2), 277 (pH 12). MS (FAB): 318 (M + $H^+$), 112 (cytosine + $H^+$). $^1$H NMR spectrum: 1.40–2.00 m, 10 H ($CCH_2$); 3.35 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 13.2 and 3.61 dd, 1 H, *J*(P,CH) = 9.5, *J*(gem) = 13.2 ($PCH_2$); 3.78 m, 1 H (OCH); 4.41 m, 1 H (NCH); 6.05 d, 1 H, *J*(5,6) = 7.6 (H-5); 7.72 d, 1 H, *J*(6,5) = 7.6 (H-6).

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