Synthesis and Conformational Study of 3-Hydroxy-4-(Hydroxymethyl)-1-Cyclohexanyl Purines and Pyrimidines

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The cyclohexane nucleosides with a 1,4-relationship between nucleoside base and hydroxymethyl moiety were synthesized using a conjugated addition reaction of the nucleobases to ethyl 1,3-cyclohexadiene-1-carboxylate and hydroboration of the cyclohexenyl precursor. The lack of antiviral activity of the compounds was correlated with the conformation of these nucleosides as deduced from NMR and X-ray analysis.

Introduction

Carbocyclic nucleosides are analogues of natural nucleosides where the ring oxygen is replaced by a methylene group. Main efforts in this field were made to obtain cyclopentane derivatives of the natural furanose nucleosides.[1] The interest in the chemistry of cyclohexane and cyclohexene counterparts has increased recently.[2−10] One of the reasons is the significant antiviral activity reported for 1,5-anhydrohexitol nucleosides,[11,12] such as 1,5-anhydro-2,3-dideoxy-2-(5-ethyluracil-1-yl)-D-*arabino*-hexitol. Therefore, we started synthesis of carbocyclic nucleosides with a six-membered carbohydrate mimic,[7−9] represented here by 3-hydroxy-4-(hydroxymethyl)-1-cyclohexyl purines and pyrimidines, and we tried to correlate structure with biological activity. Nucleophilic substitution in a cyclohexane ring is more difficult than in a cyclopentane ring because of steric hindrance, and this hampers introduction of nucleoside bases on the six-membered ring structure. This was experienced during the synthesis of 4,4-bis(hydroxymethyl) cyclohexane nucleosides[9] and during introduction of nucleoside bases in saturated six-membered carbocycles using Mitsunobu conditions.[7] Several solutions to this problem are possible. In our hands, a Pd(0)-catalyzed alkylation of heterocyclic bases by allylic epoxide afforded low yield.[7] Better results were obtained using a Mitsunobu-type condensation of nucleoside bases with an unsaturated alcohol. The allylic alcohol has higher reactivity in nucleophilic substitution reactions, and the saturated compound could be obtained after catalytic hydrogenation.[7] Another possibility is to introduce the base moiety by a Michael-type addition which likewise works efficiently.[4] This method was used here to synthesize the carbocyclic analogues of anhydrohexitol nucleosides. Hydroboration of the resulting cyclohexenyl derivatives was investigated to obtain the desired trans-relationship between the 3′-hydroxyl group and the 4′-hydroxymethyl functionality in a reaction which is not obvious in the presence of reactive heterocycles like pyrimidines and purines. NMR and X-ray analysis demonstrated an opposite conformation between anhydrohexitol nucleosides and their carbocyclic congeners, which may explain their difference in biological activity.

Results and Discussion

Synthesis. Two main strategies were used for the synthesis of cyclohexyl nucleosides. The first method was based on a gradual build-up of the purine heterocycle starting from aminocyclohexanols.[8,13−16] The alternative way consisted in the reaction of purines or pyrimidines with cyclohexyl[6] or cyclohexenyl[3,4,9] epoxides, Mitsunobu-type condensation of the heterocycle with cyclohexyl alcohols,[7] or Michael-type addition of the nucleoside base on cyclohexadienyl derivatives.[2,4] The latter method was chosen as the most appropriate for the synthesis of the cyclohexyl nucleosides, as the presence of a double bond in the reaction product allowed us to further introduce the 3′-secondary alcohol function.

Initially ethyl 1,3-cyclohexadienecarboxylate (**1**)[17] (Scheme 1) was reacted with adenine **2a**, 2-amino-6-

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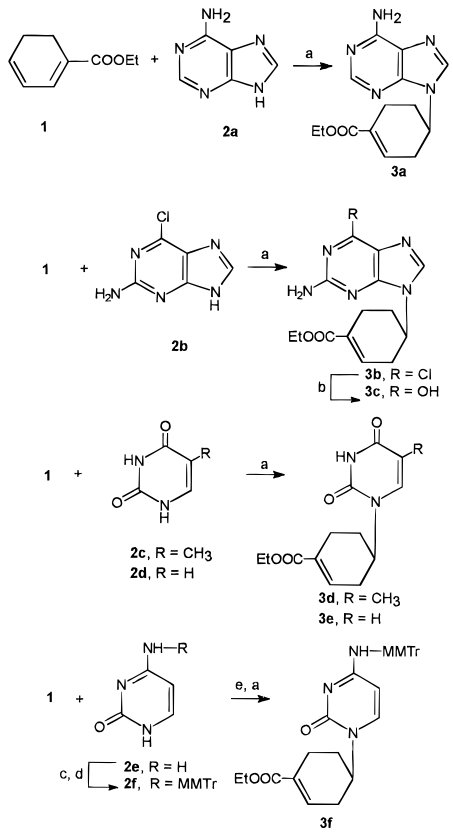
Scheme 1[a]



[a] (a) DBU·DMF/Δ; (b) CF_3COOH/H_2O; (c) BSA/Py; (d) MMTrCl/Py; (e) BSA/DMF.

chloropurine **2b**, thymine **2c**, uracil **2d**, or cytosine **2e** following an earlier described method using methyl 1,3-cyclohexadienecarboxylate.[4] The Michael-type addition of **2a** or **2b** on **1** in DMF in the presence of 0.25 equiv of DBU proceeded smoothly at 75 °C giving as the sole product compound **3a** (85%) or **3b** (74%). Compound **3b** was converted into the guanine derivative **3c** by treatment with TFA/H_2O.[7] Likewise, the thymine derivative **3d** could be obtained following this procedure. However, the uracil and cytosine bases gave only traces of the desired products, but higher yields could be obtained under modified conditions. Reaction of ethyl 1,3-cyclohexadienecarboxylate with an excess of uracil at 50 °C and 2.0 equiv of DBU yielded **3e** in 28%. For the synthesis of the cytosine analogue, the nucleoside base was first protected with a monomethoxytrityl group (83% yield) via a transient silylation procedure (BSA, pyridine). N^4-Monomethoxytritylated cytosine was used in the Michael-type reaction (30% yield) using 6 molar excess of **1** in the presence of DBU after silylation with BSA in DMF.

Attempts to prepare the hydroxymethylene derivative by reduction of the ester function of 9-[4-(ethoxycarbonyl)-3-cyclohexenyl]adenine (**3a**) using $LiAlH_4$ were unsuccessful due to the poor solubility of the reaction product in organic solvents and, hence, purification problems. Therefore we preferred to increase the lipophilicity of the compound by introducing a monomethoxytrityl protecting group and investigated the reduction reaction with DIBAL in dichloromethane (Scheme 2). This procedure afforded **5** in 75% yield from **4**. To avoid possible side reactions during hydroboration,[18] the primary hydroxyl function of **5** was first protected with a trityl group to obtain **6**. Hydroboration of **6** using BH_3−THF followed by a hydrogen peroxide basic workup gave a separable mixture of **7** (32%) and **8a** (28%). To obtain an analytical sample of the 1′,3′-cis isomer, **8a** had to be first acetylated giving **8b**, which after chromatographic purification was converted to **10** by deprotection. Deprotection of **7** with 80% aqueous acetic acid yielded the desired (1*RS*,3*SR*,4*RS*)-9-[4-(hydroxymethyl)-3-hydroxycyclohexyl]-adenine (**9**) as an enantiomeric mixture. The same sequence of reactions was used for the guanine derivative **3c** (Scheme 2). Monomethoxytritylation of **3c** yielded **11**. Following reduction with DIBAL, **12** was obtained in 87% yield. Protection of the 4′-hydroxymethyl group as in **6** led to **13**, which was hydroborated with the BH_3−THF complex, followed by treatment with H_2O_2. The only product which could be isolated in 40% yield was compound **14**. Deprotection of **14** with 80% aqueous acetic acid afforded the guanine derivative (±)-**15**.

As pyrimidine bases are more sensitive to addition reactions, the reaction conditions to obtain hydroxylated cyclohexyl pyrimidines have to be carefully controlled. With the thymine base, the reaction time had to be reduced to 1 h as compared to 7 h for the purine congeners. With the uracil and cytosine derivatives the reaction was conducted at lower temperature (−10 °C to 5 °C) for a total time of 6 h. While separation of the two 1-[4-(hydroxymethyl)-3-hydroxycyclohexyl]thymine isomers **18** (34%) and **19** (21%) was possible, this was not the case for the uracil and N^4-monomethoxytrityl cytosine derivatives. The inseparable mixtures **24/25** and **30/31** were first treated with 80% acetic acid, and separation of both diastereoisomers was conducted at the level of the deprotected target compounds. All other reactions with pyrimidine bases went as smoothly as the reactions with the purine nucleosides.

Alternatively, **26** was acetylated with Ac_2O, treated with 1*H*-1,2,4-triazole/$POCl_3$,[19] followed by displacement of the 4-triazolyl substituent with 25% ammonia in 1,4-dioxane. Final deprotection using 25% NH_4OH−MeOH−1,4-dioxane gave (1*RS*,3*SR*,4*RS*)-1-[4-(hydroxymethyl)-3-hydroxycyclohexyl]cytosine (**32**).

Conformational Analysis. The configurations of the synthesized diastereoisomeric pairs of cyclohexyl nucleosides **9**/**10**, **20**/**21**, **26**/**27**, **32**/**33**, and guanine derivative **15** were confirmed by NMR spectroscopy. The data are given for each compound in Experimental Section. A detailed NMR conformational study was carried out on the pairs **9**/**10** and **20**/**21** in D_2O at 33 °C. A standard numbering system is used here for carbon atoms as exemplified for the cyclohexyl rings of **9** and **10** in Figure 1.

All ^{13}C NMR lines and all multiplets in ^1H NMR spectra were consistently assigned by a combination of (^{13}C−^1H) heteronuclear correlation (GHSQC[20]) and double-quantum filtered COSY[21] (GMQFCOPS[22]) experiments.

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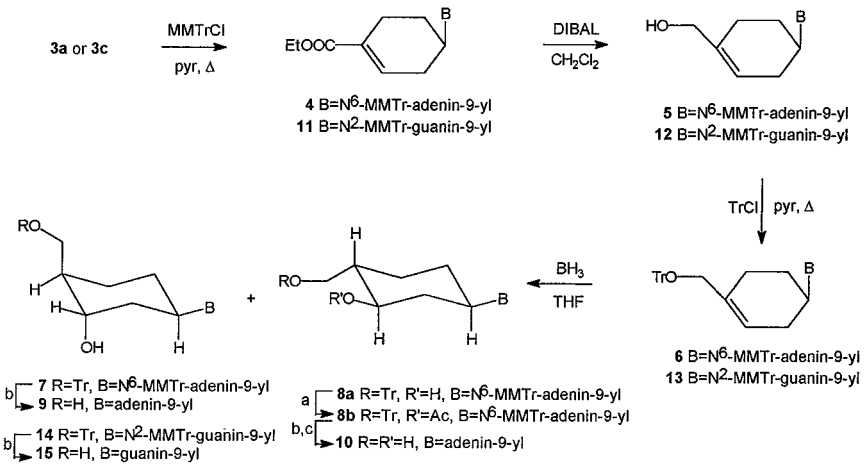
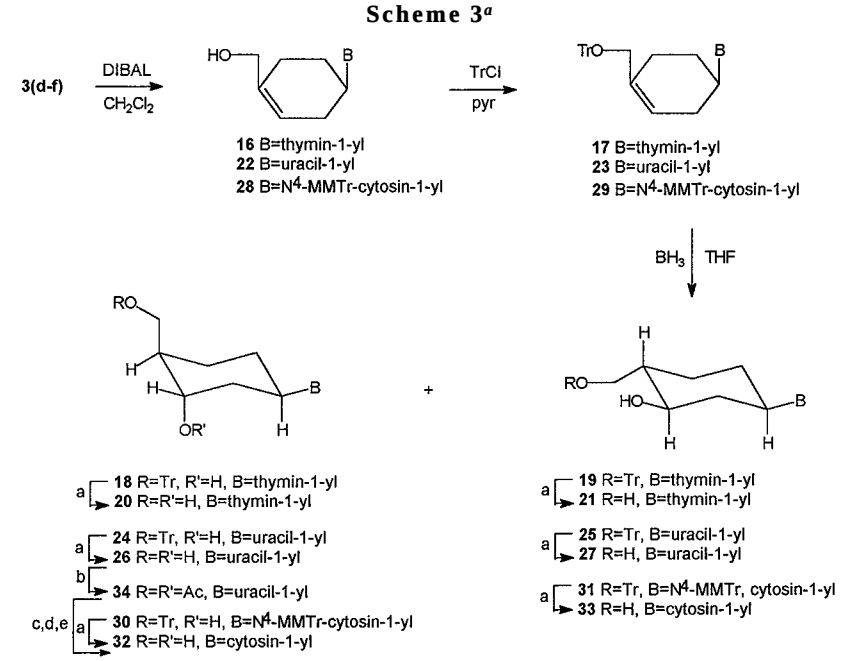
Scheme 2[a]



[a] (a) Ac_2O, pyridine; (b) 80% aqueous HOAc; (c) NH_3 (25%), dioxane, MeOH.

Scheme 3[a]



[a] (a) 80% aqueous HOAc; (b) Ac_2O, pyridine, CH_2Cl_2; (c) 1*H*-1,2,4-triazole, $POCl_3$, TEA, pyridine, CH_3CN; (d) NH_3 (25%), dioxane; (e) NH_3 (25%), dioxane, MeOH.

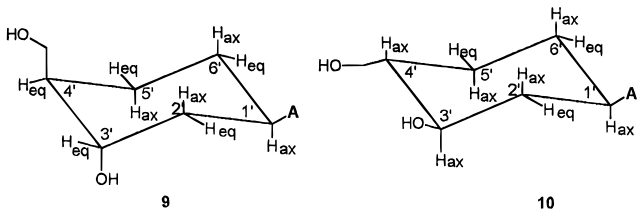


Figure 1. Structure of diastereoisomers **9** and **10** (only the 1′*R*-isomer is shown).

Proton chemical shifts and coupling constants were verified by spectral simulation of 1D spectra and iterative fitting in the case of strong coupling.

The results are summarized in Tables 1 and 2. The values of one-bond $^{13}C-^{1}H$ coupling constants (Table 2) show little variation and, consequently, are of no diagnostic value regarding molecular conformation. Due to an extensive accidental degeneracy of ^{1}H NMR spectra, full spectral analysis was not possible in the cases of compounds **9** and **20** (for a comparison see Figure 2). In these spectra the chemical shifts of protons 4′, 5′A, 5′B, 6′A, and 6′B are so close that even ^{13}C satellites seen in the GHSQC spectra do not exhibit sufficient structure to permit analysis. In the case of **9** it was, however, possible to extract the conformationally significant coupling between protons 3′ and 4′ from the 1D spectrum measured with multisite selective decoupling[23] of the protons 2′A and 2′B (see Experimental Section). In the case of **20** even such an approach was not possible because of almost complete overlap of signals due to protons 2′ and proton 4′; hence, only the upper limit of this coupling is listed as follows from the bandwidth of the multiplet.

Coupling constants in the cyclohexyl parts of **10** and **21** are essentially the same; hence, the conformational

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Table 1. ^{1}H NMR Chemical Shifts (δ) and Coupling Constants (J) in Cyclohexyl Parts of Diastereomeric Pairs 9/10 and 20/21[a]

		9 JM-21		**10** JM-20		**20** JM-19		**21** JM-24	
proton	coupling	δ	J	δ	J	δ	J	δ	J
1′	–	4.681		4.398		4.651		4.332	
	1′–2′A		4.7		12.3		4.9		12.3
	1′–2′B		10.2		3.6		13.2[b]		3.6
	1′–6′A		*c*		13.3		*c*		12.3
	1′–6′B		*c*		3.6		*c*		3.6
2′A	–	2.032		1.885		1.817		1.624	
	2′A–2′B		−13.8		−11.6		−13.2		−11.3
	2′A–3′		4.8		10.9		3.4[b]		10.6
2′B	–	2.185		2.390		1.877		2.109	
	2′B–3′		3.3		4.2		2.9		4.4
	2′B–6′B		*c*		2.9		*c*		1.9[b]
3′	–	4.047		3.651		4.138		3.558	
	3′–4′		4.8		11.0		<5		10.7
4′	–	1.86[d]		1.586		1.881		1.470	
	4′–CH_2OA		7.2[b]		6.5		7.2		6.6
	4′–CH_2OB		6.7[b]		4.0		6.7		4.0
	4′–5′A		*c*		13.3		*c*		13.3[b]
	4′–5′B		*c*		3.6		*c*		3.4[b]
5′A	–	1.60[d]		1.303		1.695		1.201	
	5′A–5′B		−14.9		−13.4		−13.7		−13.2
	5′A–6′A		*c*		13.0		*c*		13.3[b]
	5′–6′B		*c*		3.1		*c*		3.5[b]
5′B	–	1.93[d]		1.977		1.890		1.921	
	5′B–6′A		*c*		3.5		*c*		3.4
	5′B–6′B		*c*		3.5		*c*		3.4
6′A	–	1.91[d]		1.813		1.66[d]		1.585	
	6′A–6′B		*c*		−12.6		*c*		−12.7
6′B	–	1.91[d]		2.109		1.66[d]		1.838	
CH_2OA	–	3.638		3.616		3.624		3.566	
	CH_2OA–CH_2OB		−11.4		−11.2		−11.4		−11.1
CH_2OB	–	3.697		3.789		3.645		3.755	

[a] Chemical shifts of the proton indicated in the first column are values in the δ scale relative to HDO at 4.640 ppm; estimated precision ±0.001 ppm unless otherwise noted. Coupling constants between the protons indicated in the second column are values in hertz; estimated precision ±0.2 Hz unless otherwise indicated. Protons are labeled by the number of the carbon atom to which they are bonded; if two protons are bonded to the same carbon atom the one resonating at a higher field is denoted by A and the other by B. Geminal coupling constants are assumed to be negative. [b] Error up to 1 Hz possible either because of overlap or strong coupling. [c] Not determined. [d] Possible error up to 0.02 ppm.

Table 2. ^{13}C NMR Chemicals Shifts (δ) and One-Bond ^{13}C–^{1}H Coupling Constants (J) in Diastereomeric Pairs 9/10 and 20/21[a]

cyclohexane carbon no.	**9** JM-21		**10** JM-20		**20** JM-19		**21** JM-24	
	δ	J	δ	J	δ	J	δ	J
1′	50.78	145.3	52.97	141.7	51.35	142.1	53.53	142.8
2′	35.05	128.4	40.39	127.4	33.16	130.0	39.22	133.4
3′	67.68	143.9	69.90	147.6	68.03	144.7	70.04	139.7
4′	42.35	127.7	45.50	127.4	41.05	128.9	45.42	124.2
5′	21.64	129.8	25.45	132.4	21.36	130.5	25.41	130.2
6′	27.50	129.2	31.23	134.0	25.65	128.1	29.79	130.6
CH_2-O	62.38	141.8	63.55	142.8	61.97	140.6	63.51	142.8
base	adenine				thymine			
2	152.48	202.1	152.60	202.5	152.66	–	152.62	–
4	148.98	–	148.93	–	166.91	–	166.88	–
5	118.91	–	119.03	–	111.26	–	111.39	–
6	155.81	–	155.97	–	140.01	179.1	139.69	178.3
8/CH_3	140.72	*b*	*c*	*b*	11.79	129.3	11.79	129.1

[a] Chemical shifts are in the δ scale; estimated precision ±0.02 ppm. One-bond coupling constants are in hertz units; estimated precision ±0.5 Hz. [b] Not determined. [c] Not visible in deuterium-exchanged sample.

conclusions for compound **10** apply to compound **21** as well. Proton 1′ in **10** exhibits two large coupling constants to two vicinal protons (2′A and 6′A). That is possible only if all three protons assume axial positions in a chair conformer (if one does not consider the much less favorable boat conformations) and thus with the base in an equatorial position. Since protons 3′ and 4′ are also both axial according to their couplings with protons 2′A and 3′, respectively, this fixes the configuration of the compound as the 1′,3′-cis, 3′,4′-trans isomer as depicted for **10** in Figure 1. These conclusions are further supported by the observed transient NOEs (DPFGNOE[24]). Inversion of protons 2′A and 6′A yields NOE on proton 4′ as all three protons are mutually in a 1,3 diaxial arrangement. This finding, which in fact definitely excludes any boatlike conformation, is in agreement with the solid state structure determined by X-ray diffraction

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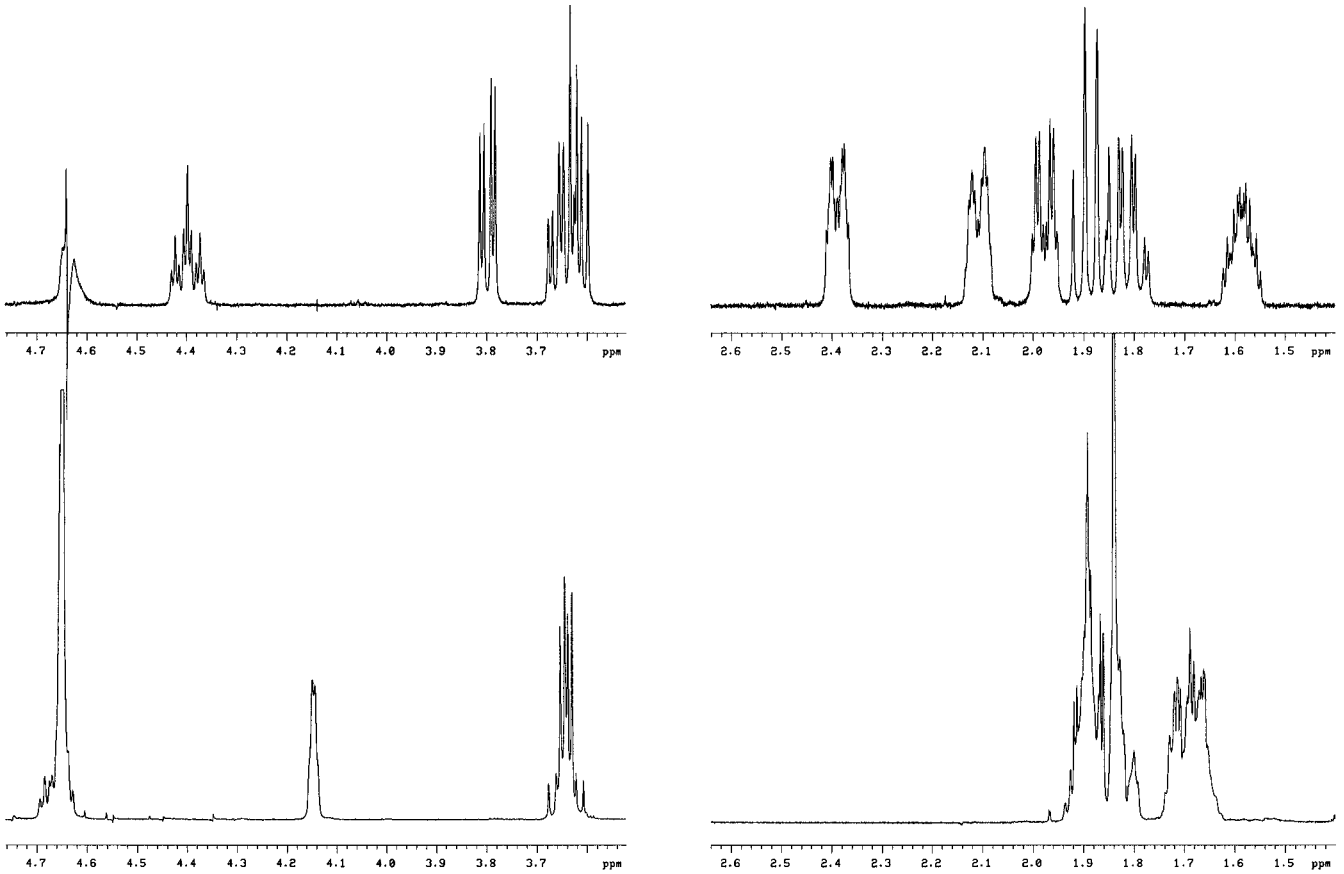

Figure 2. Relevant parts of 500 MHz ^{1}H NMR spectra of compound **10** (top) and **20** (bottom) in D_2O at 33 °C (water presaturation cannot be used in the measurements of **20** because of overlap with proton 1′ multiplet).

(Figure 3), and thus the molecules maintain their chair conformation (Figure 1) in water solutions.

In compound **9** the coupling between proton 1′ and 2′B indicates, according to the Karplus equation, the dihedral angle between C′1-H and C′2-HB to be close to 180°, an angle found in an axial−axial arrangement of these two bonds in a classical chair conformation. Again this points to an equatorially oriented base in the molecule. The small value of the *J*(2′B-3′) coupling together with the observed coupling between protons 3′ and 4′ (or its upper limit in **20**) indicates these two protons to be in equatorial arrangements and thus leads to a 1′,3′-trans, 3′,4′-trans structure, as shown for **9** in Figure 1. DPFGNOE spectra show the same NOE buildup rate for protons 4′ and 2′A when proton 3′ is selectively inverted, lending thus support to the proposed chair conformer.

Summarizing, the values of the vicinal H,H-coupling constants and NOE measurements lead to the conclusion that both **9** and **10** as well as **20** and **21** are in chair conformations with the bases (adenine and thymine) in equatorial positions. The other ring substituents (OH and CH_2OH) are axial in **9** and **20** and equatorial in **10** and **21**.

Further confirmation of this structural analysis is evident from the ^{13}C chemical shifts (Table 2), where for the isomers (**9** or **20**) with axial substituents a typical 2−5 ppm upfield shift is observed with respect to the isomer with no axial substituents. The same preferential conformation of **10** and **20** was found in the solid state. Figure 3A shows the X-ray analysis of **10** in the chair conformation and all substituents equatorially oriented. Figure 3B gives the solid state conformation of **20**, having both the hydroxymethyl group and hydroxyl group axially oriented and the base moiety equatorially positioned.

These data for the 1′,3′-trans isomer **9** indicate that the conformational preference of the six-membered carbocyclic nucleosides is opposite to that of the anhydrohexitol nucleosides.[11,12] By replacement of the ring oxygen atom by a methylene group, the base moiety is changing preferably from an axial orientation to the equatorial orientation. Two reasons may be given for this observation. First, the unfavorable 1,3-diaxial interaction between the nucleoside base and the hydrogen atoms in the 3′- and 5′-position when a carbocyclic nucleoside with an axially oriented heterocycle is considered. With an equatorially oriented heterocycle, this unfavorable interaction is present between the 4-hydroxymethyl function and the hydrogen atoms in position 2′ and 6′ and also between 3′-OH and H-5′ and H-1′. These latter interactions may be less unfavorable than with the nucleoside base. Considering the anhydrohexitol nucleosides, only one sterically unfavorable 1,3-diaxial interaction is present when the nucleoside base is oriented axially. The opposite conformation is disfavored by three undesired interactions (CH_2OH group versus two hydrogen atoms (H1′, H3′) positioned in an axial orientation and 4′OH versus H2′). Secondly, the C−O bond lengths in the hexitol nucleosides are 0.1 Å shorter than the C−C bond lengths in the cyclohexane derivatives.[12,26] This means that with an equatorially oriented base moiety, the 1,3-diaxial interactions of the hydroxymethyl group

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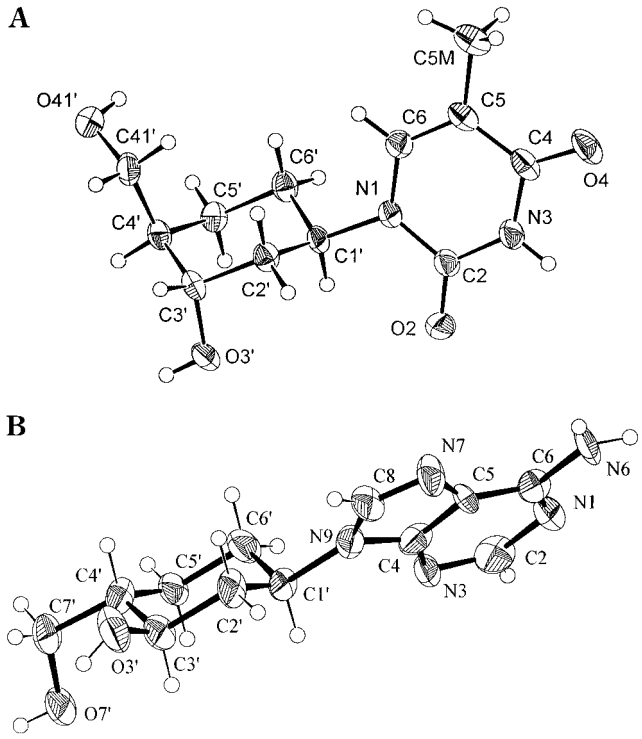


Figure 3. (A) Compound **10**. Molecular structure with atom-labeling scheme.[36] Displacement ellipsoids are plotted at the 40% probability level. H atoms are drawn as small circles of arbitrary radii. (B) Compound **20**. Molecular structure with atom-labeling scheme.[36] Displacement ellipsoids are plotted at the 40% probability level. H atoms are drawn as small circles of arbitrary radii. Only the part of the molecule with the highest occupation factor is shown for clarity.

are more disfavored in the hexitol ring than in the cyclohexane ring with its longer bonds. Finally, weak interactions between the axial base and the ring oxygen in the hexitol may not be totally excluded.

Antiviral Activity. All compounds (**3a**−**e**, **9**, **10**, **15**, **16**, **20**−**22**, **26**, **27**, **32**−**34**) were evaluated for their antiviral activity against herpes simplex virus-1 (HSV-1), herpes simplex virus-2 (HSV-2), vaccinia virus, vesicular stomatitis virus, Coxsackie virus B4, respiratory syncytial virus (RSV), parainfluenza-3 virus, reovirus-1, Sindbis virus, and Punta Toro virus and for their cytotoxicity in E_6SM cell cultures, Hela cell cultures, and Vero cell cultures. None of the compounds demonstrated any toxicity, and all compounds were completely inactive, with the exception of **3a** [minimal inhibitory concentration (MIC) against HSV-1: 10 μg/mL, against thymidine kinase deficient (TK^-) HSV-1: 20 μg/mL, against vaccinia virus: 20 μg/mL] and **15** (MIC against HSV-1: 7 μg/mL and against TK^- HSV-1: 20 μg/mL).

Conclusions

The differences in the antiviral activity between the anhydrohexitol nucleosides and their carbocyclic congeners are presented in Table 3. It is clear that nearly all activity disappears when the oxygen atom is replaced by a methylene function. This loss in antiviral activity also parallels a change in conformation. The structure of the anhydrohexitol nucleosides with their axially positioned base moiety resembles the structure of a furanose nucleoside in its 2′exo/3′endo conformation, which is not the case with the carbocyclic analogue. This is shown in Figure 4. This figure indeed shows that the three-dimensional structure of the anhydrohexitol pyrimidine nucleosides resembles that of C3′-endo puckered furanosyl nucleosides, but not of C2′-endo puckered furanoses. In contrast, no structural similarity at all is found between the carbocyclic pyrimidine nucleosides and normal furanosyl nucleoside (Figure 4). The high structural similarity between anhydrohexitol nucleosides and C3′-endo puckered furanose nucleosides, and the lack thereof in the case of carbocyclic nucleosides, might explain their differences in activity against human herpes simplex virus type 1 and 2 (Table 3).

Experimental Section

All experiments were carried out using instrumentations and manipulations as described previously.[7]

NMR Experiments. The samples for NMR conformational study were lyophilized three times from 99.98% D_2O (Aldrich); the measured solutions contained 4 mg of the compound in 0.7 mL of D_2O in a 5 mm Wilmad tube. All the NMR spectra were measured on a Varian Unity 500 spectrometer operating at 499.693 MHz for ^{1}H NMR and at 125.652 MHz for ^{13}C NMR. All the spectra were run at 33 °C, samples not spinning. ^{1}H NMR spectra were referenced to the line of water (internal) at $\delta = 4.64$, and ^{13}C NMR spectra were referenced to external acetone at $\delta = 30.70$. Standard Varian software version vnmr 5.1 was used throughout. All experiments (including GHSQC (edited),[20] GMQFCOPS,[22] and DPFGNOE[24]) were performed in a 5 mm "inverse detection" probe (with typical values for 90° pulses, 7.4 μs for ^{1}H pulses, and 14.0 μs for ^{13}C pulses) equipped with pulsed magnetic field *z*-gradient coils. Gradient pulses were performed by Performa II PFG source (Varian), and shaped pulses were generated by a waveform generator (Varian) using the shapes calculated by Pandora box program.

Heteronuclear (^{13}C−^{1}H) correlation (in a gradient enhanced variant, GHSQC[20]) and double-quantum filtered COSY[21] (DQF-COSYPS, again in gradient enhanced version GMQFCOPS[22]) experiments were used for assignments of ^{13}C NMR lines and all multiplets in ^{1}H NMR spectra. Proton chemical shifts and coupling constants derived from 1D spectra and assigned according to the DQFCOSYPS spectra were confirmed by spectral simulation and iterative fitting to 1D spectra using the vnmr simulation programs.

In order to extract a reliable value of the coupling constant between protons 3′ and 4′ in compound **9** selective multisite decoupled ^{1}H NMR spectra had to be recorded.[23] The splitting (4.1 Hz in **9**) observed in these spectra in the multiplet of proton 3′ is the residual splitting corresponding to the residual coupling constant J' with proton 4′. To get the true value of the coupling constant we took advantage of the residual couplings observed in the spectra of CH_2O protons which are also coupled to proton 4′. Since the decoupling field employed (γB_2 in Hz units) was much larger than the difference between the true (J) and the residual coupling constant (J') we could use Pachler's approximation[25] $J = J'[(1 + a^2)/a^2]^{1/2}$, where $a = \Delta\nu/\gamma B_2$. The decoupling offset ($\Delta\nu$ in Hz) and the decoupling field are the constants for the given experiment and the coupling partner (proton 4′) concerned, hence all the couplings to proton 4′ are reduced by the same factor. This yields true value $J(3',4') = 4.6$ Hz in **9**.

(±)-9-[4-(Ethoxycarbonyl)-3-cyclohexenyl]adenine (3a). A mixture of adenine **2a** (5.95 g, 44.0 mmol), ethyl 1,3-cyclohexadiene-1-carboxylate (**1**) (20.09 g, 132.0 mmol), DBU (1.65 mL, 11.0 mmol), and DMF (40 mL) was stirred at 75 °C for 48 h. After addition of AcOH (0.7 mL) and removal of volatile materials *in vacuo*, the residue was treated with MeOH (30 mL), and the resulting white crystals were filtered off, affording 10.8 g (85%) of **3a**: mp 212−213 °C. LSIMS (THGLY) 288 $[M + H]^+$, 136 $[B + 2H]^+$. UV λ_{max} (MeOH) = 262 nm (ϵ 14900). ^{1}H NMR ($CDCl_3$) δ 1.34 (3H), 2.10−3.0 (6H), 4.27 (2H), 4.81(1H), 5.89 (2H), 7.05 (1H), 7.87 (1H), 8.37 (1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 23.4, 27.9, 31.9, 50.0, 60.7, 120.0, 130.7, 135.5, 138.4, 149.9, 152.9, 155.6, 166.5. Anal. Calcd for $C_{14}H_{17}N_5O_2$: C, 58.52; H, 5.96; N, 24.37. Found: C, 58.48; H, 5.96; N, 24.37.

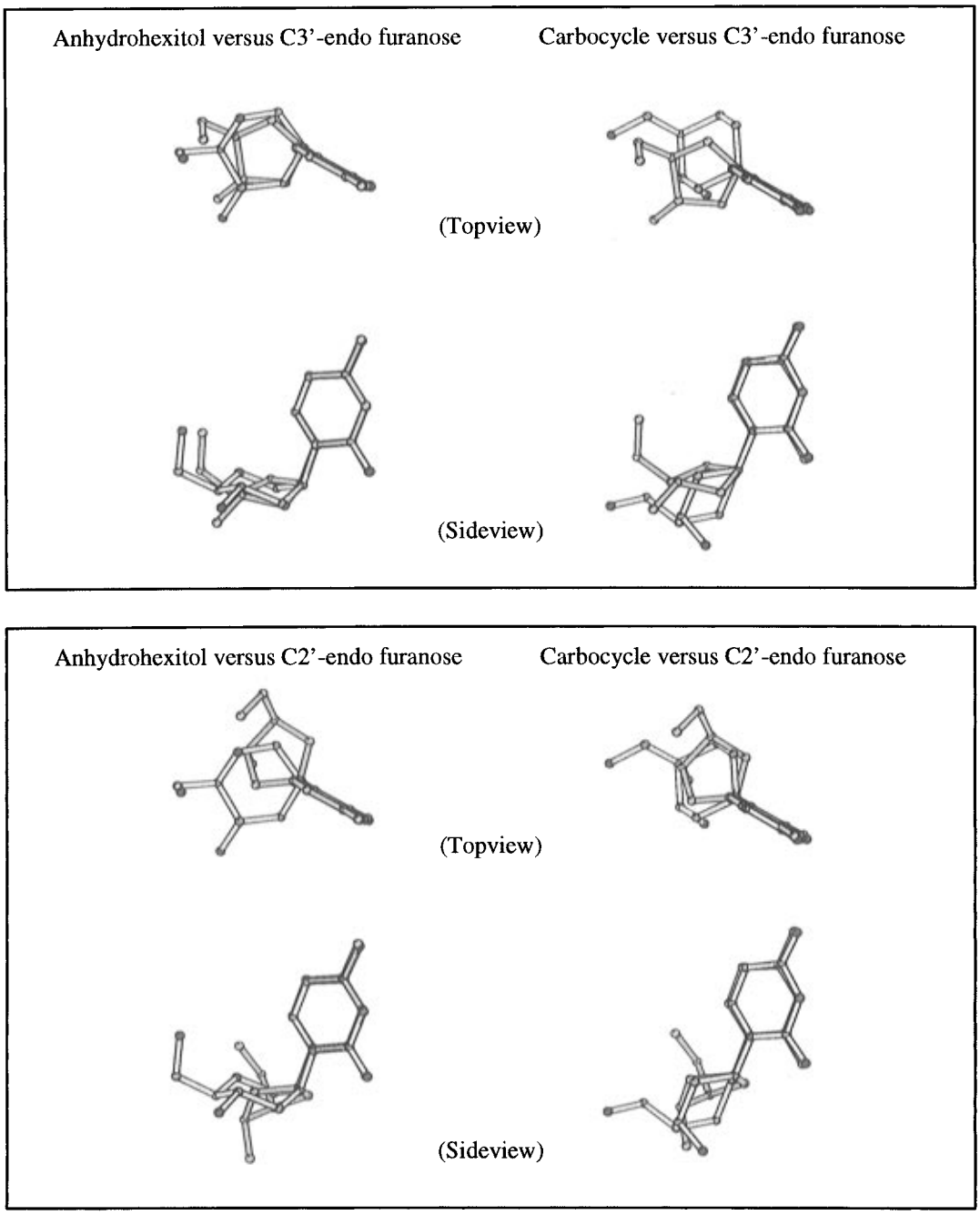


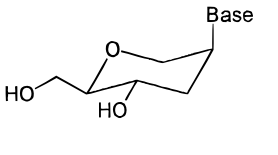
Figure 4. Comparison between the three-dimensional conformations of the six-membered sugar ring nucleosides (anhydrohexitol and carbocyclic) *versus* a normal nucleoside with its sugar moiety modeled in the two most common puckering conformations (C2′-endo and C3′-endo). All non-H atoms of the nucleobases were used in the fitting procedure. Figure produced with a locally modified version of Molscript.[37]

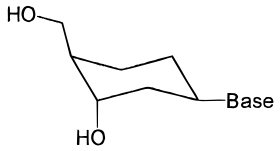
(±)-2-Amino-6-chloro-9-[4-(ethoxycarbonyl)-3-cyclohexenyl]purine (3b). Compound **3b** was obtained from 2-amino-6-chloropurine (**2b**) and **1** as described for the synthesis of **3a**. The crude product was purified by column chromatography (CH_2Cl_2−MeOH, 98:2) and crystallized from MeOH−Et_2O, affording 74% **3b**: mp 159−160 °C. LSIMS (THGLY) 322 $[M + H]^+$, 170 $[B + 2H]^+$. UV λ_{max} (MeOH) = 249 nm (ϵ 5300), 311 nm (ϵ 8100). ^{1}H NMR ($CDCl_3$) δ 1.25 (3H), 2.00−2.90 (6H), 4.15 (2H), 4.52 (1H), 6.92 (3H), 8.19 (1H). ^{13}C NMR ($CDCl_3$) δ 14.6, 23.9, 27.3, 31.0, 50.2, 60.8, 124.1, 130.0, 135.3, 142.1, 150.0, 154.1, 159.9, 166.5. Anal. Calcd for $C_{14}H_{16}N_5O_2Cl$: C, 52.26; H, 5.01; N, 21.77. Found: C, 52.28; H, 5.06; N, 21.72.

(±)-9-[4-(Ethoxycarbonyl)-3-cyclohexenyl]guanine (3c). A solution of **3b** (1.0 g, 3.10 mmol) in $CF_3COOH-H_2O$ (1:1, 15 mL) was stirred at rt for 48 h. The solvents were evaporated, and the residue was reevaporated from H_2O (30 mL × 3). The residue was treated with MeOH−NH_4OH (10:1, 15 mL) and evaporated. The solid was purified by column chromatography (CH_2Cl_2−MeOH, 4:1) to give 0.8 g (85%) of **3c**: mp >300 °C. LSIMS (THGLY) 607 $[2M + H]^+$, 304 $[M + H]^+$, 152 $[B + 2H]^+$. UV λ_{max} (MeOH) = 256 nm (ϵ 14000). ^{1}H NMR (DMSO-d_6) δ 1.24 (3H), 1.9−2.9 (6H), 4.14 (2H), 4.41 (1H), 6.42 (2H), 6.90 (1H), 7.74 (1H), 10.55 (1H). ^{13}C NMR (DMSO-d_6) δ 14.26, 23.7, 27.4, 31.2, 49.1, 60.2, 116.9, 129.6, 135.6, 136.9, 150.9, 153.4, 156.9, 166.0. Anal. Calcd for $C_{14}H_{17}N_5O_3 \cdot 0.25H_2O$: C, 54.63; H, 5.73; N, 22.75. Found: C, 54.66; H, 5.72; N, 22.49.

(±)-1-[4-(Ethoxycarbonyl)-3-cyclohexenyl]thymine (3d). Compound **3d** was prepared from thymine **2c** and **1** as described for synthesis of **3a** in 67% yield: mp 233−234 °C. LSIMS (THGLY) 557 $[2M + H]^+$, 279 $[M + H]^+$, 127 $[B + 2H]^+$. UV λ_{max} (MeOH) = 272 nm (ϵ 10300). ^{1}H NMR ($CDCl_3$) δ 1.33 (3H), 1.85−2.10 (5H), 2.22−2.78 (4H), 4.24 (2H), 4.75 (1H), 6.97 (1H), 7.03 (1H), 9.14 (1H). ^{13}C NMR ($CDCl_3$) δ 12.6, 14.2, 24.2, 27.0, 30.7, 50.6, 60.7, 111.2, 130.5, 135.8, 136.1, 150.9, 163.6,

Table 3. Activity against Herpes Simplex Virus of Anhydrohexitol Nucleosides and Their Carbocyclic Congeners[a] [minimal inhibitory concentration (μg/mL) or concentration required to reduce virus-induced cytopathicity by 50%]





	Base moiety					Base moiety				
	A	G	C	T	U	A (9)	G (15)	C (32)	T (20)	U (26)
HSV-1 (KOS)	7[b]	0.2[b]	0.7[b]	40[b]	>400[c]	>400	7	>400	>200	>400
HSV-2 (G)	7[b]	0.1[b]	0.04[b]	150[b]	>400[c]	300	>400	>400	>200	>400

[a] carbocyclic nucleosides as enantiomeric mixtures. [b] ref. 11. [c] ref. 12.

166.4. Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.23; H, 6.50; N, 10.12.

(±)-1-[4-(Ethoxycarbonyl)-3-cyclohexenyl]uracil (3e). A mixture of uracil **2d** (17.93 g, 160.0 mmol), **1** (12.18 g, 80.0 mmol), DBU (20.9 mL, 160.0 mmol), and DMF (80 mL) was stirred at 50 °C for 24 h. After addition of AcOH (8 mL), the volatiles were removed *in vacuo*, and the residue was suspended in CH_2Cl_2. Unreacted **2d** was filtered off, and the solution was washed with H_2O. The organic phase was dried with $MgSO_4$, evaporated, and purified by column chromatography (CH_2Cl_2−MeOH, 95:5) to give, after crystallization (CH_2Cl_2−Et_2O), 6.0 g (28%) of **3c**: mp 158−159 °C. LSIMS (THGLY) 529 $[2M + H]^+$, 265 $[M + H]^+$. UV λ_{max} (MeOH) = 267 nm (ϵ 11300). ^{1}H NMR ($CDCl_3$) δ 1.31 (3H), 1.8−2.8 (6H), 4.23 (2H), 4.76 (1H), 5.78 (1H), 6.95 (1H), 7.21 (1H), 7.79 (1H). ^{13}C NMR ($CDCl_3$) δ 14.2, 23.9, 26.9, 30.7, 50.8, 60.7, 102.7, 130.6, 135.7, 140.4, 151.0, 163.3, 166.3. Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.00; H, 6.15; N, 10.71.

(±)-*N*^{4}-(Monomethoxytrityl)cytosine (2f). Cytosine **2e** (2.22 g, 20.0 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (12.36 mL, 50.0 mmol) in pyridine (50 mL) was stirred at rt for 2 h. Monomethoxytrityl chloride (MMTrCl) (9.26 g, 30.0 mmol) and DMAP (30 mg) were added to the solution. After 16 h the reaction mixture was diluted with CH_2Cl_2 and washed twice with a saturated $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$, evaporated, and coevaporated with toluene. The residue was dissolved in CH_2Cl_2 (50 mL) and added with stirring to Me_2CO−Et_2O (1:1, 400 mL). The deposited crystals of **2f** were filtered off, washed with cold CH_2Cl_2 (30 mL), and dried to give 6.39 g (83%) of **2f**: mp 255−258 °C. LSIMS (THGLY + NaOAc) 428 $[M - H + 2Na]^+$, 406 $[M + Na]^+$, 273 $[MMTr]^+$. UV λ_{max} (MeOH) = 273 nm (ϵ 12000). ^{1}H NMR (DMSO-d_6) δ 3.74 (3H), 6.08 (1H), 6.83 (3H), 7.1−7.35 (12H), 8.25 (1H), 10.23 (1H). ^{13}C NMR (DMSO-d_6) δ 56.4, 69.6, 94.7, 112.7, 126.1, 127.3, 128.4, 129.8, 136.8, 140.9, 144.8, 155.5, 157.6, 164.3. Anal. Calcd for $C_{24}H_{21}N_3O_2$: C, 75.18; H, 5.52; N, 10.96. Found: C, 75.28; H, 5.55; N, 11.00.

(±)-*N*^{4}-(Monomethoxytrityl)-1-[4-(ethoxycarbonyl)-3-cyclohexenyl]cytosine (3f). A mixture of BSA (1.97 mL, 8.0 mmol) and **2f** (1.53 g, 4.0 mmol) in DMF (20 mL) was stirred at rt for 30 min. To the resulting solution were added **1** (3.64 g, 24.0 mmol) and DBU (0.15 mL, 1.0 mmol), and the reaction mixture was stirred at 75 °C for 48 h. After addition of AcOH (0.1 mL) and evaporation, the residue was purified by column chromatography, eluting with CH_2Cl_2 (300 mL) and CH_2Cl_2−MeOH 98:2 (500 mL), to give 0.64 g (30%) of **3f** as a foam: LSIMS (THGLY + NaOAc) 558 $[M + Na]^+$, 273 $[MMTr]^+$. UV λ_{max} (MeOH) = 286 nm (ϵ 15000). ^{1}H NMR ($CDCl_3$) δ 1.28 (3H), 1.65−2.85 (6H), 3.80 (3H), 4.19 (2H), 4.85 (1H), 5.04 (1H), 6.75−6.95 (5H), 7.10−7.40 (12H). ^{13}C NMR ($CDCl_3$) δ 14.2, 23.8, 26.9, 31.2, 51.2, 55.2, 60.5, 70.3, 94.6, 113.5, 127.4, 128.3, 128.5, 128.9, 129.9, 130.3, 135.9, 136.3, 140.9, 144.2, 155.8, 158.6, 164.8, 166.4. Anal. Calcd for $C_{33}H_{33}N_3O_4 \cdot 0.5H_2O$: C, 72.77; H, 6.29; N, 7.72. Found: C, 73.06; H, 6.14; N, 8.00.

(±)-*N*^{6}-(Monomethoxytrityl)-9-[4-(ethoxycarbonyl)-3-cyclohexenyl]adenine (4). A mixture of **3a** (5.75 g, 20.0 mmol) and MMTrCl (9.27 g, 30.0 mmol) in pyridine (100 mL) was stirred at 60 °C for 3 h. Another portion of MMTrCl (3.09 g, 10.0 mmol) was added, and the solution was heated at 60 °C overnight. The reaction was quenched with MeOH (10 mL) and evaporated. The residue was dissolved in CH_2Cl_2 (300 mL) and treated with a saturated $NaHCO_3$ solution (50 mL). The organic layer was dried over $MgSO_4$, evaporated, and coevaporated with toluene. The residue was purified by column chromatography (hexane to hexane−EtOAc, 1:3) to afford 9.30 g (83%) of **4** as a foam: LSIMS (THGLY + NaOAc) 560 $[M + H]^+$, 273 $[MMTr]^+$, 136 $[B + 2H]^+$. UV λ_{max} (MeOH) = 276 nm (ϵ 23400). ^{1}H NMR ($CDCl_3$) δ 1.34 (3H), 2.15−2.95 (6H), 3.82 (3H), 4.27 (2H), 4.77 (1H), 6.83 (2H), 6.99 (1H), 7.05 (1H), 7.20−7.45 (12H), 7.80 (1H), 8.10 (1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 23.4, 27.9, 31.9, 50.0, 55.2, 60.7, 71.0, 113.1, 121.2, 126.8, 127.9, 128.9, 130.2, 130.6, 135.6, 137.2, 137.6, 145.2, 148.7, 152.1, 154.2, 158.3, 166.5. Anal. Calcd for $C_{34}H_{33}N_5O_3 \cdot 0.25H_2O$: C, 72.39; H, 5.98; N, 12.41. Found: C, 72.39; H, 6.03; N, 12.38.

(±)-*N*^{6}-(Monomethoxytrityl)-9-[4-(hydroxymethyl)-3-cyclohexenyl]adenine (5). To a solution of **4** (6.2 g, 11.0 mmol) in CH_2Cl_2 (100 mL) under N_2 at 0 °C was added DIBAL (1.0 M solution in hexane, 44 mL, 44.0 mmol) in 20 min, and the reaction mixture was stirred 20 min longer. Excess of DIBAL was destroyed by slow addition of MeOH (20 mL) at 0 °C. The resulting suspension was adsorbed on silica gel (30 mL) and put on top of a silica gel column. Elution with CH_2Cl_2−MeOH 95:5 afforded after crystallization (AcOEt−hexane) 4.3 g (75%) of **5**: mp 119−121 °C. LSIMS (THGLY + NaOAc) 540 $[M + Na]^+$, 518 $[M + H]^+$, 273 $[MMTr]^+$. UV λ_{max} (MeOH) = 277 nm (ϵ 23500). ^{1}H NMR ($CDCl_3$) δ 2.1−2.8 (7H), 3.82 (3H), 4.09 (2H), 4.79 (1H), 5.80 (1H), 6.83 (2H), 7.05 (1H), 7.20−7.45 (12H), 7.84 (1H), 8.10 (1H). ^{13}C NMR ($CDCl_3$) δ 24.4, 28.2, 31.2, 50.5, 55.2, 66.4, 71.0, 113.1, 119.3, 121.0, 126.8, 127.8, 128.9, 130.2, 137.3, 137.9, 138.0, 145.2, 148.7, 152.0, 154.1, 158.3. Anal. Calcd for $C_{32}H_{31}N_5O_2 \cdot 0.5H_2O$: C, 72.98; H, 6.12; N, 13.30. Found: C, 72.77; H, 6.20; N, 12.93.

(±)-*N*^{6}-(Monomethoxytrityl)-9-[4-(trityloxymethyl)-3-cyclohexenyl]adenine (6). A mixture of **5** (2.06 g, 4.0 mmol) and trityl chloride (TrCl) (1.12 g, 6.0 mmol) in pyridine (30 mL) was stirred at 70 °C for 3 h. After workup of the reaction mixture as described for **4**, crude compound **6** was purified by column chromatography (hexane−EtOAc, 4:1 to 1:1) affording 2.57 g (85%) as a foam: LSIMS (THGLY + NaOAc) 760 $[M + H]^+$, 273 $[MMTr]^+$, 243 $[Tr]^+$, 136 $[B + 2H]^+$. UV λ_{max} (MeOH) = 276 nm (ϵ 25700). ^{1}H NMR ($CDCl_3$) δ 2.0−2.8 (6H), 2.53 (2H), 3.08 (3H), 4.76 (1H), 5.90 (1H), 6.80 (2H), 6.92 (1H),

7.20−7.45 (27H), 7.82 (1H), 8.10 (1H). ^{13}C NMR ($CDCl_3$) δ 25.0, 28.2, 31.3, 50.5, 55.2, 67.0, 70.9, 86.6, 113.1, 119.1, 120.9, 126.8, 126.9, 127.8, 128.6, 128.8, 130.2, 135.7, 137.2, 137.9, 144.0, 145.2, 148.7, 152.0, 154.1, 158.2. Anal. Calcd for $C_{51}H_{45}N_5O_2\cdot0.5H_2O$: C, 79.66; H, 6.03; N, 9.11. Found: C, 79.77; H, 6.19; N, 8.73.

(1*RS*,3*SR*,4*RS*)-9-[4-(Hydroxymethyl)-3-hydroxycyclohexyl]adenine (9) and (1*RS*,3*RS*,4*SR*)-9-[4-(Hydroxymethyl)-3-hydroxycyclohexyl]adenine (10). To a stirred solution of **6** (3.04 g, 4.0 mmol) in THF (50 mL) under N_2 was added BH_3−THF (1 M solution in THF, 18.0 mL) at 0 °C. After being stirred at rt for 7 h, the solution was diluted with H_2O (20 mL) and EtOH (20 mL), made basic with a 3 M aqueous NaOH solution (30 mL), and 35% H_2O_2 (35 mL) was slowly added. The mixture was stirred at 45 °C for 20 h. To the solution was added saturated aqueous Na_2SO_3 (35 mL). The mixture was extracted with CH_2Cl_2 (100 mL × 3), dried over $MgSO_4$, and evaporated. The residue was chromatographed (CH_2Cl_2−EtOAc, 4:1 to 1:1) to obtain 1.0 g (32%) of **7** and 0.87 g (28%) of **8a** as foams. For **7**: LSIMS (THGLY + NaOAc) 822 $[M - H + 2Na]^+$, 800 $[M + Na]^+$, 778 $[M + H]^+$, 273 $[MMTr]^+$, 243 $[Tr]^+$, 136 $[B + 2H]^+$. UV λ_{max} (MeOH) = 276 nm (ϵ 24200). ^{1}H NMR ($CDCl_3$) δ 1.3−2.15 (7H), 3.10−3.22 (2H), 3.46 (1H), 3.78 (3H), 4.10 (1H), 4.81 (1H), 6.78 (2H), 6.93 (1H), 7.15−7.52 (27H), 7.62 (1H), 7.98 (1H). ^{13}C NMR ($CDCl_3$) δ 21.9, 27.9, 35.6, 40.9, 50.0, 55.2, 64.8, 68.7, 70.9, 86.9, 113.1, 121.0, 126.5, 126.8, 127.2, 127.9, 128.6, 128.9, 129.2, 130.2, 137.2, 137.9, 143.7, 145.2, 148.6, 151.8, 154.1, 158.3. Anal. Calcd for $C_{51}H_{47}N_5O_3\cdot0.5H_2O$: C, 77.84; H, 6.15; N, 8.90. Found: C, 77.53; H, 6.14; N, 8.71.

Compound **7** (1.0 g, 1.3 mmol) was deprotected by treatment with 80% aqueous AcOH at 60 °C for 4 h. After removal of AcOH by evaporation and coevaporation with toluene, the residue was dissolved in MeOH (10 mL) and adsorbed on silica gel, and the silica was placed on top of a silica gel column. Elution with CH_2Cl_2−MeOH (95:5 to 85:15) afforded after crystallization (MeOH−H_2O) 0.23 g (68%) of **9**: mp 229−230 °C. LSIMS (THGLY) 264 $[M + H]^+$, 136 $[B + 2H]^+$. UV λ_{max} (H_2O) = 263 nm (ϵ 13300). ^{1}H NMR (DMSO-d_6) δ 1.55−2.05 (6H), 2.23 (1H), 3.56 (2H), 3.95 (1H), 4.43 (1H), 4.62 (1H), 4.71 (1H), 7.07 (2H), 8.10 (1H), 8.22 (1H). ^{13}C NMR (DMSO-d_6) δ 21.4, 27.6, 35.0, 42.3, 49.5, 61.3, 66.1, 118.9, 139.5, 149.3, 152.1, 156.1. Anal. Calcd for $C_{12}H_{17}N_5O_2$: C, 54.74; H, 6.51; N, 26.60. Found: C, 54.76; H, 6.58; N, 26.91.

To crude **8a** (1.0 g, 1.3 mmol), dissolved and stirred at 0 °C in pyridine (10 mL) were added Ac_2O (1 mL) and DMAP (10 mg). The reaction mixture was stirred overnight at rt, evaporated, and partitioned between CH_2Cl_2 and H_2O. The organic layer was washed with a saturated $NaHCO_3$ solution (20 mL), dried over $MgSO_4$, and evaporated. Chromatographic purification (hexane to hexane−Et_2O, 1:3) of the residue afforded 0.77 g (84%) of **8b** as a foam: LSIMS (THGLY + NaOAc) 842 $[M + Na]^+$, 273 $[MMTr]^+$, 243 $[Tr]^+$. UV λ_{max} (MeOH) = 276 nm (ϵ 25100). ^{1}H NMR ($CDCl_3$) δ 1.80 (3H), 1.85−2.60 (7H), 3.15 (2H), 3.78 (3H), 4.57 (1H), 5.0 (1H), 6.78 (2H), 6.92 (1H), 7.10−7.45 (27H), 7.78 (1H), 8.08 (1H). ^{13}C NMR ($CDCl_3$) δ 20.9, 26.2, 37.4, 52.6, 55.2, 62.2, 70.9, 86.2, 113.1, 121.2, 126.8, 126.9, 127.8, 127.9, 128.4, 128.7, 130.2, 137.3, 137.7, 143.9, 145.2, 148.5, 152.0, 154.2, 158.3, 170.0. Anal. Calcd for $C_{53}H_{49}N_5O_4\cdot0.1H_2O$: C, 77.46; H, 6.03; N, 8.52. Found: C, 77.08; H, 6.08; N, 8.50. Compound **8b** (0.77 g, 0.94 mmol) was deprotected by the treatment with 80% HOAc at 60 °C for 4 h. After removal of AcOH by evaporation and coevaporation with toluene, the residue was deacetylated by treatment with a mixture of NH_3 (25%)−MeOH−1,4-dioxane (1:1:1, 30 mL) at rt overnight. Solvents were removed by evaporation, and the solid residue was purified chromatographically as described for **9**, yielding after crystallization (H_2O−MeOH−Et_2O) 0.14 g (56%) of **10**: mp 232−233 °C. LSIMS (THGLY) 264 $[M + H]^+$, 136 $[B + 2H]^+$. UV λ_{max} (H_2O) = 263 nm (ϵ 14000). ^{1}H NMR (DMSO-d_6) δ 1.1−2.2 (7H), 3.3 (2H), 3.69 (1H), 4.35 (1H), 4.44 (1H), 4.82 (1H), 7.20 (2H), 8.13 (1H), 8.22 (1H). ^{13}C NMR (DMSO-d_6) δ 25.9, 31.2, 41.2, 46.2, 52.1, 62.9, 69.0, 119.1, 139.1, 149.2, 152.2, 156.1. Anal. Calcd for $C_{12}H_{17}N_5O_2\cdot0.25H_2O$: C, 53.82; H, 6.49; N, 26.15. Found: C, 53.68; H, 6.53; N, 26.14.

(±)-*N*^{2}-(Monomethoxytrityl)-9-[4-(ethoxycarbonyl)-3-cyclohexenyl]guanine (11). Compound **11** was obtained by reaction of **3c** with MMTrCl as described for **4**. Chromatographic purification (EtOAc−hexane, 1:1 to 4:1) afforded **11** in 80% yield as a foam: LSIMS (THGLY + NaOAc) 620 $[M - H + 2Na]^+$, 598 $[M + Na]^+$, 273 $[MMTr]^+$. UV λ_{max} (MeOH) = 262 nm (ϵ 14300). ^{1}H NMR ($CDCl_3$) δ 1.36 (3H), 1.64 (2H), 2.22 (4H), 3.76 (3H), 3.79 (1H), 4.26 (2H), 6.70 (3H), 7.00−7.40 (13H), 8.03 (1H), 11.8 (1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 23.6, 26.9, 30.6, 50.6, 55.1, 60.6, 70.4, 112.8, 118.0, 126.4, 127.5, 127.9, 128.1, 128.9, 129.8, 130.3, 135.5, 136.2, 137.1, 145.0, 152.2, 158.1, 159.3, 166.7. Anal. Calcd for $C_{34}H_{33}N_5O_4\cdot0.25H_2O$: C, 70.39; H, 5.78; N, 12.07. Found: C, 70.61; H, 5.84; N, 11.67.

(±)-*N*^{2}-(Monomethoxytrityl)-9-[4-(hydroxymethyl)-3-cyclohexenyl]guanine (12). Compound **12** was obtained by reaction of **11** with DIBAL as described for **5**. Chromatographic purification (CH_2Cl_2−MeOH, 95:5 to 4:1) and crystallization (EtOAC−hexane) afforded 87% of **12**: mp 173−175 °C. LSIMS (THGLY + NaOAc) 1133 $[2M - 2H + 3Na]^+$, 578 $[M - H + 2Na]^+$, 556 $[M + Na]^+$, 273 $[MMTr]^+$. UV λ_{max} (MeOH) = 262 nm (ϵ 13700). ^{1}H NMR (DMSO-d_6) δ 1.35−2.3 (6H), 3.72 (3H), 3.80 (3H), 4.75 (1H), 5.42 (1H), 6.8−7.35 (15H), 7.60 (1H), 10.55 (1H). ^{13}C NMR (DMSO-d_6) δ 24.8, 27.1, 29.4, 51.2, 55.1, 64.5, 69.7, 113.0, 117.7, 126.6, 127.7, 128.5, 129.9, 136.4, 137.0, 137.9, 145.1, 149.4, 150.2, 156.7, 157.8. Anal. Calcd for $C_{32}H_{31}N_5O_3\cdot0.5H_2O$: C, 70.83; H, 5.94; N, 12.91. Found: C, 70.78; H, 5.74; N, 13.02.

(±)-*N*^{2}-(Monomethoxytrityl)-9-[4-(trityloxymethyl)-3-cyclohexenyl]guanine (13). Compound **13** was obtained after reaction of **12** with TrCl as described for **6**. Chromatographic purification (EtOAc−hexane, 4:1) gave 90% of **13** as a foam: LSIMS (THGLY + NaOAc) 820 $[M - H + 2Na]^+$, 798 $[M + Na]^+$, 273 $[MMTr]^+$, 243 $[Tr]^+$. UV λ_{max} (MeOH) = 261 nm (ϵ 14200). ^{1}H NMR ($CDCl_3$) δ 1.6−2.35 (6H), 3.49 (2H), 3.75 (3H), 4.05 (1H), 5.75 (1H), 6.80 (2H), 7.20−7.60 (29H), 10.80 (1H). ^{13}C NMR ($CDCl_3$) δ 25.3, 27.3, 30.1, 51.3, 55.0, 67.1, 70.2, 86.6, 112.7, 117.9, 119.5, 126.1, 127.0, 127.3, 127.8, 128.6, 128.9, 130.1, 130.4, 135.0, 135.6, 137.2, 144.2, 145.1, 150.1, 150.6, 157.8, 159.4. Anal. Calcd for $C_{51}H_{45}N_5O_3\cdot0.5H_2O$: C, 78.03; H, 5.91; N, 8.92. Found: C, 77.67; H, 5.82; N, 9.11.

(1*RS*,3*SR*,4*RS*)-*N*^{2}-(Monomethoxytrityl)-9-[4-(trityloxymethyl)-3-hydroxycyclohexyl]guanine (14). Compound **14** was obtained by reaction of **13** with BH_3−THF as described in the procedure for synthesis of **7**. Column chromatography (CH_2Cl_2−MeOH, 97:3) afforded **14** (40%) as a foam: LSIMS (THGLY + NaOAc) 794 $[M + H]^+$, 273 $[MMTr]^+$, 243 $[Tr]^+$. UV λ_{max} (MeOH) = 263 nm (ϵ 14200). ^{1}H NMR ($CDCl_3$) δ 1.2−2.4 (7H), 3.10 (2H), 3.46 (1H), 3.62 (3H), 3.76 (1H), 3.98 (1H), 6.65 (2H), 7.00−7.50 (28H), 11.84 (1H). ^{13}C NMR ($CDCl_3$) δ 21.9, 26.8, 36.0, 40.7, 49.3, 55.1, 65.1, 68.5, 70.4, 86.9, 112.7, 117.3, 126.6, 127.2, 127.4, 127.9, 128.6, 129.0, 130.6, 134.8, 137.0, 143.8, 144.2, 144.9, 145.1, 150.1, 150.6, 157.9, 159.4. Anal. Calcd for $C_{51}H_{47}N_5O_4\cdot1.5H_2O$: C, 74.61; H, 6.13; N, 8.53. Found: C, 74.72; H, 5.91; N, 8.75.

(1*RS*,3*SR*,4*RS*)-9-[4-(Hydroxymethyl)-3-hydroxycyclohexyl]guanine (15). Compound **15** was obtained in 72% yield from **14** as described in the procedure for synthesis of **9**. **15**: mp 255−257 °C. LSIMS (THGLY) 280 $[M + H]^+$, 152 $[B + 2H]^+$. UV λ_{max} (H_2O) = 253 nm (ϵ 13200). ^{1}H NMR (DMSO-d_6) δ 1.5−2.2 (7H), 3.53 (2H), 3.97 (1H), 4.54 (2H), 4.72 (1H), 6.44 (2H), 7.86 (1H), 10.53 (1H). ^{13}C NMR (DMSO-d_6) δ 21.5, 28.1, 35.1, 42.2, 48.4, 61.2, 66.1, 116.6, 135.8, 150.8, 153.4, 157.0. Anal. Calcd for $C_{12}H_{17}N_5O_3\cdot H_2O$: C, 48.48; H, 6.44; N, 23.55. Found: C, 48.13; H, 6.43; N, 23.28.

(±)-1-[4-(Hydroxymethyl)-3-cyclohexenyl]thymine (16). Compound **16** was obtained from **3d** in 79% yield after reaction with DIBAL as described for **5**: mp 201−202 °C. LSIMS (THGLY) 237 $[M + H]^+$, 127 $[B + 2H]^+$. UV λ_{max} (MeOH) = 272 nm (ϵ 8800). ^{1}H NMR (DMSO-d_6) δ 1.5−2.3 (9H), 3.80 (2H), 4.45 (1H), 4.73 (1H), 5.56 (1H), 7.60 (1H), 11.21 (1H). ^{13}C NMR (DMSO-d_6) δ 12.2, 25.6, 26.7, 29.5, 51.1, 64.5, 109.1, 118.2, 137.9, 138.3, 151.0, 163.9. Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.93; H, 6.93; N, 11.87.

(±)-1-[4-(Trityloxymethyl)-3-cyclohexenyl]thymine (17). Compound **17** was obtained in the reaction of **16** with TrCl as described for **6** in 56% yield as a foam: LSIMS (THGLY + NaOAc) 501 $[M + Na]^+$, UV λ_{max} (MeOH) = 271 nm (ϵ 8600). ^{1}H NMR ($CDCl_3$) δ 1.8−2.55 (9H), 3.52 (2H), 4.76 (1H), 5.78 (1H), 7.05 (1H), 7.15−7.50 (15H), 8.98 (1H). ^{13}C NMR ($CDCl_3$) δ 12.7, 25.8, 27.3, 30.2, 51.1, 67.1, 86.6, 110.8, 119.5, 127.0, 127.8, 128.6, 135.7, 136.6, 144.1, 151.1, 163.8. Anal. Calcd for $C_{31}H_{30}N_2O_3 \cdot 0.4H_2O$: C, 76.65; H, 6.39; N, 5.77. Found: C, 76.78; H, 6.38; N, 5.72.

(1*RS*,3*SR*,4*RS*)-1-[4-(Trityloxymethyl)-3-hydroxycyclohexyl]thymine (18) and (1*RS*,3*RS*,4*SR*)-1-[4-(Trityloxymethyl)-3-hydroxycyclohexyl]thymine (19). Compounds **18** and **19** were obtained in the reaction of **17** with BH_3−THF as described in the procedure for the synthesis of **7** and **8** (reaction time 1 h). Column chromatography (CH_2Cl_2−MeOH, 99:1) afforded **18** (34%) and **19** (21%) as foams. **18**: LSIMS (NBA) 497 $[M + Na]^+$, 243 $[Tr]^+$. UV λ_{max} (MeOH) = 271 nm (ϵ 9400). ^{1}H NMR ($CDCl_3$) δ 1.0−2.0 (10H), 3.18 (2H), 3.92 (1H), 4.60 (1H), 4.78 (1H), 6.98 (1H), 7.15−7.50 (15H), 11.17 (1H). ^{13}C NMR ($CDCl_3$) δ 12.5, 21.6, 26.1, 33.9, 38.9, 49.5, 62.9, 68.0, 86.6, 110.5, 127.0, 127.8, 128.7, 136.4, 143.9, 150.9, 163.7. Anal. Calcd for $C_{31}H_{32}N_2O_4 \cdot 1.3H_2O$: C, 71.60; H, 6.71; N, 5.39. Found: C, 71.47; H, 6.52; N, 5.47. **19**: LSIMS (TDG) 497 $[M + H]^+$, 243 $[Tr]^+$. UV λ_{max} (MeOH) = 271 nm (ϵ 9300). ^{1}H NMR ($CDCl_3$) δ 1.1−2.2 (10H), 3.10 (1H), 3.41 (1H), 3.62 (1H), 3.78 (1H), 4.47 (1H), 7.03 (1H), 7.2−7.3 (15H), 8.55 (1H). ^{13}C NMR ($CDCl_3$) δ 12.6, 25.1, 30.4, 38.9, 43.5, 51.7, 67.7, 72.7, 87.6, 110.9, 127.2, 127.5, 128.0, 128.4, 136.0, 143.3, 150.6, 163.2. Anal. Calcd for $C_{31}H_{32}N_2O_4 \cdot 1.4H_2O$: C, 71.35; H, 6.45; N, 5.37. Found: C, 71.54; H, 6.72; N, 5.39.

(1*RS*,3*SR*,4*RS*)-1-[4-(Hydroxymethyl)-3-hydroxycyclohexyl]thymine (20). Compound **20** was obtained by deprotection of **18** with 80% aqueous HOAc as described for **9**. The yield of **20** after crystallization (MeOH−H_2O−Et_2O) was 72%: mp 218−220 °C. LSIMS (THGLY) 255 $[M + H]^+$, 127 $[B + 2H]^+$. UV λ_{max} (H_2O) = 274 nm (ϵ 9100). ^{1}H NMR (DMSO-d_6) δ 1.3−1.9 (10H), 3.46 (2H), 3.98 (1H), 4.46 (1H), 4.65 (2H), 7.64 (1H), 11.13 (1H). ^{13}C NMR (DMSO-d_6) δ 12.0, 21.4, 26.1, 33.5, 41.7, 49.1, 61.0, 66.3, 108.8, 138.2, 150.9, 163.8. Anal. Calcd for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.56; H, 7.23; N, 10.93.

(1*RS*,3*RS*,4*SR*)-1-[4-(Hydroxymethyl)-3-hydroxycyclohexyl]thymine (21). Compound **21** was obtained after deprotection of **19** with 80% HOAc as described for **9**. The yield of **21** after crystallization (MeOH−H_2O−Et_2O) was 81%: mp 234−236 °C. LSIMS (GLY) 255 $[M + H]^+$. UV λ_{max} (H_2O) = 275 nm (ϵ 9100). ^{1}H NMR (DMSO-d_6) δ 1.0 −1.9 (10H), 3.34 (2H), 3.67 (1H), 4.28 (1H), 4.42 (1H), 4.82 (1H), 7.63 (1H). ^{13}C NMR (DMSO-d_6) δ 12.2, 25.5, 29.7, 38.8, 45.9, 51.8, 62.8, 69.1, 109.0, 137.8, 150.7, 163.8. Anal. Calcd for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.34; H, 7.24; N, 10.90.

(±)-1-[4-(Hydroxymethyl)-3-cyclohexenyl]uracil (22). Compound **22** was obtained from **3e** in 69% yield after reaction with DIBAL as described for **5**: mp 167−168 °C. LSIMS (THGLY) 445 $[2M + H]^+$, 223 $[M + H]^+$, 113 $[B + 2H]^+$. UV λ_{max} (MeOH) = 268 nm (ϵ 8900). ^{1}H NMR (DMSO-d_6) δ 1.6−2.35 (6H), 3.80 (2H), 4.45 (1H), 4.73 (1H), 5.56 (2H), 7.68 (1H), 11.24 (1H). ^{13}C NMR (DMSO-d_6) δ 25.4, 26.6, 29.5, 51.4, 64.5, 101.4, 118.1, 138.4, 142.3, 151.1, 163.3. Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.25; H, 6.53; N, 12.64.

(±)-1-[4-(Trityloxymethyl)-3-cyclohexenyl]uracil (23). Reaction of **22** with TrCl as described for **6** afforded **23** in 71% yield as a foam: LSIMS (NPOE) 465 $[M + H]^+$, 243 $[Tr]^+$. UV λ_{max} (MeOH) = 267 nm (ϵ 9300). ^{1}H NMR ($CDCl_3$) δ 1.8−2.7 (6H), 3.56 (2H), 4.81 (1H), 5.79 (1H), 5.85 (1H), 7.2−7.55 (16H), 9.38 (1H). ^{13}C NMR ($CDCl_3$) δ 25.5, 27.2, 30.2, 51.3, 67.0, 86.7, 102.4, 119.2, 127.1, 127.8, 128.3, 128.6, 135.8, 140.8, 144.1, 151.0, 163.3. Anal. Calcd for $C_{30}H_{28}N_2O_3 \cdot 0.5H_2O$: C, 76.09; H, 6.17; N, 5.92. Found: C, 76.30; H, 6.20; N, 6.14.

(1*RS*,3*SR*,4*RS*)-1-[4-(Hydroxymethyl)-3-hydroxycyclohexyl]uracil (26) and (1*RS*,3*RS*,4*SR*)-1-[4-(Hydroxymethyl)-3-hydroxycyclohexyl]uracil (27). To a stirred solution of **23** (3.25 g, 7.0 mmol) in THF (50 mL) under N_2 was added BH_3−THF (1 M solution in THF, 17.5 mL) at −10 °C. After being stirred at −10 °C for 2 h and at 5 °C for 4 h, the solution was cooled to −30 °C, diluted with H_2O (15 mL) and EtOH (15 mL), and made basic with 3 M aqueous NaOH (10 mL) after which 35% H_2O_2 (5 mL) was slowly added. The mixture was stirred at −30 °C for 15 min and then saturated aqueous Na_2SO_3 (5 mL) was added. The solution was extracted with CH_2Cl_2 (100 mL × 3), the combined extracts were dried over $MgSO_4$, and the solvent was evaporated. The residue was chromatographed through a short column of silica gel (2.5 × 10 cm, CH_2Cl_2−MeOH, 95:5) to give a mixture of **24** and **25** (1.8 g), which was deprotected by treatment of 80% aqueous AcOH at 60 °C for 1 h. After removal of HOAc by evaporation, the residue was purified by column chromatography as described for compound **9**, affording after crystallization (MeOH−H_2O−Et_2O) 0.31 g (18%) of **26** and 0.26 g (15%) of **27**. For **26**: mp 208−210 °C. LSIMS (GLY) 241 $[M + H]^+$. UV λ_{max} (H_2O) = 269 nm (ϵ 8900). ^{1}H NMR (DMSO-d_6) δ 1.4−1.95 (7H), 3.50 (2H), 3.98 (1H), 4.50 (1H), 4.71 (2H), 5.55 (1H), 7.80 (1H), 11.20 (1H). ^{13}C NMR (DMSO-d_6) δ 21.4, 26.1, 33.5, 41.7, 49.6, 61.1, 66.3, 101.1, 142.8, 151.1, 163.2. Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.88; H, 6.83; N, 11.46. For **27**: mp 209−211 °C. LSIMS (GLY) 241 $[M + H]^+$. UV λ_{max} (H_2O) = 269 nm (ϵ 9300). ^{1}H NMR (DMSO-d_6) δ 1.0−1.95 (7H), 3.31 (2H), 3.62 (1H), 4.25 (1H), 4.40 (1H), 4.81 (1H), 5.55 (1H), 7.74 (1H), 11.23 (1H). ^{13}C NMR (DMSO-d_6) δ 25.5, 29.7, 40.0, 45.9, 52.2, 62.8, 69.1, 101.3, 142.2, 150.9, 163.2. Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.01; H, 6.79; N, 11.62.

(±)-*N*^{4}-(Monomethoxytrityl)-1-[4-(hydroxymethyl)-3-cyclohexenyl]cytosine (28). As described for **5** compound **28** was obtained from **3f** in 55% yield as a foam after reaction with DIBAL: LSIMS (THGLY + NaOAc) 516 $[M + Na]^+$, 273 $[MMTr]^+$. UV λ_{max} (MeOH) = 286 nm (ϵ 15800). ^{1}H NMR ($CDCl_3$) δ 1.80−2.50 (6H), 2.95 (1H), 3.81 (3H), 4.00 (2H), 4.80-(1H), 5.03 (1H), 5.65 (1H), 6.84−6.98 (4H), 7.15−7.36 (12H). ^{13}C NMR ($CDCl_3$) δ 25.0, 27.3, 30.5, 51.7, 55.2, 66.1, 70.4, 94.5, 113.5, 119.6, 127.4, 127.7, 128.2, 128.5, 129.9, 135.9, 137.7, 141.3, 144.2, 155.9, 158.6, 164.7. Anal. Calcd for $C_{31}H_{31}N_3O_3$: C, 75.43; H, 6.33; N, 8.51. Found: C, 75.72; H, 6.42; N, 8.90.

(±)-*N*^{4}-(Monomethoxytrityl)-1-[4-(trityloxymethyl)-3-cyclohexenyl]cytosine (29). Compound **29** was obtained after reaction of **28** with TrCl as described for **6** in 72% yield as a foam: LSIMS (NBA) 735 $[M + H]^+$, 273 $[MMTr]^+$, 243 $[Tr]^+$. UV λ_{max} (MeOH) = 286 nm (ϵ 14300). ^{1}H NMR ($CDCl_3$) δ 1.7−2.65 (6H), 3.49 (2H), 3.82 (3H), 4.90 (1H), 5.05 (1H), 5.80 (1H), 6.86−6.99 (4H), 7.20−7.55 (27H). ^{13}C NMR ($CDCl_3$) δ 25.5, 27.3, 30.6, 51.6, 55.2, 67.0, 70.3, 86.6, 113.5, 119.6, 126.9, 127.4, 127.7, 128.3, 128.5, 129.9, 135.4, 136.0, 141.3, 144.1, 144.3, 156.0, 158.6, 164.7. Anal. Calcd for $C_{50}H_{45}N_3O_3 \cdot 0.5H_2O$: C, 80.62; H, 6.22; N, 5.64. Found: C, 80.47; H, 6.22; N, 5.51.

(1*RS*,3*SR*,4*RS*)-1-[4-(Hydroxymethyl)-3-hydroxycyclohexyl]cytosine (32) and (1*RS*,3*RS*,4*SR*)-1-[4-(Hydroxymethyl)-3-hydroxycyclohexyl]cytosine (33). Method 1. A mixture of compounds **30** and **31** was obtained after reaction of **29** with BH_3−THF as described for the synthesis of **24** and **25**. Basic oxidation with H_2O_2 was performed at 40 °C for 2 h. The inseparable mixture of **30** and **31**, after isolation by short column chromatography (2.5 × 10 cm, CH_2Cl_2−MeOH, 99.5:0.5), was deprotected with 80% aqueous AcOH at 60 °C for 3 h. Chromatographic purification as described for **9** and crystallization (MeOH) afforded title compounds **32** (10%) and **33** (30%). For **32**: mp 264−266 °C. LSIMS (NBA) 240 $[M + H]^+$, 112 $[B + 2H]^+$. UV λ_{max} (H_2O) = 275 nm (ϵ 9500). ^{1}H NMR (DMSO-d_6) δ 1.4−1.8 (7H), 3.46 (2H), 3.94 (1H), 4.46 (1H), 4.61 (1H), 4.74 (1H), 5.62 (1H), 6.89 (2H), 7.64 (1H). ^{13}C NMR (DMSO-d_6) δ 21.5, 26.7, 33.9, 41.8, 49.6, 61.2, 66.4, 93.3, 142.9, 155.6, 165.1. Anal. Calcd for $C_{11}H_{17}N_3O_3$: C, 55.22; H, 7.16; N, 17.56. Found: C, 55.08; H, 7.17; N, 17.76. For **33**: mp 240−241 °C. LSIMS (GLY) 240 $[M + H]^+$, 112 $[B + 2H]^+$. UV λ_{max} (H_2O) = 275 nm (ϵ 9700). ^{1}H NMR (DMSO-d_6) δ 0.95−1.9 (7H), 3.32 (2H), 3.63 (1H), 4.23−4.43 (2H), 4.76 (1H), 5.63 (1H), 6.95 (2H), 7.63 (1H). ^{13}C NMR (DMSO-d_6) δ 25.7, 30.2, 39.8, 46.0, 52.2, 62.7, 69.1, 93.5, 142.3, 155.6, 165.0.

Anal. Calcd for $C_{11}H_{17}N_3O_3 \cdot 0.5H_2O$: C, 53.22; H, 7.31; N, 16.92. Found: C, 52.90; H, 7.33; N, 17.19.

Method 2. To a solution of **26** (0.48 g, 2.0 mmol) in pyridine/CH_2Cl_2 (1:1, 20 mL) were added Ac_2O (0.12 mL) and DMAP (10 mg) with stirring at 0 °C. The resulting solution was stirred at rt for 4 h, poured on ice, and extracted with CH_2Cl_2 (50 mL × 3). The pooled extracts were washed with a saturated aqueous $NaHCO_3$ and H_2O, dried over $MgSO_4$, and the solvent evaporated. The residue was purified by column chromatography (CH_2Cl_2−MeOH, 95:5) to give 0.48 g (74%) of (1*RS*,3*SR*,4*RS*)-1-[4-(acetoxymethyl)-3-acetoxycyclohexyl]-uracil (**34**) as a foam: LSIMS (GLY) 325 $[M + H]^+$, 113 $[B + 2H]^+$. UV λ_{max} (MeOH) = 267 nm (ϵ 9500). ^{1}H NMR ($CDCl_3$) δ 1.65−2.3 (13H), 4.17 (1H), 4.78 (1H), 5.20 (1H), 5.75 (1H), 7.25 (1H), 9.38 (1H). ^{13}C NMR ($CDCl_3$) δ 20.8, 21.2, 22.1, 26.0, 30.9, 35.6, 50.7, 63.3, 69.8, 102.5, 140.5, 150.7, 163.0. 170.0, 171.0. Anal. Calcd for $C_{15}H_{20}N_2O_6$: C, 55.55; H, 6.22; N, 8.64. Found: C, 55.36; H, 6.40; N, 8.55.

To a solution of 1*H*-1,2,4-triazole (1.34 g, 20.0 mmol) and $POCl_3$ (0.63 mL, 6.8 mmol) in CH_3CN (20 mL) was added TEA (2.77 mL, 20.0 mmol) dropwise at 0 °C. Compound **34** (0.64 g, 2.0 mmol) in CH_3CN/pyridine (1:1, 20 mL) was added, and the reaction mixture was stirred at room temperature overnight. After addition of H_2O, the solvents were evaporated and the resulting residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$ and evaporated. The residue was dissolved in aqueous ammonia (25%, 10 mL) and 1,4-dioxane (40 mL). After 6 h the mixture was evaporated and the residue partitioned between CH_2Cl_2 and saturated $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$, evaporated, and chromatographed on short silica gel column (2.5 × 10 cm, CH_2Cl_2−MeOH, 9:1). The residue left over after evaporation of the desired fractions was deacetylated by treatment with NH_3 (25%)−MeOH−1,4-dioxane (1:1:1, 60 mL) at room temperature overnight. The solution was evaporated and purified by column chromatography as described for **26** and **27** affording 0.19 g (40%) of **32**, which was chromatographically and spectroscopically indistinguishable from **32** obtained by method 1.

X-ray Diffraction Studies.[27] Colorless single crystals were grown by slow evaporation from water−methanol solutions. Both data collections and subsequent structure determinations were performed under identical condtions unless specified. Crystal data for compound **10**: $C_{24}H_{38}N_{10}O_6$, MW = 562.64, monoclinic, C*c*, a = 21.5520(9), b = 10.9723(3), c = 14.8578(5) Å, β = 128.893(3)°, V = 2734.6(2) Å^3, D_c = 1.367 g cm^{-3}, Z = 4, $F(000)$ = 1200, μ = 0.839 mm^{-1}, λ = 1.54178 Å, T = 293 K, crystal size: 0.4 × 0.20 × 0.10 mm. Crystal data for compound **20**: $C_{12}H_{18}N_2O_4$, MW = 254.28, monoclinic, *C*2/*c*, a = 18.487(2), b = 11.3955(8), c = 11.7345(7) Å, β = 94.510(5)°, V = 2464.4(4) Å^3, D_c = 1.371 g cm^{-3}, Z = 8, $F(000)$ = 1088, μ = 0.861 mm^{-1}, λ = 1.54178 Å, T = 293 K, crystal size: 0.5 × 0.25 × 0.05 mm.

Data Collection. Crystals were mounted on a Siemens P4 four-circle diffractometer with graphite monochromator and Cu Kα radiation. Unit cell parameters were obtained from a least-squares analysis of 35 reflections. Intensity data were collected using the ω−2θ scan technique. Three standard reflections monitored every 100 reflections did not reveal a significant change in intensity. The 2θ range of measured reflections was 4 ≤ 58°. The index range was, −1 ≤ h ≤ 23, −1 ≤ k ≤ 11, −16 ≤ l ≤ 12 for compound **10** and −1 ≤ h ≤ 20, −1 ≤ k ≤ 12, −12 ≤ l ≤ 12 for compound **20**. For compound **10**, 2275 reflections were collected, 2017 were unique reflections (R_{int} = 0.0202); for compound **20**, 2071 reflections were collected and 1663 were unique reflections (R_{int} = 0.0548). In both cases absorption corrections by the method of North[28] were applied.

Structure Refinements. The structures were solved using SIR92,[29] and full-matrix least-squares refinement on F^2 using SHELXL-93[30] were carried out. For compound **10** the refinement converged at $R[I > 2\sigma(I)]$ = 0.0520 with GOF on F^2 = 1.092, extinction coefficient: 0.0009(2), largest diff peak and hole: 0.204 and −0.232 e Å^{-3}. For compound **20** the refinement converged at $R[I > 2\sigma(I)]$ = 0.0408 with GOF on F^2 = 1.105, extinction coefficient: 0.0017(2), largest diff peak and hole: 0.192 and −0.200 e Å^{-3}. H atoms were positioned geometrically assuming fixed C−H, O−H, and N−H distances of 0.96, 0.82, and 0.86 Å, respectively, and were constrained to ride on their parent atoms. H atoms of the water molecule were located by difference Fourier methods. PARST[31] was used for geometry calculations.

In compound **10** molecules A and B form a pseudo-centrosymmetric dimer. The two independent molecules have only slightly different conformations. The cyclohexane rings in the two molecules A and B have a chair conformation with puckering parameters according to Cremer and Pople:[32] Q_T = 0.58(1) Å, θ = 178.3(9)° and Q_T = 0.58(1) Å, θ = 5.31(10)°, respectively. The intermolecular hydrogen-bond network involves solvent H_2O molecules resulting in a three-dimensional structure. The H_2O molecule acts as a receptor for O3′−H···O hydrogen bonds and as a donor for O−H···N3 and O−H···O7′ hydrogen bonds.

In compound **20** the cyclohexane moiety is disordered and has the chair conformation: Q_T = 0.564(8) Å, θ = 176.8(9)°. Intermolecular hydrogen bonds determine the stacking of the molecules.

Modeling Methods. C2′- and C3′-endo puckered furanosyl nucleoside structures were modeled in their idealized Arnott geometry.[33] Anhydrohexitol and carbocyclic nucleosides were model built using MacroModel,[34] and energy-minimized using the AMBER* force field supplied with MacroModel. A distance-dependent dielectric constant of $\epsilon = r$ was applied. Global energy minimum conformations were found by rotating around the χ and γ torsions in steps of 10°, each time minimizing the energy while keeping the χ and γ torsion angles fixed. The global energy minimum conformations of the anhydrohexitol and carbocyclic nucleosides were used for structural comparison with both puckered forms of the furanosyl nucleosides.

Antiviral Activity. Antiviral activity assays with herpes simplex virus (HSV-1 and HSV-2) were done using a methodology (viruses, cells, assays) that has been previously described.[35]

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(27) The authors have deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2, 1EZ, U.K.

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