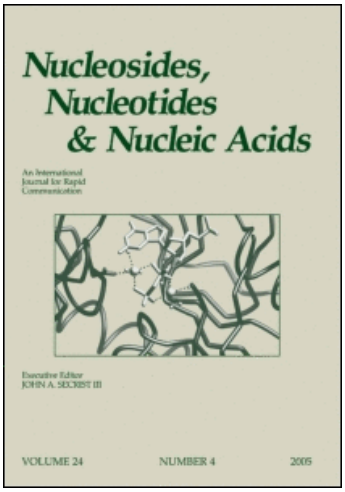

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Synthesis and Conformational Analysis of a Locked Analogue of Carbovir Built on a Bicyclo[3.1.0]-hex-2-enyl Template

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NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
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Synthesis and Conformational Analysis of a Locked Analogue of Carbovir Built on a Bicyclo[3.1.0]-hex-2-enyl Template[#]

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ABSTRACT

The synthesis and biological evaluation of a carbovir analogue (**5**) built on a bicyclo[3.1.0]hex-2-enyl template is described. A conformational analysis using density functional theory at the B3LYP/6-31G* level has been carried out on the rigid pseudosugar template of **5**, the cyclopentene moiety of carbovir and the bicyclo[3.1.0]hex-2-yl pseudosugars of two isomeric carbonucleosides (**12** and **13**) containing exo- and endo-fused cyclopropane rings. The results show that while the planar configuration of the fused cyclopentane ring of compound **5** helps retain weak anti-HIV activity, the ability of the cyclopentene ring of carbovir to easily adopt a planar or puckered conformation with little energy penalty may prove to be a crucial advantage. The bicyclo[3.1.0]hex-2-yl nucleosides

[#]In honor and celebration of the 70th birthday of Professor Leroy B. Townsend.

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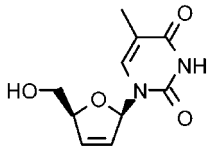
12 and **13** that were inactive against HIV exhibited stiffer resistance to having a planar, fused cyclopentane moiety.

Key Words: Carbocyclic nucleosides; Carbovir analogue; Bicyclo[3.1.0]hex-2-enyl template; Conformationally locked; Anti-HIV.

INTRODUCTION

Stavudine (**1**, D4T) is a very effective antiretroviral agent that is used as a component of many highly active antiretroviral therapy (HAART) regimens for the treatment of AIDS.[1] Recently, we synthesized a carbocyclic version of D4T (**2**) on a bicyclo[3.1.0]hex-2-enyl platform, which showed good anti-HIV activity in vitro.[2] We postulated that the rigid planarity of the embedded five member ring of **2** imposed by the combination of the fused cyclopropane ring and the double bond—which approximated that of D4T— was the reason for its activity.[2] Abacavir (**3a**), a pro-drug of carbovir (**3b**),[3] has been recently approved by the FDA as another important drug in the fight against AIDS.[4–6] At first glance, the structure of its pseudosugar ring, save for the lack of the endocyclic oxygen, resembles the planar dihydrofuran moiety of D4T. However, examination of the X-ray structures shows that while the five-member rings of D4T (**1**) and its guanine counterpart D4G (**4**) are indeed planar in the crystal environment,[7,8] that of carbovir is not.[9]



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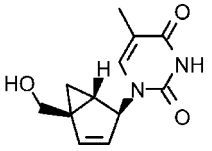

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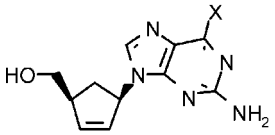
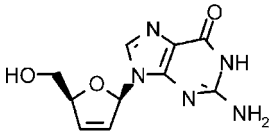


3a, X = N

3b, X = OH



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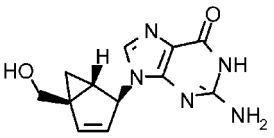

5

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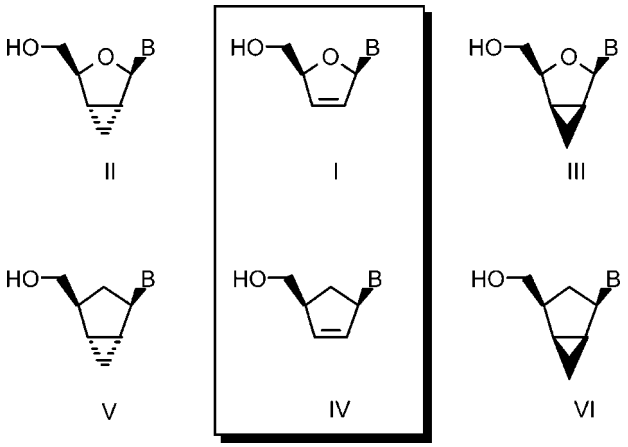
Since the relationship between planarity and biological activity for these two classes of molecules appears to be an important parameter in the design of antivirally active compounds, the synthesis of the guanosine analogue **5**, constructed on a bicyclo [3.1.0]hex-2-enyl template, has been pursued to address this issue.

The sugar and pseudosugar templates represented in Sch. 1 comprise active anti-HIV compounds such D4T (**1**) and D4G (**4**) (template I), and abacavir (**3a**) and carbovir (**3b**) (template IV). Since cyclopropanes behave in some respects like double-bond compounds, bicyclo[3.1.0]hexane nucleosides with exo (α-face, templates II and V) or endo (β-face, templates III and VI) stereochemistries have been synthesized and evaluated as anti-HIV agents. Unfortunately, for the most part the results have been disappointing.[10–14] Of the 3-oxabicyclo[3.1.0]hexane templates II and III, only the former has a planar pseudosugar with a maximum puckering amplitude (ν_{max}) of only 8.8° and a phase angle of pseudorotation (P) of 273.3°,[13],[a] corresponding to the West hemisphere of the pseudorotational cycle.[15] The pseudosugar template in III is puckered with a ν_{max} of 34.5° and with $P = 91.7°$, thus located in the East hemisphere.[14] For nucleosides built with bicyclo[3.1.0]hexane templates V and VI the embedded cyclopentane ring is not planar either. They have puckered cyclopentane rings with ν_{max} values of 25.81°[16] and 29.84°,[17] respectively. These templates display antipodal preferences for the West (template V, $P = 269.52°$)[b] and East (template VI, $P = 92.5°$)



Scheme 1.

[a]The pseudorotational parameter P for template II in Ref.[13] appears incorrectly listed as 86.7°. The correct calculated value is 273.3° (see also Ref.[14]).
[b]The pseudorotational parameter P for template V in Ref.[17] appears incorrectly listed as 91.89°. The correct calculated value is 269.52°.

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hemispheres, a conformational feature that becomes important given that the value of ν_{max} is large. Based on these data, it can be concluded that the isolated presence of either a double bond or a fused cyclopropane ring in the sugar or pseudosugar moiety does not insure planarity of the cyclopentane ring.

In the new bicyclo[3.1.0]hex-2-enyl template of compounds **2**[2] and **5**, the critical double bond is maintained, while the fused cyclopropane ring insures that the five member ring will remain planar. Therefore, compound **5** has a specific locked conformation corresponding to one of a possible set of conformations available to carbovir.

RESULTS AND DISCUSSION

1. Chemical Synthesis

We started with our previously synthesized pseudosugar precursor **6**,[2] and coupled it with *N*-(6-chloropurin-2-yl)acetamide under Mitsunobu conditions to afford both α- and β-anomers of N^9-alkylated products in a 2.5:1 ratio in favor of the β-anomer (Sch. 2). This result was unusual since the Mitsunobu reaction normally proceeds with inversion of configuration and only β-anomers are obtained. Since the starting carbocyclic alcohol **6** is allylic, it was seen as a possibility that, in addition to the expected S_N2 pathway with no allylic rearrangement, a S_N2' mechanism with allylic rearrangement or even a S_N1 mechanism could be operating. These questions and the other important issue of the site of alkylation (N^9 vs. N^7) were satisfactorily resolved by the crystal structure of compound **10** (Fig. 1). Anomers **7** and **8** could not be resolved; but after the removal of the *t*-butyldiphenylsilyl group, the resulting mixture of **9** and **10** was readily separated by column chromatography. Alkaline hydrolysis gave the desired target **5** and the α-anomer **11**; which, as expected, had identical UV spectra with a λ_{max} at 254 nm. Besides the critical information provided by the X-ray structure of **10**, ^{1}H NMR-COSY was used to confirm all the proton assignments.

2. Antiviral Activity

The antiviral activity of **5** was rather weak. In human T-lymphocyte (CEM) cells, the EC_{50} values against HIV-1 and HIV-2 were 50 μM and 30 μM, respectively. As expected, activity in CEM/TK$^-$ cells was completely absent ($EC_{50} > 250$ μM). In MT-2 cells, the EC_{50} was reached at 100 μM but with some apparent toxicity, and in MT-4 cells no anti-HIV activity was detected even at 100 μM.

3. Conformational Analysis

The X-ray structure of carbovir shows two non-planar molecules **3b** and **3b′** (two molecules in the crystallographic unit cell) in a nearly perfect East conformation ($P = 89°$–$92°$, Table 1) with the tip of the five member ring "up". Therefore,

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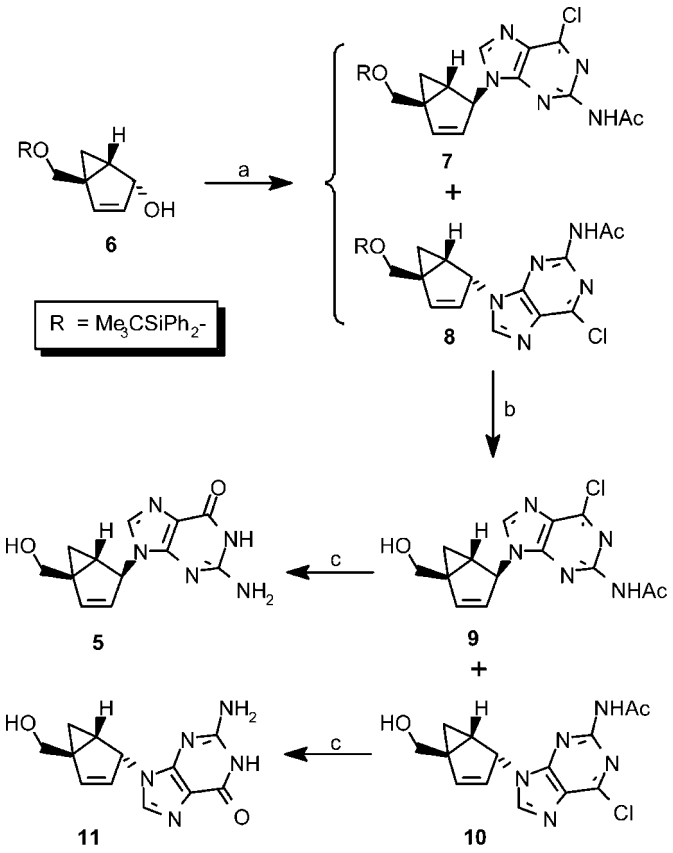

a. PPh_3, DEAD, *N*-(6-chloropurin-2-yl)acetamide, THF
b. *n*-$(Bu)_4NF$, THF
c. 1*N* NaOH, Δ

Scheme 2.

we considered it important to determine the cost in energy of generating a flat conformation of carbovir, as well as an antipodal West conformation produced by moving the tip of the five member ring "down". The two extreme conformations of the pseudosugar ring of carbovir in the East and West hemispheres are expected to approximate the conformations already achieved with templates V and VI, both of which produced inactive anti-HIV compounds with guanine and adenine nucleobases.[16,17] The energy of carbovir (**3b**) and that of its new conformers was calculated using density functional theory at the B3LYP/6-31G* level for a series of structures where the C3′-C4′-C5′-C1′ torsion angle (ν_4) was varied from $-36°$ to 36° in 3° increments (Fig. 2). Since the four-atom fragment incorporating the double bond is rigid, this operation allowed the tip of the five member ring of carbovir to move "up" or "down". We also calculated the cost of varying ν_4 in templates V and

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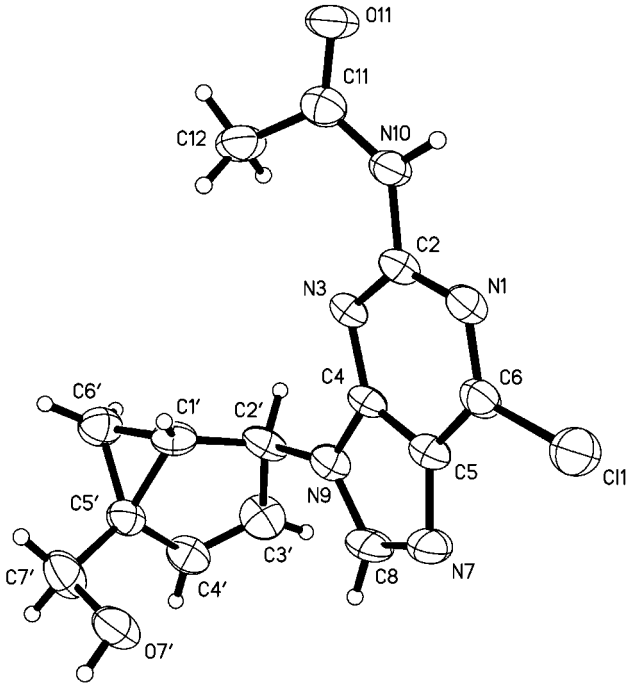

Figure 1. Displacement ellipsoid plot of one of the two molecules of **10** in the crystallographic asymmetric unit. (See Tables 2 and 3 in experimental section.)

VI, which are represented by the corresponding guanosine analogues **12** and **13**, respectively (Table 1, Fig. 2).

The computed potential energy surfaces and the planarity around C2′-C3′ (torsion angle ν_2) for carbovir, compounds **12** and **13** and the new compound **5** (vide infra) are shown in Fig. 3.

Table 1. Calculated pseudorotational parameters from the X-ray structures of **2**,[2] compounds **12**[16] and **13**,[17],[b] and two molecules of carbovir (**3b**, **3b′**).[9]

	ν_0[a]	ν_1	ν_2	ν_3	ν_4	P[b]	ν_{max}[b]	χ[c]	γ[d]
2	6.56	−5.83	2.67	1.68	−5.20	293.14	6.81	−119.12	56.17
3b	−26.47	17.89	−1.09	−16.02	25.68	92.23	27.98	−86.24	−177.76
3b′	−27.22	17.21	0.23	−17.56	26.98	89.55	28.91	−52.63	−82.90
12	24.50	−15.08	−0.21	15.25	−24.61	269.52	25.81	−74.31	−69.08
13	−28.90	18.59	−1.24	−16.49	27.79	92.38	29.84	−62.55	166.98

[a]ν_0–ν_4 represent the torsion angles of the five member ring.
[b]P and ν_{max} have been defined in the text.
[c]χ is the glycosyl torsion angle.
[d]γ is the hydroxymethyl torsion angle.
Numbers represent degrees (°).

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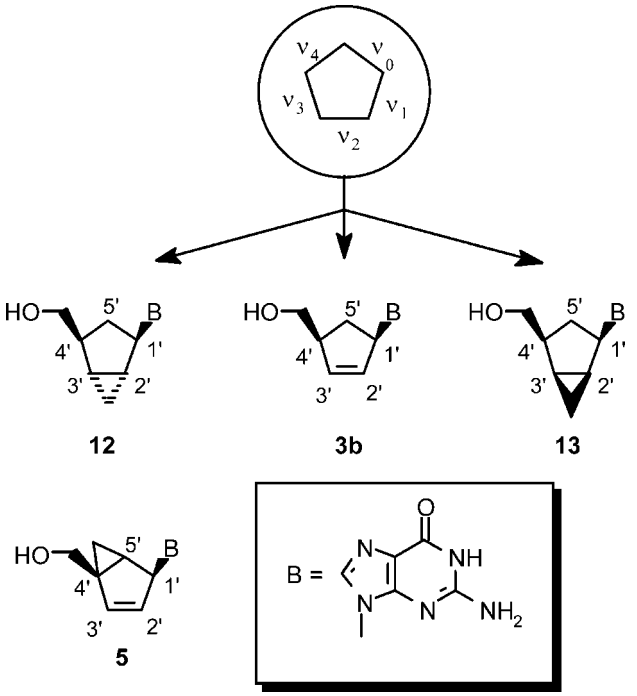

Figure 2. Structures of compounds with templates IV (**3b**), V (**12**), VI (**13**), and the bicyclo[3.1.0]hex-2-enyl nucleoside **5** depicted using a nucleoside numbering system. The corresponding torsion angles along the cyclopentane ring are indicated in the circle.

Tracing the potential energy of carbovir as the tip of the five member ring flips "up" or "down" one obtains essentially a flat curve (Fig. 3A) over a substantial range of ν_4 values. The relative energy does not change much and remains below 1 kcal/mol within the range of ν_4 from $-20°$ to 30°. The optimized value for ν_4 (17.2°) is different from the value in the crystal structure ($\nu_4 = 25.68°$ and 26.98°, Table 1), but since ν_4 can freely change from $-20°$ to 30°, crystal packing forces could account for this difference. The torsion angle ν_2, which incorporates the double bond, remains very close to zero within this range (Fig. 3E). An increase or decrease of ν_4 beyond the $-20°$ to 30° boundary dramatically changes the energy. This result demonstrates that the pseudosugar ring moiety of carbovir is indeed quite flexible and that any conformation in the range from $-20°$ to 30° for ν_4 would be energetically quite accessible. A similar exercise for compound **12** (template V) shows an optimized value for ν_4 of $-23.3°$, very close to the value observed in the crystal structure (Fig. 3B, Table 1). In contrast to carbovir, twisting the conformation of this pseudosugar template introduces large energy changes. For example, flattening the molecule ($\nu_4 = 0$) or moving the tip "up" to generate a chair conformation increases the relative energy to about $2 \sim 3$ kcal/mol. Despite this change in energy, the torsion angle ν_2 remains close to zero for a significant range of ν_4

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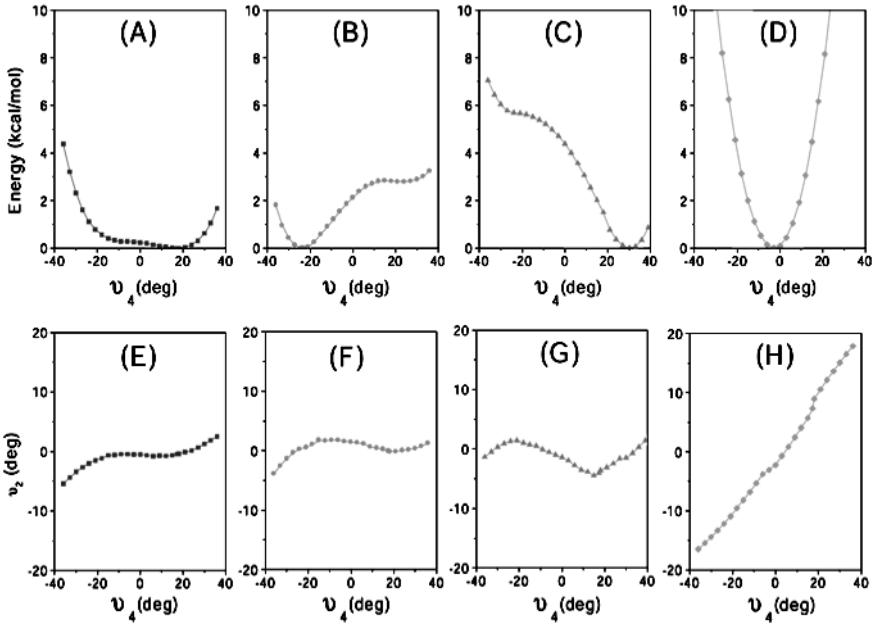

Figure 3. Relaxed potential energy surfaces for: (A) **3b** (carbovir, template IV); (B) **12** (template V); (C) **13** (template VI), and (D) **5** (bicyclo[3.1.0]hex-2-enyl template). Changes in torsion angle ν_2 as a function of ν_4 for: (E) **3b** (carbovir, template IV); (F) **12** (template V); (G) **13** (template VI), and (H) **5** (bicyclo[3.1.0]hex-2-enyl template).

(Fig. 3F). Compound **13** gave a curve resembling the mirror image of the curve obtained for **12** with an optimized $\nu_4 = 30.4°$, also quite close to the value observed in the crystal structure (Fig. 3C, Table 1). The cost of flattening the five member ring ($\nu_4 = 0°$) or moving the tip down ($\nu_4 = -24°$) is much higher for this system as reflected by the larger energy values of 4.38 and 5.68 kcal/mol, respectively. Changes in ν_2 are relatively modest from the optimized value of $-1.5°$ to $1.3°$ (Fig. 3G). The small variation in ν_2 in both cases (compounds **12** and **13**) means that the tip of the five member ring can move quite independently and without causing large distortions of the cyclopropane ring, although the required energy is significantly larger than that for carborvir.

The case of the bicyclo[3.1.0]hex-2-enyl template of compounds **2** (Table 1) and **5** has to be considered differently since the combination of the double bond and the fused cyclopropane ring strongly forces a planar configuration on the embedded cyclopentene ring. Thus, the fused cyclopentene ring has no "free" tip, and the rigidity of the system is such that any deviation from planarity is bound to be costly. Indeed, changing ν_4 from the optimized value of $-2.7°$, where the five-member ring is nearly planar, results in potential energy increases that are very steep (Fig. 3D). These high energy changes are accompanied by a large, unacceptable distortion of the dihedral angle ν_2 which centers at the C=C bond (Fig. 3H). Both the cost in

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energy and the large distortion of ν_2 illustrate the rigidity of the fused cyclopentene ring in compounds **2** and **5**.

CONCLUSIONS

From the above results, we conclude that carbovir has the most flexible conformation of the templates examined. Although in the solid state it crystallizes with its ring puckered, a planar conformation is easily accessible and probably plays an important role in the biological activity of the drug. Replacing the double bond by a fused cyclopropane ring with either an exo (compound **12**) or an endo (compound **13**) stereochemistry reduces the flexibility of the pseudosugar ring considerably, and the resulting low energy conformers no longer have a planar five member ring geometry. In each case, both low-energy conformations are confined to a narrow energy well and a substantial energy penalty has to be paid when the cyclopentane ring is made flat or the configuration of the tip reversed. The bicyclo[3.1.0]hex-2-enyl template of **2**, which served as a good surrogate scaffold of D4T, does not work as well for carbovir since the anti-HIV activity of **5** can only be described as weak. Several factors could explain these results. First, determining the proper experimental conditions for testing the anti-HIV activity of guanosine analogues can be difficult, as it was in the case of D4G.[18] Accordingly, additional anti-HIV assays under different conditions should be performed with compound **5**. Alternatively, it is well known that purine nucleosides are activated by a different set of kinases.[19] Therefore, what worked for D4T and compound **2**, does not necessarily have to translate to carbovir and compound **5**. Furthermore, the structure of the five member ring of **5** is strictly planar, whereas in carbovir it is flexible enough that it can significantly deviate from the planar state without paying a high energy penalty. The biologically active conformation of carbovir may be flat or may lie within the range from $-20°$ to $30°$ of ν_4. Therefore, if at any stage during activation, a non-planar geometry of the pseudosugar ring fits better into the receptor, the rigid conformation of **5** stands to lose binding affinity as it would resist any "molding" attempts by the enzymes. The ability of carbovir to easily adopt a planar or puckered conformation as needed with little or no energy penalty is probably advantageous.

EXPERIMENTAL

1. General Procedures

All chemical reagents were commercially available. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Column chromatography was performed on silica gel 60, 230–400 mesh (E. Merck), and analytical TLC was performed on Analtech Uniplates silica gel GF. Routine ^{1}H (400 MHz) spectra were recorded using standard methods. Chemical shifts are reported in parts per million (δ) and signals are quoted as s (singlet), d (doublet),

t (triplet), q (quartet), m (multiplet). Specific rotations were measured in a Perkin-Elmer model 241 polarimeter. Positive-ion fast-atom bombardment mass spectra (FAB-MS) were obtained on a VG 7070E-HF double-focusing mass spectrometer operated at an accelerating voltage of 6 kV. Either glycerol or 3-nitrobenzyl alcohol was used as a sample matrix, and ionization was effected by a beam of xenon atoms generated in a saddle-field ion gun at 8.0 ± 0.5 kV. Nominal mass spectra were obtained at a resolution of 1200, while accurate mass analysis (HRMS) was carried out at a resolution of 5000. For the latter, a limited-range V/E scan was employed under control of a MASPEC-II data system for Windows (Mass Spectrometry Services, Ltd.) Matrix-derived ions were used as the internal mass references for accurate mass determinations. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

2. Chemical Synthesis

(1′*S*,2′*S*,5′*R*)-*N*-(9-{5′-[(2,2-dimethyl-1,1-diphenyl-1-silapropoxy)methyl]bicyclo-[3.1.0]hex-3′-en-2′-yl}-6-chloropurin-2-yl)acetamide (7) and (1′*S*,2′*R*,5′*R*)-*N*-(9-{5′-[(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)methyl]bicyclo[3.1.0]hex-3′-en-2′-yl}-6-chloropurin-2-yl)acetamide (8). A mixture of allylic alcohol **6** (0.353 g, 0.968 mmol), triphenylphosphine PPh_3 (0.509 g, 1.94 mmol) and *N*-(6-chloropurin-2-yl)acetamide (0.307 g, 1.45 mmol) in THF (30 mL) was cooled to 0°C and treated dropwise with diethyl azodicarboxylate (DEAD, 0.31 mL, 1.94 mmol). After 1 h stirring at 0°C and 2 h stirring at room temperature, the mixture was filtered through a Celite® pad and the filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexanes/EtOAc; 2/1) to give an inseparable mixture of β- and α-alkylated products (0.253 g, 47%) in ca. 2.5:1 ratio as a white solid: ^{1}H NMR ($CDCl_3$) for the major β-isomer (**7**): δ 8.09 (s, 1 H, H-8), 8.02 (br s, 1 H, NHAc), 7.28–7.64 (m, 10 H, ArH), 6.42 (dd, $J = 5.5$, 0.9 Hz, 1 H, H-4′), 5.51 (dt, $J = 5.5$, 1.9 Hz, 1 H, H-3′), 5.42 (br s, 1 H, H-2′), 4.14 (d, $J = 11.3$ Hz, 1 H, C*H*HO), 3.55 (d, $J = 11.3$ Hz, 1 H, CH*H*O), 2.53 (s, 3 H, NHCOCH_3), 1.68 (irregular dd, 1 H, H-1′), 1.12 (dd, $J = 8.4$, 4.5 Hz, 1 H, H-6′$_a$), 0.50 (t, $J = 4.5$ Hz, 1 H, H-6′$_b$).

(1′*S*,2′*S*,5′*R*)-*N*-{6-Chloro-9-[5′-(hydroxymethyl)bicyclo[3.1.0]hex-3′-en-2′-yl]purin-2-yl}acetamide (9) and (1′*S*,2′*R*,5′*R*)-N-{6-Chloro-9-[5′-(hydroxymethyl)bicyclo[3.1.0]-hex-3′-en-2′-yl]purin-2-yl}acetamide (10). The mixture of β/α-isomers (**7**/**8**) was dissolved in THF (20 mL), treated with tetra-*n*-butylammonium fluoride (TBAF, 1 M solution in THF, 0.54 mL) and stirred at room temperature for 1 h. After removing the solvent under vacuum, the residue was purified by column chromatography on silica gel (CH_3Cl/MeOH, 25/1) and the isomers separated. β-Isomer (**9**, 65 mg, 45%): $[\alpha]_D^{24} = +37.1°$ (*c*, 0.14, MeOH); UV (MeOH) λ_{max} 288 nm; ^{1}H NMR (CD_3OD) δ 8.33 (s, 1 H, H-8), 6.51 (dm, $J = 5.0$ Hz, 1 H, H-4′), 5.61 (br d, $J = 1.2$ Hz, 1 H, H-2′), 5.58 (m, 1 H, H-3′), 4.06 (d, $J = 11.9$ Hz, 1 H, C*H*HO), 3.46 (d, $J = 11.9$ Hz, 1 H, CH*H*O), 2.28 (s, 3 H, NHCOCH_3), 1.87 (irregular dd, 1 H, H-1′),

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1.23 (dd, $J = 8.6$, 4.3 Hz, 1 H, H-6′$_a$), 0.56 (t, $J = 4.3$ Hz, 1 H, H-6′$_b$); FAB-MS (relative intensity) 320.1 (^{35}Cl MH^+, 100), 212 (^{35}Cl bH_2^+, 35); Anal. Calcd. for $C_{14}H_{14}ClN_5O_2 \cdot 0.1$ hexanes: C, 53.40; H, 4.73; N, 21.33. Found: C, 53.48; H, 4.62; N, 21.27. α-Isomer (**10**, 30 mg, 18%): UV (MeOH) λ_{max} 288 nm; ^{1}H NMR (CD_3OD) δ 8.22 (s, 1 H, H-8), 6.32 (dd, $J = 5.6$, 1.7 Hz, 1 H, H-4′), 5.97 (dm, $J = 6.8$ Hz, 1 H, H-2′), 5.67 (dt, $J = 5.4$, 1.4 Hz, 1 H, H-3′), 3.75 (d, $J = 11.9$ Hz, 1 H, C*H*HO), 3.53 (d, $J = 11.9$ Hz, 1 H, CH*H*O), 2.24 (s, 3 H, NHCOCH_3), 2.08 (m, 1 H, H-1′), 0.79 (dd, $J = 7.8$, 4.3 Hz, 1 H, H-6′$_a$), 0.56 (irregular t, $J = 4.5$, 4.3 Hz, 1 H, H-6$_b$); FAB-MS (relative intensity) 320.1 (^{35}Cl MH^+, 100), 212 (^{35}Cl bH_2^+, 36).

(1′*S*,2′*S*,5′*R*)-2-Amino-9-[5′-(hydroxymethyl)bicyclo[3.1.0]hex-3′-en-2′-yl]hypoxanthin-6-one (5). The β-isomer (**9**, 0.019 g, 0.059 mmol) was dissolved in 1 *N* NaOH (2 mL) and refluxed for 2 h. After cooling to room temperature the solution was neutralized with 1 *N* HCl and reduced to dryness under vacuum. The solid residue was purified by column chromatography on silica gel ($CHCl_3$:MeOH, 8:1) to give **5** (15 mg, 96%) as a white solid, mp 235°C (dec); UV (H_2O) λ_{max} 254 nm; $[\alpha]_D^{20} = +74.0°$ (*c*, 0.1, $CHCl_3$:MeOH, 1:2); ^{1}H NMR (DMSO-d_6) δ 10.6 (s, 1 H, NH), 7.51 (s, 1 H, H-8), 6.48 (br s, 2 H, NH_2), 6.41 (dm, $J = 5.5$ Hz, 1 H, H-4′), 5.52 (dm, $J = 5.3$ Hz, 1 H, H-3′), 5.08 (br s, 1 H, H-2′), 4.81 (t, $J = 5.8$ Hz, 1 H, OH), 3.84 (dd, $J = 11.5$, 5.7 Hz, 1 H, C*H*HO), 3.41 (dd, $J = 11.7$, 5.6 Hz, 1 H, CH*H*O), 1.71 (dd, $J = 8.0$, 3.9 Hz, 1 H, H-1′), 1.14 (dd, $J = 8.2$, 4.1 Hz, 1 H, H-$_6$′a), 0.37 (t, $J = 4.1$ Hz, 1 H, H-$_6$′b); FAB-MS (relative intensity) 260.2 (MH^+, 30); HRMS (FAB) calcd. for $C_{12}H_{13}N_5O_2$: 260.1148. Found: 260.1141.

(1′*S*,2′*R*,5′*R*)-2-Amino-9-[5′-(hydroxymethyl)bicyclo[3.1.0]hex-3′-en-2′-yl]hypoxanthin-6-one (11). Following a similar procedure for the synthesis of **5**, compound **11** was obtained: UV (H_2O) λ_{max} 254 nm; ^{1}H NMR (DMSO-d_6) δ 10.7 (br s, 1 H, NH), 7.48 (s, 1 H, H-8), 7.48 (br s, 2 H, NH_2), 6.28 (dd, $J = 5.5$, 1.7 Hz, 1 H, H-4′), 5.57 (d, $J = 6.8$ Hz, 1 H, H-2′), 5.51 (d, $J = 5.5$ Hz, 1 H, H-3′), 4.58 (br s, 1 H, OH), 3.60 (dd, $J = 11.5$, 4.5 Hz, 1 H, C*H*HO), 3.42 (dd, $J = 11.5$, 2.7 Hz, 1 H, CH*H*O), 1.81 (dd, $J = 11.1$, 7.0 Hz, 1 H, H-1′), 0.71 (dd, $J = 8.0$, 4.1 Hz, 1 H, H-6′$_a$), 0.44 (m, 1 H, H-6′$_b$); FAB-MS (relative intensity) 260.1 (MH^+, 10); HRMS (FAB) calcd. for $C_{12}H_{13}N_5O_2$: 260.1148. Found: 260.1147.

3. Computational Methods

The potential energy surfaces of carbovir (**3b**), compounds **12** and **13** and the new compound **5** were computed employing density functional theory[20] where the C3′-C4′-C5′-C1′ torsion angle (ν_4, Fig. 2) was varied from −36° to 36° in 3° increments. Partial geometry optimizations were performed using Gaussian 98 suite of program.[21] The B3LYP functional[22,23] together with the 6-31G* basis set were used, as this level of theory represents a reasonable compromise of accuracy and performance. The reported relative energy is based on the total electronic energy. The change in the planarity around C2′-C3′ was monitored by the change in ν_2, also

4. X-Ray Analysis

Table 2. Crystal data and structure refinement for compound **5**.

Empirical formula	$C_{14}H_{14}ClN_5O_2$
Formula weight	319.75
Temperature	295(2) K
Wavelength	1.54178 Å
Crystal system	Triclinic
Space group	P1
Unit cell dimensions	a = 7.182(1) Å α = 86.649(1)°
	b = 9.554(1) Å β = 76.348(1)°
	c = 11.326(1) Å γ = 88.965(1)°
Volume	753.9(2) Å^3
Z	2
Density (calculated)	1.409 mg/m^3
Absorption coefficient	2.382 mm^{-1}
F(000)	332
Crystal size	0.28×0.05×0.02 mm^3
Theta range for data collection	4.02 to 67.15°
Index ranges	$-6 \Leftarrow h \Leftarrow 8$, $-11 \Leftarrow k \Leftarrow 11$, $-13 \Leftarrow l \Leftarrow 12$
Reflections collected	3683
Independent reflections	3688 [R(int) = 0.0000]
Completeness to theta = 67.15°	81.0%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.953 and 0.513
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3688/3/415
Goodness-of-fit on F^2	0.980
Final R indices [I > 2sigma(I)]	R1 = 0.0381, wR2 = 0.1027
R indices (all data)	R1 = 0.0413, wR2 = 0.1049
Absolute structure parameter	0.07(2)
Largest diff. peak and hole	0.166 and −0.205 e·Å^{-3}

Table 3. Atomic coordinates (×10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for compound **5**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	5302(7)	5570(5)	6047(4)	54(2)
C(2)	5552(9)	4174(7)	6057(5)	53(2)
N(3)	5412(8)	3264(5)	7016(4)	50(1)
C(4)	4919(9)	3942(7)	8056(5)	51(2)
C(5)	4590(10)	5356(7)	8177(5)	60(2)
C(6)	4823(10)	6134(7)	7099(6)	60(2)
Cl(1)	4559(4)	7940(2)	7059(2)	96(1)
N(7)	4085(10)	5673(6)	9398(5)	77(2)

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Table 3. Continued.

	x	y	z	U(eq)
C(8)	4124(12)	4468(8)	9953(6)	78(2)
N(9)	4634(8)	3352(6)	9216(5)	60(2)
N(10)	6067(8)	3677(6)	4897(5)	57(2)
C(11)	6090(10)	2373(8)	4464(7)	65(2)
O(11)	6603(8)	2232(6)	3389(4)	86(2)
C(12)	5441(13)	1097(7)	5331(6)	81(3)
C(1′)	3047(11)	1084(7)	9521(5)	59(2)
C(2′)	4799(10)	1840(7)	9588(6)	64(2)
C(3′)	4857(12)	1686(8)	10913(6)	77(2)
C(4′)	3292(10)	1065(7)	11539(6)	68(2)
C(5′)	1994(10)	671(6)	10816(5)	57(2)
C(6′)	2793(12)	−447(7)	9932(6)	72(2)
C(7′)	−122(12)	887(8)	11229(8)	83(3)
O(7′)	−539(7)	2341(5)	11305(4)	78(2)
N(1A)	9603(8)	2399(6)	8027(5)	54(2)
C(2A)	9879(9)	3794(6)	7989(5)	47(2)
N(3A)	10464(8)	4653(6)	6991(5)	51(1)
C(4A)	10723(9)	4006(7)	5974(5)	47(2)
C(5A)	10452(10)	2551(7)	5867(6)	52(2)
C(6A)	9904(10)	1800(6)	6981(6)	54(2)
Cl(1A)	9596(4)	12(2)	7031(2)	90(1)
N(7A)	10835(9)	2228(6)	4658(5)	68(2)
C(8A)	11280(11)	3445(7)	4078(6)	63(2)
N(9A)	11290(8)	4545(6)	4798(4)	52(1)
N(10A)	9506(9)	4323(6)	9133(5)	61(2)
C(11A)	9157(11)	5647(8)	9512(6)	63(2)
O(11A)	8831(10)	5811(6)	10598(4)	96(2)
C(12A)	9149(13)	6835(8)	8628(7)	74(2)
C(1′A)	9796(11)	6866(6)	4620(5)	56(2)
C(2′A)	11684(9)	6041(7)	4419(6)	57(2)
C(3′A)	12457(10)	6232(7)	3083(6)	64(2)
C(4′A)	11274(11)	6894(8)	2508(6)	63(2)
C(5′A)	9487(10)	7323(7)	3377(6)	59(2)
C(6′A)	9901(15)	8386(7)	4203(7)	78(2)
C(7′A)	7575(10)	7212(7)	3105(6)	65(2)
O(7′A)	7111(7)	5819(5)	2974(4)	65(1)

shown in Fig. 3. All calculations were performed on Linux machines equipped with dual AMD Athlon CPUs.

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