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# North- and South-Bicyclo[3.1.0] Hexene Nucleosides. The Effect of Ring Planarity on Anti-HIV Activity

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## Abstract

The syntheses of new conformationally locked North and South bicyclo[3.1.0]hexene nucleosides is reported. The North analogues were synthesized by a convergent approach from the known (1*S*, 2*R*,5*R*)-5-[(*tert*-butyldiphenylsilyloxy)methyl]bicyclo[3.1.0]hex-3-en-2-ol (**7**) via Mitsunobu coupling with the nucleobases. The South analogues were synthesized from their bicyclo[3.1.0]hexane nucleoside precursors by the selective protection of the primary hydroxyl group, conversion of the secondary alcohol into a good leaving group, and base-catalyzed elimination to generate the olefin. The transformation of a bicyclo[3.1.0]hexane nucleoside into a bicyclo[3.1.0]hexene nucleoside flattens the five-membered ring of the bicyclic system and rescues anti-HIV activity for North-D4T (**4a**), North-D4A (**4c**), and South-D4C (**6d**). The relationship between planarity and the anti/syn disposition of the nucleobase that is favored by a particular pseudosugar platform are proposed as key parameters in controlling biological activity.

### Keywords

nucleosides; carbocycles; conformationally locked; antiviral agents; pseudorotational cycle

## Introduction

Recognition by cellular kinases and the viral enzyme, reverse transcriptase (RT), are essential prerequisites for a nucleoside drug to display good anti-HIV activity. Provided that the drug is efficiently metabolized to the 5′-triphosphate, the ensuing incorporation of the 5′-monophosphate into the DNA primer and interference with the proper functioning of HIV-1 RT– either by direct or delayed chain termination – stops viral replication. For HIV-1

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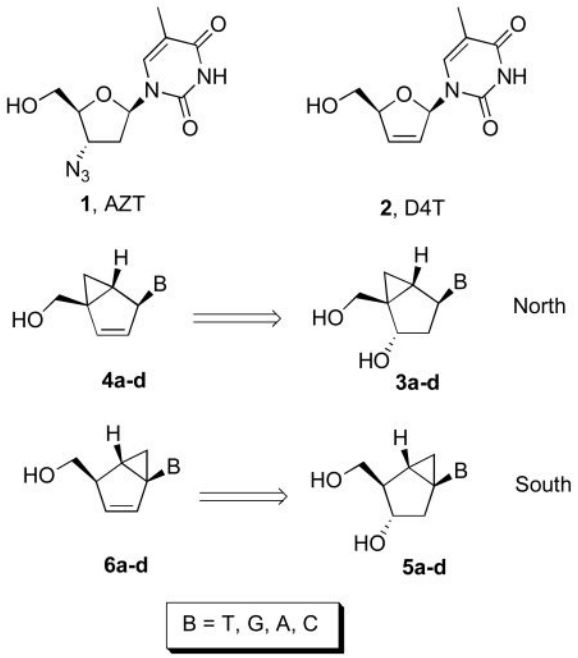
RT, we have provided evidence that the conformation of the sugar moiety preferred by the polymerase is proximate to the North ($^3T_2$, $P = 0°$) conformation.[1, 2] However, in the case of AZT (**1**), the strong gauche effect between the 3′-azido group and the ribose O4'oxygen forces the nucleoside and the corresponding 5′-triphosphate (AZTTP) to instead adopt the antipodal South ($_3T^2$, $P = 180°$) conformation (Figure 1A).[3] This conformational preference is opposite of that favored by the polymerase, which explains why AZTTP is incorporated less efficiently than the natural substrate TTP during DNA- or RNA-directed DNA synthesis.[4, 5] The ability of HIV-1 RT to distinguish between the antipodal North and South conformations of AZTTP was studied in our laboratory with two bicyclo[3.1.0]hexane analogues of AZT built on a platform that, contrary to the normal riboside ring of nucleosides, is not in a dynamic N ⇆ S equilibrium (Figure 1B). Those results showed conclusively that HIV-1 RT prefers the North conformation.[1]

Intriguingly, the 5′-triphosphate of a nucleoside with a pseudoribose ring that has virtually no puckering, stavudine (**2**, D4T), was shown to be incorporated as efficiently as the natural substrate TTP during both DNA- and RNA-dependent DNA polymerization.[6] However, counter to the ability of D4TTP to interact efficiently with HIV-1 RT is the finding that phosphorylation of D4T by the critical cellular thymidine kinase (TK) is 500-fold less efficient than for AZT.[7, 8] Indeed, the South conformation of AZT, which is detrimental for its interaction with HIV-1 RT, facilitates its interaction with the cellular thymidine kinase (TK) by displaying an affinity for the enzyme equivalent to that of thymidine itself.[7, 8] This means that South nucleoside conformers are preferred by cellular kinases and that either North or planar sugar conformations with no puckering are better substrates for the polymerases.

During the course of our investigations with bicyclo[3.1.0]hexane models of 2′-deoxynucleosides, we found that while chemically synthesized 5′-triphosphates that were restricted in the North conformation (**3a**–**3d**) were readily incorporated by HIV-1 RT and other polymerases, none of the nucleosides were effective anti-HIV agents due to inefficient cellular phosphorylation.[1, 2] On the other hand, the conformational constraint in South bicyclo[3.1.0]hexane nucleosides, which influences the nucleobase to adopt the biologically unsuitable syn conformation that is favored by intramolecular hydrogen bonding in a hydrophobic environment — such as the enzyme's binding site— resulted in compounds (**5a–d)** that were not phosphorylated by cellular kinases despite their excellent substrate recognition by the more tolerant, viral HSV-1 kinase.[9]




The incorporation of the main structural feature of D4T, which is its planarity, into the structure of the very potent anti-HSV compound, North-methanocarbathymidine (N-MCT, **3a**, B = T)[10] resulted in the very effective anti-HIV thymidine analogue (**4a**, B = T) with a novel bicyclo[3.1.0]hexene pseudosugar that included the critical double bond.[11] The 4 to 10-fold decrease in potency of **4a** relative to D4T was tentatively correlated with the nearly 10-fold reduction in the level of planarity ($\nu_{max}$ = 6.81°) of the embedded five-membered ring segment of the bicyclo[3.1.0]hexene template relative to the nearly flat pseudosugar ring of D4T ($\nu_{max}$ = 0.61°). Interestingly, in this particular case, it was planarity that converted the inactive **3a** into an active anti-HIV agent by allowing a significant level of recognition by the cellular TK resulting in the production of higher levels of the requisite 5′-triphosphate metabolite.

Because each of the cellular kinases that perform the critical first phosphorylation step have different preferences for the various nucleobases, we decided to complete our study by incorporating the rest of the nucleobases (A, C, and G) to the same bicyclo[3.1.0]hexene template (Table 1, 4a–**d**) derived from the conformationally locked North-bicyclo[3.1.0]hexane nucleosides (**3a**–**d**). It is important to remember that in terms of sugar conformation, once the amplitude of the puckering measured by $\nu_{max}$ reaches a small value, such as ~6° in **4a–d**, the designation of North and South loses its significance. Based on that argument, we decided to investigate the synthesis and anti-HIV activities of the complementary set of bicyclo[3.1.0]hexene nucleosides (Table 1, **6a–d)** derived from the antipodal, conformationally locked, South-bicyclo[3.1.0]hexane nucleosides (**5a–d**) bearing the four natural nucleobases.

## Results and Discussion

### Synthesis of "North-derived" bicyclo[3.1.0]hexene nucleosides

The syntheses of the thymidine (**4a**) and guanosine (**4b**) nucleosides were derived from the syntheses of their respective conformationally locked North conformers, which have been published.[11, 12] In a similar manner, the adenine (**4c**) and cytosine (**4d**) analogues were assembled from the bicyclo-cyclopentenol **7,** which was prepared as described previously.[11] Reaction of **7** with 6-chloropurine under Mitsunobu conditions gave **8** with the expected inversion of configuration. Subsequent displacement of the chloride with $NH_4OH$/dioxane in a pressure bomb gave the corresponding amine **9**, which after fluoride-catalyzed deprotection of the silyl group gave the target **4c** (Scheme 1). The characteristic UV $\lambda_{max}$ at 262 nm confirmed that the adenine ring in **4c** was connected to the pseudosugar through the N9 nitrogen. In a similar manner, compound **10** was assembled from the same bicyclo-cyclopentenol **7** after coupling with *N*-benzoyluracil[13] under Mistunobu conditions. Subsequent deprotection of the benzoyl group was followed by formation of the 4-(1,2,4-triazol-1-yl) intermediate **12** according to the method of Reese.[14] Ammonolysis of this intermediate provided the penultimate cytosine analogue which required only deprotection of the silyl ether to give the target compound **4d (**Scheme 2).

### Synthesis of "South-derived" bicyclo[3.1.0]hexene nucleosides

The construction of carbocyclic nucleosides (**6a–d**) derived from their respective conformationally locked South conformers is reported here for the first time. The syntheses of the precursors to generate these South conformers were performed as described previously.[15] The same methodology was used for the entire series and involved the selective protection of the primary hydroxyl group and conversion of the secondary alcohol into a good leaving group, such as the methanesulfonate ester, by standard chemistry. This was followed by base-catalyzed elimination, which in most cases occurred with the simultaneous deprotection of the silyl group, to give the desired target compounds **6b–d**. In the case of the thymine analogue (**6a**), the base-catalyzed elimination did indeed result in the desired olefin but an additional step using *n*-tetrabutylammonium fluoride (TBAF) was required to remove the silyl protecting group.

### X-ray Structures and Conformational Analysis

We have shown earlier that in the case of the North-derived D4T analogue (**4a**), the nearly planar structure of its fused cyclopentene ring nullifies the relevance of its location in the pseudorotational cycle.[11] The puckering amplitude ($\nu_{max}$) of the cyclopentene ring in **4a** was only 6.81° with a mean deviation from planarity of 0.025 Å. As expected, the compound was superimposed nicely with D4T with an RMS deviation of only 0.039 Å and its activity paralleled that of D4T.[11] Unfortunately, we were unable to grow good quality crystals of the corresponding South-derived D4T analogue (**6a**), but the guanine analogue (**6b**) provided good crystals for X-ray analysis. The crystal structure (Figure 2) validated all of the spectral assignments for this compound and the oher targets derived from the South template.

While both compounds **4a** and **6b** are similarly planar ($\nu_{max}$ ~ 7°, Table 2), as we expected, some of the pseudorotational parameters are quite different (Table 2). According to the value of *P*, **4a** is in the North hemisphere ($^1T_o$) and **6b** is in the South ($^4E$) hemisphere, although both conformations are in reality closer to the West end of the pseudorotational cycle. As mentioned before, their very planar structures with a $\nu_{max}$ ~ 7°, which corresponds to the radius of the pseudorotational cycle, makes the differences in *P* irrelevant. However, a significant divergence is found in the value of $\chi$. The purine ring of **6b** occupies the syn region as opposed to the pyrimidine ring in **4a**, which prefers the anti region. This penchant for the syn conformation is an interesting remnant from the saturated bicyclo[3.1.0]hexane scaffold in the South hemisphere which tends to favor the orientation of the base in the syn conformation.[9]

## Anti-HIV Activity

The anti-HIV activity was determined using an HIV-1 based vector containing wild-type (wt) HIV-1 RT that lacks a functional Env coding region and contains a luciferase reporter gene in the nef coding region.[16–18] This vector is pseudotyped with the vesicular stomatitis virus G protein (VSV-G) and is limited to a single replication cycle. The vector was used to infect conventional human osteosarcoma (HOS) cells or a modified HOS cell line containing and expressing the herpes simplex virus 1 thymidine kinase (HSV-1 TK).[19] Because HSV-1 TK is able to phosphorylate a wider range of nucleosides, cells that express HSV-1 TK can be used to analyze the anti-HIV activity of nucleosides that are not readily phosphorylated.[2] The HOS cell line expressing the HSV-1 TK has been designated HOS-313. Either HOS or HOS-313 cells were plated in 96 well luminescence cell culture plates and treated with each compound at different concentrations. After 48 h, anti-HIV activity was determined by measuring the reduction in the luciferase activity in infected cells. Only cells, which contain integrated viral DNA, will produce luciferase in the infectivity assay. Cytotoxicity, in the absence of virus, was determined by measuring the amount of ATP in the cells using a luciferase-based assay.[20] The amount of light produced by the reaction of the ATP from the cells with added luciferase and D-luciferin is proportional to the amount of ATP. ATP is required for vital cellular processes and the ATP concentration declines rapidly when cells undergo necrosis or apoptosis. Thus, cellular ATP levels serve as a sensitive indicator of cytotoxicity. Viral infectivity and cellular cytotoxicity is expressed on the Y-axis of the graphs as “Relative Infectivity (or Cell Health)”, respectively. In both assays, the results were normalized to a value of 1.0 representing the luciferase signal in the absence of compound. Among the bicyclo[3.1.0]hexene nucleosides (**4a**–**d**) derived from North templates, we have already reported that North-D4T (**4a**) was active, whereas North-D4G (**4b**) was not.[11, 12]

In three independent experiments using a regression analysis with a 4 parameter decay model, the North-D4A analogue (**4c**) was active in HOS cells (Figure 3A, $EC_{50(HOS)}$ = 16.7 μM). Regression analysis on cytotoxicity data was performed using a simple exponential decay model and indicated a 25-fold difference in cytotoxicity versus infectivity (Figures 3A, $CC_{50(HOS)}$ = 423 μM). The compound was slightly more potent in HOS-313 cells (Figure 3B, $EC_{50(HOS\text{-}313)}$ = 11.1 μM and $CC_{50(HOS\text{-}313)}$ = 246 μM) with a similar selectivity index of 24.

The North-D4C (**4d**) analogue was inactive and relatively non-toxic (data not shown) suggesting the possibility that neither HOS cells nor the HSV-1 TK transfected HOS-313 cells were capable of efficiently phosphorylating the compound.

With the exception of South-D4C (**6d**), all South analogues were inactive and non-toxic (data not shown). As seen in Figure 4, South-D4C had an $EC_{50}$ = 26.8 μM in HOS cells, which was reduced to 3.0 μM in HOS-313 infected cells. Selectivity indices for the compound in HOS and HOS-313 cells were 15.8 and 130, respectively.

## Conclusions

The transformation of a bicyclo[3.1.0]hexane nucleoside into a bicyclo[3.1.0]hexene nucleoside by the addition of a double bond flattens the five-membered ring of the bicyclic system and rescues anti-HIV activity for North-D4T (**4a**), North-D4A (**4c**), and South-D4C (**6d**). North-D4A (**4c**) and South-D4C (**6d**), both of which were active in non-transfected HOS cells, demonstrate the existence of a significant level of substrate recognition by both cellular kinases and HIV-1 RT. Based on the known anti-HIV activity of North-D4T (**4a**)[11] we expected that other related North analogues would also be active. However, only the North-D4A was active; the rest of this series of North analogues (G[12] and C) failed to show activity. Only one of the compounds in the South series, South-D4C (**6d**), was active. This was surprising in view of the lack of activity of North-D4C (**4d**), particularly when one assumes that the cyclopentene ring would be equally flat in both compounds. Other structural elements, such as the location of the fused cyclopropane ring and the rotational freedom around the C–N bond may be contributing factors.

## Experimental Section

### General Techniques

All reagents and solvents purchased were of the highest commercial quality and used without further purification unless otherwise stated. Column chromatography was performed on silica gel 60, 230–400 mesh (E. Merck). $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian Unity Inova instrument at 400 and 100 MHz, respectively. Spectra are referenced to the solvent in which they were run (7.24 ppm for $CDCl_3$). Infrared spectra were recorded on a Jasco model 615 FT-IR instrument. Positive-ion fast-atom bombardment mass spectra (FAB MS) were obtained on a VG 70-SE double-focusing mass spectrometer operated at an accelerating voltage of 8 kV under the control of a MASPEC-II[32] data system for Windows (MasCom GmbH, Bremen, Germany). Either glycerol or 3-nitrobenzyl alcohol was used as the 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. The FAB mass spectra of all analyzed compounds indicated a molecular species ($[M+H]^+$ or $[M+Na]^+$) as well as fragment ions highly indicative of structure. Nominal mass MS were obtained at a resolution of 1500, and matrix-derived ions were background subtracted during data system processing. Accurate mass analyses (HR-FAB-MS) were carried out under data system control at a resolution of approximately 7000 employing a limited-range V/E scan. For these analyses, matrix-derived ions were utilized as the internal mass references for accurate mass determination. Both $^{1}H$ and $^{13}C$ NMR data, in conjunction with the observed isotopic distribution of $[M+H]^+$, were

used to set constraints for the calculation of all possible elemental compositions within 20 ppm of the measured accurate mass. In all cases, a unique molecular formula could be determined by consideration of the molecular ion species and appropriate fragment ions. Optical rotations were recorded on a Jasco P-1010 polarimeter. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

**9-((1′*S*, 2′*S*, 5′*R*)-5-((*tert*-Butyldiphenylsilyloxy)methyl)bicyclo[3.1.0]hex-3-en-2-yl)-6-chloro-9H-purine (8)—**Under argon, DIAD (0.53 mL, 2.67 mmol) was added to a 0 °C solution of triphenylphosphine (718 mg, 1.16 mmol) in THF (25 mL). The resultant yellow solution continued to stir at 0 °C for 20 minutes and was then added to a 0 °C mixture of **7** (423 mg, 1.16 mmol) and 6-chloropurine (287 mg, 1.86 mmol) in THF (25 mL). The resulting solution was stirred at 0 °C for 1 h and then warmed to room temperature overnight. Concentration in vacuo and purification of the residue by silica gel flash chromatography ($CH_2Cl_2$ and 10% $Et_2O/CH_2Cl_2$, followed by 10%MeOH/$CH_2Cl_2$) gave an impure product. Further purification by silica gel flash chromatography (5% and 20% EtOAc/hexanes) gave **8** (88 mg, 17% yield) as a sticky foam; $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.74 (s, 1 H, H-2), 8.23 (s, 1 H, H-8), 7.59 (m, 4 H, Ph), 7.36 (m, 6 H, Ph), 6.46 (d, *J* = 4.4 Hz, 1 H, H-4′), 5.54 (m, 2 H, H-2′ and H-3′), 4.16 (d, *J* = 11.2 Hz, 1 H, $CH_{2a}$), 3.58 (d, *J* = 11.2 Hz, 1 H, $CH_{2b}$), 1.69 (dd, *J* = 4.2, 8.4 Hz, 1 H, H-1′), 1.15 (dd, *J* = 4.5, 8.4 Hz, 1 H, H-6′$_a$), 1.05 (s, 9 H, $C(CH_3)_3$), 0.52 (t, *J* = 4.4 Hz, 1 H, H-6′$_b$); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 151.73, 151.06, 150.82, 144.05, 143.39, 135.55, 135.44, 133.09, 133.08, 131.90, 129.83, 129.77, 127.73, 127.68, 124.89, 64.53, 60.09, 38.51, 28.35, 26.87, 24.25, 19.13; FAB MS: *m/z* (%) 501 (100) $[M+H]^+$; Anal. calcd for $C_{28}H_{29}ClN_4O_2$: C 67.11, H 5.83, N 11.18, found: C 67.16, H 6.16, N 10.59.

**9-((1′*S*, 2′*S*, 5′*R*)-5-((*tert*-Butyldiphenylsilyloxy)methyl)bicyclo[3.1.0]hex-3-en-2-yl)-9H-purin-6-amine (9)—**A solution of **8** (54 mg, 0.11 mmol) in concentrated $NH_4OH$ (3 mL) and dioxane (3 mL) was heated to 70° C in a glass pressure bomb overnight. After cooling to room temperature, the reaction mixture was concentrated in vacuo. Purification of the residue by silica gel flash chromatography (2.5% and 5% MeOH/$CHCl_3$) gave **9** (41 mg, 79% yield) as a colorless foam; $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.37 (s, 1 H, H-2), 7.92 (s, 1 H, H-8), 7.61 (m, 4 H, Ph), 7.35 (m, 6 H, Ph), 6.41 (dd, *J* = 1.4, 5.5 Hz, 1 H, H-4′), 6.05 (br s, 2 H, $NH_2$), 5.54 (dt, *J* = 1.9, 5.4 Hz, 1 H, H-3′), 5.47 (br s, 1 H, H-2′), 4.13 (d, *J* = 11.1 Hz, 1 H, $CH_{2a}$), 3.56 (d, *J* = 11.2 Hz, 1 H, $CH_{2b}$), 1.69 (dd, *J* = 4.1, 8.1 Hz, 1 H, H-1′), 1.10 (irr dd, 1 H, H-6′$_a$), 1.05 (s, 9 H, $C(CH_3)_3$), 0.48 (t, *J* = 4.4 Hz, 1 H, H-6′$_b$); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 155.57, 152.83, 149.32, 142.47, 139.29, 135.58, 135.47, 133.21, 129.79, 129.75, 127.72, 127.68, 125.58, 119.80, 64.80, 59.45, 38.34, 28.73, 26.86, 24.26, 19.16; FAB MS: *m/z* (%) 482 (57) $[M+H]^+$, 136 (100); Anal. calcd for $C_{28}H_{31}N_5OSi \cdot 0.9H_2O$: C 67.55, H 6.64, N 14.07, found: C 67.36, H 6.25, N 13.83.

**((1′*R*, 4′*S*, 5′*S*)-4-(6-Amino-9H-purin-9-yl)bicyclo[3.1.0]hex-2-en-1-yl)methanol (4c)—**A mixture **9** (107 mg, 0.22 mmol) and triethylamine trihydrofluoride (0.22 mL, 1.33 mmol) in acetonitrile (10 mL) was refluxed overnight. After cooling to room temperature, the reaction mixture was diluted with water (10 mL) and stirred for 1 h at room temperature. Concentration in vacuo and purification of the residue by silica gel flash chromatography

(2.5%, 5%, and 10% MeOH/$CHCl_3$) followed by a second silica gel flash chromatography (2.5%, 5%, and 10% MeOH/$CHCl_3$) purification gave **4c** (41 mg, 76% yield) as a white solid. Treatment of this solid with methanol/diethyl ether gave 32 mg (59% yield) of analytically pure **4c**; mp 201–203 °C; $[\alpha]_D^{19}$ = +208.69 (c 0.17, $CH_3OH$); UV (MeOH:$H_2O$, 1:1) $\lambda_{max}$ = 262 nm ($\varepsilon$ = 1.40 × $10^4$ $mol^{-1}cm^{-1}$); $^1$H NMR (400 MHz, $CD_3OD$): δ = 8.19 (s, 1 H, H-2), 8.11 (s, 1 H, H-8), 6.51 (dm, *J* = 5.4 Hz, 1 H, H-2′), 5.59 (dt, *J* = 1.9, 5.4 Hz, 1 H, H-3′), 5.43 (br t, *J* = 1.8 Hz, 1 H, H-4′), 4.14 (d, *J* = 11.8 Hz, 1 H, $CH_{2a}$), 3.50 (d, *J* = 11.8 Hz, 1 H, $CH_{2b}$), 1.93 (m, 1 H, H-5′), 1.27 (dd, *J* = 4.4, 8.4 Hz, 1 H, H-6′$_a$), 0.58 (t, *J* = 4.4 Hz, 1 H, H-6′$_b$); $^{13}$C NMR (100 MHz, $CD_3OD$): δ = 157.52, 153.59, 149.98, 143.84, 141.47, 127.13, 120.54, 64.71, 62.32, 40.20, 29.45, 25.58; FAB MS: *m/z* (%) 244 (100) [M +H]$^+$; Anal. calcd for $C_{12}H_{13}N_5O$: C 59.25, H 5.39, N 28.79, found: C 59.05, H 5.28, N 28.79.

**3-Benzoyl-1-((1′*S*, 2′*S*, 5′*R*)-5-((*tert*-butyldiphenylsilyloxy)methyl)bicyclo[3.1.0]hex-3-en-2-yl)pyrimidine-2,4(1*H*, 3*H*)-dione (10)—**Under argon, DIAD (0.54 mL, 2.70 mmol) was added to a 0 °C solution of triphenylphosphine (707 mg, 2.70 mmol) in THF (20 mL). The resultant yellow solution continued to stir at 0 °C for 30 min. A solution of **7** (393 mg, 1.08 mmol) in THF (30 mL) was added to the 0 °C solution immediately followed by *N*-3-benzoyl uracil (350 mg, 1.62 mmol) and the resultant solution was stirred at 0 °C for 1 h, and then warmed to room temperature overnight. Concentration in vacuo and purification of the residue by silica gel flash chromatography ($CH_2Cl_2$ and 5% $Et_2O/CH_2Cl_2$) gave a crude product which was subjected to a second purification by silica gel flash chromatography ($CH_2Cl_2$ and 5% $Et_2O/CH_2Cl_2$) to give **10** (187 mg, 31% yield) as a colorless foam; $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.95 (m, 2 H, H-6), 7.63 (m, 7 H, Ph), 7.44 (m, 8 H, Ph), 6.38 (d, *J* = 5.4 Hz, 1 H, H-4′), 5.54 (d, *J* = 8.1 Hz, 1 H, H-5), 5.49 (br s, 1 H, H-2′), 5.41 (m, 1 H, H-3′), 4.33 (d, *J* = 11.3 Hz, 1 H, $CH_{2a}$), 3.39 (d, *J* = 11.3 Hz, 1 H, $CH_{2b}$), 1.64 (dd, *J* = 4.0, 8.2 Hz, 1 H, H-1′), 1.07 (s, 9 H, $C(CH_3)_3$), 1.05 (m, 1H, H-6′$_a$), 0.42 (t, *J* = 4.5 Hz, 1 H, H-6′$_b$); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 169.07, 162.24, 149.73, 143.32, 141.63, 135.59, 135.43, 134.98, 133.09, 132.86, 131.60, 130.48, 130.05, 129.98, 129.10, 127.87, 127.86, 125.96, 102.51, 65.43, 60.47, 38.46, 27.87, 26.91, 23.90, 19.31; FAB MS: *m/z* (%) 563 (43) [M+H]$^+$, 105 (100); Anal. calcd for $C_{34}H_{34}N_2O_4Si$•0.3$H_2O$: C 71.88, H 6.14, N 4.93, found: C 71.55, H 6.12, N 4.78.

**1-((1′*S*, 2′*S*, 5′*R*)-5-((*tert*-Butyldiphenylsilyloxy)methyl)bicyclo[3.1.0]hex-3-en-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (11)—**Concentrated $NH_4OH$ (4 mL) was added to a solution of **10** (182 mg, 0.32 mmol) in methanol (30 mL) and stirred for 2 h in a capped vessel at room temperature. Concentration in vacuo and purification of the residue by silica gel flash chromatography ($CH_2Cl_2$ and 5% MeOH/$CH_2Cl_2$, followed by a second silica gel flash chromatography 20% and 50% EtOAc/hexanes) gave **11** (134 mg, 90% yield) as a colorless foam; $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.75 (br s, 1 H, NH), 7.64 (q, *J* = 1.6, 1 H, Ph), 7.62 (m, 1 H, Ph), 7.60 (q, *J* = 1.5, 1 H, Ph), 7.58 (m, 1 H, Ph), 7.40 (m, 7 H, Ph and H-6), 6.34 (ddd, *J* = 0.7, 1.5, 5.5 Hz, 1 H, H-4′), 5.50 (br t, *J* = 1.7 Hz, 1 H, H-2′), 5.44 (dd, *J* = 2.3, 8.0 Hz, 1 H, H-5), 5.36 (dt, *J* = 1.9, 5.4 Hz, 1 H, H-3′), 4.30 (d, *J* = 11.3 Hz, 1 H, $CH_{2a}$), 3.36 (d, *J* = 11.3 Hz, 1 H, $CH_{2b}$), 1.57 (dd, *J* = 4.3, 8.2 Hz, 1 H, H-1′), 1.05 (s, 9 H,

$C(CH_3)_3$), 1.01 (dd, *J* = 4.6, 8.5 Hz, 1 H, H-6′$_a$), 0.41 (t, *J* = 4.5 Hz, 1 H, H-6′$_b$); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.15, 150.69, 142.99, 141.89, 135.59, 135.42, 133.12, 132.91, 130.00, 129.93, 127.84, 127.81, 126.11, 102.55, 65.41, 60.19, 38.40, 27.90, 26.88, 23.86, 19.29; FAB MS: *m/z* (%) 459 (100) $[M+H]^+$; Anal. calcd for $C_{27}H_{30}N_2O_3Si•1H_2O$: C 68.04, H 6.77, N 5.88, found: C 67.91, H 6.39, N 5.71.

**1-((1′*S*, 2′*S*, 5′*R*)-5-((*tert*-Butyldiphenylsilyloxy)methyl)bicyclo[3.1.0]hex-3-en-2-yl)-4-(1*H*-1,2,4-triazol-1-yl)pyrimidin-2(1*H*)-one (12)—**Phosphorous oxychloride (0.064 mL, 0.70 mmol) was added dropwise to a solution of **11** (132 mg, 0.29 mmol), 1,2,4-triazole (457 mg, 6.62 mmol) and triethylamine (0.93 mL, 6.62 mmol) in acetonitrile (10 mL) and stirred for 2 h at room temperature. The reaction mixture was then poured into a solution of chloroform (30 mL) containing triethylamine (2 mL), extracted with saturated aqueous $NaHCO_3$ (3 ×10 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by silica gel flash chromatography (20%, 50% and 75% EtOAc/hexanes) gave **12** (140 mg, 96% yield) as a colorless glass; $^1$H NMR (400 MHz, $CDCl_3$): δ = 9.27 (s, 1 H, triazole-H), 8.10 (overlapping s and d, *J* = 7.1 Hz, 2 H, H-6, triazole-H), 7.60 (m, 3 H, Ph), 7.44 (m, 2 H, Ph), 7.37 (m, 5 H, Ph), 6.71 (d, *J* = 7.1, 1 H, H-5), 6.41 (ddd, *J* = 0.8, 1.4, 5.4 Hz, 1 H, H-4′), 5.78 (br s, 1 H, H-2′), 5.44 (dt, *J* = 2.0, 5.4 Hz, 1 H, H-3′), 4.34 (d, *J* = 11.3 Hz, 1 H, $CH_{2a}$), 3.38 (d, *J* = 11.3 Hz, 1 H, $CH_{2b}$), 1.65 (dd, *J* = 4.1, 8.4 Hz, 1 H, H-1′), 1.07 (m containing s at 1.07, 10 H, H6′$_a$ and $C(CH_3)_3$), 0.50 (t, *J* = 4.5 Hz, 1 H, H-6′$_b$); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 158.72, 155.14, 153.88, 148.88, 143.77, 135.56, 135.42, 133.12, 132.89, 130.07, 129.99, 127.88, 127.85, 126.42, 95.12, 65.37, 62.45, 38.65, 28.69, 26.94, 24.27, 19.33; FAB MS: *m/z* (%) 510 (100) $[M+H]^+$; HRMS-FAB: *m/z* $[M+H]^+$ calcd for $C_{29}H_{31}N_5O_2Si$: 510.2325, found: 510.2306.

**4-Amino-1-((1′*S*, 2′*S*, 5′*R*)-5-((*tert*-butyldiphenylsilyloxy)methyl)bicyclo[3.1.0]hex-3-en-2-yl)pyrimidin-2(1*H*)-one (13)—**A solution of **12** (136 mg, 0.27 mmol) and concentrated $NH_4OH$ (5 mL) in dioxane (20 mL) was stirred in a capped vessel overnight at room temperature. Concentration in vacuo and purification of the residue by silica gel flash chromatography (5% and 10% MeOH/$CHCl_3$) gave **13** (134 mg, 90% yield) as a colorless foam; $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.63 (m, 1 H, Ph), 7.61 (m, 1 H, Ph), 7.59 (m, 1 H, Ph), 7.57 (m, 1 H, Ph), 7.52 (d, *J* = 7.3 Hz, 1 H, H-6), 7.39 (m, 6 H, Ph), 6.29 (ddd, *J* = 0.8, 1.6, 5.5 Hz, 1 H, H-4′), 5.67 (br s, 1 H, H-2′), 5.37 (m, 2 H, H-5 and H-3′), 4.26 (d, *J* = 11.2 Hz, 1 H, $CH_{2a}$), 3.34 (d, *J* = 11.2 Hz, 1 H, $CH_{2b}$), 1.56 (dd, *J* = 4.3, 8.4 Hz, 1 H, H-1′), 1.04 (s, 9 H, $C(CH_3)_3$), 0.96 (dd, *J* = 4.5, 8.5 Hz, 1 H, H-6′$_a$), 0.38 (t, *J* = 4.4 Hz, 1 H, H-6′$_b$); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 165.16, 156.35, 143.56, 141.94, 135.60, 135.45, 133.37, 133.04, 129.91, 129.77, 127.80, 127.74, 127.24, 94.04, 65.62, 60.87, 38.19, 28.80, 26.90, 23.89, 19.30; FAB MS: *m/z* (%) 458 (100) $[M+H]^+$; HRMS-FAB: *m/z* $[M+H]^+$ calcd for $C_{27}H_{33}N_5O_2Si$: 458.2264, found: 458.2267.

**4-Amino-1-((1′*S*, 2′*S*, 5′*R*)-5-(hydroxymethyl)bicyclo[3.1.0]hex-3-en-2-yl)pyrimidin-2(1*H*)-one (4d)—**Under argon, triethylamine trihydrofluoride (0.177 mL, 1.09 mmol) was added to a mixture of **13** (83 mg, 0.18 mmol) in acetonitrile (10 mL) and refluxed overnight. After cooling to room temperature, the reaction mixture was diluted with

water (10 mL) and stirred for 1 h at room temperature. Concentration in vacuo and purification of the residue by silica gel flash chromatography (15% MeOH/$CHCl_3$) followed by recrystallization from (MeOH/$CH_2Cl_2$) gave **4d** (30 mg, 75% yield) as a white solid; mp 250 °C (dec); $[\alpha]_D^{19}$ = −21.91 (c 0.13, MeOH); $^1$H NMR (400 MHz, $d_6$-DMSO): δ = 7.03 (d, *J* = 7.3 Hz, 1 H, H-6), 7.01 (br s, 1 H, NHH), 6.83 (br s, 1 H, NHH), 6.06 (dm, *J* = 5.4 Hz, 1 H, H-4′), 5.41 (d, *J* = 7.2 Hz, 1 H, H-5), 5.02 (dt, *J* = 1.7, 5.1 Hz, 1 H, H-3′), 4.49 (t, *J* = 5.2 Hz, 1 H, OH), 3.56 (dd, *J* = 4.7, 11.6 Hz, 1 H, $CH_{2a}$), 3.03 (dd, *J* = 4.8, 11.6 Hz, 2 H, $CH_{2b}$), 1.23 (dd, *J* = 4.0, 8.1 Hz, 1 H, H-1′), 0.77 (dd, *J* = 4.0, 8.4 Hz, 1 H, H-6′$_a$), 0.01 (t, *J* = 4.1 Hz, 1 H, H-6′$_b$); $^{13}$C NMR (100 MHz, $d_6$-DMSO): δ = 164.62, 154.52, 142.59, 142.24, 126.60, 93.84, 62.00, 60.31, 38.52, 27.78, 23.66; FAB MS: *m/z* (%) 220 (100) [M +H$^+$]; HRMS-FAB: *m/z* [M+H]$^+$ calcd for $C_{11}H_{13}N_5O_2$: 220.1086, found: 220.1127; HRMS-FAB: *m/z* [M+Na]$^+$ calcd for $C_{11}H_{13}N_5O_2Na$: 242.0905, found: 242.0906.

**1-[(1′*S*, 3′*S*, 4′*R*, 5′*S*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-3-hydroxybicyclo-[3.1.0]hexan-1-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (14a)—**4-Dimethyl-aminopyridine (DMAP, 31 mg, 0.25 mmol) was added to a solution of **5a** (126 mg, 0.5 mmol) in pyridine (5 mL) and TBDPSCl (0.52mL, 2.0 mmol) was added dropwise to this solution. After stirring overnight at room temperature, the mixture was concentrated in vacuo. Purification of the residue by silica gel flash chromatography ($CHCl_3$, 2% and 5% MeOH/$CHCl_3$) followed by a second silica gel flash chromatography ($CHCl_3$, 2% and 5% MeOH/$CHCl_3$) gave **14a** (0.242g, 98 %) as a colorless foam; $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.91 (s, 1 H, NH), 7.66 (m, 4 H, Ph), 7.38 (m, 6 H, Ph), 7.08 (d, *J* = 1.3 Hz, 1 H, H-6), 4.36 (dd, *J* = 0.9, 6.9 Hz, 1 H, H-3′), 3.84 (d, *J* = 7.0 Hz, 2 H, $CH_2$), 2.35 (ddd, *J* = 2.2, 7.1, 13.7 Hz, 1 H, H-2′$_a$), 2.09 (m, 2 H, H-4′, H-2′$_b$), 1.76 (d, *J* = 1.2 Hz, 3 H, $CH_3$), 1.64 (ddd, *J* = 0.9, 4.8, 9.8 Hz, 1 H, H-5′), 1.48 (m, 1 H, H-6′$_a$), 1.09 (m, 10 H, H-6′$_b$ and C($CH_3$)$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.69, 150.48, 149.81, 135.57, 135.48, 133.53, 133.45, 129.82, 129.81, 127.78, 110.27, 74.58, 65.11, 53.37, 48.25, 40.04, 27.35, 26.99, 19.40, 19.34, 12.12; FAB MS: *m/z* (%) 491 (41) [M+H]$^+$, 243 (100); HRMS-FAB: *m/z* [M+H]$^+$ calcd for $C_{28}H_{34}N_2O_4Si$: 491.2366, found: 491.2385.

## General procedure A

Atmospheric water was azeotropically removed from a mixture of starting material (**5b**–**5d**) (1 equiv) and imidazole (2.2 equiv) by evaporation with DMF (2 × 10 mL). The residue was then re-dissolved in DMF and TBDPSCl (1.1 equiv) was added under argon. After stirring 3 h to overnight at room temperature, the reaction mixture was concentrated in vacuo. Purification of the residue by silica gel flash chromatography (2.5%, 5% and 10% MeOH/ $CHCl_3$) gave product (**14b–14d**).

**2-Amino-9-((1′*S*, 3′*S*, 4′*R*, 5′*S*)-4-((*tert*-butyldiphenylsilyloxy)-methyl)-3-hydroxybicyclo-[3.1.0]hexan-1-yl)-1*H*-purin-6(9*H*)-one (14b)—**According to general procedure A, **5b** (150 mg, 0.54 mmol), imidazole (83 mg, 1.19 mmol) and TBDPSCl (200 μL, 0.77 mmol) were combined in DMF (10 mL) overnight to give **14b** (247 mg, 86%) as a white solid, which was recrystallized from MeOH; mp >300 °C; $^1$H NMR (400 MHz, $d_6$-DMSO): δ = 10.53 (br s, 1 H, NH), 7.66 (m, 4 H, Ph), 7.45 (m, 7H, H-8 and Ph), 6.28 (br s, 2 H, $NH_2$), 4.78 (d, *J* = 3.2 Hz, 1 H, H-3′), 4.16 (br s, 1 H, OH), 3.82 (dd, *J* =

7.5, 10.4 Hz, 1 H, $CH_{2a}$), 3.77 (dd, *J* = 6.7, 10.3 Hz, 1H, $CH_{2b}$), 2.19 (m, 2 H, H-2′), 2.11 (t, *J* = 7.1 Hz, 2 H, H-4′), 1.85 (irr dd, 1 H, H-5′), 1.49 (t, *J* = 4.9 Hz, 1 H, H-6′$_a$), 1.17 (dd, *J* = 5.0, 9.4 Hz, 1 H, H-6′$_b$), 1.02 (s, 9 H, $C(CH_3)_3$); $^{13}$C NMR (100 MHz, $d_6$-DMSO): δ = 156.67, 153.28, 152.22, 137.07, 137.02, 135.10, 133.11, 133.08, 129.85, 127.90, 117.07, 72.43, 51.97, 42.31, 40.96, 26.74, 25.14, 18.84, 17.65; FAB MS: *m/z* (%) 516 (100) $[M+H]^+$; Anal. calcd for $C_{28}H_{33}N_5O_3Si$: C 65.21, H 6.45, N 13.58, found: C 65.03, H 6.44, N 13.55.

**(1′*S*, 3′*S*, 4′*R*, 5′*S*)-1-(6-Amino-1*H*-purin-9(6*H*)-yl)-4-((*tert*-butyldiphenylsilyloxy)-methyl)bicyclo[3.1.0]hexan-3-ol (14c)—**According to general procedure A, **5c** (164 mg, 0.63 mmol), imidazole (94 mg, 1.38 mmol) and TBDPSCl (180 μL, 0.69 mmol) were combined in DMF (10 mL) to give **14c** (265 mg, 82%) as a white solid; mp 189–191 °C; $^1$H NMR (400 MHz, $d_6$-DMSO): δ = 8.00 (s, 1 H, H-2), 8.01 (s, 1 H, H-8), 7.67 (dd, *J* = 1.4, 7.9, 4 H, Ph), 7.45 (m, 6 H, H-8 and Ph), 7.15 (s, 2 H, $NH_2$), 4.83 (d, *J* = 3.0 Hz, 1 H, OH), 4.19 (br dd, *J* = 2.4, 6.0 Hz, 1 H, H-3′), 3.97 (d, *J* = 7.7 Hz, 2 H, $CH_2$), 2.44 (ddd, *J* = 1.3, 6.4, 13.0 Hz, 1 H, H-2′$_a$), 2.19 (t, *J* = 7.5 Hz, 1 H, H-4′), 2.11 (d, *J* = 13.3 Hz, 1 H, H-2′$_b$), 1.84 (irregular dd, 1 H, H-5′), 1.56 (t, *J* = 5.0 Hz, 1 H, H-6′$_a$), 1.37 (ddd, *J* = 1.6, 4.9, 9.3 Hz, 1 H, H-6′$_b$), 1.02 (s, 9 H, $C(CH_3)_3$); $^{13}$C NMR (100 MHz, $d_6$-DMSO): δ = 155.94, 152.24, 150.23, 140.92, 135.08, 135.04, 133.30, 133.26, 129.78, 127.86, 127.82, 119.18, 71.89, 65.08, 52.14, 42.39, 40.43, 26.71, 25.53, 18.91, 16.71; FAB MS: *m/z* (%) 500 (100) $[M+H]^+$; Anal. calcd for $C_{28}H_{33}N_5O_2Si$: C 67.30, H 6.66, N 14.02, found: C 67.06, H 6.65, N 14.01.

**4-Amino-1-((1′*S*, 3′*S*, 4′*R*, 5′*S*)-4-((*tert*-butyldiphenylsilyloxy)methyl)-3-hydroxybicyclo-[3.1.0]hexan-1-yl)pyrimidin-2(1*H*)-one (14d)—**According to general procedure A, **5d** (241 mg, 1.02 mmol), imidazole (155 mg, 2.28 mmol) and TBDPSCl (290 μL, 1.11 mmol) were combined in DMF (20 mL) to give **14d** (447 mg, 94%) as a colorless glass; mp 168–170 °C; $^1$H NMR (400 MHz, $CD_3OD$): δ = 7.72 (m, 4 H, Ph), 7.65 (d, *J* = 7.5 Hz, 1 H, H-6), 7.44 (m, 6 H, Ph), 5.81 (d, *J* = 7.5 Hz, 1 H, H-5), 4.28 (d, *J* = 6.9 Hz, 1 H, H-3′), 3.90 (m, 2 H, $CH_2$), 2.33 (irregular dd, 1 H, H-2′$_a$), 2.20 (t, *J* = 7.1 Hz, 1 H, H-4′), 2.10 (d, *J* = 13.6 Hz, 1 H, H-2′$_b$), 1.74 (dd, *J* = 4.8, 9.7 Hz, 1 H, H-5′), 1.52 (t, *J* = 5.2 Hz, 1 H, H-6′$_a$), 1.16 (m, 1 H, H-6′$_b$), 1.09 (s, 9 H, $C(CH_3)_3$); $^{13}$C NMR (100 MHz, $CD_3OD$): δ = 164.80, 154.76, 149.54, 136.94, 136.87, 135.05, 134.95, 131.07, 129.01, 129.00, 95.30, 74.91, 66.58, 54.46, 50.95, 40.62, 28.50, 27.64, 20.29, 19.69; 476 FAB MS: *m/z* (%) 476 (100) $[M+H]^+$; HRMS-FAB: *m/z* $[M+H]^+$ calcd for $C_{27}H_{33}N_3O_3Si$: 476.2370, found: 476.2384.

**(1′*S*, 3′*S*, 4′*R*, 5′*S*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-1-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)bicyclo[3.1.0]hexan-3-yl methanesulfonate (15a)—**Methanesulfonyl chloride (252 μL, 3.26 mmol) was added dropwise to a solution of **14a (**400 mg, 0.82 mmol) in pyridine (16 mL). After stirring at room temperature for 2 h, the mixture was concentrated in vacuo. Purification by silica gel flash chromatography (5% $MeOH/CH_2Cl_2$) gave **15a** (426 mg, 92%) as a white solid; mp 93–95 °C; $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.27 (br s, 1 H, NH), 7.65 (m, 4 H, Ph), 7.40 (m, 6 H, Ph), 7.05 (d, *J* = 1.2 H z, 1 H, H-6), 5.14 (d, *J* = 6.9 Hz, 1 H, H-3′), 3.91 (m, 2 H, $CH_2$), 2.90 (s, 3 H, $CH_3$),

2.52 (irregular ddd, 1 H, H-2′$_a$), 2.43 (m, 2 H, H-2′$_b$ and H-4′), 1.77 (d, *J* = 1.0 Hz, 3 H, $CH_3$), 1.61 (m, 1 H, H-5′), 1.34 (dd, *J* = 5.1, 6.3 Hz, 1 H, H-6′a), 1.11 (m, 10 H, H-6′$_b$ and $C(CH_3)_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.60, 150.32, 140.56, 135.54, 135.50, 133.06, 133.03, 129.97, 129.95, 127.88, 127.86, 110.74, 83.50, 63.85, 51.73, 47.58, 38.36, 37.87, 27.00, 26.85, 19.31, 17.84, 12.14; FAB MS: *m/z* (%) 569 (81) $[M+H]^+$, 217 (100); HRMS-FAB: *m/z* $[M+H]^+$ calcd for $C_{29}H_{36}N_2O_6Si$: 569.2142, found: 569.2101.

**(1′*S*, 3′*S*, 4′*R*, 5′*S*)-1-(2-Amino-6-oxo-1H-purin-9(6*H*)-yl)-4-((*tert*-butyldiphenylsilyloxy) methyl)bicyclo[3.1.0]hexan-3-yl methanesulfonate (15b)**—Atmospheric water was azeotropically removed from **14a** (79 mg, 0.15 mmol) by evaporation with pyridine (3 × 4 mL), and then **14a** was dissolved in pyridine (5 mL) under argon. Methanesulfonyl chloride (24 μL, 0.31 mmol) was added dropwise and the reaction stirred at room temperature. After 1 h, additional methanesulfonyl chloride (12 μL, 0.15 mmol) was added and the reaction stirred for an additional 30 mins. The reaction mixture was then concentrated in vacuo and purified by silica gel flash chromatography (5% and 10% MeOH/$CHCl_3$) to give **15b** (80 mg, 88%) as a white solid; mp 218–220 °C; $^1$H NMR (400 MHz, $CD_3OD$): δ = 10.58 (s, 1 H, NH), 7.68 (m, 4 H, Ph), 7.46 (m, 7 H, Ph and H-8), 6.27 (s, 2 H, $NH_2$), 5.14 (d, *J* = 4.6 Hz, 1 H, H-3′), 3.93 (dd, *J* = 6.0, 10.6 Hz,1 H, $CH_{2a}$), 3.84 (dd, *J* = 8.7, 10.6 Hz, 1H, $CH_{2b}$), 3.16 (s, 3 H, $CH_3$), 2.55 (m, 2 H, H-2′$_a$), 2.50 (m, 2 H, H-2′$_b$, H-4′), 1.97 (dd, *J* = 4.7, 9.4 Hz, 1 H, H-5′), 1.30 (dd, *J* = 6.0, 10.6 Hz, 1H, H-6′$_a$), 1.21 (t, *J* = 5.7 Hz, 1H, H-6′$_b$), 1.02 (s, 9H, $C(CH_3)_3$); $^{13}$C NMR (100 MHz, $CD_3OD$): δ = 167.74, 159.19, 147.53, 136.97, 134.69, 134.65, 131.19, 129.12, 129.08, 96.05, 85.24, 65.58, 53.49, 50.25, 38.89, 38.75, 27.81, 27.69, 20.25, 18.77; FAB MS: *m/z* (%) 594 (100) $[M+H]^+$; Anal. calcd for $C_{29}H_{35}N_5O_5SSi$: C 58.66, H 5.94, N 11.79, found: C 58.43, H 5.83, N 11.68.

**(1′*S*, 3′*S*, 4′*R*, 5′*S*)-1-(6-Amino-1*H*-purin-9(6*H*)-yl)-4-((*tert*-butyldiphenylsilyloxy)-methyl)bicyclo[3.1.0]hexan-3-yl methanesulfonate (15c)**—Atmospheric water was azeotropically removed from **14c** (255 mg, 0.51 mmol) by evaporation with pyridine (2 × 10 mL), and then **14c** was dissolved in pyridine (15 mL) under argon. Methanesulfonyl chloride (77 μL, 1.00 mmol) was added dropwise and the resulting yellow solution stirred at room temperature. After 1.25 h, additional methanesulfonyl chloride (35 μL, 0.45 mmol) was added and the reaction stirred for an additional 30 min. The reaction mixture was then concentrated in vacuo and purified by silica gel flash chromatography (5% and 10% MeOH/$CHCl_3$) followed by a second purification (5% MeOH/$CHCl_3$) to give **15c (**291 mg, 98%) as a colorless foam; $^1$H NMR (400 MHz, $d_6$-DMSO): δ = 8.05 (s, 1 H, H-2), 7.95 (s, 1 H, H-8), 7.69 (m, 4 H, Ph), 7.46 (m, 6 H, Ph), 7.20 (br s, 2 H, $NH_2$), 5.21 (d, *J* = 6.7 Hz, 1 H, H-3′), 4.12 (irr t, 1 H, $CH_{2a}$), 4.01 (dd, *J* = 6.5, 10.5 Hz, 1 H, $CH_{2b}$), 3.19 (s, 3 H, $CH_3$), 2.76 (dd, *J* = 6.1, 14.1 Hz, 1 H, H-2′$_a$), 2.58 (dd, *J* = 6.6, 9.0 Hz, 1 H, H-4′), 2.50 (d, overlapped with DMSO, *J* = 14.1 Hz, 1 H, H-2′$_b$), 1.88 (dd, *J* = 4.8, 9.2 Hz, 2 H, H-5′), 1.54 (m, 1 H, H-6′$_a$), 1.27 (m, 1 H, H-6′$_b$), 1.03 (s, 9 H, $C(CH_3)_3$); $^{13}$C NMR (100 MHz, $d_6$-DMSO): δ = 155.96, 152.28, 150.16, 140.85, 135.12, 135.09, 132.88, 132.79, 129.90, 127.93, 127.88, 119.12, 82.69, 63.84, 50.76, 41.83, 38.21, 37.89, 26.64, 24.84, 18.81; FAB MS: *m/z* (%) 578 (100) $[M+H]^+$. The unstable mesylate was used in the following elimination step without further purification.

**(1′*S*, 3′*S*, 4′*R*, 5′*S*)-1-(4-Amino-2-oxopyrimidin-1(2*H*)-yl)-4-((*tert*butyldiphenylsilyloxy) methyl)bicyclo[3.1.0]hexan-3-yl methanesulfonate (15d)—**Atmospheric water was azeotropically removed from **14d** (447 mg, 0.94 mmol) by evaporation with pyridine (2 × 20 mL), and then **14d** was dissolved in pyridine (25 mL) under argon. Methanesulfonyl chloride (300 μL, 3.87 mmol) was added dropwise and the resulting solution stirred at room temperature for 1 h. The reaction mixture was then concentrated in vacuo and purified by silica gel flash chromatography (5% MeOH/$CHCl_3$) to give **15d** (428 mg, 82%) as a colorless glass. Treatment with 5% MeOH/$Et_2O$ gave colorless crystals; mp 120 °C; $^1$H NMR (400 MHz, $CD_3OD$): δ = 7.73 (m, 4 H, Ph), 7.45 (m, 7 H, Ph and H-6), 5.75 (d, *J* = 7.3 Hz, 1 H, H-5), 5.19 (d, *J* = 6.8 Hz, 1 H, H-3′), 4.06 (irr t, 1 H, $CH_{2a}$), 3.97 (dd, *J* = 5.6, 10.7 Hz, 1 H, $CH_{2b}$), 3.02 (s, 3 H, $CH_3$), 2.52 (m, 2 H, H-2′$_a$, H-4′), 2.38 (d, *J* = 14.8 Hz, 1 H, H-2′$_b$), 1.64 (dd, *J* = 4.7, 9.7 Hz, 1 H, H-5′), 1.30 (irr t, 1 H, H-6′$_a$), 1.19 (m, 1 H, H-6′b), 1.11 (s, 9 H, $C(CH_3)_3$); $^{13}$C NMR (100 MHz, $CD_3OD$): δ = 167.74, 159.19, 147.53, 136.97, 134.69, 134.65, 131.19, 129.12, 129.08, 96.05, 85.24, 65.58, 53.49, 50.25, 38.89, 38.75, 27.81, 27.69, 20.25, 18.77; FAB MS: *m/z* (%) 554 (100) $[M+H]^+$; Anal. calcd for $C_{28}H_{35}N_3O_2SSi$: C 60.73, H 6.37, N 7.59, found: C 60.73, H 6.42, N 7.51.

**1-((1′*S*, 4′*R*, 5′*S*)-4-((*tert*-Butyldiphenylsilyloy)methyl)bicyclo[3.1.0]hex-2-en-1-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)dione (16a)—**Under argon, DBU (0.50 mL, 3.21 mmol) was added to a solution of **15a** (234 mg, 0.41 mmol) in toluene (10 mL) and heated to reflux overnight. After cooling to room temperature, the reaction mixture was diluted with EtOAc and washed with water (2 × 10 mL). The combined aqueous washings were extracted with EtOAc (2 × 10 mL) and the combined organic extracts were further washed with brine (2 × 10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by silica gel flash chromatography (5%, 20%, 50% and 75% EtOAc/hexanes) gave **16a** along with unreacted **15a**, which was recycled through the same procedure and combined with the first batch to give **16a** (93 mg, 53% yield) as a white solid; mp 175–177 °C; $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.04 (br s, 1 H, NH), 7.67 (m, 4 H, Ph), 7.39 (m, 6 H, Ph), 6.99 (q, *J* = 1.1 Hz, 1 H, H-6), 5.99 (ddd, *J* = 0.6, 1.9, 5.6 Hz, 1 H, H-3′), 5.46 (dt, *J* = 2.1, 5.6 Hz, 1 H, H-2′), 3.86 (dd, *J* = 5.3, 10.0 Hz, 1 H, $CH_{2a}$), 3.72 (dd, *J* = 7.2, 10.0 Hz, 1 H, $CH_{2b}$), 2.72 (m, 1 H, H-4′), 1.70 (d, *J* = 1.2 Hz, 3 H, $CH_3$), 1.49 (dd, *J* = 5.2, 9.3 Hz, 1 H, H-5′), 1.08 (m, 10 H, H-6′$_a$ and $C(CH_3)_3$), 0.86 (t, *J* = 5.2 Hz, 1 H, H-6′$_b$); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.70, 150.79, 140.99, 135.57, 135.53, 133.95, 133.67, 133.54, 130.51, 129.79, 129.75, 127.75, 127.71, 110.36, 66.53, 52.25, 51.13, 26.99, 26.66, 24.88, 19.43, 12.02; FAB MS: *m/z* (%) 473 (86) $[M+H]^+$, 135 (100); Anal. calcd for $C_{28}H_{32}N_2O_3Si•0.1H_2O$: C 70.88, H 6.84, N 5.90, found: C 70.63, H 6.85, N 5.83.

**4-Amino-1-((1′*S*, 4′*R*, 5′*S*)-4-(hydroxymethyl)bicyclo[3.1.0]hex-2-en-1-yl)pyrimidin-2(1*H*)-one (6d)—**Atmospheric water was azeotropically removed from **15d** (82 mg, 0.144 mmol) by evaporation with DMF (2 × 5 mL), and then **15d** was dissolved in DMF (7 mL) under argon, treated with treated with DBU (0.44 mL, 2.88 mmol) and heated to 100 °C. After stirring at 100 °C for 4 days, the reaction mixture was concentrated in vacuo and the residue triturated with $Et_2O$ (3 × 25 mL). Purification by silica gel flash chromatography (10% and 15% MeOH/$CHCl_3$) gave **6d** (14 mg, 45% yield) as a white solid

after a second purification (same conditions) and treatment with $Et_2O$; mp 222–224 °C; $[\alpha]_D^{20}$ = +1.37° (c 0.47, $CH_3OH$); $^1H$ NMR (400 MHz, $CD_3OD$): δ = 7.67 (dd, *J* = 0.5, 7.3 Hz, 1 H, H-6), 6.05 (dd, *J* = 1.9, 5.6 Hz, 1 H, H-3′), 5.86 (dd, *J* = 0.5, 7.3 Hz, 1 H, H-5), 5.51 (dt, *J* = 2.0, 5.6 Hz, 1 H, H-3′), 3.77 (dd, *J* = 4.2, 10.9 Hz, 1 H, $CH_{2a}$), 3.70 (dd, *J* = 5.3, 10.9 Hz, 1 H, $CH_{2b}$), 2.72 (m, 1 H, H-4′), 2.05 (m, 1 H, H-5′), 1.48 (dd, *J* = 5.0, 9.2 Hz, 1 H, H-6′$_a$), 0.80 (t, *J* = 5.0 Hz, 1 H, H-6′$_b$); $^{13}C$ NMR (100 MHz, $CD_3OD$): δ = 167.86, 159.89, 147.85, 136.01, 130.93, 96.24, 65.65, 55.13, 52.40, 28.04, 25.27; FAB MS: *m/z* (%) 220 (100) $[M+H]^+$; Anal. calcd for $C_{11}H_{13}N_3O_2 \cdot 0.2H_2O$: C 59.29; H 6.06, N 18.86, found: C 59.24, H 6.12, N 18.81.

**2-Amino-9-((1′*S*, 4′*R*, 5′*S*)-4-(hydroxymethyl)bicyclo[3.1.0]hex-2-en-1-yl)-1H-purin-6(9H)-one (6b)—**Under argon, DBU (1.1 mL, 7.2 mmol) was added to **15b** (221 mg, 0.36 mmol) in DMF (15 mL) and heated to 100 °C for 3 days. After cooling to room temperature, the reaction mixture was concentrated in vacuo. Purification by silica gel flash chromatography (5%, 10% and 15% MeOH/$CHCl_3$) gave **6b** (41 mg, 44% yield) as a tan solid along with the 5′-protected analogue (19 mg, 10% yield) as a white solid. Recrystallization from MeOH/$Et_2O$ afforded pure **6b** as tan crystals; mp 142–143 °C; $[\alpha]_D^{19}$ = +21.74° (c 0.1, $CH_3OH$); $^1H$ NMR (400 MHz, $d_6$-DMSO): δ = 10.55 (br d, *J* = 1.2, 1 H, NH), 7.63 (d, *J* = 0.6 Hz, 1 H, H-8), 6.38 (s, 2 H, $NH_2$), 6.06 (dd, *J* = 1.9, 5.6 Hz, 1 H, H-3′), 5.50 (dt, *J* = 2.0, 5.5 Hz, 1 H, H-2′), 4.77 (t, *J* = 5.7 Hz, 1 H, OH), 3.65 (dt, *J* = 5.3, 10.6 Hz, 1 H, $CH_{2a}$), 3.52 (m, 1 H, $CH_{2b}$), 2.60 (m, 1 H, H-4′), 2.13 (br dd, *J* = 5.1, 8.2 Hz, 1 H, H-5′), 1.62 (dd, *J* = 4.7, 9.1 Hz, 1 H, H-6′$_a$), 0.69 (t, *J* = 4.9 Hz, 1 H, H-6′$_b$); $^{13}C$ NMR (100 MHz, $d_6$-DMSO): δ = 156.68, 153.41, 152.31, 137.87, 134.18, 130.25, 116.88, 63.99, 51.11, 46.28, 40.14, 39.93, 39.72, 39.51, 39.30, 39.19, 39.09, 38.88, 25.07, 23.10; FAB MS: *m/z* (%) 260 (100) $[M+H]^+$; HRMS-FAB: *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}N_5O_2$: 260.1147, found: 260.1155.

**((1′*S*, 2′*R*, 5′*S*)-5-(6-Amino-9H-purin-9-yl)bicyclo[3.1.0]hex-3-en-2-yl)methanol (6c)—**Under argon, DBU (1.1 mL, 7.2 mmol) and **15c** (210 mg, 0.36 mmol) were combined in DMF (20 mL) and heated to 100 °C for 4 days. After cooling to room temperature, the reaction mixture was concentrated in vacuo. Purification of the residue by silica gel flash chromatography (5% and 10% MeOH/$CHCl_3$) followed by a second purification by silica gel flash chromatography (5% MeOH/$CHCl_3$) gave **6c** (97 mg, 87% yield) as an ivory solid along with the 5′-protected analogue (28 mg, 13% yield). An analytically pure sample of **6c** was obtained by triturating with dichloromethane; mp 170–171 °C; $[\alpha]_D^{19}$ = +1.32° (c 0.33, $CH_3OH$); $^1H$ NMR (400 MHz, $d_6$-DMSO): δ = 8.13 (s, 1 H, H-2), 8.11 (s, 1 H, H-8), 7.21 (br s, 2 H, $NH_2$), 6.09 (br dd, *J* = 1.8, 5.6 Hz, 1 H, H-3′), 5.54 (dt, *J* = 2.0, 5.5 Hz, 1 H, H-4′), 4.90 (dd, *J* = 4.8, 6.5 Hz, 1 H, OH), 3.70 (overlapping dt, *J* = 4.9, 10.1 Hz, 1 H, $CH_{2a}$), 3.59 (dt, *J* = 6.8, 10.6 Hz, 1 H, $CH_{2b}$), 2.66 (m, 1 H, H-2′), 2.15 (m, 1 H, H-1′), 1.76 (dd, *J* = 4.8, 9.1 Hz, 1 H, H-6′$_a$), 0.77 (t, *J* = 4.9 Hz, 1 H, H-6′$_b$); $^{13}C$ NMR (100 MHz, $d_6$-DMSO): δ = 155.98, 152.50, 150.51, 141.33, 134.16, 130.37, 118.95, 64.02, 51.03, 46.52, 25.21, 22.65. FAB MS: *m/z* (%) 244 (100) $[M+H]^+$; HRMS-FAB: *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}N_5O$: 244.1198, found: 244.1201.

**1-((1′*S*, 4′*R*, 5′*S*)-4-(Hydroxymethyl)bicyclo[3.1.0]hex-2-en-1-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (6a)—**TBAF (0.4 mL, 1 M in THF) was added to a solution of **16a (66O170**) (87 mg, 0.18 mmol) in THF (5 mL). After stirring at room temperature for 1h, the reaction mixture was concentrated in vacuo. Purification by silica gel flash chromatography (5%, 20%, 50% and 75% EtOAc/hexanes) gave **6a** (46 mg) as a colorless foam. Recrystallization from EtOAc followed by hexanes gave **6a** (34 mg, 79% yield) as a white crystalline solid; mp 142–143 °C; $[\alpha]_D^{19}$ = −190.82° (c 0.09, $CH_3OH$); $^1H$ NMR (400 MHz, $CDCl_3$): δ = 8.30 (br s, 1 H, NH), 7.21 (q, *J* = 1.2 Hz, 1 H, H-6), 5.99 (ddd, *J* = 0.6, 2.0, 5.6 Hz, 1 H, H-3′), 5.53 (dt, *J* = 2.1, 5.6 Hz, 1 H, H-2′), 3.83 (d, *J* = 3.3, 2 H, $CH_2$), 2.76 (m, 1 H, H-4′), 2.08 (m, 1 H, H-5′), 1.91 (d, *J* = 1.2 Hz, 3 H, $CH_3$), 1.43 (dd, *J* = 4.8, 9.3 Hz, 1 H, H-6′$_a$), 0.78 (t, *J* = 5.0 Hz, 1 H, H-6′$_b$); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 163.50, 151.69, 140.83, 133.88, 130.52, 111.31, 77.32, 77.00, 76.68, 64.56, 52.73, 50.77, 27.59, 23.92, 12.32. FAB MS: *m/z* (%) 235 (100) $[M+H]^+$; Anal. calcd for $C_{12}H_{14}N_2O_3$•0.1$H_2O$: C 61.06, H 6.06, N 11.87, found: C 60.80, H 5.99, N 11.53.

## Cell-based Assays

The human embryonic kidney cell culture line 293T was obtained from the American Type Culture Collection (ATCC). The human osteosarcoma cell line, HOS, was obtained from Dr. Richard Schwartz (Michigan State University, East Lansing, MI). The HOS-313 cells expressing herpes simplex virus-1 thymidine kinase were previously prepared by infecting HOS cells with a previously described MLV-vector.[19,21] Cell lines were maintained in Dulbecco's modified Eagle's medium (Invitrogen, Carlsbad, CA) supplemented with 5% (v/v) fetal bovine serum, 5% newborn calf serum, and penicillin (50 units/mL) plus streptomycin (50 μg/mL) (Quality Biological, Gaithersburg, MD). VSV-g –pseudotyped HIV was produced by transfection of 293T cells. On the day prior to transfection, 293T cells were plated in 100 mm dishes at a density of $9\times10^5$ cells per plate and transfected with 10 μg of pNLNgoMIVR$^+$ ΔEnv.LUC (wild-type or NRTI resistant mutant) and 3 μg of pHCMV-g (obtained from Dr. Jane Burns, University of California, San Diego) using calcium phosphate precipitation.[16, 18] After 48 hours, virus-containing supernatants were harvested, clarified by low-speed centrifugation and filtration and diluted 1-to-5 in preparation for infection assays. HOS cells were plated in 96 well luminescence cell culture plates at a density of 4000 cells in 100 μL per well the day prior to infection. On the day of infection, cells were pretreated with the target compounds for 3 h. Infections were carried out by adding 100 μL of virus-containing supernatants to each well and incubating for 48 h. Infectivity was determined using a luciferase reporter assay.[22] Luciferase activity was measured by adding 100 μL of steadylite plus reagent (PerkinElmer, Waltham, MA) directly to the cells and measuring luminescence using a microplate reader. Activity was normalized to infections done in the absence of target compounds for the appropriate NRTI variant. Regression analysis on the data was performed using a 4-parameter sigmoidal binding model, $f(x) = a + b/(1+(x/c)^d)$ and $EC_{50}$ values were determined from the fit. Cytotoxic effects were determined by measuring the effects of the compounds on the ATP levels in the cells. After treating HOS (or HOS-313) cells with the target compounds ATP levels were determined by measuring the relative luciferase activity using the PerkinElmer ATPlite kit. Luminescence data was normalized to cell data in the absence of target compound. The data was fit as above and $CC_{50}$ values were determined from the fit.

### X-ray Crystal Structure of compound 6b

Single-crystal X-ray diffraction data on compound **6b** were collected at 173 °K using CuKα radiation and a Bruker Proteum Diffractometer equipped with Helios optics and a Platinum 135 CCD area detector. A 0.237 × 0.167 × 0.019 $mm^3$ crystal was prepared for data collection coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was mounted on MicroMesh mount (MiTeGen, Ithaca, NY) and transferred to the cold stream (173 °K) on the diffractometer. The crystal was orthorhombic in space group $P2_12_12_1$ with unit cell dimensions $a$ = 10.7840(3) Å, $b$ = 10.8458(3) Å, and $c$ = 21.3305(6) Å. Corrections were applied for Lorentz, polarization, and absorption effects. Data were 92.9% complete to 25.00° θ (approximately 0.83 Å) with an average redundancy of 5.2. The structure was solved by direct methods and refined by full-matrix least squares on $F^2$ values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS Inc., Madison, WI). Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with C-H distance set at 0.96 Å. The relative configuration was C1 = *S*, C4 = *R*, C5 = *S*. The asymmetric unit contains two molecules with the same relative configuration. Atomic coordinates for compound **6b** have been deposited with the Cambridge Crystallographic Data Centre (deposition number 727856). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk

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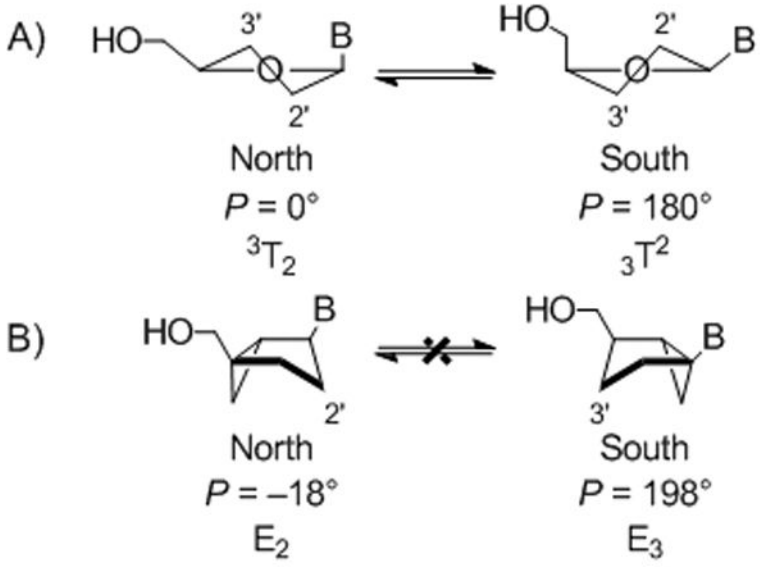



**Figure 1.**

(**A**) Rapidly interconverting North and South conformations in conventional nucleosides defined by changes in the pseudorotational angle (*P*). (**B**) Bicyclo[3.1.0]hexane nucleosides locked in North and South conformations located 18° away from the ideal *P* values of 0° and 180°.

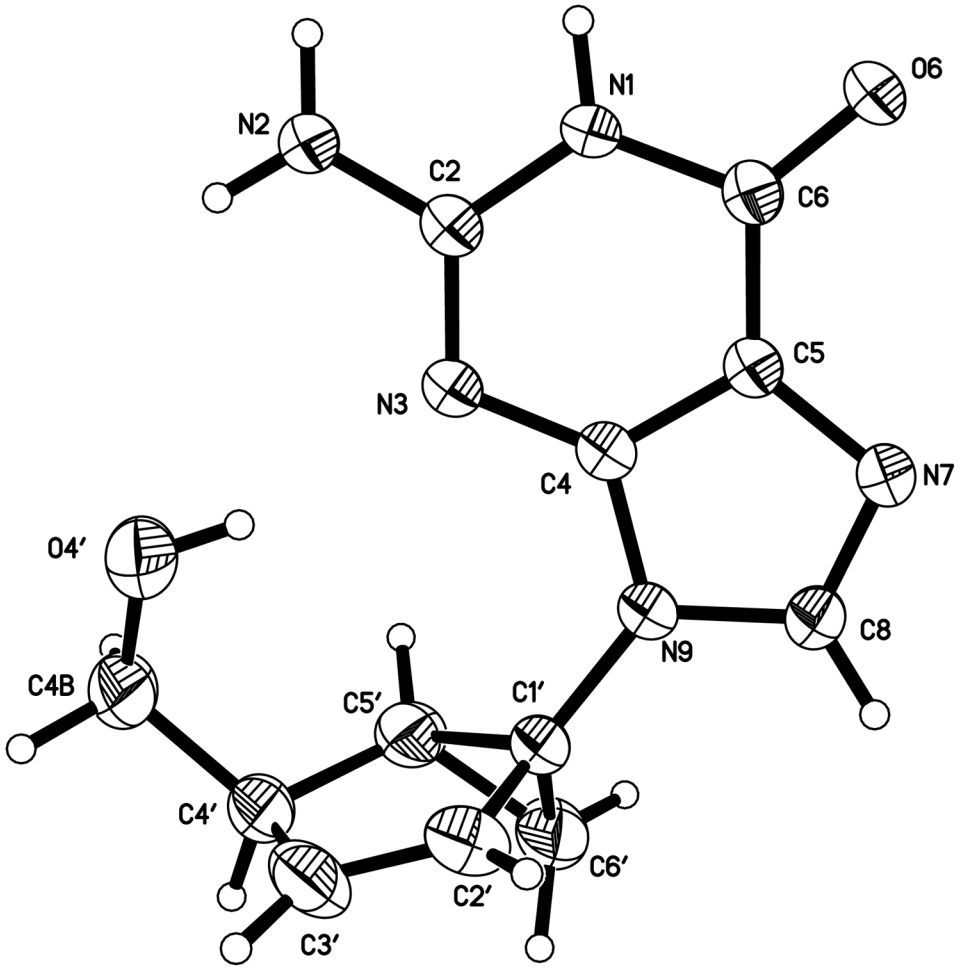
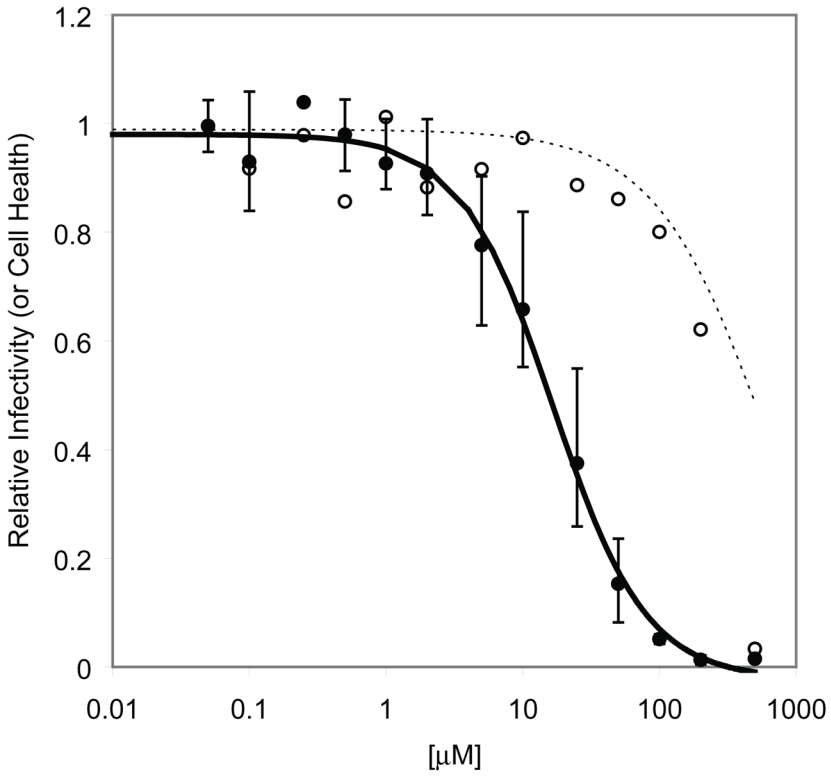



**Figure 2.**
Displacement ellipsoid plot of **6b** drawn at the 50% probability level.



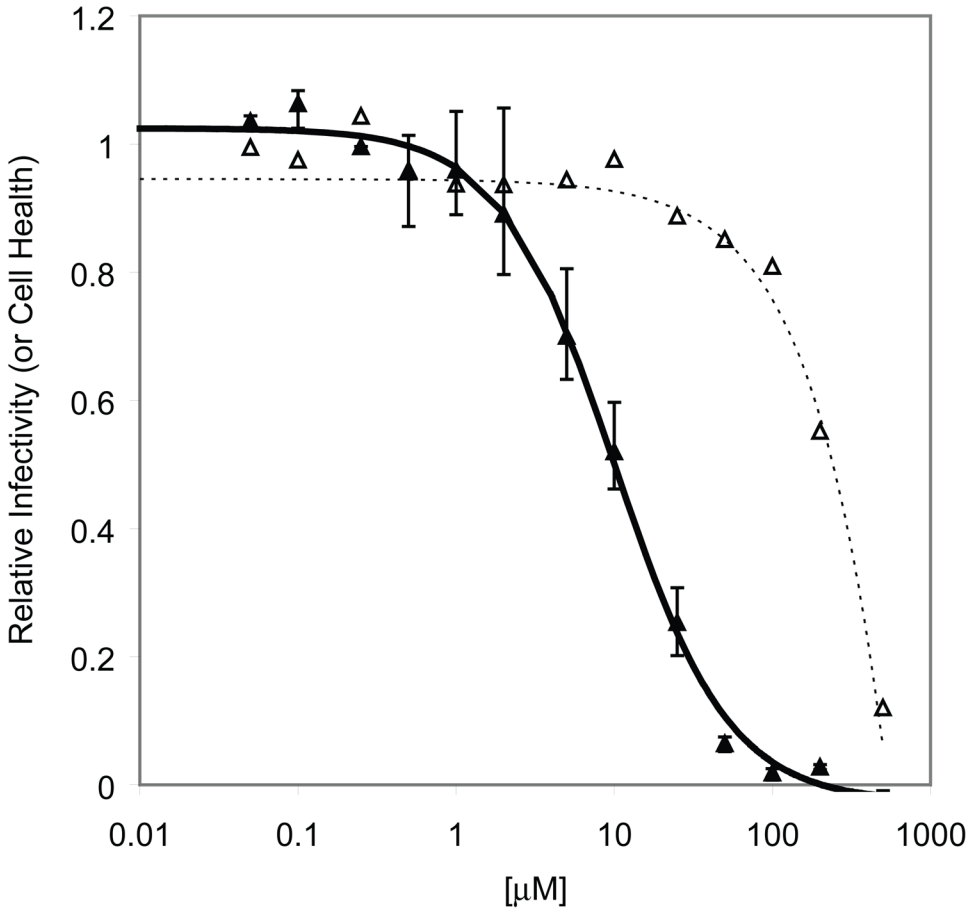



**Figure 3.**

Cell-based assay of North-D4A (**4c**) on the replication of an HIV-1 vector containing wt HIV-1 RT in HOS cells [(**A)** ● = infectivity; ○ = cytotoxicity) and HOS-313 cells [(**B**), ▲ = infectivity; △ = cytotoxicity). Luciferase activity in the absence of compound was considered to be 100 and the luciferase activity in the presence of different concentrations of **4c** was normalized to this value to give relative infectivity or cytotoxicity in the absence of the vector.

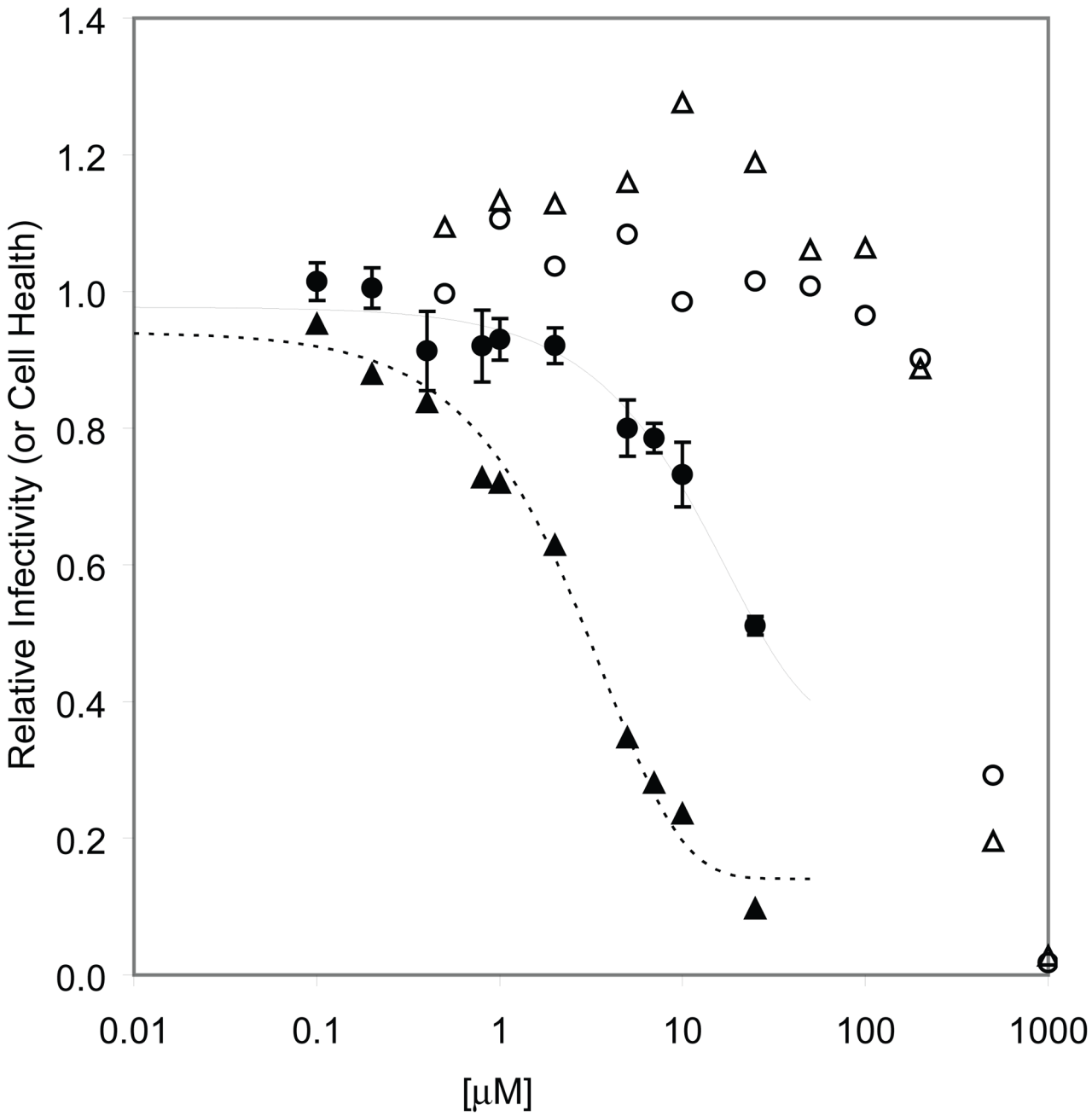
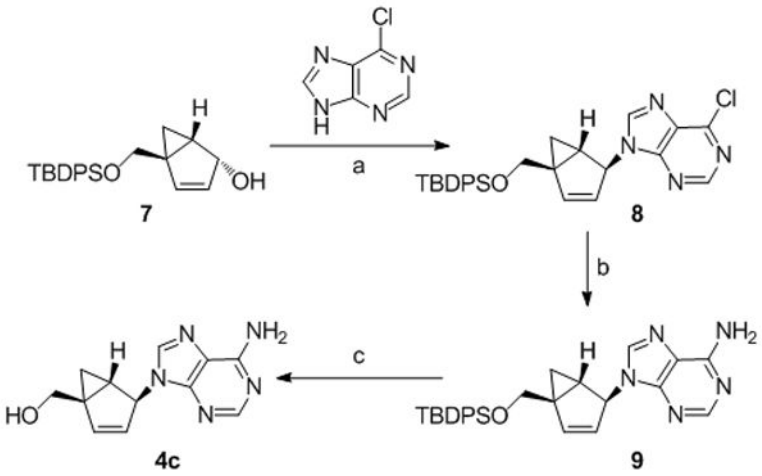


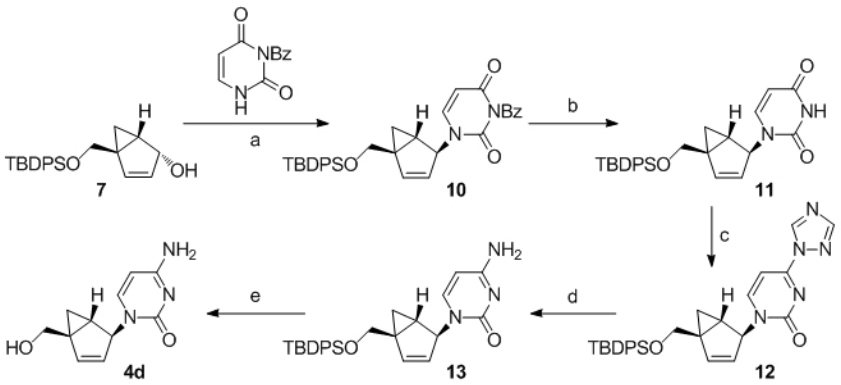

**Figure 4.**

Cell-based assay of South-D4C (**6d**) on the replication of an HIV-1 vector containing wt HIV-1 RT in HOS-313 cells and HOS cells. Luciferase activity in the absence of compound was considered to be 100 and the luciferase activity in the presence of different concentrations of **6d** was normalized to this value to give relative infectivity or cytotoxicity in the absence of the vector (● = HOS infectivity; ▲ = HOS-313 infectivity; ○ = HOS cytotoxicity; △ = HOS-313 cytotoxicity).



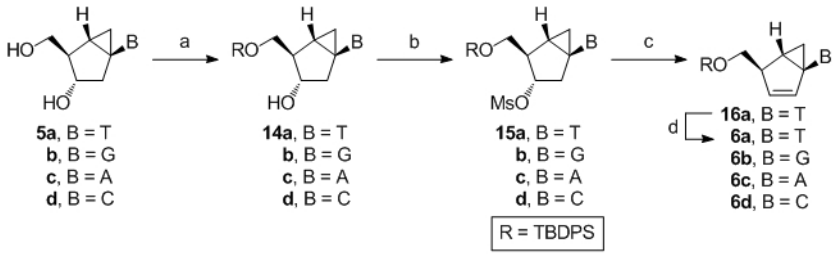

**Scheme 1.**

*Reagents and conditions:* (*a*) diisopropyl azodicarboxylate (DIAD), $PPh_3$, THF, 0 °C → rt; (*b*) $NH_4OH$, dioxane, 70 °C; (*c*) $Et_3N{\bullet}3HF$, MeCN, Δ.




**Scheme 2.**

*Reagents and conditions:* (*a*) diisopropyl azodicarboxylate (DIAD), $PPh_3$, THF, 0 °C - rt; (*b*) $NH_4OH$, MeOH, rt; (*c*) $POCl_3$, 1,2,4-triazole, $Et_3N$, MeCN; (*d*) $NH_4OH$, dioxane, rt; (*e*) $Et_3N$•HF, MeCN.




**Scheme 3.**

*Reagents and conditions:* (*a*) *tert*-butyldiphenylsilyl chloride (TBDPSCl), imidazole, DMF or TBDPSCl, DMAP, pyridine; (*b*) MsCl, pyridine; (*c*) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), PhMe or DMF, Δ; (*d*) TBAF, THF.

## Table 1

Structures of North-derived (**4a–d**) and South-derived (**6a–d**) bicyclo[3.1.0]hexene nucleosides.

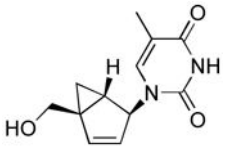
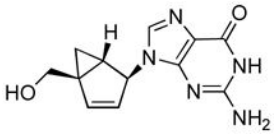
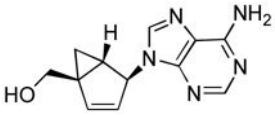
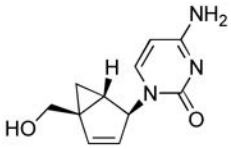
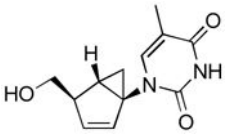
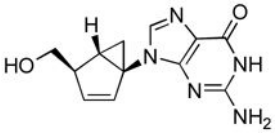
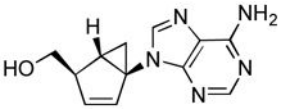
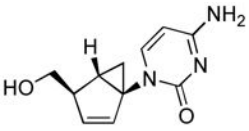
| Compound # | Structure | Base | Anti-HIV activity |
|---|---|---|---|
| **4a**[11] |  | **T** | active |
| **4b**[12] |  | **G** | inactive |
| **4c** |  | **A** | active |
| **4d** |  | **C** | inactive |
| **6a** |  | **T** | inactive |
| **6b** |  | **G** | inactive |
| **6c** |  | **A** | inactive |
| **6d** |  | **C** | +/− active |

**Table 2**

Pseudorotational parameters (in degrees) for North-derived **4a** and South-derived **6b**[a].

| | $\nu_0$ | $\nu_1$ | $\nu_2$ | $\nu_3$ | $\nu_4$ | *P* | $\nu_{max}$ | χ | γ | type |
|---|---|---|---|---|---|---|---|---|---|---|
| **4a** | 6.56 | −5.38 | 2.67 | 1.68 | −5.20 | 293.14 | 6.81 | −119.12 | 56.17 | $^{1}T_{O}$ (N) |
| **6b** | 4.05 | −0.14 | −4.05 | 6.38 | −6.05 | 233.11 | 6.75 | 48.43 | 52.58 | $^{4}E$ (S) |

[a] ν0–ν4 represent the torsion angles of the embedded cyclopentene ring.