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Synthesis and biological evaluation of 5*R*- and 5*S*-methyl substituted D- and L-configuration 1,3-dioxolane nucleoside analogs

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Abstract—1,3-Dioxolane and 1,3-oxathiolane nucleoside analogs play an important role in anti-viral and anti-neoplastic chemotherapy. We report here the synthesis of 2-hydroxymethyl-5-methyl-1,3-dioxolanylpurine nucleosides from 4-acetoxy-2-(benzyloxymethyl)-5-methyldioxolane. Dioxolanes of α-D-, β-D-, α-L-, and β-L-configuration were prepared, that included 5-methyl derivatives of both 5*R* and 5*S* configuration. Molecular mechanics calculations indicate that the 5*S* and 5*R* diastereoisomeric 1,3-dioxolanes possess distinct conformational bias, suggesting that methyl substitution may alter the conformational preference of 1,3-dioxolanes. The ability of the 1,3-dioxolanes to inhibit HCV RNA replication was evaluated in a cell-based, subgenomic replicon assay. In addition, activity against vaccinia and HIV was evaluated in cell-based assays. The 2-hydroxymethyl-5-methyl-1,3-dioxolanes were found to be inactive.

1. Introduction

Nucleoside analogs play a central role in anti-viral and anti-neoplastic chemotherapy. Examples of nucleoside analogs approved by the FDA for the treatment of viral conditions include Zidovudine (AZT, Retrovir®), Didanosine (ddI, Videx®), Zalcitabine (ddC, Hivid®), Lamivudine (3TC, Epivir®), and Stavudine (4dT, Zerit®), that are approved for the treatment of HIV infection. In addition, Fludarabine (Fludara®), Cladribine (2-CdA, Leustatin®), and Pentostatin (DCF, Nipent®) are examples of nucleoside analogs approved for the treatment of neoplastic conditions. Subsequent to the successful introduction of AZT for the treatment of HIV infection, significant effort has been put toward the discovery and development of more efficacious and selective nucleoside analogs. A particularly successful class of nucleoside analogs incorporates a heteroatom such as oxygen or sulfur in place of the 3′-methylene carbon. The best known example of this class of compounds is Lamivudine also known as 3TC or (−)-L-β-1,3-oxathiolanyl cytosine.[1–8] The 1,3-dioxolane and 1,3-oxathiolane nucleoside analogs display broad antiviral and anti-neoplastic activities (Fig. 1). Lamivudine, **1**, is efficacious against immunodeficiency virus (HIV) and hepatitis B virus (HBV) infections. The corresponding oxa derivative, (−)-L-β-1,3-dioxanyl cytosine, **2**, possesses anti-neoplastic activity,[9] in addition to its activity against HIV and HBV.[5] In the purine series, (−)-D-β-1,3-dioxanylguanine (DGX), **3**, and (−)-D-β-1,3-dioxanyl-2,6-diaminopurine (DAPG), **4**[10] (Fig. 1), are undergoing pre-clinical evaluation as anti-HIV[11] and anti-HBV agents.[11,12] In addition, (+)-L-β-1,3-oxathionyl adenine, **5**,[13] has demonstrated anti-HIV activity in PBMCs. Furthermore, dioxolane based nucleoside triphosphates have been reported to be inhibitors of RNA synthesis mediated by the hepatitis C virus RNA-dependent RNA polymerase (HCV RdRp).[14,15]

We recently described the methyl substituted nucleosides 2′-*C*-methyladenosine and 2′-*C*-methylguanosine as

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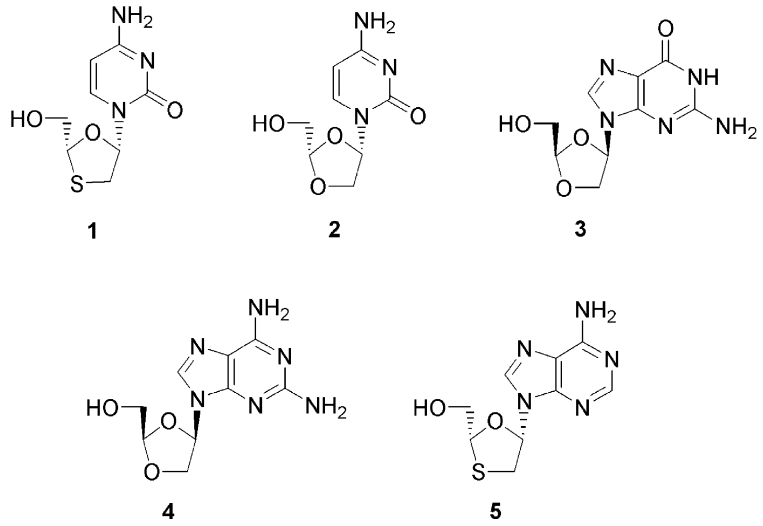


Figure 1. Examples of 1,3-dioxolane and 1,3-oxathiolane nucleosides that display anti-viral or anti-neoplastic activities: (**1**) Lamivudine, 3TC, (−)-β-L-(2*R*,5*S*)-oxathiolanyl-cytosine; (**2**) O-ddC, (−)-β-L-(2*S*,4*S*)-dioxolanyl-cytosine; (**3**) DXG, (−)-β-D-(2*R*,4*R*)-dioxolanyl-guanine; (**4**) DAPD, (−)-β-D-(2*R*,4*R*)-dioxolanyl-2,6-diaminopurine; (**5**) (+)-β-L-(2*R*,5*S*)-oxathiolanyl-adenine.

inhibitors of HCV RNA replication in cells.[16–18] The triphosphates of these nucleosides were found to be competitive inhibitors of the HCV polymerase, suggesting that the 2′-*C*-methyl modification is tolerated by the HCV viral polymerase, as well as by the kinases responsible for the metabolism of the 2′-*C*-methylribonucleosides to their triphosphates. Moreover, inclusion of the methyl substituent in the C2′ position was found to promote a conformational bias toward the C3′-*endo* (north) ribonucleoside conformer,[16] and was found to attenuate cytotoxicity for a nucleoside that incorporated a modified purine heterobase (Olsen et al. unpublished results; Eldrup et al., unpublished results).

Dioxolane based nucleoside analogs that incorporate methyl substitutions in positions that correspond to the ribonucleoside C4′ and C3′ positions have been reported.[19,20] However, dioxolanes with methyl substituents in what would correspond to the nucleoside C2′ position have not been described. Based on the findings outlined above, we recently reported preliminary work toward the synthesis of 2*S*-hydroxymethyl-1,3-dioxolanes (β-D-configuration) and (2*S*,5*R*)-2-hydroxymethyl-5-methyl-1,3-dioxolanes (β-D-configuration) that carried pyrrolo[2,3-*d*]pyrimidine heterobases.[21] We now report the synthesis and biological evaluation of 5-methyl substituted L- and D-configuration dioxolane nucleosides carrying purine heterobases. Compounds

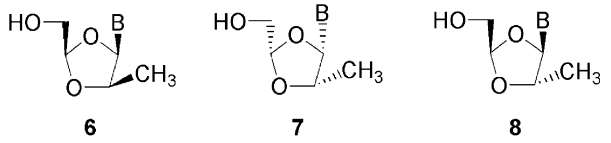


Figure 2. Target compounds: (2*R*,4*R*,5*R*)-5-methyl-1,3-dioxolanyl-purinenucleosides (β-D-configuration) **6**, (2*S*,4*S*,5*S*)-5-methyl-1,3-dioxolanyl-purinenucleosides (β-L-configuration) **7**, and (2*R*,4*R*,5*S*)-5-methyl-1,3-dioxolanyl-purinenucleosides (β-D-configuration) **8**. Nucleobase, B, is either adenine, diaminopurine or guanine.

Table 1.

	HCV replicon % inhibition at 100 μM	Vaccinia % inhibition at 100 μM	HIV spread IC_{95} (μM)
25a	No data	<30	No data
25b	<30	<30	>10
26a	46	54	>10
26b	<30	<30	>10
30a	<30	<30	>10
30b	<30	<30	>10
31a	<30	<30	>10
31b	<30	<30	>10
34	<30	<30	>10
35	<30	<30	>10

of general structure **6**, **7**, and **8** (Fig. 2) were selected as synthetic targets to ensure variations in configuration (D and L) and in the stereochemical positioning (5*R*/beta face or 5*S*/alpha face) of the methyl substituent. A change in conformational bias might affect biological activity and specificity and hence, molecular mechanics calculations were applied to assess the effect of 5-methyl substitution on conformational preference. Compounds were evaluated as inhibitors of HCV RNA replication in a replicon assay in HB-1 cells, as inhibitors of HIV spread in human T-lymphoid cells and as inhibitors of vaccinia virus replication (Table 1).

2. Results

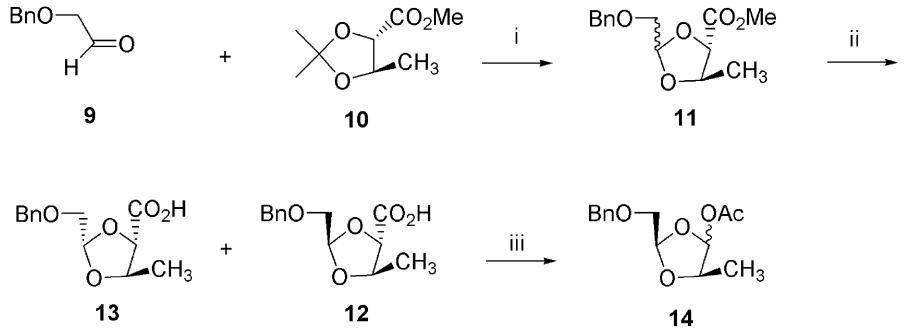
2.1. Chemistry

For the precursor for the D-configuration dioxolanes of general structure **6** (Fig. 2), 2-benzoyloxyacetaldehyde **9** was condensed[22] with commercially available (4*S*,5*R*)-methyl-2,2,5-trimethyl-1,3-dioxalane-4-carboxylate **10** in the presence of *para*-toluenesulfonic acid to give **11** as an inseparable 2*R*,2*S* diastereoisomeric mixture in 9:1 ratio (Scheme 1). Saponification of the methyl esters

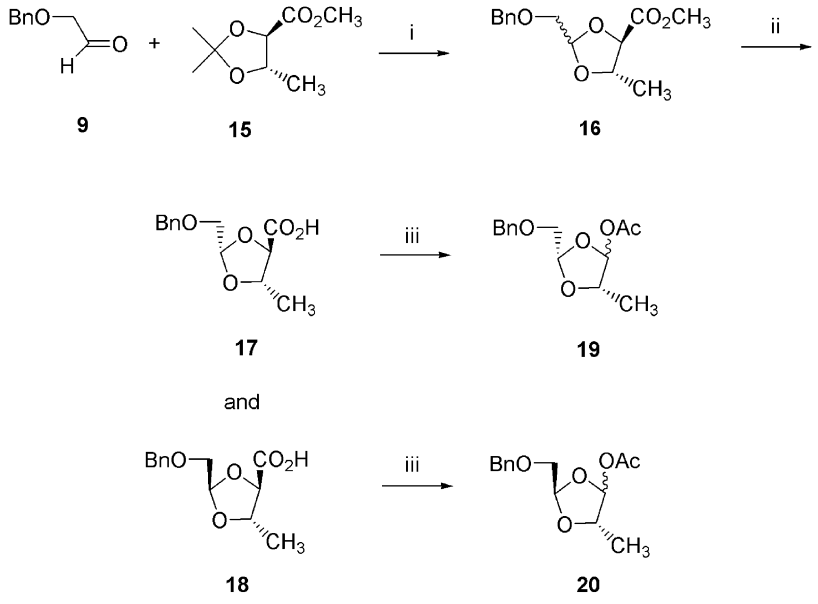
11 with lithium hydroxide in aqueous tetrahydrofuran, followed by acidification gave a mixture of the carboxylic acids **12** and **13**, which were separated by silica gel column chromatography. The stereochemistry of the carboxylic acid derivative **12** was confirmed by NOE (upon which irradiation of H-2 resulted in enhancement of the H-5 signal, confirming the β-configuration of the benzyloxymethyl substituent at C-2). Oxidative decarboxylation of the β-configuration (2,4-*trans*) carboxylic acid derivative **12** with lead tetraacetate in acetonitrile, in the presence of pyridine, gave acetyl intermediate **14** as a 4*R*,4*S*-diastereoisomeric mixture. Compound **14** served as the starting material for the synthesis of the D-configuration, 5*R*-methyl dioxolanes **25a**,**b** and **26a**,**b** (Scheme 3).

Using a similar methodology to the one described above, the precursors for the L-configuration dioxolane derivatives of general structure **7** and the D-configuration dioxolane derivatives of general structure **8** (Fig. 2) were available from the commercially available (4*R*,5*S*)-methyl-2,2,5-trimethyl-1,3-dioxolane-4-carboxylate **15**. Condensation of **15** with benzyloxyaldehyde **9** resulted in a 2*R*,2*S* diastereoisomeric mixture of the methylester derivatives **16** in 1:8 ratio (Scheme 2). Saponification of the methyl ester with aqueous lithium hydroxide was followed by acidification to afford the carboxylic acid derivatives **17** and **18**, which were separable by silica gel column chromatography. The assignment of the stereochemistry of the major isomer of **17** was performed by NOE. Conversion of **17** and **18**, respectively, to their corresponding diastereomeric mixtures of the acetoxy derivatives **19** and **20** was achieved by lead tetraacetate mediated oxidation in acetonitrile, in the presence of pyridine. Compounds **19** and **20** served as precursors for the L-configuration 5*S*-methyl dioxolanes (**30a**,**b** and **31a**,**b**, Scheme 4) and the D-configuration 5*S*-methyl dioxolanes (**34** and **35**, Scheme 5), respectively.

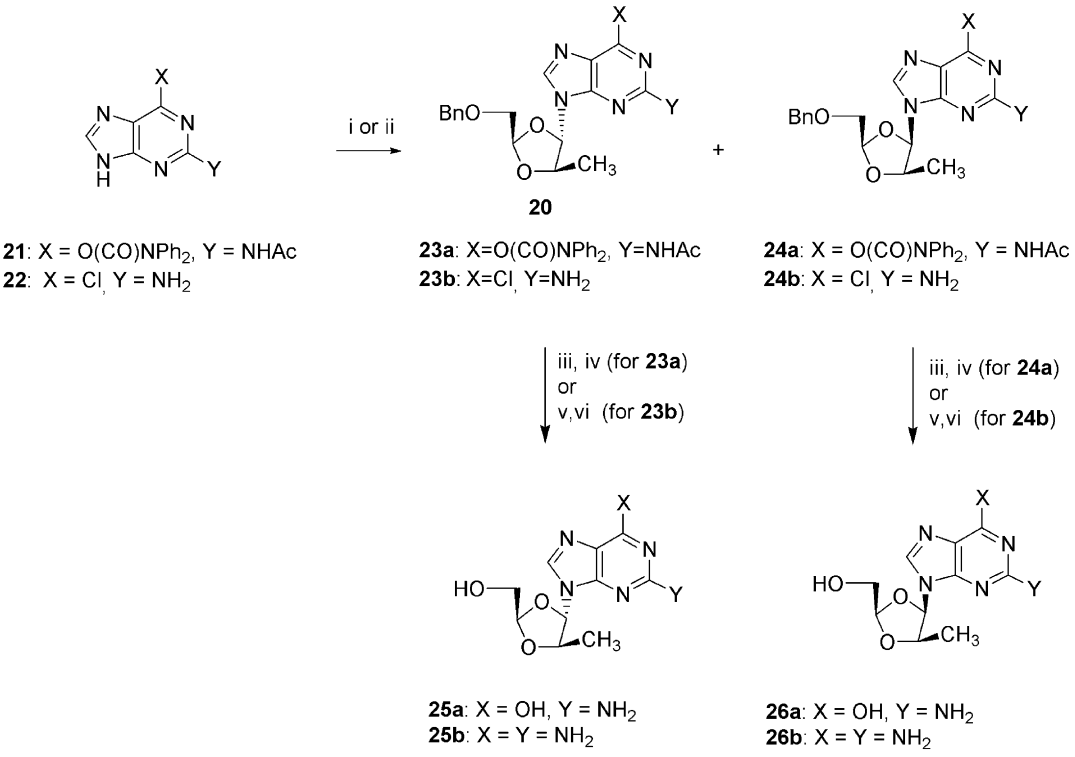
Guanine and 2,6-diaminopurine derivatives of D-configuration dioxolanes were synthesized that contained



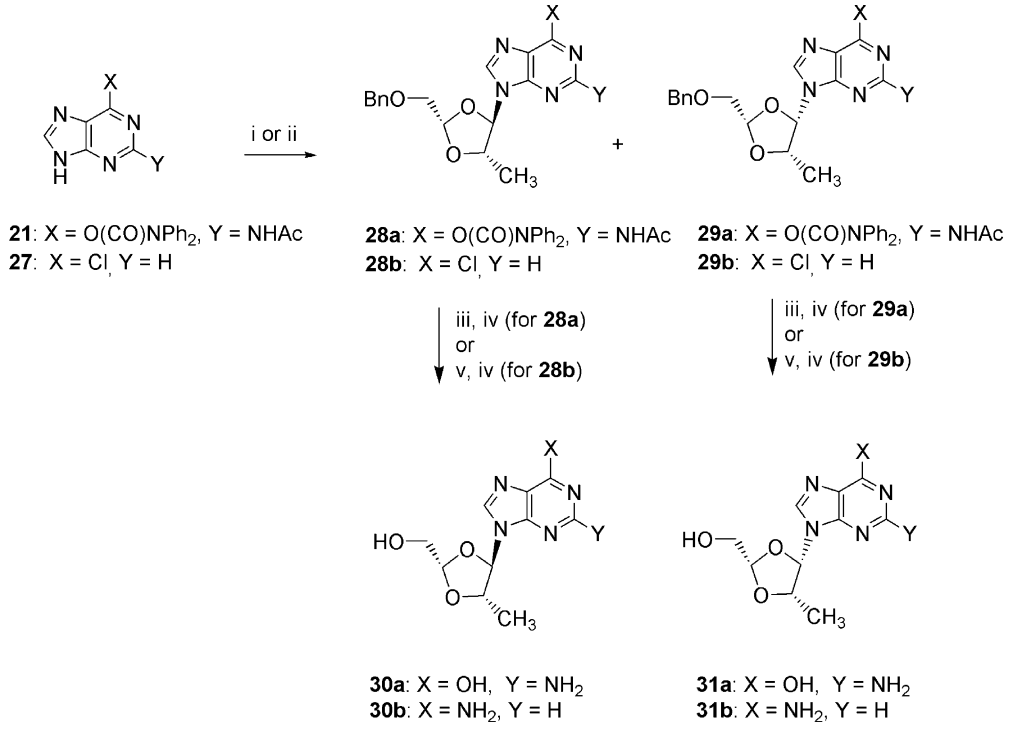
Scheme 1. Reagents and conditions: (i) *para*-toluenesulfonic acid, toluene, 80 °C, 1 h; (ii) a. 1 M aqueous lithium hydroxide/tetrahydrofuran (1:1), b. 1 N HCl or sulfuric acid (pH 2–3); (iii) lead tetraacetate, acetonitrile, pyridine.



Scheme 2. Reagents and conditions: (i) *para*-toluenesulfonic acid, toluene, 80 °C, 1 h; (ii) a. 1 M aqueous lithium hydroxide/tetrahydrofuran (1:1), b. 1 N HCl or H_2SO_4 (pH 2–3); (iii) lead tetraacetate, acetonitrile, pyridine.

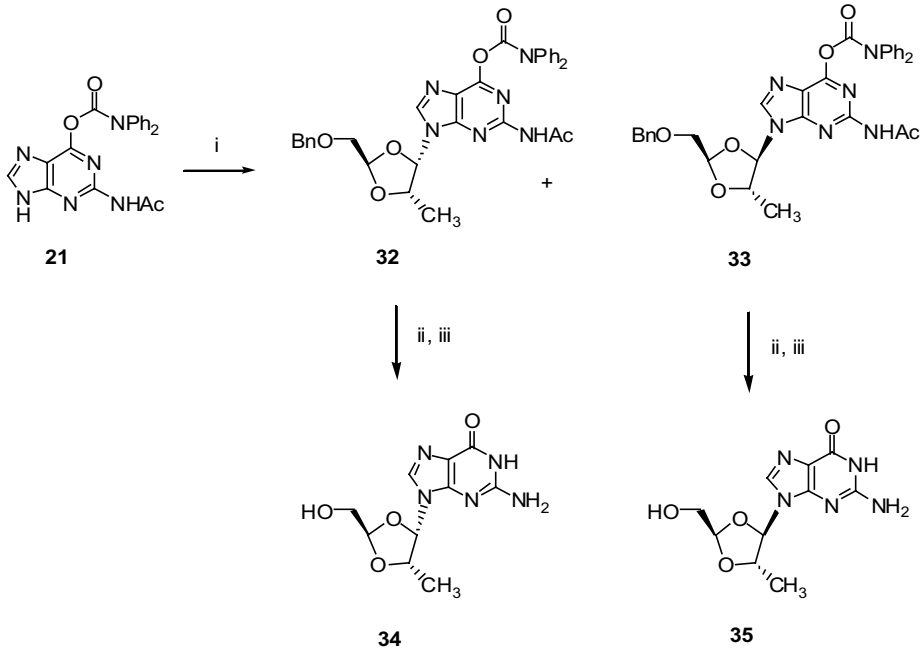


Scheme 3. Reagents and conditions: (i) a. bis-(trimethylsilyl)acetamide, 1,2-dichloroethane, b. trimethylsilyl triflate, **14**, reflux (for **21**); (ii) a. **14**, bromotrimethylsilane, dichloromethane, 0 °C to rt, b. tris-[2-(2-methoxyethoxy)ethyl]amine, KOH, **22**, acetonitrile (for **22**); (iii) hydrazine hydrate, tetrahydrofuran, reflux; (iv) palladium hydroxide/C, H_2, methanol; (v) methanolic ammonia, 55 °C; (vi) ammonium formate, Pd/C, methanol.



Scheme 4. Reagents and conditions: (i) a. bis-(trimethylsilyl)acetamide, 1,2-dichloroethane, b. **19**, trimethylsilyl triflate, reflux (for **21**); (ii) a. **19**, bromotrimethylsilane, dichloromethane, 0 °C to rt, b. **27**, tris-[2-(2-methoxyethoxy)ethyl]amine, KOH, acetonitrile; (iii) hydrazine hydrate, tetrahydrofuran, reflux; (iv) palladium hydroxide/C, ethanol, cyclohexene, (v) liquid ammonia, 80 °C.

methyl substituents of 5*R* configuration. For the guanine derivatives, silylated N^2-acetyl-O^6-diphenylcarbamoylguanine (**21**) was reacted with **14** in the presence of trimethylsilyl triflate[23] to furnish a separable 1:1 mixture of the *N*-9 'glycosylated', diastereoisomeric dioxolanes **23a** and **24a**. Separate deprotection of **23a**



Scheme 5. Reagents and conditions: (i) a. bis-(trimethylsilyl)acetamide, 1,2-dichloroethane, b. **20**, trimethylsilyl triflate, reflux; (ii) hydrazine hydrate, tetrahydrofuran, reflux; (iii) palladium hydroxide/C, ethanol, cyclohexene.

and **24a** with hydrazine hydrate, followed by transfer hydrogenolysis, produced the guanine derivatives **25a** (2*R*,4*S*,5*R*; α-D) and **26a** (2*R*,4*R*,5*R*, β-D), respectively (Scheme 3). For the synthesis of 2,6-diaminopurine derivatives, the acetate **14** was treated with bromotrimethylsilane[24] and the thus formed bromide was treated with 2-amino-6-chloropurine (**22**) under phase transfer conditions[25,26] (tris-[2-(2-methoxyethoxy)ethyl]amine and KOH in acetonitrile) to give an inseparable mixture of **23b** and **24b** (1.2:1). Treatment of this mixture with methanolic ammonia at elevated temperature produced the corresponding 2,6-diaminopurine derivatives. The benzyl protection group was subsequently removed by transfer hydrogenolysis using Pd/C and ammonium formate in refluxing methanol to give the diastereoisomeric **25b** (2*R*,4*S*,5*R*; α-D) and **26b** (2*R*,4*R*,5*R*; β-D), which were separated by preparative HPLC (see experimental).

Adenine and guanine L-configuration dioxolanes were synthesized that contained methyl substituents of 5*S* configuration. The synthesis of the guanine derivative commenced from the acetate derivative **19**, which upon treatment with a silylated diphenylcarbamoyl purine derivative (**21**) in the presence of trimethylsilyl triflate gave a 1:1 mixture of **28a** and **29a** (Scheme 4). Chromatographic separation and removal of the heterobase protection groups with hydrazine gave the α and β configuration guanine derivatives. Removal of the benzyl protection group was subsequently performed by transfer hydrogenolysis to give **30a** (2*S*,4*R*,5*S*; α-L) and **31a** (2*S*,4*S*,5*S*; β-L), respectively. For the adenine derivatives, treatment of **19** with bromotrimethylsilane gave the bromo derivative, which upon reaction with 6-chloropurine **27**, under phase transfer conditions, gave an inseparable mixture of the dioxolane derivatives **28b** and **29b** in 1:2 ratio. Treatment of this mixture with ammonia was followed by catalytic hydrogenation to afford the adenine derivatives **30b** (2*S*,4*R*,5*S*; α-L) and **31b** (2*S*,4*S*,5*S*; β-L), which were separated by preparative HPLC to afford the pure diastereoisomers (see experimental).

The D-configuration 5*S*-methyl guanine derivatives **34** and **35** were obtained by treatment of the acetate **20** with silylated purine derivative **21** under Vorbruggen condition.[23] Thus treatment of **20** with **21** under reflux with trimethylsilyl triflate in 1,2-dichloroethane produced an inseparable, 1:1 mixture of the α- and β-nucleoside derivatives **32** and **33**. This mixture was treated with hydrazine to give the corresponding guanine derivatives. Removal of the benzyl protection group was performed by transfer hydrogenolysis to yield a diastereoisomeric mixture of **34** and **35**. Chromatographic separation gave the desired **34** (2*R*,4*S*,5*S*; α-D) and **35** (2*R*,4*R*,5*S*; β-D).

The structure of the 1,3-dioxolane derivatives were determined by proton NMR and high resolution mass spectroscopy. The assignment of the 'anomeric' configuration was performed on the basis of the previously reported characteristics of the proton NMR spectra.[8,13,27] The chemical shifts of anomeric proton (H-4′) of the 2,4-*cis* derivatives (based on the orientation of 2′-hydroxymethylene and the 4′-heterobase) appeared downfield relative to the H-4′ of the *trans* isomers. Furthermore, the 2′-proton of *cis* derivatives appeared upfield from that observed for *trans* isomers, and the hydroxymethylene protons of *cis* derivatives appeared downfield from those observed for *trans* derivatives. These shifts were attributed to the fact that the protons at the *syn*-position relative to the purine base are more

cmpd	Northern anti	Northern syn	Southern anti	Southern syn
3	+0.00	+0.18	+0.31	+0.07
26a	+0.00	+0.56	+0.65	+0.95
35	+1.57	+1.77	+0.16	+0.00

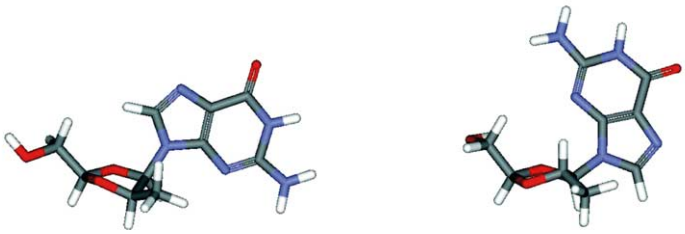


Figure 3. Relative energies in kcal/mol of canonical conformations of **3**, **26a**, and **35** calculated by molecular mechanics. Global minima of **26a** and **35** calculated by molecular mechanics. Methyl substitution of the 1,3-dioxolanes induce different conformational preferences in response to 5*R*- or 5*S*-methyl substitution.

deshielded than those in an *anti*-position relative to the base.

2.2. Molecular mechanics calculations

In order to assess the effect of the stereochemistry of the 5-methyl substitution on conformational preference, molecular mechanics calculations were performed to determine the relative energies of northern- and southern-type conformers of **26a** and **35**, which incorporate methyl substituents of 5*R* and 5*S* configuration, respectively (Fig. 3 and Methods). While the unsubstituted dioxolane **3** is calculated to have nearly equal preference for northern and southern conformation, introduction of the methyl substituent causes a modest preference for northern pucker in the case of **26a** and southern in the case of **35**.

2.3. Biological evaluation

Compounds were evaluated as inhibitors of HCV replication in a cell-based replicon assay,[17] against HIV spread in human T-lymphoid cells (see Methods) and against vaccinia in HeLa cells (see Methods).[28] None of the described compounds displayed significant activity in these assays.

3. Discussion

1,3-Dioxolanes and 1,3-oxathiolanes play a central role in anti-viral and anti-neoplastic therapies. In light of their importance, we decided to synthesize and evaluate their 5-methyl derivatives. A versatile strategy for the synthesis of L- as well as D-configuration 1,3-dioxolanes that incorporate methyl substituents of both 5*R* and 5*S* configuration was devised. It was anticipated that the inclusion of a 5-methyl substituent might impose a conformational preference distinct from that of the unsubstituted derivatives. If so, such a conformational preference could contribute to improved affinity and selectivity for the target polymerases. In order to assess the effect of 5-methyl substitution on conformational preference, molecular mechanics calculations were performed on the guanine derivatives **3**, **26a**, and **35**, respectively (Fig. 3 and experimental section). Our calculations predicted distinct conformational preferences for **26a** and **35**, suggesting that the stereochemical placement of the methyl substituent is decisive for conformational preference and that 5-substitution can be applied to alter conformational preference relative to the otherwise conformationally unbiased dioxolane, **3**.

The 1,3-dioxolanes were evaluated in vitro as inhibitors of HCV RNA replication, against HIV spread in human T-lymphoid cells and against vaccinia. Viral targets were chosen that encode polymerases that might be expected to display differences in substrate specificity: HCV encodes an RNA-dependent RNA polymerase, HIV encode an RNA- or DNA-dependent DNA polymerase (reverse transcriptase), whereas vaccinia encodes a DNA-dependent DNA polymerase as well as a DNA-dependent RNA polymerase. Despite the fact that both unsubstituted 1,3-dioxolanes and 1,3-oxathiolanes display biological activities, none of the methyl substituted derivatives displayed significant inhibitory activity in any of the assays tested. This inactivity may be due to inability on part of these polymerases to accept the methyl substituted derivatives as substrates. Alternatively, mechanisms of cellular uptake and/or nucleoside kinases may be unwilling to accept the methyl derivatives as substrates. Based on the fact that 1,3-dioxolanes were tested that displayed variance in conformational preference, it seems less likely that unsuitable conformational bias is the underlying explanation for the observed inactivity.

4. Methods

4.1. General methods

Diphenylcarbamic acid 2-acetylamino-*9H*-purin-6-yl ester **21** was prepared as described. TLC was performed on silica 60 (Merck 5554 aluminum sheet), column chromatograpy on silica 60 (230–400 mesh ASTM) (Merck 9385). ^{1}H and ^{13}C NMR spectra were obtained at 200 MHz (Varian Mecury VX) in 5 mm tubes unless otherwise indicated; chemical shifts are positive in the low-field direction. FAB mass spectra were recorded on a Jeol Hx110/110 mass spectrometer.

4.2. Molecular mechanics calculations

The relative energies of northern- and southern-type conformers for **26a** and **35** were calculated and compared to that of the unsubstituted derivative. Nucleoside conformational preferences were calculated by molecular mechanics using the MMFFs force field and a dielectric constant of 50. For each nucleoside, 1000 conformers were generated using the JG distance geometry program[29] and minimized to low gradient using BatchMin.[30] To estimate the barrier to interconversion between the northern and southern conformers and the steepness of the minima, the conformers generated by distance geometry were also subjected to constrained minimization, holding one of the ribose ring dihedral angles at a random value between −42° and +42° by means of a harmonic force constant of $1000\,kJ\,mol^{-1}\,rad^{-2}$.

4.3. Assay for inhibition of HCV replication

Inhibition of HCV replication was evaluated in a subgenomic replicon harbored in HB-1 cells as previously described.[17]

4.4. Assay for inhibition of HIV spread

Inhibition of viral spread assays were conducted using methods previously published.[28] Briefly, MT4 human T-lymphoid cells were infected at a multiplicity of infection of ~0.01, incubated overnight then washed extensively and plated into 96 well plates. Test compounds were diluted by twofold serial dilutions and mixed with the cells. Cultures were incubated an additional 72 h and then assayed for viral production by a commercial HIV viral core p24 assay kit (Coulter Immunology). Endpoint titers were recorded as the compound dilution in which 95% or greater of the viral antigen production was inhibited as compared to untreated viral growth control wells.

4.5. Single-cycle vaccinia infectivity assay

HeLa cells were maintained at 37 °C/5% CO_2 in phenol red-free Dulbecco's modified Eagle's Medium media (InVitrogen) containing 10% heat-inactivated fetal bovine serum (Hyclone) and 1X penicillin–streptomycin (InVitrogen). For vaccinia infection, cells were seeded in Costar 3917 plates at 5×10^3 cells/well. After overnight incubation, the medium was removed and the cells were infected in the presence or absence of test compounds with 500 pfu/well recombinant vaccinia virus Venv-5.[31] This virus expresses β-galactosidase under the control of the vaccinia 11K promoter.[32] After 48 h, β-galactosidase expression was detected using the Gal-Screen kit (Tropix) according to the manufacturer's instructions.

4.6. (2*R*,4*S*,5*R*)-2-Benzyloxymethyl-5-methyl-1,3-dioxolane-4-carboxylic acid (12)

To a solution of (4*S*,5*R*)-methyl-2,2,5-trimethyl-1,3-dioxolane-4-carboxylate **10** (5.25 g, 30.1 mmol) and benzyloxyacetaldehyde **9** (4.53 g, 30.1 mmol) in toluene (60 mL) was added *para*-toluenesulfonic acid (0.25 g, 1.33 mmol). The reaction mixture was heated at 80 °C under vacuum for 1 h. The reaction mixture was cooled down to room temperature and evaporated to dryness. The residue was purified over silica gel (ethyl acetate/hexane 1:3) to give the ester derivatives **11** (4.01 g, 50%) as a mixture of diastereoisomers. To a solution of **11** (4.01 g, 15.1 mmol) in tetrahydrofuran (8 mL) was added 1 M aqueous LiOH (8 mL) at 0 °C. The reaction mixture was stirred at room temperature 1 h, tetrahydrofuran was removed in vacuo and the solution was acidified to pH 2 by using 30% aqueous HCl. The solution was extracted with ethyl acetate (3×60 mL), the combined organic phase was dried over sodium sulfate, and evaporated to dryness. The residue was purified over silica gel (dichloromethane/acetic acid 49:1) to give carboxylic acid derivative **12** (2.5 g, 65%) as a major isomer. ^{1}H NMR ($CDCl_3$): 7.33 (m, 5H), 5.28 (t, J = 3.9 Hz, 1H), 4.62 (s, 2H), 4.13 (m, 2H), 3.63 (dd, J = 1, 3.9 Hz, 2H), 1.51 (d, J = 5.8 Hz, 3H).

4.7. (2*R*,4*RS*,5*R*)-4-Acetoxy-2-benzyloxymethyl-5-methyl-1,3-dioxolane (14)

To a pre-cooled solution of compound **12** (2.50 g, 9.92 mmol) and pyridine (1.13 g, 14.3 mmol) in acetonitrile (70 mL) was added lead tetraacetate (5.50 g, 12.4 mmol) portion wise over a period of 10 min. The reaction mixture was stirred at room temperature overnight. The white precipitate was filtered and the filtrate was evaporated to dryness. The residue was partitioned between ethyl acetate (200 mL) and saturated aqueous sodium bicarbonate (150 mL). The organic phase was washed with brine, dried over sodium sulfate, and evaporated to dryness. The residue was purified over silica gel (ethyl acetate/hexane 1:3) to give **14** (1.01 g, 38%) as oil. ^{1}H NMR ($CDCl_3$) (major isomer): 7.33 (m, 5H), 5.93 (d, J = 2.6 Hz, 1H), 5.33 (t, J = 4 Hz, 1H), 4.61 (s, 2H), 4.18 (m, 1H), 3.62 (d, J = 4.4 Hz, 2H), 2.09 (s, 3H), 1.35 (d, J = 6.4 Hz, 3H), LRMS-FAB $(M+Li)^+$ 273.1.

4.8. (2*S*,4*R*,5*S*)-2-Benzyloxymethyl-5-methyl 1,3-dioxolane-4-carboxylic acid (17) and (2*R*,4*R*,5*S*)-2-benzyloxymethyl-5-methyl-1,3-dioxolane-4-carboxylic acid (18)

To a solution of methyl-(4*R*,5*S*)-2,2,5-trimethyl-1,3-dioxolane-4-carboxylate **15** (3.58 g, 23.2 mmol) and benzyloxyacetaldehyde **9** (4.23 g, 23.2 mmol) in toluene (50 mL) was added *para*-toluenesulfonic acid (0.25 g, 1.33 mmol). The reaction mixture was heated at 80 °C under vacuum for 1 h. The reaction mixture was cooled down to room temperature, diluted with ethyl acetate (150 mL), and washed with saturated sodium bicarbonate (150 mL). The organic phase was dried over sodium sulfate, evaporated to dryness, and purified over silica gel (ethyl acetate/hexane 1:9) to give the ester derivatives **16** (3.8 g, 57%) as a mixture of diastereoisomers.

To a solution of **16** (3.8 g, 14.28 mmol) in tetrahydrofuran (15 mL) was added aqueous LiOH (1 M, 15 mL) dropwise at 0 °C. The reaction mixture was stirred at

room temperature for 1 h. The pH of the solution was adjusted to 2–3 by addition of 1 N aqueous HCl and extracted with ethyl acetate (3 × 100 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and evaporated to dryness. The residue was purified over silica gel (dichloromethane–acetic acid 49:1) to give **17** (2.8 g, 78%) and **18** (0.45 g, 12%). Compound **17**: ^{1}H NMR($CDCl_3$): δ 7.33 (m, 5H), 5.97 (br s, 1H), 5.28 (t, J = 3.9 Hz, 1H), 4.62 (s, 2H), 4.07–4.21 (m, 2H), 3.64 (dd, J = 0.8, 3.8 Hz, 2H), 1.51 (d, J = 5.8 Hz, 3H). Compound **18**: ^{1}H NMR($CDCl_3$): δ 7.35 (m, 5H), 5.39 (m, 1H), 4.69 (d, J = 6.6 Hz, 2H), 4.60 (m, 1H), 4.27 (d, J = 2.8 Hz, 1H), 3.75 (m, 2H), 1.39 (d, J = 6.4 Hz, 3H).

4.9. (2*S*,4*RS*,5*S*)-4-Acetoxy-2-benzyloxymethyl-5-methyl-1,3-dioxolane (19)

To a solution of **17** (1.76 g, 6.98 mmol) in acetonitrile (60 mL) were added pyridine (0.88 mL) and lead tetraacetate (3.87 g, 8.73 mmol) portion wise over a period of 10 min. The reaction mixture was stirred at room temperature overnight. The white precipitate was filtered and the filtrate was evaporated to dryness. The residue was partitioned between ethyl acetate (200 mL) and saturated aqueous sodium bicarbonate (150 mL). The organic phase was washed with brine, dried over sodium sulfate, and evaporated to dryness. The residue was purified over silica gel (ethyl acetate/hexane 1:9) to give **19** (1.04 g, 56%) as oil. ^{1}H NMR ($CDCl_3$): δ 7.34 (m, 5H), 5.93 (d, J = 2.6 Hz, 1H), 5.33 (t, J = 4 Hz, 1H), 4.61 (s, 2H), 4.18 (m, 1H), 3.62 (d, J = 3.8 Hz, 2H), 2.09 (s, 3H), 1.35 (d, J = 6.4 Hz, 3H); other isomer: 7.34 (m, 5H), 6.21 (d, J = 3.4 Hz, 1H), 5.23 (t, J = 4.2 Hz, 1H), 4.62 (s, 2H), 4.14 (m, 1H), 3.61 (d, J = 4 Hz, 2H), 2.04 (s, 3H), 1.33 (d, J = 6.4 Hz, 3H), LRMS-FAB $(M+Li)^+$ 273.1.

4.10. (2*R*,4*RS*,5*S*)-4-Acetoxy-2-benzyloxymethyl-5-methyl-1,3-dioxolane (20)

Compound **20** was obtained 55% yield from **18** following the procedure described for **19**. ^{1}H NMR ($CDCl_3$): δ 7.33 (m, 5H), 5.99 (s, 1H), 5.47 (m, 1H), 4.61 (m, 2H), 4.38 (m, 1H), 3.58 (d, J = 4.6 Hz, 2H), 2.02 (s, 3H), 1.28 (d, J = 6.6 Hz, 3H); minor isomer: 7.33 (m, 5H), 6.31 (d, J = 3.6 Hz, 1H), 5.47 (m, 1H), 4.61 (m, 2H), 4.38 (m, 1H), 3.53 (d, J = 3.8 Hz, 2H), 2.11 (s, 3H), 1.28 (d, J = 6.6 Hz, 3H), LCMS $(M+H)^+$ 267.2.

4.11. (2*R*,4*S*,5*R*)-9-[2-Hydroxymethyl-5-methyl-1,3-dioxolan-4-yl]guanine (25a) and (2*R*,4*R*,5*R*)-9-[2-hydroxymethyl-5-methyl-1,3-dioxolan-4-yl]guanine (26a)

To diphenylcarbamic acid 2-acetylamino-9*H*-purin-6-yl ester **21** (0.266 g, 1.00 mmol) in dichloroethane (8 mL) was added bis-(trimethylsilyl)acetamide (0.81 g, 4.00 mmol) at rt. The mixture was stirred at room temperature for 2 h, then the acetate derivative **14** (0.27 g, 1.00 mmol) in dichloroethane (3 mL), and then dropwise trimethylsilyl triflate (0.23 g, 1.05 mmol), was added. The resulting mixture was stirred at rt for 30 min and then heated to reflux overnight. The reaction mixture was poured into a stirred mixture of dichloromethane (100 mL) and saturated aqueous sodium bicarbonate (100 mL), the organic phase was separated, dried over magnesium sulfate, and evaporated in vacuo. The crude product was purified on silica gel using hexane/ethyl acetate (1:1 through 1:2) to give the desired diastereoisomeric compounds **23a** and **24a** (0.18 g, 30% and 0.12 g, 20%, respectively) as colorless oils.

To the individual compounds (0.18 g, 0.30 mmol and 0.12 g, 0.20 mmol, respectively) in tetrahydrofuran (10 mL) was added hydrazine hydrate (0.50 mL). The resulting solutions were stirred under reflux for 5 h, then evaporated in vacuo and the crude products purified on silica gel using dichloromethane/methanol (9:1) as the eluent. Fractions containing the products were pooled and evaporated in vacuo to give the desired compounds (0.113 and 0.080 g, respectively) as white powder.

To a solution of the individual compounds (0.113 and 0.08 g, respectively) in methanol (4 mL) was added palladium hydroxide (10–15 mg). The mixtures were stirred under hydrogen for 24 h, filtered through Celite and evaporated in vacuo. The crude products were purified on silica gel using dichloromethane/methanol (4:1) as the eluent. Fractions containing the products were pooled and evaporated in vacuo to give the desired compounds **25a** and **26a** (0.044 g, 55% and 0.029 g, 54%, respectively) as white powder. Compound **25a**: ^{1}H NMR (200 MHz, methanol-d_4): 7.89 (s, 1H), 5.73 (d, J = 5.6 Hz, 1H), 5.59 (t, J = 3 Hz, 1H), 4.71 (m, 1H), 3.66 (d, J = 3.2 Hz, 2H), 1.43 (d, J = 6.2 Hz, 3H), HRMS-FAB $(M+H)^+$ calcd for $C_{10}H_{14}N_5O_4$ 268.1045, found 268.1042; **26a**: ^{1}H NMR (200 MHz, methanol-d_4): δ 8.21 (d, 1H), 6.21 (d, 1H), 5.06 (t, 1H), 4.40 (m, 1H), 3.85 (m, 2H), 0.99 (d, 3H), HRMS-FAB $(M+H)^+$ calcd for $C_{10}H_{14}N_5O_4$ 268.1045, found 268.1044.

4.12. (2*R*,4*S*,5*R*)-2,6-Diamino-9-[2-hydroxymethyl-5-methyl-1,3-dioxolan-4-yl]purine (25b) and (2*R*,4*R*,5*R*)-2,6-diamino-9-[2-hydroxymethyl-5-methyl-1,3-dioxolan-4-yl]purine (26b)

To a pre-cooled (0 °C) solution of **14** (0.266 g, 1.00 mmol) in dichloromethane (5 mL) was added bromotrimethylsilane (0.46 g, 3.00 mmol). The resulting solution was stirred at 0 °C for 15 min, then at room temperature for 15 min. The solution was evaporated in vacuo and co-evaporated twice from acetonitrile. The residue was taken up in acetonitrile (5 mL) and added to a vigorously stirred mixture of 2-amino-6-chloropurine **22**, powdered KOH, and tris-[2-(2-methoxyethoxy)ethyl]amine in acetonitrile (5 mL). The mixture was stirred for 20 min at room temperature and poured into a stirred mixture of diethyl ether (100 mL) and saturated aqueous bicarbonate (100 mL). The organic phase was separated, washed once with water (100 mL), dried over magnesium sulfate, and evaporated under vacuo. The residue was purified on silica gel using ethyl acetate/hexane (1:1) as the eluent. Fractions containing the product were pooled and evaporated under vacuo to give the desired compound (0.065 g) as a inseparable mixture of diastereoisomers **23b** and **24b** (0.065 g, 17.3%).

A solution of **23b** and **24b** (0.065 g, 0.17 mmol) in methanolic ammonia (4 mL) was heated in a closed container overnight at 55 °C. The mixture was cooled and evaporated in vacuo. The residue was purified on silica gel using methanol/dichloromethane (1:9) as the eluent. Fractions containing the product were pooled and evaporate in vacuo to give the desired 2,6-diamino intermediate (0.037 g) as a mixture of diastereoisomers. To this compound in methanol (12 mL) was added ammonium formate (0.04 g) and Pd/C (10%) (0.040 g). The resulting mixture was heated under reflux for 2 h. The mixture was allowed to come to room temperature, filtered through Celite and evaporated under vacuo. The residue was purified on silica gel using methanol/dichloromethane (1:4) as the eluent. Fractions containing the product were pooled and evaporated in vacuo to give the desired compound (0.017 g, 34% in two steps) as a mixture of diastereoisomers **25b** and **26b**. A fraction of the diastereoisomeric mixtures (0.013 g) were separated by HPLC [column: ChiralPak AD (4.6 mm × 250 mm × 10 μ); flow: 1 mL/min; eluent: 100% EtOH; detection 250 nm] to give **25b** (0.0045 g) and **26b** (0.0018 g). Compound **25b**: ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.89 (s, 1H), 6.69 (s, 2H), 5.79 (s, 2H), 5.61 (d, J = 5.8 Hz, 1H), 5.41 (t, J = 3.6 Hz, 1H), 4.95 (br s, 1H), 4.71 (m, 1H), 3.43 (m, 2H), 1.25 (d, J = 6.2 Hz, 3H), HRMS-FAB $(M+H)^+$ calcd for $C_{10}H_{15}N_6O_3$ 267.1205, found 267.1211; **26b**: ^{1}H NMR (200 MHz, d_6-DMSO): δ 7.92 (s, 1H), 6.68 (s, 2H), 6.05 (d, J = 4.8 Hz, 1H), 5.76 (s, 2H), 5.27 (br s, 1H), 4.94 (m, 1H), 4.33 (m, 1H), 3.66 (m, 2H), 0.81 (d, J = 6.2 Hz, 3H), HRMS-FAB $(M+H)^+$ calcd for $C_{10}H_{15}N_6O_3$ 267.1205, found 267.1209.

4.13. (2*S*,4*R*,5*S*)-9-[12-Hydroxymethyl-5-methyl-1,3-dioxolan-4-yl]guanine (30a) and (2*S*,4*S*,5*S*)-9-[2-hydroxymethyl-5-methyl-1,3-dioxolan-4-yl]guanine (31a)

A suspension of **21** (0.24 g, 0.61 mmol) and bis-(trimethylsilyl)acetamide (0.6 mL, 2.44 mmol) in 1,2-dichloroethane (8 mL) was stirred at room temperature for 1.5 h. To this clean solution was added **19** (0.11 g, 0.41 mmol) in 1,2-dichloroethane (5 mL) followed by trimethylsilyl triflate (0.086 mL, 0.47 mmol). The reaction mixture was heated under reflux for 4 h. The solution was poured into saturated aqueous sodium bicarbonate and extracted with dichloromethane (2 × 50 mL). The combined organic phase was dried over sodium sulfate, evaporated, and the residue was purified over silica gel (ethyl acetate/hexane 1:1) to give **28a** (0.031 g, 13%) and **29a** (0.03 g, 12.5%).

To a solution of **28a** (0.028 g, 0.077 mmol) in tetrahydrofuran (4 mL) was added hydrazine hydrate and the solution was refluxed for 3 h. The solvent was evaporated under reduced pressure and the residue was purified over silica gel to give the guanine derivative. This was dissolved in ethanol (5 mL) and cyclohexene (2.5 mL) and to this solution was added palladium hydroxide on charcoal (20% Pd, 0.025 g). The suspension was heated under reflux for 5 h, cooled down and filtered. The filtrate was evaporated to dryness and the residue was purified over silica gel (dichloromethane/methanol 9:1) to give **30a** (0.006 g, 29% in two steps). Following the same procedure as described for **30a**, the *cis* derivative **29a** (0.028 g) was converted to **31a** (0.008 g, 39% in two steps). Compound **30a**: ^{1}H NMR(200 MHz, methanol-d_4): δ 7.68 (s, 1H), 5.70 (d, J = 5.6 Hz, 1H), 5.55 (t, J = 3.2 Hz, 1H), 4.68 (m, 1H), 3.62 (d, J = 3.4 Hz, 2H), 1.39 (d, J = 6.2 Hz, 3H), HRMS-FAB $(M+H)^+$ calcd for $C_{10}H_{14}N_5O_4$ 268.1045, found 268.1047; **31a**: ^{1}H NMR (200 MHz, d_4-MeOH): δ 8.21 (s, 1H), 6.21 (d, J = 4.8 Hz, 1H), 5.06 (t, J = 2.2 Hz, 1H), 4.40 (m, 1H), 3.85 (m, 2H), 1.00 (d, J = 6.2 Hz, 3H), HRMS-FAB $(M+H)^+$ calcd for $C_{10}H_{14}N_5O_4$ 268.1045, found 268.1049.

4.14. (2*S*,4*R*,5*S*)-6-Amino-9-[2-hydroxymethyl-5-methyl-1,3-dioxolan-4-yl]purine (30b) and (2*S*,4*S*,5*S*)-6-amino-9-[2-hydroxymethyl-5-methyl-1,3-dioxolan-4-yl]purine (31b)

To a solution of **19** (0.21 g, 0.79 mmol) in dichloromethane (4 mL) was added bromotrimethylsilane (0.21 mL, 1.6 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 45 min. Solvent was evaporated, co-evaporated with acetonitrile. The residue was dissolved in acetonitrile and added to a vigorously stirred solution of 6-chloropurine **27** (0.125 g, 0.8 mmol), KOH (0.13 g), and tris-[2-(2-methoxyethoxy)ethyl]amine (0.05 mL) in acetonitrile (4 mL). The reaction mixture was stirred at room temperature for 45 min. The solution was taken in ethyl acetate (100 mL) and washed with water (100 mL) and brine (100 mL). The organic phase was dried over sodium sulfate, evaporated to dryness and purified over silica gel to give an inseparable mixture **28b** and **29b**. (0.086 g, 30%).

A solution of a mixture of **28b** and **29b** (0.075 g, 0.21 mmol) in dioxane (3 mL) and liquid ammonia (8 mL) was heated at 80 °C in a steel bomb overnight. The reaction mixture was cooled down, evaporated to dryness, and purified over silica gel to give a diastereoisomeric mixture of adenine derivatives, which was dissolved in ethanol (10 mL) and cyclohexene (5 mL). To this solution was added palladium hydroxide on charcoal (20% Pd, 0.05 g) and the suspension was under reflux for 5 h. The reaction mixture was filtered, the filtrate was evaporated, and the residue was purified over silica gel (dichloromethane/methanol 47:3) to give inseparable mixture of **30b** and **31b** (0.036 g, 69% in two steps). A fraction of the diastereoisomeric mixtures (0.019 g) were separated by HPLC [column: Chiralcel OJ (2 cm × 25 cm × 10 μ); flow: 1 mL/min; eluent: 20% EtOH/hexane; detection 260 nm] to give **30b** (0.0055 g) and **31b** (0.011 g) as white powder. Compound **30b**: ^{1}H NMR (200 MHz, methanol-d_4): δ 8.31 (s, 1H), 8.20 (s, 1H), 5.91 (d, J = 5.4 Hz, 1H), 5.62 (t, J = 3.2 Hz, 1H), 4.81 (m, 1H), 3.68 (d, J = 3.2 Hz, 2H), 1.45 (d, J = 6.4 Hz, 3H), HRMS-FAB $(M+H)^+$ calcd for $C_{10}H_{14}N_5O_3$ 252.1096, found 252.1092; **31b**: ^{1}H NMR (200 MHz, methanol-d_4): δ 8.67 (s, 1H), 8.19 (s, 1H), 6.41 (d, J = 4.8 Hz, 1H), 5.12 (t, J = 2 Hz, 1H), 4.47 (m, 1H), 3.91 (m, 2H), 0.95 (d, J = 6.4 Hz, 3H), HRMS-FAB $(M+H)^+$ calcd for $C_{10}H_{14}N_5O_3$ 252.1096, found 252.1089.

4.15. (2*R*,4*S*,5*S*)-9-[2-Hydroxymethyl-5-methyl-1,3-dioxolan-4-yl]guanine (34) and (2*R*,4*R*,5*S*)-9-[2-hydroxymethyl-5-methyl-1,3-dioxolan-4-yl]guanine (35)

A suspension of **21** (0.485 g, 1.25 mmol) and BSA (0.7 mL, 2.84 mmol) in 1,2-dichloroethane (8 mL) was stirred at room temperature for 1.5 h. To this clean solution was added **20** (0.19 g, 0.71 mmol) in 1,2-dichloroethane (5 mL) followed by trimethylsilyl triflate (0.15 mL, 0.81 mmol). The reaction mixture was heated under reflux for 4 h. The solution was poured into saturated aqueous sodium bicarbonate and extracted with dichloromethane (2×80 mL). The combined organic phase was dried over Na_2SO_4, evaporated and the residue was purified over silica gel (ethyl acetate/hexane: 1/1) to give inseparable mixture (4:3) of α and β nucleoside derivatives **32** and **33** (0.08 g, 19%). The mixture of **32** and **33** (0.07 g, 0.118 mmol) in tetrahydrofuran (8 mL) was added hydrazine hydrate (0.4 mL) and the reaction mixture was heated under reflux for 3 h. The solution was evaporated to dryness and the residue was purified over silica gel (dichloromethane/methanol 93:7) to give a mixture of nucleoside derivatives, which was dissolved in ethanol (8 mL) and cyclohexene (4 mL). To this solution was added palladium hydroxide on charcoal (20% Pd, 0.03 g) and the suspension was refluxed for 40 h. The reaction mixture was cooled down to room temperature, filtered, and the filtrate was evaporated to dryness. The residue was purified over silica gel (dichloromethane/methanol 9:1) to give **34** (0.0047 g, 15% in two steps) and **35** (0.0065, 21% in two steps). Compound **34**: ^{1}H NMR (200 MHz, methanol-d_4): δ 7.94 (s, 1H), 5.81 (d, $J = 2.8$ Hz, 1H), 5.24 (t, $J = 2.8$ Hz, 1H), 4.61 (m, 1H), 3.63 (d, $J = 2.8$ Hz, 2H), 1.31 (d, $J = 6.6$ Hz, 3H), HRMS-FAB $(M+H)^+$ calcd for $C_{10}H_{14}N_5O_4$ 268.1045, found 268.1049; **35**: ^{1}H NMR (200 MHz, methanol-d_4): δ 7.62 (s, 1H), 6.27 (d, $J = 4.4$ Hz, 1H), 5.64 (t, $J = 3.6$ Hz, 1H), 4.63 (m, 1H), 3.66 (d, $J = 3.8$ Hz, 2H), 1.02 (d, $J = 6.4$ Hz, 3H), HRMS-FAB $(M+H)^+$ calcd for $C_{10}H_{14}N_5O_4$ 268.1045, found 268.1042.

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