Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 3304–3314

Enantiomeric synthesis of carbocyclic D-4′-*C*-methyl-ribonucleosides as potential antiviral agents

Peng Liu, Ashoke Sharon and Chung K. Chu*

The University of Georgia, College of Pharmacy, Athens, GA 30602, USA

Received 15 November 2006; accepted 1 December 2006

Abstract—An efficient synthetic approach for the preparation of enantiomerically pure carbocyclic D-4′-*C*-methylribonucleosides **3a**–**f** is reported. The key intermediate, D-2,3-*O*-cyclohexylidene-4-methylcyclopentenone **8**, was prepared starting from D-ribose in eight steps via an oxidative rearrangement. Conjugate addition of a catalytic vinylcopper(I) reagent to the α,β-unsaturated ketone **8** yielded cyclopentyl alcohol **10**, which bears a quaternary stereogenic carbon at the C4-position. The cyclopentyl alcohol **10** was subsequently coupled with 6-chloropurine or 2-amino-6-chloropurine via an S_N2 reaction, followed by a series of functional group transformations and deprotections to furnish purine ribonucleosides **3a**–**c**. Pyrimidine bases were constructed on cyclopentylamine **29** using a linear approach, which furnished the pyrimidine nucleosides **3d**–**f**.

1. Introduction

The threat of acquired immunodeficiency syndrome (AIDS), which has become the leading cause of death for young adults worldwide, has stimulated a burst of extensive drug discovery efforts over the past two decades.[1,2] Currently, there are more than 20 FDA approved anti-HIV drugs, including eight nucleoside reverse transcriptase inhibitors (NRTIs), which are available for the treatment of AIDS.[3] These drugs are being used in combination with protease inhibitors, as well as non-nucleoside reverse transcriptase inhibitors to enhance therapeutic efficacy and to reduce drug resistance. The NRTIs are the backbone of this combination chemotherapy, in which two NRTIs are generally being used in the drug cocktail.[4,5] To treat patients who have developed drug-resistant mutations, novel agents with new mechanisms of action as well as unique resistance profiles are needed.

4′-Substituted nucleosides were first investigated by Maag et al.[6] in 1992, and it was found that some 4′-azido-2′-deoxynucleosides **1a** (Fig. 1) exerted potent activity against HIV-1. Extensive structure–activity studies found that other 4′-position substituents, such as methyl **1b**,[7] fluoromethyl **1c**,[8] ethynyl **1d**,[9] and cyano **1e**[10] also exhibited high antiviral activity against HIV. The 4′-substituted nucleosides are believed to function as delayed chain terminators,[11] which may be related to the rigid north conformation of their sugar rings.[12,13] They have a novel mechanism of viral nucleic acid chain termination, which differs from the conventional 2′,3′-dideoxynucleosides. Based on these observations, the synthesis and biochemistry of 4′-substituted carbocyclic nucleoside analogues have been studied.[14,15] In view of some of the interesting biological activities of the 4′-substituted nucleosides, it was of interest to synthesize carbocyclic 4′-methylribonucleosides as potential antiviral agents. While the biological tests of compounds **3a**–**f** were in progress, a short communication for the preparation of **3a** appeared.[15c] However, the physicochemical data reported for **3a** differ from the data we observed. Herein, we report the asymmetric synthesis of D-4′-*C*-methyl carbocyclic ribonucleosides **3a**–**f**.

2. Results and discussion

2.1. Synthesis of cyclopentyl alcohol 10 bearing a chiral quaternary carbon

L-Cyclopentenone **4** was efficiently prepared from D-ribose according to our previous method,[16] via a ring-closing metathesis in six steps in 42% overall yield. Treatment of the L-enone **4** with methyllithium in THF at −78 °C yielded the tertiary allylic alcohol **5** in 94% yield, as a single

* Corresponding author. Tel.: +1 706 542 5379; fax: +1 706 542 5381; e-mail: dchu@rx.uga.edu

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.12.007

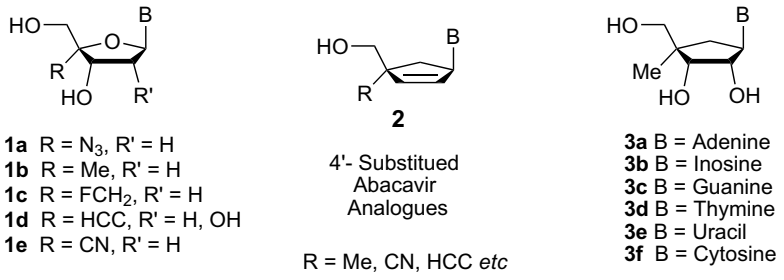
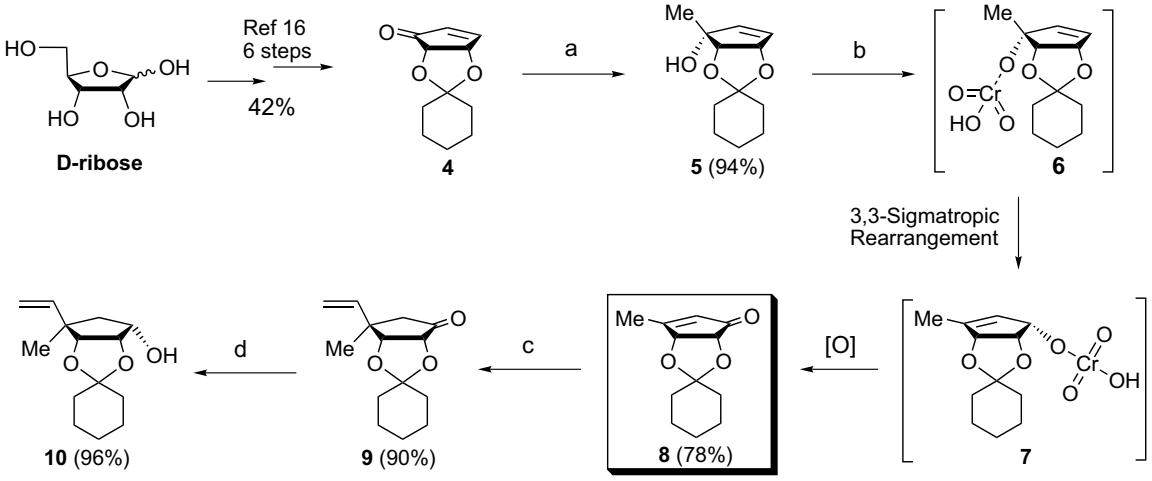


Figure 1.



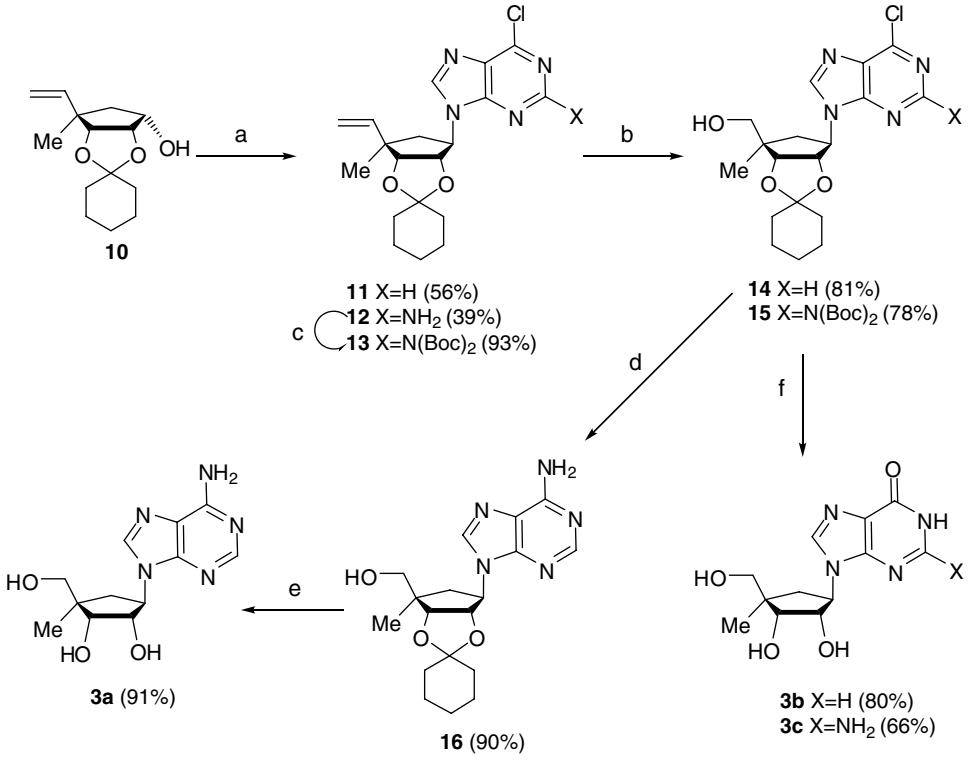
Scheme 1. Synthesis of cyclopentyl alcohol **10** bearing a chiral quaternary carbon. Reagents and conditions: (a) MeLi, THF, −78 °C, 1 h; (b) PDC, Ac_2O, 4 Å molecular sieves, CH_2Cl_2, rt, overnight; (c) vinylmagnesium bromide, TMSCl, HMPA, CuBr–Me_2S, THF, −78 °C, 3 h; (d) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −30 °C, 30 min.

diastereoisomer (Scheme 1). Although chromium oxidants (PDC, PCC, and CrO_3) are prone to induce oxidative rearrangement of tertiary allylic alcohols,[17] the transformation of alcohol **5** to D-4-methylcyclopentenone **8** was problematic. Due to the steric hindrance of the 2,3-cyclohexylidene group, the formation of intermediate **6** became difficult, and therefore may have prevented the subsequent 3,3′-sigmatropic rearrangement as well as the oxidation to form the D-4-methylcyclopentenone **8**. The inertness of a similar tertiary *endo*-OH for oxidative rearrangement was observed by another investigator.[18] By using PDC with acetic anhydride[19] however, compound **5** was successfully converted to 4-methylcyclopentenone **8** in CH_2Cl_2 at rt in 78% yield. TMSCl/HMPA accelerated the conjugate addition reaction[20] of vinylmagnesium bromide to 4-methylcyclopentenone **8** in the presence of CuBr–Me_2S as the catalyst to furnish the ketone **9** in 90% yield. The Luche reduction[21] of **9** afforded the key 4-C-methylated carbocyclic intermediate **10** in 96% yields. The relative configuration of the *C*-4 quaternary stereocenter in **10** was verified by a NOESY experiment.

2.2. Synthesis of carbocyclic 4′-methyl purine ribonucleosides

Coupling of cyclopentyl alcohol **10** with 6-chloropurine under standard Mitsunobu conditions failed to give nucleoside **11**. However, when alcohol **10** was converted to its triflate with trifluoromethanesulfonic anhydride, the subsequent S_N2 substitution of the triflate with a sodium salt of 6-chloropurine in the presence of 18-crown-6 in DMF led to nucleoside **11**, 56% yield in two steps (Scheme 2). Transformation of the vinyl group of **11** to an hydroxymethylene group was accomplished in two steps, oxidative cleavage of the double bond with $NaIO_4$–OsO_4 followed by $NaBH_4$ reduction, to give nucleoside **14** in 81% overall yield. Amination of **14** with saturated methanolic ammonia and subsequent deprotection of **16** with 1 M HCl provided the desired adenine analogue **3a**. Direct hydrolysis of **14** in formic acid at 90 °C for 4 h afforded the hypoxanthine analogue **3b** with 80% yield.

The aforementioned convergent synthetic method is also applicable to the preparation of guanine analogue **3c** with minor changes. Alcohol **10** and 2-amino-6-chloropurine were reacted via an S_N2 reaction to give nucleoside **12** in 39% yield in two steps. After Boc-protection of the 2-amino group of guanine, the double bond of the nucleoside **13** was oxidized with $NaIO_4$–OsO_4 and then reduced to the hydroxymethylene side chain by $NaBH_4$ in 78% yield in two steps. Compound **15** was subsequently hydrolyzed in hot formic acid in 6 h to give **3c** in 66% yield.



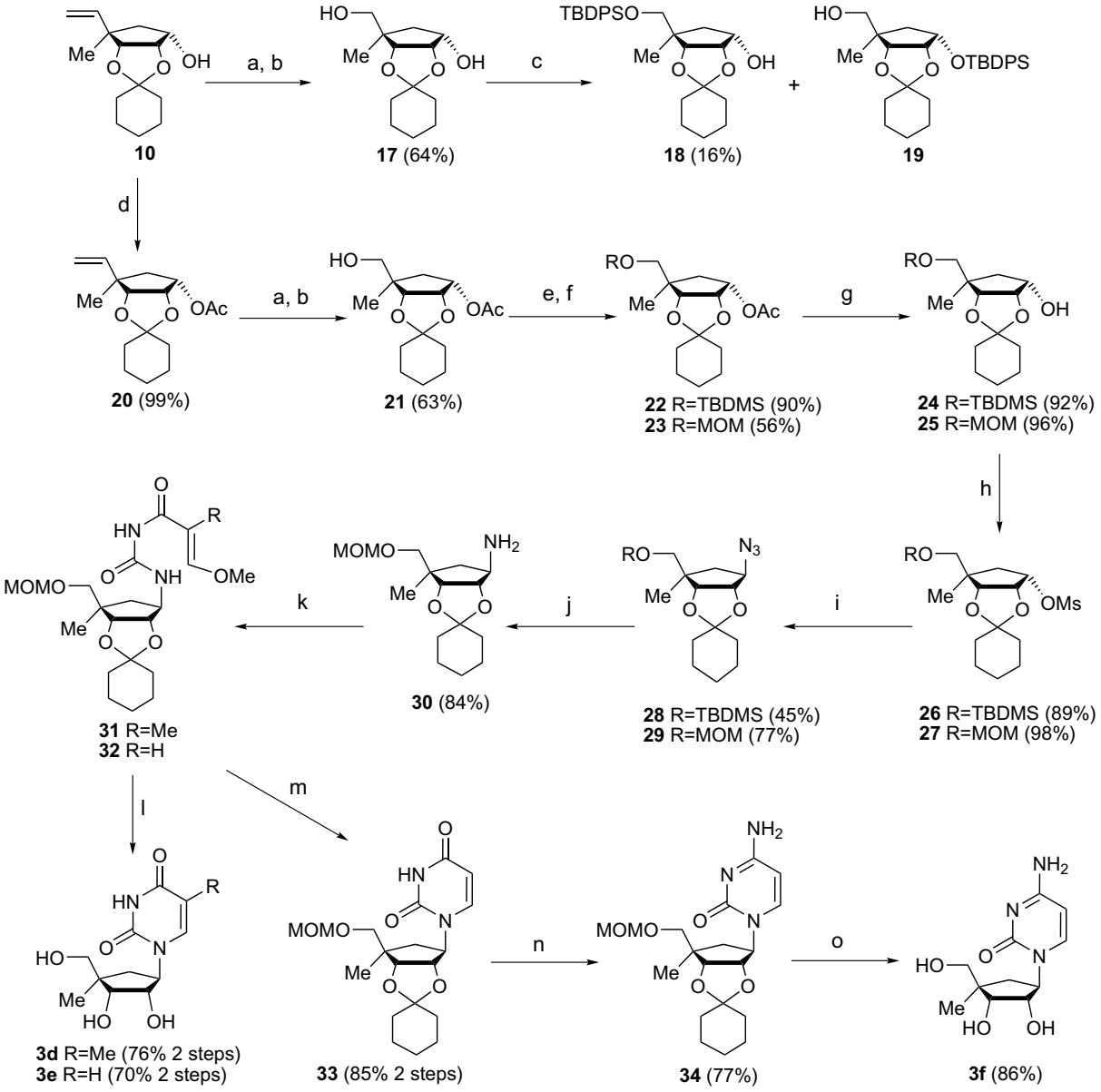
Scheme 2. Synthesis of 4′-methyl carbocyclic purine ribonucleosides. Reagents and conditions: (a) (i) Tf_2O, Py, CH_2Cl_2, 0 °C, 50 min; (ii) 6-chloropurine for **11** or 2-amino-6-chloropurine for **12**, NaH, 18-crown-6, DMF, 0 °C overnight then rt 2 days; (b) (i) $NaIO_4$, OsO_4, THF–H_2O (3:1), rt, 3 h; (ii) $NaBH_4$, MeOH, −30 °C, 30 min; (c) $(Boc)_2O$, Py, CH_2Cl_2, rt, overnight; (d) satd methanolic ammonia, 100 °C, 2 days; (e) aq 2 N HCl–MeOH (1:1), rt, overnight.

2.3. Synthesis of carbocyclic 4′-methyl pyrimidine ribonucleosides

To prepare pyrimidine nucleosides, cyclopentyl alcohol **10** was reacted under Mitsunobu reaction conditions or a substitution reaction without success. It is known that saturated cyclopentyl alcohols, which bear a side chain adjacent to the OH-group, such as functionalized carbocyclic pseudo ribofuranose skeleton, usually exhibit poor coupling reactivity.[22] Therefore, linear constructions of the pyrimidine bases on 4′-methylcyclopentylamine **30** was conducted to synthesize 4′-*C*-methyl carbocyclic ribonucleosides **3d**–**f** (Scheme 3).

The C4-vinyl group of **10** was converted to an hydroxymethylene group according to the same procedure for **14** to produce diol **17** in 64% yield for two steps. However, the selective protection of the primary hydroxyl group of diol **17** with bulky *tert*-butyldiphenylsilyl chloride in the presence of imidazole in CH_2Cl_2 gave a poor yield of alcohol **18**, along with a secondary hydroxyl protected product **19**, which were difficult to separate by chromatography. Obviously, the C-5 primary hydroxyl group of diol **17** was deactivated by the steric effect of the C-4-methyl, and therefore exhibited similar reactivity to C-1 OH. Compound **10** was therefore treated with acetic anhydride in the presence of DMAP and Et_3N in dry CH_2Cl_2, and the resulting acetate **20** was obtained in quantitative yield. Compound **21** was prepared in two steps with 63% yield by transforming the double bond of **20** to the hydroxymethylene side chain. Alcohol **21** was treated with TBDMSOTf and MOMCl to protect the C-5 hydroxyl group to give **22** and **23**, respectively. Deacetylation was conducted by treating compounds **22** and **23** with saturated methanolic ammonia in the presence of K_2CO_3 at rt for 2 days to afford cyclopentyl alcohols **24** and **25**, respectively. The Mitsunobu coupling of N^3-benzoyluracil with either alcohol **24** or **25** according to the reported procedures[22] failed. Treatment of **24** with methanesulfonyl chloride in the presence of Et_3N afforded mesylate **26** in quantitative yield, whereas the subsequent substitution of **26** with NaN_3 in DMF at 150 °C gave only 37% yield of azide **28**. In contrast, MOM protected cyclopentyl alcohol **25** was readily converted to azide **29** by the same method, 75% yield for two steps. Hydrogenation of **29** in the presence of 10% Pd/C at 35 psi for 3 h gave the cyclopentylamine **30** in 84% yield. Cyclopentylamine **30** was treated with β-methoxyacryloyl isocyanate and β-methoxy-α-methacryloyl isocyanate to obtain acryloyl ureas **31** and **32**, respectively. Ring-closure hydrolyses of **31** and **32** were conducted under acidic conditions[23] (3 M HCl–dioxane, 1:4) to prepare thymine **3d** and uracil analogue **3e**, respectively. On the another hand, by choosing a basic ring-closure methodology,[24] uracil nucleoside **33** was obtained without removal of the 2′,3′-*O*-cyclohexylidene group. The heterocyclic ring of uracil derivative **33** was converted to the corresponding cytosine base by the reported method,[25] followed by deprotection to obtain the cytosine analogue **3f** in 86% yield.

The nucleosides obtained were characterized by spectroscopic methods, and the structure of compound **3d** was fur-



Scheme 3. Synthesis of 4′-methyl carbocyclic pyrimidine ribonucleosides. Reagents and conditions: (a) $NaIO_4$, OsO_4, THF–H_2O (3:1), 0 °C to rt, 3 h; (b) $NaBH_4$, MeOH, −30 °C, 30 min; (c) TBDPSCl, imidazole, THF, rt, 24 h; (d) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, overnight; (e) TBDMSOTf, Py, CH_2Cl_2, 0 °C, 1 h; (f) MOMCl, $^iPr_2NEt$, THF, rt, 12 h; (g) satd MeOH–NH_3, K_2CO_3, rt, 24 h; (h) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 50 min; (i) NaN_3, DMF, 150 °C, 8 h; (j) H_2, 10% Pd/C, EtOH, rt, 30 psi, 3 h; (k) β-methoxy-α-methacryloyl isocyanate, DMF, −20 to 20 °C, 10 h for **30** or β-methoxyacryloyl isocyanate, DMF, −20 to 20 °C, 10 h for **31**; (l) 3 M HCl–dioxane (1:4), rt, overnight; (m) 30% NH_4OH, dioxane–EtOH (3:1), 100 °C, 12 h; (n) 2,4,6-triisopropylbenzenesulfonyl chloride, DMAP, Et_3N, MeCN, 0 °C to rt, 24 h then 30% NH_4OH, rt, 5 h; (o) CF_3CO_2H–H_2O (2:1), 50 °C, 3 h.

ther confirmed by a single-crystal X-ray diffraction study[26a] and the ORTEP diagram[26b] as shown in Figure 2 with its corresponding atomic numbering system. The crystal structural studies clearly reveal the 2′-*endo* conformation (C11) with antibase disposition.

2.4. Antiviral activity

The synthesized nucleosides were evaluated for their antiviral activity against yellow fever, Dengue, Punta Toro virus, measles, WNV, VEE as well as their cytotoxicity in Vero and MK2 cells. The results are summarized in Table 1. Only weak antiviral activities were exhibited.

3. Conclusion

In conclusion, we have developed an efficient methodology for the synthesis of carbocyclic 4′-*C*-methylribonucleosides **3a**–**f**. D-4-Methyl-2,3-*O*-cyclohexylidene cyclopentenone **8** was synthesized in eight steps from D-ribose via an oxidative rearrangement step. By conjugate addition of a vinylcopper(I) reagent onto cyclopentenone **8**, cyclopenyl alcohol **10** bearing a stereogenic quaternary carbon was prepared in high yield. Through a convergent approach, carbocyclic 4′-methyl purine ribonucleosides **3a**–**c** were synthesized, while carbocyclic 4′-methyl pyrimidine ribonucleosides **3d**–**f** were synthesized via a linear approach.

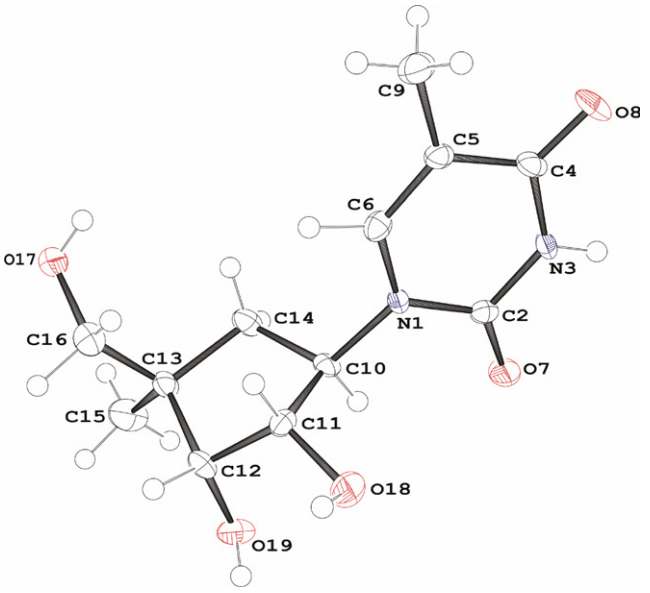


Figure 2. ORTEP diagram showing the displacement ellipsoid plot of the X-ray crystal structure of compound **3d**.

Table 1.

Compound	Cell	Virus	Activity EC_{50} (μg/mL)	Cytotoxicity IC_{50} (μg/mL)
Adenine **3a**		Yellow fever	32	>100
	Vero	Dengue	21	>100
		VEE	>100	>100
		WNV	>100	>100
Guanine **3c**		Yellow fever	>100	>100
	Vero	Dengue	>100	>100
		VEE	83.5	>100
	CV-1	Measles	60	>100
Thymine **3d**		Yellow fever	>100	>100
	Vero	Dengue	>100	>100
		VEE	>100	>100
		WNV	40	>100
	LLC-MK2	Punta Toro	72	>100
Cytosine **3f**		Yellow fever	>100	>100
	Vero	Dengue	35	>100
		VEE	>100	>100
		WNV	>100	>100

The antiviral activities of **3a**–**f** were evaluated against yellow fever, Dengue, VEE, West Nile, measles, and Punta Toro virus; however only weak antiviral activity against these viruses was detected.

4. Experimental

4.1. General

Melting points were determined on a Mel-temp II and are uncorrected. NMR spectra were recorded on a Varian 500 MHz spectrometer in the indicated solvents with TMS as the internal standard. UV spectra were obtained on a Beckman DU-650 spectrophotometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Mass spectra were recorded on a Micromass Autospec high resolution mass spectrometer with ESI. Elemental analyses were performed by Atlantic Microlab, Inc. Automated flash chromatography on Redi*Sep* Amine column was performed on a Teledyne Isco Combi*Flash* Companion purification system.

4.1.1. (3a′*R*,4′*R*,6a′*R*)-4′-Methyl-4′,6a′-dihydro-3a′*H*-spiro-[cyclohexane-1,2′-cyclopenta[*d*][1,3]dioxol]-4′-ol 5. MeLi (52 mL, 1.6 M, 51.5 mmol) was added to a solution of **4** (5.0 g, 25.8 mmol) in dry THF (200 mL) at −78 °C dropwise. After stirring at −78 °C for 30 min, the reaction mixture was warmed to rt and stirred for 1 h. The reaction was quenched by the addition of aqueous NH_4Cl (100 mL) at 0 °C, the aqueous phase was extracted with ethyl acetate (100 mL × 3), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexanes–EtOAc = 5:1) to give **5** (5.0 g, 92%) as a white solid: mp 33–34 °C; $[\alpha]_D^{23} = +47.9$ (*c* 0.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.70–6.62 (m, 2H), 6.00–5.96 (m, 1H), 5.25–5.19 (m, 1H), 4.21–4.14 (m, 1H), 2.54 (s, 8H), 2.32–2.21 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 142.28, 131.77, 114.84, 84.93, 81.05, 80.29, 78.88, 39.32, 37.96, 27.85, 26.86, 25.56; HR-ESI MS calcd for $C_{12}H_{19}O_3$ 211.1334 (M+H), found 211.1330.

4.1.2. (3a′*S*,6a′*S*)-6′-Methyl-3a′*H*-spiro[cyclohexane-1,2′-cyclopenta[*d*][1,3]dioxol]-4′(6a′*H*)-one 8. A mixture of **5** (7.0 g, 33.3 mmol), PDC (25.08 g, 66.7 mmol), 4 Å molecular sieves (6.0 g), and Ac_2O (25.2 mL, 267 mmol) in dichloromethane (300 mL) was stirred at rt overnight. The solvent was removed in vacuo and the residue partitioned between saturated aqueous Na_2CO_3 (100 mL) and CH_2Cl_2 (100 mL). The aqueous layer was washed with CH_2Cl_2 (100 mL × 2) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexanes–EtOAc = 10:1) to afford **8** (4.86 g, 70%) as a white solid: mp 80–81 °C; $[\alpha]_D^{27} = -35.3$ (*c* 0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.90 (d, $J = 1.5$ Hz, 1H), 5.00 (d, $J = 5.5$ Hz, 1H), 4.46 (d, $J = 5.5$ Hz, 1H), 2.21 (s, 3H), 1.67–1.55 (m, 8H), 1.38–1.37 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 202.78, 184.33, 174.75, 130.01, 116.02, 80.72, 37.29, 35.89, 24.94, 23.91, 23.66, 17.04; Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.08; H, 7.83.

4.1.3. (3a′*S*,4′*R*,6a′*S*)-4′-Methyl-4′-vinyldihydro-3a′*H*-spiro-[cyclohexane-1,2′-cyclopenta[*d*][1,3]dioxol]-6′(6a′*H*)-one 9. Vinylmagnesium bromide (3.6 mL, 1.0 M, 3.6 mmol) and HMPA (1.8 mL, 10 mmol) were added to a suspension of CuBr·Me_2S (50 mg, 0.24 mmol) in dry THF (20 mL) at −78 °C over 10 min. After stirring at −78 °C for 15 min, a solution of **8** (350 mg, 1.68 mmol) and TMSCl (1.05 mL, 8.4 mmol) in dry THF (10 mL) was added dropwise over 30 min. The reaction mixture was stirred at −78 °C for 2 h, and then quenched by the addition of saturated NH_4Cl (5 mL). The reaction mixture was extracted with EtOAc (40 mL × 3), the combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel

(EtOAc–hexanes = 1:10) to give **9** (352 mg, 90%) as a colorless oil: $[\alpha]_D^{27} = -209.5$ (*c* 0.76, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.80–5.74 (m, 1H), 5.10–4.99 (m, 2H), 4.42 (d–d, $J = 5.0$, 1.0 Hz, 1H), 4.21–4.19 (m, 1H), 2.57 (d, $J = 17.5$ Hz, 1H), 2.34 (d–t, $J = 18.5$, 1.5 Hz, 1H), 1.64–1.56 (m, 8H), 1.39–1.37 (m, 2H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 213.66, 142.88, 114.43, 113.28, 82.77, 79.19, 44.51, 41.62, 36.73, 34.60, 25.02, 23.93, 23.70, 21.47; Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.08; H, 8.83.

4.1.4. (3a′*S*,4′*R*,6′*S*,6a′*R*)-4′-Methyl-4′-vinyltetrahydro-3a′-*H*-spiro[cyclohexane-1,2′-cyclopenta[*d*][1,3]dioxol]-6′-ol 10. $CeCl_3{\cdot}7H_2O$ (660 mg, 1.77 mmol) was added to a solution of **9** (610 mg, 2.54 mmol) in MeOH (50 mL) at −30 °C. After stirring for 15 min at −30 °C, $NaBH_4$ (190 mg, 5.08 mmol) was added carefully and the reaction mixture was warmed to rt for 30 min. The reaction was quenched by the addition of hexanes–EtOAc (50 mL, 1:1), the reaction mixture was filtered through silica gel. The filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography (hexanes–EtOAc = 5:1) to give **10** (580 mg, 96%) as a colorless oil: $[\alpha]_D^{26} = -9.1$ (*c* 1.46, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.72–5.66 (m, 1H), 5.03–4.99 (m, 2H), 4.45 (t, $J = 6.0$ Hz, 1H), 4.32 (d, $J = 5.5$ Hz, 1H), 4.03–3.99 (m, 1H), 2.51 (d, $J = 10.0$ Hz, 1H), 1.98–1.94 (m, 1H), 1.72–1.52 (m, 9H), 1.43–1.38 (m, 2H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.88, 112.90, 111.24, 84.72, 78.46, 70.82, 44.19, 41.89, 35.85, 33.86, 25.22, 24.08, 23.67, 21.61; HR-ESI MS calcd for $C_{14}H_{23}O_3$ 239.1647 ($M+H^+$), found 239.1645.

4.1.5. 6-Chloro-9-((3a′*S*,4′*R*,6′*R*,6a′*R*)-4′-methyl-4′-vinyltetrahydro-3a′*H*-spiro[cyclohexane-1,2′-cyclopenta[*d*][1,3]-dioxole]-6′-yl)-9*H*-purine 11. Tf_2O (0.44 mL, 2.62 mmol) was added to a solution of **10** (310 mg, 1.30 mmol) and pyridine (0.35 mL, 4.34 mmol) in dry dichloromethane (20 mL) at 0 °C. After stirring for 50 min at 0 °C, cold dichloromethane (20 mL) and ice-water (30 mL) were added. The aqueous layer was washed with cold dichloromethane (15 mL) and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated to give the crude triflate, which was dried in vacuo at 0 °C for 1 h.

A solution of 6-chloropurine (400 mg, 2.59 mmol), NaH (115 mg, 60% dispersion in mineral oil, 2.87 mmol), and 18-crown-6 (690 mg, 2.61 mmol) in DMF (7 mL) was heated at 70 °C for 4 h and then cooled to 0 °C. To this mixture was added the solution of previously prepared triflate in DMF (3 mL), and the reaction mixture was allowed to stir at 0 °C for 12 h and then at rt for 2 days. DMF was removed in vacuo and the residue was purified by silica gel column chromatography (hexanes–EtOAc = 10:1 to 7:1) to give **11** (273 mg, 56%) as a colorless oil: $[\alpha]_D^{26} = -3.65$ (*c* 0.52, THF); ^1H NMR ($CDCl_3$) δ 8.76 (s, 1H), 8.19 (s, 1H), 6.01–5.95 (m, 1H), 5.14–5.06 (m, 3H), 5.02–4.98 (m, 1H), 4.69 (d, $J = 6.5$ Hz, 1H), 2.69–2.64 (m, 1H), 2.30–2.26 (m, 1H), 1.82–1.80 (m, 2H), 1.69–1.64 (m 2H), 1.59–1.48 (m, 4H), 1.41–1.1.38 (m, 2H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 151.81, 151.74, 151.32, 144.72, 144.66, 132.32, 114.84, 113.00, 84.91, 83.85, 61.51, 46.30, 42.79, 36.10, 34.16, 25.08, 23.96, 23.74, 21.05; HR-ESI MS calcd for $C_{19}H_{24}ClN_4O_2$ 375.1588 (M+H), found 375.1538.

4.1.6. ((3a′*R*,4′*R*,6′*R*,6a′*S*)-4′-(6-Chloro-9*H*-purin-9-yl)-6′-methyltetrahydro-3a′*H*-spiro[cyclohexane-1,2′-cyclopenta[*d*]-[1,3]dioxole]-6′-yl)methanol 14. $NaIO_4$ (257 mg, 1.2 mmol) and OsO_4 (0.1 mL, 0.2 M, 0.02 mmol) were added to a solution of **11** (225 mg, 0.6 mmol) in THF–H_2O (2:1, 30 mL) at 0 °C, respectively. The reaction mixture was stirred at 0 °C for 1 h and then at rt for an additional 2 h. The white solid formed was removed by filtration and the filtrate was partially concentrated in vacuo. The aqueous phase was extracted with CH_2Cl_2 (25 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give the crude aldehyde, which was used for the next step without further purification.

The crude aldehyde was dissolved in MeOH (15 mL). $NaBH_4$ (50 mg, 1.32 mmol) was added to this solution portionwise at 0 °C. After the reaction mixture was stirred at 0 °C for 1 h, hexanes–EtOAc (1:1, 20 mL) was added and the mixture was filtered through a short pad of SiO_2. The solvent was removed in vacuo and the residue was purified by silica gel flash column chromatography (CH_2Cl_2–MeOH = 100:1 to 50:1) to give **14** (184 mg, 81% for two steps) as a white foam: $[\alpha]_D^{28} = -28.0$ (*c* 0.92, EtOAc); ^1H NMR ($CDCl_3$) δ 8.75 (s, 1H), 8.34 (s, 1H), 5.05 (t, $J = 6.0$ Hz, 1H), 5.01–4.96 (m, 1H), 4.60 (d, $J = 6.0$ Hz, 1H), 3.64–3.62 (m, 2H), 3.29 (t, $J = 5.0$ Hz, 1H), 2.65–2.61 (m, 1H), 2.31–2.26 (m, 1H), 1.87–1.81 (m, 2H), 1.70–1.66 (m, 2H), 1.59–1.50 (m, 4H), 1.42–1.38 (m, 2H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 151.60, 151.51, 151.34, 145.04, 132.39, 113.82, 84.97, 83.46, 70.23, 63.15, 45.36, 39.76, 37.17, 34.41, 25.04, 24.04, 23.52, 19.04; HR-ESI MS calcd for $C_{18}H_{24}ClN_4O_3$ (M+H) 379.1537, found 379.1506; Anal. Calcd for $C_{18}H_{23}ClN_4O_3{\cdot}0.3Et_2O$: C, 57.50; H, 6.53; N, 13.97. Found: C, 57.51; H, 6.42; N, 13.95.

4.1.7. ((3a′*R*,4′*R*,6′*R*,6a′*S*)-4′-(6-Amino-9*H*-purin-9-yl)-6′-methyltetrahydro-3a′*H*-spiro[cyclohexane-1,2′-cyclopenta[*d*]-[1,3]dioxole]-6′-yl)methanol 16. A solution of **14** (120 mg, 0.32 mmol) in saturated methanolic ammonia (20 mL) was heated at 100 °C in a steel bomb for 48 h. The solution was concentrated to dryness and the residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH = 30:1) to give **16** (105 mg, 92%) as a white solid: mp 242–244 °C; $[\alpha]_D^{28} = -32.4$ (*c* 0.76, MeOH–CH_2Cl_2 1:1); ^1H NMR (DMSO-d_6) δ 8.32 (s, 1H), 8.16 (s, 1H), 7.27 (s, 2H), 5.09 (t, $J = 6.0$ Hz, 1H), 4.98 (t, $J = 5.5$ Hz, 1H), 4.95–4.90 (m, 1H), 4.55 (d, $J = 6.0$ Hz, 1H), 3.33–3.31 (m, 2H), 2.42 (t, $J = 12.5$ Hz, 1H), 1.93–1.89 (m, 1H), 1.75–1.73 (m, 2H), 1.59–1.33 (m, 8H), 1.05 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 156.55, 152.84, 149.88, 142.33, 140.27, 119.67, 113.58, 83.88, 81.92, 68.35, 59.78, 44.76, 36.70, 34.48, 25.08, 24.14, 23.65, 19.29; HR-ESI MS calcd for $C_{18}H_{25}N_5O_3$ (M) 359.1957, found 359.2007.

4.1.8. (1*R*,2*S*,3*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3-(hydroxymethyl)-3-methylcyclopentane-1,2-diol 3a. A solution of **16** (65 mg, 0.18 mmol) in 2 N HCl–MeOH (1:1, 5 mL) was stirred at rt overnight. Solid Na_2CO_3 was carefully

added to neutralize the reaction mixture. The neutral suspension was evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2–MeOH = 5:1) to obtain **3a** (41 mg, 81%) as a white solid: mp 208–209 °C; $[\alpha]_D^{24} = -29.6$ (*c* 0.32, MeOH); UV (H_2O) λ_{max} 259 nm (1377, pH 2), 261 nm (2004, pH 7), 260 nm (2160, pH 11); ^{1}H NMR (DMSO-d_6) δ 8.26 (s, 1H), 8.18 (s, 1H), 7.26 (s, br, 2H, D_2O-exchangeable), 5.03 (s, br, 1H, D_2O-exchangeable), 4.96 (s, br, 1H, D_2O-exchangeable), 4.78–4.82 (m, 1H), 4.74 (s, br, 1H, D_2O-exchangeable), 4.60–4.62 (m, 1H), 3.82 (d, $J = 5.0$ Hz, 1H), 3.39 (d–d, $J = 48.0$, 11.0 Hz, 2H), 1.84–1.98 (m, 2H), 1.05 (s, 3H); ^{13}C NMR (MeOH-d_4) δ 155.83, 151.93, 149.45, 140.61, 119.16, 75.69, 74.50, 69.39, 60.41, 44.42, 36.70, 18.43; HR-ESI MS calcd for $C_{12}H_{17}N_5O_3$ (M+H) 280.1410 (M+Na) 302.1229, found 280.1331, 302.1200; Anal. Calcd for $C_{12}H_{17}N_5O_3 \cdot 0.4H_2O$: C, 50.31; H, 6.26; N, 24.44. Found: C, 50.40; H, 6.22; N, 24.04.

4.1.9. (1*R*,2*S*,3*R*,5*R*)-5-(6-Hydroxy-9*H*-purin-9-yl)-3-(hydroxymethyl)-3-methylcyclopentane-1,2-diol 3b. Compound **14** (110 mg, 0.29 mmol) was dissolved in formic acid (10 mL) and the mixture was heated at 90 °C for 2.5 h. The solvent was removed in vacuo and co-evaporated twice with toluene (10 mL × 2). The residue was dissolved in saturated methanolic ammonia (15 mL) and the solution was stirred at rt overnight. After removing the solvent in vacuo, the residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH = 5:1) to afford **3b** (70 mg, 87%) as a white solid: mp 265 °C dec; $[\alpha]_D^{24} = -37.8$ (*c* 0.25, MeOH–CH_2Cl_2 1:1); UV (H_2O) λ_{max} 252 nm (9641, pH 2), 250 nm (7235, pH 7), 255 nm (7164, pH 11); ^{1}H NMR (DMSO-d_6) δ 8.19 (s, 1H), 8.04 (s, 1H), 4.95 (d, $J = 7.5$ Hz, 1H, D_2O-exchangeable), 4.86 (t, $J = 5.5$ Hz, 1H, D_2O-exchangeable), 4.73–4.77 (m, 1H), 4,67 (d, $J = 4.5$ Hz, 1H, D_2O-exchangeable), 4.46–4.51 (m, 1H), 3.75–3.77 (m, 1H), 3.34–3.38 (m, 2H), 3.25–3.28 (m, 1H, D_2O-exchangeable), 1.80–1.85 (m, 2H), 0.99 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 20.18, 38.19, 44.41, 59.69, 69.18, 73.81, 75.63, 124.84, 139.69, 145.55, 149.10, 157.13; HR-ESI MS calcd for $C_{12}H_{16}N_4O_4$ (M) 280.1172, found 280.1126; Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.73; H, 5.84; N, 19.57.

4.1.10. 6-Chloro-9-((3a′*S*,4′*R*,6′*R*,6a′*R*)-4′-methyl-4′-vinyltetrahydro-3a′*H*-spiro[cyclohexane-1,2′-cyclopenta[*d*][1,3]dioxole]-6′-yl)-9*H*-purin-2-amine 12. Tf_2O (313 μL, 1.87 mmol) was added to a solution of **10** (222 mg, 0.93 mmol) and pyridine (225 μL, 2.8 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After stirring for 50 min, cold CH_2Cl_2 (10 mL) and water (10 mL) were added into the reaction mixture. The aqueous phase was extracted with CH_2Cl_2 (15 mL × 2), the combined organic phases were dried over $MgSO_4$, filtered, and concentrated to afford the crude triflate, which was dried in vacuo at 0 °C for 2 h and used for the next step without further purification.

A solution of 2-amino-6-chloropurine (318 mg, 1.87 mmol), NaH (78 mg, 60% dispersion in mineral oil, 1.99 mmol), and 18-crown-6 (493 mg, 1.87 mmol) in dry DMF (3 mL) was heated at 70 °C for 4 h and then cooled to 0 °C. To this suspension was added triflate in DMF (3 mL) at 0 °C, stirred at 0 °C overnight and rt for 48 h. The DMF was removed by vacuum distillation and the residue was purified by silica gel chromatography (hexanes–EtOAc = 5:1) to afford **12** (140 mg, 39%) as a white solid: mp 192–193 °C; $[\alpha]_D^{23} = +4.0$ (*c* 0.38, EtOAc); UV (MeOH) λ_{max} 247, 310 nm; ^{1}H NMR ($CDCl_3$) δ 7.82 (s, 1H), 5.93–5.99 (m, 1H), 5.23 (s, br, 2H), 5.05–5.08 (m, 3H), 4.80–4.84 (m, 1H), 4.63 (d, $J = 7.5$ Hz, 1H), 2.54–2.58 (m, 1H), 2.17–2.21 (m, 1H), 1.78–1.81 (m, 2H), 1.37–1.50 (m, 8H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.79, 153.69, 151.51, 144.92, 141.74, 125.92, 114.67, 112.81, 84.93, 83.70, 60.50, 46.21, 42.70, 36.04, 34.18, 25.10, 23.97, 23.48, 21.05; Anal. Calcd for $C_{19}H_{24}ClN_5O_2$: C, 58.53; H, 6.20; N, 17.96. Found: C, 58.78; H, 6.28; N, 17.81.

4.1.11. 2-*N*,*N*-Bis(*tert*-butoxycarbonyl)amino-6-chloro-9-((3a′-*S*,4′*R*,6′*R*,6a′*R*)-4′-methyl-4′-vinyltetrahedro-3a′*H*-spiro[cyclohexane-1,2′-cyclopenta[*d*][1,3]dioxole]-6′-yl)-9*H*-purine 13. A solution of **12** (136 mg, 0.35 mmol), DMAP (5 mg, 0.04 mmol), and Boc_2O (460 mg, 2.10 mmol) in THF (5 mL) was stirred at rt overnight. The solvent was evaporated in vacuo, and the residue chromatographed on silica gel (hexanes–EtOAc = 4:1) to furnish **13** (198 mg, 96%) as a colorless oil: $[\alpha]_D^{26} = +0.6$ (*c* 0.48, EtOAc); ^{1}H NMR ($CDCl_3$) δ 8.22 (s, 1H), 5.92–5.98 (m, 1H), 5.11–5.14 (m, 1H), 5.04–5.08 (m, 2H), 4.94–4.99 (m, 1H), 4.66 (d, $J = 7.5$ Hz, 1H), 2.60–2.64 (m, 1H), 2.24–2.28 (m, 1H), 1.38–1.80 (m, 26H), 1.25–1.28 (m, 2H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.41, 151.59, 151.29, 150.56, 145.53, 144.63, 130.58, 114.81, 112.95, 84.83, 83.62, 83.61, 61.50, 60.40, 46.17, 42.87, 36.05, 34.12, 27.90, 25.04, 23.91, 23.41, 21.07, 21.05, 14.21; HR-ESI MS calcd for $C_{29}H_{41}ClN_5O_6$ (M+H) 590.2745, found 590.2690.

4.1.12. ((3a′*R*,4′*R*,6′*R*,6a′*S*)-4′-(2-*N*,*N*-Bis(*tert*-butoxycarbonyl)amino-6-chloro-9*H*-purin-9-yl)-6′-methyltetrahydro-3a′*H*-spiro[cyclohexane-1,2′-cyclopenta[*d*][1,3]dioxole]-6′-yl)-methanol 15. A solution of **13** (80 mg, 0.13 mmol) and $NaIO_4$ (58 mg, 0.27 mmol) in THF–H_2O (3:1, 8 mL) was treated with aqueous OsO_4 (0.2 M, 135 μL, 0.027 mmol) at 0 °C and stirred at rt for 2 h. The white precipitate was filtered off, and the filtrate concentrated in vacuo. The residue was partitioned between water (10 mL) and CH_2Cl_2 (20 mL × 2), and the separated organic phase was concentrated to give a crude aldehyde, which was used for the next step without further purification.

$NaBH_4$ (27 mg, 0.63 mmol) was added to a solution of the aforementioned crude aldehyde in MeOH (5 mL) at 0 °C. The mixture was stirred at rt for 1 h. hexanes–EtOAc (1:1, 10 mL) was added and the mixture filtered through a short pad of SiO_2. The filtrate was concentrated in vacuo and the residue purified by silica gel chromatography (hexanes–EtOAc = 1:1) to give **15** (44 mg, 55%) as a white solid: mp 99–101 °C; $[\alpha]_D^{24} = -13.0$ (*c* 0.9, EtOAc); ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H), 5.05 (t, $J = 6.0$ Hz, 1H), 4.87–4.89 (m, 1H), 4.58 (d, $J = 6.0$ Hz, 1H), 3.54–3.60 (m, 2H), 2.59–2.64 (m, 2H), 2.19–2.23 (m, 1H), 1.25–1.81 (m, 28H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.25, 151.43, 151.29, 150.64, 145.74, 130.62, 113.89, 84.59, 83.83, 83.19, 70.03, 63.14, 60.45, 45.14, 39.77, 37.14, 34.42, 27.99, 27.89, 25.05, 24.02, 23.49, 19.01, 14.23; Anal. Calcd

for $C_{28}H_{40}ClN_5O_7$: C, 56.61; H, 6.79; N, 11.79. Found: C, 56.67; H, 6.91; N, 11.60.

4.1.13. 2-Amino-9-((1*R*,2*R*,3*S*,4*R*)-2,3-dihydroxy-4-(hydroxymethyl)-4-methylcyclopentyl)-1*H*-purin-6(9*H*)-one 3c. A mixture of **15** (190 mg, 0.32 mmol) in formic acid (5 mL) was heated at 90 °C for 6 h. The solvent was removed in vacuo and the residue was treated with methanolic ammonia (10 mL) at rt overnight. The reaction mixture was concentrated to dryness, and the residue was loaded on a 4.7 g Redi*Sep* Amine column eluted with CH_2Cl_2–MeOH (2:1) to obtain **3c** (82 mg, 56%) as a pale yellowish solid: mp >290 °C dec; $[\alpha]_D^{26} = -6.45$ (*c* 0.12, MeOH); UV (H_2O) λ_{max} 256 nm (15,840, pH 2), 252 nm (12,340, pH 7), 268 nm (10,316, pH 11); ^{1}H NMR (DMSO-d_6) δ 10.61 (s, 1H, D_2O-exchangeable), 7.81 (s, 1H), 6.48 (s, 2H, D_2O-exchangeable), 4.92 (d, $J = 6.5$ Hz, 1H, D_2O-exchangeable), 4.85 (t, $J = 5.5$ Hz, 1H, D_2O-exchangeable), 4.56–4.63 (m, 2H, 1H, D_2O-exchangeable), 4.36–4.41 (m, 1H), 3.71–3.73 (m, 1H), 3.23–3.33 (m, 2H), 1.67–1.78 (m, 2H), 0.97 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 157.39, 153.51, 151.99, 136.63, 116.97, 75.50, 73.85, 69.06, 58.48, 44.20, 38.10, 20.05; Anal. Calcd for $C_{12}H_{17}N_5O_4$: C, 48.81; H, 5.80; N, 23.72. Found: C, 48.80; H, 6.20; N, 23.49.

4.1.14. (3a′*S*,4′*R*,6′*S*,6a′*R*)-4′-Methyl-4′-vinyltetrahydro-3a′*H*-spiro[cyclohexane-1,2′-cyclopenta[*d*][1,3]dioxole]-6′-yl ethanoate 20. Ac_2O (3.9 mL, 38.4 mmol) was added dropwise to a solution of **10** (6.1 g, 25.6 mmol), DMAP (317 mg, 2.6 mmol), and Et_3N (5.4 mL, 38.4 mmol) in CH_2Cl_2 (300 mL). The mixture was stirred at rt for 12 h. Solid $NaHCO_3$ was added carefully to neutralize the solution. The solvent was removed in vacuo and the residue was purified by silica gel chromatography (hexanes–EtOAc = 10:1) to give **20** (6.9 g, 96%) as a white solid: mp 44–45 °C; $[\alpha]_D^{27} = -66.0$ (*c* 0.44, EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.68–5.74 (m, 1H), 5.04–5.07 (m, 2H), 4.75–4.80 (m, 1H), 4.66 (t, $J = 5.0$ Hz, 1H), 4.27 (d, $J = 5.0$ Hz, 1H), 2.08 (s, 3H), 1.87–1.96 (m, 2H), 1.54–1.70 (m, 8H), 1.37–1.40 (m, 2H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.86, 150.01, 143.42, 113.24, 111.50, 84.84, 73.12, 43.85, 37.74, 35.85, 34.43, 25.24, 24.12, 23.75, 21.70, 20.93; Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.55; H, 8.66.

4.1.15. (3a′*S*,4′*R*,6′*S*,6a′*R*)-4′-(Hydroxymethyl)-4′-methyltetrahydro-3a′*H*-spiro[cyclohexane-1,2′-cyclopenta[*d*][1,3]dioxole]-6′-yl ethenoate 21. OsO_4 (0.2 M, 5 mL, 1 mmol) was added to a mixture of **20** (5.6 g, 20 mmol) and $NaIO_4$ (8.56 g, 40 mmol) in THF–H_2O (2:1, 100 mL) at 0 °C. After stirring at 0 °C for 30 min, an additional 5 mL of OsO_4 (0.2 M, 1 mmol) was added. The reaction mixture was stirred at rt for 3 h. The mixture was filtered through a short pad of silica gel, and the filtrate was extracted with EtOAc (100 mL × 3). The organic layer was dried over $MgSO_4$, and concentrated in vacuo to give the crude aldehyde, which was used for the next step without purification.

$NaBH_4$ (1.52 g, 40 mmol) was added to a solution of the crude aldehyde in MeOH (100 mL) at 0 °C, and the solution was stirred at rt for 30 min. The reaction mixture was quenched by the addition of hexanes–EtOAc (1:1, 100 mL) and the mixture was filtered through a short pad of silica gel. The filtrate was concentrated to dryness and the residue was purified by silica gel flash chromatography (hexanes–EtOAc = 2:1) to furnish **21** (3.41 g, 60% for two steps) as a white solid: mp 119–121 °C; $[\alpha]_D^{27} = -79.5$ (*c* 0.34, EtOAc); ^{1}H NMR ($CDCl_3$) δ 4.97–5.02 (m, 1H), 4.74 (t, $J = 5.0$ Hz, 1H), 4.27 (d, $J = 5.0$ Hz, 1H), 3.41 (s, 2H), 2.17 (t, $J = 5.0$ Hz, 1H), 2.11 (s, 3H), 1.83–1.97 (m, 2H), 1.54–1.72 (m, 8H), 1.39–1.42 (m, 2H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.12, 111.26, 83.85, 78.44, 73.48, 69.42, 43.88, 37.90, 35.85, 34.37, 25.24, 24.13, 23.75, 21.00, 18.33; Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.03; H, 8.43.

4.1.16. (3a′*S*,4′*R*,6′*S*,6a′*R*)-4′-((Methoxymethoxy)methyl)-4′-methyltetrahydro-3a′*H*-spiro[cyclohexane-1,2′-cyclopenta-[*d*][1,3]dioxol]-6′-ol 25. Chloromethyl methyl ether (1.8 mL, 23.2 mmol) was added dropwise to a solution of **21** (1.32 g, 4.65 mmol) and diisopropylethylamine (4.1 mL, 23.2 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The reaction mixture was stirred at rt for 4 h. The crude MOM protected product **23** was obtained by removing the reaction solvent in vacuo.

Crude **23** was dissolved in saturated methanolic ammonia (50 mL) and stirred at rt in the presence of K_2CO_3 (650 mg, 4.70 mmol) for 48 h. After the solvent was removed in vacuo, the residue was purified by silica gel flash chromatography (hexanes–EtOAc = 5:1) to give compound **25** (1.21 g, 91% for two steps) as a colorless oil: $[\alpha]_D^{27} = +6.7$ (*c* 0.97, EtOAc); ^{1}H NMR ($CDCl_3$) δ 4.57 (s, 2H), 4.52 (t, $J = 6.0$ Hz, 1H), 4.27 (d, $J = 6.0$ Hz, 1H), 4.20–4.24 (m, 1H), 3.35 (s, 3H), 3.24 (s, 2H), 2.63 (d, $J = 10.0$ Hz, 1H), 1.94–1.98 (m, 1H), 1.53–1.74 (m, 9H), 1.40–1.45 (m, 2H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 111.10, 96.55, 84.14, 79.47, 74.69, 70.95, 55.30, 43.05, 42.97, 35.88, 33.77, 25.21, 24.07, 23.65, 18.67; Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 62.80; H, 9.01.

4.1.17. (3a′*S*,4′*R*,6′*S*,6a′*R*)-6′-Azido-4′-((methoxymethoxy)-methyl)-4′-methyltetrahydro-3a′*H*-spiro[cyclohexane-1,2′-cyclopenta[*d*][1,3]dioxole] 29. MsCl (0.4 mL, 5.0 mmol) was added to a solution of **25** (1.2 g, 4.2 mmol) and Et_3N (0.7 mL, 5.0 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 50 min, and then quenched by the addition of cold water (30 mL). The aqueous layer was extracted with CH_2Cl_2 (50 mL × 2), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexanes–EtOAc = 5:1) to furnish methylate **27** (1.42 g, 93%).

Methylate **27** (1.42 g, 3.90 mmol) was heated with NaN_3 (2.60 g, 40 mmol) in dry DMF (50 mL) at 150–160 °C for 6 h. The solvent was removed in vacuo, the residue was purified by silica gel flash chromatography (hexanes–EtOAc = 50:1 to 30:1) to afford azide **29** (910 mg, 75%) as a colorless oil: $[\alpha]_D^{25} = -34.05$ (*c* 0.53, EtOAc); IR (cm^{-1}) 2102; ^{1}H NMR ($CDCl_3$) δ 4.63 (s, 2H), 4.46 (d, $J = 6.0$ Hz, 1H), 4.31 (d, $J = 6.0$ Hz, 1H), 3.96–3.98 (m, 1H), 3.33–3.39 (m, 5H), 1.92–1.96 (m, 1H), 1.81–1.85 (m,

1H), 1.50–1.68 (m, 8H), 1.30–1.42 (m, 2H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 112.08, 96.77, 85.70, 83.37, 73.27, 66.60, 55.32, 46.28, 38.50, 36.37, 33.84, 25.16, 24.02, 23.62, 19.32. HR-ESI MS calcd for $C_{15}H_{26}N_3O_4$ (M+H) 312.1923, found 312.1866.

4.1.18. (3a′*S*,4′*R*,6′*S*,6a′*R*)-4′-((Methoxymethoxy)methyl)-4′-methyltetrahydro-3a′*H*-spiro[cyclohexane-1,2′-cyclopenta-[*d*][1,3]dioxol]-6′-amine 30. Compound **29** (1.2 g, 3.86 mmol) was hydrogenated in EtOH (120 mL) over 10% Pd/C (400 mg) at 35 psi at rt for 3 h. The catalyst was filtered off and the filtrate was concentrated to dryness. The residue was purified by silica gel flash chromatography (CH_2Cl_2–MeOH = 30:1 to 10:1) to afford **30** (1.0 g, 91%) as a colorless oil: $[\alpha]_D^{26} = +11.3$ (*c* 0.38, EtOAc); ^{1}H NMR ($CDCl_3$) δ 4.63 (s, 2H), 4.39 (d, $J = 6.5$ Hz, 1H), 4.26 (dd, $J_1 = 6.5$ Hz, $J_2 = 3.0$ Hz, 1H), 3.40–3.44 (m, 3H), 3.37 (s, 3H), 1.91–1.95 (m, 1H), 1.48–1.70 (m, 11H, 2H, D_2O-exchangeable), 1.35–1.41 (m, 2H), 1.06 (s, 3H); HR-ESI MS calcd for $C_{15}H_{28}NO_4$ (M+H) 286.2018, found 286.2014.

4.1.19. 1-((1*R*,2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-(hydroxymethyl)-4-methylcyclopentyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione 3d. Silver cyanate (72 mg, 0.48 mmol) was added to a solution of β-methoxy-α-methacryloyl chloride (65 mg, 0.48 mmol) in dry benzene (2 mL). The mixture was refluxed for 30 min and cooled to rt. After the solid phase settled down, the supernant solution, which contained isocyanate, was transferred into a solution of **30** (46 mg, 0.16 mmol) in THF (2 mL) at −15 °C under N_2. The reaction mixture was stirred at −15 °C for 2 h, and at rt overnight. The solvent was removed in vacuo and the residue was chromatographed on silica gel (hexanes–EtOAc = 5:1) to afford **31** (56 mg, 82%) as a colorless oil: $[\alpha]_D^{25} = +10.2$ (*c* 0.85, EtOAc); ^{1}H NMR ($CDCl_3$) δ 9.03 (d, $J = 8.5$ Hz, 1H), 8.07 (s, 1H), 7.32 (d, $J = 1.0$ Hz, 1H), 4.75 (d, $J = 6.5$ Hz, 1H), 4.70 (d, $J = 6.5$ Hz, 1H), 4.51 (dd, $J_1 = 6.5$ Hz, $J_2 = 2.0$ Hz, 1H), 4.32–4.36 (m, 2H), 3.87 (s, 3H), 3.37 (dd, $J_1 = 36$ Hz, $J_2 = 9.5$ Hz, 2H), 3.36 (s, 3H), 2.18–2.21 (m 1H), 1.35–1.76 (m, 11H), 1.08 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 168.83, 158.27, 153.52, 111.74, 107.17, 96.54, 88.12, 84.65, 75.01, 61.55, 56.27, 55.34, 45.95, 41.47, 36.55, 34.07, 25.23, 24.05, 23.66, 19.51, 8.87.

Compound **31** (56 mg, 0.13 mmol) was treated with 3 M HCl (1 mL) in dioxane (4 mL) at rt overnight. The solvent was removed in vacuo. The residue was dissolved in MeOH (5 mL), and neutralized by solid $NaHCO_3$. The methanolic suspension was concentrated to dryness, and the crude product was purified by preparative silica gel TLC (CH_2Cl_2–MeOH = 5:1) to obtain **3d** (33 mg, 94%) as a white solid: mp 222–223 °C; $[\alpha]_D^2 = -81.8$ (*c* 1.4, MeOH); UV (H_2O) λ_{max} 273 nm (20,646, pH 2), 274 nm (16,921, pH 7), 273 nm (11,959, pH 11); ^{1}H NMR (DMSO-d_6) δ 11.19 (s, 1H, D_2O-exchangeable), 7.56 (s, 1H), 4.81–4.86 (m, 2H, D_2O-exchangeable), 4.67–4.73 (m, 1H), 4.52 (d, $J = 4.0$ Hz, 1H, D_2O-exchangeable), 4.14–4.17 (m, 1H), 3.64–3.66 (m, 1H), 3.18–3.29 (m, 2H), 1.80 (s, 3H), 1.45–1.58 (m, 2H), 0.93 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 164.48, 151.74, 138.92, 109.57, 73.90, 73.56, 69.05, 60.19, 43.83, 35.90, 19.96, 12.47; Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.16; H, 6.84; N, 10.01.

4.1.20. 1-((3a′*S*,4′*R*,6′*S*,6a′*R*)-4′-((Methoxymethoxy)methyl)-4′-methyltetrahydro-3a′*H*-spiro[cyclohexane-1,2′-cyclopenta-[*d*][1,3]dioxole]-6′-yl)pyrimidine-2,4(1*H*,3*H*)-dione 33. Using the same procedure as that described for compound **31**, compound **30** (145 mg, 0.51 mmol) was treated with β-methoxyacryloyl chloride (185 mg, 1.53 mmol) to give **32** as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 10.03 (s, 1H), 9.00 (d, $J = 8.0$ Hz, 1H), 7.65 (d, $J = 12.0$ Hz, 1H), 5.43 (d, $J = 12.5$ Hz, 1H), 4.73 (dd, $J = 22.0$, 7.0 Hz, 2H), 4.51–4.53 (m, 1H), 4.30–4.35 (m, 2H), 3.73 (s, 3H), 3.37 (s, 3H), 3.33–3.42 (m, 2H), 2.16–2.20 (m, 1H), 1.52–1.93 (m, 9H), 1.38 (s, br, 2H), 1.08 (s, 3H).

Compound **32** was dissolved in dioxane (3 mL), EtOH (3 mL), and 28–30% ammonium hydroxide (6 mL). The solution was heated in a steel bomb at 110 °C for 2 days. The solution was evaporated to dryness and the residue was chromatographed on silica gel (CH_2Cl_2–MeOH = 50:1) to give **33** (156 mg, 83% for two steps) as a white solid: mp 66–68 °C; $[\alpha]_D^{24} = -29.3$ (*c* 0.63, EtOAc); UV (MeOH) λ_{max} 266 nm; ^{1}H NMR ($CDCl_3$) δ 9.27 (s, 1H), 7.31 (d, $J = 8.5$ Hz, 1H), 5.75 (dd, $J = 8.5$, 1.5 Hz, 1H), 4.82–4.88 (m, 1H), 4.76 (t, $J = 6.0$ Hz, 1H), 4.65–4.68 (m, 2H), 4.49 (d, $J = 6.5$ Hz, 1H), 3.41 (dd, $J = 35.0$, 9.0 Hz, 2H), 3.38 (s, 3H), 2.19 (t, $J = 12.0$ Hz, 1H), 1.95–2.00 (m, 1H), 1.77–1.80 (m, 2H), 1.36–1.66 (m, 8H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.20, 150.74, 142.33, 114.25, 102.66, 96.70, 83.21, 82.45, 74.82, 62.70, 55.48, 43.22, 39.76, 36.57, 34.47, 25.07, 23.97, 23.53, 19.44; Anal. Calcd for $C_{19}H_{28}N_2O_6$: C, 59.98; H, 7.42; N, 7.36. Found: C, 59.61; H, 7.45; N, 7.12.

4.1.21. 1-((1*R*,2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-(hydroxymethyl)-4-methylcyclopentyl)pyrimidine-2,4(1*H*,3*H*)-dione 3e. H_2SO_4 (1 M, 1 mL) was added to a solution of compound **32** (100 mg, 0.24 mmol) in dioxane (4 mL), and the mixture was refluxed for 2 h. The volatiles were evaporated under reduced pressure, and the residue was neutralized by methanolic ammonia. The solvent was removed in vacuo and the crude product was purified by preparative silica gel TLC (CH_2Cl_2–MeOH = 4:1) to give **3e** (52 mg, 84%) as a white solid: mp 179–181 °C; $[\alpha]_D^{24} = -42.4$ (*c* 0.46, MeOH); UV (H_2O) λ_{max} 266 nm (8621, pH 11), 268 nm (11,280, pH 7), 267 nm (15,638, pH 2.0); ^{1}H NMR (DMSO-d_6) δ 11.23 (s, 1H, D_2O-exchangeable), 7.70 (d, $J = 8.0$ Hz, 1H), 5.62 (d, $J = 8.0$ Hz, 1H), 4.85–4.87 (m, 2H, D_2O-exchangeable), 4.67–4.73 (m, 1H), 4.55 (d, $J = 4.5$ Hz, 1H, D_2O-exchangeable), 4.17–4.20 (m, 1H), 3.63–3.65 (m, 1H), 3.18–3.27 (m, 2H), 1.47–1.61 (m, 2H), 0.93 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 163.71, 151.85, 143.16, 101.73, 74.19, 73.87, 69.31, 60.37, 43.89, 36.23, 20.22; Anal. Calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.19; H, 6.41; N, 10.57.

4.1.22. 4-Amino-1-((3a′*S*,4′*R*,6′*S*,6a′*R*)-4′-((methoxymethoxy)methyl)-4′-methyltetrahedro-3a′*H*-spiro[cyclohexane-1,2′-cyclopenta[*d*][1,3]dioxole]-6′-yl)pyrimidin-2(1*H*)-one 34. A mixture of **33** (209 mg, 0.55 mmol), 2,4,6-triisopropylbenzenesulfonyl chloride (330 mg, 1.09 mmol), DMAP

(133 mg, 1.09 mmol), and Et_3N (127 μL, 1.09 mmol) in acetonitrile (16 mL) was stirred at rt for 24 h. Ammonium hydroxide (28–32%, 4 mL) was added and the resulting solution was stirred for 5 h. After the solvent was removed in vacuo, the residue was purified by silica gel flash chromatography (CH_2Cl_2–MeOH = 50:1 to 30:1) to give **34** (194 mg, 93%) as a white solid: mp 87–89 °C; UV (MeOH) λ_{max} 278 nm; ^{1}H NMR ($CDCl_3$) δ 7.33 (d, $J = 7.5$ Hz, 1H), 5.74 (d, $J = 7.5$ Hz, 1H), 4.94–4.96 (m, 1H), 4.63–4.66 (m, 3H), 4.54 (d, $J = 7.0$ Hz, 1H), 3.39–3.44 (m, 2H), 3.36 (s, 3H), 2.36 (t, $J = 12.0$ Hz, 1H), 1.91–1.95 (m, 1H), 1.75–1.78 (m, 3H), 1.30–1.66 (m, 9H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.27, 156.04, 144.72, 114.02, 96.67, 94.35, 83.04, 82.62, 75.04, 65.10, 55.36, 43.70, 40.25, 36.26, 34.35, 25.17, 24.01, 23.52, 19.58; Anal. Calcd for $C_{19}H_{29}N_3O_5$: C, 60.14; H, 7.70; N, 11.07. Found: C, 60.25; H, 7.47; N, 10.89.

4.1.23. 4-Amino-1-((1*R*,2*R*,3*S*,4*R*)-2,3-dihydroxy-4-(hydroxymethyl)-4-methylcyclopentyl)pyrimidine-2(1*H*)-one 3f. A solution of **34** (50 mg, 0.13 mmol) in 3 M HCl–MeOH (1:1) was stirred at rt overnight. The reaction mixture was concentrated to dryness under reduced pressure and the residue was neutralized with methanolic ammonia. The solvent was removed in vacuo and the residue was purified by preparative silica gel TLC (CH_2Cl_2–MeOH = 2.5:1) to obtain **3f** (32 mg, 94%) as a white solid: mp >210 °C dec; $[\alpha]_D^{26} = -39.15$ (*c* 0.51, MeOH); UV (H_2O) λ_{max} 285 nm (13,182, pH 2), 276 nm (9035, pH 7), 274 nm (9140, pH 11); ^{1}H NMR (MeOH-d_4) δ 7.75 (d, $J = 7.5$ Hz, 1H), 5.97 (d, $J = 7.5$ Hz, 1H), 4.85–4.87 (m, 1H), 4.42–4.45 (m, 1H), 3.92 (d, $J = 6.0$ Hz, 1H), 3.45 (s, 2H), 1.79–1.84 (m, 2H), 1.09 (s, 3H); ^{13}C NMR (MeOH-d_4) δ 165.74, 143.74, 95.02, 74.66, 74.23, 69.13, 62.80, 60.16, 44.12, 35.47, 18.23; Anal. Calcd for $C_{11}H_{17}N_3O_4 \cdot 0.6H_2O$: C, 49.65; H, 6.89; N, 15.79. Found: C, 49.47; H, 7.01; N, 15.94.

Acknowledgments

This research was supported by the National Institute of Health (NIH) grant I UO 19 AI 056540. We thank Dr. Robert W. Sidwell of Utah University and Dr. Earl R. Kern of University of Alabama for the biological testing.

References

1. Dutschman, G. E.; Grill, S. P.; Gullen, E. A.; Haraguchi, K.; Takeda, S.; Tanaka, H.; Baba, M.; Cheng, Y.-C. *Antimicrob. Agents Chemother.* **2004**, *48*, 1640–1646.
2. Dalton, L. W. *Chrm. Eng. News* **2004**, *82*, 45–53.
3. De Clercg, E. *J. Clin. Viral.* **2004**, *30*, 115–133.
4. *Textbook of AIDS Medicine*; Merigan, T. C., Bartlet, J. G., Bolognesi, D., Eds.; Williams & Wilkins: Baltimore, MD, 1999, pp 751–780.
5. Fischl, M. A. *AIDS* **1999**, *13*, s49–s59.
6. Maag, H.; Rydzewski, R. M.; McRoberts, M. J.; Crawford-Ruth, D.; Verheyden, J. P. H.; Prisbe, E. J. *J. Med. Chem.* **1992**, *35*, 1440–1451.
7. (a) Sugimoto, I.; Shuto, S.; Mori, S.; Shigeta, S.; Matsuda, A. *Bioorg. Med. Chem. Lett.* **1999**, 385–388; (b) Strerath, M.; Cramer, J.; Restle, T.; Marx, A. *J. Am. Chem. Soc.* **2002**, *124*, 11231–11232; (c) Waga, T.; Ohrui, H.; Meguro, H. *Nucleosides Nucleotides* **1996**, *15*, 287; (d) Yamaguchi, T.; Tomikawa, A.; Hirai, T.; Kawaguchi, T.; Ohrui, H.; Saneyoshi, M. *Nucleosides Nucleotides* **1997**, *16*, 1347; (e) Waga, T.; Nishizaki, T.; Ohrui, H.; Meguro, H. *Biosci., Biotechnol., Biochem.* **1993**, *57*, 1433.
8. Kitano, K.; Miura, S.; Ohrui, H.; Meguro, H. *Tetrahedron* **1997**, *53*, 53315–53322.
9. (a) Ohrui, H.; Kohgo, S.; Kitano, K.; Kodama, E.; Yoshimura, K.; Matsuoka, M.; Shigeta, S.; Mitsuya, H. *J. Med. Chem.* **2000**, *43*, 4516–4525; (b) Summerer, D.; Marx, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 869–871; (c) Nomura, M.; Shuto, S.; Tanaka, M.; Sasaki, T.; Mori, S.; Shigeta, S.; Matsuda, A. *J. Med. Chem.* **1999**, *42*, 2901–2908; (d) Kodama, E.; Kohgo, S.; Kitano, K.; Machida, H.; Gatanaga, H.; Shigeta, S.; Matsuoka, M.; Ohrui, H.; Mitsuya, H. *Antimicrob. Agents Chemother.* **2001**, *45*, 1539–1546.
10. Kohgo, S.; Yamada, K.; Kitano, K.; Iwai, Y.; Sakata, S.; Ashida, N.; Hayakawa, H.; Nameki, D.; Kadama, E.; Matsuka, M.; Mitsuya, H.; Ohrui, H. *Nucleosides Nucleotides Nucleic Acids* **2004**, *23*, 671–690.
11. (a) Waga, T.; Ohrui, H.; Meguro, H. *Nucleosides Nucleotides* **1996**, *15*, 287; (b) Yamaguchi, T.; Tomikawa, A.; Hirai, T.; Kawaguchi, T.; Ohrui, H.; Saneyoshi, M. *Nucleosides Nucleotides* **1997**, *16*, 1347; (c) Waga, T.; Nishizaki, T.; Ohrui, H.; Meguro, H. *Biosci., Biotechnol., Biochem.* **1993**, *57*, 1433.
12. (a) Chen, M. S.; Suttmann, R. T.; Wu, J. C.; Prisbe, E. J. *J. Biol. Chem.* **1992**, *267*, 257–260; (b) Chen, M. S.; Suttmann, R. T.; Papp, E.; Cannon, P. D.; McRobierts, M. J.; Bach, C.; Copeland, W. C.; Wang, T. *Biochemistry* **1993**, *32*, 6002–6010.
13. Siddiqui, M. A.; Hughes, S. H.; Boyer, P. L.; Mitsuya, H.; Van, Q. N.; George, C.; Sarafinanos, S. G.; Marquez, V. E. *J. Med. Chem.* **2004**, *47*, 5041–5048.
14. (a) Hegedus, L. S.; Cross, J. *J. Org. Chem.* **2004**, *69*, 8492–8495; (b) Ko, O. H.; Hong, J. H. *Tetrahedron Lett.* **2002**, *43*, 6399–6402; (c) Kim, A.; Hong, J. H. *Nucleosides Nucleotides Nucleic Acids* **2004**, *23*, 813–822; (d) Baik, G. H.; Chung, B. Y.; Oh, C.-H.; Cho, J.-H.; Ko, O. H.; Hong, J. H. *Nucleosides Nucleotides Nucleic Acids* **2003**, *22*, 1781–1788; (e) Kumamoto, H.; Haraguchi, K.; Tanaka, H.; Nitanda, T.; Baba, M.; Dutschman, G. E.; Cheng, Y.-C.; Kato, K. *Nucleosides Nucleotides Nucleic Acids* **2005**, *24*, 73–83.
15. (a) Kato, K.; Suzuki, H.; Tanaka, H.; Miyasaka, T. *Tetrahedron: Asymmetry* **1998**, *9*, 911–914; (b) Kim, H. S.; Jacobson, K. A. *Org. Lett.* **2003**, *5*, 1665–1668; (c) Yin, K.-Q.; Schneller, S. W. *Tetrahedron Lett.* **2006**, *47*, 4057–4059.
16. Liu, P.; Chu, C. K. *Can. J. Chem.* **2006**, *84*, 748–754.
17. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ley, S. V., Eds.; Pergamon Press: New York, 1991; pp 252–278.
18. Choi, W. J.; Moon, H. R.; Kim, H. O.; Yoo, B. N.; Lee, J. A.; Shin, D. H.; Jeong, L. S. *J. Org. Chem.* **2004**, *69*, 3985.
19. Andersson, F.; Samuelsson, B. *Carbohydr. Res.* **1984**, *129*, C1.
20. (a) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025–4028; (b) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349–362.
21. Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
22. Antle, V. D.; Caperelli, C. A. *Nucleosides Nucleotides* **1999**, *18*, 1911–1928.
23. (a) Shealy, Y. F.; O'Dell, C. A. *J. Heterocycl. Chem.* **1976**, *13*, 1015–1020; (b) Lin, T.-S.; Zhang, X.-H.; Wang, Z.-H.; Prusoff, W. H. *J. Med. Chem.* **1988**, *31*, 484–486.
24. Wang, P.; Agrofoglio, L. A.; Newton, M. G.; Chu, C. K. *J. Org. Chem.* **1999**, *64*, 4173–4178.
25. Shuto, S.; Obara, T.; Saito, Y.; Andrei, G.; Snoeck, R.; De Clercq, E.; Matsuda, A. *J. Med. Chem.* **1996**, *39*, 2392–2399.

26. (a) *Crystal data of* **3d**: $C_{12}H_{18}N_2O_5$, $M = 270.28$, monoclinic, space group $P2(1)$, $a = 7.888(2)$, $b = 6.293(1)$, $c = 12.513(3)$ Å, $\beta = 94.02(3)°$, $V = 619.6(2)$ Å^3, $T = 293$ K, $Z = 2$, $R1 = 0.0442$ for $948F_o > 4\text{sig}(F_o)$ and 0.0456 for all 981 data. CCDC 628156 contains the supplementary crystallographic data. These data can be obtained free of charge from www.ccdc.cam.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; e-mail: deposit@ccdc.cam.ac.uk]; (b) Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.