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8-METHYL DERIVATIVES OF ARISTEROMYCIN, NEPLANOCIN, 3-DEAZANEPLANOCIN AND RELATED ANALOGS

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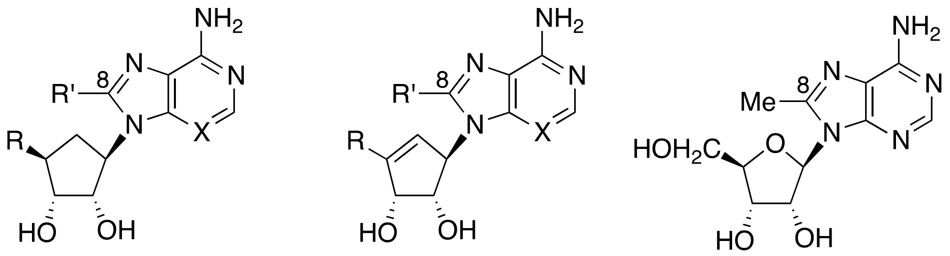
Abstract – The promising biological properties of 8-methyladenosine prompted a study of the related carbocyclic analogs based on aristeromycin and neplanocin. These target compounds have been prepared from strategically protected parent carbocyclic nucleoside derivatives or built up from suitable cyclopentanols and cyclopentenols. Several of these nucleosides were evaluated against a variety of RNA and DNA viruses to determine the potential of the 8-methyl series as a source for new antiviral agents. Encouraging results towards Epstein-Barr virus, cowpox, vaccinia virus, Ebola, and the flaviviruses (dengue and yellow fever) suggests more extensive studies.

INTRODUCTION

Because of the biological and therapeutic potential of aristeromycin (**1a**)[1] and neplanocin A (**2a**)[2] (Figure 1) numerous structural modifications have been carried out on these prototype structures[1b,3] including their 3-deaza congeners (**3a** and **4a**).[3a,4] Limited in that regard, however, has been attention to the purine C-8 center of **1a** and **2a**.[5] The promising antiviral activity of 8-methyladenosine (**5**)[6] suggested that the 8-methyl derivatives **1b-d**/**2b-c** and **3b**/**4b-d** would be worthy targets. These derivatives represent the focus of this report.



1 series X=N; **3** series X=CH

1a, R=CH_2OH; R'=H
b, R=CH_2OH; R'=Me
c, R=H; R'=Me
d, R=OH; R'=Me[5]

3a, R=CH_2OH; R'=H
b, R=CH_2OH; R'=Me

2 series X=N; **4** series X=CH

2a, R=CH_2OH; R'=H
b, R=CH_2OH; R'=Me
c, R=H; R'=Me

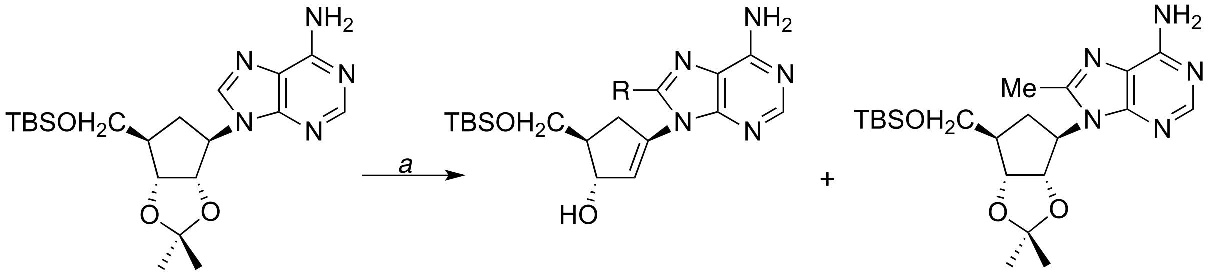
4a, R=CH_2OH; R'=H
b, R=CH_2OH; R'=Me
c, R=CH_2CH_2OH; R'=Me
d, R=H; R'=Me

5

Figure 1

RESULTS AND DISCUSSION

Chemistry. Our initial plan to the 8-methyl targets considered C-8 lithiation followed by methyl iodide alkylation. Thus, reaction of **6**[7] using 5 equivalents of lithium di*iso*propylamide (LDA) and subsequent treatment with methyl iodide provided the desired precursor **7** (Scheme 1) (37%). A careful analysis of the product mixture revealed two additional products, **8** and **9**, which likely[8] arose from elimination as illustrated with structure **i** (Figure 2). Acidic deprotection of **7** yielded **1b**.



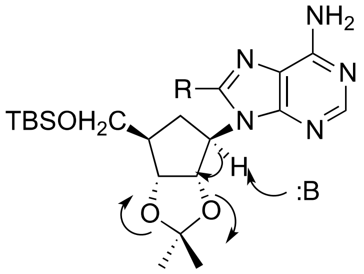
6[7]

8, R=Me
9, R=H

7 $\xrightarrow{b}$ **1b**

[a]Reagents and conditions: *a*, LDA then MeI, THF, 37% for **7**, 8% for **8,** 25% for **9**; *b*, 1 N HCl in MeOH, 95%.

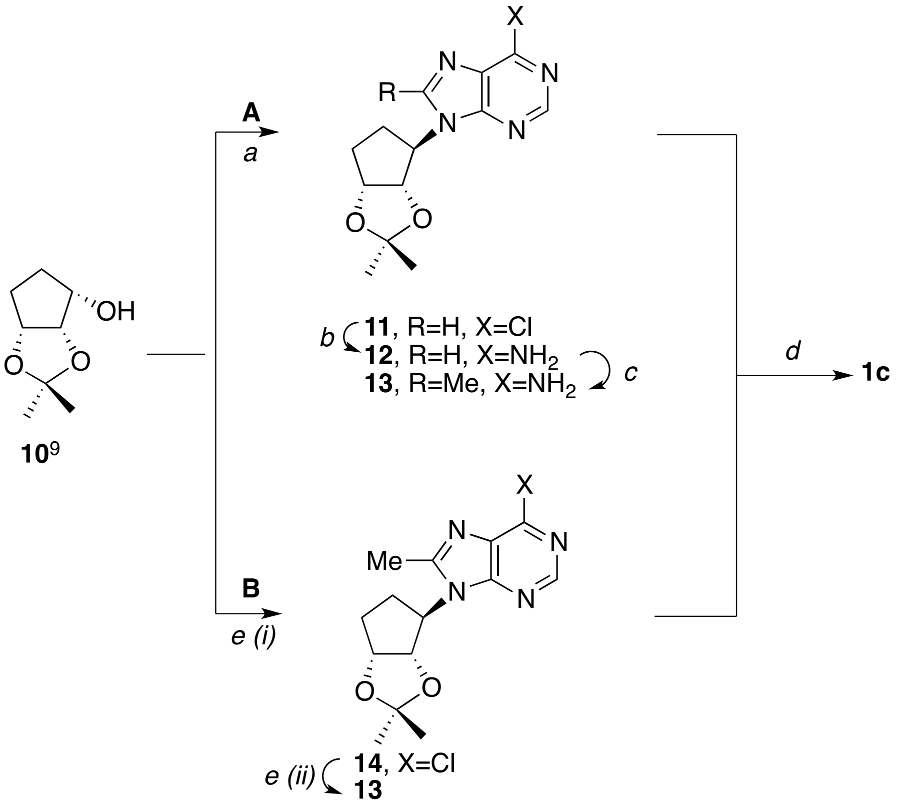
Scheme 1[a]



i (R=Me, H)

Figure 2

Initially, a similar approach to **1c** was undertaken by subjecting the protected cyclopentanol **10**[9] to a Mitsunobu reaction[10] with 6-chloropurine to give **11** (Scheme 2). Ammonolysis of **11** to **12** followed by, first, LDA and then methyl iodide yielded **13**. Deprotection of **13** produced the desired **1c**.

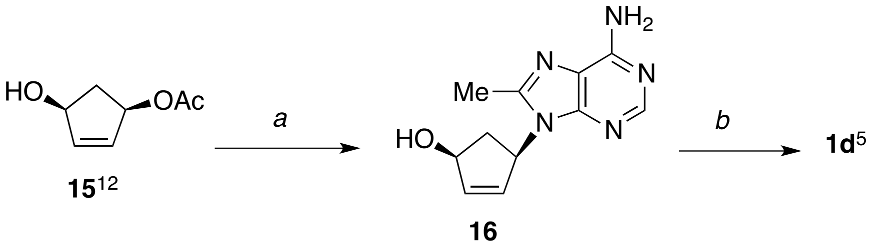


^{a}Reagents and conditions: *a,* 6-chloropurine, Ph_3P, DIAD, THF, 86%; *b*, NH_3 in MeOH, 120 °C, 91%; *c*, LDA then MeI, THF, 43%; *d*, 1N HCl in MeOH, 92% from **13**; *e*, (i) 6-chloro-8-methylpurine, Ph_3P, DIAD, THF; (ii) NH_3 in MeOH, 120 °C, 57% from **10** to **13**.

Scheme 2^a

To shorten the pathway to **1c** and, at the same time, address the low yield of the LDA/methyl iodide reaction (as, possibly, due to unwanted elimination products as illustrated in Figure 2), **10**[9] was reacted with 6-chloro-8-methylpurine[11] in a Mitsunobu process[10] to give **14** (Scheme 2). Amination of **14** resulted in **13**, which was deprotected as before to produce **1c**.

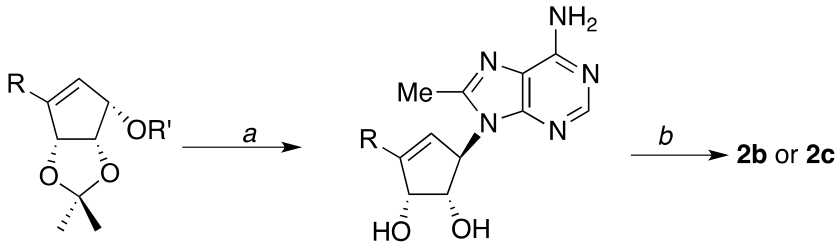
Analog **1d** arose from the palladium catalyzed coupling of the allylic acetate **15**[12] with 8-methyladenine[13] to result in **16** (Scheme 3). Dihydroxylation of **16** produced **1d**.[5]



[a]Reaction conditions: *a,* 8-methyladenine, NaH, $Pd(PPh_3)_4$, PPh_3, DMSO, 48%; *b*, NMO, OsO_4, THF/H_2O, 70%.[5]

Scheme 3[a]

Achieving targets **2b** and **2c** began with mesylation of the requisite allylic alcohols **17a**[14] and **18a**[15] to **17b** and **18b**, respectively (Scheme 4). Reaction of these mesylates with the sodium anion of 8-methyadenine[13] produced **19** and **20**. Deprotection of **19** with trifluoroacetic acid and **20** with hydrochloric acid formed **2b** and **2c**, respectively.



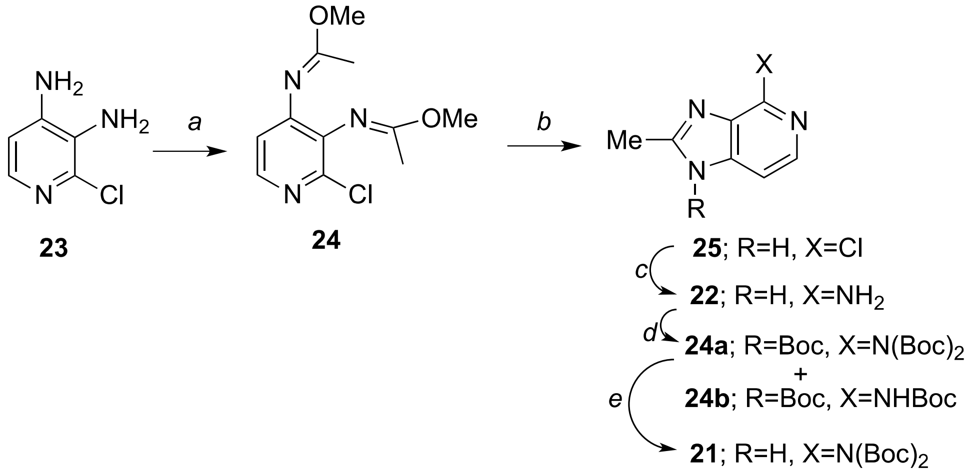
17a, R=CH_2OTBS; R'=H[9]
b, R=CH_2OTBS; R'=Ms
18a, R=R'=H
b, R=R'=Ms

19, R=CH_2OTBS[9]
20, R=H

[a]Reagents and conditions: *a*, (i) MsCl, Et_3N, DMAP, CH_2Cl_2; (ii) NaH, 8-methyladenine, 15-C-5, DMF; *b*, **19**, TFA, H_2O, 35% for 3 steps from **17**; *c*, **20**, 1N HCl in MeOH, 36% from **18a**.

Scheme 4[a]

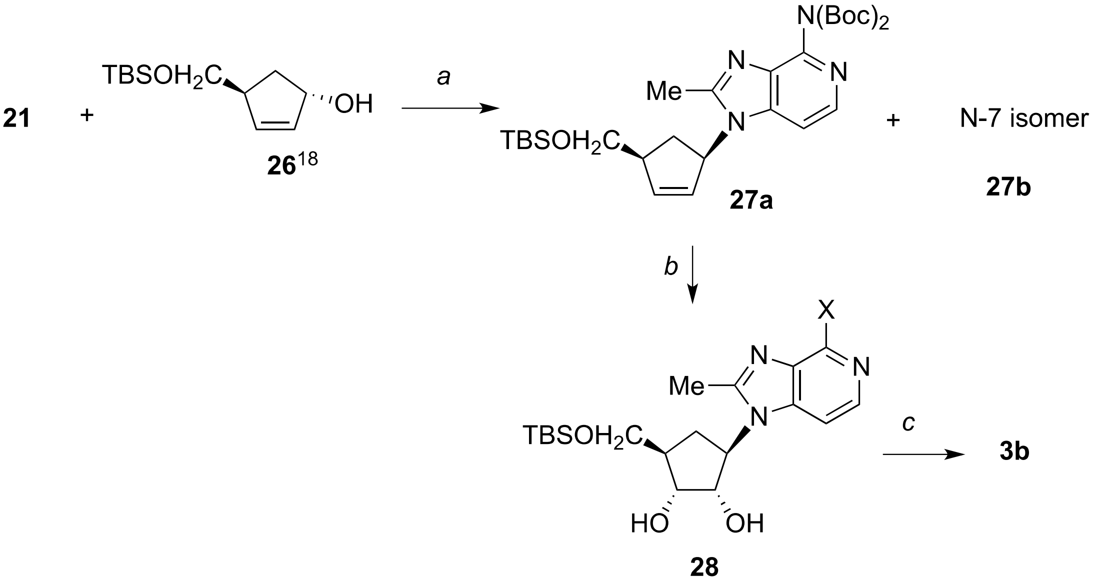
The synthesis of targets **3b** and **4b-c** required[16] the bis-Boc protected 8-methyl-3-deazaadenine (**21**) (Scheme 5) for subsequent Mitsunobu processes. For this purpose, the availability of 6-chloro-8-methyl-3-deazaadenine (**22**) was required, which was accomplished from 3,4-diamino-2-chloropyridine (**23**) via the bis-imino vinyl ether **24** using a more accessible route (Scheme 5) than reported in the literature.[17] Reaction of **22** with di-*tert*-butyl dicarbonate gave a mixture of **24a** and **24b** in 9:1 ratio (Scheme 5). Upon separation, treatment of **24a** with tetrabutylammonium fluoride yielded the requisite **21**.



[a]Reaction conditions: *a,* $MeC(OMe)_3$, formic acid, 78%; *b,* NaOH, H_2O, 96%; *c*, NH_2NH_2, propan-1-ol, Raney Ni, 92%; *d*, $(Boc)_2O$, DMAP, THF, for **24a**, 83%; *e*, TBAF, THF, 81%.

Scheme 5[a]

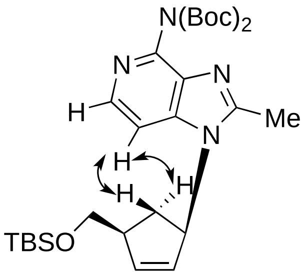
Mitsunobu coupling of **21** with the cyclopentenol **26**[18] resulted in a mixture of N-9 and N-7 products (**27a** and **27b**, Scheme 6) followed by dihydroxylation of separated **27a** to **28** and removal of protecting groups yielded **3b**.



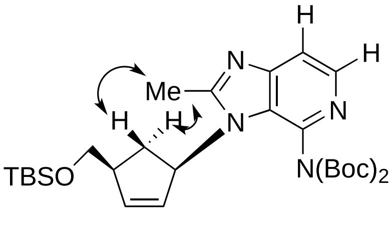
[a]Reaction conditions: *a,* Ph_3P, DIAD, THF, **27a** for 48%, **27b** for 12%; *b,* NMO, OsO_4, CH_2Cl_2/H_2O, 83%; *c*, HCl, MeOH, 70%.

Scheme 6[a]

Structural distinction of **27a** and **27b** was accomplished by NOESY spectral analysis (Figure 3). The methyl group on the C-8 position of **27a** can be expected[19] to give a *syn* conformation while the N-7 is **27b** would be in the more preferred *anti* conformation due to the bulky Boc protecting group on the C-6 position.[19] A consequence of these conformations a strong NOESY relationship between the hydrogen at C-3 with the C-6' hydrogens in **27**a and a NOESY correlation between he C-8 methyl group and the C-6 protons of **27b** was seen.



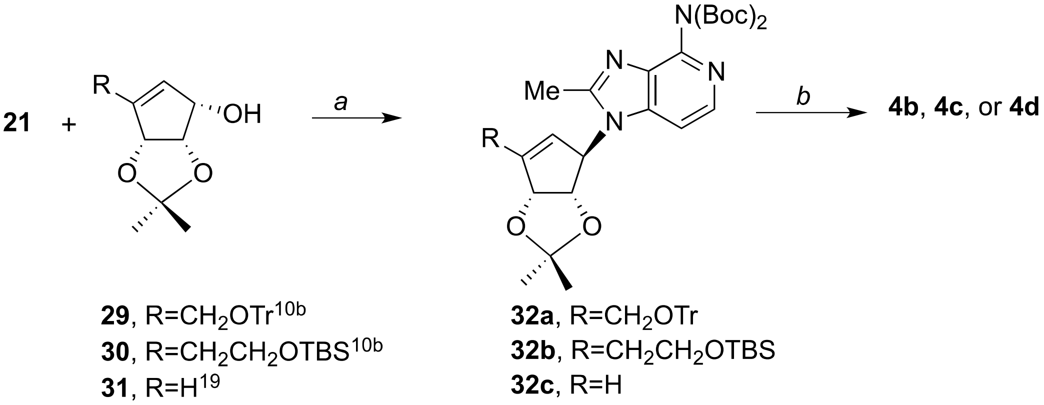
27a



27b

Figure 3

Similarly, with one less step and no N-7 product contamination, Mistunobu coupling of **21** with the cyclopentenols **29**,[10b] **30**,[10b] and **31**[20] produced **32a-c** (Scheme 7). Deprotection of the latter three products gave the sought **4b-d**.



[a]Reaction conditions: *a*, Ph_3P, DIAD, THF, **32a** for 68%, **32b** for 48%, **32c** for 77%; *b*, HCl, MeOH, **4b** for 78%, **4c** for 80%, **4d** for 65%.

Scheme 7[a]

Antiviral results. Compounds **1b**, **1c**, **1d**, **2b** and **2c** were subjected to broad spectrum antiviral analysis (positive controls included within each result).[21] Compound **1b** was active against EBV (IC_{50}, 10.3 µg/mL; cidofovir, IC_{50}, 1.0 µg/mL; CC_{50} >50 µg/mL), cowpox virus (IC_{50}, 43.1 µg/mL; CC_{50}, >50 µg/mL; cidofovir, IC_{50}, 1.0 µg/mL; CC_{50} >100 µg/mL) and vaccinia virus (IC_{50}, 14.2 µg/mL; CC_{50}, >100 μg/mL; cidofovir, IC_{50}, 1.3 μg/mL; CC_{50} >100 μg/mL). Compound **2c** displayed activity against Ebola virus (IC_{50}, 2.3 μg/mL; CC_{50}, 20 μg/mL; Favipiravir, IC_{50}, 155 μg/mL; CC_{50} >1000 μg/mL).

Most significantly, compound **1c** exhibited potent antiviral properties against several virus species in the *flaviviridae* family (Vis = visual; NR = neutral red: dengue, IC_{50}, Vis 1.9 μg/mL; NR 5.3 μg/mL; and, yellow fever, IC_{50} Vis, 10 μg/mL, NR, 8.0 μg/mL.

The controls for these assays were: dengue (6-azauridine, IC_{50}, 0.25 μg/mL; 47.7 μg/mL) and yellow fever (Infergen, IC_{50}, 3.8×10^{-5} μg/mL; CC_{50} >0.01 μg/mL. The CC_{50} for the flavi assays >100 μg/mL.

Compounds **1d** and **2b** were inactive while the antiviral data for **3b**, and **4b-c** will be the subject of future work.

Conclusion. A class of novel 8-methylated adenine-derived carbocyclic nucleoside analogs have been successfully synthesized. The convergent syntheses reported provides guidelines for further functionalization at the purine C-8 position. The meaningful antiviral activity for **1b**, **1c**, and **2c** offers new structural leads for viral drug therapeutic discovery, which precedence[22] suggests will be a fruitful pursuit. Furthermore, an analysis[19,23] of the conformational preference (*syn* versus *anti*) of the 8-methylated targets described may provide for a correlation with their antiviral activity for extension into other C-8 derivatives and into the 3-deazapurine series (represented by **3b** and **4b-d**).[24]

EXPERIMENTAL

Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV- 400 spectrometer (operated at 400 or 250 MHz, respectively). All ^1H chemical shifts are reported in δ relative to internal standard tetramethylsilane (TMS, δ 0.00). ^{13}C chemical shifts are reported in δ relative to $CDCl_3$ (center of triplet, δ 77.23) or relative to DMSO-d_6 (center of septet, δ 39.51). The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublet) and br (broad). The mass spectral data was determined using a Waters Micromass Q-TOF Premier Mass Spectrometer. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Georgia. Reactions were monitored by thin layer chromatography (TLC) using 0.25 mm E. Merck silica gel 60-F_{254} precoated silica gel plates with visualization by irradiation with a Mineral light UVGL-25 lamp or exposure to iodine vapor. Column chromatography was performed on Whatman silica gel (average particle size 5-25 μm, 60 Å) and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials. The reactions were generally carried out in a N_2 atmosphere under anhydrous conditions.

9-[(1′*R*,2′*S*,3′*R*,4′*R*)-2′,3′-Dihydroxy-4′-(hydroxymethyl)cyclopent-1′-yl]-8-methyladenine (1b). Di*iso*propylamine (2.5 mL, 17.5 mmol) was added to a solution of 2.5 M BuLi (7.0 mL, 17.5 mmol) in

THF (25 mL) at -78 ºC. The resulting mixture was stirred for 5 min, and then a solution of **6**[7] (1.48 g, 3.50 mmol) in THF (15 mL) was added. After the dark solution was stirred for 30 min, MeI (0.6 mL, 10.5 mmol) was added. The reaction mixture was stirred at -78 ºC for additional 3 h and quenched by sat. aq. NH_4Cl solution. Following extraction with EtOAc, the organic phase was washed with brine and dried (anhydrous $MgSO_4$). Filtration and concentration followed by purification by column chromatography (twice) (EtOAc-hexanes, 4:1, then CH_2Cl_2-MeOH, 30:1) gave **7** (560 mg, 37%), **8** (30 mg, 8%) and **9** (90 mg, 25%) as white solids.

9-[(1′*R*,2′*S*,3′*R*,4′*R*)-2′,3′-*O*-*Iso*propylidene-4′-(*tert*-butyldimethylsilyloxymethyl)cyclopent-1′-yl]-8-methyladenine (7): ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.17 (s, 1H), 6.41 (s, 2H), 5.25-5.20 (m, 1H), 4.68-4.56 (m, 2H), 3.76-3.73 (m, 2H), 2.85-2.79 (m, 1H), 2.56 (s, 3H), 2.32-2.28 (m, 1H), 2.15-2.09 (m, 1H), 1.51 (s, 3H), 1.25 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.0, 151.8, 151.1, 149.3, 118.9, 113.3, 83.0, 80.8, 63.4, 61.8, 46.3, 32.7, 27.9, 25.9, 25.4, 18.4, 14.7, -5.3. Anal. Calcd for $C_{21}H_{35}N_5O_3Si\cdot 0.7H_2O$: C, 56.52; H, 8.24; N, 15.70. Found: C, 56.81; H, 7.96; N, 15.63.

9-[(3′*S*,4′*R*)-2′-Hydroxy-4′-(*tert*-butyldimethylsilyloxymethyl)cyclopent-1′-en-1′-yl]-8-methyladenine (8): ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.29 (s, 1H), 5.99 (m, 3H), 4.92 (m, 1H), 3.86-3.73 (m, 3H), 3.03-3.00 (m, 1H), 2.72-2.64 (m, 1H), 2.57 (s, 3H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.8, 152.6, 151.4, 149.0, 137.6, 129.4, 119.0, 78.1, 64.6, 50.1, 35.1, 26.1, 18.5, 15.3, -5.2.

9-[(3′*S*,4′*R*)-2′-Hydroxy-4′-(*tert*-butyldimethylsilyloxymethyl)cyclopent-1′-en-1′-yl]-adenine (9): ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.86 (s, 1H), 6.62 (s, 1H), 6.37 (s, 2H), 4.87 (br, 1H), 3.75 (d, *J*=6.3 Hz, 2H), 3.19-3.08 (m, 1H), 2.74-2.65 (m, 1H), 2.54-2.46 (m, 1H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.9, 153.7, 150.1, 138.4, 136.5, 120.4, 119.5, 78.5, 64.5, 49.2, 33.8, 26.1, 18.5, -5.2.

To a solution of **7** (390 mg, 0.90 mmol) in MeOH (8 mL) was added 1 N HCl (8 mL) and this was stirred at room temperature for 3 h. This reaction mixture was then neutralized with Amberlite IR-67 resin. Filtration and evaporation followed by flash chromatography (MeOH–EtOAc, 1:5) afforded **1b** (240 mg, 95%) as a white solid, mp 216-218 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.00 (s, 2H), 4.84 (d, *J*=6.5 Hz, 1H), 4.74 (m, 1H), 4.64-4.53 (m, 3H), 3.82 (br, 1H), 3.53-3.34 (m, 2H), 2.50 (s, 3H), 2.10-2.06 (m, 3H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 155.0, 151.0, 150.4, 149.4, 118.1, 73.1, 71.5, 63.3, 60.3, 45.7, 27.1, 14.3. Anal. Calcd for $C_{12}H_{17}N_5O_3\cdot 1.2H_2O$: C, 47.89; H, 6.51; N, 23.28. Found: C, 47.96; H, 6.48; N, 23.03. EI-MS $[M]^+$ Calcd: 279.1330; Found: 279.1331.

9-((3a*S*,4*R*,6a*R*)-Tetrahydro-2,2-dimethyl-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-9*H*-purin-6-amine (12). To a stirred suspension of 6-chloropurine (3.07 g, 20 mmol) and triphenylphosphine (5.24 g, 20 mmol) in THF (20 mL) at 0 °C di*iso*propyl azodicarboxlate (DIAD) (4.08 g, 20 mmol) was added dropwise. To this mixture was added a solution of **10**[9] (2.8 g, 18.4 mmol) in dry THF (20 mL). The new mixture was stirred at 55 °C for 48 h and concentrated under reduced pressure (4.5 g, 86%). The residue was purified by column chromatography (hexanes-EtOAc, 4:1 to 2:1) to provide **11** as a white solid, mp 97-98 °C; ^{1}H NMR (CDCl$_3$, 250 MHz) δ 8.78 (s, 1H), 8.08 (s, 1H), 5.02 (m, 2H), 4.95 (dd, *J*=7.1, 3.9 Hz, 1H), 2.61 (m, 1H), 2.24-2.15 (m, 3H), 1.57 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (CDCl$_3$, 62.5 MHz) δ 152.4, 152.0, 151.7, 144.2, 132.4, 111.9, 85.2, 81.0, 63.4, 31.8, 29.9, 27.0, 24.6. Anal. Calcd for $C_{13}H_{15}ClN_4O_2$: C, 52.98; H, 5.44; N, 19.01; Cl, 12.03. Found: C, 52.90; H, 5.13; N, 18.79; Cl, 12.08.

A solution of **11** (1.0 g, 3.4 mmol) in dry MeOH (30 mL) was saturated with NH_3 and this mixture was kept at 120 °C for 48 h in a Parr stainless steel, sealed reaction vessel. The reaction mixture was then evaporated under reduced pressure and the residue purified by column chromatography (EtOAc-MeOH, 20:1) to give **12** (0.85 g, 91%), mp 193-195 °C; ^{1}H NMR (CDCl$_3$, 250 MHz) δ 8.35 (s, 1H), 7.87 (s, 1H), 5.84 (brs 2H), 5.01 (m, 2H), 4.84 (d, *J*=5.52 Hz, 1H), 2.54 (m, 1H), 2.26 (m 3H), 1.54 (m, 3H), 1.28 (s, 3H); ^{13}C NMR (CDCl$_3$, 62.5 MHz) δ 155.5, 153.0, 152.0, 139.0, 120.0, 111.2, 85.0, 80.7, 62.2, 31.4, 29.5, 26.6, 24.2. Anal. Calcd for $C_{13}H_{17}N_5O_2$: C, 55.12; H, 6.36; N, 24.73. Found: C, 55.15; H, 6.29; N, 24.66.

9-((3a*S*,4*R*,6a*R*)-Tetrahydro-2,2-dimethyl-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-8-methyl-9*H*-purin-6-amine (13). By method A: Di*iso*propylamine (1.63 mL, 12.0 mmol) was added to a solution of *n*-butyllithium (4.8 mL, 2.5 M in hexanes, 12 mmol) in dry THF (20 mL) at -78 °C. The resulting mixture was stirred for 5 min, then a solution of **12** (650 mg, 2.36 mmol) in dry THF (10 mL) was added. The resultant yellow reaction mixture was stirred for 30 min and then methyl iodide (0.9 mL, 13.1 mmol) was added. This reaction mixture was stirred at same temperature for 3 h before it was treated with sat. aq. NH_4Cl (15 mL). Following extraction of this mixture with EtOAc (3×20 mL), the organic solution was washed with ice H_2O (2 × 20 mL) and the EtOAc dried (anhydrous Na_2SO_4). The organic layer was filtered and concentrated under reduced pressure to give a yellow oil that was purified by column chromatography (EtOAc-MeOH, 30:1 to 2:1) to give desired product contaminated (^{1}H NMR) with a small amount of starting material. Purification by recrystallization (EtOAc) gave **13** (310 mg, 43%) as a yellow solid, mp 200-202 °C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.22 (s, 1H), 5.45 (brs, 2H), 5.35 (d, *J*=5.74 Hz, 1H), 5.15 (m, 1H), 4.53 (m, 1H), 2.63 (s, 3H), 2.37 (m, 2H), 2.10 (m, 1H), 2.00 (m, 1H), 1.54 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 154.4, 151.7, 151.0, 149.6, 118.7, 110.0, 84.2, 81.6, 63.0, 31.4, 30.6, 26.9, 24.4, 14.8. Anal. Calcd for $C_{14}H_{19}N_5O_2\cdot 0.1H_2O$: C, 57.74; H, 6.59; N, 24.06. Found: C, 57.63; H, 6.63; N, 24.11.

By method B: To a stirring suspension of 6-chloro-8-methylpurine[11] (0.41 g, 2.44 mmol) and triphenylphosphine (0.93 g, 3.80 mmol) in THF (20 mL) at 0 °C DIAD (0.76 g, 3.80 mmol) was added dropwise. To this mixture was then added a solution of **10** (500 mg, 3.16 mmol) in dry THF (20 mL). This new mixture was stirred at 55 °C for 48 h and concentrated under vacuum. The residue was purified by column chromatography (hexanes-EtOAc, 4:1 to 2:1) to result in a yellow oil (800 mg) contaminated with hydrazine by-product.

A solution of the above oil in dry MeOH (30 mL) saturated with NH_3 was kept at 120 °C for 48 h in a Parr stainless steel, sealed reaction vessel. The reaction mixture was evaporated to dryness and the residue was evaporated and the residue was purified by column chromatography (EtOAc-MeOH, 20:1) to **13** (0.4 g, 57%) whose NMR spectral data was identical to **13** from method A.

(1*R*,2*S*,3*R*)-3-(6-Amino-8-methyl-9*H*-purin-9-yl)cyclopentane-1,2-diol (1c). Compound **13** (300 mg, 1.09 mmol) was for 0.5 h and then evaporated to dryness under reduced pressure. The residue was then dissolved in MeOH (10 mL) and neutralized with IRA-67 resin. The residue from a subsequent evaporation was purified by column chromatography (MeOH–EtOAc, 1:5) to give **1c** (250 mg, 92 %) as white solid, mp >220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (s, 1H), 7.00 (brs, 2H), 4.90 (d, *J*=6.79 Hz, 1H), 4.69 (d, *J*=3.35 Hz, 1H), 4.57 (m, 2H), 4.00 (s, 1H), 2.48 (s, 3H), 2.28 (m, 3H), 1.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.1, 151.1, 149.4, 146.2, 117.5, 75.5, 70.7, 60.1, 29.2, 23.8, 14.3. Anal. Calcd for $C_{11}H_{15}N_5O_2 \cdot 0.55\ H_2O$: C, 50.75 H, 6.22 N, 26.82. Found: C, 50.82 H, 5.98 N, 26.55. EI-MS $[M]^+$ Calcd: 249.1221; Found: 249.1226.

(1*S*,2*R*,3*S*,4*R*)-4-(6-Amino-8-methyl-9*H*-purin-9-yl)cyclopentane-1,2,3-triol (1d). To a solution of 8-methyladenine[13] (319 mg, 2.1 mmol) in DMSO (5 mL) was added NaH (2.1 mmol). After the mixture was stirred at room temperature for 0.5 h, $Pd(PPh_3)_4$ (228 mg, 0.2 mmol), triphenylphosphine (78.6 mg, 0.3 mmol) and **15** (426 mg, 3.0 mmol) in THF (20 mL) was added. The resulting mixture was then stirred at 50 °C for 48 h and evaporated to dryness. The black residue was treated with H_2O (10 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layers were dried (anhydrous Na_2SO_4), filtered and the filtrate concentrated under reduced pressure. The resultant residue was purified by column chromatography (MeOH-CH_2Cl_2, 1:10) to give a white solid (320 mg, 48%), which was assumed to be **16** and was used directly in next reaction.

To an ice-H_2O cooled solution of the above solid (320 mg, 1.42 mmol) in THF/H_2O (20 mL, 10:1) was added *N*-methylmorpholine *N*-oxide (0.6 mL, 50% aqueous) and osmium tetroxide (20 mg). This mixture was then stirred at room temperature for 24 h and the solvent removed under reduced pressure. Purification of the residue by column chromatography (MeOH-EtOAc, 4:1) provided **1d** as a white solid (260 mg, 70%), which was purified by recrystalization from MeOH and hexanes, mp >250 °C (dec.). The NMR data agree with reported value.[5] Anal. Calcd for $C_{11}H_{15}N_5O_3 \cdot 0.58\ H_2O$: C, 47.87; H, 5.86; N, 25.38. Found: C, 48.26; H, 5.74; N, 24.99. EI-MS $[M]^+$ Calcd: 265.1175; Found: 265.1175.

(1*S*,2*R*,5*R*)-5-(6-Amino-8-methyl-9*H*-purin-9-yl)-3-(hydroxymethyl)-cyclopent-3-ene-1,2-diol (2b). To a solution of **17a**[14] (1.13 g, 4.0 mmol) and triethylamine (0.80 mL) in anhydrous CH_2Cl_2 (20 mL) was added MsCl (0.33 mL, 4.48 mmol) at 0 °C. The reaction mixture became a yellow solution after stirring 1 h at room temperature. It was then diluted with CH_2Cl_2 (20 mL) and washed with ice H_2O (20 mL), dried (anhydrous Na_2SO_4) and filtered. Evaporation of filtrate provided a sticky yellow oil (1.40 g; assumed to be **17b**), which was used directly for the next step.

To a solution of 8-methyladenine[13] (752 mg, 4.48 mmol) in dry DMF (20 mL) was added NaH (108 mg, 4.48 mmol) and 15-crown-5 (0.1 mL). This mixture became a clear dark solution after 0.5 h at room temperature and the above yellow oil in DMF (20 mL) was added. The reaction mixture was then kept at 80 °C for 36 h and then evaporated under reduced pressure to give a black residue. Water (20 mL) was added and aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried (anhydrous $NaSO_4$), filtered and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography with (CH_2Cl_2-MeOH, 20:1 to 1:1) to give a yellow oil (assumed to be **19**), which was contaminated with 15-crown-5. ^{1}H NMR (DMSO-d_6, 250 MHz) δ 7.27 (s, 1H), 5.82 (s, 1H), 5.50 (s, 2H), 5.60 (s, 1H), 5.35 (d, *J*=6.0 Hz, 1H), 4.72 (d, *J*=6.0 Hz, 1H), 4.20 (m, 2H), 2.03 (s, 3H), 1.49 (s, 3H), 1.37 (s, 3H), 1.27 (s, 9H), 0.06 (s, 6H).

This oil was dissolved in trifluoroacetic acid and H_2O (20 mL, 1:1). This mixture was stirred at overnight for 0.5 h and then evaporated to dryness under reduced pressure. The residue was then dissolved in MeOH and neutralized with IRA-67 resin and this mixture evaporated to dryness under reduced pressure. The residue was purified by column chromatography (EtOAc-MeOH, 5: 1) to give **2b** (380 mg, 35%) as a yellow solid (recrystallized from MeOH-ether), mp >210°C (dec.); ^{1}H NMR (DMSO-d_6, 250 MHz) δ 8.01 (s, 1H), 7.00 (brs, 2H), 5.69 (s, 1H), 5.32 (m, 1H), 5.08 (d, *J*=7.5 Hz, 1H), 4.92 (m, 2H), 4.49 (q, *J*=7.5 Hz, 1H), 4.36 (m, 1H), 4.10 (s, 2H), 2.50 (s, 3H); ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ 154.9, 151.3, 150.7, 149.9, 147.6, 124.4, 117.7, 75.4, 71.7, 69.7, 64.4, 14.7. Anal. Calcd for $C_{12}H_{15}N_5O_3 \cdot 0.34MeOH$: C, 51.42 H, 5.44; N, 24.31. Found: C, 51.45 H, 5.66 N, 24.31. EI-MS $[M]^+$ Calcd: 277.1172; Found: 277.1175.

(1*S*,2*R*,5*R*)-5-(6-Amino-8-methyl-9*H*-purin-9-yl)cyclopent-3-ene-1,2-diol (2c). Following the procedure for preparing **17b**, to a solution of **18a**[15] (700 mg, 4.48 mmol), triethylamine (0.80 ml) in anhydrous CH_2Cl_2 (20 mL) was added MsCl (0.35 mL, 4.48 mmol) at 0 °C to give **18b** as a sticky yellow oil, which was directly used in the next step.

Following the preparation of **19**, a solution of 8-methyladenine[13] (752 mg, 4.48 mmol) in dry DMF (20 mL) containing NaH (108 mg, 4.48 mmol) and 15-crown-5 (0.1 mL) was stirred for 0.5 h at room temperature and the **18b** in DMF (20 mL) was added. The reaction was then kept at 80 °C for 36 h and evaporated to give a black residue. H_2O (20 mL) was added and aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried (anhydrous Na_2SO_4), filtered and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography with (EtOAc-MeOH, 20:1 to 5:1) to give a yellow oil, which was contaminated with 15-crown-5. This oil was dissolved in 1 N HCl in MeOH (total volume 20 mL). This mixture was stirred at room temperature for 0.5 h and then evaporated to dryness under reduced pressure. The residue was dissolved in MeOH and neutralized with IRA-67 resin. The residue following evaporation of the solvent was purified by column chromatography (MeOH-EtOAc, 1:5) to give **2c** (400 mg, 36 %) as a yellow solid, mp >202 °C (dec.); ^{1}H NMR (DMSO-d_6, 250 Hz) δ 7.98 (s, 1H), 6.99 (brs, 2H), 6.04 (m, 2H), 5.31 (m, 1H), 5.05 (d, *J*=7.8 Hz, 1H), 4.91 (d, *J*=5.7 Hz, 1H), 4.46-4.37 (m, 2H), 2.49 (s, 3H); ^{13}C NMR (DMSO-d_6, 62.5 Hz) δ 151.3, 150.7, 149.0, 140.9, 133.8, 133.6, 117.8, 75.5, 72.0, 69.8, 14.5. Anal. Calcd for $C_{11}H_{13}ClN_5O_2 \cdot 0.25\ H_2O$: C, 45.83; H, 4.68; N, 24.30. Found: C, 46.15; H, 4.81; N, 24.02. EI-MS [M]$^+$ Calcd: 247.1062; Found: 247.1069.

4-(bis(*tert*-Butoxycarbonyl)amino)-2-methyl-1*H*-imidazo[4,5-*c*]pyridine-1-carboxylate (21). 2-Chloro-3,4-diaminopyridine (**23**, 10.0 g, 69.6 mmol) was added to trimethyl orthoacetate (161 mL) and the mixture was heated to 80 °C. After the solution was mostly clear, formic acid (4.2 mL) was added dropwise and the solution was continued to heat to 100 °C for 8 h. Upon cooling to room temperature, the solvent was evaporated and the crude product purified by column chromatography (EtOAc-hexanes, 1:1) to give **24** (13.9 g, 78.0%) as white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.87 (d, *J*=5.2 Hz, 1H), 6.56 (d, *J*=5.2 Hz, 1H), 3.71 (s, 3H), 3.64 (s, 3H), 1.74 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 164.0, 162.2, 148.9, 143.7, 133.8, 116.4, 116.3, 53.8, 53.7, 17.3, 17.0.

Compound **24** (13.9 g, 54.36 mmol) was dissolved in aqueous NaOH solution (1.5 N, 110 mL) and the reaction mixture was heated to reflux for 10 min. After cooling to the room temperature the solution was extracted by EtOAc (4 × 100 mL). The combined organic phases were dried (anhydrous Na_2SO_4). The solvent was evaporated and the crude product purified by column chromatography (EtOAc-MeOH, 8:1) to give **25** (11.2 g, 96.0%) as white solid. ^{1}H NMR (400 MHz, MeOD) δ 8.07 (d, *J*=5.6 Hz, 1H), 7.49 (d, *J*=5.6 Hz, 1H), 2.64 (s, 3H).

Compound **25** (2.42 g, 14.4 mmol) was dissolved to a mixture of anhydrous hydrazine (99%, 18.8 mL) and propan-1-ol (14.0 mL). The solution was brought to reflux overnight. After the reaction mixture was cooled to room temperature, the residual hydrazine and propan-1-ol was evaporated under reduced pressure. Water (38 mL) was added to dissolve the residues, followed by addition of Raney nickel (1.91 g) portionwisely. The mixture was heated to reflux for 1 h and the reaction mixture was filtered through a celite pad. The filtrate was evaporated under reduced pressure to afford **22** (1.96 g, 91.6%). ^{1}H NMR (250 MHz, MeOD) δ 8.00 (d, *J*=5.8 Hz, 1H), 7.42 (d, *J*=5.8 Hz, 1H), 2.57 (s, 3H).

Compound **22** (1.7 g, 11.3 mmol) and 4-(dimethylamino)pyridine (DMAP, 0.134 g, 1.1 mmol) were dissolved in dry THF (50 mL) at room temperature, followed by addition of Boc_2O (10 mL, 44 mmol) at the same temperature. The resulting suspension was stirred for two days under nitrogen atmosphere. TLC analysis (EtOAc) showed **24a** was obtained (Rf = 0.9) with appearance of a little **24b** (Rf = 0.6). The ratio was approximately 9:1 (detected by ^{1}H NMR). After evaporation of the solvent, the mixture was separated by chromatography (EtOAc-hexanes, 2:1) to give **24a** (4.22 g, 83.0%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J*=5.6 Hz, 1H), 7.75 (d, *J*=5.6 Hz, 1H), 2.84 (s, 3H), 1.73 (s, 9H), 1.42 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 151.4, 146.4, 142.9, 140.4, 110.2, 86.8, 83.1, 77.4, 28.3, 28.1, 18.6, 0.21. By-product **24b**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.29 (d, *J*=6.0 Hz, 1H), 7.43 (d, *J*=6.0 Hz, 1H), 2.82 (s, 3H), 1.71 (s, 9H), 1.55 (s, 9H).

Compound **24a** (2.84 g, 6.34 mmol) was dissolved under Ar in dry THF (100 mL). A 1 M solution of Bu_4NF in THF (1 M in THF, 19.7 mL, 19.7 mmol) was added and the reaction mixture was stirred for 12 h. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexanes-EtOAc, 1:2) to afford **21** (1.79 g, 81.1%) as a white foam. ^{1}H NMR NMR (250 MHz, MeOD) δ 8.16 (d, *J*=5.8 Hz, 1H), 7.54 (d, *J*=5.8 Hz, 1H), 2.64 (s, 3H), 1.33 (s, 18H). ^{13}C NMR (100 MHz, MeOD) δ 160.1, 139.6, 135.3, 124.6, 121.9, 110.6, 73.5, 36.6, 23.6, 16.8. EI-MS [$(M + H)^+$] Calcd: 349.1876. Found: 349.1878.

(1*R*,2*S*,3*R*,5*R*)-3-(4-Amino-2-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-5-(hydroxylmethyl)cyclopentane-1,2-diol (3b). To a suspension of **26**[18] (0.32 g, 1.40 mmol), Ph_3P (0.55 g, 2.10 mmol), and **21** (0.57 g, 1.64 mmol) in THF (40 mL) at 0 °C was added a solution of DIAD (0.42 g, 2.10 mmol). The mixture was warmed to room temperature and then stirred at this temperature for 2 h. The solvent was removed and the residue purified by column chromatography (EtOAc-hexanes, 1:4) to afford **27a** (0.37g, 48%) and **27b** (93.9 mg, 12%) as white foams. **27a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J*=5.6 Hz, 1H), 7.23 (d, *J*=5.6 Hz, 1H), 6.15 (m, 1H), 5.74 (dt, *J*=5.6, 2.0 Hz, 1H), 5.51 (dt, *J*=6.0, 2.4 Hz, 1H), 3.72 (dd, *J*=10, 4.4 Hz, 1H), 3.63 (dd, *J*=10, 6.0, 1H), 2.80 (m, 1H), 2.68 (s, 3H), 2.64 (m, 1H), 2.38 (m, 1H), 1.44 (s, 18H), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 151.8, 143.5, 141.4, 139.9, 136.2, 135.2, 129.0, 106.9, 82.8, 64.1, 63.7, 47.0, 34.9, 28.1, 26.1, 18.5, 14.9, -5.1, -5.3. **27b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J*=5.6 Hz, 1H), 7.28 (d, *J*=5.6 Hz, 1H), 6.19 (td, *J*=5.6, 2.4 Hz, 1H), 5.92 (td, *J*=5.6, 2.0 Hz, 1H), 5.60 (m, 1H), 3.69 (d, *J*=5.2, 1.2 Hz, 2H), 3.28 (m, 1H), 2.65 (s, 3H), 2.37 (m, 1H), 2.13 (m, 1H), 1.45 (s, 18H), 0.95 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 151.8, 143.5, 141.0, 139.9, 137.9, 136.1, 130.6, 106.9, 82.8, 65.9, 62.2, 48.3, 33.6, 28.1, 26.0, 22.1, 14.9, -5.2, -5.1.

4-Methylmorpholine *N*-oxide (31.7 mg, 0.27 mmol) was added to a solution of **27a** (50.0 mg, 0.089 mmol) in CH_2Cl_2 (5 mL), which contained a small amount of H_2O (0.05 mL). After the solution was cooled to 0 °C, a catalytic amount of solid OsO_4 (0.9 mg, 0.003 mmol) was added and the solution was stirred for 4 h at room temperature. The reaction was quenched by addition of $NaHSO_3$. The solvent was removed and the residue was purified by column chromatography (EtOAc-hexanes, 1:2) to give the **28** (43.8 mg, 83%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J*=5.6 Hz, 1H), 7.09 (d, *J*=5.6 Hz, 1H), 4.60 (m, 1H), 4.50 (m, 1H), 4.17 (m, 1H), 3.60 (dd, *J*=10.0, 4.8 Hz, 1H), 3.52 (dd, *J*=10, 4.0 Hz, 1H), 3.48 (m, 1H), 2.62 (m, 1H), 2.49 (s, 3H), 2.38 (m, 1H), 2.00 (br, 1H), 1.80 (m, 1H), 1.47 (s, 18H), 0.87 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 152.1, 151.9, 143.4, 139.8, 106.4, 83.3, 83.3, 75.9, 71.1, 64.4, 63.5, 40.1, 32.5, 28.1, 26.0, 18.5, 14.8, -5.27, -5.34.

Compound **28** (40.0 mg, 0.089 mmol) was dissolved in a mixture of MeOH (5.0 mL) and 1 N HCl (5.0 mL) and the resulting solution was stirred at room temperature for 5 h. After addition of basic resin (Amberlite IR67) for neutralization of the solution and filtration, the solvent was removed under reduced pressure and the residue purified by column chromatography (EtOAc-MeOH-$NH_3 \cdot H_2O$, 8:2:1) to give **3b** (17.3 mg, 70.0%) as white solid. ^{1}H NMR (400 MHz, MeOD) δ 7.62 (d, *J*=6.0 Hz, 1H), 6.86 (d, *J*=6.0 Hz, 1H), 4.62 (m, 1H), 4.55 (dd, *J*=9.6, 4.4 Hz, 1H), 4.15 (m, 1H), 3.63-3.55 (m, 2H), 2.69 (m, 1H), 2.64 (s, 3H), 2.40 (m, 1H), 1.63 (ddd, *J*=14.8, 4, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, MeOD) δ 153.9, 152.8, 140.0, 139.7, 127.0, 99.9, 77.3, 72.6, 66.2, 65.9, 41.2, 33.4, 14.5. EI-MS Calcd for $C_{13}H_{18}N_4O_3$: [(M + H)$^+$]: 279.1412. Found: 279.1574.

8-Methyl-1-((3a*S*,4*R*,6*S*,6a*S*)-6-(trityloxymethyl)-2,2-dimethyl-tetrahydro-3a*H*-cyclopenta[*d*][1,3]-dioxol-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-bis-Boc-4-amine (32a). To a solution of **29**[10b] (0.80 g, 1.86 mmol), Ph_3P (0.53 g, 2.02 mmol), and **21** (0.80 g, 2.30 mmol) in dry THF (40 mL) at 0 °C was added dropwise a solution of DIAD (0.41 mL, 2.02 mmol) in THF (5 mL). The mixture was then stirred at the same temperature for 30 min and warmed to room temperature for 12 h. The solvent was removed under the reduced pressure, and the residue purified by column chromatography (EtOAc-hexanes, 1:4) to afford **32a** (0.96 g, 68%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.19 (d, *J*=5.7 Hz, 1H), 7.48 (d, *J*=7.0 Hz, 6H), 7.31-7.15 (m, 10H), 6.08 (s, 1H), 5.48 (s, 1H), 5.31 (d, *J*=6.0 Hz, 1H), 4.69 (d, *J*=6.0 Hz, 1H), 3.97 (s, 2H), 2.69 (s, 3H), 1.45 (s, 18H), 1.30 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.6, 151.3, 147.8, 143.4, 140.8, 140.0, 135.7, 128.2, 127.7, 127.1, 123.6, 112.6, 106.2, 87.1, 84.5, 83.8, 82.4, 61.1, 61.0, 60.0, 27.7, 20.7, 14.6. Anal. Calcd for $C_{45}H_{50}N_4O_7 \cdot 0.6H_2O$: C, 70.49; H, 6.84; N, 7.15. Found: C, 70.47; H, 6.75; N, 7.20.

(1*S*,2*R*,5*R*)-5-(4-Amino-2-methyl-1*H*-imidazo[4,5-c]pyridin-1-yl)-3-(hydroxymethyl)cyclopent-3-ene-1,2-diol (4b). Compound **32a** (1.31 g, 2.34 mmol) was dissolved in a mixture of MeOH (23.4 mL) and 1 N HCl (23.4 mL) and the resulting solution was stirred at room temperature for 5 h. After addition of basic resin (Amberlite IR67) and filtration, the solvent was removed under reduced pressure and the residue purified by column chromatography (EtOAc-MeOH-$NH_3 \cdot H_2O$, 8:2:1) to give **4b** (0.50 g, 78%) as white solid. ^{1}H NMR (400 MHz, MeOD) δ 7.57 (d, *J*=6.0 Hz, 1H), 6.80 (d, *J*=6.0 Hz, 1H), 5.98 (dd, *J*=3.3, 1.5 Hz, 1H), 5.44 (d, *J*=5.4 Hz, 1H), 4.54 (d, *J*=5.8 Hz, 1H), 4.34-4.31 (m, 3H), 2.65 (s, 3H); ^{13}C NMR (62.9 MHz, MeOD) δ 153.1, 150.2, 148.0, 140.6, 140.2, 128.5, 126.8, 100.2, 78.4, 73.6, 67.5, 60.4, 14.3. Anal. Calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.07; H, 5.82; N, 19.94.

(1*S*,2*R*,5*R*)-5-(4-Amino-2-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-3-(2-hydroxyethyl)cyclopent-3-ene-1,2-diol (4c). To a suspension of **30**[10b] (0.97 g, 3.1 mmol), Ph_3P (0.98 g, 3.72 mmol), and **21** (1.29 g, 3.72 mmol) in THF (40 mL) at 0 °C was added a solution of DIAD (0.75 g, 3.72 mmol). The mixture was warmed to room temperature and then stirred for 2 h. The solvent was removed and the residue was purified by column chromatography (EtOAc-hexanes, 1:4) to afford **32b** (0.99 g, 48%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J*=5.6 Hz, 1H), 7.13 (d, *J*=6.0 Hz, 1H), 5.62 (s, 1H), 5.34 (s, 1H), 5.29 (d, *J*=6.0 Hz, 1H), 4.56 (d, *J*=6.0 Hz, 1H), 3.97-3.84 (m, 2H), 2.68 (s, 3H), 2.51 (t, *J*=5.6 Hz, 2H), 1.44 (s, 3H), 1.38 (s, 18H), 1.30 (s, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 151.5, 148.4, 143.5, 141.2, 140.2, 135.8, 124.1, 112.7, 106.3, 85.8, 84.5, 82.7, 67.7, 60.9, 32.3, 28.0, 27.3, 26.0, 25.9, 15.0, -5.2.

Compound **32b** (0.43 g, 0.65 mmol) was dissolved in a mixture of MeOH (6.5 mL) and 1 N HCl (6.5 mL) and the resulting solution was stirred at room temperature for 5 h. After addition of basic resin (Amberlite IR67) for neutralization of the solution and filtration, the solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc-MeOH-$NH_3 \cdot H_2O$, 8:2:1) to give **4c** (0.15 g, 80%) as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 7.47 (d, *J*=6.4 Hz, 1H), 6.78 (d, *J*=6.4 Hz, 1H), 5.78 (d, *J*=1.6 Hz, 1H), 5.38 (dd, *J*=6.0, 1.2 Hz, 1H), 4.46 (d, *J*=5.6 Hz, 1H), 4.26 (t, *J*=6.0 Hz, 1H), 3.78 (td, *J*=6.2, 1.6 Hz, 2H), 2.57 (s, 3H), 2.50-2.47 (m, 2H); ^{13}C NMR (100 MHz, MeOD) δ 153.4, 152.1, 148.0, 140.7, 138.9, 128.5, 126.8, 100.3, 78.4, 75.9, 68.0, 61.0, 34.0, 14.4. Anal. Calcd for $C_{14}H_{18}N_4O_3 \cdot 0.57$ HCl: C, 53.74; H, 6.00; N, 17.90. Found: C, 53.83; H, 6.32; N, 17.83.

(1*S*,2*R*,5*R*)-5-(4-Amino-2-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)cyclopent-3-ene-1,2-diol (4d). To a solution of **21** (2.24 g, 6.44 mmol), Ph_3P (1.48 g, 5.66 mmol), and **31**[20] (0.81 g, 5.19 mmol) in dry THF (100 mL) at 0 °C, DIAD (1.14 mL, 5.65 mmol) was added dropwise. The mixture was then stirred at the same temperature for 30 min and warmed to room temperature for 12 h. The solvent was removed under reduced pressure, and the residue purified by column chromatography (EtOAc-hexanes, 1:2) to afford **32c** (1.94 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J*=5.6 Hz, 1H), 7.04 (d, *J*=5.6 Hz, 1H), 6.29 (dt, *J*=5.6, 2.0 Hz, 1H), 5.95 (dd, *J*=6.0, 2.4 Hz, 1H), 5.50-5.48 (m, 2H), 4.64 (dd, *J*=6.0, 1.2 Hz, 1H), 2.63 (s, 3H), 1.48 (s, 3H), 1.39 (s, 18H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 151.4, 143.4, 140.9, 140.1, 136.1, 135.7, 131.0, 112.6, 106.0, 84.4, 84.0, 82.6, 68.2, 27.8, 27.0, 25.1, 14.7.

Compound **32c** (1.95 g, 4.00 mmol) was dissolved in a mixture of MeOH (42 mL) and 1 N HCl (42 mL). The resulting solution was stirred at room temperature for 12 h and brought to reflux for another 3 h. Basic resin (Amberlite IR67) was added and this was followed by filtration. The filtrate was removed under reduced pressure and residue was purified by chromatography (EtOAc-MeOH-$NH_3 \cdot H_2O$, 8:2:1) to give **4d** (0.64 g, 65%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J*=6.0 Hz, 1H), 6.61 (d, *J*=6.0 Hz, 1H), 6.17 (td, *J*=2.8, 6.4 Hz, 1H), 6.09 (dd, *J*=1.6, 6.4 Hz, 1H), 5.34 (m, 1H), 4.49 (ddd, *J*=1.2, 3.0, 6.0 Hz, 1H), 4.21 (dd, *J*=5.6, 6.4 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 152.5, 140.5, 140.3, 136.4, 135.2, 126.8, 99.9, 78.1, 74.0, 67.5, 14.3. Anal. Calcd for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.37; H, 5.83; N, 22.52.

Antiviral assays. The antiviral data was obtained following the reported protocols.[21]

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