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Tetrahedron 60 (2004) 3451–3455
Tetrahedron

5′-Noraristeromycin possessing a C-1′ cyclopentyl double bond: a new carbanucleoside structural prototype

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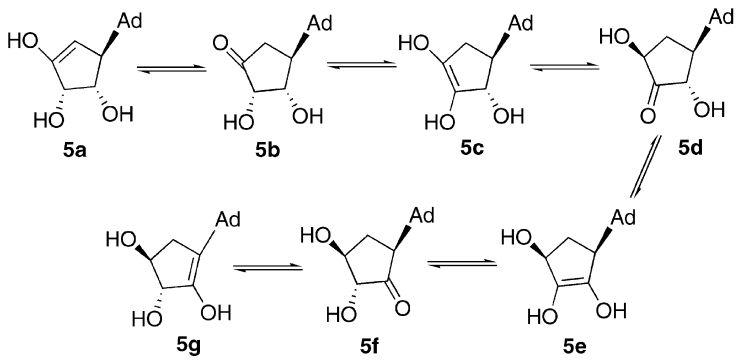
Received 12 January 2004; revised 13 February 2004; accepted 13 February 2004

Abstract—Prior to this work only two examples of carbanucleosides possessing a C-1′/C-6′ double bond had been reported and they were minor derivatized side products arising during other targeted syntheses. To develop this structural feature into a new class of potential antiviral agents, the 5′-nor derivative of aristeromycin with such an olefinic structure (**6**) represents the first example. In this regard, treatment of (1′*S*,2′*S*,3′*S*,4′*R*,5′*S*)-6-chloro-9-(2′,3′-*iso*propylidenedioxy-6′-oxabicyclo[3.1.0]hex-4′-yl)purine (**7**) with sodium methoxide yielded **6** via an E_2'-like elimination pathway. A convenient way to the C-4′ epimer of **6** (that is, **17**) also arose during these studies and is described. Antiviral analysis of **6** and **17** failed to produce any significant activity.

1. Introduction

Carbanucleosides have moved to a prominent position in biochemistry and medicinal chemistry.[1] Within this class of compounds are the unsaturated neplanocins (**1**-**3**)[1a] and the 5′-nor carbanucleosides (for example, 5′-noraristeromycin, **4**).[2,3] Imposing the neplanocin structure on 5′-nor carbanucleosides (for example, **5a**) would be complicated by the participation of **5a** in the enol–keto tautomeric cascade[4] depicted in Scheme 1. However, the allylic alcoholic isomer of the **5**-series, **6** (Scheme 2), with the C-1′/C-6′ (herein designated C-1′/C-2′) double bond,[3] would be a neplanocin-related analogue that would not be vulnerable to the alkene relocations of **5**. This class of carbanucleosides has received very little attention.[5] It is with this and the biological properties of **4** in mind that compound **6** was sought. Its synthesis and that of its C-3′-epimer (**17**) and their antiviral properties are described here (Fig. 1).

A key step in our retrosynthetic analysis to **6** (Scheme 2) was the selective epoxide ring opening of **7** using alkoxide[6] in an E_2' process involving base abstraction of the C-4′ hydrogen. Compound **7** was foreseen to be available in several steps from 6-chloropurine (**8**) and (−)-(4*R*,5*R*)-4,5-(*iso*propylidenedioxy)cyclopent-2-en-1-one (**9**).[7] Two alternative procedures were considered for modifying **9**



Scheme 1.

Keywords: Neplanocin analogs; Mitsunobu coupling; Epoxide ring opening; Antiviral.
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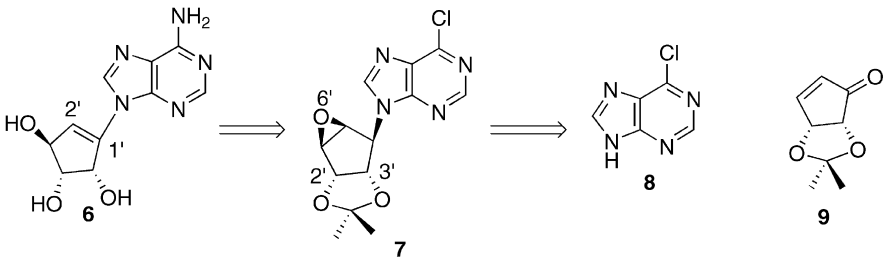
doi:10.1016/j.tet.2004.02.032



Scheme 2.

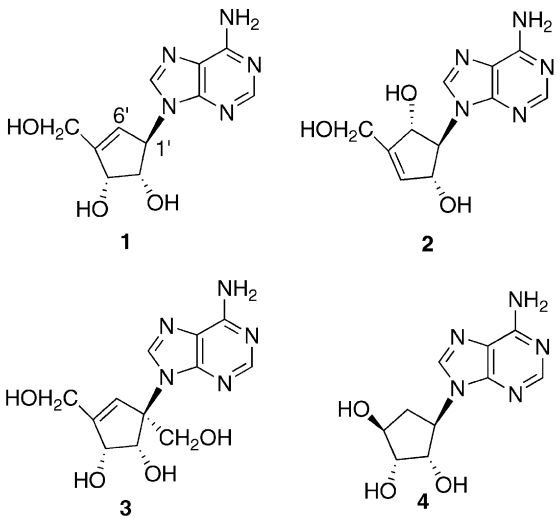
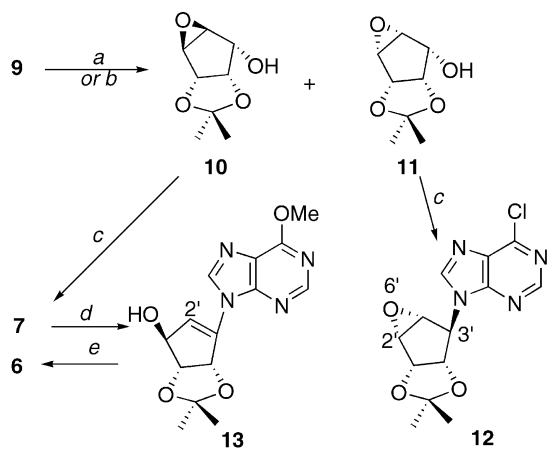


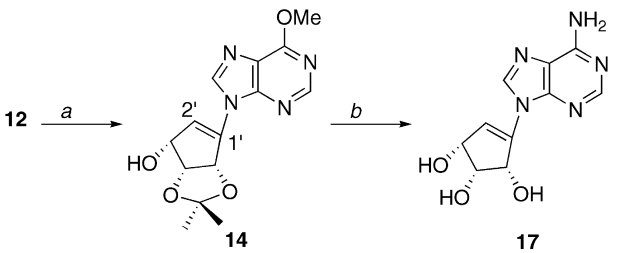
Figure 1. Ref. 3.

prior to a coupling with **8** (Scheme 3): (i) olefinic epoxidation[8] followed by carbonyl reduction (path a) and, conversely, (ii) reduction of the ketone followed by epoxidation (path b). In the former case, only the β-epoxide **10** was obtained whereas, via the latter method, both **10** and the α-epoxide **11** were realized.[9] Mitsunobu coupling of **10** (obtained from either method but pathway *a* was preferred because of higher yield in less reaction time) with **8** provided **7**. In a similar way, **11** yielded **12**.



Scheme 3. Reaction conditions: (a)(i) *t*-BuOOH, Triton B, THF, MeOH (92%); (ii) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH (**10** only, 75%); (b)(i) same as (a)(ii); (ii) *m*-CPBA, CH_2Cl_2 (**10**, 37%; **11**, 12%); (c) 6-chloropurine, Ph_3P, DIAD, THF (63% for **7**; 56% for **12**); (d) NaOMe, MeOH, 2 h, rt (89%); (e)(i) NH_3, MeOH; (ii) 0.5 N HCl, MeOH (73%).

Treatment of **7** with sodium methoxide at room temperature for 2 h gave **13** (Scheme 3). On the other hand, similar reaction conditions with epoxide **12** led to only methoxy substitution of the 6-chloro substituent; only by refluxing for 15 h could **12** be converted to **14** (Scheme 4).



Scheme 4. Reaction conditions: (a) NaOMe, MeOH, reflux, 15 h (93%); (b)(i) NH_3, MeOH; (ii) 0.5 N HCl, MeOH (56%).

The structure of **13** was assigned by NMR methods. In that regard, D_2O exchange of the hydroxyl hydrogen along with ^{1}H COSY permitted assignment of the hydrogens of the cyclopentenyl ring. HMBC then showed correlation between H-8 (8.3 ppm) and C-2′ (121 ppm) (Fig. 2). The C-2′ was assigned by correlation (HMQC) with the olefinic H-2′ (assigned by ^{1}H COSY). All other HMBC and HMQC correlations support **13** as the structure. Furthermore, NOE measurements demonstrated a correlation between H-4′ and H-5′ (cyclopentenyl numbering) but no correlation between H-3′ and H-4′ (Fig. 2). Thus, H-3′ and H-4′ are *anti* to each other.

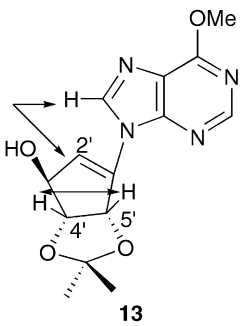
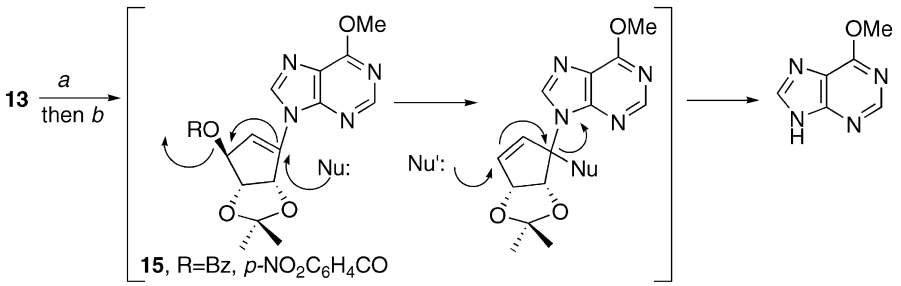


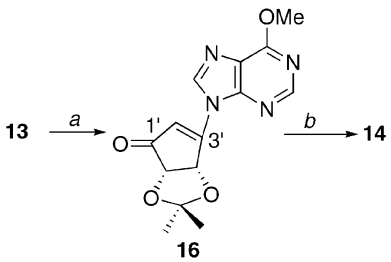
Figure 2.

In contrast to **13**, the structure of **14** was difficult to confirm by NMR. Thus, a chemical structure proof was sought. For that purpose, attempts to employ a Mitsunobu inversion of the 3′-hydroxyl of **13** to compare to **14** consistently led to loss of the cyclopentenyl ring and isolation of 6-methoxypurine (Scheme 5). This result is postulated to have occurred via dual attack of **15** by the nucleophiles present under the



Scheme 5. Reaction conditions: (a) $PhCO_2H$ or p-$NO_2C_6H_4CO_2H$, DIAD, PPh_3; (b) for R=Bz, Nu=NH_3/MeOH or NaOMe/MeOH; for R=p-$NO_2C_6H_4CO$, Nu=K_2CO_3/MeOH.

Mitsunobu inversion conditions. Alternatively, oxidation of **13** with pyridinium chlorochromate to **16** was followed by stereoselective reduction of this enone with Luche's reagent[10] to yield a product whose spectral data was identical to that previously assigned as **14** (Scheme 6).



Scheme 6. Reaction conditions: (a) PCC, Celite, CH_2Cl_2 (88%); (b) $NaBH_4$; $CeCl_3{\cdot}7H_2O$, MeOH (85%).

The desired **6** was obtained by ammonolysis of **13** with subsequent removal of the *iso*propylidene protecting group with 0.5 N hydrochloric acid (Scheme 3).

The epimer **17** was synthesized from **14** by a route similar to that for obtaining **6** from **13** (Scheme 4).

If desired, the L-like derivatives of **6** and **17** could be prepared by beginning with the enantiomer of **9**.[11] This procedure is also adaptable to other heterocyclic bases.[12]

Compounds **6** and **17** were subjected to antiviral analysis[13] and found to be inactive and to display no cytotoxicity except for **6** towards the Daudi host cells (IC_{50} 11.3 μg/mL; ganciclovir IC_{50} 40 μg/mL, acyclovir IC_{50}>50 μg/mL) used in the Epstein-Barr assay.

2. Experimental

2.1. Materials and methods

Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer (operated at 250 or 62.5 MHz, respectively). All ^{1}H 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), dd (doublet of doublets), t (triplet), m (multiplet), and br (broad). Coupling constants (J) are expressed in Hz. Atlantic Microlabs, Atlanta, Georgia, performed the elemental analyses. 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 (^{1}H and ^{13}C NMR) homogeneous materials. The reactions were generally carried out in a N_2 atmosphere under anhydrous conditions.

2.1.1. (1*S*,2*R*,3*S*,4*S*,5*S*)-4-Hydroxy-2,3-*iso*propylidenedioxy-6-oxabicyclo[3.1.0]-hexane (10) and (1*R*,2*R*,3*S*,4*S*,5*R*)-4-hydroxy-2,3-*iso*propylidenedioxy-6-oxa-bicyclo[3.1.0]hexane (11). *Method a*. To a solution of enone **9** (0.72 g, 4.5 mmol) and *t*-butyl hydrogen peroxide (0.63 mL, 4.5 mmol, 70% wt in H_2O) in THF (20 mL) in a salt-ice bath was added Triton B (1.08 mL, 40% in MeOH) dropwise. The reaction was then stirred for 2 h at the same temperature. The reaction mixture was quenched by adding ice H_2O (5 mL) and the solvents removed. The residue was extracted with EtOAc (2×10 mL) and dried ($MgSO_4$). The organic solvent was evaporated to give a pale yellow oil (700 mg, 92%), which was used directly in the next step without further purification.

To the solution of the yellow oil (600 mg, 3.52 mmol) and $CeCl_3{\cdot}7H_2O$ (1.31 g) at 0 °C in MeOH (10 mL) was added $NaBH_4$ (170 mg, 4.59 mmol) portionwise. The reaction mixture was stirred at 0 °C for 10 min and evaporated. The residue was diluted with H_2O (10 mL), extracted with EtOAc (3×20 mL) and dried ($MgSO_4$). Evaporation of the organic solvent gave the β-epoxide **10** as a light yellow oil (450 mg, 75%), which was pure enough for the use in the preparation of **7**: ^{1}H NMR ($CDCl_3$) δ 4.70 (d, J=5.5 Hz, 1H), 4.49 (t, J=5.7 Hz, 1H), 4.09 (t, J=5.5 Hz, 1H), 3.64 (s, 1H), 3.62 (s, 1H), 2.86 (d, J=5.4 Hz, 1H), 1.59 (s, 3H), 1.39 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 113.8, 80.5, 77.7, 68.9, 60.8, 58.4, 26.4, 24.7.

Method b. To a solution of the allylic alcohol (from reduction of the enone **9**[14]) (6.0 g, 38.9 mmol) in CH_2Cl_2 (100 mL) was added *m*-CPBA (5.25 g, 75% max by weight) at room temperature. The mixture was refluxed for 5 days. The reaction mixture was then diluted with CH_2Cl_2 (100 mL), washed with saturated Na_2CO_3 solution

(3×100 mL), brine (100 mL) and dried ($MgSO_4$). The organic layer was filtered and evaporated. The resulting residue was purified by column chromatography (EtOAc/hexanes, 1:10 and 1:2) to give some remaining starting material, β-epoxide **10** (2.43 g, 37%) and α-epoxide **11** (0.74 g, 12%) as a light yellow oil; **11**: ^{1}H NMR ($CDCl_3$) δ 4.65 (d, J=6.7 Hz, 1H), 4.48 (t, J=6.8 Hz, 1H), 4.23 (d, J=6.7 Hz, 1H), 3.53 (d, J=2.0 Hz, 1H), 3.49 (d, J=2.0 Hz, 1H), 2.77 (brs, 1H), 1.59 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 114.8, 79.3, 76.3, 70.8, 62.3, 56.7, 26.5, 26.2. Both **10** and **11** were too unstable for microanalysis but were of sufficient purity to use in the synthesis of **7** and **12**, respectively.

2.1.2. (1′*S*,2′*S*,3′*S*,4′*R*,5′*S*)-6-Chloro-9-(2′,3′-*iso*propylidenedioxy-6′-oxabicyclo-[3.1.0]hex-4′-yl)purine (7). To a stirred suspension of 6-chloropurine (2.05 g, 13.62 mmol) and triphenylphosphine (3.58 g, 13.62 mmol) in THF (20 mL) at −10 °C was added, dropwise, di*iso*propyl azodicarboxylate (2.48 g, 13.62 mmol). This mixture was stirred at −10 °C for 10 min and then stirred at room temperature for 15 min. To this mixture was added a solution of **10** (2.3 g, 13.72 mmol) in dry THF (10 mL). The new mixture was stirred at room temperature for 48 h and concentrated under vacuum. Column chromatography with hexanes–EtOAc (4:1) provided a white solid of desired **7** (2.7 g, 63%), mp 142–143 °C; ^{1}H NMR ($CDCl_3$) δ 8.80 (s, 1H), 8.39 (s, 1H), 5.35 (t, J=1.2 Hz, 1H), 4.94 (d, J=3.5 Hz, 1H), 4.47 (d, J=2.8 Hz, 1H), 3.93 (s, 1H), 3.92 (s, 1H), 1.61 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.6, 152.2, 151.5, 143.9, 131.5, 114.1, 85.8, 79.5, 77.4, 62.3, 59.0, 27.2, 24.7. Anal. Calcd for $C_{13}H_{13}ClN_4O_3$: C, 50.58; H, 4.24; N, 18.15. Found: C, 50.76; H, 4.32; N, 18.07.

2.1.3. (1′*R*,2′*S*,3′*S*,4′*R*,5′*S*)-6-Chloro-9-(2′,3′-*iso*propylidenedioxy-6′-oxabicyclo-[3.1.0]hex-4′-yl)purine (12). To a stirring suspension of 6-chloropurine (0.635 g, 4.27 mmol) and triphenylphosphine (1.12 g, 4.27 mmol) in THF (10 mL) at −10 °C was added, dropwise, di*iso*propyl azodicarboxylate (0.8 g, 4.27 mmol). This mixture was stirred at −10 °C for 10 min and then stirred at room temperature for 15 min. To this mixture was then added a solution of **11** (0.74 g, 4.3 mmol) in dry THF (5 mL). The new mixture was stirred at room temperature for 48 h and concentrated under vacuum. Column chromatography with hexanes–EtOAc (4:1) provided a white solid of desired **12** (0.76 g, 56%), mp 175–176 °C; ^{1}H NMR ($CDCl_3$) δ 8.74 (s, 1H), 8.14 (s, 1H), 5.33 (d, J=7.0 Hz, 1H), 5.08 (s, 1H), 4.80 (d, J=6.99 Hz, 1H), 3.92 (s, 1H), 3.68 (s, 1H), 1.60 (s, 3H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.4, 152.0, 151.5, 144.7, 114.3, 86.7, 80.2, 77.4, 60.6, 60.6, 60.4, 26.3, 26.6. Anal. Calcd for $C_{13}H_{13}ClN_4O_3$: C, 50.58; H, 4.24; N, 18.15. Found: C, 50.36; H, 4.24; N, 18.39.

2.1.4. (3′*S*,4′*R*,5′*S*)-9-(3′-Hydroxy-4′,5′-isopropylidenedioxycyclopenten-1′-yl)6-methoxypurine (13). To a stirred solution of epoxide **7** (110 mg, 0.36 mmol) in dry THF (5 mL) at room temperature under N_2 was added sodium methoxide solution (0.217 mmol, 25% wt in MeOH). The mixture was stirred at room temperature for 2 h and evaporated. Water (5 mL) was added to the residue and extracted with EtOAc (3×10 mL). The combined extracts were dried (Mg_2SO_4), filtered, and evaporated to provide **13** as a white solid (97 mg, 89%), mp 154 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H, H-2), 8.36 (s, 1H, H-8), 6.92 (d, J=2.4 Hz, 1H, H-2′), 5.69 (d, J=5.6 Hz, 1H, H-5′), 4.98 (m, 1H, H-3′), 4.71 (d, J=5.7 Hz, 1H, H-4′), 4.21 (s, 3H, OMe), 2.25 (d, J=5.7 Hz, 1H, OH), 1.43 (s, 3H, Me), 1.40 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 163.1, 154.7, 140.0, 140.0, 124.0, 121.1, 115.1, 86.7, 84.0, 80.3, 79.1, 56.2, 29.1, 27.8. Anal. Calcd for $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.26; 18.42. Found: C, 55.09; H, 5.31; N, 18.22.

2.1.5. (3′*R*,4′*R*,5′*S*)-9-(3′-Hydroxy-4′,5′-isopropylidenedioxycyclopenten-1′-yl)6-methoxypurine (14). To a stirring solution of epoxide **12** (480 mg, 1.57 mmol) in 10 mL of dry THF at room temperature under N_2 was added sodium methoxide solution (1 mL, 3.14 mmol, 25% wt in MeOH). The mixture was refluxed overnight at 70 °C and the solvents removed. To the residue was added H_2O (10 mL) and this mixture extracted with EtOAc (3×10 mL). The combined extracts were evaporated and further purified by column chromatography with hexanes–EtOAc (1:2) to give **14** as a white solid (450 mg, 93%), mp 147–148 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 8.37 (s, 1H), 6.85 (s, 1H), 5.46 (d, J=5.5 Hz, 1H), 4.93 (t, J=5.5 Hz, 1H), 4.90 (m, 1H), 4.21 (d, J=0.7 Hz, 3H), 2.81 (brs, 1H, OH), 1.49 (s, 3H), 1.45 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.5, 153.1, 152.1, 140.5, 135.4, 122.3, 122.2, 114.0, 81.8, 77.7, 72.4, 54.6, 27.8, 26.7. Anal. Calcd for $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.26; 18.42. Found: C, 55.45; H, 5.36; N, 18.20.

Compound **14** was also prepared from **16** in the following way: To a stirring solution of **16** (100 mg, 0.33 mmol) (preparation below) and $CeCl_3{\cdot}7H_2O$ (130 mg) in MeOH (10 mL) was added, portionwise, $NaBH_4$ (35 mg) at 0 °C. The mixture was then stirred at the same temperature for 10 min. The mixture was evaporated. The residue was diluted by addition of saturated aq. NH_4Cl (10 mL) and this extracted with EtOAc (30 mL) and dried (Na_2SO_4). Evaporation of solvent gave **14** as a white solid (85 mg, 85%) whose spectral properties were identical to **14** obtained from **12**.

2.1.6. (4′*S*,5′*S*)-9-(4′5′-Isopropylidenedioxy-1′-oxocyclopent-2-enyl)-6-methoxypurine (16). To a solution of **13** (152 mg, 0.5 mmol) in dry CH_2Cl_2 under N_2 was added PCC (324 mg, 1.5 mmol). The mixture was stirred for 1 h, filtered with Celite and evaporated. The resulting residue was purified by column chromatography using hexanes–EtOAc (1:1) to give **16** as a white solid (130 mg, 88%), mp 195 °C; ^{1}H NMR ($CDCl_3$) δ 8.67 (s, 1H), 8.45 (s, 1H), 7.32 (s, 1H), 5.69 (d, J=5.7 Hz, 1H), 4.74 (d, J=5.6 Hz, 1H), 4.23 (s, 3H), 1.52 (s, 3H), 1.45 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 199.0, 161.7, 159.8, 154.0, 152.2, 139.9, 122.9, 117.8, 116.9, 77.5, 54.9, 27.5, 26.4.[15] Anal. Calcd for $C_{14}H_{14}N_4O_4$: C, 55.63; H, 4.67; N; 18.53. Found: C, 55.71; H, 4.68; N, 18.50.

2.1.7. (3′*S*,4′*R*,5′*S*)-9-(3′,4′,5′-Trihydroxycyclopent-1-enyl)purine (6). A solution of **13** (160 mg, 0.53 mmol) in MeOH (20 mL) saturated with NH_3 was heated at 120 °C for three days in a Parr stainless steel sealed reaction vessel. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (MeOH–CH_2Cl_2, 1:20) to give protected **6** as a white solid, mp

219–220 °C; ^{1}H NMR (DMSO) δ 8.30 (s, 1H), 8.25 (s, 1H), 7.47 (s, 2H), 6.63 (d, J=3.1 Hz, 1H), 5.88 (dd, J=1.0, 6.9 Hz, 1H), 5.47 (d, J=5.8 Hz, 1H), 4.66 (m, 1H), 4.53 (d, J=5.8 Hz, 1H), 1.35 (s, 3H), 1.28 (s, 3H).

The white solid from the last step was dissolved in 0.5 N HCl solution in MeOH (20 mL). This mixture was stirred at room temperature for 0.5 h. The mixture was evaporated to dryness to give a solid (100 mg, 76% after 2 steps) that was recrystallized from MeOH/H_2O to provide **6** as a white solid, mp 167 °C dec.; $[\alpha]_D^{22.9}$=+42.702 (c, 0.187 DMSO); ^{1}H NMR (DMSO) δ 8.32 (s, 1H), 8.23 (s, 1H), 7.43 (s, 2H), 6.56 (d, J=1.6 Hz, 1H), 5.24 (s, 3H), 5.01 (d, J=5.7 Hz, 1H), 4.60 (s, 1H), 3.80 (t, J=4.9 Hz, 1H); ^{13}C NMR (DMSO) δ 155.9, 152.9, 149.2, 138.3, 136.0, 120.8, 119.0, 78.3, 77.1, 71.4. Anal. Calcd for $C_{10}H_{11}N_5O_3 \cdot 1.1H_2O$: C, 44.62; H, 4.90; N, 26.02. Found: C, 44.47; H, 4.74; N, 25.89.

2.1.8. (3′*R*,4′*R*,5′*S*)-9-(3′,4′,5′-Trihydroxycyclopent-1-enyl)purine (17). Compound **17** was achieved as a white solid from **14** in 56% yield using the same method as for the synthesis of **6** from **13**, mp 208 °C dec.; $[\alpha]_D^{22.9}$=−2.81 (c, 0.121 DMSO); ^{1}H NMR (DMSO) δ 8.37(s, 1H), 8.23 (s, 1H), 7.42, (s, 2H), 6.68 (s, 1H), 5.17 (s, 1H), 4.87 (m, 2H), 4.47 (s, 2H), 4.11 (t, J=5.3 Hz, 1H); ^{13}C NMR (DMSO) δ 156.1 (2C), 153.2, 149.4, 138.7, 138.1, 119.3, 119.0, 71.4, 69.5.[15] Anal. Calcd for $C_{10}H_{11}O_3N_5 \cdot 0.2H_2O$: C, 47.50; H, 4.51, N, 27.71. Found: C, 47.47, H, 4.45, N, 27.44.

Acknowledgements

This research was supported by funds from the Department of Health and Human Services (AI 48495 and AI 56540), which is appreciated. We are also indebted to the following individuals for providing the antiviral data[13] following their standard procedures: Dr. Erik De Clercq, the Rega Institute, Leuven Belgium; Dr. Earl Kern, University of Alabama at Birmingham, Birmingham, AL; Dr. Brent Korba, Georgetown University, Washington, DC; and, Dr. Robert Sidwell, Utah State University, Logan, UT. The assistance of Dr. Lyle Castle of the Idaho State University, Pocatello, Idaho, in using NMR to determine the structure of **13** is gratefully acknowledged.

References and notes

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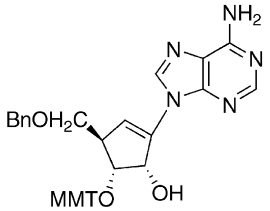
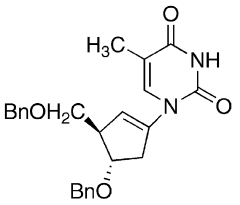


i



ii

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13. Viruses subjected to **6** and **17** were influenza A (H1N1 and H3N2), influenza B, parainfluenza-3 virus, respiratory syncytial virus, vesicular stomatitis virus, herpes simplex virus 1 (TK^+ and TK^-) and 2, human cytomegalovirus, varicella zoster virus, Epstein-Barr virus, vaccinia virus, cowpox virus, West Nile virus, Sindbis virus, adenovirus type 1, measles, Punta Toro virus, rhinovirus type 2, Venezuelan equine encephalitis, yellow fever, and HIV-1 and HIV-2. Compound **17** was also evaluated against coxsackie virus B4 and reovirus-1.
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