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A flexible synthesis of carbanucleosides and 5′-nor-1′-homo carbanucleosides from a common precursor

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Abstract—Enzymatic resolution of (±)-1-acetoxy-4-(nitromethyl)-2-cyclopentene (**4**) provides entry into a facile 10-step route to carbanucleosides and a practical 7-step procedure to 5′-nor-1′-homo carbanucleosides. These routes are illustrated for adenine derivatives but they are adaptable to any heterocyclic base.

As a naturally occurring carbocyclic nucleoside (carbanucleoside) aristeromycin (**1**)[1] possesses numerous biological properties, which have stimulated studies with other carbanucleosides.[2] Our own research in this area[3] has recently required access to an efficient and flexible synthesis of **1** and analogs of **1** altered in the heterocyclic ring (Fig. 1).

Concurrent with this effort has been an ongoing investigation at Auburn of 5′-nor carbanucleosides (represented by **2**).[4] The biological characteristics of this collection of molecules prompted the search for structurally varied derivatives, including the 1′-homo series (illustrated by **3**), which are isomeric to the conventional carbanucleosides. The 1′-homo compounds were also important to our studies of oligomers possessing the 5′-nor building block.[5] Such units would render an oligomer with the same inter-base distance as traditional oligomers, which is an arrangement that is not possible for regular 5′-nor oligomers[5] due to the hemiacetal functionality at C-4′.

Both the goal of an efficient preparation of carbanucleosides and the desire to have 1′-homo 5′-nor analogs were conceived to be accessible from a common point, namely racemic 1-acetoxy-4-(nitromethyl)-2-cyclopentene (**4**)[6] and to be based on modifying and improving upon the notable work of Deardorff[7] and Trost[8] and their co-workers. Thus, the syntheses began by treating of (±)-**4** with *Pseudomonas cepacia* lipase[9] (Scheme 1) to provide (+)-**4**[10] and (−)-**5** with compound (+)-**4**, in turn, serving as the entry into the carbanucleosides (Scheme 2) and (−)-**5** being the starting point for the 1′-homo derivatives (Scheme 3). Confirmation that this resolution led to the enantiomers shown occurred with the conversion of (+)-**4** to (−)-**1** (vide infra).

Glycolization/protection of (+)-**4** yielded **6** as the major product[7] along with a small amount of **7**. Cyanide promoted hydrolysis of **6** to **8** was followed by oxidation using pyridinium chlorochromate to result in **9**. Reduction of **9**

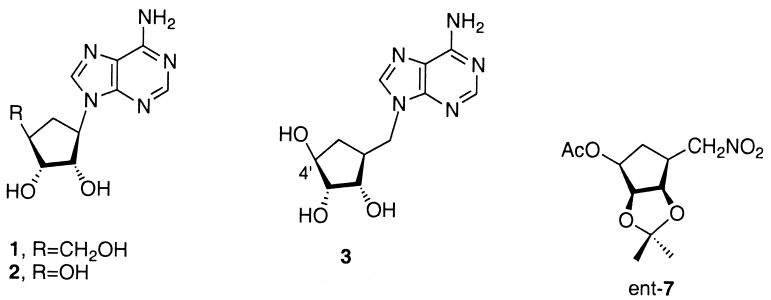

Figure 1.

Keywords: carbocyclic nucleosides; antiviral; enzyme resolution.

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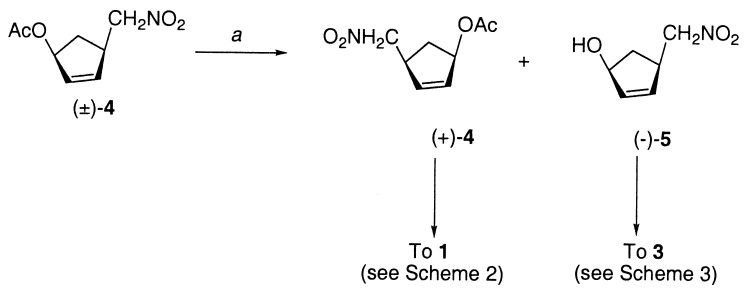
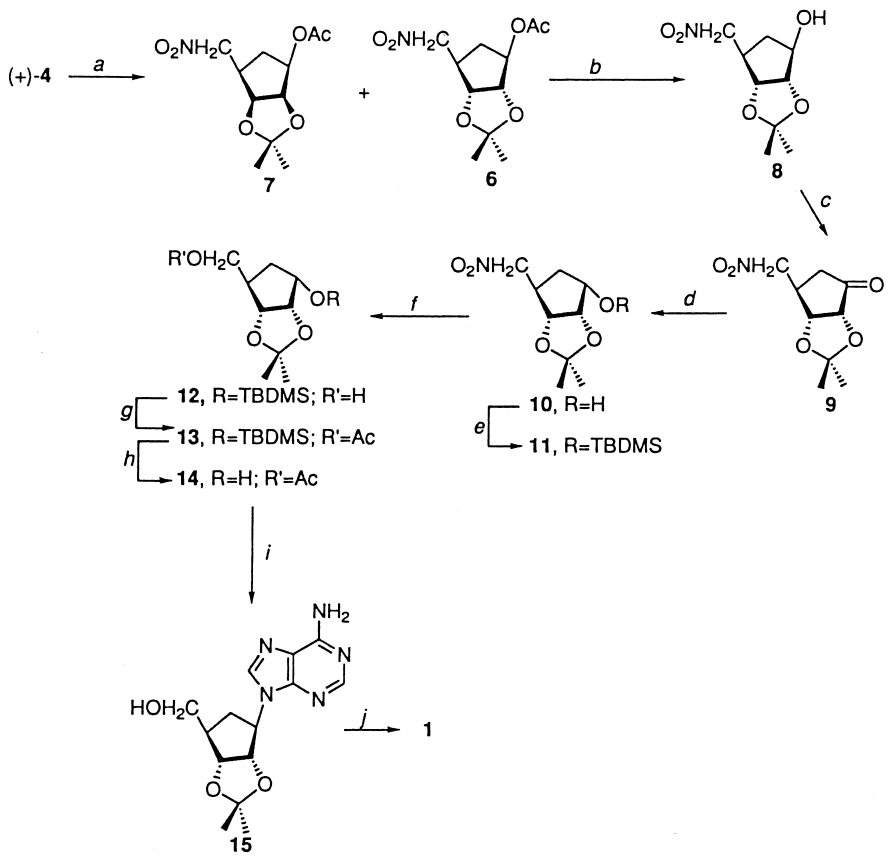


Scheme 1. *Reaction condition*: *a*, *Pseudomonas cepacia* lipase, NaOH, acetone/phosphate buffer, pH 7.0–7.2.



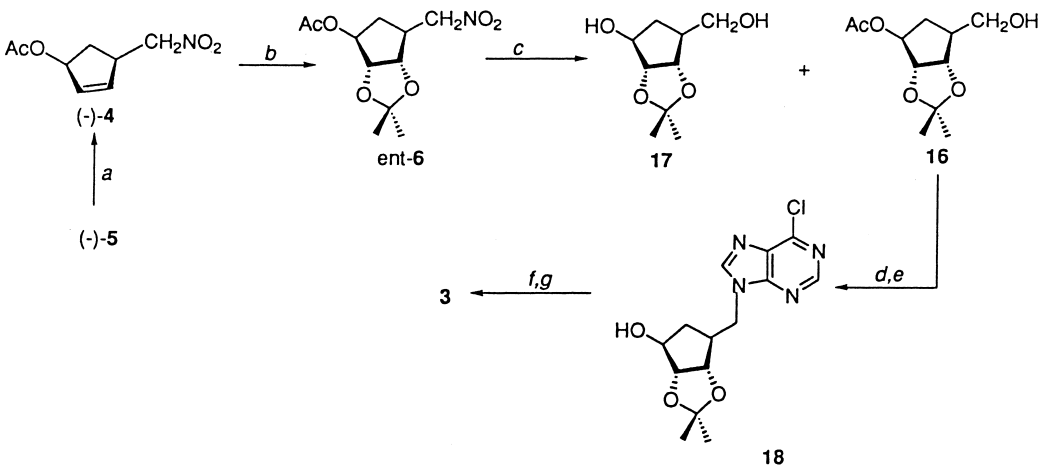
Scheme 2. *Reaction conditions*: *a*, (i) OsO_4, NMO; (ii) acetone, 2,2-dimethoxypropane, H^+; *b*, on **6**, KCN (cat.); *c*, PCC and Celite; *d*, $NaBH_4$ and $CeCl_3$; *e*, TBDMSCl/imidazole; *f*, on **11** (i) $KMnO_4$, KOH, $MgSO_4$; (ii) $NaBH_4$; *g*, Ac_2O, pyridine; *h*, Bu_4NF; *i*, (i) on **14**, 6-chloropurine, DIAD, Ph_3P; (ii) NH_3; *j*, TFA-H_2O.

with sodium borohydride selectively[11] led to **10**. Protection of the newly produced secondary alcohol of **10** as the *tert*-butyldimethylsilyl derivative **11** permitted a successful Nef[7] reaction. Subsequent reduction of the resulting aldehyde occurred to give the requisite hydroxymethylene subsituent of **12**. Acetylation of **12** (to **13**) and then desilylation produced **14**. Subjecting **14** to a Mitsunobu reaction with 6-chloropurine followed by ammonolysis gave the aristeromycin precursor **15**. Acid deprotection[12] of **15** yielded **1**,[13] whose $[\alpha]_D^{25}$ agreed with the literature value.[14]

The synthesis of **3** (Scheme 3) began with the acetylation of (−)-**5** to (−)-**4**, which was converted to *ent*-**6** via the standard oxidation/protection sequence. Following the Nef reaction and reduction tandem procedure of Scheme 2, ent-**6** gave **16** along with a small amount of the deacetylated derivative **17**. Derivative **16** led to the desired **3** by the following sequence: (i) Mitsunobu coupling with 6-chloropurine, (ii) deacetylation (to **18**), (iii) ammonolysis,[15] and (iv) deprotection of the 2′,3′-glycol.

The enantiomers of **1** and **3** would be available by treating (±)-**4** with pig liver esterase[16] to give (−)-**4** and (+)-**5** and then following Schemes 2 and 3, respectively. Also, the means illustrated herein for achieving **1** and **3** can be used to readily[11,12,17] obtain derivatives with other heterocyclic moieties.

Analogs **3** and *ent*-**3** were subjected to antiviral analysis[18] and found to be inactive. Neither compound was cytotoxic to the cells that served as hosts to the viral assays.



Scheme 3. *Reaction conditions*: *a*, Ac_2O, pyridine, CH_2Cl_2; *b*, (i) OsO_4, NMO; (ii) acetone, 2,2-dimethoxypropane, *p*TSA; *c*, (i) KOH, $KMnO_4$, $MgSO_4$; (ii) $NaBH_4$; *d*, 6-chloropurine, DIAD, Ph_3P; *e*, K_2CO_3, MeOH; *f*, NH_3, MeOH (ref. 14); *g*, 0.5 N HCl.

1. Experimental

1.1. General

Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. Combustion analyses were performed by Atlantic Microlabs, Inc. Norcross, GA. ^{1}H and ^{13}C spectra were recorded on a Bruker AC 250 spectrometer (operated at 250 and 62.5 MHz, respectively) all referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt (doublet of triplet), t (triplet), and m (multiplet). The optical rotations were measured on a Jasco P-1010 polarimeter. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Whatman Diamond silica gel 60-F_{254} precoated plates or using Silicycle (60 Å) with visualization by irradiation with a Mineralight UVGL-25 lamp or exposure to iodine vapor. Column chromatography was performed on Whatman silica, 230–400 mesh, 60 Å or Silicycle Å (200–400 mesh) and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials.

1.1.1. (+)-(1*R*,4*S*)-1-Acetoxy-4-(nitromethyl)-2-cyclopentene ((+)-4) and (−)-(1*S*,4*R*)-4-(nitromethyl)-2-cyclopenten-1-ol ((−)-5). To a 1 L three-necked round-bottomed flask fitted with a mechanical stirrer, a pH electrode and a dropping funnel was added acetone (40 mL), (±)-**4**[6] (23 g, 124 mmol) and 0.1 M phosphate buffer (200 mL). To this mixture *P. cepacia* lipase (PCL) (600 mg) was added in one portion. The pH of the solution was maintained between 7.0 and 7.2 by slow and intermittent addition of 1N (62 mmol) NaOH. When the NaOH solution addition was completed, EtOAc (500 mL) was added and the mixture filtered through a pad of Celite. The pad was washed with EtOAc (2×150 mL). The EtOAc layer was separated and the aqueous layer was extracted with EtOAc (3×150 mL). The combined EtOAc extracts were dried (anhydrous $MgSO_4$), filtered and the filtrate evaporated to get a light brown oil. Purification via silica gel column chromatography by elution with hexanes–EtOAc (5:1) afforded (+)-**4** (12 g, 52%, 90% ee[19]); $[\alpha]_D^{25}$=+40.14 (*c* 0.4733, MeOH), lit.[7] $[\alpha]_D^{25}$=+83.4 (*c* 1.535, CH_2Cl_2): ^{1}H NMR ($CDCl_3$) δ 6.01 (br, s, 2H), 5.63 (dd, *J*=10, 3 Hz, 1H), 4.53–4.34 (m, 2H), 3.40 (m, 1H), 2.57 (dt, *J*=15, 8 Hz, 1H), 2.03 (s, 3H), 1.62 (dt, *J*=15, 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 171.0, 135.5, 132.8, 79.4, 78.5, 42.6, 34.1, 21.1; Anal. calcd for $C_8H_{11}NO_4$**:** C, 51.89; H, 5.99; N, 7.56. Found: C, 52.14; H, 5.99; N, 7.38.

Elution of (−)-**5** was achieved using hexanes–EtOAc (1:1) (8 g, 45%, >98% ee[19]), $[\alpha]_D^{25}$=−10.72 (*c* 0.3735, MeOH): ^{1}H NMR ($CDCl_3$) δ 5.97 (ddd, *J*=9.2, 5.5, 2 Hz, 1H), 5.85 (dd, *J*=5.5, 2 Hz, 1H), 4.85 (dd, *J*=5.2, 4 Hz, 1H), 4.54–4.37 (m, 2H), 3.32 (m, 1H), 2.57 (ddd, *J*=15, 8, 1 Hz, 1H), 1.93 (s, 1H), 1.54 (dt, *J*=15, 4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 136.7, 132.1, 79.8, 74.6, 42.8, 37.3; Anal. calcd for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.24; H, 6.34; N, 9.53.

1.1.2. (1*R*,2*S*,3*R*,4*R*)-1-Acetoxy-2,3-(*iso*propylidenedioxy)-4-(nitromethyl)cyclopentane (6). To an ice-H_2O cooled solution of (+)-**4** (22 g, 71 mmol) in acetone-H_2O (256:44) (300 mL) was added *N*-methylmorpholine *N*-oxide (37 mL, 50% aq) and OsO_4 (100 mg). The mixture was then stirred at rt for 24 h. The acetone was evaporated under reduced pressure and the residue cooled in an ice-H_2O bath and saturated $Na_2S_2O_3$ solution (23 mL) added. This mixture was stirred for 15 min and then extracted with EtOAc (3×50 mL). The combined organic layers were washed with ice-cold 1N HCl (2×20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a colorless oil (21.5 g). The presumed diol was then transferred to a dry flask and dissolved in anhydrous acetone (50 mL). To this was added 2,2-dimethoxypropane (35 mL) followed by *p*-TSA (460 mg). The reaction was stirred at rt for 20 h. The mixture was then neutralized (dilute NH_4OH) to pH 7. After evaporation of the solvent, the residue was extracted with Et_2O (200 mL) and washed with brine (2×100 mL). The aqueous layer was then extracted with EtOAc (100 mL). The combined organic layers were dried ($MgSO_4$), filtered and the filtrate concentrated under vacuum. Column chromatography with hexanes–EtOAc (8:1) provided **6**, R_f=0.5 (20.16 g, 68% for two steps) and **7** (20:1): ^{1}H NMR for **6** ($CDCl_3$) δ 5.10 (dd,

J=5, 1 Hz, 1H), 4.58 (s, 2H), 4.56–4.38 (m, 2H), 2.97 (dd, J=7.5, 5 Hz, 1H), 2.50 (m, 1H), 2.07 (s, 3H), 1.70 (dd, J=14, 6.5 Hz, 1H), 1.49 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.7, 111.5, 84.7, 82.6, 78.9, 77.4, 43.8, 32.3, 26.5, 24.1, 21.3; Anal. calcd for $C_{11}H_{17}NO_6$: C, 50.96; H, 6.61; N 5.40. Found: C, 51.03; H 6.68; N 5.31.

Minor isomer **7** (1.25 g, 3.4%): ^{1}H NMR ($CDCl_3$) δ 4.99 (m, 1H), 4.76 (dd, J=6.7, 3.5 Hz, 1H), 4.68 (m, 2H), 4.54 (dd, J=7.5, 7.7 Hz, 1H), 3.10 (m, 1H), 2.12 (s, 3H), 1.95 (m, 2H), 1.52 (s, 3H), 1.31 (m, 3H).

1.1.3. (1*R*,2*S*,3*R*,4*R*)-1-Hydroxy-2,3-(*iso*propylidenedioxy)-4-(nitromethyl)cyclopentane (8). To a solution of **6** (1 g, 3.8 mmol) in MeOH (20 mL) was added KCN (50 mg). The mixture was stirred at rt for 2 h. The solvent was removed under reduced pressure and the residue obtained was loaded on a silica gel column. Elution of an impurity using a mixture of hexanes–EtOAc (7:1) was followed by elution with a different mixture of hexanes–EtOAc (4:1). Evaporation of the solvent from this elution afforded **8** (850 mg) as a viscous liquid. Further purification on a silica gel column gave an analytically pure sample of **8** (768 mg, 93%): ^{1}H NMR ($CDCl_3$) δ 4.67–4.44 (m, 3H), 4.27 (d, J=2.5 Hz, 1H), 4.10 (d, J=7 Hz, 1H), 2.92 (dt, J=12.5, 4.7 Hz, 1H), 2.30 (m, 2H), 1.63 (d, J=14.4 Hz, 1H), 1.42 (s, 3H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 111.3, 87.1, 83.4, 78.5, 77.0, 44.4, 34.9, 26.8, 24.4; Anal. calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.57; H, 7.05; N, 6.36.

1.1.4. (2*R*,3*R*,4*R*)-2,3-(*iso*Propylidenedioxy)-4-(nitromethyl)cyclopentan-1-one (9). To a stirred suspension of Celite (10 g) and PCC (9.27 g, 43 mmol) in anhydrous CH_2Cl_2 (100 mL) was added, dropwise, over a period of 15 min, a solution of **8** (4.67 g, 21.5 mmol) in anhydrous CH_2Cl_2. After 15 h of stirring at rt, the suspension was filtered through a pad of Celite and the pad was washed with ether (500 mL). The combined filtrates were evaporated, the residue was washed, sequentially, with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and filtered. The filtrate was evaporated in vacuo to afford a light brown residue, which was purified via column chromatography (hexanes–EtOAc, 7:3) to give **9** (3.5 g, 76%) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 4.72 (d, J=5.7 Hz, 1H), 4.56 (d, J=5.7 Hz, 2H), 4.44 (d, J=5.7 Hz, 1H), 2.98–2.91 (m, 2H), 2.29 (d, J=14 Hz, 1H), 1.45 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 210.6, 113.0, 79.9, 78.8, 60.5, 37.9, 36.6, 26.8, 24.8. Anal. calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.39; H, 6.24; N, 6.39.

1.1.5. (1*S*,2*S*,3*R*,4*R*)-1-Hydroxy-2,3-(*iso*propylidenedioxy)-4-(nitromethyl)cyclopentane (10). A solution of **9** (3.23 g, 15 mmol) and $CeCl_3{\cdot}7H_2O$ (5.59 g, 15 mmol) in MeOH (60 mL) was cooled to 0°C and $NaBH_4$ (681 mg, 18 mmol) was added slowly. The mixture was stirred at 0°C for 45 min and then neutralized with saturated aqueous NH_4Cl. The solvent was evaporated, the residue suspended in H_2O (100 mL) and this suspension extracted with EtOAc (3×60 mL). The combined extracts were washed with brine, dried ($MgSO_4$), filtered and the filtrate evaporated in vacuo. The residue was purified by column chromatography (hexanes–EtOAc, 3:1). Evaporation of the combined eluents gave **10** as a light yellow viscous liquid (2.75 g, 84%): ^{1}H NMR ($CDCl_3$) δ 4.58 (m, 1H), 4.40 (d, J=2 Hz, 1H), 4.36 (d, J=1.25 Hz, 2H), 4.08 (dt, J=10.5, 5.7 Hz, 1H), 2.90 (m, 1H), 2.55 (d, J=5.7 Hz, 1H), 2.11 (m, 1H), 1.73 (m, 1H), 1.53 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 113.5, 82.2, 79.7, 77.0, 70.5, 41.2, 35.6, 26.3, 24.6. Anal. calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.57; H, 6.99; N, 6.37.

1.1.6. (1*S*,2*S*,3*R*,4*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-(*iso*propylidenedioxy)-4-(nitromethyl)cyclopentane (11). To a solution of **10** (10 g, 46 mmol) and imidazole (3.74 g, 55 mmol) in anhydrous DMF (100 mL) was added *tert*-butyldimethylsilyl chloride (8.22 g, 54 mmol). The reaction mixture was stirred, under N_2, at rt for 12 h. After evaporation of the solvent on a rotary evaporator, the residue was dissolved CH_2Cl_2 (150 mL) and this solution washed with brine (1×100 mL) and then H_2O (1×80 mL). The organic extract was dried ($MgSO_4$), filtered and the filtrate evaporated in vacuo. The viscous residue was purified by column chromatography (20:1, hexanes–EtOAc). Evaporation of the eluent afforded **11** as a colorless syrup (11 g, 72%): ^{1}H NMR ($CDCl_3$) δ 4.45–4.27 (m, 4H), 4.10 (dt, J=11.7, 5 Hz, 1H), 2.87 (dt, J=10, 5 Hz, 1H), 2.17 (dt, J=13, 6 Hz, 1H), 1.66 (m, 1H), 1.61 (s, 3H), 1.31 (s, 3H), 0.91 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 113.0, 81.8, 80.8, 77.6, 72.0, 41.2, 35.3, 26.6, 26.1, 25.1, 18.5, −4.3, −4.7. Anal. calcd for $C_{15}H_{29}NO_5Si$: C, 54.35; H, 8.75; N, 4.22. Found: C, 54.57; H, 8.86; N, 4.18.

1.1.7. (1*S*,2*S*,3*R*,4*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-(*iso*propylidenedioxy)-4-(hydroxymethyl)cyclopentane (12). A solution of **11** (1.22 g, 3.7 mmol) in MeOH (25 mL) at 0°C was mixed with a solution of KOH (85%) (243 mg, 3.7 mmol) in MeOH (5 mL). The mixture was stirred at 0°C for 20 min and a freshly prepared solution of $KMnO_4$ (537.3 mg, 3.4 mmol) and $MgSO_4$ (397.2 mg, 3.3 mmol) in H_2O (25 mL) was added dropwise, over 40 min, to the above mixture. After the mixture was stirred at 0°C for an additional hour, the mixture was diluted with EtOAc (100 mL) and filtered through a pad of Celite. The Celite pad was washed with EtOAc (3×60 mL). The combined filtrates were washed with brine (1×100 mL) and H_2O (1×100 mL), dried ($MgSO_4$), filtered and the filtrate evaporated in vacuo. The residue obtained was dissolved in 2-propanol (50 mL) and brought to 0°C. Sodium borohydride (239 mg, 6.3 mmol) was added slowly to the solution. The reaction was stirred at 0°C for 60 min and then neutralized with saturated aqueous solution of NH_4Cl. The insoluble materials were removed by filtration, H_2O was added to the filtrate and this mixture extracted with EtOAc (3×60 mL). The combined extracts were dried ($MgSO_4$), filtered and the filtrate evaporated in vacuo. The residue was loaded on a silica gel column and eluted first with hexanes–EtOAc (10:1) to elute unreacted starting material and impurities, and then with hexanes–EtOAc (4:1) to elute, after evaporation of the solvent mixture, **12** as a colorless syrup (710 mg, 66%): ^{1}H NMR ($CDCl_3$) δ 4.41 (m, 3H), 4.13 (dd, J=4.2 Hz, 1H), 3.60–3.52 (m, 2H), 2.22 (m, 1H), 2.03 (dt, J=12.2, 4 Hz, 1H), 1.66 (m, 1H), 1.50 (s, 3H), 1.32 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 111.9, 82.2, 81.1, 72.9, 64.6, 44.9, 34.5, 26.7, 26.2, 25.1, 18.6, −4.2. Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 9.99. Found: C, 59.28; H, 10.01.

1.1.8. (1*S*,2*S*,3*R*,4*R*)-4-(Acetoxymethyl)-1-(*tert*-butyldimethylsilyloxy)-2,3-(*iso*propylidenedioxy)cyclopentane (13). Acetic anhydride (5 mL, 50 mmol) was added to a mixture of **12** (3.2 g, 10.6 mmol) and pyridine (6.4 mL, 80 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0°C. The mixture was stirred at rt for 16 h. It was then brought to 0°C and a cold, saturated aqueous solution of $NaHCO_3$ was added and this stirred for 30 min. The organic layer was separated, washed with cold 1N HCl (2×50 mL) and H_2O (1×50 mL), dried ($MgSO_4$), filtered and evaporated under vacuum to give a colorless liquid, which was further purified as **13** (3.12 g, 85%) by column chromatography (hexanes–EtOAc, 10:1): ^{1}H NMR ($CDCl_3$) δ 4.43 (m, 3H), 4.11 (m, 2H), 3.99 (ddd, J=11, 6, 6 Hz, 1H), 2.73 (m, 1H), 2.07 (s, 3H), 1.58 (m, 1H), 1.49 (s, 3H), 1.31 (s, 3H), 1.15 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.2, 111.8, 82.0, 80.9, 72.9, 65.8, 41.5, 34.4, 26.7, 26.2, 25.0, 21.1, 18.6, −4.2. Anal. calcd for $C_{17}H_{32}O_5Si$: C 59.27; H 9.29. Found: C 59.56; H 9.30.

1.1.9. (1*S*,*RS*,3*R*,4*R*)-4-(Acetoxymethyl)-2,3-(*iso*propylidenedioxy)cyclopentan-1-ol (14). To a solution of **13** (2.4 g, 6.9 mmol) in freshly distilled THF (50 mL) was added a 1N solution of tetrabutylammonium fluoride in THF (9 mL). The mixture was stirred at rt for 2 h. After evaporation of the solvent, the residue was loaded on a silica gel column and the product eluted using hexanes–EtOAc (8:1 followed by 5:1). Evaporation of the second eluent stage gave **14** (1.4 g, 88%) as colorless syrup, which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 4.50–4.46 (m, 3H), 4.11 (dd, J=7, 6 Hz, 1H), 4.03 (m, 2H), 2.42 (m, 1H), 2.07 (s, 3H), 1.95 (m, 1H), 1.78 (m, 1H), 1.51 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.4, 112.1, 82. 5, 79.6, 71.5, 65.3, 41.3, 35.0, 26.3, 24.5, 21.1. Anal. Calcd for $C_{11}H_{18}O_5 \cdot 0.1H_2O$: C, 56.93; H, 7.90. Found: C, 56.64; H, 7.81.

1.1.10. 9-[(1′*R*,2′*S*,3′*R*,4′*R*)-(4′-Hydroxymethyl)-2′,3′-(*iso*propylidinedioxy)cyclo-pentan-1′-yl]adenine (15). Di*iso*propyl azodicarboxylate (DIAD) (1.01 g, 5.2 mmol) was added dropwise to a solution of triphenylphosphine (1.34 g, 5.2 mmol) in freshly distilled THF (80 mL) kept under N_2 atmosphere. The mixture was stirred for 20 min and then a solution of **14** (1.28 g, 5.6 mmol) in dry THF (20 mL) was added slowly. The mixture was stirred at rt for an additional 20 min and then 6-chloropurine (787 mg, 5.2 mmol) was added. The mixture was stirred at 55°C for 18 h. The solvent was evaporated and the residue was loaded onto a silica gel column. The faster moving impurities were successively eluted with CH_2Cl_2–EtOAc (first at 50:1 and then 25:1). This was followed by CH_2Cl_2–EtOAc (10:1) to elute product and triphenylphosphine oxide, which could not be separated under various conditions. After evaporation of the eluent, the residue obtained (assumed to contain 5′-acetylated **15**) was dried under vacuum (P_2O_5) and used directly in the next reaction.

The above residue was dissolved in MeOH (30 mL) saturated with anhydrous NH_3 and heated at 110°C for 48 h in a sealed pressure apparatus. After cooling the solution to rt and removing the insoluble material by filtration, the solvent was evaporated and the residue was loaded on a silica gel column. The triphenylphosphine was eluted first with CH_2Cl_2–MeOH (25:1) followed by fractions containing product. Evaporation of these fractions afforded **15** as a white powder (980 mg, 62% for two steps based on 6-chloropurine), mp 204–206°C: ^{1}H NMR (DMSO-d_6) δ 8.28 (s, 1H), 8.16 (s, 1H), 7.26 (s, 2H), 5.04 (dd, J=8, 4 Hz, 1H), 4.80 (m, 2H), 4.56 (dd, J=4, 2 Hz, 1H), 3.51 (s, 2H), 2.27 (m, 3H), 1.49 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 155.9, 152.2, 149.2, 139.7 119.1, 112.3, 82.8, 80.6, 61.8, 60.3, 45.3, 33.6, 27.3, 25.0. Anal. calcd for $C_{14}H_{19}N_5O_3$: C, 55.07; H, 6.27; N, 22.94. Found: C, 54.85; H, 6.13; N, 22.73.

1.1.11. 9-[(1′*R*,2′*S*,3′*R*,4′*R*)-[(2′,3′-(Dihydroxy)-4′-(hydroxymethyl)cyclopentan-1′-yl]adenine (1, aristeromycin). Compound **15** (500 mg, 1.6 mmol) was dissolved in a mixture of trifluoroacetic acid–H_2O (2:1) and this solution stirred at rt for 2 h. The solvent was removed under vacuum and the residue was repeatedly dissolved in MeOH and evaporated (4 times). The solid obtained in this manner was adsorbed on silica gel and this mixture loaded on a silica gel column. Evaporation of the product containing fractions using CH_2Cl_2–MeOH (3:1) afforded **2** (360 mg 84%) as a white solid, mp. 215–218°C. (lit.[12a] 214–216°C); $[\alpha]_D^{25}$=−59.6 (c 0.1362, DMF), lit.[14] $[\alpha]_D^{25}$=−56 (c 0.366, DMF): ^{1}H NMR (DMSO-d_6) δ 8.19 (s, 1H), 8.11 (s, 1H), 7.18 (s, 2H), 4.95 (d, J=6.5 Hz, 1H), 4.73 (t, J=6 Hz, 1H), 4.71–4.66 (m, 2H), 4.35 (dt, J=6, 9 Hz, 1H), 3.84 (m, 1H), 3.48–3.38 (m, 2H), 2.25 (dt, J=12, 8 Hz, 1H), 2.04–2.01 (m, 1H), 1.73–1.70 (dt, J=12, 8.2 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 155.9, 152.0, 149.7, 140.0, 119.3, 74.5, 71.6, 63.0, 59.2, 45.3, 29.2; Anal. calcd $C_{11}H_{15}N_5O_3 \cdot 1.4\ H_2O$: C, 45.48; H, 6.18; N, 24.11. Found: C, 45.81; H, 5.83; N, 23.77.

1.1.12. (−)-(1*S*,4*R*)-1-Acetoxy-4-(nitromethyl)-2-cyclopentene ((−)-4). To a solution of (−)-**5** (10 g, 53.9 mmol) and Ac_2O in dry CH_2Cl_2 (200 mL) at 0°C was added pyridine (4 g). The mixture was then stirred at rt for 20 h, washed with ice-cooled saturated Na_2CO_3 (3×50 mL), 1N HCl (3×50 mL), brine (50 mL) and dried ($MgSO_4$). The CH_2Cl_2 was evaporated under reduced pressure. The residue was purified by Kugelrohr distillation (120–140°C/0.25 mm Hg) to give (−)-**4** (9.5 g, 90%), whose NMR spectral properties matched those of (+)-**4**.

1.1.13. (1*S*,2*R*,3*S*,4*S*)-1-Acetoxy-2,3-(*iso*propylidenedioxy)-4-(nitromethyl)cyclopentane (ent-6) and (1*S*,2*S*,3*R*,4*S*)-1-acetoxy-2,3-(*iso*propylidenedioxy)-4-(nitromethyl)cyclopentane (ent-7). Following the same procedure as described for preparing **6**, (−)-**4** (11 g, 0.071 mol) provided ent-**6** (10.47 g, 57%) and ent-**7** (625 mg, 3.4%) (Fig. 1) as colorless oils following purification by silica gel column chromatography with hexanes–EtOAc (8;1). ent-**6**: ^{1}H NMR ($CDCl_3$) δ 5.14 (d, J=5 Hz, 1H), 4.35–4.64 (m, 4H), 2.99 (m, 1H), 2.50 (m, 1H), 2.11 (s, 3H), 1.70 (d, J=6.5 Hz, 1H), 1.49 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.7, 111.6, 84.7, 82.6, 79.0, 77.5, 43.9, 32.4, 26.6, 24.2, 21.3. Anal. calcd for $C_{11}H_{17}NO_6$: C, 50.96; H, 6.61; N, 5.40. Found: C, 51.25; H, 6.62; N, 5.29.

ent-**7**: ^{1}H NMR ($CDCl_3$) δ 4.99 (m, 1H), 4.76 (dd, J=6.7, 3.5 Hz, 1H), 4.68 (m, 2H), 4.54 (dd, J=7.5, 7.7 Hz, 1H), 3.10 (m, 1H), 2.12 (s, 3H), 1.95 (m, 2H), 1.52 (s, 3H), 1.31 (m, 3H).

1.1.14. (1*R*,2*S*,3*R*,4*S*)-4-Acetoxy-1-(hydroxymethyl)-2,3-(*iso*propylidenedioxy)cyclopentane (16). To a stirring ice-H_2O cooled solution of ent-**6** (5.9 g, 22.7 mmol) in MeOH (50 mL) was added, dropwise, over 5 min a freshly prepared solution of KOH (1.633 g, 0.025 mol) in MeOH (100 mL). After an additional 15 min, a freshly prepared solution of $KMnO_4$ (2.84 g, 17 mmol) and $MgSO_4$ (2.01 g, 16 mmol) in H_2O (160 mL) was added dropwise over 15 min. This mixture was stirred at 0°C for 45 min and then quenched by passing through a pad of Celite and washing the pad with ether. The resultant filtrate was extracted with EtOAc (3×100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellow oil (4.0 g). This unstable aldehyde was immediately dissolved in 2-propanol (40 mL) and cooled in an ice-H_2O bath. To this was added, in one portion, $NaBH_4$ (908 mg, 0.0227 mol). The reaction mixture was stirred at rt for 1 h, cooled in an ice-H_2O bath and then quenched with saturated NH_4Cl solution to pH 7. This mixture was extracted with EtOAc (3×200 mL). The combined organic layers were dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo. Purification via column chromatography with hexanes–EtOAc (1:1) provided **16** and **17** as colorless oils. Compound **16** (1.25 g, 24%): ^{1}H NMR (DMSO) δ 4.83 (s, 1H), 4.69 (t, J=5 Hz, 1H), 4.5 (d, J=6.25 Hz, 1H), 4.41 (d, J=6.0 Hz, 1H), 3.31 (m, 2H), 2.10–2.16 (m, 2H), 1.98 (s, 3H), 1.50 (d, J=8.5 Hz, 1H), 1.35 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (DMSO) δ 169.5, 109.8, 84.2, 81.7, 78.9, 61.9, 47.2, 31.1, 26.5, 24.1, 21.0; Anal. calcd for $C_{11}H_{18}O_5 \cdot 0.2H_2O$: C, 56.52; H, 7.87. Found: C, 56.61; H, 7.94.

Compound **17** (2.0 g, 39%): ^{1}H NMR (DMSO) δ 4.95 (d, J=3.9 Hz, 1H), 4.68 (t, J=7.0 Hz, 1H), 4.46 (d, J=6.0 Hz, 1H), 4.24 (d, J=5.6 Hz, 1H), 3.90 (d, J=3.7 Hz, 1H), 3.32 (m, 2H), 1.99 (m, 2H), 1.37 (s, 1H), 1.32 (s, 3H), 1.19 (s, 3H).

1.1.15. 6-Chloro-9-{(1′*S*,2′*R*,3′*S*,4′*S*)-[4′-hydroxy-2′,3′-(*iso*propylidenedioxy)cyclopent-1′-yl]methyl}purine (18). To a stirring suspension of 6-chloropurine (1.12 g, 7.27 mmol) and triphenylphosphine (1.91 g, 7.27 mmol) in THF (20 mL) at −10°C was added dropwise diisopropyl azodicarboxylate (1.47 g, 7.27 mmol). This mixture was stirred at −10°C for 10 min and then stirred at rt for 15 min. To this mixture was added a solution of **16** (1.25 g, 5.5 mmol) in dry THF (10 mL) and the new mixture stirred at rt for 2 h, followed by stirring at 55°C for another 1 h. The mixture was concentrated in vacuo. Purification of the residue via column chromatography with hexanes–EtOAc (1:1) provided a mixture of the desired product and triphenylphosphine oxide (2.2 g). To this mixture in MeOH (100 mL) was added K_2CO_3 (0.90 g). The resultant mixture was stirred at rt for 1 h and then concentrated under vacuum. Column chromatography of the residue with hexanes–EtOAc (1:1) provided **18** (705 mg, 41%) as a white solid: mp 161°C; ^{1}H NMR (DMSO) δ 8.79 (s, 1H), 8.76 (s, 1H), 5.20 (d, J=3.0 Hz, 1H), 4.4–4.53 (m, 3H), 4.22 (dd, J=6.75, 6.75 Hz, 1H), 4.0 (d, J=7.2 Hz, 1H), 2.62 (d, J=7.5 Hz, 1H), 1.98 (m, 1H), 1.44 (d, J=13.5 Hz, 1H), 1.26 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (DMSO) δ 152.0, 151.5, 149.0, 147.7, 130.8, 109.8, 86.6, 82.4, 75.3, 46.8, 45.1, 34.4, 26.4, 24.0; Anal. calcd for $C_{14}H_{17}ClN_4O_3 \cdot 0.2H_2O$: C, 51.22; H, 5.30; N, 17.06. Found: C, 51.27; H, 5.31; N, 16.96.

1.1.16. 9-[(1′*S*,2′*R*,3′*S*,4′*R*)-(2′,3′,4′-Trihydroxycyclopent-1′-yl)methyl]adenine (3). A solution of **18** (720 mg, 2.21 mmol) in MeOH (50 mL) saturated with NH_3 was heated at 120°C for two days in a Parr stainless steel sealed reaction vessel. The solvent was evaporated under reduced pressure and the mixture dissolved in 0.5N HCl solution (40 mL) in MeOH. This mixture was stirred at rt for 0.5 h and then evaporated to dryness under reduced pressure. The residue was purified by column chromatography (MeOH–EtOAc, 1:5) to give **3** (210 mg, 36%), which was purified further by recrystallization from MeOH–H_2O to provide **3** as a white solid, mp 200°C: ^{1}H NMR (DMSO) δ 8.13 (s, 1H), 8.12 (s, 1H), 7.17 (s, 2H), 4.73 (d, J=4.1 Hz, 1H), 4.46 (m, 2H), 4.22 (dd, J=6.7, 6.9 Hz, 1H), 4.02 (dd, J=6.7, 6.9 Hz, 1H), 3.72 (m, 2H), 3.54 (d, J=3.7 Hz, 1H), 2.30 (m, 1H), 1.86 (m, 1H), 1.03 (m, 1H); ^{13}C NMR (DMSO) δ 155.8, 152.2, 149.7, 141.02, 118.6, 77.9, 74.4, 74.0, 46.5, 42.3, 33.9; Anal. calcd for $C_{11}H_{15}N_5O_3 \cdot 0.5H_2O$: C, 48.17; H, 5.88; N, 25.53. Found: C, 48.04; H, 5.58; N, 25.31.

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19. Enantiomeric purity was determined by proton NMR spectroscopy in the presence of chiral shift reagent *tris*[3-(heptafluoropropylhydroxymethylene)-*d*-camphorate. europium (III) [Eu(hfc)$_3$].