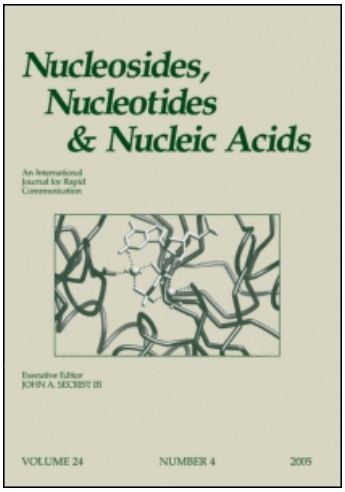

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1-Deaza-5'-noraisteromycin

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1-Deaza-5′-noraisteromycin[†]

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ABSTRACT

(±)-1-Deazaaristeromycin (**4**) has been reported to be an inactivator of S-adenosylhomocysteine (AdoHcy) hydrolase and, as a consequence, to affect S-adenosylmethionine (AdoMet) mediated macromolecular biomethylations. To extend this to our program focused on 5′-noraristeromycin derivatives as inhibitors of the same hydrolase enzyme as potential antiviral agents, both enantiomers of 1-deaza-5′-noraristeromycin (**5** and **20**) have been prepared. Compounds **5** and **20** were evaluated against the following viruses: vaccinia, cowpox, monkeypox, Ebola, herpes simplex type 1 and 2, human cytomegalovirus, Epstein Barr, varicella zoster, hepatitis B, hepatitis C, HIV-1 and HIV-2, adenovirus type 1, measles, Pichinde, parainfluenza type 3, influenza A (H1N1 and H3N2), influenza B, Venezuelan equine encephalitis, rhinovirus type 2, respiratory syncytial, yellow fever, and West Nile. No activity was found nor was there any cytotoxicity to the viral host cells.

Key Words: 1-Deazaaristeromycin; AdoHcy; AdoMet.

INTRODUCTION

Carbocyclic nucleosides (carbanucleosides) have long been synthesized as potential antiviral agents. Examples are aristeromycin (**1**),[1] neplanocin A,[2] carbovir,[3]

[†]In honor and celebration of the 70th birthday of Professor Leroy B. Townsend.

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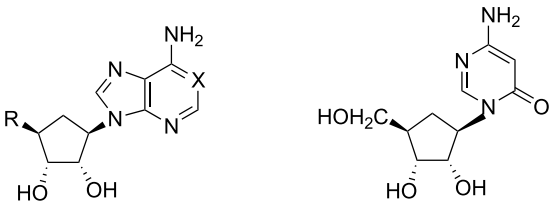
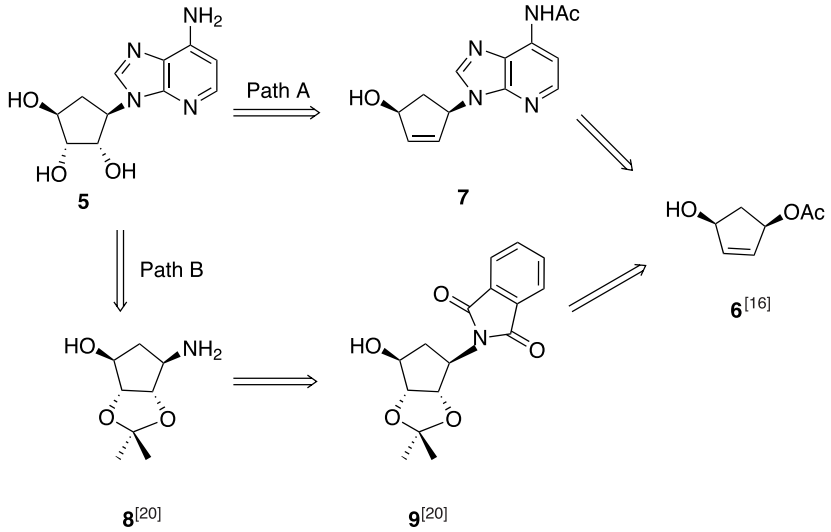


1, X=N; R=CH_2OH
3, X=N; R=OH
4, X=CH; R=CH_2OH
5, X=CH; R=OH

2

Figure 1. Aristeromycin and related carbanucleosides.

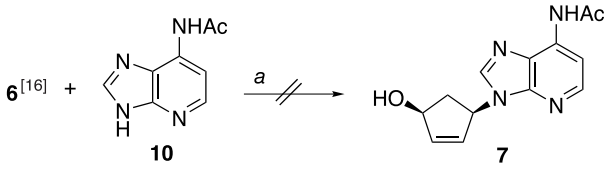
carbodine (**2**),[4] and carbooxetancin G (for a leading reference see Ref. [5]). Modification of these lead compounds has occurred in the heterocyclic base portion and/or in the cyclopentane.[6] In this direction and motivated by the desire to limit 5′-phosphorylation of aristeromycin and, in turn, its cyctotoxicity, 5′-noraristeromycin (**3**)[7,8] and its 3-deaza,[9] 7-deaza[10] and 4′-deoxy[11] analogs were prepared and found to have significant biological (including antiviral) properties. Like aristeromycin, the activity of these compounds has been attributed to their inhibition of *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase,[12] an enzyme that modulates biomethylations mediated by *S*-adenosylmethionine (AdoMet).[13] With this observation, our attention was recently drawn to (±)-1-deazaaristeromycin (**4**), which has been reported to be an irreversible inactivator of AdoHcy hydrolase.[14] Thus, as part of a program seeking inhibitors of viruses sensitive to perturbation of AdoHcy hydrolase[15] and as an extension of our 5′-nor carbanucleoside studies, the synthesis and antiviral properties of both enantiomers of 1-deaza-5′-noraristeromycin (**5** and **20**) were sought. The results of this effort are described (Figure 1).



5 **7** **6**[16]

8[20] **9**[20]

Scheme 1.



Reaction conditions: *a*, for example, $Pd(PPh_3)_4$, NaH, DMF, 60 °C

Scheme 2.

Chemistry

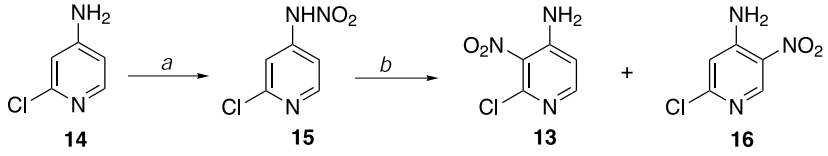
To achieve the target compound 1-deaza-5′-noraristeromycin (**5**), two different routes were designed (Scheme 1) from a common precursor **6**:[16] Path A requires a preformed imidazo[4,5-*b*]pyridine (1-deazapurine); Path B follows a de novo plan by constructing the heterocyclic base from a cyclopentane derivative.

Path A

Pathway A seemed to embody the fewest steps and was considered first. Following a standard procedure in our laboratory (for a leading reference see Ref. [17]) that involves a Pd(0) mediated coupling of a heterocyclic base with a cyclopentyl allylic acetate, reaction of monoacetate **6**[16] with 7-acetamido-3*H*-imidazo[4,5-*b*]pyridine (N^6-acetyl-1-deazaadenine, **10**)[18] was carried out (Scheme 2). However, the expected product **7** could not obtained employing a variety of conditions. Attention then turned to Path B.

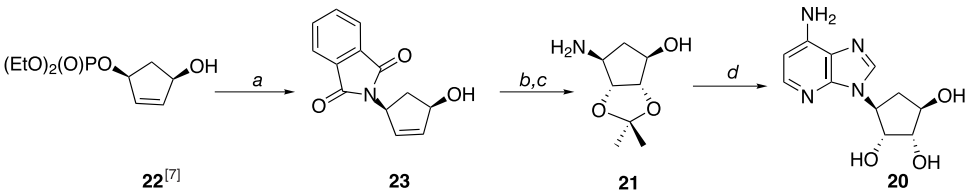
Path B

The two building blocks for this route were seen as 4-amino-2-chloro-3-nitropyridine (**13**)[19] and the protected cyclopentylamine **8**.[20] Compound **13** was achieved in two steps from commercially available 2-chloro-4-aminopyridine (**14**) as shown in Scheme 3.[19] In that regard,[19] the nitration of **14**, followed by rearrangement of nitramine **15**, gave two products, **13** and **16** (6:1). The ratio of the products was determined by NMR in which the C-5 and C-6 hydrogens appeared as doublets for



Reaction conditions: *a*, fuming HNO_3, conc. H_2SO_4, 0 °C, 15 min; *b*, conc. H_2SO_4, 0 °C to 75 °C, 3h

Scheme 3. (From Ref. [19].)



22[7] **23** **21** **20**

Reaction conditions: *a*, potassium phthalimide, $Pd(PPh_3)_4$, DMSO/THF, 60 °C[20]; *b*, (i) N-methylmorpholine, N-oxide, OsO_4, acetone; (ii) 2,2-dimethoxypropane, *p*-toluenesulfonic acid, acetone, 15 h[20]; *c*, NH_3, MeOH, 6 h; *d*, see Scheme 4 where **21** replaces **8**

Scheme 4.

13 (δ 7.89 and 6.81 ppm) while the C-3 and C-6 hydrogens of **16** were singlets (δ 8.84 and 6.95 ppm).

With **13** available it was reacted with amine **8**[20] in the presence of triethylamine following a general method[7] to give **17**. Reduction of **17** followed by fused imidazole ring formation with formamidine acetate resulted in two products (**18** and **19**) instead of one as suggested by the literature.[14] These isomeric compounds were distinguished by observing a broad 2-proton amine singlet (δ 6.33 ppm) in the NMR spectrum of **18**. In this regard, compound **19** displayed a one proton NH singlet at 12.52 ppm. Deprotection of **18** with 0.5 N HCl provided the desired **5**.

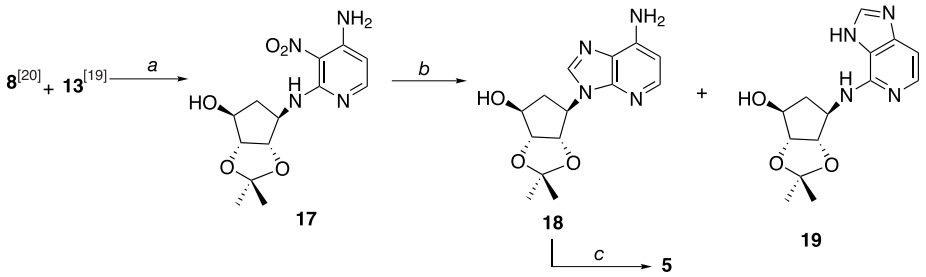
The L-like enantiomer **20** was synthesized from **21** (Scheme 4) via a similar sequence of reactions for achieving **5** (Scheme 5). A means to the requisite **21** was modeled after our literature procedure to **8**[20] but beginning with **22**.[7]

With the intention of obtaining **5** and **20** from a common precursor, Scheme 6 was considered. In that regard, racemic **24** was prepared from cyclopentadiene following a literature procedure.[21] Acetylation of (±)-**24** with subsequent chiral-selective hydrolysis using *Pseudomonas cepacia* lipase yielded **25** and **26** with high ee (NMR analysis).[a] While **25** and **26** could be converted into **5** and **20**, respectively, as shown in Scheme 6, the long time required for the enzymatic resolution reaction rendered this plan of employing (±)-**24** as a common precursor unfavorable for further consideration.

Antiviral Analysis

Compounds **5** and **20** were evaluated against the following viruses[10,11] (for leading references on the procedures used for the assays see Refs. [22–24]): vaccinia, cowpox, monkeypox, Ebola, herpes simplex type 1 and 2, human cytomegalovirus, Epstein Barr, varicella zoster, hepatitis B, hepatitis C, HIV-1 and HIV-2, adenovirus type 1, measles, Pichinde, parainfluenza type 3, influenza A (H1N1 and H3N2), influenza B, Venezuelan equine encephalitis, rhinovirus type 2, respiratory syncytial, yellow fever, and West Nile. No activity was found nor was there any cytotoxicity to

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



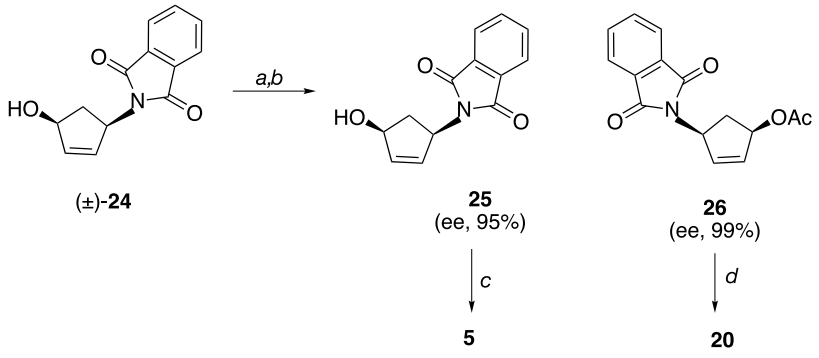
Reaction conditions: *a*, Et_3N, 1-BuOH, reflux, 36 h; *b*, (i) H_2, Pd/C, EtOH, rt, overnight; (ii) formamidine acetate, 2-methoxyethanol, refluxing, 2 h; *c*, 0.5 N HCl, MeOH, rt, 30 min

Scheme 5.

the viral host cells. From this, it can be concluded that N-1 is essential for 5′-norariste romcyin (**3**) to exert its antiviral properties. Also the structural prototype represented by **5** and **20** does not lend itself to development for inhibiting the orthopox or flaviviruses, which are particular interest to our group.

EXPERIMENTAL SECTION

General methods. Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. Combustion analyses were performed by Atlantic Microlab, Inc., Norcross, GA. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer (operated at 250 and 62.5 MHz, respectively) and are referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The spin multiplicities are indicated by



Reaction conditions: *a*, Ac_2O, pyridine, DMAP, CH_2Cl_2; *b*, *Pseudomonas cepacia* lipase, NaOH, NaH_2PO_4 buffer, acetone; *c*, (i) see steps b and c of Scheme 5; (ii) steps a, b, and c of Scheme 4; *d*, steps b, c, and d of Scheme 5

Scheme 6.

the symbols s (singlet), d (doublet), t (triplet), m (multiplet), and br (broad). Reactions were monitored by thin-layer chromatography (TLC) using 0.5-mm Whatman Diamond silica gel 60-F_{254} precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous) materials.

(1*S*,2*R*,3*S*,4*R*)-4-(4′-Amino-3′-nitro-2′-pyridyl)amino-2,3-*iso*propylidene-dioxycyclopentane-1, 2, 3-triol (17). To a solution of 4-amino-2-chloropyridine (**14**) (2.0 g, 15.6 mmol) in conc. sulfuric acid (96%, 20 mL) at 0°C was added fuming nitric acid (10 mL, 90%) in a dropwise manner. The reaction was stirred for 30 min at the same temperature and then poured into crushed ice in a beaker. This pH of the mixture was adjusted to 3 by cautiously adding conc. ammonium hydroxide while maintaining the temperature below 10°C. The resulting solid was filtered and washed with ice-H_2O (2×10 mL) to give **15** as an off-white solid, which was directly used in the next step without further purification.

The nitramine from the last step was added, in small portions to well-stirred, ice-cooled conc. sulfuric acid (40 mL, 96%). The mixture was heated at 75°C for 1.5 h and then poured into crushed ice in a beaker. This mixture was basified to pH 8 by adding, cautiously, conc. ammonium hydroxide while maintaining the temperature below 10°C. The resulting solid was recovered by filtration and dried to give a yellow solid (1.8 g, 74%) that was purified by column chromatography with hexanes-EtOAc (1:1) to give 4-amino-2-chloro-3-nitropyridine (**13**)[19] as a yellow solid, mp, 202–203°C (lit.[25] 205–207°C): ^{1}H NMR (DMSO) δ 7.89 (d, $J = 5.90$ Hz, 1H), 7.35 (brs, 2H), 6.81(d, $J = 5.90$ Hz, 1H) and 4-amino-2-chloro-5-nitropyridine (**16**) also as a yellow solid, mp, 153–154°C (lit.[25] 155–156°C): ^{1}H NMR (DMSO) δ 8.84 (s, 1H), 8.10 (brs, 2H), 6.95 (s, 1H).

A mixture of **8**[20] (519 mg, 3 mmol) and the newly prepared **13** (622 mg, 3.6 mmol) in 1-butanol (10 mL) containing triethylamine (0.2 mL) was refluxed for 36 h. The mixture was then evaporated and purified by column chromatography (hexanes-EtOAc, 10:1) to give **17** as a yellow solid (0.75 g, 81%), mp, 174–175°C: ^{1}H NMR (DMSO) δ 9.27 (d, $J = 8.10$ Hz, 1H), 8.08 (s, 2H), 7.66 (d, $J = 8.10$ Hz, 1H), 6.09 (d, $J = 5.84$ Hz, 1H), 5.49 (d, $J = 2.47$ Hz, 1H), 4.57 (t, $J = 9.29$, 7.16 Hz, 1H), 4.38 (m, 2H), 4.07 (m, 1H), 3.30 (s, 1H), 2.10 (m, 1H), 1.60 (d, $J = 14.0$ Hz, 1H), 1.33 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (DMSO) δ 153.231, 152.898, 151.014, 115.828, 109.043, 101.027, 85.552, 85.362, 75.871, 55.279, 34.770, 26.153, 23.709. Anal. Calcd for $C_{13}H_{18}O_5N_4$: C, 50.31; H, 5.84, N, 18.05; Found: C, 50.57; H, 5.94, N, 18.06.

(1′*R*,2′*S*,3′*R*,4′*S*)-7-Amino-3-(2′,3′,4′-trihydroxycyclopent-1′-yl)-3*H*-imidazo[4,5-*b*]pyridine (5). Compound **17** (630 mg, 2.1 mmol) in absolute EtOH (30 mL) was hydrogenated overnight at 40 psi in the presence of palladium on charcoal (10% wt, 300 mg). The catalyst was removed by filtration through a pad of Celite and the filtrate removed under reduced pressure to give the triamino-derivative as colorless solid. A mixture of this solid and formamidine acetate (340 mg, 3.0 mmol) in 2-methoxyethanol (10 mL) was refluxed for 3 h under a N_2 atmosphere. The reaction mixture was concentrated in vacuo to give a residue, which was purified by column chromatography (CH_2Cl_2/MeOH, 10:1) to give (1′*R*,2′*S*,3′*R*,4′*S*)-7-amino-3-(4′-hydroxy-2′,3′-*O*-*iso*propylidenedioxycyclopent-1′-yl)-3*H*-imidazo[4,5-*b*]pyridine (**18**) as a white solid (320 mg,

53%) and **19** (180 mg, 30%). **18**, ^{1}H NMR (DMSO) δ 8.15 (s, 1H), 7.76 (d, $J = 5.40$ Hz, 1H), 6.30 (m, 3H), 5.64 (s, 1H), 4.88 (m, 1H), 4.80 (m, 1H), 4.49 (d, $J = 7.45$Hz, 1H), 4.12 (s, 1H), 2.43 (m, 1H), 2.11 (m, 1H), 1.40 (s, 3H), 1.18 (s, 3H); **19**, ^{1}H NMR (DMSO) δ 12.52 (brs, 1H), 8.02 (s, 1H), 7.69 (d, $J = 5.80$ Hz, 1H), 6.71 (d, $J = 5.80$ Hz, 1H), 6.40 (d, $J = 9.27$ Hz, 1H), 5.55 (s, 1H), 4.55(m, 1H), 4.43 (s, 2H), 4.08 (d, $J = 3.12$ Hz, 1H), 2.16 (m, 1H), 1.63 (d, $J = 14.00$ Hz, 1H), 1.33 (s, 3H), 1.16 (s, 3H). Compound **18** was used for the next step without further characterization.

Compound **18** (200 mg, 0.69 mmol) was dissolved in 0.5 N HCl (20 mL) in MeOH. This mixture was stirred at rt for 0.5 h and then evaporated to dryness under reduced pressure. The residue was dissolved in MeOH again and neutralized with IRA-67 resin. The mixture was filtered and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (EtOAc-MeOH, 10:1) to give 5 (130 mg, 75%) as a white solid, mp > 230°C dec: ^{1}H NMR (DMSO) δ 8.08 (s, 1H), 7.69 (d, $J = 5.43$ Hz, 1H), 6.41 (s, 2H), 6.33 (d, $J = 5.43$ Hz, 1H), 5.93 (s, 1H), 5.02 (d, $J = 4.65$ Hz, 1H), 4.84 (d, $J = 3.2$ Hz, 1H), 4.63 (m, 1H), 4.57 (s, 1H), 3.88 (s, 1H), 3.75 (s, 1H), 2.57 (m, 1H), 1.79 (m, 1H); ^{13}C NMR (DMSO) δ 147.50, 146.28, 143.47, 140.03, 123.57, 101.86, 76.99, 75.35, 73.92, 58.83, 36.35; Anal. Calcd for $C_{11}H_{14}N_4O_3 \cdot 0.05H_2O$: C, 52.58; H, 5.61; N, 22.30. Found: C, 52.93; H, 5.69; N, 21.97.

(1*R*, 4*S*)-4-(*N*-Phthalimidyl)-2-cyclopenten-1-ol (23). To a solution of the potassium salt of phthalimide (6.56 g, 34.6 mmol) in anhydrous DMSO (40 mL) was added triphenyl phosphine (518 mg, 6 mol%) and *tetrakis*(triphenylphosphine)palladium (1.38 g, 4 mol%). The mixture was stirred for 5 min and a solution of **22**[7] (8.5 g, 34.6 mmol) in freshly distilled THF (200 mL) was added to the above mixture. The resulting mixture was immediately transferred to a preheated oil bath at 50°C and the mixture was stirred for 16 h. The solvent was removed at reduced pressure and the residue was slurried in CH_2Cl_2 (200 mL) and filtered. The filtrate was washed with brine (150 mL), dried (Na_2SO_4) and filtered. After removal of the solvent, the residue was purified by column chromatography with hexanes-EtOAc (10:1 → 5: 1) to give **23** as a light yellow solid (3.70 g, 57%) whose ^{1}H and ^{13}C NMR spectra were identical with reported value.[20]

(1′*S*,2′*R*,3′*S*,4′*R*)-7-Amino-3-(2′,3′,4′-trihydroxycyclopent-1′-yl)-3*H*-imidazo[4,5-*b*]pyridine (20). Compound **20** was synthesized from **23** by the method described for the preparation of **5**. Anal. Calcd for $C_{11}H_{14}N_4O_3 \cdot 0.25H_2O$: C, 51.88; H,5.69; N, 21.99. Found: C, 51.87; H, 5.74; N, 21.72.

(±)-4-(*N*-Phthalimidyl)-2-cyclopenten-1-ol (24). To an ice-cold mechanically stirred mixture of freshly cracked cyclopentadiene (23.50 g, 0.35 mol), Na_2CO_3 (106 g, 1.00 mol) and CH_2Cl_2 (500 mL) was added dropwise 32% peracetic acid (47.89 mL) that had been pretreated with NaOAc (2.66 g). After the addition was complete, the reaction was stirred at rt for 6 h, until a negative starch-iodide test was obtained. The mixture was filtered, and the filtrate evaporated under reduced pressure to afford crude cyclopentene-3,4-epoxide, which was used directly in the next step.

A solution of the crude epoxide in dry THF (200 mL) and DMSO (30 mL) was treated with potassium salt of phthalimide (52.3 g, 276 mmol) and *tetrakis*(triphenylphosphine)palladium (1.4 g, 1.21 mmol). The mixture was refluxed under N_2

atmosphere for 3 h and at rt for overnight. The solid was then filtered and solvent was removed under reduced pressure. The residue was dissolved in EtOAc (500 mL), washed with brine (2 × 100 mL) and dried (Na_2SO_4). The mixture was filtered and the filtrate evaporated. The residue was purified by column chromatography with hexanes-EtOAc (3:1) to give a light yellow solid (33 g, 41%, two steps), which was recrystallized from EtOAc and hexanes to give a white solid, whose ^1H and ^{13}C NMR spectra were identical with reported values.[20]

(1*S*, 4*R*)-4-(*N*-Phthalimidyl)-2-cyclopenten-1-ol (25) and (1*R*, 4*S*)-1-Acetoxy-4-(*N*-phthalimidyl)-2-cyclopentene (26). To a solution of **24** (11.4 g, 50 mmol) and Ac_2O (6.3 mL) in dry CH_2Cl_2 (200 mL) at 0°C was added pyridine (4.68 g) and DMAP (250 mg). The mixture was then stirred at rt for 20 h, washed with ice-cooled saturated $NaHCO_3$ (3 x 50 mL), 1N HCl (3 × 50 mL), brine (50 mL) and dried ($MgSO_4$). The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography with hexanes-EtOAc (3:1) to give the monoacetate as a white solid racemate (12.0 g, 89%).

The pH of a suspension of this racemic acetate (2.7 g, 10 mmol) in phosphate buffer solution (0.1 M, 17 mL) and acetone (5 mL) was adjusted to 7 with 6 M NaOH solution and to the stirred mixture was added *Pseudomonas cepacia* lipase (PCL) (Amano International Enzyme Corporation) (200 mg). During the hydrolysis, the continuous addition of NaOH (10 mL, 0.5 M, 1.05 equiv) maintained the pH *ca.* 7. After 18 h, the mixture was filtered over a pad of Celite, the filtrate extracted with EtOAc (3 × 50 mL), and the combined extracts dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography using hexanes-EtOAc (3:1) to give **26** (1.3 g, 48%) as a white solid and **25** (1.0 g, 45%) as a white solid. **26**: ee,[a] 99%, mp 223°C dec; ^1H NMR ($CDCl_3$) δ 7.80 (m, 2H), 7.71 (m, 2H), 6.10 (m, 1H), 5.99 (m, 1H), 5.68 (m, 1H), 5.26 (m, 1H), 2.86 (m, 1H), 2.17 (m, 1H), 2.04 (s, 3H). **25**: ee,[a] 95%; the ^1H and ^{13}C NMR spectra of **25** were identical with reported values.[20]

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REFERENCES

1. Shealy, J.D.; Clayton, J.D. 9-[β-DL-2α,3α-dihydroxy-4β-(hydroxymethyl)-cyclopentyl]adenine, the carbocyclic analog of adenine. J. Am. Chem. Soc. **1966**, *88*, 3885–3887.

2. Lim, M.-I.; Marquez, V.E. Total synthesis of (−)-neplanocin A. Tetrahedron Lett. **1984**, *25*, 5559–5562.
3. Vince, R.; Hua, M. Synthesis and anti-HIV activity of carbocyclic 2′,3′-didehydro-2′,3′-dideoxy-2,6-disubstituted purine nucleosides. J. Med. Chem. **1990**, *33*, 17–21.
4. De Clercq, E.; Bernaerts, R.; Shealy, Y.F.; Montgomery, J.A. Broad-spectrum antiviral activity of carbodine, the carbocyclic analogue of cytidine. Biochem. Pharmacol. **1990**, *39*, 319–325.
5. Wu, J.; Schneller, S.W.; Seley, K.L.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. Carbocyclic oxetanocins lacking the C-3′-methylene. J. Med. Chem. **1997**, *40*, 140101406.
6. Crimmins, M.T. New developments in the enantioselective synthesis of cyclopentyl carbocyclic nucleosides. Tetrahedron **1998**, *54*, 9229–9272.
7. Siddiqi, S.M.; Chen, X.; Schneller, S.W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. Antiviral enantiomeric preference for 5′-noraristeromycin. J. Med. Chem. **1994**, *37*, 551–554.
8. Seley, K.L.; Schneller, S.W.; Korba, B. A 5′-noraristeromycin enantiomer with activity towards hepatitis B virus. Nucleosides Nucleotides **1997**, *16*, 2095–2099.
9. Siddiqi, S.M.; Chen, X.; Rao, J.; Schneller, S.W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. 3-Deaza- and 7-deaza-5′-noraristeromycin and their antiviral properties. J. Med. Chem. **1995**, *38*, 1035–1038.
10. Seley, K.L.; Schneller, S.W.; Rattendi, D.; Bacchi, C.J. (+)-7-Deaza-5′-noraristeromycin as an anti-trypanosomal agent. J. Med. Chem. **1997**, *40*, 622–624.
11. Seley, K.L.; Schneller, S.W.; Korba, B. Does the anti-hepatitis B virus activity of (+)-5′-noraristeromycin exist in its 4′-epimer and 4′-deoxygenated derivatives? J. Med. Chem. **1998**, *41*, 2168–2170.
12. Patil, S.D.; Schneller, S.W.; Hosoya, M.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. Synthesis and antiviral properties of (±)-5′-noraristeromycin and related purine carbocyclic nucleosides. A new lead for anti-human cytomegalovirus agent design. J. Med. Chem. **1992**, *35*, 3372–3377.
13. Wolfe, M.S.; Borchardt, R.T. S-Adenosyl-L-homocysteine hydrolase as a target for antiviral chemotherapy. J. Med. Chem. **1991**, *34*, 1521–1523.
14. Ohno, H.; Itoh, T.; Nomura, A.; Mizuno, Y. Studies on the chemical synthesis of potential antimetabolites. Nucleosides Nucleotides **1984**, *3*, 345–351.
15. De Clercq, E. Vaccinia virus inhibitors as a paradigm for the chemotherapy of poxvirus infections. Clin. Microbiol. Rev. **2001**, *14*, 382–397.
16. Siddiqi, S.M.; Chen, X.; Schneller, S.W. Enantiospecific synthesis of 5′-noraristeromycin and its 7-deaza derivative and a formal synthesis of (−)-5′-homoaristeromycin. Nucleosides Nucleotides **1993**, *12*, 267–278.
17. Rajappan, V.; Schneller, S.W.; Williams, S.L.; Kern, E.R. The enantiomers of carbocyclic 5′-norguanosine: activity towards Epstein–Barr virus. Bioorg. Med. Chem. **2002**, *10*, 883–886.
18. Antonini, I.; Cristalli, G.; Franchetti, P.; Grifantini, M.; Martelli, S.; Petrelli, F. Deaza analogs of adenosine as inhibitors of blood platelet aggregation. J. Pharm. Sci. **1984**, *73*, 366–369.
19. Deady, L.W.; Korytsky, O.L.; Rowe, J.E. Substituent effects on the isomer ratios in the rearrangement of some 2- and 4-nitraminopyridines. Aust. J. Chem. **1982**, *35*, 2025–2034.

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20. Rajappan, V.P.; Hegde, V.R.; Schneller, S.W. A protected form of (1*S*,2*R*,3*S*,4*R*)-4-aminocyclopentane-1,2,3-triol, a useful precursor to 5′-nor carbocyclic nucleosides. Synth. Commun. **2001**, *31*, 2849–2854.
21. Deardorff, D.R.; Linde, R.G., II; Martin, A.M.; Shulman, M.J. Enantioselective preparation of functionalized cyclopentanoids via a common chiral (π-allyl)palladium complex. J. Org. Chem. **1989**, *54*, 2759–2762.
22. Das, S.R.; Schneller, S.W.; Balzarini, J.; De Clercq, E. A mercapto analog of 5′-noraristeromycin. Bioorg. Med. Chem. **2002**, *10*, 457–460.
23. Barnard, D.L.; Stowell, V.D.; Seley, K.L.; Hegde, V.R.; Das, S.R.; Rajappan, V.P.; Schneller, S.W.; Smee, D.F.; Sidwell, R.W. Inhibition of measles virus replication by 5′-nor carbocyclic adenosine analogues. Antivir. Chem. Chemother. **2001**, *12*, 241–250.
24. Das, S.R.; Schneller, S.W.; Balzarini, J.; De Clercq, E. 5′-Nor carbocyclic 5′-deoxy-5′-(*iso*butylthio)adenosine and a 2′,3′-dideoxy-2′,3′-didehydro derivative. Antivir. Chem. Chemother. **2001**, *12*, 119–124.
25. Talik, Z.; Plazek, E. Rocz. Chem. **1956**, *30*, 1139–1149.

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