Notes

5′-Amino-5′-deoxy-5′-noraristeromycin

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Introduction

In 1990[1] we became interested in investigating nucleosides lacking the C-5′ methylene group. In visualizing the target compounds, it was apparent that such derivatives based on the common furanose framework would not be possible due to the presence of the hemiacetal center (as represented by the adenine system **1**) that would simply unravel to the heterocyclic base and a 1,4-dialdehyde. This limitation was circumvented by considering the carbocyclic relative, with **2** (5′-noraristeromycin) as the parent compound. This has been a fruitful pursuit.[2]

We have been equally interested in 5′-amino-5′-deoxy derivatives (e.g., **3**), but recognizing that similar stability problems as with **1** were likely, the 5′-nor carbocyclic derivative **4** became a target compound. The synthesis of **4**[3] has been accomplished, as reported here.

Chemistry

A review of the literature[4] suggested that the most straightforward pathway to **4** should begin with the palladium-catalyzed amination of the allylic acetate **6** (which is obtained from the known[5] alcohol **5**) to **7** using NaN_3 (Scheme 1). Compound **7** was indeed obtained; however, attempts to convert **7** into glycol **8** were unsuccessful. Our attention then turned to a more stepwise route whereby the intermediate azide **9** (Scheme 2) was obtained using $Pd_2(dba)_3(CHCl_3)$[4] as the catalyst. Debenzoylation of **9** afforded **10**, which upon glycolization gave **11**. Catalytic hydrogenation of **11** produced the desired **4**.

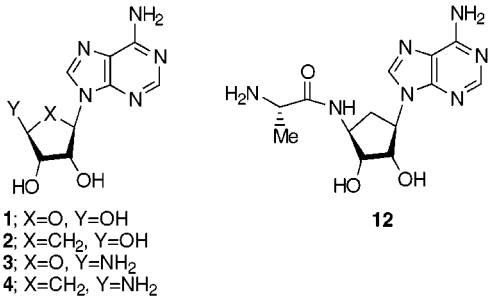
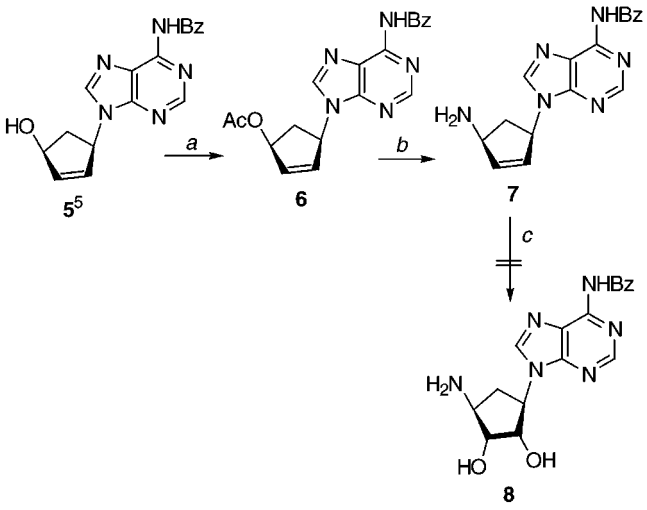


Figure 1.

Scheme 1[a]



[a] Reaction conditions: *a*, Ac_2O, pyridine, DMAP; *b* NaN_3 $Pd(PPh_3)_4$, 50 °C; *c*, OsO_4, 60% aq 4-methylmorpholine *N*-oxide in THF/H_2O.

Although the literature[4] suggests that the coupling of the azide (as in the synthesis of **9**) can produce either epimer at the C-4′ position, an NMR analysis utilizing COSY techniques showed that the product obtained had the desired stereochemistry. A coupling constant of 2.8 Hz between the protons on C-3′ and C-4′ is consistent with a trans configuration according to Karplus correlations measuring the dihedral angles.

Although precedence in our laboratory[6] and the research of others[7] indicates that the configuration of the 4′-amino group of **4** is as shown, this was initially confirmed by the use of COSY NMR techniques to assign the cyclopentyl protons and coupling constants. Concurrent with the NMR analysis, construction of an energy-minimized computer molecular model[8] provided a heat of formation of −32.0 kcal/mol for **4**. Next, using the Karplus equation and the dihedral angles present in the aforementioned molecular model, the theoretical coupling

(1) Koga, M.; Schneller, S. W. *Tetrahedron Lett.* **1990**, *31*, 5861.
(2) (a) Siddiqi, S. M.; Chen, X.; Schneller, S. W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1994**, *37*, 551. (b) Seley, K. L.; Schneller, S. W.; Rattendi, D.; Bacchi, C. J. *J. Med. Chem.* **1997**, *40*, 622. (c) Seley, K. L.; Schneller, S. W.; Korba, B. *Nucleosides Nucleotides* **1997**, *16*, 2095.
(3) Reports on derivatives of **4**, but not the free amine, have appeared in the literature. For a leading reference, see: Vogt, P. F.; Hansel, J.-G.; Miller, M. J. *Tetrahedron Lett.* **1997**, *38*, 2903.
(4) Murahashi, S.-I.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292.
(5) Siddiqi, S. M.; Chen, X.; Schneller, S. W. *Nucleosides Nucleotides* **1993**, *12*, 267.
(6) Koga, M.; Schneller, S. W. *J. Org. Chem.* **1993**, *58*, 6471.
(7) Trost, B. M.; Kuo, G.-H.; Benneche, T. A. *J. Am. Chem. Soc.* **1988**, *110*, 621.
(8) Stewart, J. J. P. *J. Comput.-Aided Mol. Des.* **1980**, *4*, 1.

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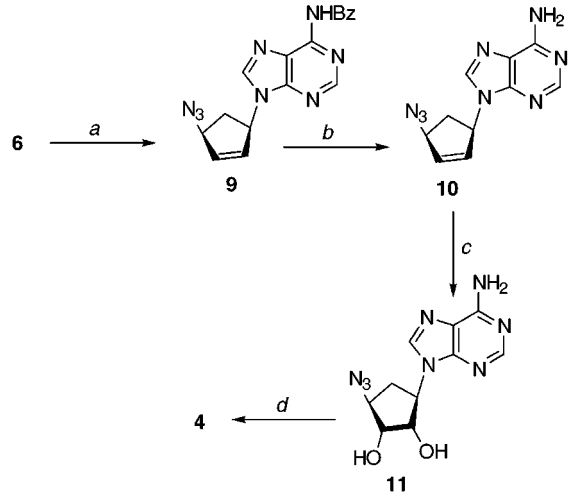
Scheme 2[a]



[a] Reaction conditions: *a*, NaN_3, $Pd_2(dba)_3$ ($CHCl_3$), 1,3-bis-(diphenyl)phosphinopropane, 50 °C; *b*, NH_4OH/MeOH, 110 °C, 3 h; *c*, OsO_4, 60% aq 4-methylmorpholine *N*-oxide in THF/H_2O; *d*, Pd/C, MeOH, H_2, 15 psi, 2 days.

constants were determined.[9] These new latter coupling constants closely matched the observed constants. Using these latter constants, new dihedral angles were determined[9] and utilized for a revised computer model of **4**.[8] This gave a heat of formation of −29.5 kcal/mol, which is acceptably close to the −32.0 kcal/mol of the theoretical model.

Computer modeling of the epimer of **4** provided theoretical coupling constants that were different from those observed for **4**. In addition, the calculated heat of formation for the epimer, −11.0 kcal/mol, was less favorable than that of **4**. Thus, from this analysis, it is concluded that the 4′-amino compound is correctly depicted as **4**.

To ensure that the 2′,3′-diol function of **4** was in the desired configuration (rather than the "up" orientation), the ^{13}C NMR spectrum of **4** was found to be in agreement with that of **12**.[10]

Results

Compounds **4** and **11** were evaluated for their effectiveness toward HBV, influenza A, influenza B, adenovirus, respiratory syncytial virus, measles, varicella zoster virus, cytomegalovirus, vesicular stomatitis, sindbis virus, punta toro virus, coxsackie B4 virus, reovirus, HSV, HIV, and vaccinia virus. Neither of these agents proved as effective as the control drugs.

The azide derivative **11** is also foreseen as a potential photoaffinity label for determining the mechanism by which **2** is active toward cytomegalovirus.[2a] It is also worth noting that the moderate activity of **4** toward vesicular stomatitis virus (0.13 μg/mL) and vaccinia virus (0.64 μg/mL) suggests[11] that it may be acting via inhibition of *S*-adenosylhomocysteine hydrolase. More detailed biological studies will be forthcoming.

(9) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.
(10) Ghosh, A.; Ritter, A. R.; Miller, M. J. *J. Org. Chem.* **1995**, *60*, 5808.
(11) Siddiqi, S. M.; Chen, X.; Schneller, S. W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1994**, *37*, 1382.

Experimental Section

General. Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. Combustion analyses were performed by M-H-W Laboratories, Phoenix, AZ. ^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 the symbols s (singlet), d (doublet), t (triplet), p (pentet), m (multiplet), and br (broad). IR spectra were recorded on a Nicolet 5PC spectrometer. Reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm Whatman Diamond silica gel 60-F_{254} precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. Column chromatography was performed on Whatman silica, 230−400 mesh, 60 Å, and elution was with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials.

(1*R*,4*S*)-4-Acetoxy-1-(6-amino-9*H*-purin-9-yl)cyclopent-2-ene (6). To a solution of **5**[5] (2.5 g, 7.77 mmol) in anhydrous CH_2Cl_2 (150 mL) and anhydrous DMF (30 mL) stirring at 0 °C were added anhydrous pyridine (0.73 g, 9.2 mmol), (dimethylamino)pyridine (0.02 g, 1.6 mmol), and acetic anhydride (0.92 g, 9.2 mmol). The reaction mixture was stirred at 0 °C for 30 min, followed by stirring at room temperature for 3 h. The reaction mixture was cooled to 0 °C and quenched with a saturated $NaHCO_3$ solution (150 mL), and the organic layer was separated and washed with ice-cold 1 N HCl (2 × 150 mL). The organic layer was then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified via column chromatography, eluting with CH_2Cl_2/MeOH (98:2) to afford 2.6 g (92%) of **6** as an off-white foam: ^1H NMR ($CDCl_3$) δ 1.95 (dt, 1H), 2.09 (s, 3H), 3.11 (p, 1H), 5.78 (m, 2H), 6.22 (d, 1H), 6.37 (d, 1H), 7.44−7.55 (m, 3H), 8.02 (m, 2H), 8.08 (s, 1H), 8.79 (s, 1H), 9.40 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 20.9, 38.6, 57.0, 76.8, 122.2, 127.9 (2), 128.8 (2), 132.4, 133.6, 133.8, 135.9, 141.3, 149.6, 151.5, 152.6, 164.8, 170.5. Anal. Calcd for $C_{19}H_{17}N_5O_3 \cdot H_2O$: C, 60.01; H, 5.00; N, 18.29. Found: C, 60.03; H, 5.22; N, 18.52.

(1*R*,4*S*)-*N*-[9-(4-Amino-2-cyclopentenyl)-9*H*-purin-6-yl]-benzamide (7). A solution of **6** (1.40 g, 4.0 mmol) in THF (50 mL) was treated with $Pd(PPh_3)_4$ (0.23 g, 0.2 mmol), followed by the addition of a solution of NaN_3 (0.26 g, 4.0 mmol) in 5 mL of H_2O, and stirred overnight at room temperature. The reaction mixture was then treated with Ph_3P (1.15 g, 4.4 mmol) and stirred at 50 °C for 2 h. The mixture was then extracted with 2 N HCl (3 × 20 mL), and the combined aqueous layers were made strongly basic with NaOH and extracted further with benzene (3 × 20 mL). The combined organic layers were washed with brine (3 × 20 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was then purified via column chromatography eluting with EtOAc/MeOH (9:1) to give 0.14 g (11.4%) of **7** as a yellow solid; mp 152−154 °C; ^1H NMR ($CDCl_3$) δ 2.22 (dt, 1H), 3.17 (dt, 1H), 5.38 (m, 1H), 5.54 (m, 1H), 5.85 (dd, 1H), 5.93 (br, 2H), 6.23 (dd, 1H), 7.46 (m, 3H), 7.88 (m, 2H), 7.99 (s, 1H), 8.27 (s, 1H), 9.50 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 36.8, 53.8, 61.3, 121.3, 127.3, 128.3, 128.7, 130.1, 130.7, 131.6, 135.2, 137.9, 141.1, 149.2, 152.5, 155.9, 166.8. Anal. Calcd for $C_{17}H_{16}N_6O \cdot 1.5$ MeOH: C, 60.32; H, 5.97; N, 22.83. Found: C, 60.27; H, 5.61; N, 23.06.

(1*R*,4*S*)-*N*-[9-(4-Azido-2-cyclopentenyl)-9*H*-purin-6-yl]-benzamide (9). A solution of **6** (2.18 g, 6.0 mmol) in THF (15 mL) was treated with $Pd_2(dba)_3(CHCl_3)$[4] (0.16 g, 2.5 mol %) and 1,3-bis(diphenyl)phosphinopropane (0.25 g, 10 mol %) dissolved in THF (5 mL). To that solution was added NaN_3 (0.72 g, 7.2 mmol) in 15 mL of water, and the reaction mixture was stirred at 50 °C under N_2 for 10 h. The THF was evaporated under reduced pressure, and the aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). The organic layers were then combined, washed with brine (50 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was further purified by column chromatography, eluting with EtOAc/MeOH (9:1) to afford 1.5 g of **9** (75%) as a yellow foam: mp >50 °C dec; ^1H NMR ($CDCl_3$) δ 1.95 (dt, 1H), 3.13 (dt, 1H), 4.64 (m, 1H), 5.80 (m, 1H), 6.20 (dd, 1H), 6.35 (dd, 1H), 7.55 (m, 3H), 8.02 (m, 2H), 8.05 (s, 1H), 8.08 (s, 1H), 8.80 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 38.7, 57.6, 65.2, 123.2, 128.1, 128.4, 128.9, 132.8, 133.0, 133.9, 135.1, 135.8, 141.2, 149.8, 151.8, 152.6, 165.0; IR (Nujol) 2093 cm^{-1} (azide). Anal. Calcd for $C_{17}H_{14}N_8O \cdot$

0.25 MeOH: C, 58.47; H, 4.23; N, 31.63. Found: C, 58.67; H, 4.58; N, 31.57.

(1*R*,4*S*)-4-Azido-1-(6-amino-9*H*-purin-9-yl)cyclopent-2-ene (10). A solution of **9** (1.5 g, 4.33 mmol) in NH_4OH/MeOH (1:1, 20 mL) was sealed in a steel vessel and heated at 110 °C for 3 h. The vessel was cooled to 0 °C, and the solvents were removed under reduced pressure. The residue was then purified via column chromatography, eluting with EtOAc/MeOH (4:1). Fractions containing product were combined and evaporated to give 1.0 g (97%) of **10** as a white crystalline solid, mp 170−172 °C; ^{1}H NMR ($CDCl_3$) δ 1.96 (dt, 1H), 3.10 (dt, 1H), 4.61 (m, 1H), 5.70 (m, 1H), 6.17 (dd, 1H), 6.29 (dd, 1H), 6.38 (s, 2H), 7.88 (s, 1H), 8.37 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 38.9, 57.4, 65.3, 119.9, 133.5, 135.3, 138.6, 149.9, 153.2, 156.0. Anal. Calcd for $C_{10}H_{10}N_8$: C, 49.58; H, 4.16; N, 46.26. Found: C, 49.72; H, 4.22; N, 46.36.

(1*R*,2*R*,3*R*,4*S*)-4-Azido-1-(6-amino-9*H*-purin-9-yl)cyclopentane-2,3-diol (11). To a solution of **10** (1.0 g, 4.13 mmol) in THF/H_2O (20 mL, 10:1) were added OsO_4 (0.05 g) and 4-methylmorpholine *N*-oxide (1.5 mL). The mixture was stirred at room temperature for 5 h until TLC (EtOAc/MeOH, 4:1) showed no remaining starting material. The solvent was evaporated, and the residue was purified via column chromatography, eluting with EtOAc/MeOH (4:1). Fractions containing product were combined and evaporated to afford 1.10 g (100%) of **11** as a white solid: mp >158 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.04 (dt, 1H), 2.57 (dt, 1H), 3.95 (br, 1H), 4.05 (br, 1H), 4.35 (dd, 1H), 5.00 (dd, 1H), 5.25 (m, 1H), 5.37 (m, 1H), 7.25 (s, 2H), 8.12 (s, 1H), 8.20 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 31.5, 58.6, 63.7, 73.7, 74.6, 119.3, 140.3, 149.4, 152.2, 156.0. Anal. Calcd for $C_{10}H_{12}N_8O_2 \cdot 0.5\ H_2O$: C, 42.28; H, 4.93; N, 39.16. Found: C, 42.56; H, 4.69; N, 38.88.

(1*R*,2*R*,3*R*,4*S*)-4-Amino-1-(6-amino-9*H*-purin-9-yl)cyclopentane-2,3-diol (4). To a solution of **11** (0.64 g, 2.31 mmol) in MeOH (50 mL) was added Pd/C (0.25 g), and the mixture was placed under H_2 and shaken for 48 h at 15 psi. The mixture was filtered over a Celite pad, the pad was rinsed with MeOH, and the filtrate was evaporated under reduced pressure. The residue was then purified via column chromatography, eluting with EtOAc/MeOH (7:3). Fractions containing product were combined and evaporated to afford 0.55 g (95%) of **4** as a white crystalline solid, mp 192−194 °C; $[\alpha]^{23}_D$ −38.3° (*c* 1.04, DMSO); ^{1}H NMR (DMSO-d_6) δ 1.66 (dt, 1H), 2.48 (dt, 1H), 3.11 (br, 1H), 3.67 (dd, 1H), 4.04 (dd, 1H), 4.43 (br, 1H), 4.53 (m, 1H), 4.66 (m, 1H), 7.22 (s, 4H), 8.12 (s, 1H), 8.23 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 36.4, 55.6, 59.1, 75.0, 78.1, 119.3, 140.4, 149.6, 152.2, 156.0. Anal. Calcd for $C_{10}H_{14}N_6O_2 \cdot 0.5\ H_2O$: C, 46.33; H, 5.83; N, 32.41. Found: C, 46.35; H, 5.78; N, 32.80.

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