A Methylated Derivative of 5′-Noraristeromycin

Katherine L. Seley and Stewart W. Schneller*

Department of Chemistry, Auburn University, Auburn, Alabama 36849-5312

Erik De Clercq

Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium

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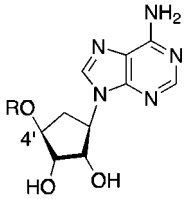
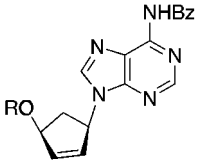
5′-Noraristeromycin in the D-like configuration **1** has been reported by us[1] to possess potent, selective antiviral activity, which correlated with its ability to inhibit *S*-adenosyl-L-homocysteine hydrolase. To determine if a free hydroxyl hydrogen at C-4′ was necessary for the biological properties of **1**, its methyl derivative **2** was sought. The results of this effort are described here.



1, R=H
2, R=Me

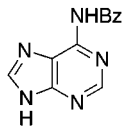


3, R=Me
4, R=H
5, R=Ac

The plan to **2** was to employ a standard glycolization[2] of the 2′,3′-dideoxy-2′,3′-didehydro precursor **3** followed by debenzoylation. The first approach to **3** was to explore direct methylation of compound **4**.[2] Simple base-promoted methylation[3] led to elimination of the heterocyclic base (Scheme 1) while application of less common methylation procedures (for example, using trimethylsilyl diazomethane[4,5]) were unsuccessful.

A second approach to **3** was to consider the palladium(0)-catalyzed coupling of the allylic acetate **5** (obtained from **4**) with methoxide ion.[6] In that effort only compound **4** resulted due to simple deacetylation of **5** by methoxide.

With these difficulties in preparing **3** from **4**, attention turned to the palladium-promoted coupling of **6**[7] and **7**. The initial attempt to compound **7** via a simple methylation of the known[2] (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (**8**) resulted in the base-catalyzed elimination of acetic acid to give cyclopentadiene monoepoxide, in a manner likely to be similar to Scheme 1.



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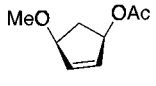

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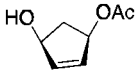

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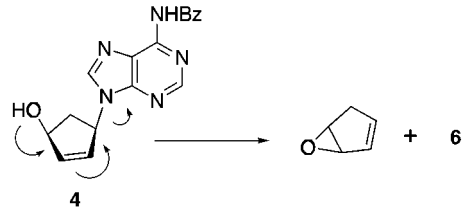
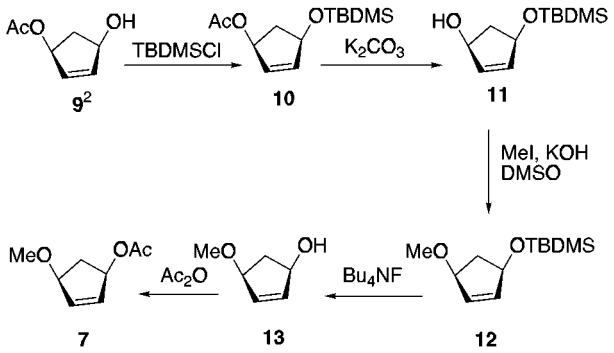
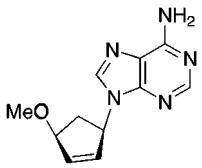
Scheme 1



Scheme 2



Success to **7** was achieved using the tedious series of steps presented in Scheme 2[8] beginning with silylation of the known **9**[2] (the enantiomer of **8**) to **10**. Hydrolysis of **10** provided **11**, which was not susceptible to elimination when treated with standard base-promoted methylation to **12**. Desilylation of **12** gave **13**, which was acetylated to **7**. With the requisite **7** available, the synthesis of **2** was then accomplished by, first, its palladium-catalyzed coupling with N^6-benzoyladenine (**6**) to afford **3**. Subsequent debenzoylation of **3** using ammonium hydroxide in methanol to **14** was followed by glycolization with osmium tetraoxide to give **2**.



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Compound **2** was much less effective against those viruses that were most susceptible to **1** and lacked the potent inhibitory property of **1** toward *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase.[10] Possible reasons for the decreased activity of **2** may be attributed to (1) the steric interference exhibited by the newly introduced methyl group when **2** interacts with the hydrolase and/or (2) loss of the biologically necessary proton from the 4′-hydroxyl of **1**. Regardless, this data indicates that

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(2) Siddiqi, S. M.; Chen, X.; Schneller, S. W. *Nucleosides Nucleotides* **1993**, *12*, 267.
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(8) For related work see: Nokami, J.; Matsuura, H.; Nakasima, K.; Shibata, S. *Chem. Lett.* **1994**, 1071.
(9) Siddiqi, S. M.; Chen, X.; Rao, J.; Schneller, S. W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1995**, *38*, 1035.
(10) These assays were conducted using methods previously described by us (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).

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preservation of the proton on the 4′-hydroxyl of **1** is important for its antiviral activity and inhibition of the hydrolase.

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. ^{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), t (triplet), q (quartet), m (multiplet), and br (broad). Optical rotations were measured on a JASCO DIP-370 polarimeter. 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 or exposure to iodine vapor. Column chromatography was performed on Whatman silica, 230−400 mesh, 60 Å, and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials.

(1*R*,4*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-methoxycyclopent-2-ene (12). A solution of (−)-(1*S*,4*R*)-4-hydroxy-2-cyclopenten-1-yl acetate[2] (24.66 g, 0.17 mol) in anhydrous DMF (300 mL) was treated with imidazole (29.5 g, 0.43 mol) and TBDMSCl (31.45 g, 0.21 mol) and the clear solution stirred at rt for 6 h under N_2.[8] The reaction mixture was treated with 300 mL of ice−water and 300 mL of ether and the organic layer separated, washed with brine (3 × 500 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with hexane/EtOAc (4:1) to afford 44.0 g of **10** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ -0.08 (s, 6H), 0.86 (s, 9H), 1.57 (dt, 1H), 2.06 (s, 3H), 2.83 (dt, 1H), 4.72 (t, 1H), 5.48 (t, 1H), 5.87 (d), 5.98 (d, 1H); ^{13}C NMR ($CDCl_3$) δ −4.7, 18.1, 25.7, 41.1, 74.8, 76.89, 131.1, 138.8, 170.8.

To a suspension of K_2CO_3 (5.4 g, 39.0 mmol) in MeOH (100 mL) was added **10** (10.0 g, 39.0 mmol) and stirred at rt for 30 min.[8] The solvent was removed under reduced pressure and the residue dissolved in ether (300 mL) and washed with brine (300 mL). The organic layers were combined, dried (Na_2SO_4), and evaporated to afford **11** (7.7 g crude) as a colorless syrup which was used immediately in the next step.

To a suspension of crushed KOH (8.06 g, 61.70 mmol) in DMSO (50 mL) that had been stirring at rt for 15 min was added **11**, obtained in the previous step, followed immediately by the dropwise addition of MeI (10.21 g, 71.94 mmol).[3] The reaction mixture was then stirred at rt for 4 h, after which it was poured onto ice and extracted with CH_2Cl_2 (3 × 200 mL). The organic layers were combined and washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified via column chromatography eluting with hexane/EtOAc (10:1, followed by 4:1) to afford 5.1 g (62%) of **12** as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ −0.08 (s, 6H), 0.86 (s, 9H), 1.57 (dt, 1H), 2.65 (dt, 1H), 3.33 (s, 3H), 4.26 (t, 1H), 4.67 (t, 1H), 5.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −4.7, 18.1, 25.8, 40.8, 55.7, 74.8, 83.0, 132.4, 137.5. Anal. Calcd for $C_{12}H_{24}O_2Si$: C, 63.28; H, 10.54. Found: C, 63.13, H, 10.61.

(1*R*,4*S*)-4-Methoxy-2-cyclopenten-1-yl Acetate (7). A solution of **12** (5.1 g, 22.2 mmol) and Bu_4NF (1.0 M sol in THF, 47 mL, 47 mmol) was stirred at rt for 3 h. The solvent was evaporated under reduced pressure and the residue was purified via column chomatography eluting with hexane/EtOAc (5:1, followed by 2:1) to afford 1.5 g (59%) of **13** as a colorless syrup, which was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 1.57 (dt, 1H), 2.65 (dt, 1H), 3.06 (br, 1H), 3.34 (s, 3H), 4.24 (q, 1H), 4.60 (q, 1H), 6.01 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 40.1, 56.1, 74.5, 83.3, 133.2, 137.4.

To a chilled stirring solution of **13** (1.5 g, 13.1 mmol) in dry CH_2Cl_2 (30 mL) were added pyridine (1.5 g, 19.5 mmol), DMAP (0.05 g), and acetic anhydride (1.9 g, 19.5 mmol).[9] The reaction mixture was stirred overnight at rt, at which point it was treated with saturated $NaHCO_3$ solution (50 mL) and stirred vigorously for 15 min. The organic layer was separated, washed with ice-cold 1 N HCl (50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified via column chromatography, eluting with hexane/EtOAc (19:1) to give 1.2 g (58%) of **7** as a yellow syrup: ^{1}H NMR ($CDCl_3$) δ 1.57 (dt, 1H), 1.97 (s, 3H), 2.66 (m, 1H), 3.30 (s, 3H), 4.24 (t, 1H), 5.44 (t, 1H), 6.05 (dd, 2H); ^{13}C NMR ($CDCl_3$) δ 21.0, 36.8, 56.1, 76.5, 82.9, 132.9, 135.7, 170.7. Anal. Calcd for $C_8H_{12}O_3$: C, 61.70; H, 7.71. Found: C, 61.60, H, 7.68.

(1*R*,4*S*)-4-Methoxy-1-(6-amino-9*H*-purin-9-yl)cyclopent-2-ene (14). To a solution of N^6-benzoyladenine[7] (2.02 g, 8.41 mmol) in dry DMSO (30 mL) was added NaH (0.23 g, 8.62 mmol, 95%). The mixture was stirred at rt under an argon atmosphere for 30 min. Tetrakis(triphenylphosphine)palladium (0.61 g, 0.53 mmol), Ph_3P (0.23 g, 0.88 mmol), and a solution of **7** (1.2 g, 7.65 mmol) in dry THF (30 mL) was added.[2] The mixture was stirred at 55 °C for 2 days. The volatiles evaporated under reduced pressure, and the residue was slurried in CH_2Cl_2 and filtered. The filtrate was washed with brine and evaporated. The residue was purified via column chromatography eluting with EtOAc/MeOH (19:1, followed by 9:1) to afford 2.2 g of **3** as a gum, which was used directly in the next reaction, without further purification.

A solution of **3** (2.2 g, 4.09 mmol) in NH_4OH/H_2O (1:1, 100 mL) was sealed in a steel vessel and heated at 110 °C for 2 days. 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 (19:1, followed by 10:1). Fractions containing product were combined and evaporated to give 0.69 g (39% from N^6-benzoyladenine) of **14** as a white crystalline solid: mp 155−156 °C; ^{1}H NMR (DMSO-d_6) δ 1.80 (dt, 1H), 2.87 (m, 1H), 3.27 (s, 3H), 4.45 (t, 1H), 5.48 (t, 1H), 6.20 (dd, 2H), 7.25 (br, 2H), 7.95 (s, 1H), 8.15 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 37.9, 55.9, 56.5, 83.1, 118.8, 132.8, 135.8, 138.6, 149.1, 152.4, 156.0. Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.31; H, 5.64; N, 30.16. Found: C, 57.06; H, 5.60; N, 30.35.

(1*R*,2*R*,3*R*,4*S*)-4-Methoxy-1-(6-amino-9*H*-purin-9-yl)cyclopentane-2,3-diol (2). To a solution of **14** (0.50 g, 2.15 mmol) in THF/H_2O/acetone (75 mL, 1:1:1) were added OsO_4 (0.03 g) and 4-methylmorpholine *N*-oxide (1 mL).[2] The mixture was stirred at rt overnight until TLC (EtOAc/MeOH, 5:1) showed no remaining starting material. The solvent was evaporated, and the residue was purified via column chromatography, eluting with EtOAc/MeOH (9:1). Fractions containing product were combined and evaporated to afford 0.17 g (30%) of **2** as a white solid: mp 230−231 °C; $[\alpha]^{23}_D$ 37.6° (*c* 0.20, DMF); ^{1}H NMR (DMSO-d_6/D_2O) δ 1.99 (m, 1H), 2.61 (m, 1H), 3.31 (s, 3H), 3.64 (d, 1H), 3.91 (d, 1H), 4.42 (q, 1H), 4.63 (q, 1H), 8.14 (s, 1H), 8.17 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 33.1, 56.5, 58.1, 73.3, 74.3, 84.0, 119.3, 140.1, 149.8, 152.2, 156.0. Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.98; H, 5.68; N, 26.31. Found: C, 49.85; H, 5.65; N, 26.14.

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