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# The Importance of the 4′-Hydroxyl Hydrogen for the Anti-Trypanosomal and Antiviral Properties of (+)-5′-Noraristeromycin and Two 7-Deaza Analogues

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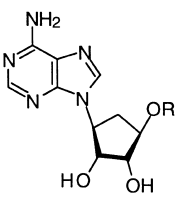
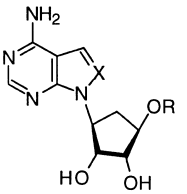
**Abstract**—(+)-5′-Noraristeromycin (**1**) has shown significant antiviral activity while its 7-deaza analogue **2** is an anti-trypanosomal candidate. To determine the relevance of the 4′-hydroxyl hydrogen in these activities, a derivative of **1** (that is, **3**) where the C-4′ hydroxyl hydrogen has been replaced by a methyl group has been prepared beginning with palladium (0) mediated coupling of the sodium salt of $N^6$-benzoyladenine (**9**) and (1*S*,4*R*)-4-methoxy-2-cyclopenten-1-yl acetate (**5**). The synthesis of compound **5** is described from (1*S*,4*R*)-1-[(*tert*-butyldimethylsilyl)oxy]-4-hydroxy-cyclopent-2-ene (**6**) in three steps. Analogous preparations of the 7-deaza and 8-aza-7-deaza derivatives of **3** related to **2** (that is, **4** and **12**) are also reported. The new derivatives (**3**, **4**, and **12**) failed to show improved antiviral activity. Compound **12** was the only derivative with some anti-trypanosomal activity, giving 40% inhibition of growth at 100 μM against bloodstream forms of a *Typanosoma brucei brucei* isolate in a standard in vitro screen. This study indicated that the C-4′-hydroxyl hydrogen plays a role in the medicinal properties of **1** and **2**. 

## Introduction

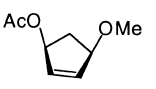
In the search for new medicinal agents derived from nucleosides, recent successes with analogues in the L-configuration have been surprising due to their unnatural structure.[1] Our investigations have uncovered two L-like carbocyclic nucleosides with promising activity: (+)-5′-noraristeromycin (**1**) with potency towards hepatitis B virus[2] and (+)-7-deaza-5′-noraristeromycin (**2**) with effectiveness as an anti-trypanosomal candidate.[3] To explore the structural features of **1** and **2** that are necessary for their respective activities, attention has focused on the role of the C-4′ hydroxyl hydrogen by considering the methyl derivatives (**3** and **4**). The results of this investigation are described.




**1**, R = H
**3**, R = Me




**2**, X = CH; R = H
**4**, X = CH; R = Me
**12**, X = N; R = Me




**5**

## Chemistry

To achieve the desired compounds **3** and **4**, sights were first set on the preparation of the cyclopentene derivative **5** for coupling[4] with an appropriate heterocyclic base. Scheme 1 shows that the synthesis of **5** began with

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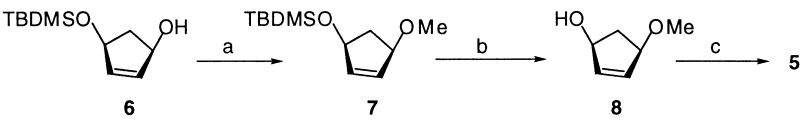



**Scheme 1.** Reaction conditions: (a) MeI, KOH, DMSO; (b) $Bu_4NF$; (c) $Ac_2O$.

methylation of the known[5] silylated derivative **6** to give **7**. Desilylation of **7** provided **8**, which was then acetylated to **5**.

With **5** available, its coupling with the sodium salt of $N^6$-benzoyladenine (**9**) provided **10** (Scheme 2). Debenzoylation of **10** to **11** followed by glycolization yielded (+)-**3**. Synthesis of **4** and its 8-aza analogue[6] **12**, was accomplished in a similar manner, but utilizing the sodium salt of 4-chloropyrrolo[2,3-*d*]pyrimidine[7] (**13**) or the sodium salt of 4-methoxypyrazolo[3,4-*d*]pyrimidine[8] (**14**), respectively, for the initial palladium coupling step to **15** and **16**, respectively (Scheme 2). Ammonolysis and glycolization afforded the desired **4** and **12**.

## Antiviral Results

Compounds **1**, **2**, **3**, **4**, and **12** were assayed against herpes simplex virus type 1 (strain KOS) and type 2 (strain g), vaccinia virus, and vesicular stomatitis virus in human embryonic skin-muscle ($E_6SM$) fibroblasts, vesicular stomatitis virus in HeLa cells, parainfluenza type 3 virus, reovirus type 1, and Sindbis virus in Vero cells, human immunodeficiency virus type 1 (strain IIIB) and type 2 (strain ROD) in CEM cells, and cytomegalovirus (strains AD-169 and Davis) and varicella-zoster virus (strains Oka and YS) in human embryonic lung (HEL) cells. Whereas compound **1** showed activity against vaccinia, vesicular stomatitis, parainfluenza-3, and reo-1 at a 50% inhibitory concentration ($IC_{50}$) of 0.7, 2, 0.2 and 7 μg/mL, no antiviral activity was noted with compounds **2**, **3**, **4** and **12** up to the highest concentrations tested (50 μg/mL in HEL, 250 μg/mL in CEM, >400 μg/mL in the other cells).

## Anti-HBV Results

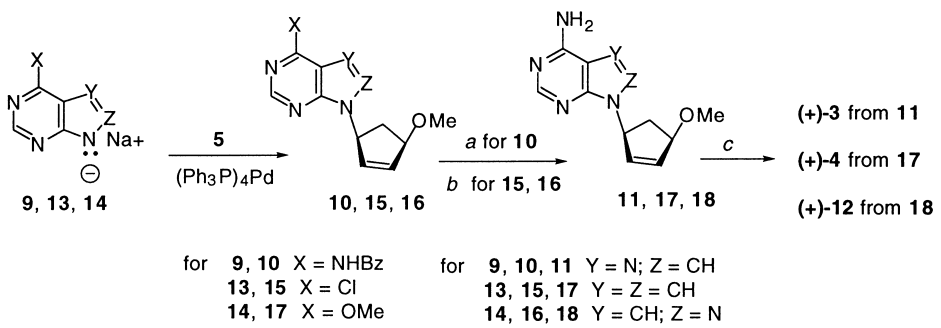
Modification of **1** by the replacement of the C-4′ hydrogen by a methyl group (compound **3**) reduced anti-HBV activity (see Table 1). Further modifications of **1** to either the 7-deaza (**4**) or the 8-aza-7-deaza (**12**) derivatives completely abolished anti-HBV activity (Table 1). However, the replacement of the C-4′ hydrogen by a methyl group (compounds **3** and **12**) significantly reduced cytotoxicity to human hepatoblastoma cells.

## Anti-Trypanosomal Results

Compounds **3**, **4**, and **12** were tested for in vitro growth inhibition of two trypanosome isolates in a standard screen. *Trypanosoma brucei brucei* Lab 110 EATRO is a standard isolate used for routine testing, while *Trypanosoma brucei rhodesiense* KETRI 243 is a clinical isolate from East Africa. Although none of the compounds were highly effective, with activities of only 9% and 22% (at 100 μM) being noted for compounds **3** and **4**, respectively, compound **12** was 40% inhibitory to *T. b. brucei* growth at the same concentration. Compound **12** was only minimally active (16%) against the *T. b.*

**Table 1.** HBV activity in 2.2.15 cells

| Compd | $CC_{50}$(μM) | $EC_{50}$(μM) | $EC_{90}$(μM) |
|---|---|---|---|
| **1** | 466 ± 20 | 1.4 ± 0.1 | 9.6 ± 0.8 |
| **2** | 277 ± 21 | > 100 | > 100 |
| **3** | > 1000 | 41 ± 4.3 | 119 ± 10 |
| **4** | 666 ± 31 | > 10 | > 10 |
| **12** | > 1000 | > 10 | > 10 |




**Scheme 2.** Reaction conditions: (a) $NH_4OH$:MeOH; (b) $NH_3$ in MeOH; (c) $OsO_4$/60% aq 4-methylmorpholine *N*-oxide.

*rhodesiense* isolate, with compounds **3** and **4** showing even less activity (12% and 11%, respectively).

## Conclusion

The biological results presented herein show that replacement of the 4′-hydroxyl hydrogen of **1** with a methyl group leads to diminished antiviral and anti-trypanosomal activity. This could be due to intolerable steric factors introduced by the methyl substituent or loss of the proton that has a necessary biological function.

## Experimental

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, USA). $^1$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), p (pentet), 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*S*,4*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-methoxycyclopent-2-ene (7).** To a suspension of crushed KOH (23.0 g, 0.41 mol) in DMSO (500 mL) that had been stirring at room temperature for 15 min was added **6**[5] (22.0 g, 0.10 mol) followed immediately by the dropwise addition of MeI (10.21 g, 0.21 mol). The reaction mixture was then stirred at room temperature for 4 h, after which it was poured onto ice and extracted with $CH_2Cl_2$ (3×500 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 8.93 g (38%) of **7** 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 −4.67, 18.10, 25.84, 40.83, 55.67, 74.84, 83.04, 132.39, 137.54. Calcd. for $C_{12}H_{24}O_2Si$: C, 63.28; H, 10.54. Found: C, 63.49, H, 10.39.

**(1*S*,4*R*)-4-Methoxy-2-cyclopenten-1-yl acetate (5).** A solution of **7** (8.93 g, 38.9 mmol) and $Bu_4NF$ (1.0 M in THF, 82 mL, 82 mmol) was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the residue was purified via column chromatography eluting with hexane:EtOAc (5:1, followed by 2:1) to afford 3.5 g (78%) of **8** 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 40.10, 56.08, 74.50, 83.33, 133.17, 137.42.

To a chilled stirring solution of **8** (3.5 g, 30.52 mmol) in dry $CH_2Cl_2$ (150 mL) was added pyridine (3.5 g, 45.5 mmol), dimethylaminopyridine (0.05 g), and acetic anhydride (4.5 g, 45.5 mmol). The reaction mixture was stirred overnight at room temperature, at which point it was treated with saturated $NaHCO_3$ solution (50 mL) and stirred vigorously for 15 min. The organic layer was separated and washed with ice-cold 1 N HCl (200 mL), brine (2×200 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified via column chromatography eluting with hexane:EtOAc (19:1) to give 2.65 g (55%) of **5** as a yellow syrup; $^1$H NMR ($CDCl_3$) δ 1.66 (dt, 1H), 2.03 (s, 3H), 2.74 (p, 1H), 3.35 (s, 3H), 4.32 (t, 1H), 5.51 (t, 1H), 6.05 (dd, 2H); $^{13}$C NMR ($CDCl_3$) δ 20.93, 36.75, 56.07, 76.49, 82.84, 132.85, 135.65, 170.58. Calcd for $C_8H_{12}O_3$: C, 61.70; H, 7.71. Found: C, 61.59, H, 7.77.

**(1*S*,4*R*)-4-Methoxy-1-(6-amino-9*H*-purin-9-yl)cyclopent-2-ene ((–)-11)**. To a solution of $N^6$-benzoyladenine (2.02 g, 8.41 mmol) in dry DMSO (30 mL) was added NaH (0.23 g, 8.62 mmol, 95%) to generate **9**. The mixture was stirred at room temperature 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 **5** (1.2 g, 7.65 mmol) in dry THF (30 mL) was added.[9] The mixture was stirred at 55 °C for 2 days. The volatiles were 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 3.8 g of **10** as a gum, which was used directly in the next reaction, without further purification.

A solution of **10** (3.8 g, 11.3 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 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

1.65 g (42% in two steps) of **11** as a white crystalline solid, mp 155–156 °C; $[\alpha]^{23}_{D}$ −73.40° (*c* 0.20, MeOH); $^1$H NMR (DMSO-$d_6$) δ 1.80 (dt, 1H), 2.87 (m, 1H), 3.30 (s, 3H), 4.44 (t, 1H), 5.47 (t, 1H), 6.23 (dt, 2H), 7.20 (br, 2H), 7.94 (s, 1H), 8.15 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) δ 37.94, 55.94, 56.51, 83.14, 118.83, 132.77, 135.81, 138.55, 149.10, 152.38, 155.95. Calcd for $C_{11}H_{13}N_5O$: C, 57.31; H, 5.64; N, 30.16. Found: C, 57.27; H, 5.73; N, 30.20.

**(1*S*,2*S*,3*S*,4*R*)-4-Methoxy-1-(6-amino-9*H*-purin-9-yl)cyclopentane-2,3-diol ((+)-3).** To a solution of **11** (0.85 g, 3.66 mmol) in THF:$H_2O$:acetone (75 mL, 1:1:1) was added $OsO_4$ (0.1 g) and 4-methylmorpholine *N*-oxide (1 mL). The mixture was stirred at room temperature 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 0.46 g (47%) **3** as a white solid, mp 230–231 °C; $[\alpha]^{21}_{D}$ +38.4° (*c* 0.20, DMF); $^1$H NMR (DMSO-$d_6$) δ 1.99 (m, 1H), 2.57 (m, 1H), 3.30 (s, 3H), 3.57 (q, 1H), 3.91 (d, 1H), 4.43 (q, 1H), 4.64 (q, 1H), 4.96 (d, 1H), 5.06 (d, 1H), 7.17 (br, 2H), 8.12 (s, 1H), 8.14 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) δ 32.96, 56.40, 57.91, 73.14, 74.05, 83.46, 119.25, 139.92, 149.72, 152.07, 155.95. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.98; H, 5.68; N, 26.31. Found: C, 49.78; H, 5.89; N, 26.33.

**(1*S*,4*R*)-4-Methoxy-1-(4-chloropyrrolo[2,3-*d*]pyrimin-7-yl)-cyclopent-2-ene (15).** To a solution of 4-chloropyrrolo-[2,3-*d*]pyrimidine[7] (2.85 g, 18.56 mmol) in dry DMSO (30 mL) was added NaH (0.48 g, 19.0 mmol, 95%) to give **13**. The mixture was stirred at room temperature under an argon atmosphere for 30 min. To this was added tetrakis(triphenylphosphine)palladium (1.35 g, 1.17 mmol), $Ph_3P$ (0.51 g, 1.94 mmol) and a solution of **5** (2.68 g, 17.09 mmol) in dry THF (30 mL).[3] The mixture was stirred at 55 °C for 2 days. The volatiles were 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 hexane/EtOAc (9:1, followed by 5:1) to afford 2.08 g (48.5%) of **15** as a colorless syrup; $^1$H NMR ($CDCl_3$) δ 1.77–1.85 (dt, 1H), 2.87–2.99 (p, 1H), 3.41 (s, 3H), 4.47 (m, 1H), 5.93 (m, 1H), 6.02 (dd, 1H), 6.33 (d, 1H), 6.60 (d, 1H), 7.40 (d, 1H), 8.63 (s, 1H); $^{13}$C NMR ($CDCl_3$) δ 38.21, 56.80, 57.05, 83.61, 99.94, 117.65, 126.95, 133.18, 135.95, 150.38, 150.48, 151.88. Calcd for $C_{12}H_{12}ClN_3O$: C, 57.90; H, 4.82; N, 16.76. Found: C, 57.86; H, 4.55; N, 16.77.

**(1*S*,4*R*)-4-Methoxy-1-(4-aminopyrrolo[2,3-*d*]pyrimin-7-yl)-cyclopent-2-ene (17).** A solution of **15** (2.0 g, 7.98 mmol) in saturated methanolic ammonia (150 mL) was sealed in a steel vessel and heated at 110 °C for 3 days. The vessel was cooled to 0 °C, and the solvents removed under reduced pressure. The residue was then purified via column chromatography, eluting with $CH_2Cl_2$:MeOH (98:2). Fractions containing product were combined and evaporated to give 1.48 g (80%) of **17** as a white sticky foam; $^1$H NMR (DMSO-$d_6$) δ 1.73–1.82 (dt, 1H), 2.87–2.99 (dt, 1H), 3.40 (s, 3H), 4.44 (br, 1H), 5.34 (br, 2H), 5.86 (br, 1H), 6.01 (dd, 1H), 6.27 (dd, 1H), 6.36 (d, 1H), 7.10 (d, 1H), 8.33 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) δ 38.55, 56.63, 56.76, 83.87, 98.07, 103.21, 122.35, 133.92, 135.25, 150.01, 151.65, 156.75. Calcd for $C_{12}H_{14}N_4O$: C, 62.76; H, 6.10; N, 24.22. Found: C, 62.49; H, 6.15; N, 24.52.

**(1*S*,2*S*,3*S*,4*R*)-4-Methoxy-1-(4-aminopyrrolo[2,3-*d*]pyrimidin-7-yl)cyclopentane-2,3-diol ((+)-4).** To a solution of **17** (1.5 g, 6.48 mmol) in THF:$H_2O$ (40 mL, 3:1) was added $OsO_4$ (0.125 g) and 4-methylmorpholine *N*-oxide (1.5 mL). The mixture was stirred at room temperature for two days until TLC ($CH_2Cl_2$:MeOH, 95:5) showed no remaining starting material. The solvent was evaporated, and the residue was purified via column chromatography, eluting with $CH_2Cl_2$:MeOH (95:5). Fractions containing product were combined and evaporated, and the residue dissolved in MeOH and treated with decolorizing charcoal, filtered and the filtrate evaporated to afford an off white solid. This was recrystallized in MeOH:EtOAc to afford 0.26 g (15%) of **4** as a white solid, mp 176–177 °C; $[\alpha]^{24}_{D}$ +32.2° (*c* 0.20, MeOH); $^1$H NMR (DMSO-$d_6$) δ 1.65–1.76 (m, 1H), 2.45–2.57 (m, 1H), 3.29 (s, 3H), 3.58 (t, 1H), 3.89 (br, 1H), 4.21–4.30 (dt, 1H), 4.90 (q, 1H), 4.94 (t, 1H), 5.56 (d, 1H), 6.55 (d, 1H), 6.94 (br, 2H), 7.18 (d, 1H), 8.03 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) δ 32.96, 56.40, 57.91, 73.14, 74.05, 83.46, 119.25, 139.92, 149.72, 152.07, 155.95. Calcd for $C_{12}H_{16}N_4O_3$: C, 54.72; H, 6.08; N, 21.12. Found: C, 54.68; H, 6.25; N, 21.09.

**(1*S*,4*R*)-4-Methoxy-1-(4-methoxypyrazolo[3,4-*d*]pyrimin-7-yl)cyclopent-2-ene (16).** To a solution of 4-methoxypyrazolo[3,4-*d*]pyrimidine[8] (3.12 g, 20.78 mmol) in dry DMSO (30 mL) was added NaH (0.54 g, 21.4 mmol, 95%) to give **14**. The mixture was stirred at room temperature under an argon atmosphere for 30 min. To this solution was added tetrakis(triphenylphosphine)palladium (1.51 g, 1.31 mmol), $Ph_3P$ (0.57 g, 2.17 mmol) and a solution of **5** (3.0 g, 19.13 mmol) in dry THF (30 mL).[10] The mixture was stirred at 55 °C for 2 days. The volatiles were 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 hexane:EtOAc (9:1, followed by 4:1) to afford 2.03 g (43%) of **16** as white crystals, mp 81–82 °C; $^1$H NMR ($CDCl_3$) δ 2.10–2.20 (dt, 1H), 2.91–3.03 (dt, 1H),

3.41 (s, 3H), 4.15 (s, 3H), 4.56 (t, 1H), 5.91 (m, 1H), 6.05 (dt, 1H), 6.30 (dt, 1H), 8.07 (s, 1H), 8.56 (s, 1H); $^{13}$C NMR ($CDCl_3$) δ 37.16, 54.10, 56.27, 59.95, 83.67, 102.86, 131.67, 132.69, 135.09, 154.27, 154.96, 163.96. Calcd for $C_{12}H_{12}N_3ClO$: C, 57.90; H, 4.82; N, 16.76. Found: C, 57.86; H, 4.55; N, 16.77.

**(1*S*,2*S*,3*S*,4*R*)-4-Methoxy-1-(4-aminopyrazolo[3,4-*d*]pyrimidin-7-yl)cyclopentane-2,3-diol ((+)-12).** A solution of **16** (1.8 g, 7.28 mmol) in saturated methanolic ammonia (150 mL) was sealed in a steel vessel and heated at 110 °C for 3 days. The vessel was cooled to 0 °C, and the solvents removed under reduced pressure. The residue was then purified via column chromatography, eluting with $CH_2Cl_2$:MeOH (95:5). Fractions containing product were combined and evaporated to give 1.3 g (77%) of **18** as a gum, which was used directly without characterization.

To a solution of **18** (1.3 g, 6.0 mmol) in THF:$H_2O$ (50 mL, 10:1) was added $OsO_4$ (0.125 g) and NMO (2 mL). The mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was purified via column chromatography, eluting with $CH_2Cl_2$:MeOH (95:5, followed by 9:1). Fractions containing product were combined and evaporated to afford a colorless syrup, which hardened upon cooling. This solid was then recrystallized in MeOH to afford 0.26 g (77% in two steps) **12** as a white solid, mp 128–129 °C; $[\alpha]^{24}_D$ +29.6° (*c* 0.20, MeOH); $^1$H NMR (DMSO-$d_6$) δ 1.78–1.88 (m, 1H), 2.41–2.53 (m, 1H), 3.27 (s, 3H), 3.30 (br, 1H), 3.59 (m, 1H), 3.89 (br, 1H), 4.33 (q, 1H), 4.89 (dd, 1H), 4.98 (q, 1H), 7.66 (br, 2H), 8.11 (s, 1H), 8.14 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) δ 32.99, 56.56, 59.18, 73.18, 74.73, 83.26, 100.36, 132.17, 153.61, 155.70, 158.11. Calcd for $C_{11}H_{15}N_5O_3 \cdot 1.0$ MeOH: C, 49.63; H, 5.88; N, 25.54. Found: C, 49.86; H, 5.62; N, 25.38.

### Antiviral

Antiviral assays were carried out in the systems described previously.[9]

### Anti-HBV

Analysis of anti-HBV activity and associated toxicity were performed following 9 days of consecutive daily administration of the test compounds to confluent cultures of the HBV-producing cell line, 2.2.15, as previously described.[11] Anti-HBV activity was determined by blot hybridization analysis of extracellular HBV virion DNA in culture medium.[11] Cytotoxicity was determined by uptake of neutral red dye on cultures maintained under conditions that were identical to those used for the antiviral assays.[11]

### Anti-trypanosomal

The compounds were dissolved in medium and added aseptically. Coulter counts were taken at 72 h as described previously.[3,10]

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### References and Notes

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