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The synthesis of the 7-cyano and 7-carboxamido derivatives of 7-deaza-5'-noraristeromycin have been prepared in 3 and 4 steps, respectively, for evaluation as anti-trypanosomal agents. Neither compound was active in the latter assay.

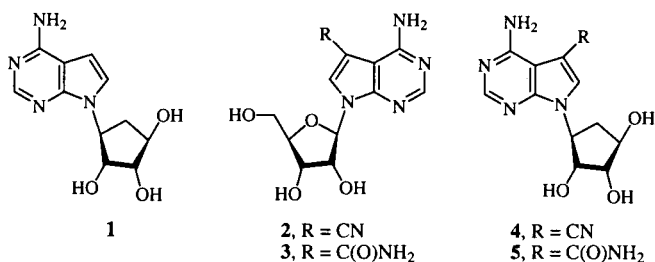
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It has recently been disclosed [1] that (+)-7-deaza-5'-noraristeromycin (**1**), which resembles an L-nucleoside, possesses activity against 4 strains of African trypanosomes including *Trypanosoma brucei brucei* and *brucei rhodesiense*. To explore ways of improving upon this effect of **1**, we were drawn to the significant biological properties [2] that have been displayed for the 7-substituted 7-deazapurine nucleosides toyocamycin (**2**) and sangivamycin (**3**). With that in mind, analogues **4** and **5**

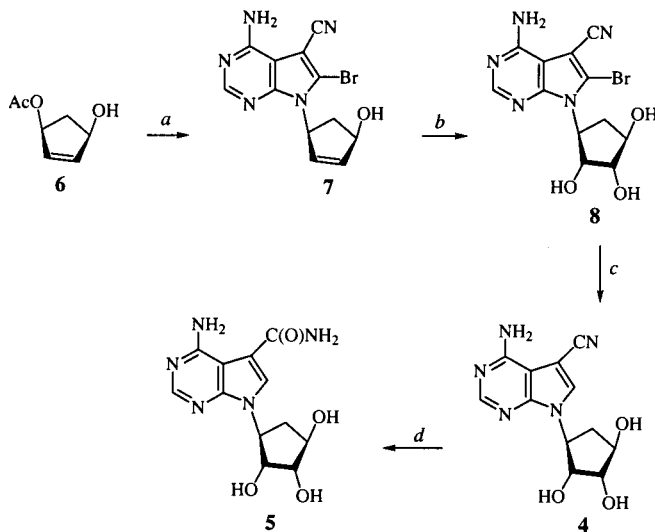
became target compounds for our anti-trypanosomal investigations.

Scheme 1 summarizes the preparation of **4** and **5**, which began with the palladium catalyzed coupling of the allylic acetate **6** [3] with 4-amino-6-bromo-5-cyanopyrrolo-[2,3-*d*]pyrimidine [4,5] to yield **7**. Glycolization of **7** to **8** followed by hydrogenolytic debromination [5] provided target **4**. Treatment of **4** with basic hydrogen peroxide [6] produced **5**.

Both compounds **4** and **5** were found to have no effect on trypanosomal growth [7].



Scheme 1



Reaction conditions: a, (i) 4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidine [4,5], NaH (Ph₃P)₄Pd, PPh₃, 55°C; b, OsO₄/60% aq. 4-methylmorpholine *N*-oxide; c, 10% Pd on C, H₂, 50 psi; d, H₂O₂, NH₄OH.

EXPERIMENTAL

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. The ¹H and ¹³C spectra were recorded on a Bruker AC 250 spectrometer (operated at 250 and 62.5 MHz, respectively) all referenced to internal tetramethylsilane 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). Reactions were monitored by thin-layer chromatography (tlc) using 0.25 mm Whatman Diamond silica gel 60-F₂₅₄ 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 with the indicated solvent system. Yields refer to chromatographically and spectroscopically (¹H and ¹³C nmr) homogeneous materials.

(1*R*,2*S*,3*R*,4*S*)-4-(4-Amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidin-7-yl)cyclopentane-1,2,3-triol (**8**).

To a stirring suspension of 4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidine [4,5] (8.4 g, 35.3 mmol) in anhydrous dimethyl sulfoxide (100 ml) was added sodium hydride (1.42 g, 35.5 mmol) and the mixture stirred at rt for 30 minutes. To this mixture was added tetrakis(triphenylphosphine)palladium (2.51 g, 2.17 mmol), triphenylphosphine (1.0 g, 3.81 mmol), and **6** [3] (4.98 g, 35.0 mmol) in anhydrous tetrahydrofuran, and the resulting suspension stirred at 55 °C for 3 days. The volatiles were removed under reduced pressure and the residue treated with methylene chloride (250 ml) and filtered. The new mixture was washed with brine (3 x 250 ml), dried (sodium sulfate) and evaporated. The residue was purified *via* column chromatography, eluting with hexane/ethyl acetate (4:1, then 1:1, then

1:4), followed by ethyl acetate. The fractions containing product were combined and evaporated to afford 6.2 g of (1*R*,4*S*)-4-(4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidin-7-yl)cyclopent-2-en-1-ol (**7**) as a yellow solid, which was slightly contaminated with uncoupled base. The product was used directly without further purification; ¹H nmr (dimethyl-*d*₆ sulfoxide): δ 1.70 (dt, 1H), 2.98 (p, 1H), 4.73 (br, 1H), 5.45 (d, 1H), 5.78 (m, 2H), 6.03 (dd, 1H), 6.28 (dt, 1H), 8.29 (s, 1H); ¹³C nmr (dimethyl-*d*₆ sulfoxide): δ 40.8, 62.0, 73.7, 83.4, 104.3, 115.8, 129.5, 132.1, 141.0, 143.3, 145.9, 155.4.

A solution of **7** (2.8 g, 8.71 mmoles) in tetrahydrofuran/water (200 ml, 9:1) was treated with osmium tetroxide (150 mg) and 4-methylmorpholine *N*-oxide (10 ml) and the reaction stirred for 3 days until no starting material remained (tlc). The solvents were removed under reduced pressure, and the residue was then purified via column chromatography eluting with ethyl acetate/methanol (19:1). The fractions containing product were evaporated under reduced pressure to afford 1.5 g of **8** (48%) after recrystallization with ethyl acetate, as a pale tan solid, dec >230°; ¹H nmr (dimethyl-*d*₆ sulfoxide): δ 2.05 (dd, 1H), 2.65 (m, 1H), 3.76 (d, 1H), 3.87 (d, 1H), 4.67 (m, 1H), 4.92 (m, 2H), 5.08 (br, 1H), 5.58 (br, 1H), 7.22 (br, 2H), 8.50 (s, 1H); ¹³C nmr (dimethyl-*d*₆ sulfoxide): δ 35.7, 64.5, 73.7, 74.5, 76.6, 83.3, 104.7, 115.7, 131.5, 144.6, 145.8, 155.5.

Anal. Calcd. for C₁₂H₁₂BrN₅O₃: C, 40.68; H, 3.41; N, 19.77. Found: C, 40.71; H, 3.41; N, 19.69.

(1*R*,2*S*,3*R*,4*S*)-4-(4-Amino-5-cyanopyrrolo[2,3-*d*]pyrimidin-7-yl)-cyclopentane-1,2,3-triol (**4**).

To a solution of **8** (3.96 g, 11.2 mmoles) in ethanol/water (300 ml, 1:1) was added sodium hydroxide (0.75 g, 18.8 mmoles) and palladium on charcoal (10%, 1.0 g), and the reaction placed under hydrogen at 50 psi and shaken overnight [5]. The mixture was filtered over a celite pad, the pad rinsed with ethanol, and the filtrate evaporated under reduced pressure. The residue was coevaporated with toluene (2 x 20 ml), and purified *via* column chromatography, eluting with ethyl acetate/methanol (9:1). Fractions containing product were combined and evaporated to give 1.8 g (48 %) of **4** after recrystallization in ethyl acetate/methanol as an off-white solid, dec >245°C; ¹H nmr (dimethyl-*d*₆ sulfoxide): δ 2.00 (dd, 1H), 2.65 (m, 1H), 3.76 (s, 1H), 3.88 (d, 1H), 4.82, (m, 2H), 4.97 (d, 1H), 5.09 (s, 1H), 6.50 (br, 1H), 7.22 (br, 2H), 8.27 (s, 1H), 8.48 (s, 1H); ¹³C nmr (dimethyl-*d*₆ sulfoxide): δ 35.0, 66.1, 73.9, 74.1, 76.9, 81.5, 103.6, 117.0, 145.0, 145.2, 145.9, 157.1.

Anal. Calcd. for C₁₂H₁₃N₅O₃·0.5 M H₂O: C, 50.69; H, 4.96; N, 24.64. Found: C, 50.62; H, 4.96; N, 24.64.

(1*R*,2*S*,3*R*,4*S*)-4-(4-Amino-5-carboxamidopyrrolo[2,3-*d*]pyrimidin-7-yl)cyclopentane-1,2,3-triol (**5**).

A solution of **4** (1.3 g, 4.72 mmoles) in ammonium hydroxide (200 ml) was treated with hydrogen peroxide (30%, 20 ml) and stirred at rt for 6 hours. During that time, a white precipitate formed. The mixture was chilled to 0° for 24 hours, followed by filtration to isolate the solid. The product was washed with ice water, and dried under vacuum to afford 0.60 g of **5** (43%) as a white solid, dec > 265°; ¹H nmr, (methanol-*d*₄:dimethyl-*d*₆ sulfoxide): δ 2.18 (dd, 1H), 2.83 (ddd, 1H), 3.85 (d, 1H), 3.97 (d, 1H), 4.71 (m, 1H), 4.97 (dd, 1H), 7.89 (s, 1H), 8.26 (s, 1H); ¹³C nmr (methanol-*d*₄:dimethyl-*d*₆ sulfoxide): δ 35.2, 67.4, 75.0, 77.9, 103.9, 111.2, 139.3, 145.5, 146.4, 147.2, 159.1, 168.5.

Anal. Calcd. for C₁₂H₁₅N₅O₄: C, 49.14; H, 5.16; N, 23.88. Found: C, 49.38; H, 5.17; N, 23.54.

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