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A CONVENIENT SYNTHESIS OF THE L-LIKE ENANTIOMER OF 4'-METHYL-3-DEAZAARISTEROMYCIN

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Abstract -- As an entry into L-like 3-deazaaristeromycins, synthesis of the enantiomer of D-like 4'-methyl-3-deazaaristeromycin is described in 11 steps from a readily accessible cyclopentenone that, in turn, is prepared from D-ribose.

The therapeutic prominence of abacavir (**1**)[1] and entecavir (**2**)[2] has placed carbocyclic nucleosides[3] at the forefront of drug discovery. The successes with **1** and **2** can be traced to the beginning of carbocyclic nucleoside research with the preparation of aristeromycin (**3**)[4] and its subsequent isolation from natural sources[5] that stimulated numerous investigations in carbocyclic nucleosides.[3] With the D-like structure of **3**, it is not surprising that most structural variation development drew attention to this configuration. It was not until sometime later that reports of the L-like enantiomer of **3** (**4**) began to appear.[6-8] The first non-enzymatic total synthesis of L-like adenine derived carbocyclic nucleosides (and other heterocyclic base variations) was from the Chu laboratories.[9] At the same time, we reported the anti-HBV activity of L-like 5'-noraristeromycin (**5**) with no similar activity with the D-like analog.[10] This was followed by our laboratory describing the anti-trypanosomal activity for L-like 7-deaza-5'-noraristeromycin (**6**) and 8-aza-7-deaza-5'-noraristeromycin (**7**) with no corresponding properties for the D-like enantiomer.[11,12]

This paper is dedicated to Prof. Dr. Ei-ichi Negishi on the occasion of his 77th birthday.

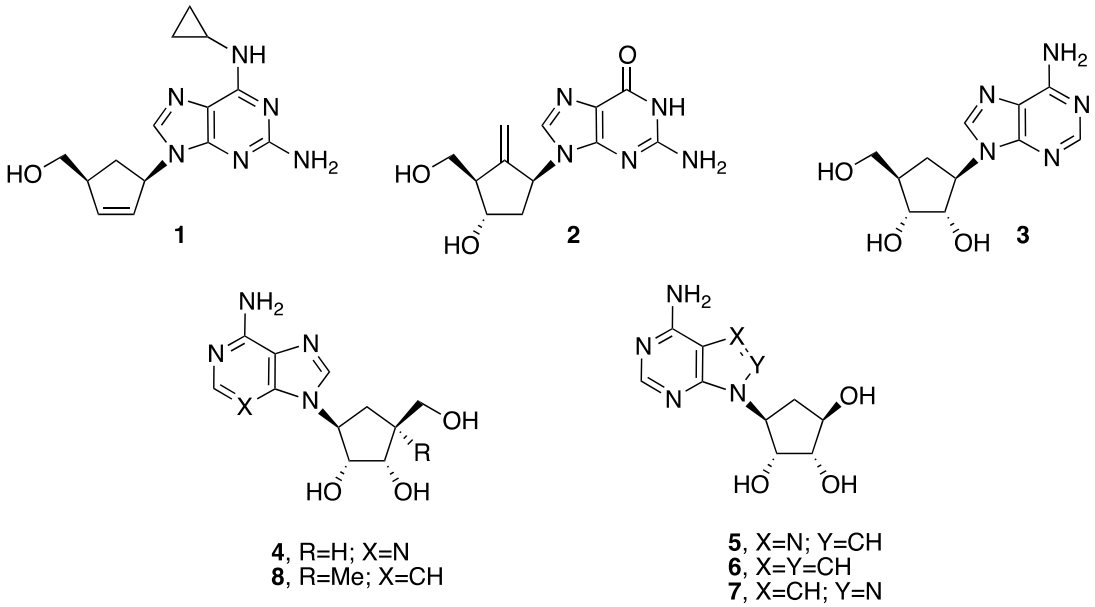


Figure 1

Our laboratory has recently returned to L-aristeromycin built around the 3-deazapurine base. This was prompted by the significant antiviral potential of 3-deazaaristeromycin[13] that has never been extended to the L-like series. In that direction, we sought a convenient way into the 4'-alkyl derivatives as represented here with the L-like 3-deazaaristeromycin possessing a C-4' methyl group (**8**).

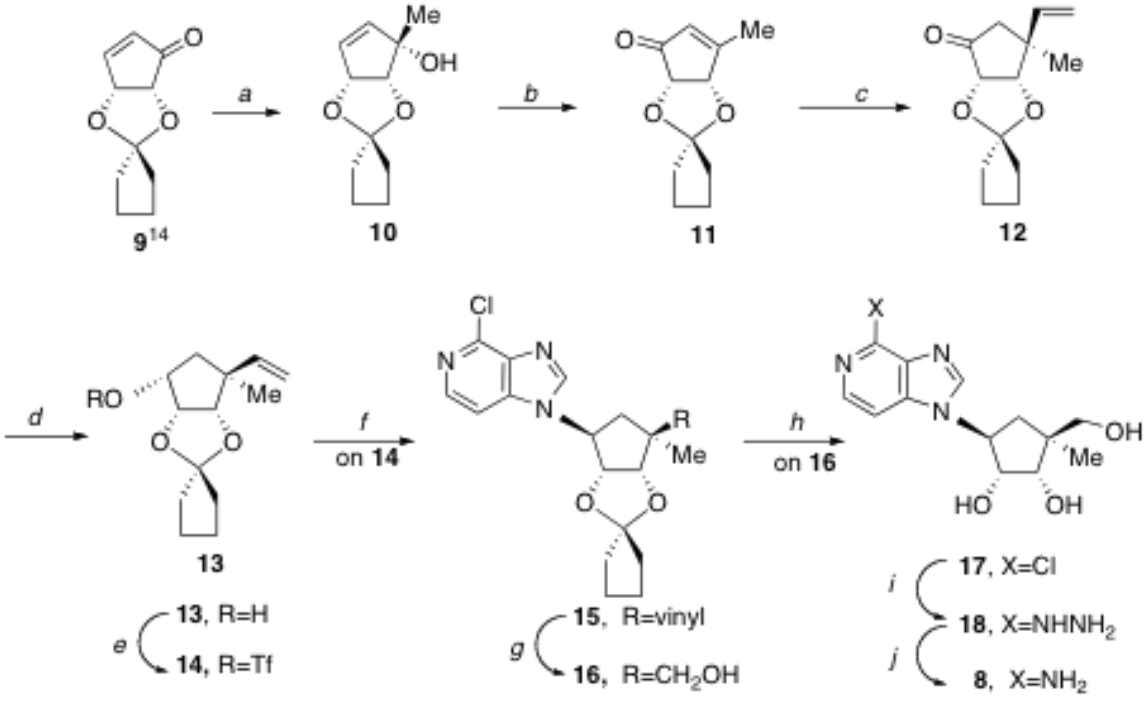
As shown in Scheme 1, the preparation of **8** began with treatment of the cyclopentenone **9**[14] with methyllithium in THF at -78 °C to yield the tertiary allylic alcohol **10** in 85% yield. Subjecting **10** to the oxidative rearrangement of tertiary allylic alcohols by pyridinium dichromate (PDC)[15] in the presence of acetic anhydride[16,17] afforded **11**. This was followed by the conjugate 1,4-addition reaction of vinylmagnesium bromide to **11** in the presence of CuBr·Me_2S as catalyst and TMSCl and hexamethylphosphoramide (HMPA) added[18] to result in ketone **12**. Luche reduction of **12** with sodium borohydride and cerium(III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$) gave the alcohol **13**. The high diastereoselectivity of this latter 1,2-reduction[19,20] was confirmed by X-ray crystallography of the eventual target **8** (Figure 2).

The alcohol **13** was converted to its triflate **14** with trifluoromethanesulfonic anhydride. A subsequent S_N2 substitution reaction of the triflate **14** with the sodium salt of 6-chloro-3-deazapurine[21] in the presence of catalytic amount of 18-crown-6 in DMF afforded carbocyclic nucleoside **15**. Transformation of the vinyl group of **15** to a hydroxyl group occurred, first, by oxidative cleavage (OsO_4/$NaIO_4$) followed by sodium borohydride reduction to obtain **16** in 66% yield. Deprotection of **16** with hydrochloric acid afforded triol **17**. Amination of **17** with hydrazine and subsequent reduction of **18** with Raney nickel produced the desired 4'-methyl-3-deazaaristeromycin (**8**) (30% yield, last two steps).[22]

In addition to NMR data, the structure of 4′-methyl-3-deazaaristeromycin (**8**) was confirmed by X-ray

crystallography (Figure 2).[23]

In conclusion, we have established a general method into the L-like 4'-alkyl-3-deaazristeromycin series that can be varied with the selection of the alkyllithium reagent employed in the first step of Scheme 1.



Scheme 1

Reaction conditions: *a*, MeLi, THF, -78 °C, 85%; *b*, PDC, Ac_2O, CH_2Cl_2, rt, 55%; *c*, vinylmagnesium bromide, HMPA, CuBr•Me_2S, THF, TMSCl, -78 °C, 70%; *d*, $NaBH_4$, $CeCl_3$•7 H_2O, MeOH, 86%; *e*, pyridine, Tf_2O, CH_2Cl_2; *f*, 6-chloro-3-deazapurine[21], NaH, 18-C-6, DMF, 55% for steps *e* and *f*; *g*, (i) OsO_4, $NaIO_4$, MeOH; (ii) $NaBH_4$, MeOH, 66%; *h*, HCl, MeOH, 0 °C, 60%; *i*, N_2H_4, 1-propanol, reflux; *j*, Raney Ni, 30% for steps *i* and *j*.

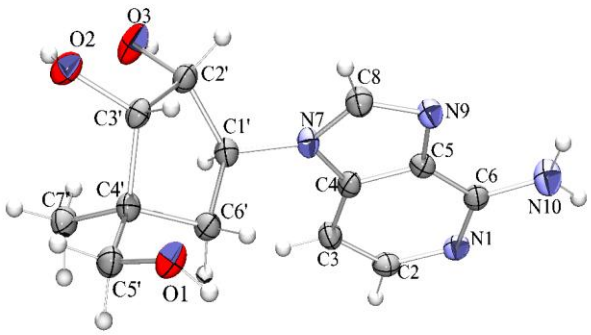


Figure 2

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were measured on a Bruker AV-400 spectrometer or Bruker AC-250 spectrometer. ^{1}H chemical shifts are reported relative to $CDCl_3$ at δ 7.27 ppm (or MeOD at δ 3.51 ppm or DMSO-d_6 at δ 2.51 ppm) and tetramethylsilane as an internal standard. ^{13}C chemical shifts are reported in relative to $CDCl_3$/MeOD/ DMSO-d_6. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), and m (multiplet). Elemental analyses were performed by Atlantic Microlabs, Atlanta, Georgia. The mass spectral data were obtained using a Waters Micromass QTOF Premier mass spectrometer. Reactions were monitored by thin layer chromatography (TLC) using 0.25 mm E. Merck silica gel 60-F254 precoated silica gel plates with visualization by irradiation with a Mineral light UVGL-25 lamp or exposure to iodine vapor. Column chromatography was performed on Whatman silica gel (average particle size 5–25 mm, 60 Å) and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials. The reactions were generally carried out in an N_2 atmosphere under anhydrous conditions.

(3a*R*,4*S*,6a*R*)-4-Methyl-4,6a-dihydro-3a*H*-spiro[cyclopenta[*d*][1,3]dioxole-2,1'-cyclopentan]-4-ol (10). Methyl lithium (31.2 mL, 1.6 M, 49.9 mmol) was added, dropwise, to a solution of **9**[14] (5.0 g, 27.7 mmol) in dry THF (50 mL) at -78 °C. After stirring at -78 °C for 30 min, the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched by the addition of aqueous NH_4Cl (50 mL) at 0 °C. The aqueous phase was extracted with EtOAc (3 × 50 mL), and the combined organic layers dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane:EtOAc = 5:1) to give **10** (4.63 g, 85%) as a white solid: mp 43-44 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (d, J = 9.2 Hz, 1H), 5.74 (d, J = 9.2 Hz, 1H), 5.04-5.07 (m, 1H), 4.24 (d, J = 9.2 Hz, 1H), 3.09 (s, 1H), 1.79-1.84 (m, 4H), 1.61-1.70 (m, 4H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ142.3, 131.7, 114.8, 84.9, 81.9, 80.3, 78.9, 39.3, 37.9, 20.3, 20.1. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.18; H, 8.13.

(3a*S*,6a*S*)-6-Methyl-3a*H*-spiro[cyclopenta[*d*][1,3]dioxole-2,1'-cyclopentan]-4(6aH)-one (11). A mixture of **10** (3.43 g, 17.6 mmol), PDC (13.26 g, 35.3 mmol), 4 Å molecular sieves (3 g), and Ac_2O (7.84 mL, 141 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature overnight. The solvent was removed in vacuo and the residue was partitioned between saturated aqueous Na_2CO_3 (100 mL) and CH_2Cl_2 (100 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane:EtOAc = 10:1) to afford **11** (1.87 g, 54.8%) as a white solid: mp 80-81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (s, 1H), 4.96 (d, J = 5.6 Hz, 1H), 4.41 (d, J = 5.6 Hz, 1H), 2.2 (s, 3H), 1.68-1.86 (m, 4H), 1.62-1.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 184.3, 174.8, 130.0,

116.0, 80.7, 37.3, 35.9, 24.9, 20.5, 20.1. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.18; H,
7.26.

(3a*S*,4*S*,6a*S*)-4-Methyl-4-vinyldihydro-3a*H*-spiro[cyclopenta[*d*][1,3]dioxole-2,1'-cyclopentan]-6(6a*H*)-one (12). Vinylmagnesium bromide (10.95 mL, 10.95 mmol, 1.0 M in THF) and HMPA (3.2 mL, 18.25 mmol) were added to a suspension of CuBr·Me_2S (150 mg, 0.73 mmol) in dry THF (20 mL) at -78 °C over 10 min. After stirring at -78 °C for 15 min, a solution of **11** (1.42 g, 7.3 mmol) and TMSCl (1.94 mL, 15.33 mmol) in dry THF (20 mL) was added dropwise over 30 min. The reaction mixture was stirred at -78 °C for 2 h, and then quenched by the addition of saturated aqueous NH_4Cl (10 mL). The reaction mixture was extracted with EtOAc (3 × 40 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane:EtOAc = 10:1) to give **12** (1.13 g, 69.8%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66-5.73 (m, 1H), 4.99-5.04 (m, 2H), 4.4-4.43 (d, *J* = 5.6 Hz, 1H), 4.11-4.22 (d, *J* = 5.6 Hz, 1H), 1.94 (d, *J* = 7 Hz, 2H), 1.68-1.86 (m, 4H), 1.62-1.67 (m, 4H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.6, 142.9, 114.4, 113.3, 82.8, 79.2, 44.5, 41.6, 36.7, 34.6, 25.0, 21.9, 21.7. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.11; H, 8.09.

(3a*S*,4*S*,6*R*,6a*R*)-4-Methyl-4-vinyltetrahydro-3a*H*-spiro[cyclopenta[*d*][1,3]dioxole-2,1'-cyclopentan]-6-ol (13). Cerium chloride heptahydrate (1.43 g, 4.95 mmol) was added to a solution of **12** (1 g, 4.5 mmol) in MeOH (10 mL) at -30 °C. After stirring for 15 min at -30 °C, $NaBH_4$ (340 mg, 9.0 mmol) was added, carefully, and the reaction mixture was warmed to room temperature for 30 min. The mixture was neutralized with conc. aqueous HCl. The volume was reduced in vacuo to 2/3, extracted with brine and Et_2O. The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane:EtOAc = 5:1) to give **13** (866 mg, 85.8%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66-5.73 (m, 1H), 4.99-5.03 (m, 2H), 4.37 (t, *J* = 6.0 Hz, 1H), 4.22 (d, *J* = 5.5 Hz, 1H), 3.99-4.03 (m, 1H), 2.41 (d, *J* = 10.0 Hz, 1H), 1.94-1.98 (m, 5H), 1.52-1.72 (m, 5H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 112.9, 111.2, 84.7, 78.5, 70.8, 44.2, 41.9, 35.9, 33.9, 25.2, 21.3, 20.99. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.73; H, 8.82.

4-Chloro-1-((3a*S*,4*S*,6*S*,6a*R*)-4-methyl-4-vinyltetrahydro-3a*H*-spiro[cyclopenta[*d*][1,3]dioxole-2,1'-cyclopentane]-6-yl)-1*H*-imidazo[4,5-*c*]pyridine (15). Triflic anhydride (1.5 mL, 8.92 mmol) was added to a solution of **13** (1 g, 4.46 mmol) and pyridine (1.44 mL, 17.83 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. After stirring for 50 min at 0 °C, cold CH_2Cl_2 (10 mL) and ice-H_2O (20 mL) were added. The aqueous layer was washed with cold CH_2Cl_2 (15 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give the crude triflate **14**, which was dried in vacuo at 0 °C for 1 h.

A solution of 6-chloro-3-deazapurine[21] (1.3 g, 8.47 mmol), NaH (357 mg, 8.92 mmol, 60% dispersion in mineral oil), and 18-crown-6 (2.36 g, 8.92 mmol) in DMF (15 mL) was heated at 70 °C for 4 h and then cooled to 0 °C. To this mixture was added the solution of previously prepared triflate in DMF (5 mL). This reaction mixture was allowed to stir at 0 °C for 12 h and then at room temperature for 2 days. The DMF was removed in vacuo and the residue purified by silica gel column chromatography (hexane:EtOAc = 5:1) to give **15** (882 mg, 55%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.65 (d, *J* = 5.6 Hz, 1H), 7.55 (d, *J* = 5.6 Hz, 1H), 5.95-6.01 (m, 1H), 5.06-5.14 (m, 3H), 4.98-5.02 (m, 1H), 4.69 (d, *J* = 6.5 Hz, 1H), 2.64-2.69 (m, 1H), 2.26- 2.3 (m, 1H), 1.80-1.82 (m, 2H), 1.64-1.69 (m 2H), 1.48-1.59 (m, 4H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ149.8, 139.7, 137.2, 136.7, 132.3, 122.6, 114.8, 113.0, 108.1, 84.9, 83.9, 61.5, 46.3, 42.8, 36.1, 34.2, 25.1, 21.9, 21.7; HRMS calcd for $C_{19}H_{22}ClN_3O_2$ 359.1488, found 359.1438.

((3a*R*,4*S*,6*S*,6a*S*)-4-(4-Chloro-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-6-methyltetrahydro-3a*H*-spiro[cyclopenta[*d*][1,3]dioxole-2,1'-cyclopentane]-6-yl)methanol (16). Compound **15** (882 mg, 2.45 mmol) was dissolved in MeOH (8 mL). To this H_2O (8.3 mL) and $NaIO_4$ (1.15 g, 5.39 mmol) were added. This mixture was cooled to 0 °C and OsO_4 (31 mg, 0.12 mmol, 5% mol) was added. The mixture was stirred at 0 °C for 2 h. The mixture was filtered and the MeOH removed under reduced pressure. The residue was extracted with CH_2Cl_2 (3×10 mL) and the organic layer washed with brine, dried (Na_2SO_4), and concentrated. The residue was dissolved in MeOH (10 mL) and to this $NaBH_4$ (232 mg, 6.13 mmol) was added, portionwise, at 0 °C. The mixture as then stirred at 0 °C for 1 h and saturated aqueous NH_4Cl solution (10 mL) added. The mixture was filtered through celite and the solvent was removed with reduced pressure. The residue was extracted with EtOAc (3 ×10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 3:1) to provide **16** as a white foam (587 mg, 65.8%); ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.27 (s, 1H), 8.22 (d, *J* = 5.6 Hz, 1H), 7.57 (d, *J* = 5.6 Hz, 1H), 4.74-4.78 (m, 1H), 4.63-4.65 (m, 1H), 4.46-4.48 (d, *J* = 6.4 Hz, 1H), 3.61 (d, *J*=5.6 Hz, 2H), 2.62-2.68 (m, 1H), 2.31-2.37 (m, 1H), 1.65-1.8 (m, 8H), 1.2 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ149.9, 139.6, 137.1, 132.2, 122.7, 113.2, 108.2, 84.7, 83.9, 67.5, 61.5, 46.2, 42.6, 36.2, 34.3, 25.2, 21.9, 21.7; Calcd HRMS for $C_{18}H_{22}ClN_3O_3$: 363.1377. Found: 363.1367.

(1*R*,2*S*,3*S*,5*S*)-5-(4-Chloro-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-3-(hydroxymethyl)-3-methylcyclopentane- 1,2-diol (17). Compound **16** (587 mg, 1.61 mmol) was dissolved in 2 N HCl (1 mL) in MeOH at 0 °C and this solution was stirred at 25 °C overnight. Sodium bicarbonate was added to neutralize the solution until it no longer bubbled. The mixture was filtered. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc:MeOH = 2:1) to provide **17** as a white solid (287 mg, 59.7%): mp 184-186 °; ^{1}H NMR (400

MHz, DMSO-d_6), δ 8.56 (s, 1H), 8.13 (d, J = 5.6 Hz, 1H), 7.82 (d, J = 5.6 Hz, 1H), 4.82-4.92 (m, 1H), 4.53-4.57 (m, 1H), 3.9-3.93 (m, 1H), 3.51 (d, J = 5.6 Hz, 1H), 3.44 (d, J = 5.6 Hz, 1H), 3.29 (s, 1H), 2.09-2.18 (m, 1H), 2.01-2.07 (m, 1H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.3, 138.4, 136.8, 132.1, 119.2, 108.4, 75.7, 74.5, 69.4, 60.4, 44.4, 36.7, 18.4; Calcd HRMS for $C_{13}H_{16}ClN_3O_3$: 297.0965. Found: 297.0961.

(1*R*,2*S*,3*S*,5*S*)-5-(4-Amino-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-3-(hydroxymethyl)-3-methylcyclopentane-1,2-diol (8). To a mixture of anhydrous hydrazine (99%, 1 mL) and 1-propanol (3 mL) was added **17** (287 mg, 1.87 mmol). The solution was brought to reflux for 8 h. The reaction was cooled to room temperature and the residual hydrazine and 1-propanol was evaporated under reduced pressure. Water (5 mL) was added to dissolve the residue and then Raney nickel (0.8 g) was added portionwise. The mixture was heated to reflux for 1 h. The reaction mixture was then filtered through a celite pad. The filtrate was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc:MeOH:NH_4OH = 20:2:1) to provide **8** as a white solid (76 mg, 30.3%): mp 208-209 °C; ^{1}H NMR (400 MHz, MeOD), δ 8.21 (s, 1H), 7.64 (d, J = 6 Hz, 1H), 7.0 (d, J = 6 Hz, 1H), 4.56-4.78 (m, 1H), 4.53-4.57 (m, 1H), 3.94 (d, J = 6 Hz, 1H), 3.51 (d, J = 5.6 Hz, 1H), 3.48 (d, J = 5.6 Hz, 1H), 2.08-2.13 (m, 1H), 1.98-2.05 (m, 1H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 176.5, 153.3, 142.3, 140.4, 128.2, 99.7, 77.5, ,76.0, 70.6, 62.7, 45.7, 37.7, 20.1; Calcd HRMS for $C_{13}H_{18}N_4O_3$: 279.1469. Found: 279.1457.

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23. The crystallographic data (excluding structure factors) for **8** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 882824. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e mail: deposit@ccdc.cam.ac.uk).