Preparation of 8-Aza-7-deazaaristeromycin and -neplanocin A and Their 5′-Homologs

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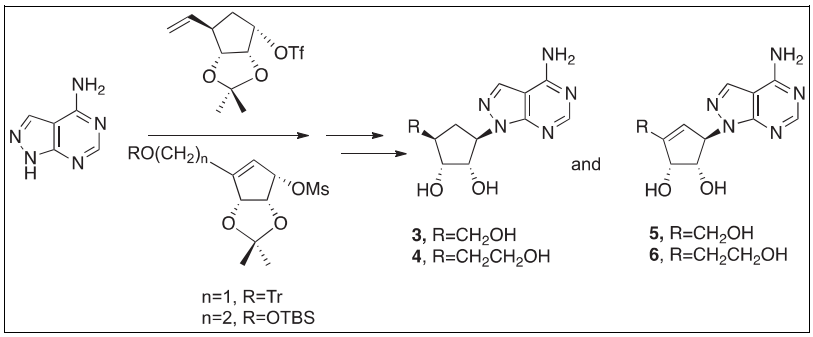


The synthesis of new members of the aristeromycin and neplaoncin A families of carbocyclic nucleosides possessing the 1*H*-pyrazolo[3,4-*d*]pyrimidine ring is reported. For this purpose, an adapted route to 4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidine is described.

INTRODUCTION

For some time, a research focus in our laboratory has been the synthesis and biological properties of 5′-noraristeromycin (**1**) [1] and related compounds [2]. Among those studies was an investigation into the anti-trypanosomal properties of compounds based on 8-aza-7-deaza-5′-noraristeromycin (**2**) [3]. At the time of those investigations, we did not have available the parent carbocyclic aristeromycin analog **3** and, for comparative purposes, the corresponding neplanocin A **5**, as the 8-aza-7-deaza analog of the naturally occurring neplanocin [4], and the side chain extended 5′-homo pair **4** and **6**, which are related to the biologically active 5′-homoaaristeromycin and 5′-homoneplanocin [5,6]. With the possibility that we will return to further work on the anti-trypanosomal properties of 8-aza-7-deazaadenine derived carbocyclic nucleosides, a synthetic means to **3–6** was sought (Figure 1). These results are described here.

RESULTS AND DISCUSSION

We first sought a cost-effective route to the requisite 1*H*-pyrazolo[3,4-*d*]-pyrimidine (7-deaza-8-azaadenine, **7**) for the subsequent coupling reactions with cyclopentyl and cyclopentenyl co-reactants. For this purpose, adaptation/combination of existing procedures was undertaken (Scheme 1).

Thus, beginning with the conversion of commercially available 4,6-dihydroxypyrimidine to 5-formyl-4,6-dichloropyrimidine (**8**) followed a literature procedure with slight modification [7]. Aminolysis of **8** with dimethylamine afforded compound **9** [8], which was treated with sodium hydroxide to provide the ring-cleaved product **10** [9]. The synthesis to **7** was completed by ring closure of **10** (to **11**) followed by treatment with formamide [10].

With **7** in hand, the Mitsunobu reaction with **12** [11] was first investigated in the presence of DIAD and PPh_3. However, only trace amounts of the desired coupled compound **13** were detected. Converting **12** to its triflate **14** [12] led successfully to **13** when reacted with **7** in the presence of sodium hydride. Oxidative cleavage of the alkenic center of **13** with osmium tetroxide/sodium periodate followed by sodium borohydride reduction yielded **15**. Acidic deprotection of **15** removed the isopropylidene protecting group to result in compound **3**. Regioselective hydroboration of **13** using 9-BBN, followed by oxidative hydrolysis to **16**, was followed by deprotection to smoothly provide **4** (Scheme 2).

The neplanocin A analogs **5** and **6** were synthesized by converting cyclopentenols **17** [13] and **18** [5] to their mesylates **19** and **20**. These latter products were reacted with **7** in the presence of sodium hydride to afford **21** and **22**. The targets **5** and **6** were achieved from **21** and **22** by deprotection using 1*N* HCl in methanol (Scheme 3).

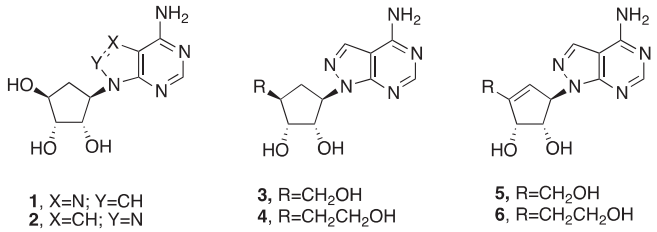
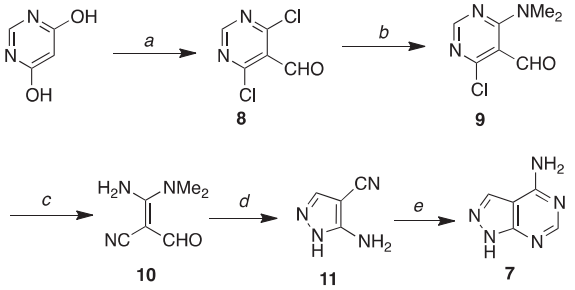


Figure 1. Adenine-based carbocyclic nucleosides

Scheme 1. Synthesis of 1*H*-pyrazolo[3,4-*d*]pyrimidine (**7**). Reagents and conditions: (a) POCl3, DMF, 63%; (b) HOAc, (CH3)2NH (aq.), 90%; (c) NaOH, H2O, product was used directly in step d; (d) NH2NH2, EtOH, 55% from 8; (e) formamidine acetate, EtOH, 75%.



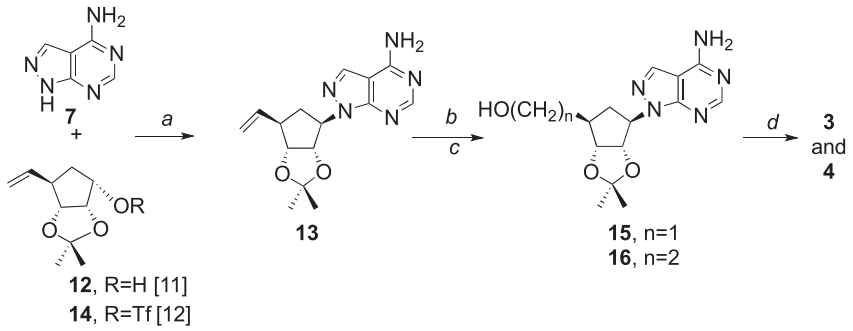
CONCLUSIONS

By adapting existing conditions for the preparation of 1*H*-pyrazolo[3,4-*d*]-pyrimidine (7-deaza-8-azaadenine, **7**), a series of carbocyclic 8-aza-7-deazaadenine derivatives **3–6** based on aristeromycin and neplanocin A has been synthesized via the S_N2-displacement between deprotonated 8-aza-7-deazaadenine and a corresponding protected cyclopentanol/cyclopentenol triflate or mesylate in the presence of sodium hydride.

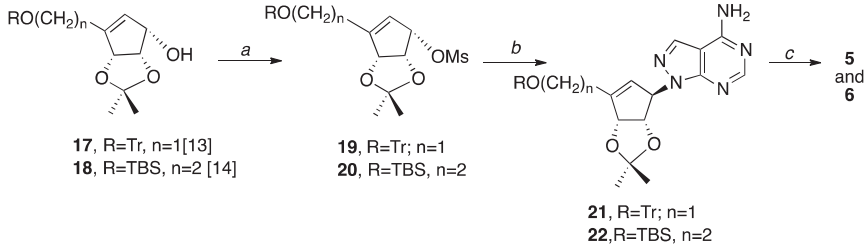
EXPERIMENTAL

Materials and methods. All melting points were recorded on a Meltemp II melting point apparatus (Barnstead/Thermolene, Dubuque, IA) and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC 250 (Bruker, Billerica, MA) spectrometer (operated at 250 and 62.9 MHz, respectively) or Bruker AV 400 (Bruker, Billerica, MA) spectrometer (operated at 400 and 100 MHz, respectively) and referenced to internal TMS at 0.0 ppm. The reactions were monitored by TLC using 0.25 mm Whatman Diamond silica gel

Scheme 2. Synthesis of compounds **3** and **4**. Reagents and conditions: (a) NaH, DMF then add 14, 0°C to room temperature, 88%; (b) for 15: (i) NaIO4, MeOH/H2O, 0°C, OsO4 added; (ii) NaBH4, 48% from 13; (c) for 16: (i) 9-BBN, THF, 0°C; (ii) NaOH, H2O2, 80% from 13; (d) 1N HCl, MeOH, 95% for both 3 and 4.



Scheme 3. Synthesis of compounds **5** and **6**. Reagents and conditions: For 5 (a) MsCl, Et3N, CH2Cl2, 0°C, 83%; (b) 7, NaH, DMF, 0°C to room temperature, 88%; (c) 1N HCl, MeOH, 95%. For 6, overall yield after steps a (using 18), b, and c is 31%.



60-F254 precoated plates (Whatman, Florham Park, NJ) with visualization by irradiation with a Mineralight UVGL-25 lamp (UVP, Upland, CA). Column chromatography was performed on Whatman silica, 230–400 mesh, 60 Å, and elution was carried out with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials.

1H-Pyrazolo[3,4-d]pyrimidin-4-amine (8-aza-7-deazaadenine, 7) [10]. To a solution of $POCl_3$ (50 mL) in anhydrous DMF (16 mL) at 0°C under N_2, 4,6-dihydroxypyrimidine (12.5 g, 112 mmol) was added portionwise, and the reaction mixture was stirred at same temperature for 30 min. Then, the heterogeneous mixture was refluxed for 5 h. The volatiles were removed under reduced pressure, the residue was poured onto ice, and the mixture neutralized by adding solid $NaHCO_3$ followed by extraction with diethyl ether. The organic phase was dried over Na_2SO_4 and concentrated, and the residue of 4,6-dichloropyrimidine-5-carbaldehyde (**8**) [7] (12.4 g, 63%) was found sufficiently pure by mp 68–70°C (lit. [7] mp 69–70°C) for use in the next step. ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.93 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 185.65, 162.73, 159.60, 124.89.

To a stirred solution of **8** (17.7 g, 100 mmol) in dioxane (200 mL) was added HOAc (5.7 mL, 100 mmol) at 0°C. To this mixture, dimethylamine (40% aq., 11.4 mL, 100 mmol) was added, dropwise. Stirring was continued at room temperature for 5 h. The reaction mixture was concentrated under reduced pressure, and the residue purified by recrystallization from EtOH to give 4-chloro-6-(dimethylamino)pyrimidine-5-carbaldehyde (**9**) [8] (16.7 g, 90%) that was used directly in the next step. ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.35 (s, 1H), 3.11 (s, 6H).

To a solution of **9** (7.5 g, 51 mol) in H_2O (5 mL) was added 2*N* NaOH (10 mL), together with dioxane (1–2 mL) to aid partial dissolution. The mixture was stirred for 24 h at room temperature and then extracted with CH_2Cl_2 (100 mL). The extracts were combined, dried (Na_2SO_4), and evaporated to dryness *in vacuo*. The residue of (*Z*)-3-amino-3-(dimethylamino)-2-formylacrylonitrile (**10**) [9] was used in the next step without purification.

To a solution of crude **10** (1.76 g, 13 mmol) in EtOH (30 mL) was added hydrazine hydrate (0.61 mL, 14 mmol), and the resultant mixture refluxed for 12 h. The mixture was concentrated *in vacuo*, and the residue purified by recrystallization from H_2O to give 2-amino-1*H*-pyrazole-3-carbonitrile (**11**) [9] as pale yellow solid (0.77 g, 55% from **8**), mp 171–173°C (lit. [9] mp 173–174°C). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.24 (s, 1H), 5.32 (s, 1H).

To a solution of **11** (1.6 g, 15 mmol) in EtOH (20 mL) was added formamidine acetate (3.0 g, 29 mmol). This mixture was heated under reflux for 5 h, and the solvent then removed *in vacuum*. The resulting residue was purified by recrystallization from H_2O to give **7** (1.5 g, 75%) as a pale solid, mp >300°C (lit. [10] mp 353–356°C). ^{1}H NMR (250 MHz, $CDCl_3$) δ 13.34 (s, 1H), 8.15 (s, 1H), 8.08 (s, 1H), 7.59 (s, br, 2H).

1-((3aS,4R,6R,6aR)-2,2-Dimethyl-6-vinyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (13). To a stirred solution of **7** (0.14 g, 1.0 mmol) in DMF (5 mL), sodium hydride (40 mg, 60% in mineral oil, 1.1 mmol) was added at 0°C. This mixture was stirred for 30 min at 0°C before a solution of **14** [12] (0.32 g, 1.0 mmol) in CH_2Cl_2 was added dropwise. After stirring the reaction at room temperature for 16 h, saturated NH_4Cl (10 mL) was added, and the resultant mixture stirred for 10 min. To this was added CH_2Cl_2 (50 mL), and the organic layer separated, washed with H_2O, and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue purified by column chromatography (5 : 1, hexanes/EtOAc) to afford **13** as a white solid (0.26 g, 88%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.99 (s, 1H), 6.82 (brs, 2H), 5.88–5.97 (m, 1H), 5.28–5.33 (m, 1H), 5.16 (td, 1H, J = 1.2 Hz, J = 13.2 Hz), 5.10–5.12 (m, 2H), 4.57 (t, 1H, J = 6.8 Hz), 2.80–2.85 (m, 1H), 2.38–2.44 (m, 1H), 2.32–2.35 (m, 1H), 1.56 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 158.1, 155.8, 153.5, 138.0, 131.7, 115.6, 113.7, 100.9, 84.0, 83.8, 61.5, 48.2, 31.5, 27.4, 25.0. HRMS Calcd. for $C_{15}H_{20}N_5O_2$ $[M+H]^+$: 302.1617; Found: 302.1605.

((3aR,4R,6R,6aS)-6-(4-Amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,2-dimethyl-tetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)methanol (15). To a mixture of **13** (4.3 g, 14.3 mmol) dissolved in MeOH (35 mL) and H_2O (18 mL) was added $NaIO_4$ (4.33 g, 20.2 mmol). After cooling the mixture to 0°C, OsO_4 (30 mg) was added. This new reaction mixture was stirred at the same temperature for 1 h and then at room temperature for 2 h. The resultant white solid was removed by filtration, and the filtrate removed *in vacuo* at ambient temperature. Methylene chloride (200 mL) was added to the residue, and the resultant organic solution washed with H_2O (30 mL) and brine (30 mL) and dried (Na_2SO_4). The CH_2Cl_2 was removed under reduced pressure at ambient temperature, and the residue dissolved in MeOH (40 mL). This new solution was cooled to 0°C, and $NaBH_4$ (1.2 g, 30.8 mmol) added portionwise. After the reaction was stirred at 0°C for 1 h, the solvent was removed, and CH_2Cl_2 (150 mL) and H_2O (30 mL) were added. The organic layer was separated and washed with brine and dried (Na_2SO_4). After removing the solvent under reduced pressure, the product was purified by chromatography with a short silica gel column (2 : 1 hexanes/EtOAc to only EtOAc) to give **15** (2.09 g, 48% from **13**) as a white solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.37 (s,1H), 7.92 (s,1H), 6.00(s, 2H), 5.29–5.33 (m, 1H), 4.99 (dd, 1H, J = 4.4 Hz, J = 6.4 Hz), 4.70 (dd, 1H, J = 3.6 Hz, J = 6.0 Hz), 3.80 (s, 2H), 2.59–2.62 (m, 1H), 2.52 (s, br, 1H), 1.59 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.8, 156.2, 153.6, 131.1, 112.9, 101.0, 85.5, 82.9, 64.4, 63.4, 46.5, 33.5, 27.6, 25.2. HRMS Calcd. for $C_{14}H_{20}N_5O_3$ $[M+H]^+$: 306.1566; Found: 306.1576.

(1R,2S,3R,5R)-3-(4-Amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-5-(hydroxymethyl)-cyclopentane-1,2-diol (3). A solution of **15** (400 mg, 1.31 mmol) dissolved in a mixture of 1*N* HCl (10 mL) and MeOH (10 mL) was stirred at room temperature for 3 h and then neutralized with basic ion-exchange resin (Amberlite IRA-67). Filtration of this mixture and followed by evaporation of this filtrate under reduced pressure afforded **3** as a white solid (330 mg, 95%); ^{1}H NMR (400 MHz, MeOD) δ 8.09 (s, 1H), 7.93 (s, 1H), 3.73–3.79 (m, 1H), 3.62 (dd, 1H, J = 4.4, 6.4 Hz), 3.80 (s, 2H), 3.30–3.32 (m, 2H), 2.18–2.22 (m, 1H), 1.70–1.71 (m, 1H); ^{13}C NMR (100 MHz, MeOD) δ 157.4, 154.4, 153.8, 133.2, 101.3, 74.4, 72.8, 65.1, 64.2, 45.6, 26.2. HRMS Calcd. For $C_{11}H_{16}N_5O_3$ $[M+H]^+$: 266.1253; Found: 266.1270.

2-((3aR,4R,6R,6aS)-6-(4-Amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2,2-dimethyl-tetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl) ethanol (16). To a solution of **13** (1.0 g, 3.13 mmol) in THF (20 mL) at 0°C under N_2 was added 9-BBN (0.5*M* in THF, 10.0 mL, 5.00 mmol), and the resultant mixture stirred at this temperature for 3 h. To this, NaOH solution (1*M*, 6 mL) was added, followed by H_2O_2 (50% in H_2O, 3 mL), and the stirring continued for an additional 30 min. The reaction mixture was diluted with CH_2Cl_2 (100 mL), and the CH_2Cl_2 solution washed with saturated $NaHCO_3$ solution (30 mL). The organic layer was

dried ($MgSO_4$) and filtered, and the filtrate concentrated *in vacuo* to give the crude product as a colorless oil, which was purified by flash column chromatography (EtOAc/hexanes, 4 : 1) to afford **16** as a white solid (0.84 g, 80%), mp 190–191°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.93 (s, 1H), 5.51 (s, br, 2H), 5.29–5.30 (m, 1H), 5.04–5.07 (m, 1H), 4.51 (t, 1H, J = 6.8 Hz), 3.75–3.79 (m, 2H), 2.42–2.48 (m, 1H), 2.17–2.22 (m, 2H), 1.74–1.82 (m, 3H), 1.57 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 156.0, 153.8, 130.7, 112.6, 100.8, 84.5, 84.3, 61.8, 61.5, 42.5, 37.7, 35.9, 27.5, 25.3. HRMS Calcd. for $C_{15}H_{22}N_5O_3$ $[M+H]^+$: 320.1723; Found: 320.1711.

Synthesis of (1R,2S,3R,5R)-3-(4-amino-1H-pyrazolo[3,4-d] pyrimidin-1-yl)-5-(2-hydroxyethyl)-cyclopentane-1,2-diol (4). Compound **16** (400 mg, 1.31 mmol) was dissolved in a mixture of 1*N* HCl (10 mL) and MeOH (10 mL). This reaction mixture was stirred at room temperature for 3 h and then neutralized with basic ion-exchange resin (Amberlite IRA-67). Filtration and evaporation of the filtrate *in vacuo* afforded **4** as a white solid (330 mg, 95%). ^{1}H NMR (400 MHz, MeOD) δ 8.17 (s, 1H), 8.09 (s, 1H), 5.08 (dd, 1H, J = 6.0 Hz, J = 8.8 Hz), 4.34 (t, 1H, J = 6.0 Hz), 3.91 (t, 1H, J = 6.0 Hz), 3.63–3.67 (m, 2H), 2.38–2.41 (m, 1H), 2.15–2.20 (m, 2H), 1.88–1.94 (m, 1H), 1.71–1.75 (m, 2H); ^{13}C NMR (100 MHz, MeOD) δ 157.4, 153.6, 151.4, 130.5, 101.2, 74.5, 74.2, 60.2, 58.8, 45.4, 38.5, 35.2. HRMS Calcd. for $C_{12}H_{18}N_5O_3$ $[M+H]^+$: 280.1410; Found: 280.1407.

1-((3aS,4R,6aR)-6-(Trityloxymethyl)-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (21). To a stirred solution of **17** [13] (1.07 g, 2.5 mmol) in CH_2Cl_2 (20 mL) and Et_3N (15 mL) at 0°C was added, dropwise, MsCl (428 mg, 3.75 mmol) in CH_2Cl_2 (5 mL). This mixture was kept at 0°C for 30 min, and to this was added cold H_2O (10 mL). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexanes, 4 : 1) to afford (3a*R*,4*S*,6a*R*)-6-(trityloxymethyl)-2,2-dimethyl-4,6a-dihydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl methanesulfonate (**19**) (1.05 g, 83%) as a white solid. This solid was used in the next step directly.

To a stirred solution of **7** (0.14 g, 1.0 mmol) in DMF (5 mL) at 0°C was added sodium hydride (40 mg, 60% in mineral oil, 1.1 mmol). This mixture was stirred for 30 min at 0°C before a solution of **19** (0.51 g, 1.0 mmol) in CH_2Cl_2 was added, dropwise. After stirring the reaction mixture at room temperature for 16 h, saturated NH_4Cl (10 mL) was added, and the stirring continued for 10 min. To this was added CH_2Cl_2 (50 mL), and the resultant organic layer separated, washed with H_2O, and dried (Na_2SO_4). Evaporation of the organic solvent under reduced pressure yielded a residue that was purified by column chromatography (EtOAc/hexanes, 4 : 1) to afford **21** as a white solid (0.48 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.92 (s, 1H), 7.40–7.47 (m, 5H), 7.19–7.30 (m, 10H), 6.05 (d, J = 9.0 Hz, 2H), 5.68 (s, br, 2H), 5.33 (d, 1H), 4.87 (d, 1H, J = 6.0 Hz), 3.97 (d, 1H, J = 15.0 Hz), 3.78 (d, 1H, J = 15.0 Hz), 1.45 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 156.0, 153.6, 148.1, 143.9, 131.0, 128.6, 127.9, 127.1, 123.6, 112.3, 100.9, 87.1, 84.6, 84.2, 66.8, 61.6, 27.6, 26.3. HRMS Calcd. for $C_{33}H_{32}N_5O_3$ $[M+H]^+$: 546.2505; Found: 546.2508.

(1S,2R,5R)-5-(4-Amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-3-(hydroxymethyl)-cyclopent-3-ene-1,2-diol (5). Compound **21** (400 mg, 1.31 mmol) was dissolved in a mixture of 1*N* HCl (10 mL) and MeOH (10 mL). This reaction mixture was stirred at room temperature for 3 h and then neutralized with basic ion-exchange resin (Amberlite IRA-67). Filtration and evaporation of the filtrate under reduced pressure afforded **5** as a pale solid (330 mg, 95%). ^{1}H NMR (400 MHz, MeOD) δ 8.25 (s, 1H), 8.01 (s, 1H), 5.56–5.59 (m, 1H), 4.54–4.56 (m, 1H), 4.19–4.23 (m, 2H), 4.09–4.11 (m, 1H), 3.72 (s, br, 1H); ^{13}C NMR (100 MHz, MeOD) δ 157.4, 154.5, 153.7, 146.7, 132.9, 121.7, 101.3, 78.8, 72.8, 69.6, 65.6. HRMS Calcd. for $C_{11}H_{14}N_5O_3$ $[M+H]^+$: 264.1097; Found: 264.1099.

(5R)-5-(4-Amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-3-(2-hydroxyethyl)cyclopent-3-ene-1,2-diol (6). Following a procedure similar to that for preparing **5**, **6** was prepared from **18** [5] as a white solid (31% in three steps): ^{1}H NMR (MeOD, 400 MHz) δ 8.27 (s, 1H), 7.98 (s, 1H), 5.38–5.36 (m, 1H), 4.50–4.56 (m, 1H), 4.07 (dd, 1H, J = 3.6 Hz, J = 6.0 Hz), 3.39–3.55 (m, 3H), 2.15–2.13 (m, 2H); ^{13}C NMR (MeOD, 100 MHz) δ 157.4, 154.7, 153.8, 144.9, 132.9, 121.0, 101.0, 82.8, 72.8, 69.6, 60.9, 29.8. HRMS Calcd. for $C_{12}H_{16}N_5O_3$ $[M+H]^+$: 278.1253; Found: 278.1247.

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