Carbocyclic 4-Deazaformycins

Yan Zhang, Wei Ye, Haisheng Wang, Stewart W. Schneller*

The Molette Laboratory for Drug Discovery, Department of Chemistry and Biochemistry, Auburn University, Auburn, AL 36849-5312, USA

Fax +1(334)8440239; E-mail: schnest@auburn.edu

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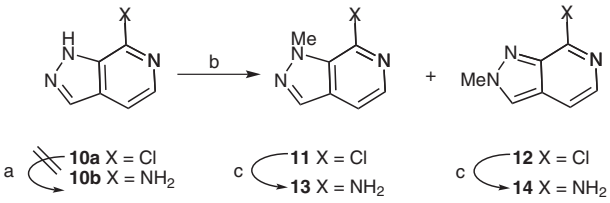
Abstract: The preparation of carbocyclic 4-deazaformycin and its 5′-homoanalogue from a common vinyl precursor, and its N-1 and N-2 methyl derivatives is reported. The syntheses began with a highly stereoselective S_N2 reaction between lithio 4-picolines and a protected 2,3-dihydroxy-4-vinylcyclopentyl triflate. The requisite fused pyrazole ring was created by an intramolecular diazonium reaction that was followed by vinyl transformation into the hydroxymethyl and the hydroxyethyl groups. The *N*-methyl derivatives arose by standard methylation conditions and the resultant *N*-Me regiochemistry was assigned by homo- and heteronuclear NMR spectroscopy.

Key words: C-nucleosides, carbocyclic nucleosides, pyrazolo[3,4-*c*]pyridines

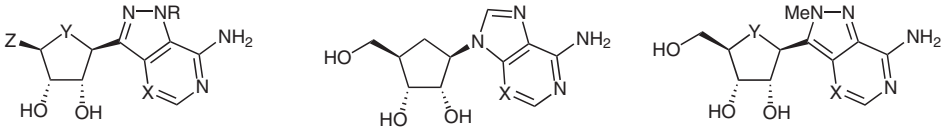
Formycin (**1**), as a C-nucleoside,[1] and aristeromycin (**2**), as a carbocyclic nucleoside,[2] represent unique natural products. Because of their structural relationship to adenosine, they have spawned numerous studies that have focused on chemotherapeutic discovery and biomechanistic endeavors.[1c,3] With formycin, for example, the N-1 and N-2 methylated derivatives, **3** and **4**, respectively, have shown biological properties different from formycin[4] while 3-deazaaristeromycin (**5**) has found its own biological place beyond aristeromycin.[5] In continuing our investigations on 3-deaza carbocyclic nucleosides,[6] we sought synthetic means that would combine all of these features into the carbocyclic C-nucleoside[7] target compounds **6–8** (Figure 1). Derivative **9** was also included in this study because of its similarity to 5′-homoaristeromycin, which has displayed an encouraging biological profile.[8] The successes in this direction are reported here.

In designing pathways to **6–9** we were well acquainted with the difficulty of converting 6-chloro-3-deazapurines to 3-deazaadenines with ammonia[6] and were uncertain if the same difficulty would be encountered in this resembling deaza study. To evaluate this possibility, a model study was carried out with 7-chloropyrazolo[3,4-*c*]pyridine (**10**),[9] which found that no reaction with ammonia occurred (Scheme 1). However, ammonolysis of the methylated derivatives **11** and **12** was successful producing **13** and **14** [the isomeric products were assigned by an X-ray crystallographic determination of the side-product **25**[10] formed by the ammonolysis of **12**]. This difference in reactivity was likely the consequence of an acid/base reaction between the pyrazole NH of **10** and ammonia that deactivated the chloro-bearing carbon to displacement by ammonia. With the methyl derivatives **11** and **12** this situation was rendered inoperative. In any case, from this observation, we concluded that a route to **7** and **8** could include an ammonolysis step, but a scheme to **6** and **9** would necessitate alternative considerations for introducing the requisite amino group. Our synthetic investigations began with seeking **6** and **9**.



Scheme 1 *Reagents and conditions*: a) NH_3–MeOH, 165 °C; b) NaH, MeI, THF, 0 °C to r.t., overnight, 24% for **11** and 64% for **12**; c) same as a, 85% for **13** and 90% for **14**.

The preparation of these latter targets was envisioned as arising from a common C-4′ substituent (as in **15**,



1 X = N; Y = O; Z = CH_2OH; R = H
3 X = N; Y = O; Z = CH_2OH; R = Me
6 X = CH; Y = CH_2; Z = CH_2OH; R = H
7 X = CH; Y = CH_2; Z = CH_2OH; R = Me
9 X = CH; Y = CH_2; Z = CH_2CH_2OH; R = H

2 X = N
5 X = CH

4 X = N; Y = O
8 X = CH; Y = CH_2

Figure 1 Aristeromycin, formycin, and related compounds

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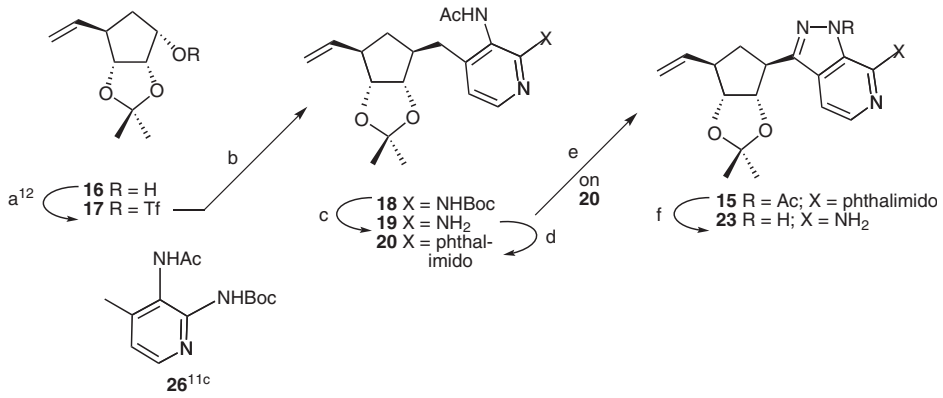
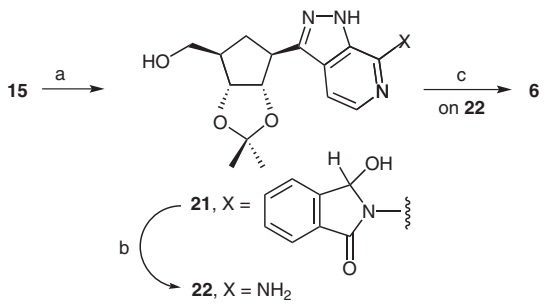


Scheme 2 *Reagents and conditions*: a) Tf_2O, Py, CH_2Cl_2, 0 °C, 30 min, 92%; b) **26**, THF, –78 °C, then *n*-BuLi followed by **17**, then r.t., 57%; c) TFA (20 equiv), 0 °C to r.t., 5 h; d) phthalic anhydride, toluene, 50 °C, 1 d, 80% for 2 steps; e) KOAc, Ac_2O, isoamyl nitrite, benzene, reflux, 79%; f) NH_3–MeOH, r.t., overnight, 84%.

Scheme 2) that was foreseen as accessible by adapting a literature procedure.[11] Thus, the synthesis of **15** began with the nucleophilic substitution reaction of the triflate **17**[12] by the lithio salt of *tert*-butyl-*N*-(3-acetamido-4-methylpyridin-2-yl) carbamate (**26** in Scheme 2),[11c] which also served as the source of the final C-7 amino substituent. This reaction proceeded from the less hindered β-face of the cyclopentyl ring of **17** (verified by NMR analysis of **27**, vide infra) to give **18**. To circumvent potential subsequent side reactions,[9] the Boc group was removed and the resulting free amine **19** protected as its *N*-phthalimino derivative **20**.

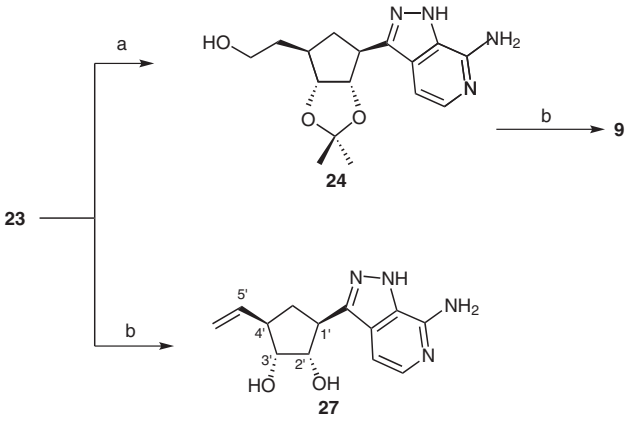
Construction of the fused pyrazole ring took place by treating **20** with isoamyl nitrite in the presence of potassium acetate and acetic anhydride in refluxing benzene to result in the desired **15** (Scheme 2).

Transformation of ethylene unit of **15** to the hydroxymethyl of **6** was achieved (Scheme 3) by, first, glycolization with *N*-methlymorpholine *N*-oxide (NMO) and osmium tetroxide followed by oxidation using sodium periodate and, then, reduction with sodium borohydride to provide **21** in which one of the carbonyl centers of the phthalimido unit was reduced. Treatment of **21** with methanolic ammonia (to **22**) and subsequent hydrolytic deprotection produced **6**.



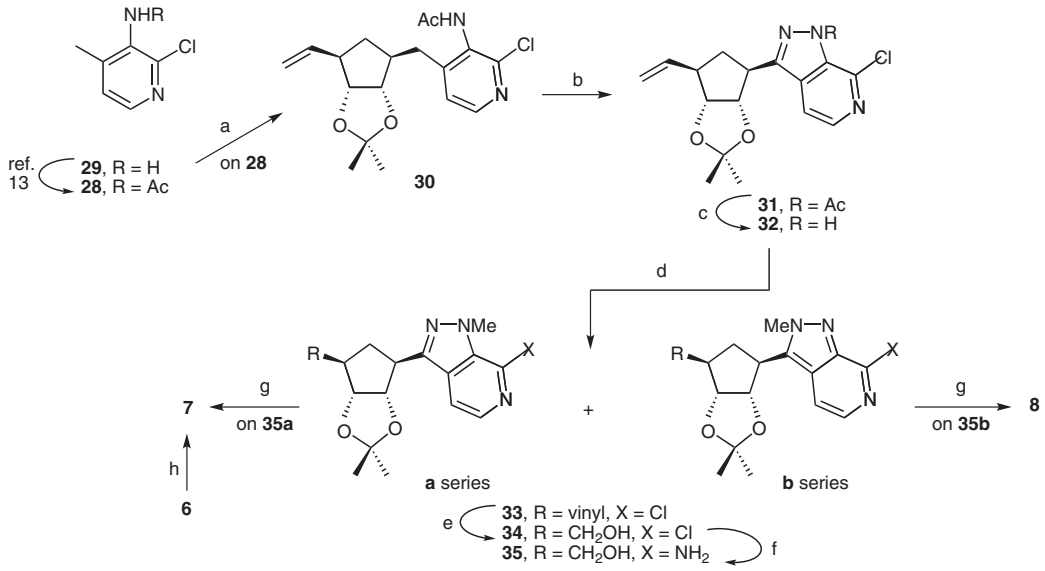
Scheme 3 *Reagents and conditions*: a) i. NMO/OsO_4 (cat.), THF, 0 °C to r.t., 12 h, ii. $NaIO_4$, CH_2Cl_2/H_2O, r.t., 1 h, iii. $NaBH_4$ (excess), 0 °C, 1 h, 51% for 3 steps; b) NH_3–MeOH, r.t., overnight, 92%; c) aq 1 M HCl–THF (1:1), r.t., 6 h, 88%.

Ammonolysis of **15** to **23** (Scheme 2) followed by a method used previously in our laboratories[6] of Brown hydroboration with 9-borabicyclo[3.3.1]nonane (BBN) and, subsequent, oxidation with hydrogen peroxide yielded **24** (Scheme 4). Deprotection of **24** formed **9**. Similarly, deprotection of **23** produced **27** whose structure was confirmed by NMR spectroscopic analysis, which established the stereochemistry of the heterocyclic ring-to-cyclopentyl unit arising out of the **17** to **18** conversion. In this direction, the vinyl H-5′ signal of **27** appeared at δ = 5.08. Using HHCOSY, the following assignments could then be made: H-4′ (2.06 ppm), H-3′ (3.70 ppm), H-2′ (4.02 ppm), and H-1′ (3.37 ppm). A NOESY correlation was found between H-4′ and H-1′ indicating they were both in the 'down' orientation.



Scheme 4 *Reagents and conditions*: a) i. 9-BBN, THF, 0 °C to r.t., 12 h, ii. 50% H_2O_2 in H_2O, NaOH, 30 min, 81% for two steps; b) TFA–H_2O (2:1), r.t., 3 h, 86% for **9**, 81% for **27**.

Construction of **7** and **8** began with 3-acetamido-2-chloro-4-picoline (**28**)[13] that was prepared from 3-amino-2-chloro-4-picoline (**29**) on treatment with Ac_2O (Scheme 5). Compound **28** was transformed to its lithio derivative and this reacted with triflate **17** in a nucleophilic substitution manner from the less hindered cyclopentyl β-face, as expected (see **18**), to yield **30** as the only product. Construction of the fused pyrazole ring onto **30** occurred via the



Scheme 5 *Reagents and conditions*: a) *n*-BuLi, THF, –78 °C, then to 0 °C, add **17**, –78 °C, then to 0 °C, 57%; b) KOAc, Ac_2O, isoamyl nitrite, benzene, reflux, 60%; c) NH_3–MeOH, r.t., quant.; d) NaH/MeI in THF, 0 °C, then to r.t., 55% for **33a**, 41% for **33b**; e) i. NMO/OsO_4 (cat.), THF, 0 °C to r.t., ii. $NaIO_4$, CH_2Cl_2/H_2O, r.t., 1 h, iii. $NaBH_4$ (excess), 86% for **34a**, 84% for **34b** for 3 steps; f) NH_3–MeOH, 0 to 165 °C, 45% for **35a**, 84% for **35b**; g) aq 1 M HCl, THF, r.t., 80% for **7**, 81% for **8**; h) i. DMFDMA, DMF, 70 °C, ii. NH_4OH, 71%.

same procedure as the **20** to **15** transformation to give **31**. The N-1/N-2 methyl derivatives **33a/33b** were prepared in the ratio of 4:3 by reacting deacetylated **32** (ammonia–methanol) with methyl iodide/sodium hydride. The vinyl unit of the products **33a/33b** was transformed to the desired hydroxymethyl functional center of **34a/34b** in the same manner as described for **15** to **21** in Scheme 3 (i.e., NMO, OsO_4; $NaIO_4$; $NaBH_4$).

Ammonolysis of **34a/34b** to **35a/35b** followed by weak acid deprotection gave **7** and **8**, respectively. A more convenient route to **7** was found by treating **6** with dimethylformamide dimethyl acetal. However, these conditions failed when applied to the protected form of **6** (that is, **22**).

The structures of isomers **33a** and **33b**, were assigned by an HMBC ^{13}C spectroscopic analysis: (i) the N-1 methyl of **33a** (δ = 38.9 ppm) displayed a strong correlation with C-7a (δ = 134.1 ppm) but no correlation with C-3, C-3a, and C-7 whereas (ii) the N-2 methyl of **33b** (δ = 39.6 ppm) offered a strong correlation with C-3 (δ = 137.2 ppm) but no correlation with C-3a, C-7a, and C-1′ (Figure 2).

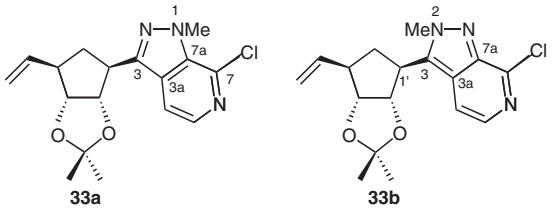


Figure 2 Relevant ring atoms for **33a** and **33b**

In conclusion, an efficient synthesis of various carbocyclic formycin derivatives related to 3-deazaaristeromycin has been developed. This offers an effective pathway into formycin analogues where substitution can occur at N-1 and N-2, C-4 (which is a nitrogen center in formycin), and the cyclopentyl ring at C-6′ (which is an oxygen in formycin).

^1H and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer or Bruker AC-250 spectrometer. ^1H chemical shifts are reported relative to $CDCl_3$ at δ = 7.27 ppm (or CD_3OD at δ = 3.51 ppm or DMSO-d_6 at δ = 2.51 ppm) and TMS as an internal standard. ^{13}C chemical shifts are reported relative to $CDCl_3$/CD_3OD/DMSO-d_6. Standard abbreviations are used to indicate spin multiplicities. The mass spectral data was determined using a Waters Micromass Q-TOF Premier Mass Spectrometer. Atlantic Microlabs, Atlanta, Georgia, performed elemental analyses. Reactions were monitored by 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 I_2 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 (^1H and ^{13}C NMR) homogeneous materials. The reactions were generally carried out in a N_2 atmosphere under anhydrous conditions.

7-Chloro-1-methylpyrazolo[3,4-*c*]pyridine (11) and 7-Chloro-2-methylpyrazolo[3,4-*c*]pyridine (12)

Compound **10**[9] (0.95 g, 6.19 mmol) was partly suspended in anhyd THF (30 mL) and cooled to 0 °C. To this, NaH (0.21 g, 8.67 mmol) was added portionwise and the mixture was kept at 0 °C for another 10 min. MeI (0.48 mL, 7.73 mmol) was added dropwise to the mixture and the system gradually warmed to r.t. and then stirred overnight to give a clear solution. After addition of sat. aq NH_4Cl (5 mL) dropwise, the solvent was evaporated under reduced pressure. To the residue was added H_2O (10 mL) and this mixture extracted by CH_2Cl_2 (30 mL), and the extracts dried (Na_2SO_4) and concentrated to dryness. The crude product was isolated by flash chromatography using a mixture of hexanes–EtOAc (2:1) to give **11** (0.25 g, 24%) and hexanes–EtOAc (1:2) to provide **12** (0.66 g, 63%).

11
Light yellow solid; mp 68–69 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.03–8.00 (m, 2 H), 7.53 (dt, *J* = 5.8, 1.0 Hz, 1 H), 4.44 (s, 3 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 138.2, 134.3, 133.7, 132.5, 130.6, 114.7, 39.3.

HRMS: *m*/*z* calcd for $C_7H_6ClN_3$: 167.0250; found: 167.0248.

12
Light yellow solid; mp 110–111 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.00 (s, 1 H), 7.88 (d, *J* = 5.8 Hz, 1 H), 7.42 (d, *J* = 6.0 Hz, 1 H), 4.29 (s, 3 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 143.3, 142.7, 137.4, 126.0, 125.2, 113.6, 41.4.

HRMS: *m*/*z* calcd for $C_7H_6ClN_3$: 167.0250; found: 167.0253.

7-Amino-1-methylpyrazolo[3,4-*c*]pyridine (13)
To MeOH saturated with NH_3 (40 mL) at 0 °C was added **11** (0.24 g, 1.56 mmol). This mixture was heated to 165 °C and then kept at this temperature for 2 d. The solvent was removed under reduced pressure and the residue purified by column chromatography using MeOH–CH_2Cl_2 (1:10) to give **13** (0.19 g, 85%) as a light yellow solid; mp 114–115 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.12 (s, 1 H), 7.35 (d, *J* = 6.8 Hz, 1 H), 6.69 (d, *J* = 6.4 Hz, 1 H), 6.37 (br, 2 H), 4.13 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6, 136.4, 133.1, 124.6, 124.5, 104.4, 40.9.

HRMS: *m*/*z* calcd for $C_7H_8N_4$: 148.0749; found: 148.0749.

7-Amino-2-methylpyrazolo[3,4-*c*]pyridine (14)
Using an identical procedure for preparing **13**, **12** (0.24 g, 1.56 mmol) yielded **14** (0.20 g, 90%) as a light yellow solid; mp 156–157 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.86 (s, 1 H), 7.50 (d, *J* = 5.6 Hz, 1 H), 6.88 (d, *J* = 5.6 Hz, 1 H), 6.20 (br, 2 H), 4.26 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.3, 137.3, 132.4, 129.7, 127.4, 107.3, 39.1.

HRMS: *m*/*z* calcd for $C_7H_8N_4$: 148.0749; found: 148.0756.

(3a*S*,4*S*,6*R*,6a*R*)-2,2-Dimethyl-4-trifluoromethanesulfonyl-6-vinyltetrahydrocyclopenta[1,3]dioxole (17)
Tf_2O (0.35 mL, 2.50 mmol) in CH_2Cl_2 (5 mL) was added to a mixture of alcohol **16**[11] (0.64 g, 3.5 mmol) and anhyd pyridine (5.61 mL, 70 mmol) in anhyd CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred for 30 min and then cold H_2O (5 mL) was added. The layers were separated and the organic layer was washed with H_2O (3 × 20 mL), dried (Na_2SO_4), and evaporated to dryness to give a brown oil, which was purified by flash column chromatography using hexanes–EtOAc (8:1) to give **17** as a colorless syrup (1.02 g, 92%) for the next step.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.77 (ddd, *J* = 27.2, 17.6, 10.0 Hz, 1 H), 5.17–5.09 (m, 3 H), 4.62 (t, *J* = 9.2 Hz, 1 H), 4.53–4.50 (m, 1 H), 2.92–2.75 (m, 1 H), 2.43–2.32 (m, 1 H), 2.12–2.05 (m, 1 H), 1.54 (s, 3 H), 1.35 (s, 3 H).

***tert*-Butyl-*N*-{3-acetamido-4-[(3a*S*,4*S*,6*R*,6a*R*)-2,2-dimethyl-6-vinyltetrahydrocyclpenta[1,3]dioxol-4-methyl]pyridin-2-yl} Carbamate (18)**
tert-Butyl-*N*-(3-acetamido-4-methylpyridin-2-yl) carbamate (**26**;[11c] 1.03 g, 3.87 mmol) dissolved in anhyd THF (100 mL) was cooled to –78 °C. To this was added *n*-BuLi (4.64 mL, 11.61 mmol, 2.5 M solution in hexanes) slowly under N_2. The resulting yellow solution was stirred at this same temperature for 15 min and then warmed to 0 °C over 30 min. The orange solution was cooled to –78 °C and a solution of the triflate **17** (1.02 g, 3.23 mmol) in anhyd THF (20 mL) added dropwise. The resulting mixture was stirred at –78 °C for 15 min and then at r.t. overnight. Sat. aq NH_4Cl (20 mL) was added to the reaction mixture at 0 °C and this mixture was stirred for 10 min. The solvent was removed under reduced pressure and to the residue H_2O (20 mL) was added. This aqueous mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated to dryness under reduced pressure. The residue was then purified by flash chromatography using a mixture of CH_2Cl_2–EtOAc (1:1) and the resultant residue, following solvent evaporation, was recrystallized from CH_2Cl_2–hexanes to give **18** as white needles (0.79 g, 57%); mp 116–118 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (br, 1 H), 8.20 (d, *J* = 5.2 Hz, 1 H), 7.71 (br, 1 H), 7.18 (d, *J* = 5.2 Hz, 1 H), 5.83 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.09 (dd, *J* = 16.9, 0.9 Hz, 1 H), 5.03 (dd, *J* = 10.4, 0.9 Hz, 1 H), 4.34 (t, *J* = 6.4 Hz, 1 H), 4.25 (dd, *J* = 6.8, 4.8 Hz, 1 H), 2.98–2.93 (m, 1 H), 2.66–2.59 (m, 2 H), 2.44–2.39 (m, 1 H), 2.14 (s, 3 H), 2.05–2.02 (m, 1 H), 1.64 (m, 1 H), 1.54 (s, 9 H), 1.51 (s, 3 H), 1.28–1.25 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 154.5, 150.4, 146.7, 146.4, 139.5, 124.7, 122.3, 115.2, 112.9, 85.8, 85.5, 82.2, 49.4, 44.4, 37.4, 35.5, 28.4 (3 ×), 27.8, 25.3, 23.6.

HRMS: *m*/*z* calcd for $C_{23}H_{33}N_3O_5$: 431.2420; found: 431.2425.

***N*-{4-[(3a*S*,4*S*,6*R*,6a*R*)-2,2-Dimethyl-6-vinyltetrahydrocyclopenta[1,3]dioxol-4-methyl]-2-phthalimidopyridin-3-yl}acetamide (20)**
Compound **18** (2.00 g, 4.63 mmol) was dissolved in CH_2Cl_2 (50 mL) and this solution was cooled to 0 °C. The yellow solution changed into bright yellow immediately when TFA (7.14 mL, 92.69 mmol) was added dropwise over 5 min. The mixture was gradually warmed to r.t., kept at this temperature for 5 h, and then poured slowly into chilled sat. aq $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 25 mL), and the combined organic phases dried (Na_2SO_4), evaporated under reduced pressure, and purified by flash chromatography using a mixture of MeOH–CH_2Cl_2 (1:10) to give crude **19** as a yellow solid. To a solution of this **19** in anhyd toluene was added phthalic anhydride (0.69 g, 4.63 mmol). The mixture was heated at 50 °C for one day, then filtered through Celite, washed with CH_2Cl_2 (25 mL), evaporated under reduced pressure, and the residue purified by flash chromatography using a mixture of EtOAc–CH_2Cl_2, (1:1) to give **20** as a white solid (1.71 g, 80% for 2 steps). Compound **20** was further purified by recrystallization from CH_2Cl_2–hexane system to form white needles; mp 202–203 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 4.8 Hz, 0.13 H), 8.52 (d, *J* = 4.8 Hz, 0.87 H), 7.98–7.95 (m, 2 H), 7.82–7.80 (m, 2 H), 7.48 (br, 1 H), 7.42 (d, *J* = 5.2 Hz, 1 H), 5.12 (dd, *J* = 16.9, 0.8 Hz, 1 H), 5.05 (dd, *J* = 10.4, 0.8 Hz, 1 H), 4.37 (t, *J* = 6.4 Hz, 1 H), 4.27 (t, *J* = 6.4 Hz, 1 H), 3.01–2.95 (m, 1 H), 2.72–2.62 (m, 2 H), 2.39 (sext, *J* = 5.6 Hz, 1 H), 2.08 (quint, *J* = 6.4 Hz, 1 H), 2.03 (s, 3 H), 1.53 (s, 3 H), 1.35 (q, *J* = 11.2 Hz, 1 H), 1.31 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 166.6, 150.7, 147.9, 143.7, 139.1, 134.8, 131.9, 129.5, 125.4, 124.1, 115.3, 113.1, 85.5, 85.4, 49.1, 44.5, 37.5, 35.1, 27.7, 25.2, 23.3.

HRMS: *m*/*z* calcd for $C_{26}H_{27}N_3O_5$: 461.1951; found: 461.1939.

Anal. Calcd for $C_{26}H_{27}N_3O_5$: C, 67.66; H, 5.90; N, 9.10; found: C, 67.73; H, 5.80; N, 8.92.

1-Acetyl-7-phthalimido-3-[(3a*S*,4*S*,6*R*,6a*R*)-2,2-dimethyl-6-vinyltetrahydrocyclopenta[1,3]dioxol-4-yl]pyrazolo[3,4-*c*]pyridine (15)

Compound **20** (1.00 g, 2.17 mmol) was suspended in anhyd benzene (100 mL) and to this was added KOAc (0.25 g, 2.23 mmol) and Ac_2O (0.61 mL, 6.46 mmol). Isoamyl nitrite (0.43 mL, 3.25 mmol) was subsequently added dropwise to the reaction mixture once it was heated to 70 °C. The resultant mixture was heated at reflux for 10 h, cooled to r.t., filtered through Celite, and washed with hot toluene (3 × 10 mL). The filtrates were evaporated and the residue was purified by flash chromatography using a mixture of EtOAc–hexanes (2:3) to give **15** as a white solid (0.81 g, 79%); mp 191–192 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.67 (d, *J* = 5.6 Hz, 1 H), 8.00–7.96 (m, 3 H), 7.81–7.79 (m, 2 H), 5.93 (ddd, *J* = 16.9, 10.4, 7.2 Hz, 1 H), 5.21 (dt, *J* = 16.9, 1.6 Hz, 1 H), 5.17 (dt, *J* = 10.0, 1.2 Hz, 1 H), 4.82 (dd, *J* = 6.8, 6.0 Hz, 1 H), 4.54 (dd, *J* = 7.2, 6.0 Hz, 1 H), 3.66 (quint, *J* = 6.0 Hz, 1 H), 2.92 (sept, *J* = 6.0 Hz, 1 H), 2.66 (s, 3 H), 2.53 (quint, *J* = 6.4 Hz, 1 H), 2.10 (dt, *J* = 12.4, 1.6 Hz, 1 H), 1.65 (s, 3 H), 1.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 166.8, 151.5, 143.1, 138.5, 135.2, 134.5, 133.7, 133.0, 132.6, 124.2, 116.3, 115.9, 113.9, 85.5, 84.6, 49.6, 44.1, 35.3, 27.8, 25.3, 23.9.

HRMS: *m*/*z* calcd for $C_{26}H_{24}N_4O_5$: 427.1747; found: 427.1748.

Anal. Calcd for $C_{26}H_{24}N_4O_5$: C, 66.09; H, 5.12; N, 11.86. Found: C, 66.18; H, 5.22; N, 11.90.

7-(2,3-Dihydro-3-hydroxy-1*H*-isoindol-1-one-2-yl)-3-[(3a*S*,4*R*,6*R*,6a*R*)-2,2-dimethyl-6-hydroxymethyltetrahydrocyclopenta[1,3]dioxol-4-yl]pyrazolo[3,4-*c*]pyridine (21)

Methylmorpholine *N*-oxide (0.49 mL 50% wet in THF, 2.38 mmol) was added to a solution of **15** (0.75 g, 1.59 mmol) in THF (20 mL). After the solution was cooled to 0 °C, a catalytic amount of solid OsO_4 (4 mg, 0.016 mmol) was added and the solution stirred for 12 h at r.t. The reaction mixture was quenched by the addition of $NaHSO_3$ (5 g). The solvent was removed under reduced pressure and the residue purified by flash column chromatography (EtOAc). To the material obtained upon evaporation of the EtOAc dissolved in CH_2Cl_2 (3.2 mL) was added $NaIO_4$ (0.68 g, 3.18 mmol) dissolved in H_2O (6.4 mL). This reaction mixture was stirred at r.t. for 1 h and then extracted with CH_2Cl_2 (3 × 20 mL), and the combined extracts were dried (Na_2SO_4). The CH_2Cl_2 was removed under reduced pressure at r.t. and the residue dissolved in anhyd MeOH (20 mL). This solution was cooled to 0 °C and $NaBH_4$ (1.2 g, 30.8 mmol) was added portionwise. After stirring the reaction at the same temperature for 1 h, the solvent was removed and CH_2Cl_2 (30 mL) and H_2O (15 mL) were added to the residue. The organic layer was separated and washed with brine (10 mL) and dried (Na_2SO_4). The existing solvent was removed under reduced pressure and the product obtained by short column chromatography (EtOAc–hexanes, 7:3) to give **21** as a white solid, which could be further purified by recrystallization from CH_2Cl_2–hexanes to form needles (0.35 g, 51% for 3 steps); mp 124–125 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 12.55 (s, 1 H, NH), 7.95–7.84 (m, 2 H), 7.65–7.50 (m, 4 H), 7.27 (s, 1 H), 6.28 (br, 1 H), 4.83–4.78 (m, 1 H), 4.58–4.52 (m, 1 H), 3.64–3.58 (m, 3 H), 3.08–3.04 (m, 1 H), 2.55–2.46 (m, 2 H), 2.19–2.08 (m, 1 H), 1.60 (s, 3 H), 1.34 (s, 3 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 166.8, 147.0, 143.0, 137.3, 135.5, 134.0, 130.8, 130.3, 129.3, 128.6, 124.4, 123.7, 112.6, 111.8, 86.0, 83.6, 83.3, 64.0, 47.7, 44.1, 32.2, 27.7, 25.2.

HRMS: *m*/*z* calcd for $C_{23}H_{24}N_4O_5$: 436.1747; found: 436.1750.

7-Amino-3-[(3a*S*,4*R*,6*R*,6a*R*)-2,2-dimethyl-6-hydroxymethyltetrahydrocyclopenta[1,3]dioxol-4-yl]pyrazolo[3,4-*c*]pyridine (22)

Compound **21** (0.35 g, 0.8 mmol) was dissolved in sat. methanolic NH_3 (50 mL) at r.t. and this solution was stirred overnight. The solvent was removed under vacuum and the residue purified by flash chromatography using a mixture of MeOH–CH_2Cl_2 (1:9) to give pure **22** (0.22 g, 92%) as a yellow powder; mp 104–106 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.45 (d, *J* = 6.0 Hz, 1 H), 7.03 (d, *J* = 6.0 Hz, 1 H), 4.81 (t, *J* = 6.4 Hz, 1 H), 4.55 (dd, *J* = 6.8, 4.0 Hz, 1 H), 3.64–3.50 (m, 3 H), 2.44–2.33 (m, 2 H), 2.00–1.92 (m, 1 H), 1.53 (s, 3 H), 1.30 (s 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 148.0, 147.4, 135.9, 130.2, 126.1, 114.0, 105.8, 86.8, 84.4 (2 ×), 64.4, 45.5, 34.5, 28.1, 25.5.

HRMS: *m*/*z* calcd for $C_{15}H_{20}N_4O_3$: 304.1535; found: 304.1532.

7-Amino-3-[(1*S*,2*S*,3*R*,5*R*)-5-hydroxymethylcyclopentane-1,2-diol-1-yl]pyrazolo[3,4-*c*]pyridine (6)

A mixture of aq 1 M HCl–THF (5 mL, 1:1) was cooled to ice bath temperature and then added to the flask containing **22** (0.15 g, 0.50 mmol). This mixture was stirred for 6 h at r.t. and the solvent removed in vacuo. The residue was purified by flash column chromatography (EtOAc–MeOH–Et_3N, 40:4:1) to afford **6** as a pale brown solid (0.12 g, 88%); mp 175–177 °C; $[\alpha]_D^{22.9}$ –45.18 (*c* 0.04, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.27 (s, 1 H), 7.41 (d, *J* = 6.0 Hz, 1 H), 6.93 (d, *J* = 6.0 Hz, 1 H), 6.77 (br, 2 H), 4.25 (br, 3 H), 4.02–3.98 (m, 1 H), 3.77–3.74 (m, 1 H), 3.51–3.33 (m, 3 H), 2.13–2.02 (m, 2 H), 1.67–1.60 (m, 1 H).

^{13}C NMR (400 MHz, DMSO-d_6): δ = 146.7, 139.3, 134.3, 128.7, 123.9, 103.9, 77.0, 73.6, 63.1, 46.6, 32.4, 29.7.

HRMS: *m*/*z* calcd for $C_{12}H_{16}N_4O_3$: 264.1222; found: 264.1224.

7-Amino-3-[(3a*S*,4*S*,6*R*,6a*R*)-2,2-dimethyl-6-vinyltetrahydrocyclopenta[1,3]dioxol-4-yl]pyrazolo[3,4-*c*]pyridine (23)

Compound **15** (0.8 g, 1.69 mmol) was dissolved in sat. methanolic NH_3 (50 mL) at r.t. and the solution was stirred overnight. The solvent was removed in vacuo and the residue purified by flash chromatography using MeOH–CH_2Cl_2 (1:9) as the eluent, to give pure **23** (0.43 g, 84%) as a yellow powder; mp 172–173 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.57 (s, 1 H, NH), 7.50 (d, *J* = 4.4 Hz, 1 H), 6.91 (d, *J* = 5.6 Hz, 1 H), 6.28 (s, 2 H, NH_2), 5.89 (ddd, *J* = 16.9, 10.0, 7.2 Hz, 1 H), 5.11 (d, *J* = 16.9 Hz, 1 H), 5.01 (d, *J* = 10.8 Hz, 1 H), 4.82 (t, *J* = 6.4 Hz, 1 H), 4.48 (t, *J* = 6.4 Hz, 1 H), 3.47 (quint, *J* = 6.0 Hz, 1 H), 2.73 (sext, *J* = 6.4 Hz, 1 H), 2.33 (quint, *J* = 6.4 Hz, 1 H), 1.94 (q, *J* = 12.0 Hz, 1 H), 1.49 (s, 3 H), 1.25 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 145.9, 145.5, 139.5, 136.7, 127.5, 124.3, 115.0, 112.3, 103.2, 84.6, 49.4, 43.6, 36.7, 27.5 25.1.

HRMS: *m*/*z* calcd for $C_{16}H_{20}N_4O_2$: 300.1586; found: 300.1586.

Anal. Calcd for $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 64.13; H, 6.71; N, 18.52.

7-Amino-3-[(1*S*,2*S*,3*R*,5*R*)-5-vinylmethylcyclopentane-1,2-diol-1-yl]pyrazolo[3,4-*c*]pyridine (27)

Following the same procedure for obtaining **9** (see below), compound **23** (0.170 g, 0.57 mmol) yielded **27** (0.12 g, 81%) as white granules following purification by flash chromatography using a mixture of EtOAc–MeOH–Et_3N (40:4:1) followed by recrystallization from MeOH–CH_2Cl_2–pentane as a white solid; mp 218–219 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.94 (br, 1 H, NH), 7.44 (d, *J* = 6.0 Hz, 1 H), 6.92 (d, *J* = 6.0 Hz, 1 H), 6.28 (br, 2 H, NH_2), 5.92

(ddd, *J* = 16.9, 10.0, 7.2 Hz, 1 H, H-5′), 5.08 (ddd, *J* = 16.9, 2.0, 1.2 Hz, 1 H), 5.00 (ddd, *J* = 9.2, 2.0, 0.8 Hz, 1 H), 4.74 (br, 2 H), 4.02 (t, *J* = 5.6 Hz, 1 H, H-2′), 3.70 (dd, *J* = 6.8, 5.6 Hz, 1 H, H-3′), 3.37 (dt, *J* = 9.2, 6.0 Hz, 1 H, H-1′), 2.60 (quint, *J* = 8.4 Hz, 1 H, H-4′), 2.19 (dt, *J* = 12.8, 8.0 Hz, 1 H, H-6′), 1.71 (dt, *J* = 12.8, 10.0 Hz, 1 H, H-6′).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 147.0, 146.7, 141.5, 134.9, 129.0, 124.3, 114.8, 104.1, 77.0, 48.6, 43.2, 32.4.

HRMS: *m*/*z* calcd for $C_{13}H_{16}N_4O_2$: 260.1273; found: 260.1274.

7-Amino-3-[(3a*S*,4*S*,6*R*,6a*R*)-2,2-dimethyl-6-hydroxyethyltetrahydrocyclopenta[1,3]dioxol-4-yl)pyrazolo[3,4-*c*]pyridine (24)

To a solution of **23** (0.30 g, 1 mmol) in THF (20 mL) at 0 °C under N_2 was added 9-BBN (0.5 M in THF, 3.2 mL, 1.5 mmol), and the resultant mixture was stirred at this temperature for 12 h. To this was added, aq NaOH (1 M, 2.4 mL) followed by H_2O_2 (50% in H_2O, 1.2 mL) and the stirring continued for an additional 30 min. The reaction mixture was diluted with CH_2Cl_2 (70 mL) and this mixture was washed with sat. aq $NaHCO_3$ (30 mL). The organic layer was dried (Na_2SO_4), filtered, and the filtrate concentrated in vacuo to give the crude product as a colorless oil, which was subsequently purified by flash column chromatography (EtOAc–hexanes, 1:4) to afford **24** as a white solid (0.27 g, 81%); mp 125–126 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.47 (br, 1 H), 7.03–7.02 (m, 1 H), 4.81 (t, *J* = 6.0 Hz, 1 H), 4.37 (t, *J* = 5.6 Hz, 1 H), 3.66–3.63 (m, 2 H), 3.51–3.46 (m, 1 H), 2.43 (quint, *J* = 6.0 Hz, 1 H), 2.30–2.18 (m, 1 H), 1.87–1.74 (m, 2 H), 1.66–1.61 (m, 1 H), 1.52 (s, 3 H), 1.29 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 148.0, 147.5, 136.4, 130.1, 126.3, 114.3, 105.8, 87.7, 86.8, 61.7, 45.5, 43.9, 38.0, 37.6, 28.1, 25.5.

HRMS: *m*/*z* calcd for $C_{16}H_{22}N_4O_3$: 318.1692; found: 318.1685.

7-Amino-3-[(1*S*,2*S*,3*R*,4*R*)-4-hydroxyethylcyclopentane-2,3-diol-1-yl]pyrazolo[3,4-*c*]pyridine (9)

A mixture of TFA–H_2O (6 mL, 2:1) was cooled and added to a flask containing compound **24** (0.20 g, 0.58 mmol). This mixture was stirred for 3 h at r.t. and the solvent was removed in vacuo. The residue was purified by flash column chromatography (EtOAc–MeOH–Et_3N, 40:4:1) to afford **9** as a white solid (0.16 g, 86%); mp 155–157 °C; $[\alpha]_D^{23.1}$ –18.81 (*c* 0.08, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.45 (br, 1 H), 7.47 (d, *J* = 4.8 Hz, 1 H), 6.87 (d, *J* = 5.2 Hz, 1 H), 6.25 (br, 2 H), 4.61–4.44 (m, 3 H), 4.01 (br, 1 H), 3.57–3.46 (m, 3 H), 3.35–3.26 (m, 1 H), 2.21–2.14 (m, 1 H), 1.98–1.94 (m, 1 H), 1.79–1.73 (m, 1 H), 1.50–1.40 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 147.4, 145.9, 136.4, 127.5, 124.5, 103.6, 77.1, 76.5, 59.9, 43.1, 40.9, 37.3, 32.8.

HRMS: *m*/*z* calcd for $C_{13}H_{18}N_4O_3$: 278.1379; found: 278.1377.

Anal. Calcd for $C_{13}H_{18}N_4O_3$: C, 56.10; H, 6.52; N, 20.13. Found: C, 56.16; H, 6.49; N, 20.06.

3-Acetamido-2-chloro-4-[(3a*S*,4*S*,6*R*,6a*R*)-2,2-dimethyl-6-vinyltetrahydrocyclopenta[1,3]dioxol-4-methyl]pyridine (30)

3-Acetamido-2-chloro-4-methylpyridine (**28**;[13] 1.04 g, 5.63 mmol) was dissolved in anhyd THF (100 mL) and cooled to –78 °C. To this was slowly added *n*-BuLi (5.18 mL, 12.96 mmol, 2.5 M solution in hexanes) under N_2. The resulting yellow solution was stirred at the same temperature for 15 min and then warmed to 0 °C for 30 min. The orange solution was cooled to –78 °C and a solution of the triflate **17** (1.48 g, 4.69 mmol) in anhyd THF (20 mL) was added dropwise. The resulting mixture was stirred at –78 °C for 15 min and then at r.t. overnight. Sat. aq NH_4Cl (25 mL) was then added to the reaction mixture at 0 °C followed by stirring for 10 min. The solvent was removed in vacuo and to the residue H_2O (25 mL) was added. This mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to dryness and the residue purified by flash chromatography using a mixture of CH_2Cl_2–EtOAc (1:1) as with subsequent recrystallization from CH_2Cl_2–hexanes to give white needles that became a foam upon attempts to dry under vacuum (0.79 g, 57%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (br, 1 H), 8.07 (d, *J* = 4.8 Hz, 1 H), 7.14 (d, *J* = 5.2 Hz, 1 H), 5.72 (ddd, *J* = 17.2, 10.4, 7.2 Hz, 1 H), 4.99 (dt, *J* = 16.9, 1.2 Hz, 1 H), 4.94 (dt, *J* = 11.6, 1.2 Hz, 1 H), 4.26 (t, *J* = 6.4 Hz, 1 H), 4.13 (dd, *J* = 7.2, 5.6 Hz, 1 H), 2.78 (dd, *J* = 10.8, 7.2 Hz, 1 H), 2.52–2.47 (m, 2 H), 2.27–2.19 (m, 1 H), 2.09 (s, 3 H), 1.92 (quint, *J* = 6.4 Hz, 1 H), 1.40 (s, 3 H), 1.19 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 151.0, 149.8, 147.2, 138.9, 130.1, 123.8, 115.1, 112.8, 85.4, 85.1, 48.8, 44.2, 37.2, 35.3, 27.4, 25.0, 22.9.

HRMS: *m*/*z* calcd for $C_{18}H_{23}ClN_2O_3$: 350.1397; found: 350.1397.

1-Acetyl-7-chloro-3-[(3a*S*,4*S*,6*R*,6a*R*)-2,2-dimethyl-6-vinyltetrahydrocyclopenta[1,3]dioxol-4-yl]pyrazolo[3,4-*c*]pyridine (31)

Compound **30** (1.32 g, 3.76 mmol) was suspended in anhyd benzene (100 mL) and to this was added KOAc (0.37 g, 3.76 mmol) and Ac_2O (1.43 mL, 11.29 mmol). Isoamyl nitrite (0.75 mL, 5.64 mmol) was added dropwise to the reaction mixture as it was heated to 70 °C. This mixture was heated at reflux for 10 h and cooled to r.t., filtered through Celite, and washed with hot toluene (3 × 10 mL). The filtrates were combined, evaporated in vacuo, and the residue purified by flash chromatography using a mixture of EtOAc–hexanes (1:4) to give (0.89 g, 60%) as a white solid, together with a small amount of **32** (0.09 g, 8%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (dd, *J* = 5.2, 0.8 Hz, 1 H), 7.72 (d, *J* = 5.2 Hz, 1 H), 5.88 (ddd, *J* = 17.2, 10.4, 7.2 Hz, 1 H), 5.16 (dt, *J* = 17.2, 1.2 Hz, 1 H), 5.07 (dt, *J* = 10.4, 1.2 Hz, 1 H), 4.78 (dd, *J* = 6.8, 6.0 Hz, 1 H), 4.51 (t, *J* = 5.6 Hz, 1 H), 3.57 (pent, *J* = 6.0 Hz, 1 H), 2.86 (pent, *J* = 6.0 Hz, 1 H), 2.78 (s, 3 H), 2.49 (pent, *J* = 6.4 Hz, 1 H), 2.14 (dt, *J* = 13.2, 11.6 Hz, 1 H), 1.60 (s, 3 H), 1.32 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 150.7, 142.2, 138.3, 137.2, 134.4, 134.1, 115.5, 113.9, 113.4, 85.2, 84.3, 49.2, 43.9, 35.0, 27.5, 25.0, 24.0.

7-Chloro-3-[(3a*S*,4*R*,6*R*,6a*R*)-2,2-dimethyl- 6-vinylmethyltetrahydrocyclopenta[1,3]dioxol-4-yl]pyrazolo[3,4-*c*]pyridine (32)

Compound **31** (0.89 g, 2.46 mmol) was dissolved in sat. methanolic NH_3 (50 mL) at r.t. and this solution was stirred overnight. The solvent was removed in vacuo and the residue purified by flash chromatography using a mixture of MeOH–CH_2Cl_2 (1:9) to give pure **32** (0.79 g, quant.) as a white powder; mp 140–141 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 12.01 (br, 1 H), 8.05 (d, *J* = 5.8 Hz, 1 H), 7.65 (d, *J* = 5.5 Hz, 1 H), 5.88 (ddd, *J* = 17.3, 10.3, 7.3 Hz, 1 H), 5.14 (td, *J* = 17.3, 1.3 Hz, 1 H), 5.08 (dd, *J* = 11.3, 1.0 Hz, 1 H), 4.90 (t, *J* = 6.6 Hz, 1 H), 4.52 (dd, *J* = 8.8, 5.8 Hz, 1 H), 3.63 (quint, *J* = 10.0 Hz, 1 H), 2.88 (sext, *J* = 6.3 Hz, 1 H), 2.51 (quint, *J* = 6.5 Hz, 1 H), 2.12 (t, *J* = 12.5 Hz, 1 H), 1.64 (s, 3 H), 1.35 (s, 3 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 148.1, 138.7, 138.2, 135.9, 134.3, 127.7, 115.6, 114.3, 113.8, 85.4, 85.3, 49.6, 44.3, 36.5, 27.8, 25.3.

HRMS: *m*/*z* calcd for $C_{16}H_{18}ClN_3O_2$: 319.1088; found: 350.1397.

7-Chloro-3-[(3a*S*,4*R*,6*R*,6a*R*)-2,2-dimethyl-6-vinylmethyltetrahydrocyclopenta[1,3]dioxol-4-yl]-1-methylpyrazolo[3,4-*c*]pyridine (33a) and 7-Chloro-3-[(3a*S*,4*R*,6*R*,6a*R*)-2,2-dimethyl-6-vinylmethyltetrahydrocyclopenta[1,3]dioxol-4-yl]-2-methylpyrazolo[3,4-*c*]pyridine (33b)

Compound **32** (0.85 g, 2.66 mmol) was dissolved in anhyd THF (30 mL) and this solution was cooled to 0 °C. NaH (0.089 g, 3.72 mmol) was then added portionwise and the mixture kept at 0 °C for another 10 min. MeI (0.21 mL, 3.32 mmol) was added dropwise to the resultant mixture and the system gradually warmed to r.t. followed by stirring overnight. After adding sat. aq NH_4Cl (5 mL) dropwise, the solvent was evaporated in vacuo. To the residue was added H_2O (10 mL) and this mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined extracts were dried (Na_2SO_4) and evaporated dryness in vacuo. The crude product was isolated by flash chromatography using a mixture of hexanes–EtOAc (1:4) to provide **33a** (0.49 g, 55%), and hexanes–EtOAc (1:2) to yield **33b** (0.36 g, 41%).

33a

White solid; mp 69–70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 5.52 Hz, 1 H, H-5), 7.62 (d, *J* = 5.5, 1 H, H-4), 5.89 (ddd, *J* = 17.3, 10.3, 7.1 Hz, 1 H, H-5′), 5.16 (dt, *J* = 17.2, 1.4 Hz, 1 H, *H*CH=CH), 5.06 (dt, *J* = 10.3, 1.3 Hz, 1 H, *H*CH=CH), 4.82 (dd, *J* = 7.1, 6.0 Hz, 1 H, H-2′), 4.48 (dd, *J* = 7.1, 5.9 Hz, 1 H, H-3′), 4.36 (s, 3 H, N1-CH_3), 3.59 (quint, *J* = 6.5 Hz, 1 H, H-1′), 2.84 (m, 1 H, H-4′), 2.45 (quint, *J* = 6.5 Hz, 1 H, H-6′α), 2.07 (q, *J* = 12.4 Hz, 1 H, H-6′β), 1.59 (s, 3 H, CCH_3), 1.32 (s, 3 H, CCH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 145.4 (C-3), 138.8 (C-5′), 137.7 (C-5), 134.6 (C-7), 134.1 (C-7a), 129.3 (C-3a), 115.6 (*C*H_2=CH), 114.5 (C-4), 113(C-4), 6 [*C*(CH_3)$_2$], 85.4 (C-2′ or C-3′), 85.3 (C-2′ or C-3′), 49.8 (C-4′), 43.9 (C-1′), 38.9 (N1-CH_3), 36.5 (C-6′), 27.8 (C*C*H_3), 25.3 (C*C*H_3).

HRMS: *m*/*z* calcd for $C_{17}H_{20}ClN_3O_2$: 333.1244; found: 333.1240.

33b

White solid; mp 110–111 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 5.6 Hz, 1 H, H-5), 7.39 (d, *J* = 6.0 Hz, 1 H, H-4), 5.93 (ddd, *J* = 16.9, 10.4, 6.8 Hz, 1 H, H-5′), 5.20 (dt, *J* = 16.9, 1.2 Hz, 1 H, *H*CH=CH), 5.13 (dt, *J* = 10.0, 1.2 Hz, 1 H, *H*CH=CH), 4.71 (t, *J* = 6.8 Hz, 1 H, H-2′), 4.53 (dd, *J* = 7.0, 6.4 Hz, 1 H, H-3′), 4.28 (s, 3 H, N2-CH_3), 3.63 (quint, *J* = 6.3 Hz, 1 H, H-1′), 2.84 (sext, *J* = 6.4 Hz, 1 H, H-4′), 2.42 (quint, *J* = 6.3 Hz, 1 H, H-6′α), 2.24 (q, *J* = 12.8 Hz, 1 H, H-6′β), 1.57 (s, 3 H, CCH_3), 1.28 (s, 3 H, CCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2 (C-7), 142.2 (C-7a), 137.8(C-5′), 137.2 (C-3), 136.6 (C-5), 123.4 (C-3a), 116.3 (*C*H_2=CH), 114.3 [*C*(CH_3)$_2$], 113.5 (C-4), 85.5 (C-2′), 84.9 (C-3′), 49.6 (C-4′), 44.0 (C-1′), 39.6 (N2-CH_3), 36.4 (C-6′), 27.7 (C*C*H_3), 25.2 (C*C*H_3).

HRMS: *m*/*z* calcd for $C_{17}H_{20}ClN_3O_2$: 333.1244; found: 333.1241.

7-Chloro-3-[(3a*S*,4*R*,6*R*,6a*R*)-2,2-dimethyl-6-hydroxymethyltetrahydrocyclopenta[1,3]dioxol-4-yl]-1-methylpyrazolo[3,4-*c*]pyridine (34a)

Methylmorpholine *N*-oxide (0.32 mL 50% wet in THF, 1.53 mmol) was added to a solution of **33a** (0.34 g, 1.02 mmol) in THF (20 mL). After the solution was cooled to 0 °C, a catalytic amount of solid OsO_4 (4 mg, 0.016 mmol) was added and the solution stirred for 12 h at r.t. The reaction mixture was quenched by addition of $NaHSO_3$ (200 mg). The solvent was removed and the residue purified by flash column chromatography (hexanes–EtOAc, 3:1). To this isolated material dissolved in CH_2Cl_2 (3.2 mL) was added $NaIO_4$ (0.44 g, 2.04 mmol) dissolved in H_2O (4 mL). This reaction mixture was stirred at r.t. for 1 h followed by extraction with CH_2Cl_2 (3 × 20 mL), and the combined extracts were dried (Na_2SO_4). The solvent was removed under reduced pressure at r.t. and the residue dissolved in anhyd MeOH (20 mL). After the solution was cooled to 0 °C, $NaBH_4$ (0.27 g, 7.13 mmol) was added portionwise. The reaction mixture was stirred at the same temperature for 1 h and after removing the solvent, CH_2Cl_2 (30 mL) and H_2O (15 mL) were added. The organic layer was separated and washed with brine (10 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the product obtained by short column chromatography (EtOAc–hexanes, 2:3) to give **34a** as a white solid (0.28 g, 86% for 3 steps); mp 108–109 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 5.6 Hz, 1 H), 7.64 (d, *J* = 5.6 Hz, 1 H), 4.77 (t, *J* = 6.4 Hz, 1 H), 4.57 (dd, *J* = 6.8, 4.0 Hz, 1 H), 4.36 (s, 3 H), 3.73–3.68 (m, 2 H), 3.62–3.56 (m, 1 H), 2.51 (m, 3 H), 2.11 (m, 1 H), 1.60 (s, 3 H), 1.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8, 137.8, 134.6, 134.1, 129.2, 114.6, 113.0, 85.9, 83.6, 64.2, 47.8, 44.2, 38.9, 32.5, 27.7, 25.2.

HRMS: *m*/*z* calcd for $C_{16}H_{20}ClN_3O_3$: 337.1193; found: 337.1189.

7-Chloro-3-[(3a*S*,4*R*,6*R*,6a*R*)-2,2-dimethyl-6-hydroxymethyltetrahydrocyclopenta[1,3]dioxol-4-yl]-2-methylpyrazolo[3,4-*c*]pyridine (34b)

Product **34b** (0.20 g, 84%) was obtained by the same method as for **34a** from **33a** (0.25 g, 0.76 mmol) and purified by short column chromatography (EtOAc–hexanes, 3:2) as a foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 6.0 Hz, 1 H), 7.64 (d, *J* = 6.0 Hz, 1 H), 4.72–4.65 (m, 2 H), 4.29 (s, 3 H), 3.92–3.60 (m, 2 H), 3.63 (quint, *J* = 6.4 Hz, 1 H), 2.70 (br, 1 H), 2.52–2.44 (m, 1 H), 2.39 (quint, *J* = 6.4 Hz, 1 H), 2.30 (quint, *J* = 12.4 Hz, 1 H), 1.58 (s, 3 H), 1.29 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2, 142.2, 137.67, 136.4, 123.5, 114.0, 113.8, 86.0, 82.7, 63.4, 47.2, 44.5, 39.6, 33.1, 27.8, 25.2.

HRMS: *m*/*z* calcd for $C_{16}H_{20}ClN_3O_3$: 337.1193; found: 337.1185.

7-Amino-3-[(3a*S*,4*R*,6*R*,6a*R*)-2,2-dimethyl-6-hydroxymethyltetrahydrocyclopenta[1,3]dioxol-4-yl]-1-methylpyrazolo[3,4-*c*]pyridine (35a)

Compound **34a** (0.20 g, 0.63 mmol) was added to MeOH 50 mL) saturated with NH_3 at 0 °C. This mixture was heated to 165 °C and kept at this temperature for 2 d. The solvent was removed under reduced pressure and the product **35a** was purified by chromatography (MeOH–CH_2Cl_2, 1:10) as a white solid (90 mg, 45%); mp 153–154 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.46 (d, *J* = 6.0 Hz, 1 H), 7.07 (d, *J* = 5.6 Hz, 1 H), 4.82 (t, *J* = 6.4 Hz, 1 H), 4.56 (m, 1 H), 4.27 (s, 3 H), 3.59 (m, 2 H), 3.49 (m, 1 H), 2.37 (m, 2 H), 1.97 (m, 1 H), 1.57 (s, 3 H), 1.28 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 148.0, 146.3, 136.0, 129.3, 128.8, 114.0, 106.9, 86.9, 84.4, 64.4, 49.2, 45.4, 39.1, 34.6, 28.1, 25.5.

HRMS: *m*/*z* calcd for $C_{16}H_{22}N_4O_3$: 318.1692; found: 318.1699.

7-Amino-3-[(3a*S*,4*R*,6*R*,6a*R*)-2,2-dimethyl-6-hydroxymethyltetrahydrocyclopenta[1,3]dioxol-4-yl]-2-methylpyrazolo[3,4-*c*]pyridine (35b)

Following an identical procedure for obtaining **35a**, compound **34b** (0.2 g, 0.63 mmol) yielded **35b** (0.17 g, 84%), which was purified by column chromatography using MeOH–CH_2Cl_2 (1:8) as a foam.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.29 (dd, *J* = 1.7, 6.4 Hz, 1 H), 6.87 (dd, *J* = 1.7, 6.4 Hz, 1 H), 4.72 (t, *J* = 6.9 Hz, 1 H), 4.62 (m, 1 H), 4.62 (s, 3 H), 3.71 (m, 2 H), 3.63 (m, 1 H), 2.38 (m, 2 H), 2.17 (q, *J* = 12.7 Hz, 1 H), 1.56 (s, 3 H), 1.29 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 152.9, 137.6, 136.8, 135.9, 122.9, 114.8, 105.0, 87.1, 83.9, 63.9, 48.8, 45.2, 39.2, 34.4, 28.1, 25.5.

HRMS: *m*/*z* calcd for $C_{16}H_{22}N_4O_3$: 318.1692; found: 318.1691.

(1*R*,2*S*,3*S*,5*R*)-3-(7-Amino-1-methyl-1*H*-pyrazolo[3,4-*c*]pyridin-3-yl)-5-(hydroxymethyl)cyclopentane-1,2-diol (7)

Method A: A mixture of aq 1 M HCl–THF (5 mL, 1:1) was cooled and added to a flask containing **35a** (85 mg, 0.27 mmol). This mixture was stirred for 6 h at r.t., neutralized with Amberlite IRA-67, and the solvent removed under vacuum. The residue was purified by flash column chromatography (EtOAc–MeOH–Et_3N, 40:4:1) to afford **7** as a light brown solid (60 mg, 80%); mp 151–153 °C; $[\alpha]_D^{22.5}$ –23.05 (*c* 0.05, MeOH).

^{1}H NMR (400 MHz, CD_3OD): δ = 7.45 (d, *J* = 1.6, 6.0 Hz, 1 H), 7.07 (dd, *J* = 1.6, 6.2 Hz, 1 H), 4.27 (s, 3 H), 4.21 (m, 1 H), 3.95 (m, 1 H), 3.65 (m, 2 H), 3.51 (m, 1 H), 2.29 (m, 2 H), 1.74 (m, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 148.3, 147.3, 136.5, 129.6, 129.2, 107.3, 79.0, 76.0, 65.4, 48.4, 44.0, 39.3, 31.3.

HRMS: *m*/*z* calcd for $C_{13}H_{18}N_4O_3$: 278.1379; found: 278.1374

Method B: By adapting a literature procedure,[14] a solution of compound **6** (200 mg, 0.76 mmol) in anhyd DMF (10 mL) containing DMF dimethyl acetal (1.6 mL) was heated at 70 °C overnight. The solvent was evaporated and the resultant syrup was dissolved in NH_4OH and stirred at r.t. for 3 d. After evaporation, the residue was purified by flash column chromatography (EtOAc–MeOH–Et_3N, 40:4:1) to afford **7** (150 mg, 71%) as a light brown solid and whose spectral properties were identical to **7** obtained above from **35a**.

(1*R*,2*S*,3*S*,5*R*)-3-(7-Amino-2-methyl-2*H*-pyrazolo[3,4-*c*]pyridin-3-yl)-5-(hydroxymethyl)cyclopentane-1,2-diol (8)

Following an identical procedure for obtaining **7**, target **8** was achieved from **35b** (150 mg, 0.47 mmol) as a light yellow solid (106 mg, 81%); mp 160–162 °C; $[\alpha]_D^{23.0}$ –43.23 (*c* 0.42, MeOH).

^{1}H NMR (400 MHz, CD_3OD): δ = 7.16 (d, *J* = 1.7, 6.4 Hz, 1 H), 6.96 (dd, *J* = 6.2 Hz, 1 H), 4.24 (m, 1 H), 4.12 (s, 3 H), 3.95 (m, 1 H), 3.64 (m, 3 H), 2.22 (m, 2 H), 1.76 (m, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 152.3, 139.7, 136.2, 131.9, 122.6, 105.8, 78.6, 75.5, 64.6, 48.4, 43.1, 39.2, 30.1.

HRMS: *m*/*z* calcd for $C_{13}H_{18}N_4O_3$: 278.1379; found: 278.1371.

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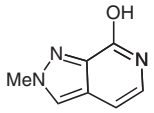
(10) Crystallographic data (Figure 3) for **25**, which was a minor product in the ammonolysis of **12** have been deposited with Cambridge Crystallographic Data Centre (e mail: ccdc@code.cam.ac.uk) and allocated the deposition number CCDC 851387.



25

Figure 3 Hydrolyis side-product from **12**

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