Syntheses of 5'-Substituted Analogues of Carbocyclic 3-Deazaadenosine as Potential Antivirals

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Various 5'-substituted derivatives (**2**, **3**, **6a**, **6b**, **9a**, **9b**, **12**, **13b**, and **15**) of carbocyclic 3-deazaadenosine (3-deaza CAdo, **1**) were prepared from 3-deaza CAdo (**1**) and evaluated as antiviral agents against a number of viruses, including HIV-1. Several of the compounds had moderate to good antiviral activity against vaccinia (VV) and vesicular stomatitis (VSV) viruses; however, the antiviral activity of the analogues did not exceed that of the parent compound. No anti-HIV activity was detected.

Introduction

Carbocyclic adenosine (C-Ado) and 3-deazaadenosine (c^3Ado), two adenosine analogues with broad-spectrum antiviral activity, are both inhibitors of *S*-adenosyl-L-homocysteine hydrolase (SAH), an established cellular target for antiviral chemotherapy.[1] However, C-Ado is rapidly metabolized in cells to the triphosphate, a poor inhibitor of SAH that is cytotoxic. c^3Ado, on the other hand, is not phosphorylated to any extent but is a relatively poor inhibitor of SAH. Carbocyclic 3-deazaadenosine (3-deaza CAdo, **1**), which combines the structural features of both C-Ado and c^3Ado, was designed to be a specific inhibitor of SAH and has been shown to have promise as an antiviral agent.[2-4] It exhibits *in vitro* activity against vaccinia, vesicular stomatitis, Sindbis, measles, parainfluenza type 3, and reo type 1 viruses.[5,6] It is also about 100 times more potent than the established broad-spectrum antiviral agents ribavirin and (*S*)-9-(2,3-dihydroxypropyl)adenine against vesicular stomatitis, parainfluenza, measles, and reo viruses. 3-Deaza CAdo is not cytotoxic at the highest levels examined which are 20–200-fold higher than its minimum inhibitory concentration (0.2–20 μg/mL).

In hopes of obtaining a more potent and selective antiviral agent, we synthesized a series of carbocyclic nucleosides related to 3-deaza CAdo upon the basis of the features or properties of that compound that appear important for its antiviral activity, which are (1) a resemblance to adenine nucleosides, (2) little or no substrate activity for adenosine deaminase, (3) little or no conversion to the 5'-phosphate by normal enzymes, and (4) resistance to cleavage by phosphorylases. On the basis of these considerations, we chose to prepare a series of 5'-modified 3-deaza CAdo derivatives. The syntheses and initial antiviral evaluation of these compounds are described herein.[7]

Chemistry

Our starting materials in the preparation of the target compounds were 3-deaza CAdo (**1**) and compound **2** (Scheme I), prepared by the procedures of Montgomery *et al.*[3] The 5'-deoxy derivative, compound **3**, was obtained by treating compound **2** with tri-*n*-butyltin hydride in the presence of the radical initiator AIBN. Heating at reflux for several days in THF resulted in 77% conversion to **3**, as judged by HPLC, with the remaining material being unreacted starting material. Employing higher boiling solvents or longer reaction times did little to improve the percent conversion and compounds **2** and **3** could not be separated chromatographically. A pure sample of **3** was therefore obtained by treating a mixture of **2** and **3** with the sodium salt of 2-methyl-1-propanethiol in alcohol. The resulting mixture of **3** and the 5'-(isobutylthio)methyl derivative **9b**[8] was resolvable by flash chromatography. However, **9b** prepared in this manner was contaminated with a non-nucleoside compound that complicated its isolation and purification.

The 5'-aminomethyl compound **6a** was prepared by first converting **1** to its isopropylidene derivative **4** with 2,2-dimethoxypropane and 70% perchloric acid in dry acetone. The hydroxymethyl group in compound **4** was then smoothly converted to a phthalimidomethyl group under Mitsunobu conditions.[9] Removal of the phthaloyl group with anhydrous hydrazine followed by hydrolysis of the isopropylidene group with 4 N HCl gave **6a** as the dihydrochloride salt. Treatment of **5** with 90% aqueous trifluoroacetic acid provided compound **6b**, which was also evaluated for antiviral activity.

Several attempts were made to convert **1** directly to the 5'-bromomethyl derivative **9a** using thionyl bromide in trimethyl phosphate under conditions similar to those used to synthesize compound **2**. In each trial, the desired product was detected by mass spectrometry; however, dibromination products were also detected and TLC indicated considerable amounts of unreacted starting material. Therefore, a more circuitous route was employed that involved blocking the reactive 6-amino function of **4a**. Thus, **4a** was treated with *N*,*N*-dimethylformamide dimethyl acetal in dry DMF at room temperature overnight to provide **7** in good yield. Reaction of **7** with trifluoromethanesulfonic anhydride and pyridine in CH_2Cl_2 produced **8a** whose triflate group was readily displaced by either LiBr in HMPA or nBu_4NBr in CH_2Cl_2 to give **8b**. Deblocking with 4 N HCl at room temperature provided **9a**. Intermediate **8b** was also used to prepare compound **9b**.[8]

Compound **15** was synthesized by the sequence of reactions (**11** → **13b** → **14** → **15**) shown in Scheme II. Initially, many attempts were made to oxidize compound **4a** or its N-6 benzoylated derivative **4b**, directly to the 5'-carboxylic acids. Thus, **1** was converted to its fully benzoylated derivative with benzoyl chloride, partially deblocked with NaOMe–MeOH–pyridine[10] and then converted to the 2',3'-isopropylidene derivative to provide **4b** in 56% yield (for 3 steps). Treatment of **4a** with KOH–$KMnO_4$, a procedure used with nucleosides,[11,12] provided, after workup, less than 10% of **13a** (as determined by ^{1}H

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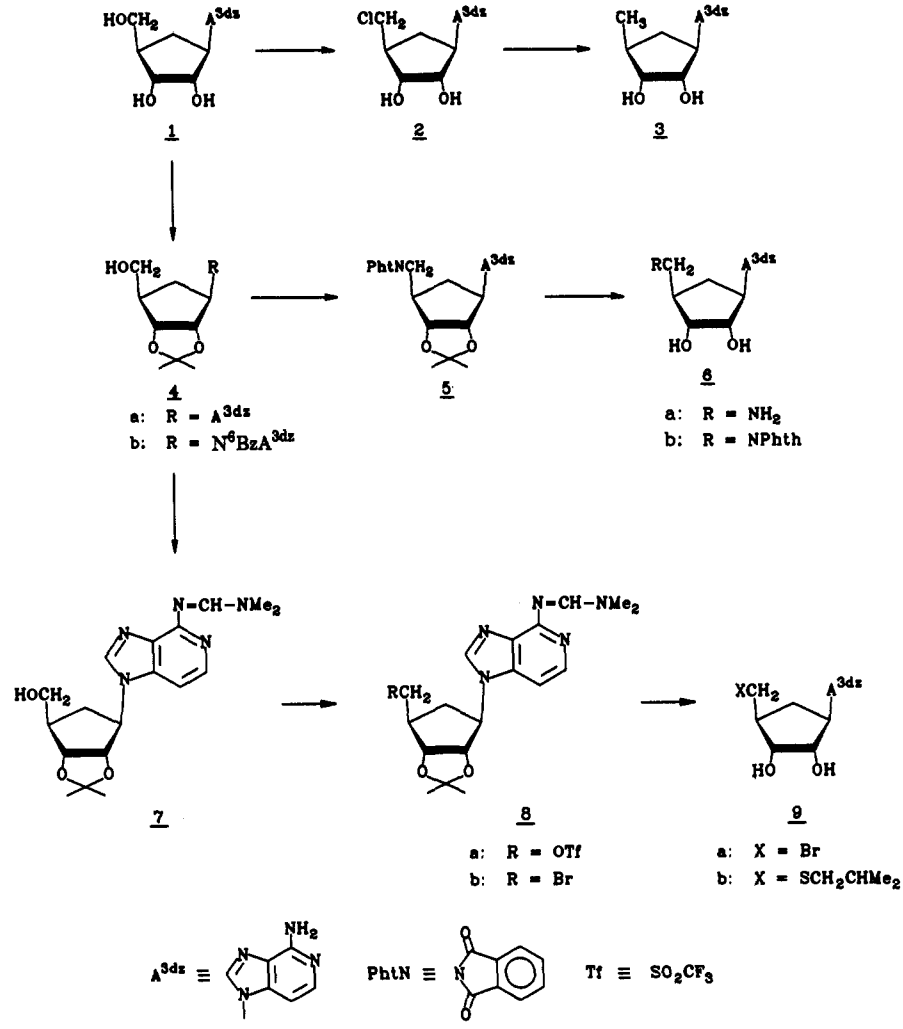
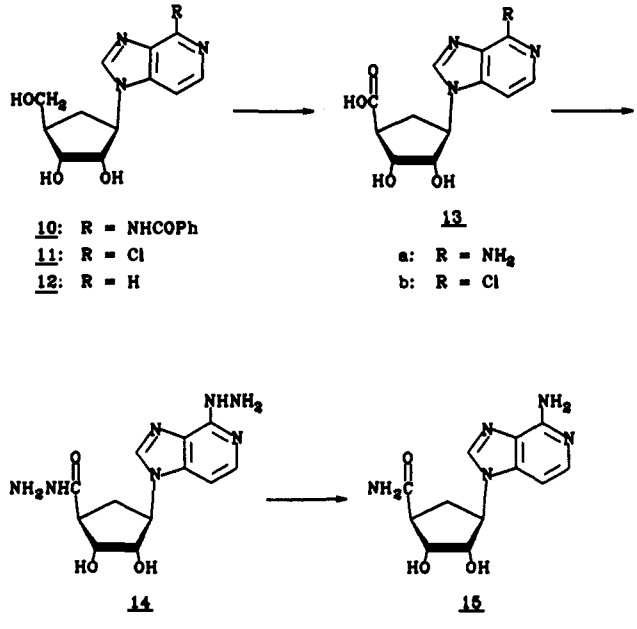
Scheme I



Scheme II



NMR and FABMS) with considerable degradation of starting material. Similar attempts were made to oxidize **4b** with no success.

Platinum-catalyzed oxidation by O_2 of **1**, **4b**, and **10** in aqueous acetone was attempted and although a small-scale reaction worked once for **4b**, the results could not be repeated despite varying the solvent, catalyst (both amount and batch number), temperature, and pH. While investigating alternative oxidative methods it was found that 3-deaza-6-chloropurine derivative **11**[3] could be oxidized readily with platinum and O_2 to give **13b** in good yield. Compound **13b** was converted to its methyl ester with diazomethane and subsequently treated with anhydrous hydrazine to effect both displacement of the 6-chloro group and conversion of the methyl ester to its hydrazide, compound **14**. Reduction of **14** with hydrogen and Raney Ni provided **15**.

Considering the number of times that 3-deaza CAdo was routinely synthesized during the course of this work, it is noteworthy that a byproduct, compound **12**, was formed in one instance. Its precursor was probably formed during the reduction of (±)-(1,4/2,3)-4-(3-nitro-2-chloro-4-pyridylamino)-2,3-dihydroxy-1-cyclopentanemethanol,[3] prior to cyclization to 3-deaza CAdo. In light of its interesting structure, compound **12** was submitted for screening.

Antiviral Evaluation

The carbocyclic nucleosides **2**, **3**, **6a**, **6b**, **9a**, **9b**, **12**, **13b**, and **15** were evaluated for antiviral efficacy against the following viruses (viral strain): (a) Japanese encephalitis virus, JE (Nakayama); (b) yellow fever virus, YF (Ashibi); (c) sandfly fever virus, SF (Sicilian); (d) Punta Toro virus, PT (Adames); (e) Venezuelan equine encephalomyelitis virus, VEE (Trinidad donkey); (f) vaccinia virus, VV

Table I. *In Vitro* Antiviral Activity of Carbocyclic Nucleosides

compd	virus	cell line	VR[a]	IC_{50} (μg/mL)[b]	MTC (μg/mL)[c]	TI[d]
2	VV	L-929	0.6	32	90	2.8
	VSV	L-929	0.4	88	283	3.2
3	VV	Vero	1.4	3.1	100	32
	VSV	L-929	1.0	100	100	10
	YF	MK2	NA[e]	23	104	5
6a	VV	Vero	1.0	18	320	18
9a	VV	Vero	0.6	87	320	3.7
	VSV	L-929	0.3	147	320	2.2
12	VV	L-929	1.0	7	249	36
	VSV	L-929	0.7	49	79	1.6
	YF	MK2	NA[e]	70	100	1.4
15	VV	Vero	0.7	32	320	10

[a] VR = virus rating. Virus ratings are calculated by the method of Huffman and Sidwell (*Appl. Microbiol.* 1971, *22*, 797–801).[15] VR > 1 indicates definite and significant to moderate activity; VR < 0.5 indicates no significant activity. [b] IC_{50} = Inhibitory concentration 50. Concentration of the drug that causes a 50% reduction in virus cytopathic effect (CPE). [c] MTC = minimum toxic concentration. The lowest concentration of the test compound that results in a 50% reduction in the percent survival of viable host cells. [d] TI = therapeutic index. A measure of the antiviral potential for the drug calculated as MTC/IC_{50}. [e] Evaluated by plaque reduction assay.

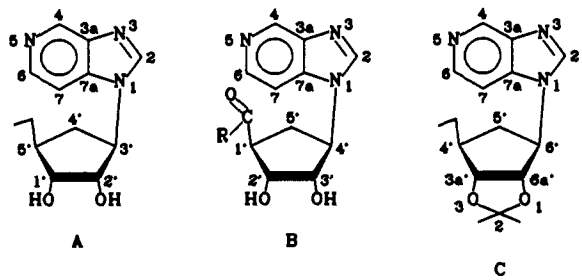
(Lederle vaccine); (g) vesicular stomatitis virus, (VSV (Indiana); (i–k) adenovirus type 2; Ad2, Rift Valley fever, RVF; and Pichinde, PIC. The results are summarized in Table I. The *in vitro* antiviral and cytotoxic effects of a test compound were measured either (a) by observing inhibition of the viral cytopathic effect (CPE)[13–15] or (b) by using a general plaque-reduction (PR) assay.[16] All plaque-reduction assays were performed with either MK2 or Vero cells. Viral CPE assays were carried out with several cell lines including (virus) ATH8 (HIV), HEP2 (Ad2), Vero (JE, PT, SF, VV, YF), L-929 (VSV), and MK2 (PT).

The only compounds that possessed moderate to significant activity included **2**, **3**, **6a**, **9a**, **12**, and **15**. All six compounds were active against VV with compounds **3** and **12** showing significant antiviral activity. Compound **3** also demonstrated significant activity against VSV while compounds **2** and **12** showed marginal activity toward this virus. None of the compounds, however, were superior to 3-deaza CAdo (**1**).

Experimental Section

Melting points were recorded on a Mel-Temp apparatus and are uncorrected. NMR spectra were recorded on a Nicolet NT 300 NB spectrometer operating at 300.635 MHz for ^1H and 75.6 MHz for ^{13}C. Chemical shifts are expressed in parts per million downfield from tetramethylsilane. Mass spectra were recorded on a Varian MAT 311A mass spectrometer in the fast-atom bombardment (FAB) mode.

The following diagrams are provided for interpretation of NMR chemical shift data. All compounds for which NMR data are reported were named as either cyclopentanediols (A) (*e.g.*, **3**, **6a**, **6b**, **9a**, **9b**, and **12**), cyclopentanecarboxylic acids (B) (*e.g.*, **13b**, and **15**), or cyclopenta-1,3-dioxoles (C) (*e.g.*, **4**, **5**, and **7**) with numbering schemes as follows:



A B C

[(±)-(1α,2α,3β,5β)]-3-(4-Amino-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-5-methyl-1,2-cyclopentanediol (3). To a suspension of 3.04 g (10.8 mmol) of **2**[9] in dry THF (800 mL) were added 2,2′-azobis(isobutyronitrile) (0.5 g, 3.0 mmol) and tri-*n*-butyltin hydride (12.52 g, 43 mmol), and the mixture was heated at reflux under a nitrogen atmosphere. Additional tri-*n*-butyltin hydride (~12 g) was added in several portions over the course of 2 days. Analysis by HPLC indicated that the reaction gradually proceeded to about 80% completion and would proceed no further. The solvent was removed under reduced pressure, and the residue was diluted with cold petroleum ether (35–60 °C). The solid was collected, dried *in vacuo*, and then dissolved in 1 N $NaOCH_3$ in ethanol (50 mL). 2-Methyl-1-propanethiol (0.9 mL, 8.31 mmol) was added, and the reaction mixture was heated at reflux for 5 h, after which time HPLC analysis showed the complete reaction of **2**. The reaction mixture was cooled in an ice bath and adjusted to pH 6 with glacial acetic acid, and the solvent was removed under reduced pressure. The nucleosides were then extracted from the solid with hot $CHCl_3$. The extracts were condensed *in vacuo*, and the residue was flash chromatographed (100 g of silica gel for ~3 g of extracts), eluting with $CHCl_3$–CH_3OH (4:1) to give 0.83 g (31%) of **3**. Final purification was achieved by recrystallization from ethanol to give 0.5 g (19%) of **3**: mp 218–219 °C; FABMS *m/z* 249; ^1H NMR (Me_2SO-d_6) δ 1.13 (d, 3, CH_3), 1.52 (q, 1, H-4′), 1.98 (m, 1, H-5′), 2.32 (m, 1, H-4′), 3.60 (t, 1, H-1′), 4.17 (t, 1, H-2′), 4.53 (m, 1, H-3′), 4.9 (br, 2, OH's), 6.13 (br s, 2, NH_2), 6.81 (d, 1, H-7), 7.66 (d, 1, H-6), 8.19 (s, 1, H-2). Anal. ($C_{12}H_{16}N_4O_2$·0.25EtOH) C, H, N.

[(±)-(3aα,4α,6α,6aα)]-4-(Hydroxymethyl)-6-(4-amino-1*H*-imidazo[4,5-*c*]pyridin-1-yl)tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole (4a). A solution of acetone (350 mL), 70% $HClO_4$ (1.6 mL, 26.7 mmol) and 2,2-dimethoxypropane (16 mL, 13.54 g, 130 mmol) was stirred at room temperature for 5 min. Solid 3-deaza CAdo hydrochloride (**1**) (2.37 g, 7.88 mmol) was added, and the burgandy solution was stirred 2 h. After the solution was chilled in an ice bath, 5% $NaHCO_3$ solution (60 mL) was added and then most of the solvents were removed. After some H_2O was added, the solution was extracted with diethyl ether and the water layer was rotovaped further precipitating the product as an off-white solid. Filtering, washing with cold water, and drying gave 2.19 g (91%) of **4a**: mp 206–207 °C; FABMS *m/z* 305; ^1H NMR (Me_2SO-d_6) δ 1.24 and 1.52 (2 s, 6, $C(CH_3)_2$), 2.16 (q, 1, H-5′), 2.28 (m, 1, H-4′), 2.38 (m, 1, H-5′), 3.54 (m, 2, 4′-CH_2), 4.55 (m, 1, H-3a′), 4.68 (m, 1, H-6′), 4.74 (q, 1, H-6a′), 4.84 (t, 1, 4′-CH_2OH), 6.15 (s, 2, 4-NH_2), 6.88 (d, 1, H-3), 7.68 (d, 1, H-6), 8.19 (s, 1, H-2).

[(±)-(3aα,4α,6α,6aα)]-4-(Phthalimidomethyl)-6-(4-amino-1*H*-imidazo[4,5-*c*]pyridin-1-yl)tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole (5). Compound **4a** (250 mg, 0.82 mmol), phthalimide (181 mg, 1.23 mmol), and triphenylphosphine (322 mg, 1.23 mmol) were suspended in 2.5 mL of dry tetrahydrofuran under a nitrogen atmosphere. Diethyl azodicarboxylate (260 μL, 286 mg, 1.64 mmol) was added dropwise *via* syringe. The reaction was stirred at room temperature for 1 h, and the yellow solid was filtered, washed with diethyl ether, and dried to give 316 mg (89%) of **5**: mp 269–270 °C (with sintering); FABMS *m/z* 434; ^1H NMR (Me_2SO-d_6) δ 1.19 and 1.43 (2 s, 6, $C(CH_3)_2$), 2.20 (q, 1, H-5′), 2.40, 2.51 (m, 2, H-4′ and H-5′), 3.80 (m, 2, CH_2-4′), 4.64 (m, 2, H-3a′, H-6′), 4.82 (m, 1, H-6a′), 6.15 (s, 2, NH_2), 6.89 (d, 1, H-7), 7.66 (d, 1, H-6), 7.88 (m, 4, phthalimide protons), 8.20 (s, 1, H-2).

[(±)-(1α,2α,3β,5β)]-3-(4-Amino-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-5-(aminomethyl)-1,2-cyclopentanediol Dihydrochloride (6a). Compound **5** (950 mg, 2.19 mmol) was suspended in absolute ethanol (13 mL), anhydrous hydrazine (1.5 mL, 1.60 g, 50 mmol) was added, and the suspension was stirred at reflux overnight (18 h) under N_2. The precipitated phthalhydrazide was removed by filtration and washed with ethanol, and the ethanol filtrate was evaporated to dryness. The resulting white solid (693 mg) represented a 100% yield (FABMS *m/z* 304). Without further purification this solid (603 mg, 1.28 mmol) was suspended in 20 mL of 4 N HCl and stirred for 3 h at room temperature. The solvent was removed *in vacuo* with mild heating (30 °C), and the resulting white solid was recrystallized from methanol to give 545 mg (81.6%) of **6a**: mp 162 °C (softening); FABMS *m/z* 264; ^1H NMR (Me_2SO-d_6) δ 1.79 (m, 1,

H-4'), 2.28 (m, 1, H-5'), 2.44 (m, 1, H-4'), 3.00 (m, 2, CH_2N), 3.90 (t, 1, H-1'), 4.19 (m, 1, H-2'), 4.73 (m, 1, H-3'), 4.0–5.4 (OH's, H^+), 7.33 (d, 1, H-7), 7.75 (m, 1, H-6), 8.20 (br s, 3, $CH_2NH_3^+$), 8.56 (br s, 2, 4-NH_2), 8.70 (s, 1, H-2). Anal. ($C_{12}H_{17}N_5O_2 \cdot 2HCl \cdot 0.75CH_3OH \cdot 0.25H_2O$) C, H, N.

[(±)-(1α,2α,3β,5β)]-3-(4-Amino-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-5-(phthalimidomethyl)-1,2-cyclopentanediol (6b). Trifluoroacetic acid (90%, 5 mL) was added to 542 mg (1.25 mmol) of **5**, and the suspension was stirred at 0 °C for 15 min. The solvent was removed by evaporation with mild heating, and the resulting syrup was crystallized from ethyl acetate providing 452 mg (71%) of **6b**: mp 228–229 °C dec; FABMS *m/z* 394; ^1H NMR (Me_2SO-d_6) δ 1.75 (m, 1, H-4'), 2.39 (m, 2, H-4' and H-5'), 3.65 (m, 1, 5'-CH_2), 3.85 (m, 2, H-1' and 5'-CH_2), 4.26 (m, 1, H-2'), 4.67 (m, 1, H-3'), 4.7–5.4 (vbs, 2, OH's), 7.31 (d, 1, H-7), 7.72 (d, 1, H-6), 7.84 (m, 4, phthalimide protons), 8.65 (s, 2, NH_2), 8.72 (s, 1, H-2). Anal. ($C_{20}H_{19}N_5O_4 \cdot 0.25CF_3CO_2H$) C, H, N.

[(±)-(3aα,4α,6α,6aα)]-4-(Hydroxymethyl)-6-[4-[[(dimethylamino)methylene]amino]-1*H*-imidazo[4,5-*c*]pyridin-1-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole (7). Compound **4a** (2.57 g, 8 mmol) was suspended in 30 mL of dry dimethylformamide, *N,N*-dimethylformamide dimethyl acetal (4.66 mL, 4.00 g, 0.034 mol) was added, and the reaction was stirred under nitrogen at room temperature overnight. The resulting white precipitate was collected providing 936 mg of **7**. A second crop (1.39 g) was obtained by evaporating DMF *in vacuo* with mild heating and triturating the residue with ethanol for a total yield of 77.3%: mp 211–213 °C; FABMS *m/z* 360; ^1H NMR (Me_2SO-d_6) δ 1.26 and 1.54 (2 s, 6, $C(CH_3)_2$), 2.26 (m, 3, H-4', H-5'), 3.08 and 3.13 (2 s, 6, NMe_2), 3.53 (t, 2, CH_2OH), 4.56 (m, 1, H-6a'), 4.74 (m, 2, H-6', H-3a'), 4.84 (t, 1, CH_2OH), 7.22 (d, 1, H-7), 7.93 (d, 1, H-6), 8.24 (s, 1, H-2), 8.63 (s, 1, N=C*H*—).

[(±)-(1α,2α,3β,5β)]-3-(4-Amino-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-5-(bromomethyl)-1,2-cyclopentanediol Hydrochloride (9a). To a chilled solution (0 °C) of dry CH_2Cl_2 (300 mL) under N_2 was added dry pyridine (1.03 g, 13.04 mmol) followed immediately by trifluoromethanesulfonyl anhydride (3.50 g, 12.41 mmol). After 5 min of stirring compound **7** (2.97 g, 8.27 mmol) was added and stirring was continued for 1 h at 0 °C under N_2. At this time TLC ($CHCl_3$–MeOH (7:1)) showed conversion to **8a** to be complete. Tetrabutylammonium bromide (2.93 g, 9.1 mmol) was added and stirring was continued at 0 °C under N_2 for 5 h. The reaction mixture was poured into a weak $NaHCO_3$ solution (cold), the layers were separated, and the aqueous solution was extracted with $CHCl_3$ (2 × 75 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the solvents were removed *in vacuo*. The residue was flash chromatographed (4 × 21 cm column, 230–400 mesh EM Reagents Silica Gel 60), eluting with $CHCl_3$–MeOH (20:1), and the purest fractions (as judged by TLC, $CHCl_3$–MeOH (7:1) were kept, and all other fractions combined and rechromatographed (two additional times, using the above conditions). The purest fractions from all three columns were combined and evaporated to dryness, and the residue was triturated with slightly basic $NaHCO_3$ solution (to remove tetrabutylammonium triflate) which precipitated compound **8b**. Filtering and drying gave 1.8 g (52%) (FABMS *m/z*: 422).

Compound **8b** (1.8 g, 4.28 mmol) was stirred in 4 N HCl overnight (16 h) and the solvent was removed *in vacuo*. Trituration of the residue with EtOH precipitated the product which was filtered and dried to provide 1.12 g of **9a**: mp 211–213 °C dec; FABMS *m/z* 327; ^1H NMR (D_2O) (compound is very reactive in Me_2SO-d_6) δ 1.92 (m, 1, H-4'), 2.57 (m, 2, H-5', H-4'), 3.70 (m, 2, $BrCH_2$), 4.13 (m, 1, H-1'), 4.41 (t, 1, H-2'), 4.83 (m, 1, H-3'), 7.24 (d, 1, H-6), 7.63 (d, 1, H-7), 8.45 (s, 1, H-2). Anal. ($C_{12}H_{15}BrN_4O_2 \cdot HCl$) C, H, N.

[(±)-(1α,2α,3β,5β)]-3-(1*H*-Imidazo[4,5-*c*]pyridin-1-yl)-5-(hydroxymethyl)-1,2-cyclopentanediol (12). A solution of (±)-(1,4/2,3)-4-(3-nitro-2-chloro-4-pyridylamino)-2,3-dihydroxy-1-cyclopentanemethanol[3] (19.6 g, 0.064 mol) in 1 L of dry ethanol with Raney nickel (60 g) was hydrogenated at atmospheric pressure and room temperature overnight. The catalyst was removed by filtration through Celite and washed with 4.5 L of hot ethanol. The combined filtrates were evaporated to dryness. The residue was dissolved in dimethylacetamide (160 mL), triethyl orthoformate (350 mL), and 12 N HCl (8 mL). The solution was stirred for 2 days at room temperature before being evaporated to dryness *in vacuo* without heat. Workup as described previously[3] provided 7 g of crude product that was purified by flash chromatography (150 g of 230–400 mesh silica gel) eluting with $CHCl_3$–MeOH (4:1). Fractions containing the product were combined, solvent was removed by evaporation, and the residue was crystallized on standing to provide 0.6 g (3.8%) of **12**: mp 196–199 °C; FABMS *m/z* 250; ^1H NMR (Me_2SO-d_6) δ 1.8 (m, 1, H-4'), 2.12 (m, 1, H-5'), 2.35 (dt, 1, H-4'), 3.54 (d, 1, 5'-CH_2), 3.86 (m, 1, H-1'), 4.24 (m, 1, H-2'), 4.76 (t, 1, H-3'), 4.8 and 5.06 (bs, 3, OH's), 7.74 (d, 1, H-7), 8.34 (d, 1, H-6), 8.50 (s, 1, H-2), 8.96 (s, 1, H-4). Anal. ($C_{12}H_{16}N_3O_2$) C, H, N.

[(±)-(1α,2β,3β,4α)]-4-(4-Chloroimidazo[4,5-*c*]pyridin-1-yl)-2,3-dihydroxycyclopentanecarboxylic Acid (13b). A suspension of platinum black (prepared from 230 mg of PtO_2) in 40 mL of water was heated to 90 °C. Oxygen was bubbled into the suspension *via* pipet for 15 min and then **11**[3] (213 mg, 0.75 mmol) was added. An aliquot of aqueous sodium bicarbonate (0.02 M) was added every 20 min for *ca.* 5 h to maintain a near neutral pH. The reaction was cooled to room temperature, the catalyst was removed by filtration and 2 mL of 1 N HCl was added to the filtrate. The aqueous layer was condensed, and the precipitate was filtered to give a white solid (60 mg, 67%): mp 185 °C (with sintering); FABMS *m/z* 298; ^1H NMR (Me_2SO-d_6) δ 2.23 and 2.56 (m, 2, H-5'), 2.85 (m, 1, H-1'), 4.17 (m, 1, H-2'), 4.24 (m, 1, H-3'), 4.81 (m, 1, H-4'), 5.3 (br s, 2, OH's), 7.83 (d, 1, H-7), 8.17 (d, 1, H-6), 8.62 (s, 1, H-2), 12.6 (br s, 1, COOH). Anal. ($C_{12}H_{12}ClN_3O_4 \cdot 0.25H_2O$) C, H, N.

[(±)-(1α,2β,3β,4α)]-4-(4-Aminoimidazo[4,5-*c*]pyridin-1-yl)-2,3-dihydroxycyclopentanecarboxamide Hydrochloride Hydrate (15). Compound **13b** (1.29 g, 4.34 mmol) was dissolved in 75 mL of *N,N*-dimethylacetamide (DMAC) and chilled to 0 °C. Ethereal diazomethane was added until a yellow color persisted. The solution was removed from the ice bath and stirred for 0.5 h. After the solution sat at room temperature overnight, the DMAC was removed *in vacuo*, and the residue was chromatographed on silica gel (4 × 20 cm) eluting with 10% MeOH–$CHCl_3$ containing 1% Et_3N. The cleanest fractions were combined and condensed providing 1.06 g (79%) of the methyl ester derivative of **13b** (FABMS *m/z* 312) which was used directly in the next step.

The methyl ester was placed in 40 mL of anhydrous hydrazine and heated near reflux for 1 h. The hydrazine was removed, the residue was taken up in 30 mL of deoxygenated water, and the solution was evaporated to dryness. This residue was dissolved in 50 mL of deoxygenated water containing 3.0 g (wet weight) of Raney nickel and was heated at reflux for 1 h. The reaction mixture was filtered while hot through Celite, and the catalyst was washed with 25 mL of hot, deoxygenated water. The filtrate and washings were condensed to dryness. Both TLC (silica gel, $CHCl_3$–MeOH–NH_4OH, 20:10:1) and FABMS indicated that two products resulted, the desired product and the partially reduced 4-amino, 5'-ester hydrazide derivative. To achieve complete hydrogenolysis of the 5'-ester hydrazide function, the two-component mixture was treated again with RaNi for 3 h as described above. The reaction vessel was briefly (15 min) stirred under hydrogen (1 atm) at the end of the first and second hours of stirring. After 3 h, the reaction was complete and the reaction was worked up as described above. The residue was crystallized from ethanol. Because C, H, N analysis indicated contamination of the product with ammonium chloride, the solid was passed down a short column (2 × 20 cm) of Bio-Beads (SM-4, Bio-Rad Labs, no. 152-4020) eluting first with water to remove inorganics and then the methanol to remove the product. The product-containing fractions were condensed, and the residue was crystallized from ethanol resulting in two crops of **15**, a total of 300 mg (21% for 3 steps): mp 229–231 °C; FABMS *m/z* 278; ^1H NMR (Me_2SO-d_6) δ 2.13 (m, 1, H-5'), 2.48 (m, 1, H-5'), 2.82 (m, 1, H-1'), 4.0 (br s, 1, H-2'), 4.24 (m, 1, H-3'), 4.78 (q, 1, H-4'), 5.24 (m, 2,2', 3'-OH's), 7.04, 7.62 (s, 2, NH_2CO), 7.43 (d, 1, H-7), 7.75 (d, 1, H-6), 8.35 (s, 2, NH_2), 8.59 (2, 1, H-2). Anal. ($C_{12}H_{14}N_5O_3 \cdot H_2O$) C, H, N.

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