72 computer at the (Sydney) University Computer Centre. Partition coefficients (log $P_{octanol/water}$) were derived or calculated from the literature[31,32] by addition of the summed hydrophobic substituent (π) values to the log P values of the parent structure as described.[31] Log P values used in calculations are shown in Table III.

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Carbocyclic Analogue of 3-Deazaadenosine: A Novel Antiviral Agent Using *S*-Adenosylhomocysteine Hydrolase as a Pharmacological Target

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The carbocyclic analogue of 3-deazaadenosine (3-deaza-C-Ado) has been synthesized and found to have antiviral activity in cell culture against herpes simplex virus type 1, vaccinia virus, and HL-23 C-type virus. It is relatively noncytotoxic at effective antiviral concentrations and is not subject to deamination or phosphorylation. It acts as a competitive inhibitor of *S*-adenosyl-L-homocysteine hydrolase, is at best a poor substrate, and does not inactivate the enzyme significantly. 3-Deaza-C-Ado may cause a selective inhibition of the methylation of the polynucleotide 5′ cap of viral mRNA via higher cellular concentrations of *S*-adenosyl-L-homocysteine, resulting from the inhibition of *S*-adenosylhomocysteine hydrolase in infected cells, since increases in the intracellular level of *S*-adenosylhomocysteine, but no effects on DNA or RNA synthesis, were observed after incubation of these cells with it.

S-Adenosylmethionine (AdoMet) dependent methylation reactions exhibit a wide range of sensitivity toward inhibition by *S*-adenosyl-L-homocysteine (AdoHcy), one of the products of methylation reactions.[1-3] Because of this variable sensitivity, analogues of adenosine or AdoHcy have been synthesized and tested for their ability to inhibit AdoHcy hydrolase,[1-3] which hydrolyzes AdoHcy to homocysteine and adenosine. Although the equilibrium of the reaction favors synthesis, physiologically the reaction proceeds in the hydrolytic direction because adenosine and homocysteine are removed by metabolism. When AdoHcy hydrolase is inhibited, cellular accumulation of AdoHcy takes place. The pharmacological consequence is a disruption of the cellular ratio of AdoMet/AdoHcy, leading to a selective perturbation of methylation reactions.[4,5] Until now, one of the more potent inhibitors found for AdoHcy hydrolase is 3-deazaadenosine,[1-5] which, depending on species and organs, can also serve as a substrate for AdoHcy hydrolase, generating 3-deaza-AdoHcy.[1-3] It is difficult to determine whether AdoHcy, 3-deaza-AdoHcy, or the combination is the pharmacological agent responsible for the biochemical and biological effects observed. These effects are inhibition of phospholipid methylation and creatine biosynthesis in vivo,[4,5] inhibition of protein carboxymethylation,[6] inhibition of chemotaxis and phagocytosis,[7,8] inhibition of histamine release by human basophils,[9] inhibition of lymphocyte-mediated cytolysis,[10] antimalarial effect in vitro,[11] conversion of 3T3-L1 fibroblasts to fat cells,[12] and antiviral effects.[13-15]

The concept of exploiting AdoHcy hydrolase as a pharmacological target for chemotherapeutic purposes has been proposed.[1-5] Particularly notable is the observation that 3-deazaadenosine is a potent antiviral agent against a variety of DNA and RNA viruses.[13-15] The RNA viruses that are affected are Rous sarcoma virus, vesicular stomatitis, Sindbis, Newcastle disease,[13,14] and HL-23.[15] The finding that 9-(±)-[(1α,2β,3β,4α)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl]adenine, the carbocyclic analogue of adenosine (C-Ado), is the most potent inhibitor for AdoHcy hydrolase thus far studied, with a K_i of 5 nm,[16]

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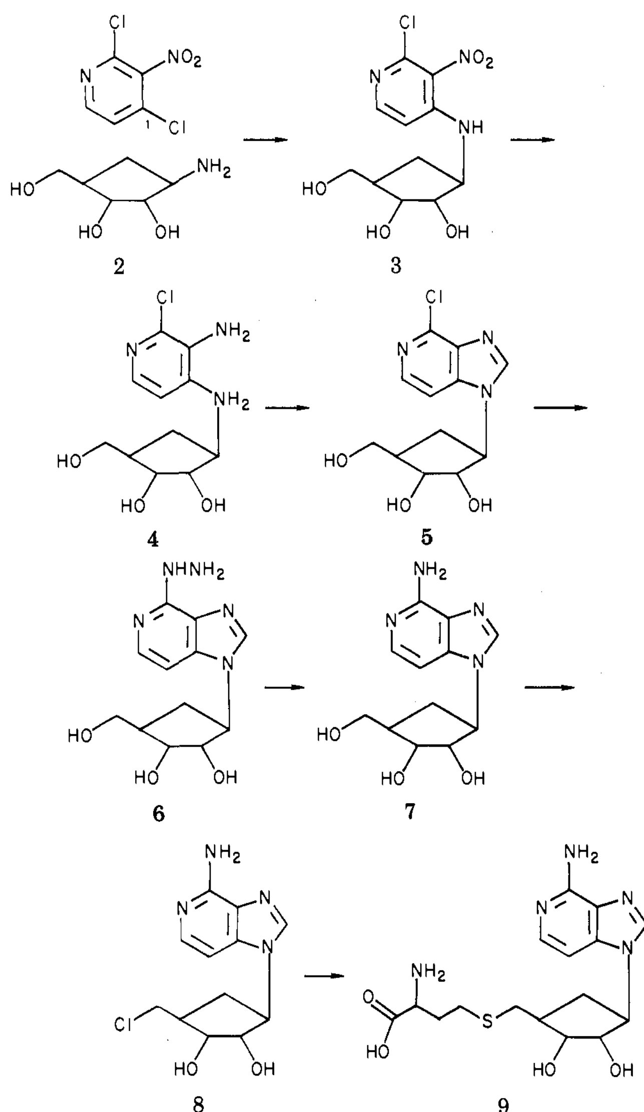
Scheme I



led us to the synthesis of (±)-4-amino-1-[(1α,2β,3β,4α)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl]imidazo[4,5-*c*]pyridine, the carbocyclic analogue of 3-deazaadenosine (3-deaza-C-Ado, **7**).

The route selected for the synthesis of **7** (Scheme I) was based on the knowledge that 2,4-dichloro-3-nitropyridine (**1**) reacts with nucleophiles preferentially at C-4.[17,18] Reaction of **1** with (±)-(1,4/2,3)-4-amino-2,3-dihydroxy-1-cyclopentanemethanol (**2**)[19-22] should then give the necessary intermediate **3**. That **3** and not its isomer was the product of this reaction was established by a comparison of its UV spectrum with the spectra of other 4-amino-2-chloro-3-nitropyridines[17,18] and with the spectrum of 2-amino-4-chloro-3-nitropyridine.[23] Reduction of **3** with hydrogen and Raney nickel catalyst gave the diamino compound **4**, which was cyclized with triethyl orthoformate and 12 N HCl in dimethylacetamide to the 3-deazapurine analogue **5**. Compound **5** was converted, by treatment with hydrazine to give **6** and Raney nickel reduction of **6**, to the desired 3-deaza-C-Ado (**7**). The UV spectrum of **7**, which agrees well with that of 3-deaza-Ado[24] and is quite different from that of 1-deaza-Ado,[25] provides final proof that amination of **1** with **2** occurred in the predicted manner. Chlorination of **7** as previously described for 3-deaza-Ado[13] gave the 5′-chloro-5′-deoxy compound **8** which on treatment with DL-homocysteine thiolactone in base gave (±)-*S*-[[(1α,2β,3β,4α)-4-(4-aminoimidazo[4,5-*c*]pyridin-1-yl)-2,3-dihydroxycyclopentyl]methyl]-DL-homocysteine (**9**), one stereoisomer of which would be formed if **7** served as a substrate for AdoHcy hydrolase.

Table I. In Vitro Antiviral Activity

compd	virus[a]	VR[b]	MIC_{50},[c] μg/mL	act.
3-deazaadenosine	herpes simplex virus, type 1	0.5		±
3-deaza-C-Ado (7)	herpes simplex virus, type 1	1.1	238	+ to ±[d]
ara-A	herpes simplex virus, type 1	3.2	2.1	+
3-deaza-C-Ado (7)	vaccinia virus	2.8	1.9	+
ara-A	vaccinia virus	1.2	19.2	+

[a] Herpes simplex virus type 1 (strain E-377) and vaccinia virus (strain Lederle chorioallantoic) both grown in mouse fibroblast cells, clone L-929. [b] VR = virus rating: A weighted measurement of in vitro antiviral activity, based on inhibition of virus-induced cytopathogenic effects [R. Sidwell et al., *Proc. Soc. Exp. Biol. Med.*, 131, 1223 (1969)]. [c] MIC_{50} = the minimum concentration of drug required for 50% inhibition of virus-induced cytopathogenic effects in infected cell cultures. [d] Observed effects diminished with time.

Biological Activity. 3-Deaza-C-Ado (**7**) is a competitive inhibitor of AdoHcy hydrolase, with K_i values of 3 μM and 1 nM for the enzyme from beef liver and from hamster liver, but it does not inactivate the enzyme to any extent. In contrast to C-Ado and in similarity to 3-deazaadenosine, it is not deaminated by calf intestinal deaminase and is not phosphorylated by L1210 leukemia cells. Conversion to the analogue (**9**) of adenosylhomocysteine was not detected in mouse L or normal rat kidney cells at the concentration investigated but did occur in 3T3 L1 mouse fibroblasts. When these latter cells were incubated with [^{35}S]methionine they produced adenosyl[^{35}S]-methionine and adenosyl[^{35}S]homocysteine, which were separated and identified by HPLC.[1] Incubation with [^{35}S]methionine plus 3-deazaadenosine gave Ado-Met, AdoHcy, and a third radioactive peak previously identified as 3-deaza-AdoHcy.[1] In a like manner, 3-deaza-C-Ado gave a third peak traveling similarly to but slightly different from 3-deaza-AdoHcy. When synthetic **9** was added to the cell extracts, it traveled with the same retention time as the radioactive peak.

3-Deaza-C-Ado (**7**) is more potent than 3-deazaadenosine against herpes simplex virus type 1 but inferior to *ara*-A. Against vaccinia, however, it is quite effective and clearly

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Table II. Inhibition by 3-Deaza-C-Ado of the Transformation of Normal Rat Kidney Cells by HL-23 Virus

concn, μM	no. of foci per dish[a]	% inhibn	% control cell number[b]
0	115	0	100
0.25	64	44	100
0.50	65	44	96
1.0	28	76	81
2.0	9	92	71
4.0	1	99	53

[a] Oncogenic transformation was assayed by infecting normal rat kidney cells (NRK 153C17) with HL-23 virus and counting the foci on day 5 after staining with Giemsa (see ref 15). [b] Determined on day 3.

better than *ara*-A (see Table I). At a concentration of 4 μM, it did not inhibit the incorporation of [^{3}H]thymidine into viral DNA. Although **7** is not toxic to L929 cells at levels that are effective against vaccinia, it is toxic to H.Ep.No.2 cells using a different type of assay.[26]

Virus production by HL-23, a C-type virus isolated from human acute myelogenous leukemia cells,[27] was inhibited by more than 85% by 0.5 μM 3-deaza-C-Ado, but incorporation of [^{14}C]uridine into viral RNA was not affected. Moreover, the induction of oncogenic transformation of normal rat kidney cells (NRK 153 Cl 7) by HL-23 virus was also inhibited (Table II). At 1 μM, 3-deaza-C-Ado (**7**) inhibited focus formation by 76% with minimal cytotoxicity. The antiviral effect of **7** against HL-23 could be correlated with the accumulation of AdoHcy in the cells (Figure 1), presumably from the inhibition of AdoHcy hydrolase. The hydrolase of NRK 153 Cl 7 cells appeared to be more sensitive than that of mouse L cells to inhibition by **7**. Two hours after administration of 1 μM **7**, a 5-fold increase in AdoHcy occurred and rose further to 10-fold after 24 h. Accompanying the increase of AdoHcy was a steady increase of AdoMet in these cells to 1.3-fold the normal level. The response of the mouse L cells to 3-deaza-C-Ado was somewhat different. Paralleling the 2- to 3-fold increase in AdoHcy was a 2-fold increase in AdoMet. Twenty-four hours after the administration of 30 μM 3-deaza-C-Ado, the level of AdoMet returned to normal, while the level of AdoHcy fell from 3 to 2 times normal. The overall increase in the cellular levels of AdoMet in these two types of cells was probably a reflection of inhibition of methylation reactions by AdoHcy.

The most likely mechanism for the antiviral activity of 3-deaza-C-Ado (**7**) is the inhibition of the methylation of the 5′ cap of mRNA of the viruses by the higher than normal accumulation of cellular AdoHcy. The methylation of the 5′ polynucleotide cap of mRNA is essential for viral replication.[28,29] One piece of evidence to support this hypothesis is that both 3-deaza-C-Ado and 3-deazaadenosine fail to inhibit the replication of poliovirus,[30] which has a polypeptide cap on the 5′ end and is not methylated.[31-33] Thus, the mechanism of the antiviral

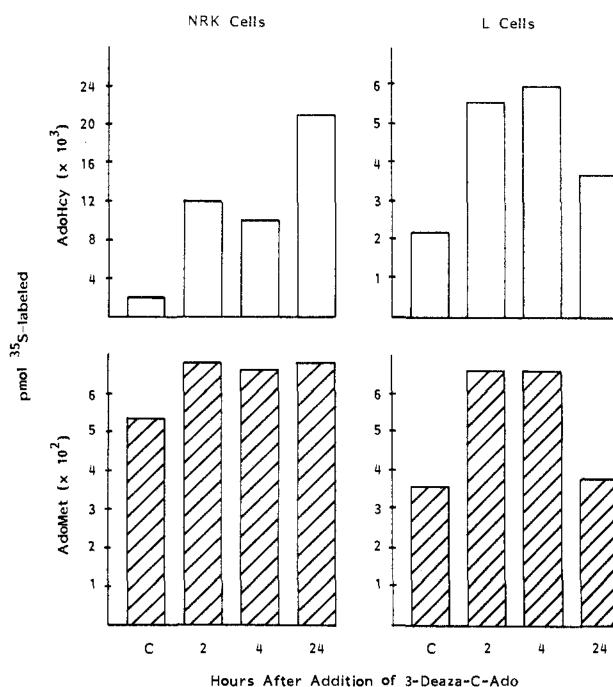

Figure 1. High-pressure liquid chromatography of [^{35}S]AdoHcy and [^{35}S]AdoMet. NRK 153 Cl 7 cells or mouse L cells were seeded at 5 × 10^5 cells in a 100-mm dish in 10 mL of minimal essential medium supplemented with 5% newborn calf serum and 31 μCi of [^{35}S]methionine. On day 6, 3-deaza-C-Ado was added to two dishes each of NRK 153 Cl 7 cells at 1 μM and mouse L cells at 30 μM and left for 24 h. The following day, the same concentrations of 3-deaza-C-Ado were also added to other dishes of cells for other time points (C = control cells). Two dishes of cells were combined for each time point, and the metabolites were determined by high-pressure liquid chromatography with VYDAC cation exchanger.[1,16]

action of **7** appears to be different from agents like *ara*-A[34] or acycloguanosine,[35] and **7** appears not to be phosphorylated and is probably not incorporated into nucleotides that can become part of the genome of the host. Furthermore, in contrast to 3-deazaadenosine,[7,8] 3-deaza-C-Ado does not inhibit chemotaxis by macrophage cell lines,[36] nor does it potentiate platelet aggregation and serotonin release induced by epinephrine or ADP.[37] Therefore, 3-deaza-C-Ado may be considered a potential antiviral agent without some of the undesirable effects of other agents.

Experimental Section

Biological Methods. AdoHcy hydrolase was prepared and assayed as described previously.[1,16,38] 3-Deaza-C-Ado (92 μg) was incubated for 1 h with an excess of adenosine deaminase (10 μg) purchased from Sigma Chemical Co. Since no change was observed another 40 μg of deaminase was added, and the mixture was allowed to stand overnight. No change in the UV spectrum or the TLC could be detected. Under the same conditions, adenosine was completely deaminated in a few minutes. TCA extracts of L1210 leukemia cells incubated with 3-deaza-C-Ado for 1 h were analyzed by HPLC as previously described.[39] 3-Deaza-C-Ado appeared with the front and no new mono-, di-, or

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triphosphates could be detected. The antiviral activities given in Table I were determined as previously described,[40] as well as inhibition of the transformation of normal rat binding cells by HL-23 virus[15] and the toxicity of 7 to H.Ep.No.2 cells in culture.[41]

Synthesis. All evaporations were carried out in vacuo with a rotary evaporator. Analytical samples were normally dried in vacuo over P_2O_5 at room temperature for 16 h. Analtech precoated (250 μm) silica gel G(F) plates were used for TLC analyses; the spots were detected by irradiation with a Mineralight and by charring after spraying with saturated $(NH_4)_2SO_4$. Compounds containing amino groups were also detected with ninhydrin spray. All analytical samples were essentially TLC homogeneous. Melting points were determined with a Mel-Temp apparatus and are not corrected. The UV absorption spectra were determined in 0.1 N HCl, pH 7 buffer, and 0.1 N NaOH with a Cary 17 spectrophotometer: the maxima are reported in nanometers ($\epsilon \times 10^{-3}$). The ^{1}H NMR spectra were determined with a Varian XL-100-15 spectrometer in Me_2SO-d_6 with tetramethylsilane as an internal reference: chemical shifts (δ, in parts per million) quoted in the case of multiplets are measured from the approximate center. The high-pressure liquid chromatographic analysis was carried out with a Waters Associates ALC-242 chromatograph with an M-6000 pump and equipped with a μPorasil column (0.25 in. × 30 cm) using $CHCl_3$ (1% EtOH) as the solvent.

(±)-(1,4/2,3)-4-(3-Nitro-2-chloro-4-pyridylamino)-2,3-dihydroxy-1-cyclopentanemethanol (3). A solution of (±)-(1,4/2,3)-4-amino-2,3-dihydroxy-1-cyclopentanemethanol (2; 294 mg, 2 mmol)[18] and 2,4-dichloro-3-nitropyridine (1; 1.12 g, 5.8 mmol) in 100 mL of absolute ethanol (dried over 3A molecular sieves) containing triethylamine, 1 mL, was protected from moisture and refluxed overnight. Thin-layer chromatography showed that the reaction was complete. The solution was evaporated to dryness, and the last of the ethanol was removed by addition of water followed by evaporation. The residue was partitioned between water and chloroform. The water was extracted once with chloroform. Evaporation of the chloroform, followed by crystallization from ethanol, gave 450 mg (40%) of 2,4-dichloro-3-nitropyridine. Evaporation of the water solution, followed by crystallization from ethanol, gave 345 mg (56.8%) of the desired product (3): mp 175–177 °C with softening from 170 °C (Mel-Temp, uncorrected); homogeneous by TLC ($CHCl_3$/MeOH, 3:1); UV λ_{max} at pH 1, 248 (14.3), 268–274 (sh), 355 (1.97); at pH 7, 248 (17.3), 375 (2.51); at pH 13, 248 (17.3), 35 (2.51); NMR (Me_2SO-d_6) δ 1.25 (br m, $H_{5'}$), 2.2 (br m, $H_{4'}$ and $H_{5'}$), 3.4 (m, 2 $H_{6'}$), 3.7 (m, $H_{1'}$, $H_{2'}$, and $H_{3'}$), 4.6 (br m, OH), 7.05 (d, H_5), 7.15 (d, NH), 8.0 (d, H_6). Anal. Calcd for $C_{11}H_{14}ClN_3O_5$: C, 43.50; H, 4.65; N, 13.84. Found: C, 43.89; H, 4.98; N, 13.90.

(±)-4-Chloro-1-[(1α,2β,3β,4α)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl]imidazo[4,5-*c*]pyridine (5). A solution of compound 3 (3.6 g, 11.8 mmol) in 250 mL of ethanol with Raney nickel (1 g) was hydrogenated at atmospheric pressure and room temperature. As soon as hydrogen uptake stopped, the catalyst was removed by filtration through Celite. The catalyst was washed with fresh ethanol, and the combined filtrates were evaporated to dryness. The residue was dissolved in a mixture of dimethylacetamide (40 mL), triethyl orthoformate (80 mL), and 12 N HCl (2 mL). The solution was stirred overnight at room temperature before being evaporated to dryness in vacuo without heat. It was then evaporated with toluene in vacuo. A solution of the residue in 50% aqueous acetic acid (50 mL) was stirred at room temperature for 4 h, evaporated in vacuo without heat, dissolved in water, and evaporated in vacuo to remove acetic acid. It was dried in vacuo overnight and dissolved in 10% ammonia in methanol (50 mL). The solution was stirred for 4 h, evaporated to dryness, dissolved in ethanol, and evaporated to dryness again. The residue was crystallized from water. The product was obtained in two crops: total yield 1.71 g (51%); mp 219–221 °C; UV λ_{max} at pH 1, 274 sh (6.16), 267 (6.4), 255–259 sh; at pH 7, 275 (5.01), 267 (6.62), 258 (6.58); at pH 13, 276 (4.96), 268 (6.56), 259 (6.42). Anal. Calcd for $C_{12}H_{14}ClN_3O_3$: C, 50.80; H, 4.97; N, 14.81. Found: C, 50.97; H, 5.16; N, 15.07.

(±)-4-Amino-1-[(1α,2β,3β,4α)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl]imidazo[4,5-*c*]pyridine (7) Hydrochloride. A solution of compound 5 (1.59 g, 5.6 mmol) in 95+% hydrazine (48 mL) was refluxed under nitrogen for 1 h. The solution was evaporated to dryness in vacuo, dissolved in water, and evaporated again. A solution of the residue in oxygen-free water was stirred under nitrogen with Raney nickel at reflux for 1 h. The mixture was filtered hot, and the catalyst was washed with boiling water. The combined filtrates were evaporated to dryness, and the residue was recrystallized from methanol using charcoal. The product was collected, washed with methanol, and dried in vacuo: yield 670 mg (40.1%); mp 236–238 °C with darkening from 230 °C. Two additional crops were obtained: yield 391 mg; total yield 1.06 g (63.5%); UV λ_{max} at pH 1, 262 (10.1), 268 (9.84); at pH 7, 263 (10.3), 268 sh; at pH 13, 267 (10.4); MS, *m/e* 264 $(M)^+$, 247 $[(M - OH)^+]$, 161 $[(B + C_2H_4)^+]$, 135 $[(B + 2H)^+]$, 36 (HCl); ^{1}H NMR (Me_2SO-d_6) δ 1.8 (m, $H_{5'}$), 2.25 (m, $H_{5'}$ and $H_{4'}$), 3.53 (d, $H_{6'}$), 3.85 (m, $H_{3'}$), 4.2 (m, $H_{2'}$), 4.75 (q, H_5), 7.33 (d, H_7), 7.78 (d, H_6), 8.48 (s, NH_2), 8.64 (s, H_2). Anal. Calcd for $C_{12}H_{16}N_4O_3\cdot HCl$: C, 47.92; H, 5.70; N, 18.63; Cl, 11.79. Found: C, 47.89; H, 5.82; N, 18.51; Cl, 11.70.

(±)-4-Amino-1-[(1α,2β,3β,4α)-2,3-dihydroxy-4-(chloromethyl)cyclopentyl]imidazo[4,5-*c*]pyridine (8). A cold (0–5 °C) mixture of 3-deaza-C-Ado (7; 298 mg, 1 mmol) in trimethyl phosphate (2.84 mL) was stirred, treated with thionyl chloride (0.64 mL), allowed to warm up to ambient temperature, and held there for 20 h. The resulting yellow mixture was diluted with 5 mL of ether and filtered. An aqueous solution of the gummy solid obtained was made basic (pH 9) with 1 N NaOH, filtered, and chilled to give a white crystalline solid: yield 184 mg (66%). A small sample was recrystallized from water for analysis: mp 323–326 °C dec.; MS (FD), *m/e* 282 (M^+); UV λ_{max} at pH 1, 263 (10.4), 270 (10.3); at pH 7, 263 (10.4); at pH 13, 267 (10.6). Anal. Calcd for $C_{12}H_{15}ClN_4O_2\cdot 0.5H_2O$: C, 49.50; H, 5.53; N, 19.21. Found: C, 49.33; H, 5.25; N, 19.26.

(±)-*S*-[[(1α,2β,3β,4α)-4-(4-Aminoimidazo[4,5-*c*]pyridin-1-yl)-2,3-dihydroxycyclopentyl]methyl]-DL-homocysteine (9). DL-Homocysteine thiolactone hydrochloride (203 mg, 1.32 mmol) was added to 1 N NaOH (4.62 mL), which had been chilled to 0.5 °C. The resulting solution was allowed to warm up to ambient temperature, kept there for 30 min, then charged with 184 mg (0.65 mmol) of the 5′-chloro compound, refluxed for 5 h, acidified (pH 2) with dilute HCl, and applied to a column of 100 mL of Dowex 50 WX4 (NH_4^+) 50–100 mesh resin. After initial water elution to remove inorganics and unreacted starting material, the column was eluted with 1 N ammonium hydroxide to give the product. Fractions containing product were combined and freeze-dried to give a glass weighing 226 mg. The glass was further purified by preparative thin-layer chromatography on silica gel using CH_3CN/1 N NH_4OH (13:7) as the developing solvent. The product band was extracted with MeOH to give a glass weighing 90 mg. The glass was recolumned on 50 mL of Dowex 50 WX4 (NH_4^+) resin. After the initial water elution, the product was obtained by eluting with 1 N NH_4OH. Evaporation gave a glass: yield 65 mg (26%); UV λ_{max} ($\epsilon \times 10^{-3}$) 263 nm at pH 1 (9.98), 264 nm at pH 7 (10.4), and 267 nm at pH 13 (10.3); HPLC t_R 10.53 min [$NH_4H_2PO_4$ (pH 5.1, 0.1 N)/MeOH (9:1)]; TLC [CH_3CN/1 N NH_4OH (13:7)]. Anal. Calcd for $C_{16}H_{23}N_5O_4S\cdot 2H_2O$: C, 46.02; H, 6.52; N, 16.77. Found: C, 46.40; H, 5.99; N, 16.38.

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