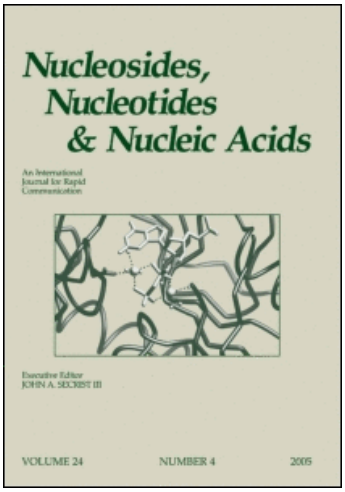

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Carbocyclic Purine Nucleosides Derived from Aristeromycin Through Two Key Intermediates, Carbocyclic 5-Amino-4-Imidazolecarboxamide Riboside and 2'-Deoxyriboside

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CARBOCYCLIC PURINE NUCLEOSIDES DERIVED FROM ARISTEROMYCIN THROUGH TWO KEY INTERMEDIATES, CARBOCYCLIC 5-AMINO-4-IMIDAZOLECARBOXAMIDE RIBOSIDE AND 2'-DEOXYRIBOSIDE

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ABSTRACT: Treating carbocyclic N^1-methoxymethyl-inosine and -2'-deoxyinosine with 1N-NaOH/aq.EtOH gave carbocyclic 5-amino-4-imidazolecarboxamide riboside and 2'-deoxyriboside, respectively. Reactions of both the useful key intermediates with benzoylisothiocyanate afforded the corresponding 5-(N-benzoylisothiocarbamoyl) derivatives. Methylation of the sulfhydryl groups, followed by treatment with NaOH, led to the purine ring-closure (guanine, isoguanine, and 3-methylxanthine) reaction. The conformational difference between 2'-deoxyguanosine and carbocyclic 2'-deoxyguanosine is also discussed.

Aristeromycin is a carbocyclic analog of adenosine in which the furanose oxygen atom is replaced with a methylene group. Surprisingly, it was isolated from the culture broth of *Streptomyces citricolor*[1] after the chemical synthesis of racemic carbocyclic adenosine[2]. Consistent with the presence of nonglycosidic structures, carbocyclic analogs are not susceptible to cleavage by nucleoside phosphorylases and hydrolases, which cleave the glycosyl bond of natural nucleosides. However, the expected conformational similarity in bond lengths and angles between the tetrahydrofuran and cyclopentane rings allows these analogs to

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This paper is dedicated to the late Professor Tohru Ueda.

have the potential to mimic or antagonize the functions of natural nucleosides against some enzymes in living cells[3].

We have already shown the synthesis of oligodeoxynucleotides carrying 2'-deoxyaristeromycin and their application to recombinant DNA techniques[4]. Furthermore, it has been found that the rates of hydrolysis by some restriction enzymes were somewhat affected by the distance between the positions of 2'-deoxyaristeromycin and the fission sites in the oligodeoxynucleotides (data not shown). To study the biochemical effects of carbocyclic nucleosides in further details, we have decided to synthesize optically active carbocyclic 2'-deoxyguanosine and guanosine from aristeromycin.

In the meantime, *Shealy et al.*[5] have reported the preparation of racemic mixtures of carbocyclic guanosine derivatives by a long synthetic sequence and the evaluation of their antiviral activities against herpes simplex virus (HSV). After the epoch-making discovery of the antiherpetic activity of acyclovir[6], several carbocyclic nucleosides as well as various acyclic ones have been evaluated against viruses: carbocyclic analogs of cytidine, 3-deazaadenosine, arabinofuranosyl adenine, and 5-substituted 2'-deoxyuridines[7]. However, all these carbocyclic nucleosides have been synthesized as racemic mixtures, and tested without optical separation procedures. Just before our short communication about optically pure carbocyclic 2'-deoxyguanosine[8], it was reported that the resolution of the racemic mixture of carbocyclic 2'-deoxyguanosine was developed using adenosine deaminase[9]. The results have shown that the *dextro*-isomer is more than three times as potent as the racemic mixture against HSV-2[10] and that the concomitant *levo*-isomer, which has the mirror image structure of a natural nucleoside, might behave like an inhibitor in regard to antiviral action[11] and gives a slight lowering of the antiviral activity.

In this paper, we describe the synthesis of optically active carbocyclic purine nucleosides in which we utilized

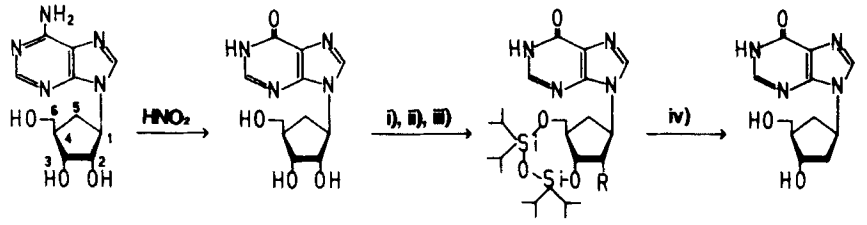
the conversion of the adenine moiety of aristeromycin and 2'-deoxyaristeromycin through the useful intermediates, carbocyclic 5-amino-4-imidazolecarboxamide (AICA) derivatives. This route is of great value because many ring-closure methodologies to form various purine nucleosides from AICA derivatives have been investigated[12]. By using these methods, we can easily obtain many kinds of optically active carbocyclic nucleosides.

RESULTS AND DISCUSSION

Carbocyclic inosine (2)[13] was obtained from aristeromycin (1) by deamination (Scheme 1) and was further converted into the 2',3'-O-isopropylidene derivative (4a)[14]. It was allowed to react with monomethoxytrityl chloride (MMTr-Cl) in pyridine to give the 5'-O-protected compound (4b) in a crystalline form (Scheme 2). The protecting group was useful for tracing the reaction processes and separation of the products. Carbocyclic 3',5'-O-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)inosine (3a) was prepared in high yield from 2 by treatment with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TPDS-Cl_2)/imidazole/DMF. Phenoxythiocarbonylation and free radical deoxygenation of 3b was performed using the procedure described by *Robins et al.*[15] to give carbocyclic 3',5'-O-protected 2'-deoxyinosine (3c) (Scheme 1).

At first we tried the direct conversion reaction from the carbocyclic inosine derivative (4a, 4b) to AICA riboside derivative (6a, 6b) by heating 4a or 4b in an aqueous alkaline solution in a sealed tube based on the experiment with inosine described previously[16]. In spite of many efforts, the yield of 6b was at most about 30%, and it was apparently impossible to separate 6b from 4b on a large scale. Therefore, we chose another method described by *Shaw*[17].

Treatment of 4b with NaH in DMF/dioxane, and subsequently methyl chloromethyl ether furnished the N^1-methoxymethylinosine derivative (5) (Scheme 2). In this reaction,

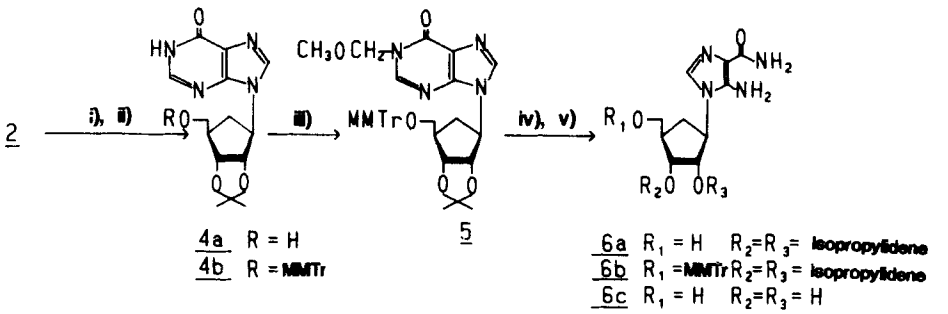


SCHEME 1

(i) $(i\text{-}Pr_2SiCl)_2O$/imidazole/DMF (ii) PhOCSCl/DMPA/MeCN (iii) Bu_3SnH/AIBN/PhMe (iv) Bu_4NF

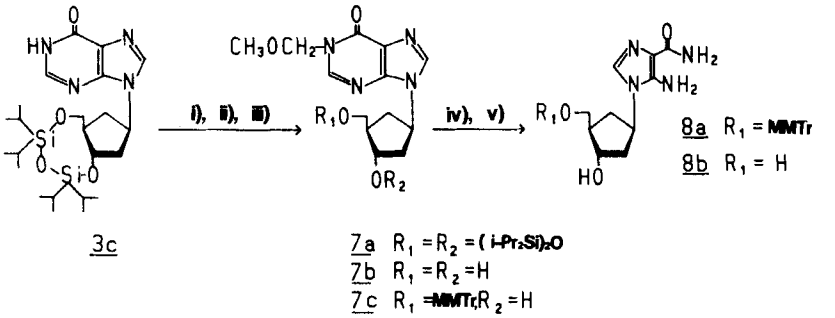
the formation of a more hydrophobic by-product was also observed (yield: ~15%). The by-product with the same molecular weight (Mass: m/e 622) as that of 5 and with one MMTr-group [^{1}H-NMR: $CDCl_3$, Me_4Si, δppm: 3.62 (s,3H), 5.83 (s,2H)] was presumed to be the carbocyclic O^6-methoxymethylinosine derivative. In the case of methoxymethylation of 3c, the analogous by-product was also detected (Scheme 3). Treatment of 5 with alkali in refluxing aq.EtOH gave the carbocyclic AICA riboside derivative (6b, yield: 45~53%) with recovery of the starting compound (4b, yield: ~11%) and some by-products (Scheme 2). The formation of 4b could be explained by the lability of the N^1-methoxymethyl group, which might lead to hydrolysis back to the hypoxanthine moiety as a competing reaction with the ring-opening. In the case of 7c, the analogous pattern was also observed (Scheme 3).

The cyclization reactions were based on the procedure described by *Yamazaki et al.*[18]. Carbocyclic 2'-deoxyriboside of 5-(N-benzoyl-S-methylisothio-carbamoyl)amino-4-imidazolecarboxamide (10b) and the corresponding riboside (14a) were prepared by treating 8b and 6a, respectively, with benzoyl isothiocyanate, followed by methylation of the crude product with dimethyl sulfate in alkali (Schemes 4



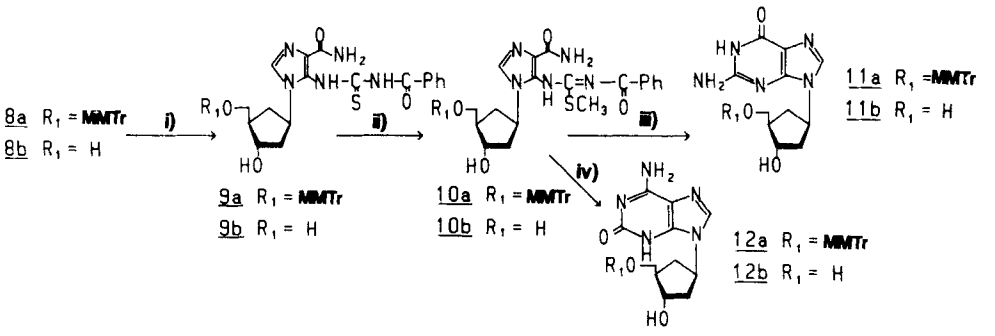
SCHEME 2

(i) 2,2-Dimethoxypropane/ p-TsOH (ii) MMTrCl/ Pyridine (iii) MeOCH₂Cl/ NaH/ Dioxane-DMF (iv) 5N-NaOH/ EtOH (v) 80% AcOH



SCHEME 3

(i) MeOCH₂Cl/ NaH/ Dioxane (ii) Bu₄NF/ THF (iii) MMTrCl/ Pyridine (iv) 5M-NaOH/ EtOH (v) 80% AcOH



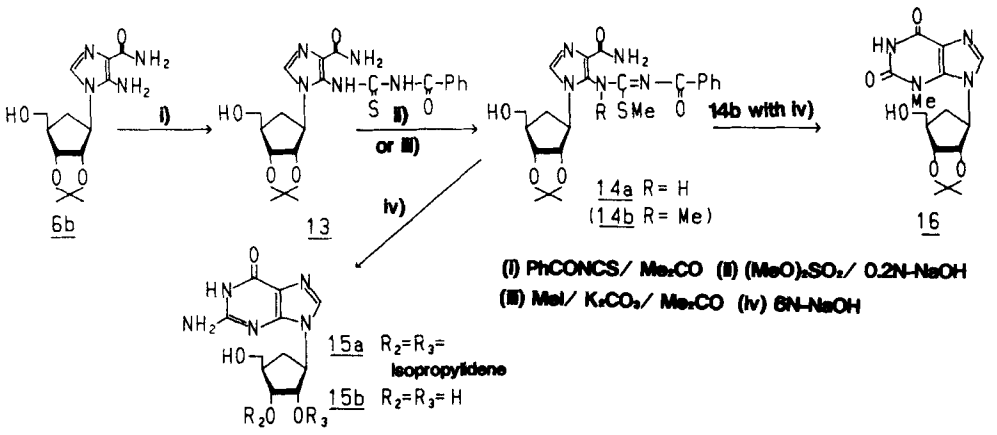
SCHEME 4

(i) PhCONCS/ Me₂CO (ii) (MeO)₂SO₂/ 0.2N-NaOH (iii) 6N-NaOH (iv) 0.1N-NaOH

and 5). Treatment of the N-benzoylisothiocarbamoyl compound (13) with excess amounts of methyl iodide in the presence of K_2CO_3/Me_2CO gave an unexpected compound as the main product, which was observed faintly as a by-product in the case of the reaction using dimethyl sulfate. The yield of the expected compound (14a) was only 10%. It was so difficult to isolate the unexpected product that the crude material was successively treated with refluxing 6N-NaOH. From the reaction mixture, a crystalline product (16, 7% from 13) and some unstable compounds were isolated. The stable 16 was assigned to be carbocyclic 2',3'-O-isopropylidene-3-methyl-xanthosine by UV (it is superimposable on that of 3-methylxanthosine[19]), ^{1}H-NMR, and elemental analyses. From the formation of 16, it can be assumed that 13 is per-methylated to give the intermediary N,S-dimethylated compound (14b), which is cyclized and hydrolysed to form a 3-methylxanthine ring (Scheme 5). The carbocyclic guanosine derivatives (11a, 11b, and 15a) were prepared by treating 10a, 10b, and 14a, respectively, with refluxing 6N-NaOH. Finally, the non-protected carbocyclic guanine nucleosides (11b,15b) were easily isolated by HP-20 chromatography followed by crystallization (Schemes 4 and 5).

Yamazaki et al.[18] reported that 5-(N-benzoyl-S-methylisothiocarbamoyl)-amino-4-imidazolecarboxamide was converted to isoguanine on refluxing in diluted alkaline. Thus, we prepared carbocyclic 2'-deoxyisoguanosine (12b) by using monomethoxytrityl derivative (10a) (Scheme 4). Treating 10a with 0.1N-NaOH in 17% aq.EtOH under refluxing gave mainly the isoguanine derivative (12a) with concomitant formation of the guanine derivative (11a). The desired carbocyclic 2'-deoxyisoguanosine (12b) was obtained by aq.AcOH hydrolysis of 12a (Scheme 4).

Carbocyclic *dextro*-2'-deoxyguanosine and -2'-deoxyinosine showed strong antiviral activity *in vivo* against HSV-1 as described previously[20]. At present, the evaluation of the other compounds described here against viruses are in progress. Recently, it has been reported that carbocyclic



SCHEME 5

2'-deoxyguanosine is phosphorylated significantly to the triphosphate in H.Ep.-2 or Vero cells infected with HSV-1, but no triphosphate was detected in uninfected cells[10]. The acceptance of nucleoside analogs by the kinase of HSV-1 is probably determined by conformational factors. In order to compare the conformations of 2'-deoxyguanosine with its carbocyclic analog, we have determined their crystal structures by X-ray structural analyses. The results have shown that 2'-deoxyguanosine adopts the standard ${}^{2}_{3}T$ (P=185.8°) form in the sugar ring pucker and a *syn* base torsion angle (χ=70.1°), whereas the carbocyclic derivative exists in the unusual high energy ${}^{1}E$ conformation (P=293.3°) and a high *anti* base torsion angle (χ=-73.7°)[21]. These results suggest that the HSV-specified thymidine kinase can preferentially phosphorylate carbocyclic 2'-deoxyguanosine with the unusual ${}^{1}E$ conformation while the host cellular one cannot.

EXPERIMENTAL

General Methods

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. UV spectra were measured with a Hitachi EPS-2T spectrophotometer.

^{1}H-NMR spectra were recorded on a Varian T-60 (60 MHz), EM-390 (90 MHz), or XL-100 (100 MHz) spectrometer using tetramethylsilane as an internal standard or on a Jeol-GX400 (400 MHz) spectrometer in D_2O using 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an internal standard. A Nichiden JMS-OISC or Hitachi M-80A mass spectrometer was used for mass spectrometry. Optical rotations were taken with a digital polarimeter model DIP-181 (Japan Spectroscopic Co. Ltd.). Column chromatographies were performed on Kieselgel-60 (0.063-0.200 mm, Merck) and LiChrosorb RP-18 (5 μm, Merck), thin layer chromatographies on Silica gel 60 F_{254}, (Merck).

Protection and Deoxygenation

(1R,8R,10R,11S)-11-hydroxy-10-(hypoxanthin-9-yl)-3,3,5,5-tetrakis(isopropyl)-2,4,6-trioxa-3,5-disila-bicyclo[6,3,0]-undecane (3a)

To 10 g (37.5 mmol) of dried 2 in anhydrous DMF (200 ml) was added 13 ml (41 mmol) of TPDS-Cl_2 and 11.3 g (165 mmol) of imidazole. The mixture was stirred at room temperature for 2.5 hr, then poured slowly to vigorously stirred H_2O (2l). The resulting precipitate was collected by filtration and washed thoroughly with H_2O, rapidly Et_2O and dried *in vacuo* over P_2O_5. The resulting amorphous product (17.2 g) was of sufficient purity for direct use in subsequent reactions. For characterization, a small aliquot was crystallized from CH_2Cl_2: mp 135-138°C.

(1R,8R,10R,11S)-10-(hypoxanthin-9-yl)-11-phenoxythiocarbonyloxy-3,3,5,5-tetrakis(isopropyl)-2,4,6-trioxa-3,5-disila-bicyclo[6,3,0]undecane (3b)

To the crude compound 3a (11.2 g, 22.3 mmol) was added anhydrous CH_3CN (300 ml), 15.89 g (53.5 mmol) of DMAP, and 5 g (29 mmol) of PhOCSCl. The solution was stirred at room temperature for 7 hr. The solvent was evaporated and the residue was partitioned between $CHCl_3$ and 0.5M-KH_2PO_4/H_2O (each 250 ml). The organic phase was washed with 0.5M KH_2PO_4/H_2O (250 ml), and H_2O (200 ml), dried (Na_2SO_4), fil-

tered, and evaporated. The resulting yellow syrup was chromatographed on silica gel (90 g, ø 5.0×8.5 cm) with $CHCl_3$ and $CHCl_3$-MeOH (60:1). Evaporation of appropriate fractions *in vacuo* gave 13.0 g (90%) of pale yellow glassy product (3b): ^{1}H-NMR (60 MHz, $CDCl_3$) δ 1.0-1.23 (28H,m, $(CH_3)_2CH\times4$), 2.13-2.43 (3H,m,H_4-,$2H_5$-), 3.93-4.10 (2H,m, H_6-), 4.80-5.20 (2H,m,H_1-,H_3-), 6.00-6.20 (1H,m,H_2-), 7.03-7.50 (5H,m,Ph), 7.87 and 8.13 (1H each, s, purine ring protons).

(1S,8R,10R)-10-(hypoxanthin-9-yl)-3,3,5,5-tetrakis(isopropyl)-2,4,6-trioxa-3,5-disila-bicyclo[6,3,0]undecane (3c)

The compound 3b was suspended in dry toluene (30 ml), co-evaporated, and then dissolved in 300 ml of dry toluene. To the solution degassed with oxygen-free N_2 for 20 min were added 11 ml (40 mmol) of n-Bu_3SnH and 820 mg (5 mmol) of AIBN. The mixture was heated at 80°C for 3 hr while stirring. The solvent was evaporated and the residue was chromatographed on silica gel (80 g, ø 5.0×7.6 cm) with $CHCl_3$ and $CHCl_3$/MeOH (60:1~30:1). Evaporation of the appropriate fractions and drying *in vacuo* gave 10.4 g of colorless glassy residue (3c). It was of sufficient purity for direct use in subsequent reactions. Crystallization of the residue from EtOH gave 5.2 g (53%) of 3c: mp 200-202°C; ^{1}H-NMR (60 MHz, $CDCl_3$) δ 0.93-1.20 (28H,m,$(CH_3)_2CH\times4$), 1.97-2.53 (5H,m,$2H_2$-,H_4-,$2H_5$-), 3.80-4.07 (2H,m,H_6-), 4.43-5.27 (2H,m,H_1-,H_3-), 7.87 and 8.20 (1H each, s, purine ring protons).

9-[(1R,2S,3R,4R)-4-Monomethoxytrityloxymethyl-2,3-(dimethylmethylenedioxy)cyclopent-1-yl]hypoxanthine (4b)

The compound 4a (8.4 g, 27 mmol) was co-evaporated with anhydrous pyridine and to this residue was added anhydrous pyridine (150 ml) and 9 g (29 mmol) of MMTr-Cl. After 13 hr at room temperature, MeOH (20 ml) was added and the solvent was evaporated. The residue was partitioned between $CHCl_3$ and 0.1M TEAB (pH 7.5) (each 100 ml). The organic phase was washed with H_2O (100 ml), dried (Na_2SO_4), filtered. Condensation of this solution under reduced

pressure gave 9.4 g (60%) of the crystals (4b): mp 194-195°C. In addition, another crop of 4b (2.7 g) was obtained as a white powder from the filtrate.

Ring Opening Reactions

9-[(1R,3S,4R)-4-(Monomethoxytrityloxy)methyl-3-hydroxycyclopent-1-yl]-1-methoxymethylhypoxanthine (7c)

The product 3c (9.8 g, 19.8 mmol) was dissolved in anhydrous dioxane (240 ml), treated with sodium hydride (NaH) (880 mg of a 60% mineral oil dispersion, 22 mmol), and left for 1.5 hr while stirring. Methyl chloromethyl ether (2 ml, 22 mmol) was added and the mixture was stirred at room temperature for 3 hr. After removal of the solvent under reduced pressure, the residue was partitioned between $CHCl_3$ (200 ml) and 0.1M TEAB (pH 7.5, 100 ml). The organic phase was washed with the same buffer (200 ml) and H_2O (200 ml), dried (Na_2SO_4), filtered, and evaporated. The resulting syrup was chromatographed on C_{18} silica gel (ø 5.3×7.0 cm) with 55-80% acetone/H_2O. Evaporation of the appropriate fractions gave 8.5 g (79%) of colorless glassy product (7a). To the above obtained 7a (8.0 g) was added THF (32 ml) and 10 g (32 mmol) of $Bu_4NF \cdot 3H_2O$. The solution was stirred at room temperature for 0.5 hr. The solvent was evaporated and the residue was dissolved in H_2O (100 ml), washed with Et_2O (2×100 ml), and applied to a column of Dowex 50 (pyridinium form) resin (60 ml) to remove tributylammonium ion. The eluate and the column washing water (240 ml) were combined and evaporated. The residue was dissolved in water and applied to a column of HP-20 resin (190 ml). The column was washed well with H_2O before elution with 30% EtOH/H_2O. After evaporation of the eluate, the residue (7b) was co-evaporated with anhydrous pyridine three times to remove residual H_2O.

To this residue was added anhydrous pyridine (100 ml) and 5.4 g (17.5 mmol) of MMTr-Cl. The solution was stirred at 37°C for 4 hr. Pyridine was evaporated and the residue was partitioned between $CHCl_3$ and 0.1M-TEAB (pH 7.5, each

100 ml). The organic phase was washed with H_2O (100 ml), dried (Na_2SO_4), filtered, and evaporated. This material (7c) was chromatographed on silica gel (80 g, ø 5.2×7.4 cm) with $CHCl_3$/MeOH (100:1~50:1). After appropriate fractions were evaporated, the residue was dissolved in CH_2Cl_2 and the solution was added dropwise to n-hexane with stirring. Filtration and drying *in vacuo* gave 6.1 g (73%) of a white powder (7c): ^{1}H-NMR (60 MHz, $CDCl_3$), δ 1.87-2.70 (5H,m, $2H_2$-,H_4-,$5H_5$-), 3.20-3.40 (2H,m,H_6-), 3.43 (3H,s,CH_2OCH_3), 3.80 (3H,s,Me), 4.30-4.57 (1H,m,H_3-), 4.87-5.10 (1H,m,H_1-), 5.47 (2H,s,CH_2OCH_3), 6.73-7.54 (14H,m,Ph's), 7.73 and 7.98 (1H each, s, purine ring protons).

1-[(1R,3S,4R)-4-(Monomethoxytrityloxy)methyl-3-hydroxy-cyclopent-1-yl]-4-carbamoyl-5-aminoimidazole (8a)

The white powder 7c (6.1 g, 10.7 mmol) was dissolved in hot EtOH (490 ml). The solution was added rapidly to 5M-NaOH (130 ml, preheated at 90°C) and the mixture was refluxed for 40 min. After removal of the solvent under reduced pressure, the residue was partitioned between $CHCl_3$ (200 ml) and H_2O (100 ml). The organic phase was washed with H_2O (100 ml), 0.1M-TEAB (pH 7.5), and saturated NaCl/H_2O, dried (Na_2SO_4), filtered, and evaporated. The resulting syrupy product was chromatographed on silica gel (90g, ø 5.3×9.0 cm) with $CHCl_3$/MeOH (100:1~20:1). Evaporation of the appropriate fractions gave 3.2 g (57%) of 8a as a colorless glassy material. A small aliquot was dissolved in $CHCl_3$ and the solution was added dropwise to n-pentane with stirring. Centrifugation, decantation of solvent and drying *in vacuo* gave 8a as a white powder: ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.40-2.52 (5H,m,$2H_2$-,H_4-,$2H_5$-), 3.00-3.40 (3H,m, H_6-,OH), 3.77 (3H,s,OMe), 4.12-4.60 (2H,m,H_1-,H_3-), 5.02 (2H,br,NH_2), 5.95 (2H,br,NH_2), 6.76-7.48 (15H,m,Ph's,H_2); *Anal.* Calcd for $C_{30}H_{32}N_4 \cdot 0.5H_2O$: C,69.08; H,6.38; N,10.74. Found: C,69.14; H,6.09; N,10.54.

1-[(1R,3S,4R)-4-Hydroxymethyl-3-hydroxycyclopent-1-yl]-4-carbamoyl-5-aminoimidazole (8b)

The product 8a (2.3 g, 4.4 mmol) was dissolved in 80% AcOH/H_2O (50 ml) and the solution was stirred at 40°C for 7

hr. After evaporation, the residue was co-evaporated with toluene, EtOH and dissolved in EtOH (12 ml). The solution was added dropwise to a mixture (130 ml) of n-hexane and diethyl ether with stirring. The obtained oil was dissolved in water and applied to a column of C_{18} silica gel (10 g, ø 3.6×2.0 cm). The column was washed with H_2O before elution was effected with 5% acetone/H_2O. After evaporation of eluate, crystallization of the residue from EtOH gave 0.93 g (87%) of 8b: mp 162-163°C; UV_{max} (pH 7) 234 (sh) nm, 268 nm; UV_{max} (pH 1) 244 nm, 269 nm; UV_{max} (pH 13) 267.5nm; ^{1}H-NMR (100 MHz, Me_2SO-d_6) δ1.30-2.52 (5H,m,$2H_{2'}$, $4H_{4'}$,$2H_{5'}$), 3.50-3.60 (2H,m,$H_{6'}$), 3.96-4.12 (1H,m,$H_{3'}$), 4.40-4.70 (3H,m,$H_{1'}$,OH), 5.71 (2H,s,NH_2), 6.59 (2H,br,NH_2), 7.20 (1H,s,H_2); *Anal.* Calcd for $C_{10}H_{16}N_4O_3$: C,49.99; H, 6.71; N,23.32. Found: C,49.32; H,6.34; N,22.92; high resolution MS, m/z 240.1227, ER 0.6 mmu[$C_{10}H_{16}N_4O_3$].

9-[(1R,2S,3R,4R)-4-Monomethoxytrityloxymethyl-2,3-(dimethylmethylenedioxy)cyclopent-1-yl]-1-methoxymethylhypoxanthine (5)

The compound 4b (19.1 g, 33 mmol) was dissolved in 360 ml of anhydrous dioxane-DMF (3:1, v/v), treated with NaH (1.47 g of a 60% mineral oil dispersion, 36.7 mmol), and stirred for 1 hr at room temperature. Then methyl chloromethyl ether (3.2 ml, 35.7 mmol) was added at 0°C and the solution was stirred for 4 hr. After the same procedure of 7a, the syrup was dissolved in $CHCl_3$ and applied to a silica gel column (100 g) and eluted by $CHCl_3$-MeOH (100:1~10:1, v/v). The appropriate fractions were collected and the solvent was removed. The residue was rechromatographed on C_{18} silica gel column (ø 5.3×7.0 cm) with 55-90% aqueous acetone to remove the small amount of by-product. Evaporation of appropriate fractions gave 16.8 g (81%) of 5: mp 97-102°C; ^{1}H-NMR (90 MHz, $CDCl_3$) δ1.28 (3H,s,Me), 1.54 (3H, s,Me), 2.33-2.60 (3H,m,$H_{4'}$,$2H_{5'}$), 3.10-3.40 (2H,m,$H_{6'}$), 3.43 (3H,s,CH_2OCH_3), 3.79 (3H,s,Me), 4.47-5.07 (3H,m,$H_{1'}$, $H_{2'}$,$H_{3'}$), 5.46 (2H,s,CH_2OCH_3), 6.79-7.57 (14H,m,Ph's), 7.82 and 8.06 (1H each, s, purine ring protons).

1-[(1R,2S,3R,4R)-4-Monomethoxytrityloxymethyl-2,3-(dimethylmethylenedioxy)cyclopent-1-yl]-4-carbamoyl-5-aminoimidazole (6b)

A similar procedure of ring opening as with the synthesis of 8a was applied to 16.8 g (26.5 mmol) of 5 in 685 ml of EtOH and 137 ml of 5M-NaOH at reflux for 20 min. Evaporation of appropriate fractions on silica gel chromatography gave 7.9 g (53%) of colorless glassy product (6b): mp 107-112°C; UV_{max} (95% EtOH), 234 nm, 267 nm; ^{1}H-NMR (90 MHz,$CDCl_3$) δ 1.27 (3H,s,Me), 1.58 (3H,s,Me), 1.90-2.67 (3H,m,H_4-,$2H_5$-) 3.23-3.40 (2H,m,H_6-), 3.80 (3H,s,Me) 4.07-4.50 (3H,m,H_1-,H_2-H_3-), 5.54 (2H,br,NH_2), 6.80-7.57 (16H,m,Ph's, H_2,NH_2).

1-[(1R,2S,3R,4R)-4-Hydroxymethyl-2,3-dihydroxycyclopent-1-yl]-4-carbamoyl-5-aminoimidazole (6c) and its 2',3'-O-isopropylidene derivative (6a)

The compound 6b (7.9 g, 13.9 mmol) was treated with 80% AcOH (120 ml) at 40°C for 7 hr while shaking. After removal of the solvent, the residue was co-evaporated with water several times and partitioned between water and ether. The water phase was washed with ether, condensed and applied to a C_8 silica gel column (ø 5.2×4 cm). The 5% aqueous acetone eluate and the column washing water was collected, evaporated, and co-evaporated with EtOH twice. Crystallization from EtOH gave 0.34 g (9%) of 6c: mp 212-214°C; ^{1}H-NMR (100 MHz, Me_2SO-d_6) δ 4.56-5.00 (3H,m,OH), 5.69 (2H,br,NH_2), 6.63 (2H,br,NH_2), 7.22 (1H,s,H_2); *Anal.* Calcd for $C_{10}H_{16}N_4O_4 \cdot 0.2C_2H_5OH \cdot 0.5H_2O$: C,45.50; H,6.63; N, 20.42. Found: C,45.98; H,6.32; N,20.07.

After isolation of 6c, the 15% aqueous acetone eluate was collected, evaporated, and co-evaporated with EtOH. Crystallization from EtOH gave 2.27 g (55%) of 6a: mp 169-171°C (decomp.); ^{1}H-NMR (100 MHz, Me_2SO-d_6) δ 1.26 (3H,s, Me), 1.50 (3H,s,Me), 1.70-2.40 (3H,m,H_4-,$2H_5$-), 3.40-3.60 (2H,m,H_6-), 4.16-4.82 (4H,m,H_1-,H_2-,H_3-,OH), 5.72 (2H,br, NH_2), 6.65 (2H,br,NH_2), 7.26 (1H,s,H_2). *Anal.* Calcd for

$C_{13}H_{20}N_4O_4 \cdot 0.2H_2O$: C,52.06; H,6.86; N,18.68. Found: C, 52.18; H,6.60; N,18.63.

Cyclization Reactions

1-[(1R,3S,4R)-4-Hydroxymethyl-3-hydroxycyclopent-1-yl]-4-carbamoyl-5-(N-benzoyl-S-methylisothiocarbamoyl)aminoimidazole (10b)

A refluxing solution of 8b (0.82 g, 3.4 mmol) in dry acetone (25 ml) was added dropwise to a mixture of dry acetone (8 ml) and benzoylisothiocyanate (0.52 ml, 3.8 mmol) over 10 min. The reaction mixture was refluxed for an additional 50 min, the solvent evaporated *in vacuo*, the residue suspended in a mixture of acetone and $CHCl_3$ (15 ml, 2:1, v/v). The solution was poured into Et_2O. Filtration, washing and drying gave 1.4 g of powder (9b). The powder was dissolved in 0.2N-NaOH (35 ml), treated with dimethylsulfate (0.34 ml, 3.6 mmol). The solution was stirred at room temperature for 1 hr and added to AcOH on ice bath, adjusting pH 4-6. The product was extracted by BuOH (3×20 ml) from the reaction mixture and the organic layer was washed with H_2O (2×10 ml), evaporated, suspended in acetone/water and chromatographed on C_{18} silica gel (10 g, ϕ 3.6×2.0 cm) with H_2O and 30% acetone/H_2O. Evaporation of the appropriate fractions and drying gave 0.92 g (65%) of pale yellow glassy product (10b). This product had sufficient purity for subsequent reactions. Crystallization of this compound from H_2O gave 0.57 g (1.4 mmol) of 10b: mp 119-120°C; ^{1}H-NMR (100 MHz, Me_2SO-d_6) δ2.52 (3H,s,SMe), 7.34-7.94 (6H,m,Ph,H_2), 11.85 (1H,br,NH); *Anal.* Calcd for $C_{19}H_{23}N_5SO_4 \cdot 0.3H_2O$: C,53.96; H,5.62; N,16.56; S,7.58. Found: C,54.03; H,5.49; N,16.44; S,7.53.

1-[(1R,3S,4R)-4-Monomethoxytrityloxymethyl-3-hydroxycyclopent-1-yl]-4-carbamoyl-5-(N-benzoyl-S-methylisothiocarbamoyl)aminoimidazole (10a)

The compound 8a (0.88 g, 1.7 mmol) was treated with benzoylisothiocyanate (0.26 ml, 1.9 mmol) by the method described for the preparation of compound 9b. The reaction

mixture was concentrated to dryness, and the residue was dissolved in $CHCl_3$ and chromatographed on a silica gel (15 g, ø 3.6×3.4 cm) with $CHCl_3$/MeOH (50:1~30:1, v/v). Evaporation of the appropriate fractions gave pale yellow glass of 9a (0.87 g, 76%): ^{1}H-NMR (100 MHz, $CDCl_3$) δ 3.78 (3H,s, Me), 6.78-7.91 (20H,m,Ph's,H_2), 9.47 and 12.03 (1H each, br, NH).

The product 9a (0.84 g, 1.2 mmol) was added to a small amount of acetone and the resultant syrup was diluted with 0.2N-NaOH (12 ml) by sonification. The solution was added to dimethylsulfate (0.13 ml, 1.4 mmol), stirred at room temperature for 1 hr and the product was extracted by $CHCl_3$ (2×15 ml) from reaction mixture. The organic phase was washed with 0.1M-TEAB (pH 7.5) (3×15 ml), saturated NaCl/H_2O, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (15 g, ø 3.6×3.4 cm) with $CHCl_3$/MeOH (100:1~60:1, v/v). The obtained glass was dissolved in a small amount of CH_2Cl_2 and the solution was poured into n-hexane. Centrifugation and drying *in vacuo* over P_2O_5 gave a powder of 10a (0.40 g, 46%): ^{1}H-NMR (100 MHz, $CDCl_3$) δ 2.52 (3H,s,SMe), 3.79 (3H,s,OMe), 5.64 (1H, br,NH_2), 6.72-7.96 (20H,m,Ph's,H_2), 11.35 (1H,br,NH); *Anal.* Calcd for $C_{39}H_{39}N_5O_5S$: C,67.90; H,5.70; N,10.15. Found: C,67.45; H,5.45; N,9.89.

9-[(1R,3S,4R)-4-Hydroxymethyl-3-hydroxycyclopent-1-yl]-guanine (11b)

To the product 10b (0.42 g, 1 mmol) was added 6N-NaOH (10 ml, preheated above 100°C) rapidly and the mixture was refluxed for 1 hr on the oil bath (130°C) with vigorous stirring. After cooling, the solution was neutralized with dilute hydrochloric acid with stirring, and applied to a column of HP-20 resin (190 ml, ø 2.0×31 cm). The column was washed well with H_2O (500 ml) before elution was effected with 10% EtOH/H_2O. Concentration of the eluate gave crystals of 11b (174 mg, 65%): mp 246-248°C $[\alpha]_D^{25}$= +7.7° (c=0.5,DMF); UV_{max} (pH 7) 255 nm (sh); UV_{max} (pH 1) 257 nm, 282 nm; UV_{max} (pH 13) 256 nm (sh), 273 nm; ^{1}H-NMR (400 MHz,

D_2O) δ 1.752 (1H, dt, J=12.9, 9.9 Hz, H_5-), 2.207 (1H,m, H_4-), 2.29 (1H, J=4.0, 14.0, 8.9 Hz, H_2-), 2.33 (1H, J=7.0, 14.0, 8.9 Hz, H_2-) 2.551 (1H, dt like, J=12.9, 7.6 Hz, H_5-), 3.687 (1H, dd, J=11.2, 6.6 Hz, H_6-), 3.763 (1H, dd, J=11.2, 5.9 Hz, H_6-), 4.310 (1H, dt, J=6.8, 4.8 Hz, H_3-), 4.917 (1H, quintet like, J=8.9 Hz, H_1-), 7.913 (1H,s,H_8); *Anal.* Calcd for $C_{11}H_{15}N_5O_3 \cdot 0.5H_2O \cdot 0.1C_2H_5OH$: C,48.24; H, 6.00; N,25.11. Found: C,48.61; H,6.41; N,25.40; High resolution MS, m/z 265.1180, ER 0.6 mmu[$C_{11}H_{15}N_5O_3$].

9-[(1R,3S,4R)-4-Monomethoxytrityloxymethyl-3-hydroxycyclopent-1-yl]guanine (11a)

The compound 10a (0.36 g, 0.53 mmol) was treated with 6N-NaOH (18 ml) by the method described for the preparation of 11b. The product was extracted by $CHCl_3$ and the organic phase was washed with 0.1M-TEAB (30 ml, pH 7.5), sat. NaCl/H_2O (30 ml), dried ((Na_2SO_4)), and chromatographed on silica gel (8 g, ϕ 3.6×1.8 cm) with $CHCl_3$/MeOH (40:1~60:1, v/v). After evaporation, the glass was dissolved in acetone and poured into n-pentane. Centrifugation of precipitate, decanting of solvent, washing with n-pentane, and drying *in vacuo* over P_2O_5 gave 0.21 g (72%) of white powder (11a): ^{1}H-NMR (100 MHz, Me_2SO-d_6) δ 3.76 (3H,s,OMe), 6.37 (2H,br,NH_2), 6.82-7.46 (14H,m,Ph's), 7.68 (1H,s,H_8), 10.60 (1H,br,NH); *Anal.* Calcd for $C_{31}H_{31}N_5O_4 \cdot H_2O$: C,67.01; H, 5.99; N,12.60. Found: C,67.01; H,5.69; N,12.42.

1-[(1R,2S,3R,4R)-4-Hydroxymethyl-2,3-(dimethylmethylenedioxy)cyclopent-1-yl]-4-carbamoyl-5-(N-benzoyl-5-methylisothiocarbamoyl)aminoimidazole (14a)

The compound 6a (0.3 g, 1 mmol) was suspended in dry acetone (18 ml) and the solution was refluxed, added dropwise to a mixture of dry acetone (5 ml) and 0.15 ml (1.1 mmol) of benzoylisothiocyanate over 10 min period. The reaction mixture was refluxed for an additional 1 hr, the solvent evaporated *in vacuo*, and then the residue dissolved in a mixture of $CHCl_3$ and acetone (5 ml, 1:1, v/v). Precipitation from n-hexane (100 ml) gave a pale yellow powder

(13): UV_{max} (EtOH) 243 nm, 281 (sh) nm. The powder (13) was dissolved in 0.2N-NaOH (10 ml), treated with dimethyl sulfate (0.11 ml, 1.1 mmol) at room temperature for 1.5 hr while stirring. To adjust the pH to 4-5, addition of AcOH on ice bath gave an insoluble compound, which was extracted with $CHCl_3$ (2×10 ml) and the organic layer was washed with H_2O (3×20 ml), dried over Na_2SO_4, condensed and chromatographed on silica gel (11 g, ϕ 3.8×2.4 cm) with $CHCl_3$/MeOH (100:1~ 40:1). The appropriate fractions were evaporated, and the colorless glassy material was dissolved in CH_2Cl_2 (6 ml) and poured into n-hexane (100 ml) to give 14a as a white powder (0.32 g, 67%): mp 97-105°C; UV_{max} (EtOH) 239 nm, 321 (sh) nm; ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.30 (3H,s,OMe), 1.54 (3H,s,OMe), 2.58 (3H,s,SMe), 5.85 (1H,br,NH_2), 7.26-7.94 (6H,m,Ph,H_2); *Anal.* Calcd for $C_{22}H_{27}N_5O_5S\cdot0.5H_2O$: C,54.76; H,5.85; N,14.51. Found: C,54.75; H,5.40; N,14.35.

9-[(1R,2S,3R,4R)-4-Hydroxymethyl-2,3-(dimethylmethylene-dioxy)cyclopent-1-yl]guanine (15a)

To 14a (0.82 g, 1.75 mmol) was added 6N-NaOH (14 ml, preheated above 100°C) rapidly and the mixture was refluxed for 1 hr on the oil bath (130°C) with vigorous stirring. After cooling, the solution was neutralized with dilute hydrochloric acid with stirring, and applied to a column of C_{18} silica gel (10 g, ϕ 3.8×2.0 cm). The column was washed with a sufficient amount of H_2O and then eluted with 20% acetonitrile. Washing with $CHCl_3$ and concentration of the eluate gave crystals of 15a (0.41 g, 73%): mp 287-288°C; UV_{max} (H_2O) 254 nm, 274 (sh) nm; UV_{max} (pH 2) 256 nm, 281 nm: UV_{max} (pH 10) 258 (sh) nm, 270 nm: ^{1}H-NMR (100 MHz, Me_2SO-d_6) δ 1.26 (3H,s,Me), 1.51 (3H,s,Me), 1.84-2.40 (3H, m,H_4-,$2H_5$-), 3.31 (1H,br,OH), 3.53 (2H,d,H_6-), 4.46-5.04 (3H,m,H_1-,H_2-,H_3-), 6.63 (2H,br,NH_2), 7.86 (1H,s,H_8), 10.85 (1H,br,NH); *Anal.* Calcd for $C_{14}H_{19}N_5O_4\cdot0.8H_2O$: C,50.08; H,6.18; N,20.86. Found: C, 50.28; H,5.89; N,20.86.

9-[(1R,2S,3R,4R)-4-Hydroxymethyl-2,3-dihydroxycyclopent-1-yl]guanine (15b)

Compound 15a (150 mg, 0.46 mmol) was dissolved in 0.05N-HCl (20 ml) and heated at 70°C for 20 min. Neutrali-

zation of this solution with 1N-NaOH on the ice bath gave crystals of 15b (91 mg, 70%): mp 268-270°C (dec.); $[\alpha]_D^{25}$ =-31.4° (c=0.67, DMF); *Anal.* Calcd for $C_{11}H_{15}N_5O_4 \cdot 0.7H_2O$: C,44.96; H,5.62; N,23.83. Found; C,45.19; H,5.95; N,23.65.

9-[(1R,2S,3R,4R)-4-Hydroxymethyl-2,3-(dimethylmethylenedioxy)cyclopent-1-yl]-3-methylxanthine (16)

To a solution of 6a (1.20 g, 3.9 mmol) in dry acetone (60 ml) with refluxing was added dropwise a mixture of dry acetone (20 ml) and 0.6 ml (4.3 mmol) of benzoylisothiocyanate over 30 min period. The reaction mixture was refluxed for an additional 40 min and the solvent was evaporated *in vacuo*. The oily syrup was again dissolved in dry acetone (45 ml). To the solution was added methyl iodide (4.5 ml) and K_2CO_3 (4.5 g). The reaction mixture was shaken at room temperature for 2 hr, filtered to remove K_2CO_3, evaporated, mixed with $NaHCO_3$ soln. The products were extracted by $CHCl_3$ (2×50 ml) and the organic layer was washed with H_2O (2×50 ml), dried over Na_2SO_4, evaporated. The oily syrup was dissolved in $CHCl_3$, and chromatographed on silica gel column (30 g, ϕ 3.8×6.5 cm) with $CHCl_3$/MeOH (40:1~10:1, v/v). Appropriate fractions were combined, evaporated, suspended in aqueous acetone and applied to a C_{18} silica gel column (10 g, ϕ 3.8×2.0 cm). The eluate with 30% aqueous acetone was evaporated to give the crude products (0.70 g). They were dissolved in 6N-NaOH (14 ml, preheated about 100°C) rapidly and the mixture was refluxed for 1 hr on the oil bath (130°C) with vigorous stirring. The solution was neutralized with N-HCl and applied to a column of HP-20 resin (ϕ 2.8×34 cm). The column was washed well with H_2O (500 ml) before elution was effected with 10% EtOH, and then 20% EtOH. Concentration of the 20% EtOH eluate and recrystallization from EtOH gave 85 mg (0.26 mmol) of 16. The overall yield from 6a was about 7%. mp 275-277°C with previous darkening above 268°C; UV_{max} (pH 7) 240 nm, 269.5 nm; UV_{max} (pH 1) 240 nm, 269.5 nm; UV_{max} (pH 13) 241.5 (sh) nm, 248 nm, 270.5 nm; ^{1}H-NMR (400 MHz, D_2O) δ 1.381 (3H,s, Me), 1.621 (3H,s,Me), 2.234 (1H, q, J=12.1 Hz, H_5-), 2.468

(1H, d quintet like, J=12.0, 5.9 Hz, H_4-), 2.621 (1H,dt, J=12.5, 6.4 Hz,H_5-), 3.767 (2H,d, J=6.1 Hz, H_6-), 3.789 (3H,s,NMe), 4.758 (1H,dd, J=7.7, 5.3 Hz, H_3-), 4.882 (1H,t, J=7.1 Hz, H_2-), 5.181 (1H, dt, J=12.0, 6.2 Hz, H_1-), 8.010 (1H,s,H_8); *Anal.* Calcd for $C_{15}H_{20}N_4O_5 \cdot 0.5H_2O$: C,52.17; H, 6.13; N,16.22. Found: C,52.22; H,5.79; N,16.06; MS, m/z 336 (M), 321 (M-CH_3).

9-[(1R,3S,4R)-4-Hydroxymethyl-3-hydroxycyclopent-1-yl]-isoguanine (12b)

A solution of 10a (580 mg, 0.85 mmol) in EtOH (10 ml) was mixed with 0.1N-NaOH (50 ml) and was refluxed for 2 hr. To this solution subsequently was added 0.1N-NaOH (60 ml) and the mixture was further refluxed for 2 hr. The solution was neutralized with 1N-HCl and the insoluble product was extracted by $CHCl_3$. The organic phase was washed with saturated NaCl/H_2O and H_2O, and condensed to give a syrup. This syrup gradually turned into white crystals (200 mg, 43%) at 4°C: *Anal.* Calcd for $C_{31}H_{31}N_5O_4$: C,69.26; H,5.81; N,13.03. Found: C,68.80; H,5.86; N,12.60. However, the crystals were found to be a mixture of 12a and its isomer 11a (2:1) from ^{1}H-NMR data (each δ 7.77 and 7.68, H_8 proton, 100 MHz, Me_2SO-d_6). To this mixture (150 mg, 0.27 mmol) was added 80% AcOH (11 ml) and the solution was stirred at 45°C for 6 hr. After removal of the solvent, the residue was co-evaporated with water and partitioned between water and ether. The water phase was condensed and the residue was suspended in a small amount of EtOH. The insoluble compound was collected by filtration (56 mg, 76%). The small amount of this mixture (12b and 11b) was dissolved in water and purified on a Nucleosil C_{18} (Machery-NaGel Co.) column (ϕ 4.0×300 mm) using a Gilson's HPLC system apparatus. The desired peak was collected, evaporated and dried *in vacuo* over P_2O_5 to give the colorless glassy product (12b): UV_{max} (H_2O) 249 nm, 253 (sh) nm, 294 nm; UV_{max} (pH 2) 236 nm, 242 (sh) nm, 283 nm; UV_{max} (pH 10) 250 nm, 285 nm; High resolution MS, m/z 265.1165 ER -0.8 mmu [$C_{11}H_{15}N_5O_3$].

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