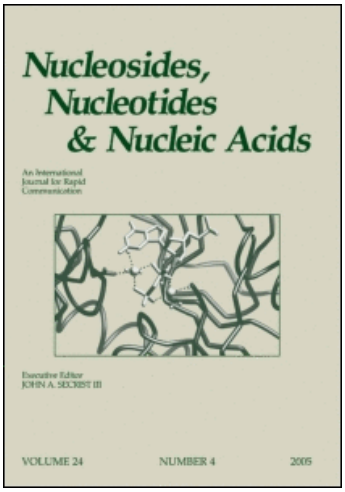


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Syntheses of 2",3"-Dideoxy-*L*-Glycero-Pentofuranosyl *C*-Nucleosides

Chang Soo Lee[a]; Jinfa Du[a]; Chung K. Chu[a]
[a] Department of Medicinal Chemistry College of Pharmacy, The University of Georgia, Athens, Georgia

To cite this Article Lee, Chang Soo , Du, Jinfa and Chu, Chung K.(1996) 'Syntheses of 2",3"-Dideoxy-*L*-Glycero-Pentofuranosyl *C*-Nucleosides', Nucleosides, Nucleotides and Nucleic Acids, 15: 6, 1223 — 1236
To link to this Article: DOI: 10.1080/07328319608007389
URL: http://dx.doi.org/10.1080/07328319608007389

NUCLEOSIDES & NUCLEOTIDES, 15(6), 1223–1236 (1996)

SYNTHESES OF 2',3'-DIDEOXY-*L*-GLYCERO-PENTOFURANOSYL *C*-NUCLEOSIDES

Chang Soo Lee, Jinfa Du and Chung K. Chu*

Department of Medicinal Chemistry
College of Pharmacy, The University of Georgia, Athens, Georgia 30602

Abstract: 2',3'-Dideoxy-*L*-*C*-nucleosides, 4-amino-8-(2,3-dideoxy-*L*-glyceropentofuranosyl)pyrazolo[1,5-a]-1,3,5-triazines (**9** and **10**), 4-amino-7-(2,3-dideoxy-*L*-glyceropentofuranosyl)-3H,5H-pyrrolo[3,2-d]pyrimidines (**17** and **18**), 7-(2,3-dideoxy-*L*-glyceropentofuranosyl)-4-oxo-3H,5H-pyrrolo[3,2-d]pyrimidines (**23** and **24**) and 2,4-diamino-5-(2,3-dideoxy-*L*-glyceropentofuranosyl)pyrimidines (**28** and **29**) have been synthesized from *L*-gulonic γ-lactone **1**.

Since the identification of human immunodeficiency virus (HIV) as the etiological agent of acquired immunodeficiency syndrome (AIDS), a significant amount of effort has been directed towards the discovery of synthetic as well as natural compounds which inhibit the replication of the virus.[1] Despite these intense efforts, for the most part only dideoxy nucleosides such as AZT, ddI, ddC and d4T are found to be clinically effective for the treatment of HIV infections.[2,3] Recently, a number of *L*-2',3'-dideoxy nucleosides, including 3'-modified nucleosides, have been synthesized as antiviral agents. Among these nucleosides, (-)-(2'*R*,5'*S*)-1-(2-hydroxymethyl-oxathiolan-5-yl)cytosine (3TC),[4] (-)-β-*L*-2',3'-dideoxy-5-fluoro-3'-thiacytidine (FTC),[5] β-*L*-2',3'-dideoxy-5-fluorocytidine (*L*-FddC)[6,7] and β-*L*-2'-fluoro-5-methylarabinofuranosyluracil (*L*-FMAU)[8] are the most interesting and promising *L*-nucleosides, that are currently undergoing preclinical and clinical trials as anti-HIV and anti-HBV agents.

C-Nucleosides are a unique class of compounds which contain a carbon-carbon bond between the carbohydrate and heterocyclic moieties instead of the carbon-nitrogen bond as in *N*-nucleosides. This isosteric replacement of the nitrogen with a carbon stabilizes the glycosyl bond, which may alter the biological profile including catabolism. Some of the *C*-nucleosides have shown very interesting antiviral and anticancer activities.[9] These include tiazofurin,[10-13] pyrazomycin[14,15] and pseudoisocytidine.[16] 2',3'-Dideoxy *C*-nucleosides, such as 2',3'-dideoxy-9-deazaadenosine[17] and 2',3'-dideoxy pseudoisocytidine[18], have already been synthesized. However, the reported procedures requiring the corresponding *C*-nucleosides as the starting material is not applicable for the synthesis of other 2',3'-

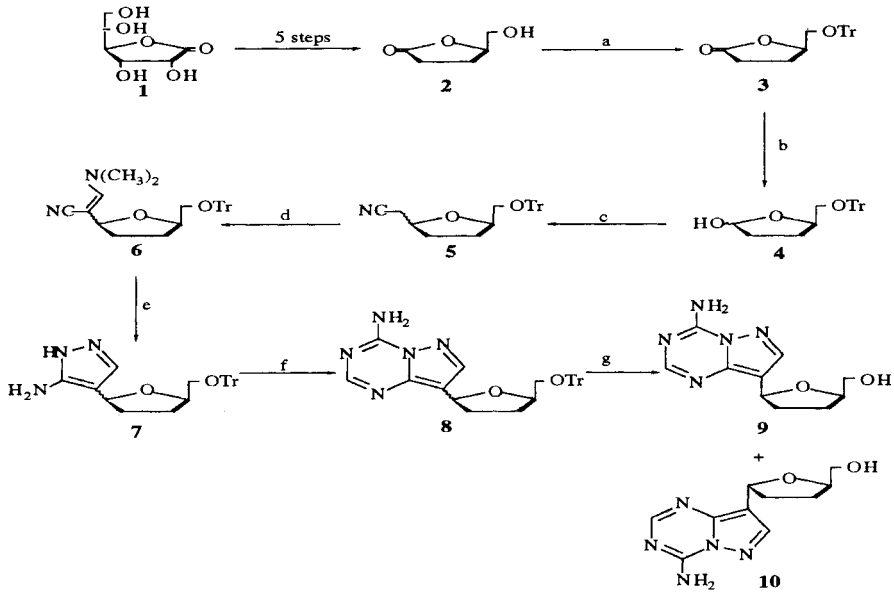
dideoxy *C*-nucleosides. Therefore, it was of interest to develop a versatile method that allows us to access various types of *L*-2',3'-dideoxy *C*-nucleosides. In this paper, we wish to report the syntheses of pyrimidine and purine 2',3'-dideoxy-*L*-*C*-nucleosides from *L*-gulonic γ-lactone **1**.

RESULTS AND DISCUSSION

The pyrazolo[1,5-a]-1,3,5-triazine *C*-nucleosides **9** and **10** have been synthesized from an acetonitrile derivative **5** (Scheme 1). γ-Lactone **2**, prepared from *L*-gulonic γ-lactone (**1**) in 5 steps,[19,20] was treated with trityl chloride in pyridine to give compound **3** in 95% yield. Reduction of **3** with DIBAL-H in CH_2Cl_2 gave γ-lactol **4** which was reacted with diethyl cyanomethyl phosphonate in 1,2-dimethoxyethane in the presence of NaH to yield the acetonitrile derivative **5** in 78% yield.[21] Compound **6**, prepared by the reaction of **5** with bis(dimethylamino)-*t*-butoxymethane in DMF, was cyclized with hydrazine to give the 3-aminopyrazole derivative **7** as an inseparable mixture of α- and β-isomers.[22] The aminopyrazole derivative **7** was condensed with methyl *N*-cyano-methanimidate in refluxing benzene to give an inseparable α- and β- mixture **8**.[22] The final nucleosides **9** (β) and **10** (α) were obtained in good yield by the removal of the trityl group in **8** with methanolic HCl followed by flash silica gel column chromatography. The structures of **9** and **10** were determined by ^{1}H NMR in which the upfield chemical shift of 4'-H (3.94 ppm) in **9** (β) was observed in comparison to that (4.10 ppm) in **10** (α).[6]

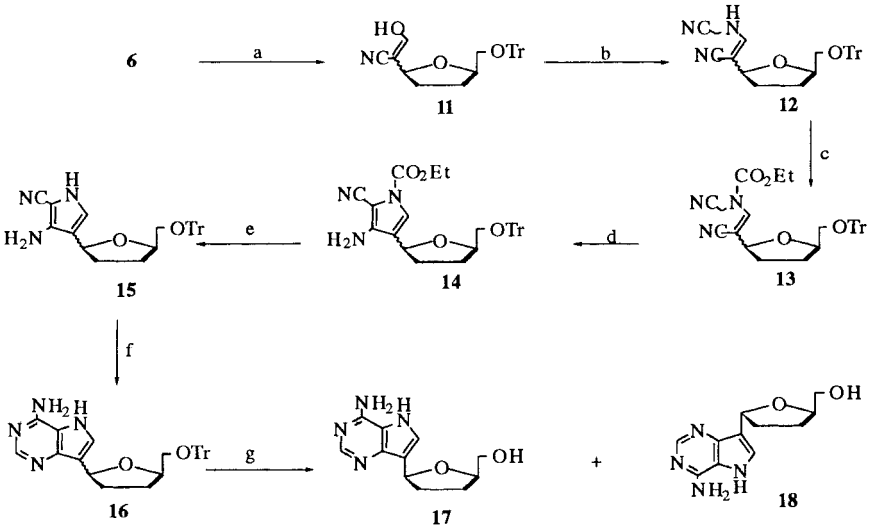
Pyrrolo[3,2-d]pyrimidine *C*-nucleosides (**17** and **18**) were synthesized as shown in Scheme 2.[23] Enamine **12** was obtained in 64% yield by hydrolysis of **6** with aqueous trifluoroacetic acid followed by the reaction with aminoacetonitrile hydrochloride in the presence of sodium acetate. *N*-Protection of the compound **12** with ethyl chloroformate followed by cyclization catalyzed by DBN gave the *N*-ethoxycarbonyl pyrrole derivative **14** in 98% yield. Compound **16** was obtained by the hydrolysis of ethoxycarbonyl group of **14** with sodium carbonate in methanol followed by the condensation with formamidine in boiling ethanol. The detritylation of **16** as described for **8** followed by flash column chromatography gave *C*-nucleosides **17** (β) and **18** (α). The structures were assigned based on the comparison of the ^{1}H NMR data with those of **9** and **10**, in which H-4' of the **17** (β) showed an upfield chemical shift (4.02 ppm) in comparison to that of the **18** (α, 4.11 ppm).

Hypoxanthine analogs **23** and **24** were also synthesized from intermediate **11** (Scheme 3).[24] Intermediate **20** was obtained by the reaction of **11** with ethyl glycinate



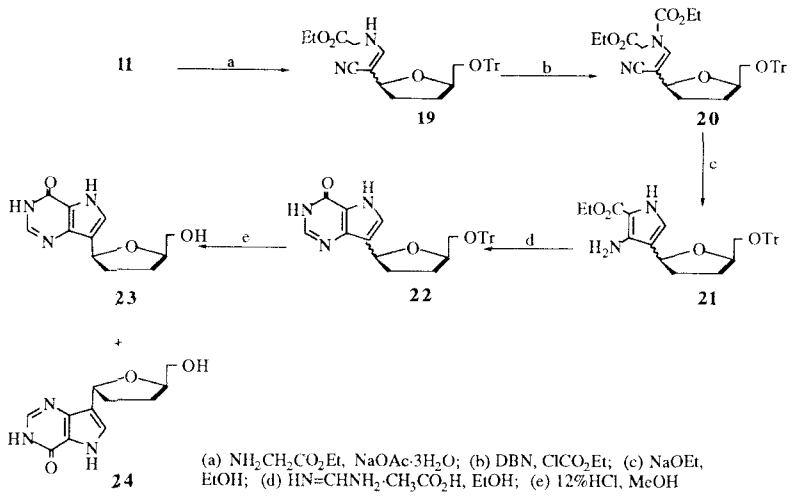
(a) TrCl, Py.; (b) DIBAL-H, CH_2Cl_2; (c) NaH, $NCCH_2PO(OCH_2CH_3)_2$, 1,2-dimethoxyethane; (d) $HC[N(CH_3)_2]_2Ot$-Bu, DMF; (e) NH_2NH_2, $NH_2NH_2 \cdot HCl$, CH_3OH, H_2O, CH_3CN; (f) $NCN{=}CHOCH_3$, benzene; (g) 12%HCl, MeOH

Scheme 1



(a) CF_3CO_2H, H_2O; (b) $NH_2CH_2CN \cdot HCl$, NaOAc; (c) DBN, $ClCO_2Et$; (d) DBN; (e) Na_2CO_3, MeOH; (f) $HN{=}CHNH_2 \cdot CH_3CO_2H$, EtOH; (g)12%HCl, MeOH;

Scheme 2

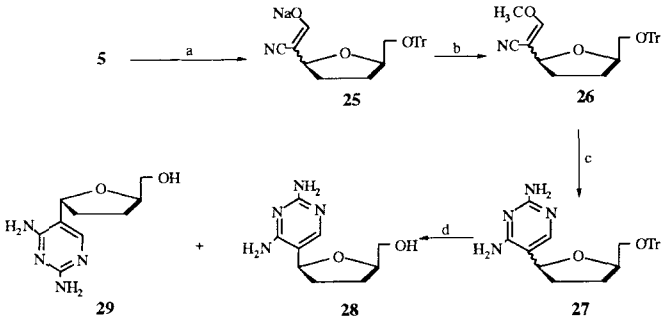


Scheme 3

hydrochloride in aqueous methanol in the presence of sodium acetate followed by the *N*-protection with ethyl chloroformate and DBN in CH_2Cl_2. Cyclization of **20** catalyzed by sodium ethoxide in ethanol followed by the condensation with formamidine in boiling ethanol gave the pyrrolo[3,2-d]pyrimidine derivative **22** as an α- and β- mixture. The final products **23** (β) and **24** (α) were obtained by detritylation of **22** followed by preparative TLC separation. The anomeric configurations of **23** and **24** were assigned based on the method as previously described above.

For the synthesis of 2,4-diamino-5-(2,3-dideoxy-*L*-glyceropentofuranosyl)pyrimidines (**28** and **29**), the intermediate **5** was formylated with ethyl formate in the presence of NaH followed by the treatment with methyl iodide in DMF to give **26** as an α- and β- mixture (Scheme 4).[21] The compound **26** was condensed with guanidine hydrochloride to give 2,4-diamino pyrimidine derivative **27**. The pyrimidine 2',3'-dideoxy-*L*-nucleosides **28** (β) and **29** (α) were obtained by the detritylation of **27** followed by preparative TLC separation. The anomeric configurations were also confirmed as described above (Table 1).

The results of 2D ROESY experiments supported the above stereochemical assignments for the nucleosides listed in Table 1. In 2D ROESY spectra, compound **9** (β) exhibited a strong correlation between signals of 1'-H (5.02 ppm) and 4'-H (3.94 ppm) while no correlation was observed between signals of 1'-H (5.12 ppm) and 4'-H (4.10 ppm) of **10**



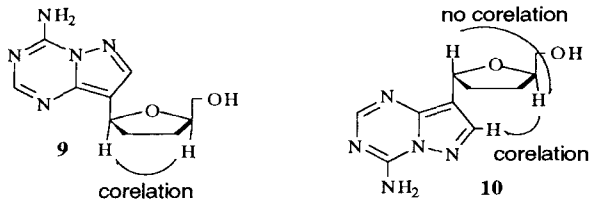
(a) NaH, HCO_2Et, ether; (b) CH_3I, DMF;
(c) $HN{=}C(NH_2)_2 \cdot HCl$, NaOEt, EtOH; (d) HCl, MeOH

Scheme 4

Table 1 Characteristic ^1H NMR Data of 4'-H

Compound	δ	Compound	δ
9	3.94	**10**	4.10
17	4.02	**18**	4.11
23	3.95	**24**	4.09
28	3.93	**29**	4.08

(α). However, a correlation between signals of 2-H (8.13 ppm) and 4'-H (4.10 ppm) of **10** (α) was observed.



Results of ROESY experiments

In summary, 2',3'-dideoxy-*L*-*C*-nucleosides of pyrazolo[1,5-a]-1,3,5-triazine, pyrrolo[3.2-d]pyrimidine, and pyrimidine have been synthesized from the common starting material *L*-γ-lactone **2**. The antiviral evaluation of the synthesized nucleosides is in progress.

EXPERIMENTAL SECTION

Melting points were determined on a Mel-temp II and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL FX 90Q fourier transform spectrometer for 90 MHz or a Bruker 250 AM for 250 MHz, 300 AC for 300 MHz or 400 AMX spectrometer for 400 MHz, with Me_4Si as internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br s (broad singlet). IR spectra were measured on a Nicolet 510P FT-IR Spectrometer. Optical rotations were performed on a Jasco DIP-370 Digital Polarimeter. TLC were performed on Uniplates (silica gel) purchased from Analtech Co. Column chromatography was performed using either silica gel 60 (220-440 mesh) for flash chromatography or silica gel G (TLC grade>440 mesh) for vacuum flash column chromatography. UV spectra were obtained on a Beckman DU-7 or a Beckman DU-650 Spectrophotometer. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. Dry 1,2-dichloroethane and methylene chloride were distilled from CaH_2. Dry tetrahydrofuran was distilled from Na/benzophenone.

2,3-Dideoxy-5-*O*-trityl-*L*-glyceropentanoic acid γ-lactone (3). A solution of the lactone **2**[19,20] (90.0 g, 0.78 mol) and trityl chloride (259 g, 0.93 mol) in pyridine (450 mL) was stirred for 24 h at 90 °C. The resulting mixture was concentrated under reduced pressure to give a solid which was redissolved in $CHCl_3$. The solution was washed with H_2O, dried ($MgSO_4$) and filtered. The filtrate was concentrated to dryness and the residue was triturated with ether to give **3** as a white solid (190 g, 95.0%). mp 143-144 °C, $[\alpha]^{25}_D$ -7.53° (c 0.17, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 1.98-2.76 (m, 4H, H-2, H-3), 3.14, 3.42 (2xm, 2H, H-5), 4.65 (m, 1H, H-4), 7.20-7.45 (m, 15H, Tr). Anal. Calcd for $C_{24}H_{22}O_3 \cdot 0.25H_2O$: C, 79.43; H, 6.25. Found: C, 79.75; H, 6.20.

2,3-Dideoxy-5-*O*-trityl-*L*-glyceropentanoic acid γ-lactol (4). To a solution of **3** (100 g, 0.28 mol) in dry CH_2Cl_2 (430 mL), DIBAL-H (1 M in hexanes, 462 mL, 462 mmol) was added dropwise, stirred under N_2 at -78 °C for 1.5 h and quenched with CH_3OH (400 mL). The reaction mixture was warmed to rt, brine was added and filtered. The organic layer was dried ($MgSO_4$) and concentrated to give an oil which was purified by silica gel column chromatography (hexanes:ethyl acetate, 1:1) to yield **4** as a syrup (98.0 g, 97.0%). ^{1}H NMR ($CDCl_3$) δ 1.64-2.15 (m, 4H, H-2, H-3), 3.08-3.30 (m, 2H, H-5), 3.34 (br s, 1H, OH, D_2O exchangeable), 4.25, 4.43 (2xm, 1H, H-4), 5.48, 5.59 (2xm, 1H, H-1), 7.19-7.47 (m, 15H, Tr). Anal. Calcd for $C_{24}H_{23}O_3 \cdot 0.25H_2O$: C, 79.21; H, 6.5. Found: C, 78.86; H, 6.87.

2,3-Dideoxy-5-*O*-trityl-*L*-glyceropentofuranosyl acetonitrile (5).[21] To a suspension of NaH (95% in oil, 19.4 g, 0.81 mol) in dry 1,2-dimethoxyethane (330 mL), diethyl cyanomethyl phosphonate (175 mL, 1.08 mol) was added dropwise at 0 °C. After evolution of H_2 had ceased, **4** (97.0 g, 0.27 mol) in 1,2-dimethoxyethane (120 mL) was

added and stirred at rt for 2.5 h. The resulting mixture was extracted with EtOAc, dried ($MgSO_4$) and filtered. The filtrate was concentrated to dryness and the residue was purified by silica gel column chromatography (hexane:ethyl acetate, 5:1) to give **5** as a white foam (83.0 g, 80.0%). ^{1}H NMR ($CDCl_3$) δ 1.71-2.23 (m, 4H, 2'-H, 3'-H), 2.56-2.67 (m, 2H, CH_2CN), 3.09-3.23 (m, 2H, H-5), 4.09-4.35 (m, 2H, H-1', H-4'), 7.19-7.48 (m, 15H, Tr). Anal. Calcd for $C_{26}H_{25}NO_2$: C, 81.44; H, 6.57; N; 3.65. Found: C, 81.28; H, 6.68; N, 3.65.

3-Dimethylamino-2-(2,3-dideoxy-5-*O*-trityl-*L*-glyceropentofuranosyl) acrylonitrile (6). To a solution of **5** (9.97 g, 0.026 mol) in dry DMF (50 mL), bis(dimethylamino)-*t*-butoxymethane (22 mL, 0.11 mol) was added at rt and stirred at 70 °C for 3.5 h under N_2. The resulting mixture was concentrated and the residue partitioned between $CHCl_3$ and H_2O. The organic layer was dried ($MgSO_4$) and filtered. The solvent was removed and the residue was purified by silica gel column chromatography (hexane:ethyl acetate, 4:1) to yield **6** as a syrup (8.10 g, 71.0%). ^{1}H NMR ($CDCl_3$) δ 1.78-2.17 (m, 4H, H-2', H-3'), 2.99, 3.05 (2xs, 6H, $2CH_3$), 3.00-3.30 (m, 2H, H-5'), 4.05-4.38 (m, 2H, H-1', H-4'), 6.46, 6.50 (2xs, 1H, CH), 7.17-7.48 (m, 15H, Tr). Anal. Calcd for $C_{29}H_{30}N_2O_2 \cdot 0.75H_2O$: C, 77.05; H, 7.02; N, 6.20. Found: C, 77.36; H, 6.76; N, 5.80.

3-Amino-4-(2,3-dideoxy-5-*O*-trityl-*L*-glyceropentofuranosyl)pyrazole (7).[22] A mixture of **6** (7.90 g, 0.02 mol), CH_3OH (40 mL), anhydrous hydrazine (14 mL, 0.42 mol), H_2O (4 mL) and hydrazine hydrochloride (1.78 g, 0.026 mol) was heated at 70 °C for 16 h. The resulting solution was evaporated in *vacuo* and the residue partitioned between CH_2Cl_2 and H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated to give a foam which was redissolved in CH_3CN (200 mL). The solution was heated at 80 °C for 21 h and concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$:CH_3OH, 50:1) to give **7** as a foam (1.40 g, 18.0%). ^{1}H NMR ($CDCl_3$) δ 1.80-2.40 (m, 4H, H-2', H-3'), 3.11-3.22 (m, 2H, H-5'), 4.02 (br s, 3H, NH, NH_2, D_2O exchangeable), 4.19, 4.34 (2xm, 1H, H-4'), 4.85, 4.97 (2xt, J=6.1, 8.0 Hz, 1H, H-1'), 7.17-7.49 (m, 16H, 2-H, Tr). Anal. Calcd for $C_{27}H_{27}N_3O_2 \cdot H_2O$: C, 73.12; H, 6.59; N, 9.47. Found: C, 73.09; H, 6.64; N, 9.20.

4-Amino-8-(2,3-dideoxy-5-*O*-trityl-*L*-glyceropentofuranosyl)pyrazolo [1,5-a]-1,3,5-triazine (8). To a solution of **7** (1.40 g, 3.29 mmol) in benzene (25 mL), methyl *N*-cyanomethanimidate (0.57 g, 6.72 mmol) was slowly added at rt, stirred at 74 °C for 17 h and concentrated to dryness. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate, 1:1) to yield **8** as a foam (0.90 g, 57.0%). ^{1}H NMR ($CDCl_3$) δ 1.77-2.40 (m, 4H, H-2', H-3'), 3.10-3.30 (m, 2H, H-5'), 4.30, 4.46 (2xm, 1H, H-4'), 5.26-5.38 (m, 1H, H-1'), 6.69 (br s, 2H, NH_2, D_2O exchangeable), 7.25-7.51 (m, 15H, Tr), 8.06, 8.10 (2xs, 1H, H-7), 8.14, 8.17 (2xs, 1H, H-2). Anal. Calcd for $C_{29}H_{27}N_5O_2 \cdot 1.65H_2O$: C, 68.67; H, 6.02; N, 13.80. Found: C, 69.02; H, 5.63; N, 13.34.

4-Amino-8-(2,3-dideoxy-β-*L*-glyceropentofuranosyl)pyrazolo[1,5-a]-1,3,5-triazine (9) and 4-amino-8-(2,3-dideoxy-α-*L*-glyceropentofuranosyl) pyrazolo[1,5-a]-1,3,5-triazine (10). A solution of **8** (0.43 g, 0.89 mmol) and 12% methanolic HCl (3 mL) in CH_3OH (3 mL) was stirred at rt for 2.5 min, neutralized with sat. $NaHCO_3$ solution and concentrated to dryness under reduced pressure. The residue was purified by flash column chromatography ($CHCl_3$: CH_3OH, 15:1) to give **9** (90 mg, 43.0%) and **10** (65 mg, 31.0%). β-isomer (**9**): mp 174-176 °C, $[\alpha]^{25}_D$ -16.3° (c 0.4, MeOH); UV (H_2O) λ_{max} 273.5 nm (pH 7), 273.5 nm (pH 11), 266.0 nm (pH 2); ^{1}H NMR (DMSO-d_6) δ 1.83-2.16 (m, 4H, H-2', H-3'), 3.43 (m, 2H, H-5'), 3.94 (m, 1H, H-4'), 4.79 (t, *J*=5.8 Hz, 1H, OH, D_2O exchangeable), 5.02 (t, *J*=7.0 Hz, 1H, H-1'), 8.03 (s, 1H, H-7), 8.17 (s, 1H, H-2), 8.37, 8.68 (2xs, 2H, NH_2, D_2O exchangeable). Anal. Calcd for $C_{10}H_{13}N_5O_2$: C, 51.06; H, 5.57; N, 29.77. Found: C, 50.81; H, 5.66; N, 29.51.

α-isomer (**10**): mp 152-154 °C, $[\alpha]^{25}_D$ 0.70° (c 0.5, MeOH); UV (H_2O-MeOH) λ_{max} 273.5 nm (pH 7), 273.5 nm (pH 11), 264.5 nm (pH 2); ^{1}H NMR (DMSO-d_6) δ 1.70-2.20 (m, 4H, H-2', H-3'), 3.38 (m, 2H, H-5'), 4.10 (m, 1H, H-4'), 4.67 (t, *J*=5.6 Hz, 1H, OH, D_2O exchangeable), 5.12 (t, *J*=7.0 Hz, 1H, H-1'), 8.03 (s, 1H, H-7), 8.13 (s, 1H, H-2), 8.32, 8.64 (2xs, 2H, NH_2, D_2O exchangeable). Anal. Calcd for $C_{10}H_{13}N_5O_2 \cdot 0.5H_2O$: C, 49.18; H, 5.77; N, 28.67. Found: C, 49.20; H, 5.83; N, 28.56.

***N*-[2-(2,3-dideoxy-5-*O*-trityl-*L*-glyceropentofuranosyl)-2-cyanovinyl] acetonitrile (12).** To a solution of **6** (13.3 g, 0.03 mol) in $CHCl_3$ (300 mL), trifluoroacetic acid (6.6 mL) in water (540 mL) was added and stirred vigorously at rt for 17 h. The organic layer was separated, dried ($MgSO_4$), filtered and concentrated to give **11** as a foam which was redissolved in MeOH (120 mL) and H_2O (7 mL). To the solution, aminoacetonitrile hydrochloride (3.70 g, 0.039 mol) and sodium acetate trihydrate (6.30 g, 0.046 mol) were added and stirred at rt for 27 h. The reaction mixture was concentrated and partitioned between $CHCl_3$ and H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate, 2:1) to give **12** as a syrup (8.40 g, 64.0%). ^{1}H NMR ($CDCl_3$) δ 1.85-2.11 (m, 4H, H-2', H-3'), 3.15 (m, 2H, H-5'), 3.70, 3.90 (2xm, 2H, CH_2N), 4.11 (m, 1H, H-4'), 4.38 (m, 1H, H-1'), 5.17 (br s, 1H, NH, D_2O exchangeable), 6.67, 6.75 (dd, *J*=12.7, 12.8 Hz, 1H, CH), 7.21-7.50 (m, 15H, Tr). Anal. Calcd for $C_{29}H_{27}N_3O_2 \cdot H_2O$: C, 74.50; H, 6.25; N, 8.99. Found: C, 74.35; H, 6.06; N, 8.65.

3-Amino-2-cyano-1-carbethoxy-4-(2,3-dideoxy-5-*O*-trityl-*L*-glycero-pentofuranosyl)-1H-pyrrole (14). To a solution of **12** (8.20 g, 0.018 mol) and 1,5-diazabicyclo[4.3.0] non-5-ene (4.5 mL, 0.036 mol) in CH_2Cl_2 (140 mL), ethyl chloroformate (2.9 mL, 0.030 mol) was added and stirred at 0 °C for 1h. Without isolation of resulting **13**, an additional portion of 1,5-diazabicyclo[4.3.0]non-5-ene (2.3 mL) was

added and stirred at rt for 19 h. The resulting mixture was washed with H_2O, dried ($MgSO_4$), filtered and concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate, 2:1) to yield **14** as a syrup (9.30 g, 98.0%). ^1H NMR ($CDCl_3$) δ 1.43 (t, J=6.8 Hz, 3H, CH_3), 1.80-2.23 (m, 4H, H-2', H-3'), 3.16 (m, 2H, H-5'), 4.27 (m, 1H, H-4'), 4.42 (m, 4H, OCH_2, NH_2, D_2O exchangeable), 4.80, 4.93 (2xt, J = 6.8, 7.0 Hz, 1H, H-1'), 7.11, 7.12 (2xs, 1H, CH), 7.21-7.48 (m, 15H, Tr). Anal. Calcd for $C_{32}H_{31}N_3O_4 \cdot 0.75H_2O$: C, 71.83; H, 6.12; N, 7.85. Found: C, 71.65; H, 5.93; N, 7.58.

3-Amino-2-cyano-4-(2,3-dideoxy-5-*O*-trityl-*L*-glyceropentofuranosyl)-1H-pyrrole (15). Compound **14** (9.10 g, 0.017 mol) and Na_2CO_3 (0.19 g, 0.0018 mol) were dissolved in MeOH (100 mL), stirred at rt for 1 h, concentrated and partitioned between H_2O and $CHCl_3$. The organic layer was dried ($MgSO_4$). The solvent was removed and the residue was chromatographed on silica gel column (hexanes:ethyl acetate, 2:1) to afford **15** as a white foam (5.80 g, 74.0%). ^1H NMR ($CDCl_3$) δ 1.79-2.21 (m, 4H, H-2', H-3'), 3.11-3.27 (m, 2H, H-5'), 4.03 (br s, 2H, NH_2, D_2O exchangeable), 4.20, 4.30 (2xm, 1H, H-4'), 4.80, 4.92 (2xm, 1H, H-1'), 6.50, 6.52 (dd, J= 3.3 Hz, 1H, H-5), 7.20-7.49 (m, 15H, Tr), 7.97, 8.07 (2xs, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{29}H_{27}N_3O_2$: C, 77.48; H, 6.05; N, 9.35. Found: C, 77.41; H, 6.08; N, 9.25.

4-Amino-7-(2,3-dideoxy-5-*O*-trityl-*L*-glyceropentofuranosyl)-3H,5H-pyrrolo[3,2-d]pyrimidine (16). A mixture of **15** (2.10 g, 4.67 mmol) and formamidine acetate (1.49 g, 3.34 mmol) in ethanol (60 mL) was heated at 80°C for 17 h and concentrated to dryness under reduced pressure. The resulting syrup was dissolved in $CHCl_3$, washed with H_2O, dried ($MgSO_4$) and filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 20:1) to afford **16** as a white foam (1.20 g, 54.0%). ^1H NMR ($CDCl_3$) δ 1.70-2.30 (m, 4H, H-2', H-3'), 2.80-3.30 (m, 2H, H-5'), 4.28, 4.50 (2xm, 1H, H-4'), 5.20 (m, 1H, H-1'), 6.89 (s, 2H, NH_2, D_2O exchangeable), 7.17-7.43 (m, 16H, H-6, Tr), 8.08 (s, 1H, H-2), 8.40 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{30}H_{28}N_4O_2 \cdot 2.1H_2O$: C, 70.00; H, 6.30; N, 10.89. Found: C, 69.76; H, 5.86; N, 10.57.

4-Amino-7-(2,3-dideoxy-β-*L*-glyceropentofuranosyl)-3H,5H-pyrrolo [3,2-d]pyrimidine (17) and 4-amino-7-(2,3-dideoxy-α-*L*-glyceropento-furanosyl)-3H,5H-pyrrolo[3,2-d]pyrimidine (18). A solution of **16** (0.50 g, 1.05 mmol) and 12% methanolic HCl (3.5 mL) in MeOH (4 mL) was stirred at rt for 3 min, neutralized with sat. $NaHCO_3$ solution and concentrated to dryness under reduced pressure. The residue was purified by flash column chromatography ($CHCl_3$: MeOH, 10:1) to afford **17** (100 mg, 41.0%) and **18** (87mg, 35.0%) as a solid. β-isomer (**17**): $[\alpha]^{25}_D$ -16.6° (c 0.2, MeOH); UV (H_2O-MeOH) λ_{max} 273.5 nm (pH 7), λ_{max} 273.5 nm (pH 11), λ_{max} 274 nm (pH 2); ^1H NMR (DMSO-d_6) δ 1.93-2.20 (m, 4H, H-2', H-3'), 3.35-3.58 (m, 2H, H-5'), 4.02 (m, 1H, H-4'), 4.98 (dd, J=5.5, 8.8 Hz, 1H, H-1'), 5.85 (br s, 1H, OH, D_2O exchangeable), 6.79 (s, 2H, NH_2, D_2O exchangeable), 7.45 (s, 1H,

H-6), 8.03 (s, 1H, H-2), 10.83 (s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.27; H, 6.08; N, 23.76.

α-isomer (**18**): $[\alpha]^{25}_D$ 9.93° (c 0.15, MeOH); UV (H_2O) λ_{max} 274 nm (pH 7), λ_{max} 273 nm (pH 11), λ_{max} 274 nm (pH 2); ^{1}H NMR (DMSO-d_6) δ 1.70-2.17 (m, 4H, H-2', H-3'), 3.29-3.50 (m, 2H, H-5'), 4.11 (m, 1H, H-4'), 4.68 (br s, 1H, OH, D_2O exchangeable), 5.13 (t, J=6.9 Hz, 1H, H-1'), 6.65 (s, 2H, NH_2, D_2O exchangeable), 7.42 (s, 1H, H-6), 8.05 (s, 1H, H-2), 10.8 (s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.33; H, 6.30; N, 23.61.

***N*-[2-(2,3-dideoxy-5-*O*-trityl-*L*-glyceropentofuranosyl)-2-cyanovinyl] glycine ethyl ester (19).** To a solution of **6** (7.70 g, 0.018 mol) in $CHCl_3$ (170 mL), trifluoroacetic acid (3.8 mL) in water (320 mL) was added and stirred vigorously at rt for 14 h. The organic layer was separated, dried ($MgSO_4$), filtered and concentrated to give crude **11** as a foam which was redissolved in MeOH (75 mL) and H_2O (4.5 mL). To the solution, glycine ethyl ester hydrochloride (3.10 g, 0.022 mol) and sodium acetate trihydrate (3.00 g, 0.022 mol) were added and stirred at rt for 22 h. The reaction mixture was concentrated and partitioned between $CHCl_3$ and H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate, 4:1) to give **19** as a syrup (3.80 g, 43.0%). ^{1}H NMR ($CDCl_3$) δ 1.20-1.34 (m, 3H, CH_3), 1.80-2.18 (m, 4H, H-2', H-3'), 3.07-3.14 (m, 2H, H-5'), 3.87, 4.40 (m, 5H, CH_2O, CH_2N, H-4'), 5.05 (m, 1H, H-1'), 6.63-6.72 (m, 1H, CH), 7.21-7.48 (m, 15H, Tr). Anal. Calcd for $C_{31}H_{32}N_2O_4 \cdot H_2O$: C, 72.36; H, 6.66; N, 5.44. Found: C, 72.27; H, 6.62; N, 5.50.

***N*-Carbethoxy-*N*-[2-(2,3-dideoxy-5-*O*-trityl-*L*-glyceropentofuranosyl)-2-cyanovinyl]glycine ethyl ester (20).** Ethyl chloroformate (0.67 mL, 6.80 mmol) was added to a solution of **19** (2.80 g, 5.64 mmol) and 1,5-diazabicyclo[4.3.0]non-5-ene (1.1 mL, 8.4 mmol) in CH_2Cl_2 (25 mL) at 0 °C and stirred at rt for 7 h. The reaction mixture was washed with water, dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on silica gel column (hexanes:ethyl acetate, 4:1) to give **20** as a syrup (2.80 g, 87.0%). ^{1}H NMR ($CDCl_3$) δ 1.23-1.38 (m, 3H, CH_3), 1.84-2.13 (m, 4H, H-2', H-3'), 3.10-3.35 (m, 2H, H-5'), 4.25-4.95 (m, 6H, H-4', H-1', 2xCH_2O), 7.08 (s, 1H, CH), 7.20-7.48 (m, 15H, Tr). Anal. Calcd for $C_{34}H_{36}N_2O_6 \cdot 0.75H_2O$: C, 70.15; H, 6.49; N, 4.81. Found: C, 69.80; H, 6.50; N, 4.81.

Ethyl 3-amino-4-(2,3-dideoxy-5-*O*-trityl-*L*-glyceropentofuranosyl)-1H-pyrrole-2-carboxylate (21). Compound **20** (2.80 g, 4.92 mmol) in ethanolic NaOEt (0.43 N, 13 mL) in EtOH (3 mL) was stirred at rt for 2 h then neutralized with 1N HCl and concentrated. The concentrate was redissolved in $CHCl_3$, dried ($MgSO_4$), filtered and the solvent was removed. The residue was chromatographed on silica gel column (hexanes:ethyl acetate, 4:1) to give **21** as a syrup (1.40 g, 57.0%). ^{1}H NMR ($CDCl_3$) δ 1.30-1.37 (m, 3H, CH_3), 1.79-2.17 (m, 4H, H-2', H-3'), 3.08-3.22 (m, 2H, H-5'), 4.27-4.32 (m, 3H, CH_2, H-4'), 4.82, 4.95 (2xm, 1H, H-1'), 6.60 (br s, 2H, NH_2, D_2O

exchangeable), 7.22-7.50 (m, 16H, H-6, Tr), 8.10 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{31}H_{32}N_2O_4 \cdot 0.5H_2O$: C, 73.64; H, 6.58; N, 5.54. Found: C, 73.82; H, 6.65; N, 5.35.

7-(2,3-Dideoxy-5-*O*-trityl-*L*-glyceropentofuranosyl)-4-oxo-3H,5H-pyrrolo[3,2-d]pyrimidine (22). A mixture of **21** (1.40 g, 2.82 mmol) and formamidine acetate (1.17 g, 11.28 mmol) in ethanol (28 mL) was heated at 80 °C for 2 days and concentrated. The concentrate was redissolved in $CHCl_3$, washed with H_2O, dried ($MgSO_4$) and filtered. The solvent was removed and the residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 10:1) to give **22** as a white foam (0.80 g, 59.0%). ^1H NMR ($CDCl_3$) δ 1.92-2.45 (m, 4H, H-2', H-3'), 3.09-3.30 (m, 2H, H-5'), 4.30, 4.46 (2xm, 1H, H-4'), 5.33 (m, 1H, H-1'), 7.13-7.50 (m, 16H, H-6, Tr), 8.09, 8.22 (2xs, 1H, H-2), 10.3, 10.5 (2xs, 1H, NH, D_2O exchangeable), 11.0, 11.1 (2xs, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{30}H_{27}N_3O_3 \cdot 0.25H_2O$: C, 74.75; H, 5.75; N, 8.72. Found: C, 74.79; H, 5.76; N, 8.67.

7-(2,3-Dideoxy-β-*L*-glyceropentofuranosyl)-4-oxo-3H,5H-pyrrolo[3,2-d]pyrimidine (23) and 7-(2,3-dideoxy-α-*L*-glyceropentofuranosyl)-4-oxo-3H,5H-pyrrolo[3,2-d]pyrimidine (24). A solution of **20** (0.30 g, 0.63 mmol) and 12% methanolic HCl (2 mL) in MeOH (2 mL) was stirred at rt for 2.5 min, neutralized with sat. $NaHCO_3$ solution and filtered. The solvent was removed and the residue was purified by preparative TLC ($CHCl_3$:MeOH, 5:1) to afford **23** (77 mg, 52.0%) and **24** (47 mg, 32.0%) as a solids. β-isomer (**23**): $[\alpha]^{25}_D$ -29.8° (c 0.33, MeOH); UV (H_2O-MeOH) λ_{max} 262.5 nm (pH 7), 267.0 nm (pH 11), 260.0 nm (pH 2); ^1H NMR (DMSO-d_6) δ 1.83-2.10 (m, 4H, H-2', H-3'), 3.34-3.46 (m, 2H, H-5'), 3.95 (m, 1H, H-4'), 5.0-4.95 (m, 2H, H-1', OH, D_2O exchangeable), 7.34 (s, 1H, H-6), 7.78 (s, 1H, H-2), 11.9 (br s, 2H, 2NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.17; H, 5.57; N, 17.86. Found: C, 56.03; H, 5.56; N, 17.74.

α-isomer (**24**): $[\alpha]^{25}_D$ -1.99° (c 0.6, MeOH); UV (H_2O-MeOH) λ_{max} 262.0 nm (pH 7), 267.0 nm (pH 11), 259.0 nm (pH 2); ^1H NMR (DMSO-d_6) δ 1.72-2.15 (m, 4H, H-2', H-3'), 3.31 (m, 2H, H-5'), 4.09 (m, 1H, H-4'), 4.65 (br s, 1H, OH, D_2O exchangeable), 5.09 (t, J=5.2 Hz, 1H, H-1'), 7.28 (s, 1H, H-6), 7.77 (s, 1H, H-2), 11.83 (br s, 1H, NH, D_2O exchangeable), 11.9 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.17; H, 5.57; N, 17.86. Found: C, 56.07; H, 5.61; N, 17.77.

2-Formyl-2-(2,3-dideoxy-5-*O*-trityl-*L*-glyceropentofuranosyl)acetonitrile sodium enolate (25). a solution of ethyl formate (26 mL, 0.32 mol) in dry ether (80 mL) was added dropwise to a mixture of **5** (20.0 g, 0.052 mol) and NaH (95% in oil, 1.92 g, 0.08 mol) in dry ether (8 mL) and absolute ethanol (1 mL) and stirred at rt for 21 h then concentrated to give a syrup which was used for the next reaction without further purification.

3-Methoxy-2-(2,3-dideoxy-5-*O*-trityl-*L*-glyceropentofuranosyl) acrylonitrile (26). To a solution of crude (**25**) in DMF (110 mL), methyl iodide (7.5

mL, 0.12 mol) was added dropwise within 5 min, stirred at rt for 22 h and then poured into ice-water. The aqueous solution was extracted with $CHCl_3$. Extracts were combined and dried ($MgSO_4$), filtered and concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate, 5:1) to give **26** as a syrup (5.40 g, 24.0%). ^{1}H NMR ($CDCl_3$) δ 1.79-2.20 (m, 4H, H-2', H-3'), 3.09-3.30 (m, 2H, H-5'), 3.78, 3.81 (2xs, 3H, CH_3), 4.10, 4.35 (2xm, 1H, H-4'), 4.79, 4.93 (2xt, J=6.3 Hz, 1H, H-1'), 6.77, 6.78 (2xs, 1H, CH), 7.13-7.50 (m, 15H, Tr); Anal. Calcd for $C_{28}H_{27}NO_3 \cdot 0.25H_2O$: C, 78.21; H, 6.44; N, 3.26. Found: C, 78.21; H, 6.62; N, 3.22.

2,4-Diamino-5-(2,3-dideoxy-5-*O*-trityl-*L*-glyceropentofuranosyl) pyrimidine (27). A mixture of **26** (5.30 g, 0.01 mol) and guanidine hydrochloride (1.97 g, 0.02 mol) in ethanolic NaOEt (60 mL, 0.75 N) was refluxed for 23 h. The reaction mixture was concentrated to 30 mL, neutralized with 1N HCl and concentrated to give a solid which was redissolved in ether. The solution was washed with water, dried ($MgSO_4$) and filtered. The solvent was removed and the residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 50:1) to afford **27** as a solid (0.63 g, 11.0%). ^{1}H NMR ($CDCl_3$) δ 1.80-2.25 (m, 4H, H-2', H-3'), 3.10-3.44 (m, 2H, H-5'), 4.15-4.35 (m, 1H, H-4'), 4.64, 4.76 (2xt, J=8.7 Hz, 1H, H-1'), 4.92, 5.60 (2xs, 4H, $2NH_2$, D_2O exchangeable), 7.20-7.43 (m, 15H, Tr), 7.66, 7.68 (2xs, 1H, H-6); Anal. Calcd for $C_{28}H_{28}N_4O_2 \cdot 0.5H_2O$: C, 72.87; H, 6.33; N, 12.14. Found: C, 72.68; H, 6.33; N, 12.08.

2,4-Diamino-5-(2,3-dideoxy-β-*L*-glyceropentofuranosyl)pyrimidine (28) and 2,4-diamino-5-(2,3-dideoxy-α-*L*-glyceropentofuranosyl)pyrimidine (29). A solution of **27** (0.20 g, 0.45 mmol) and 12% methanolic hydrogen chloride (1.5 mL) in MeOH (1.5 mL) was stirred at rt for 2 min, neutralized with sat. $NaHCO_3$ solution and concentrated to dryness under reduced pressure. The residue was purified by preparative TLC ($CHCl_3$:MeOH, 7:1, twice eluted) to give **28** (15 mg, 16.0%) and **29** (35 mg, 37.0%) as solids. β-isomer (**28**): $[\alpha]^{25}_D$ -11.6 °C (c 0.25, MeOH); UV (H_2O-MeOH) λ_{max} 275.5 nm (pH 7), 284 nm (pH 11), 269.5 nm (pH 2); ^{1}H NMR (DMSO-d_6) δ 1.84-1.90 (m, 4H, H-2', H-3'), 3.38-3.52 (m, 2H, H-5'), 3.93 (m, 1H, H-4'), 4.53 (t, J=7.4 Hz, 1H, H-1'), 5.00 (br s, 1H, OH, D_2O exchangeable), 5.82, 6.30 (2xs, 4H, $2NH_2$, D_2O exchangeable), 7.60 (s, 1H, H-6). Anal. Calcd for $C_9H_{14}N_4O_2 \cdot 0.7H_2O$: C, 48.50; H, 6.96; N, 25.10. Found: C, 48.91; H, 6.89; N, 24.48.

α-isomer (**29**): $[\alpha]^{25}_D$ -3.68 °C (c 0.35, MeOH); UV (H_2O) λ_{max} 277.5 nm (pH 7), 285.0 nm (pH 11), 270.2 nm (pH 2); ^{1}H NMR (DMSO-d_6) δ 1.65-2.14 (m, 4H, H-2', H-3'), 3.50 (m, 2H, H-5'), 4.08 (m, 1H, H-4'), 4.66 (t, J=5.2 Hz, 1H, H-1'), 5.81, 6.07 (2xs, 4H, $2NH_2$, D_2O exchangeable), 7.61 (s, 1H, H-6). Anal. Calcd for: $C_9H_{14}N_4O_2 \cdot 0.7H_2O$: C, 48.50; H, 6.96; N, 25.10. Found: C, 49.01; H, 6.94: N, 24.73.

ACKNOWLEDGMENT

This research was supported by the U. S. Public Health Service Research Grants AI 32351 and AI 33655 from the National Institute of Health, and Research Center for New Drug Development, College of Pharmacy, Seoul National University.

REFERENCES

1. De Clercq, E. *J. Med. Chem.* **1995**, *38*, 2491.
2. Nasr, M.; Litterst, C.; McGown, J. *Antiviral Res.* **1990**, *14*, 125.
3. Nasr, M.; Cradock, J.; Johnston, M. I. *AIDS Res. Human Retrovirus* **1992**, 8, 135.
4. Belleau, B.; Dixit, D.; Nguyen-Ga, N.; Kraus, J. L. *International Conference on AIDS*, Montreal, Canada, June 4-9, 1990, paper no. T.C.O.I; Coates, B. A. V.; Cammack, N.; Jenkinson, H. J.; Mutton, I. M.; Pearson, B. A.; Storer, R.; Cameron, J. M.; Penn, C. R. *Antimicrob. Agents Chemother.* **1992**, *36*, 202; Schinazi, R. F.; Chu, C. K.; Peck, A.; McMillan, A.; Mathis, R.; Cannon, D.; Jeong, L. S.; Beach, J. W.; Choi, B. G.; Yeola, S.; Liotta, D. C. *Antimicrob. Agents Chemother.* **1992**, *36*, 672.
5. Furman, P. A.; Davis, M.; Liotta, D. C.; Paff, M.; Frick, L. W.; Nelson, D. J.; Dornsife, J. E.; Wurster, J. A.; Fyfe, J. A.; Tuttle, J. V.; Miller, W. H.; Condreay, L.; Avereet, D. R.; Schinazi, R. F.; Painter, G. R. *Antimicrob. Agents Chemother.* **1992**, *36*, 2686.
6. Chu, C. K.; El-Kabbani, F. M.; Thompson, B. B. *Nucleoside & Nucleotides* **1984**, *3*, 1; Lin, T.-S.; Luo, M.-Z.; Liu, M.-C.; Pai, S. B.; Dutschman, G. E.; Cheng, Y.-C. *J. Med. Chem.* **1994**, *37*, 798.
7. Gosselin, G.; Schinazi, R. F.; Sommadossi, J.-P.; Mathe, C.; Bergogne, M.-C.; Aubertin, A.-M.; Kirn, A.; Imbach, J.-L. *Antimicrob. Agents Chemother.* **1994**, 38, 1292.
8. Chu, C. K.; Ma, T.; Shanmuganathan, K.; Wang, C.; Xiang, Y.; Pai, S. B.; Yao, G.-Q.; Sommadossi, J.-P.; Cheng, Y.-C. *Antimicrob. Agents Chemother.* **1995**, *39*, 979.
9. Watanabe, K. A. In *Chemistry of Nucleosides and Nucleotides* Vol. 3, Townsend, L. B. Ed., Plenum, New York, **1994**, p 421.
10. Srivastava, P. C.; Pickering, M. V.; Allen, L. B.; Streeter, D. G.; Campbell, M. T.; Witkowski, J. T.; Sidwell, R. W. and Robins, R. K. *J. Med. Chem.* **1977**, *20*, 256.
11. Robins, R. K.; Srivastava, P. C.; Narayanam, V. L.; Plowman, J.; Paull, K. D. *J. Med. Chem.* **1982**, *25*, 107.
12. Srivastava, P. G.; Robins, R. K. *J. Med. Chem.* **1983**, *26*, 445.

13. Streeter, P. G.; Robins, R. K. *Biochem. Biophys. Res. Commun.* **1983**, *115*, 544.
14. Sweeney, M. J.; Davis, F. A.; Gutowski, G. E.; Hamill, R. L.; Hoffman, D. H.; Poore, G. A. *Cancer Res.* **1973**, *33*, 2619.
15. Cadman, C. E.; Dix, D. E.; Handschumacher, R. E. *Cancer Res.* **1987**, *38*, 682.
16. Chu, C. K.; Wempen, I.; Watanabe, K. A.; Fox, J. J. *J. Org. Chem.* **1976**, *41*, 2793; Burchenall, J. H.; Ciovacco, K.; Kalaher, K.; O'Toole, T.; Kiefner, R.; Dowling, M. D.; Chu, C. K.; Watanabe, K. A.; Wempen, I.; Fox, J. J. *Cancer Res.* **1976**, *36*, 1520.
17. Tam, S.; Holman, M.; Klein, R. S.; Mitsuya, M.; Broder, S. *Nucleoside & Nucleotides* **1989**, *8*, 1109; Ciszewski, L.; Lipka, P.; Ren, W.-Y.; Watanabe, K. A. *Nucleoside & Nucleotides* **1993**, *12*, 487.
18. Doboszewski, B.; Chu, C. K.; Van Halbeek, H. *J. Org. Chem.* **1988**, *53*, 2777.
19. Hubschwerlin, C. *Synthesis* **1986**, 962.
20. Beach, J. W.; Kim, H. O.; Jeong, L. K.; Nampalli, S.; Islam, Q.; Ahn, S. K.; Babu, J. R.; Chu, C. K. *J. Org. Chem.* **1992**, *57*, 3887.
21. Chu, C. K.; Reichman, U.; Watanabe, K. A.; Fox, J. J. *J. Org. Chem.* **1977**, *42*, 711.
22. Tam, S. Y.-K.; Klein, R. S.; Wempen, I. Fox, J. J. *J. Org. Chem.* **1979**, *44*, 4547.
23. Lim, M.-I.; Klein, R. S. *Tetrahedron Lett.* **1981**, *22*, 25.
24. Lim, M.-I.; Ren, W.-Y.; Otter, B. A.; Klein, R. S. *J. Org. Chem.* **1983**, *48*, 780.

Received November 7, 1995
Accepted February 21, 1996