Tetrahedron Vol. 42, No. 21, pp. 5869 to 5878, 1986
Printed in Great Britain.

0040-4020/86 $3.00+.00

TOTAL SYNTHESIS OF 2'-DEOXYTOYOCAMYCIN, 2'-DEOXYSANGIVAMYCIN AND RELATED 7-β-D-ARABINOFURANOSYLPYRROLO[2,3-d]PYRIMIDINES VIA RING CLOSURE OF PYRROLE PRECURSORS PREPARED BY THE STEREOSPECIFIC SODIUM SALT GLYCOSYLATION PROCEDURE

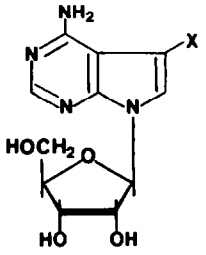
Kandasamy Ramasamy, Roland K. Robins, and Ganapathi R. Revankar*

Nucleic Acid Research Institute, 3300 Hyland Avenue, Costa Mesa, California 92626, and Department of Chemistry, Brigham Young University, Provo, Utah 84602, U. S. A.

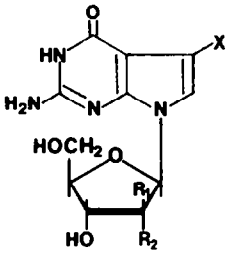
(*Received in USA* 21 *July* 1986)

ABSTRACT - A stereospecific high-yield glycosylation of a fully aromatic pyrrole, 2-bromo-(or ethylthio)-5-ethoxymethyleneamino-pyrrole-3,4-dicarbonitrile(14a and 14b) has been accomplished for the first time. Treatment of the sodium salt of 14a or 14b with 1-chloro-2-deoxy-3,5-di-O-p-toluoyl-α-D-erythro-pentofuranose(5) gave exclusively the corresponding blocked nucleosides with β-anomeric configuration (15a and 15b),which on ring closure and further functional group transformation provided the total synthesis of 2'-deoxytoyocamycin (3a) and 2'-deoxysangivamycin (3b). Similar glycosylation of the sodium salt of 14a with 1-chloro-2,3,5-tri-O-benzyl-α-D-arabinofuranose (8) furnished the corresponding blocked nucleoside (17), which on ring closure, debromination/debenzylation gave 4-amino-7-β-D-arabinofuranosylpyrrolo[2,3-d]pyrimidine-5-carboxamide (21b). The synthetic utility of this glycosylation procedure for other saturated pyrroles, pyrrole-3-carbonitrile (11) and diethyl 3,4-pyrroledicarboxylate (4) has been demonstrated.

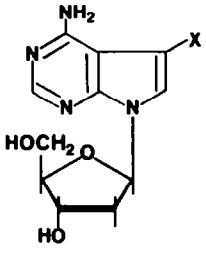
The naturally occurring cytotoxic[1,2] nucleoside antibiotic tubercidin (1a) is a structural analog of adenosine and closely related to pyrrolo[2,3-d]pyrimidine ribonucleosides toyocamycin (1b) and sangivamycin (1c), which also exhibit significant antitumor properties.[2-6] The recent isolation of nucleoside antibiotics related to 7-deazaguanosine from natural sources, e.g. nucleoside Q,[7-10] nucleoside preQ$_0$ (2a),[11,12] cadeguomycin (2b)[13-17] and kanagawamicin (2c)[18] has stimulated renewed interest in the synthesis and biological evaluation of the nucleoside derivatives of pyrrolo[2,3-d]pyrimidine ring system. From a biochemical viewpoint, these pyrrolo[2,3-d]pyrimidine nucleosides present potential advantages, since tubercidin is neither deaminated by adenosine deaminase[19] nor subject to glycosidic cleavage by purine nucleoside phosphorylase.[20] Unlike tubercidin (1a), sangivamycin (1c) is active *in vivo* against L1210 and P388 leukemias and Lewis lung carcinoma.[2]



1a, X = H
b, X = CN
c, X = $CONH_2$



2a, X = CN; R_1 = H; R_2 = OH
b, X = COOH; R_1 = H; R_2 = OH
c, X = $COOCH_3$; R_1 = NH_2; R_2 = H



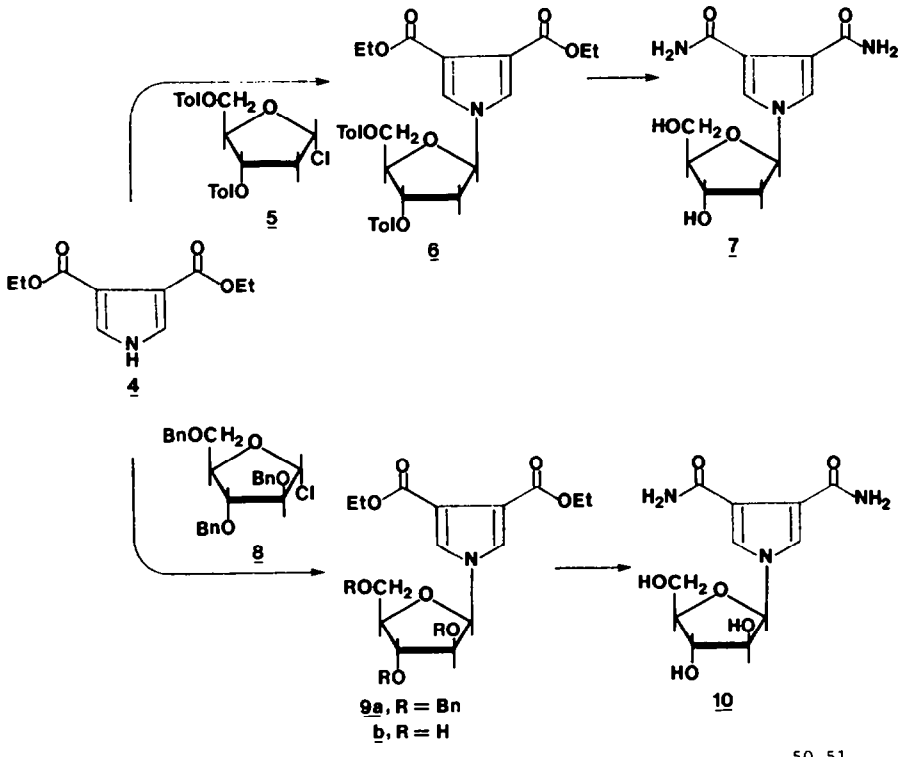
3a, X = CN
b, X = $CONH_2$

Derivatives of 2'-deoxyadenosine are of considerable current interest due to the potent antitumor effects of 2-halo-2'-deoxyadenosine.[21-23] It has recently been found[23] that 2-chloro-2'-deoxyadenosine, given on a frequent schedule, results in 60% survivors of mice injected with L1210 leukemia. These observations provide a good rationale for the synthesis of 2'-deoxytoyocamycin (3a), 2'-deoxysangivamycin (3b) and related 7-β-D-arabinofuranosyl-pyrrolo[2,3-d]pyrimidines (21) to obtain sufficient quantities for further studies of these potential chemotherapeutic agents. We now report a total synthesis of these nucleosides *via* ring closure of pyrrole nucleoside precursors.

The stereospecific synthesis of 2'-deoxyribofuranosyl nucleosides with β-anomeric configuration has been a part of our ongoing research program. Prior glycosylation procedures introducing the 2-deoxy-β-D-ribofuranosyl (2-deoxy-β-D-erythro-pentofuranosyl) moiety into an azole heterocycle reported from our laboratory[24-27] and by others[28-31] invariably suffered from the need to separate regioisomers and anomers at some stage of the synthetic sequence. In only one instance the β anomer of the 2'-deoxyribonucleoside has been claimed exclusively in 40% yield.[32] In view of these difficulties, a four-step deoxygenation procedure using phenoxythiocarbonylation[33-35] or imidazolylthiocarbonylation[36,37] of the 2'-hydroxy group of the corresponding 3',5'-diprotected β-D-ribonucleoside has been developed to provide the requisite 2'-deoxynucleoside. These latter procedures, however, require the availability of the preformed ribonucleoside. Although the synthesis of a number of analogs of 2'-deoxyadenosine by an enzymatic procedure has been reported,[38] this approach is not generally applicable to the pyrrolo[2,3-d]pyrimidine ring system.[39] We have recently employed a sodium salt glycosylation procedure[40-45] for the synthesis of several ribo and 2'-deoxyribofuranosyl derivatives of certain heterocyclic ring systems. Use of this stereospecific, single-phase sodium salt glycosylation procedure for the synthesis of pyrrole nucleosides has now been found to be remarkably successful. Further ring annulation of certain of these pyrrole nucleosides provided a route to the synthesis of 3a, 3b and 21b.

Literature search revealed that only a few pyrrole N-nucleosides have been reported[46-48] using partially hydrogenated pyrroles in the glycosylation reaction employing the "indoline-indole" method.[49] Subsequent photodehydrogenation of Δ^3-pyrroline nucleoside intermediates gave the pyrrole nucleosides. However, our synthetic pathway involves the direct attachment of a glycon moiety to a preformed fully aromatic pyrrole derivative.

Scheme I

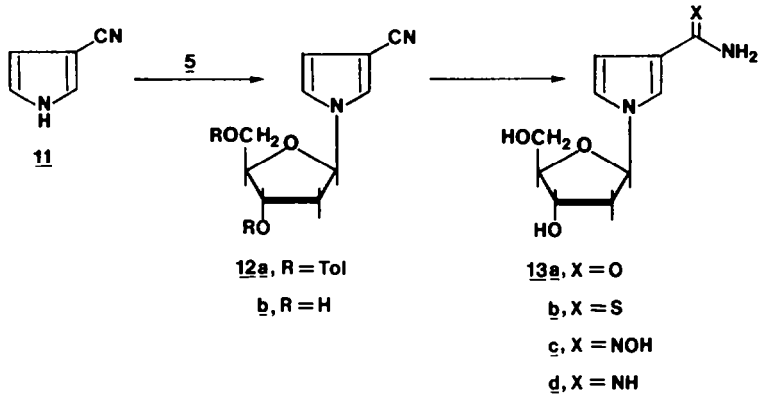


In the present work we elected to use diethyl pyrrole-3,4-dicarboxylate[50,51] (4) as one of the aglycons for glycosylation studies. The sodium salt of 4, produced in situ by NaH in anhydrous CH_3CN, was treated with 1-chloro-2-deoxy-3,5-di-O-p-toluoyl-α-D-erythro-pentofuranose[52] (5) at ambient temperature. A clean reaction was observed, and the desired diethyl 1-(2-deoxy-3,5-di-O-p-toluoyl-β-D-erythro-pentofuranosyl)pyrrole-3,4-dicarboxylate (6) was isolated in 70% yield (Scheme I). No formation of the α-anomer was detected. When 6 was

treated with MeOH/NH_3 (saturated at 0°C) at 100-110°C for two weeks, deprotection of the glycon moiety with concomitant ammonolysis of the ester functions to amide groups occurred to give 1-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrole-3,4-dicarboxamide (7) in 37% yield.

The preparation of the β-D-arabinofuranosyl derivatives of 4 was also accomplished in a manner similar to that of 6. Glycosylation of the sodium salt of 4 with 1-chloro-2,3,5-tri-O-benzyl-α-D-arabinofuranose[53] (8) in CH_3CN at ambient temperature and purification of the reaction product by flash chromatography on silica gel gave a 69% yield of diethyl 1-(2,3,5-tri-O-benzyl-β-D-arabinofuranosyl)pyrrole-3,4-dicarboxylate (9a). Debenzylation of 9a with $Pd(OH)_2$ in EtOH in the presence of cyclohexene (as hydrogen source) at reflux temperature readily gave diethyl 1-β-D-arabinofuranosylpyrrole-3,4-dicarboxylate (9b) in 75% yield. Ammonolysis of 9b with MeOH/NH_3 at 100-110°C for two weeks provided 1-β-D-arabinofuranosylpyrrole-3,4-dicarboxamide (10), which was isolated in 52% yield. The synthesis of these pyrrole nucleosides represents the first report of a direct attachment of a glycon moiety to a fully aromatic preformed pyrrole.

Scheme II

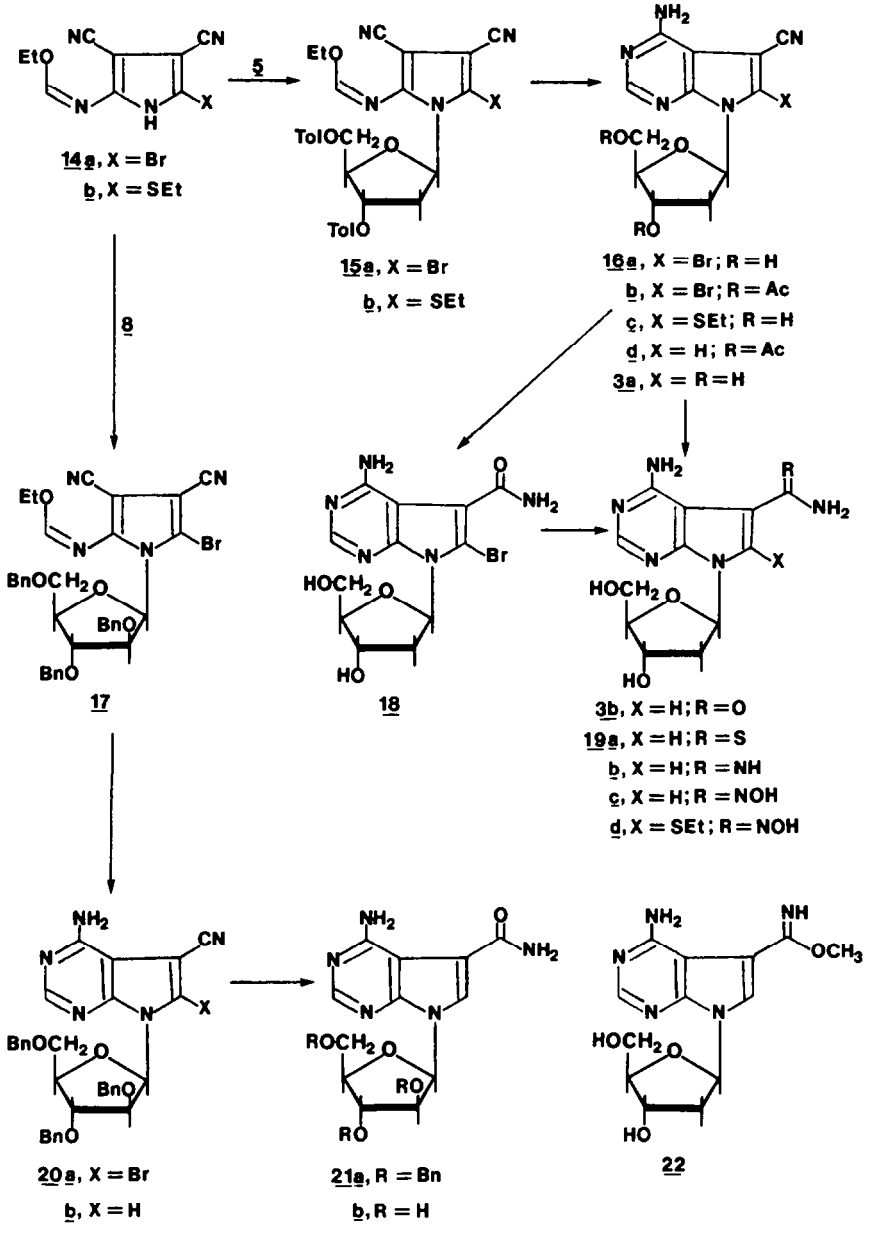


The other heterocycle that was employed for glycosylation studies was pyrrole-3-carbonitrile[54] (11). Compound 11 was chosen since brunfelsamidine, a novel convulsant isolated recently from the roots and bark of Brunfelsiagrandiflora is identified as pyrrole-3-carboxamidine.[55] Reaction of the protected halogenose 5 with the sodium salt of 11 gave a 62% yield of 1-(2-deoxy-3,5-di-O-p-toluoyl-β-D-erythro-pentofuranosyl)pyrrole-3-carbonitrile (12a) (Scheme II). As in the case of 6, no formation of the α-anomer of 12a in this reaction was observed. Deprotection of the blocking groups of the glycon moiety of 12a was accomplished by the treatment with MeOH/NH_3 at room temperature to yield 1-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrole-3-carbonitrile (12b), in which the nitrile function was available for further transformation reactions. The presence of the nitrile function in 12b was evident as confirmed by the IR spectrum, which revealed a sharp absorption band at 2215 cm^{-1}. Treatment of 12b with NH_4OH/H_2O_2 solution, and purification of the reaction product by chromatography on silica gel furnished 1-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrole-3-carboxamide (13a) in good yield. Reaction of 12b with H_2S in pyridine containing Et_3N at room temperature gave the corresponding 3-thiocarboxamide derivative (13b) in 67% yield. When 12b was allowed to react with free NH_2OH in EtOH at reflux temperature, 1-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrole-3-carboxamidoxime (13c) was formed in almost quantitative yield, which on further catalytic hydrogenation in the presence of Pd/C at 50 psi for 2 days, furnished an 80% yield of the 2'-deoxyribofuranosyl derivative of brunfelsamidine (13d).

The anomeric configuration of the isolated pyrrole-2'-deoxyribonucleosides (7 and 12b) was assigned as β by ^1H NMR, where the characteristic triplet for the anomeric proton was observed at δ5.94-6.15 with a peak width of 13.20 Hz. This pattern is similar to that observed for the anomeric proton of other 2'-deoxy-β-ribonucleosides.[25,43] Since the starting halosugar 5 has the α-configuration[56] in the solid state, the exclusive formation of the blocked 2'-deoxy-β-D-ribonucleosides in this study is believed to be due to a direct Walden

inversion (S_N2) at the C_1 carbon by the anionic heterocyclic nitrogen. The anomeric configuration of 10 was assigned as β on the basis of $J_{1',2'}$ coupling constant (4.80 Hz) observed for the anomeric proton (δ 5.74) in the ^1H NMR spectrum, which is within the region of 3.5-8.0 Hz expected for a vicinal, cis arrangement of the C_1' and C_2' protons.[57]

Scheme III



For the synthesis of the target pyrrolo[2,3-d]pyrimidine nucleosides (3a, 3b and 21b), 2-amino-5-bromopyrrole-3,4-dicarbonitrile[58] served as a useful starting material. The protection of the amino group was effected in 90% yield by the treatment of the aminopyrrole with diethoxymethylacetate in CH_3CN at reflux temperature to give 2-ethoxymethyleneamino-5-bromopyrrole-3,4-dicarbonitrile (14a) (Scheme III). Coupling of 14a with 5 in CH_3CN furnished a 75% yield of 2-ethoxymethyleneamino-5-bromo-1-(2-deoxy-3,5-di-O-p-toluoyl-β-D-erythro-pentofuranosyl)pyrrole-3,4-dicarbonitrile (15a), which cleanly cyclized to 4-amino-6-bromo-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carbonitrile (16a) on treatment with MeOH/NH_3 at room temperature. Selective acetylation of 16a with Ac_2O in pyridine gave a near quantitative yield of 4-amino-6-bromo-7-(2-deoxy-3,5-di-O-acetyl-β-D-erythro-pento-

furanosyl)pyrrolo[2,3-d]pyrimidine-5-carbonitrile (16b). Reductive debromination[59] of 16b was smoothly accomplished with N,O-bis(trimethylsilyl)acetamide (BSA) in the presence of "naked" fluoride ion in dry CH_3CN, and deacetylation of the resultant debrominated product (16d) with $MeOH/NH_3$ gave the desired 2'-deoxytoyocamycin (3a). A small amount (<10%) of the MeOH addition product presumably 2'-deoxytubercidin-5-methylformimidate (22) was also isolated from this reaction mixture. Compound 3a was found to be identical with 2'-deoxytoyocamycin previously reported.[34] Treatment of 3a with NH_4OH/H_2O_2 in MeOH/dioxane afforded 2'-deoxysangivamycin (3b) in 75% yield. A similar treatment of 16a with NH_4OH/H_2O_2 gave an excellent yield of 6-bromo-2'-deoxysangivamycin (18). Catalytic (Pd/C) hydrogenation of 18 under hydrogen atmosphere at 40 psi furnished yet another route to 3b, which as before was found to be identical with 2'-deoxysangivamycin previously prepared by deoxygenation procedure.[34]

It is of considerable interest that thiosangivamycin (4-amino-7-β-D-ribofuranosylpyrrolo [2,3-d]pyrimidine-5-thiocarboxamide), reported earlier from our laboratory,[60] exhibited a T/C of 175 against L1210 leukemia.[2] Thiosangivamycin has also shown considerable activity against the MX-1 human mammarycarcinoma xenograft.[2] However, 4-amino-7-β-D-ribofuranosylpyrrolo-[2,3-d]pyrimidine-5-carboxamidoxime,[60] at 3.12 mg/kg/day on 1x9 daily dosage treatment schedule exhibited a T/C of 204 against L1210 leukemia[2]. This carboxamidoxime has also shown activity against colon 26 and colon 38 carcinoma. In view of such antitumor activity, we have now prepared the corresponding 2'-deoxy derivatives. Treatment of 3a with H_2S in pyridine at room temperature gave 2'-deoxythiosangivamycin [4-amino-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine-5-thiocarboxamide],19a in 62% yield. Similarly, when 3a was allowed to react with free NH_2OH in EtOH at reflux temperature, 4-amino-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carboxamidoxime (19c) was formed and was isolated in 89% yield. Treatment of 3a with liquid NH_3 and NH_4Cl at elevated temperature and pressure gave the corresponding 5-carboxamidine derivative (19b), which was isolated as the hydrochloride salt.

The glycosylation studies were further extended to 2-ethoxymethyleneamino-5-ethylthio-pyrrole-3,4-dicarbonitrile (14b), which in turn was obtained by the treatment of 2-amino-5-ethylthiopyrrole-3,4-dicarbonitrile[58] with diethoxymethylacetate. Condensation of the sodium salt of 14b with 5 in CH_3CN gave the corresponding glycosyl derivative 15b, which readily cyclized to 6-ethylthio-2'-deoxytoyocamycin (16c) when treated with $MeOH/NH_3$. The isolated yield of 16c from 15b was greater than 90%. Subsequent treatment of 16c with NH_2OH in EtOH at reflux temperature resulted in the isolation of 4-amino-6-ethylthio-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carboxamidoxime (19d).

The versatile starting material (14a) that was available for glycosylation studies was also employed to obtain the arabinosyl derivatives. Thus, treatment of 14a (as the sodium salt) with 8 gave the corresponding benzyl blocked nucleoside 17, which was readily ring closed in the presence of $MeOH/NH_3$ to yield 4-amino-6-bromo-7-(2,3,5-tri-O-benzyl-β-D-arabino-furanosyl)pyrrolo[2,3-d]pyrimidine-5-carbonitrile (20a). As in the case of 16b, reductive debromination of 20a with BSA in the presence of "naked" fluoride ion gave 20b, which on oxidative hydration by the treatment of NH_4OH/H_2O_2 furnished 4-amino-7-(2,3,5-tri-O-benzyl-β-D-arabinofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carboxamide (21a). Debenzylation of 21a with $Pd(OH)_2$ in EtOH in the presence of cyclohexene at reflux temperature gave 4-amino-7-β-D--arabinofuranosylpyrrolo[2,3-d]pyrimidine-5-carboxamide[61] (21b) in greater than 94% yield. This nucleoside was found to be identical to 21b reported recently.[61]

Thus, the stereospecific attachment of 2-deoxy-β-D-ribofuranosyl and β-D-arabinofuranosyl moieties via the sodium salt of a preformed fully aromatic pyrrole and subsequent ring closure constitutes a direct route to the synthesis of 2'-deoxyribofuranosyl or arabinofuranosyl nucleosides of pyrrolo[2,3-d]pyrimidine ring system.

EXPERIMENTAL

Melting points were taken on Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^1H NMR) spectra were determined at 300 MHz with IBM NR/300 FTNMR spectrometer. The chemical shift values are expressed in δ values (parts per

million) relative to tetramethylsilane as an internal standard. Infrared spectra (IR in KBr) were obtained on a Beckman Acculab 2 spectrophotometer and ultraviolet spectra (UV; sh = shoulder) were recorded on a Cary Model 15 spectrophotometer. Elemental analyses were done by Robertson Laboratory, Florham Park, NJ. E. Merck silica gel (230-400 mesh) was used for flash column chromatography. Evaporations were carried out under reduced pressure with the bath temperature below 30°C.

Diethyl 1-(2-deoxy-3,5-di-O-p-toluoyl-β-D-erythro-pentofuranosyl)pyrrole-3,4-dicarboxylate (6). To a solution of diethyl pyrrole-3,4-dicarboxylate[51] (4, 1.60g, 7.6mmol) in dry CH_3CN (25ml) was added NaH (60% in oil, 0.40g, 10mmol) and the mixture was stirred at room temperature under a nitrogen atmosphere for 30 min. 1-Chloro-2-deoxy-3,5-di-O-p-toluoyl-α-D-erythro--pentofuranose[52] (5, 3.90g, 10mmol) was added portionwise with stirring . The reaction mixture was stirred at room temperature for 0.5h, at 50°C for 1h, and then it was filtered to remove a small amount of insoluble material. Evaporation of the filtrate gave an oily residue, which was purified by flash chromatography using hexane:acetone (7:3) as the eluent to yield 3.0g(70%) of 6 as foam. IR: ν 1715 (C=O)cm^{-1}; UV: λ max (EtOH) 240nm (ε43,000); ^1H NMR ($CDCl_3$): δ 1.26 (s, 6, $2CH_2CH_3$), 2.41 (2s, 6, $2CH_3$), 4.25 (q, 4, $2CH_2CH_3$), 6.0 (t, 1, J=7.0 Hz, $C_1'H$), 7.22-7.94 (m, 10, $2Ph+C_2H+C_5H$). Anal. Calcd for $C_{31}H_{33}NO_9$ (563.60): C, 66.06; H, 5.90; N, 2.48. Found: C, 66.03; H, 5.92; N, 2.59.

1-(2-Deoxy-β-D-erythro-pentofuranosyl)pyrrole-3,4-dicarboxamide (7). A solution of 6 (2.80g, 5mmol) in MeOH/NH_3 (saturated at 0°C, 50ml) was heated in a steel bomb at 100-110°C for 2 weeks, and the mixture was evaporated to dryness. The residue was purified by flash chromatography using $CHCl_3$:MeOH (8:2) as the eluent and crystallized from EtOH/H_2O to yield 0.50g (37%) of 7; mp 176-178°C. IR: ν 1650(C=O), 3200-3380 (NH_2,OH) cm^{-1}; UV: λ max (pH1) 256nm (ε11,000); (pH7) 252nm (ε10,700); (pH11) 251nm (ε10,700): ^1H NMR (Me_2SO-d_6):δ 6.16 (t, 1, J=6.0 Hz, $C_1'H$), 7.40 (s, 2, $CONH_2$), 7.89 (s, 2, C_2H+C_5H), 9.15 (s, 2, $CONH_2$). Anal. Calcd for $C_{11}H_{15}N_3O_5$ (269.25): C,49.07; H, 5.61; N, 15.60. Found: C,49.03; H, 5.80; N, 15.42.

Diethyl 1-(2,3,5-tri-O-benzyl-β-D-arabinofuranosyl)pyrrole-3,4-dicarboxylate (9a). In the same manner as for 6, the title compound was prepared by using 4 (4.22g, 20mmol), NaH (60% in oil, 1.0g, 25mmol), CH_3CN (150ml) and 1-chloro-2,3,5-tri-O-benzyl-α-D-arabinofuranose[53] (8,8.8g,20 mmol). After stirring the reaction mixture overnight, the product was purified by flash chromatography using hexane:EtOAc (7:3) as the eluent to yield 8.5g (69%) of 9a as oil; IR: ν 1725 (C=O) cm^{-1}; UV: λ max (EtOH) 250nm (ε 7400); ^1H NMR ($CDCl_3$): δ 1.31 (t, 6, $2CH_2CH_3$), 4.27 (q, 4, $2CH_2CH_3$), 5.71 (d, 1, J=4.5 Hz, $C_1'H$),7.02-7.44(m, 17, $3Ph+C_2H+C_5H$). Anal. Calcd for $C_{36}H_{39}NO_8$ (613.70): C, 70.45; H, 6.41; N, 2.28. Found: C, 70.60; H, 6.50; N, 2.11.

Diethyl 1-β-D-arabinofuranosylpyrrole-3,4-dicarboxylate (9b). A mixture of 9a (8.30g, 13.5 mmol),cyclohexene (30ml) and $Pd(OH)_2$ (2.50g) in EtOH (200ml) was heated under reflux for 12h. The cooled reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was purified by flash chromatography using CH_2Cl_2:acetone (8:2) as the eluent to yield 3.50g (75.4%) of 9b as amorphous foam; IR: ν 1720(C=O)cm^{-1}; UV: λ max (EtOH) 249nm (ε9000); ^1H NMR (Me_2SO-d_6): δ 1.24 (t, 6, $2CH_2CH_3$), 4.16 (q, 4, $2CH_2CH_3$), 5.82 (d, 1, J=4.8 Hz, $C_1'H$),7.58 (s, 2, C_2H+C_5H). Anal. Calcd for $C_{15}H_{21}NO_8$ (343.33): C,52.47; H,6.16; N,4.08. Found: C,52.29; H,6.21; N,3.83.

1-β-D-Arabinofuranosylpyrrole-3,4-dicarboxamide (10). Ammonolysis of 9b (3.50g, 10.2mmol) with MeOH/NH_3(100ml) at 100-110°C for two weeks in the same manner as described for 7 gave the title compound in 51.6% (1.50g) yield as foam; IR: ν 1650(C=O), 3300-3400(NH_2,OH)cm^{-1}; UV: λ max (pH1) 256nm (ε9800); (pH7) 249.5nm (ε8000);(pH11) 249nm (ε8700); ^1H NMR (Me_2SO-d_6):δ 5.74 (d, 1, J=4.8Hz, $C_1'H$), 7.09 (s, 2, $CONH_2$), 7.57 (s, 2, C_2H+C_5H), 8.91 (s, 2, $CONH_2$) Anal. Calcd for $C_{11}H_{15}N_3O_6$ (285.25): C,46.31; H,5.29; N,14.72. Found: C,46.31; H,5.30; N,14.63.

1-(2-Deoxy-3,5-di-O-p-toluoyl-β-D-erythro-pentofuranosyl)pyrrole-3-carbonitrile (12a). In the same manner as for 6, reaction of the sodium salt of pyrrole-3-carbonitrile[54] (11, 0.50g, 5.4mmol and 60% NaH in oil, 0.24g, 6mmol) with 5 (2.30g, 6mmol) in CH_3CN (50ml) gave 1.50g (62.1%) of crystalline (from acetone/hexane) 12a; mp 121-123°C; IR: ν 2210(CN), 1710(C=O)cm^{-1}; UV: λ max (EtOH) 238nm (ε39,700); ^1H NMR (Me_2SO-d_6): δ 2.38 (s, 6, $2CH_3$), 6.21 (t, 1, J=7.0 Hz, $C_1'H$), 6.52 and 7.19 (2m, 2, C_4H and C_5H), 7.34-7.81 (m, 9, $2Ph+C_2H$). Anal. Calcd for $C_{26}H_{24}N_2O_5$ (444.48): C, 70.25; H, 5.44; N, 6.30. Found: C, 70.42; H, 5.54; N, 6.26.

1-(2-Deoxy-β-D-erythro-pentofuranosyl)pyrrole-3-carbonitrile (12b). A solution of 12a (0.90g, 2mmol) in MeOH/NH_3 (50ml) was stirred at room temperature in a pressure bottle for 12h and then evaporated to dryness. The residue was purified by flash chromatography using CH_2Cl_2:MeOH (8:2) as the eluent and crystallized from $CHCl_3$ to yield 0.40g (94.9%) of 12b; mp 42-45°C; IR: ν 2215 (CN)cm^{-1}; UV: λ max (EtOH) 224nm (ε10,300); ^1H NMR (Me_2SO-d_6): δ 5.94 (t, 1, J=7.2 Hz, $C_1'H$), 6.47 (m, 1, C_4H), 7.16 and 7.83 (2m, 2, C_5H and C_2H). Anal. Calcd for $C_{10}H_{12}N_2O_3$ (208.21): C, 57.68; H, 5.81; N, 13.45. Found: C, 57.93; H, 5.66; N, 13.28.

1-(2-Deoxy-β-D-erythro-pentofuranosyl)pyrrole-3-carboxamide (13a). A solution of 12b (0.42g, 2mmol) in dioxane/MeOH (5 and 50ml each) was adjusted to pH9 with NH_4OH and treated with H_2O_2 (30%, 5ml). The mixture was stirred at room temperature for 12h and evaporated to dryness. The residue was purified by flash chromatography using $CHCl_3$:MeOH (8:2) as the eluent to yield 0.30g (66%) of 13a as foam; IR: ν 1650(C=O), 3200-3400 (NH_2,OH)cm^{-1}; UV: λ max (pH1) 232nm (ε10,700); (pH7) 231nm (ε10,700); (pH11) 230nm (ε11,400); ^1H NMR (Me_2SO-d_6): δ 5.87(t, 1, J=7.2 Hz, $C_1'H$), 6.44 (m, 1, C_4H), 6.75 and 7.32 (2br s, 2, $CONH_2$), 6.94 and 7.49 (2m, 2, C_5H and C_2H). Anal. Calcd for $C_{10}H_{14}N_2O_4$ (226.21): C, 53.09; H, 6.24; N, 12.38.

Found: C, 52.81; H, 6.26; N, 12.31.

1-(2-Deoxy-β-D-erythro-pentofuranosyl)pyrrole-3-thiocarboxamide (13b). A solution of 12b (0.90g, 4.3mmol) in anhydrous pyridine (50ml) containing Et_3N (5ml) was saturated with H_2S at room temperature. After stirring the reaction mixture in a sealed vessel at room temperature for 12h, it was evaporated to dryness. The residue was purified by flash chromatography using CH_2Cl_2:MeOH (8:2) as the eluent to give 0.70g (66.8%) of 13b as foam; IR: ν 1260 (C=S), 3200-3400 (NH_2,OH)cm^{-1}; UV: λ max (pH1) 257nm (ε8900), 304 (8800); (pH7) 257nm (ε8600), 304 (8600); (pH11) 257nm (ε9000), 302 (7200); ^1H NMR (Me_2SO-d_6): δ 5.88 (t, 1, J=7.0 Hz, $C_1'H$), 6.58 (m, 1, C_4H), 6.97 and 7.62 (2m, 2, C_5H and C_2H), 8.81 and 9.0 (2br s, 2, $CSNH_2$). Anal. Calcd for $C_{10}H_{14}N_2O_3S$ (242.21): C, 49.58; H, 5.83; N, 11.56; S, 13.21. Found: C, 49.33; H, 5.88; N, 11.31; S, 13.02.

1-(2-Deoxy-β-D-erythro-pentofuranosyl)pyrrole-3-carboxamidoxime (13c). A solution of 12b (0.50g, 2.4mmol) and free NH_2OH (0.50g) in absolute EtOH (25ml) was heated under reflux for 3h and allowed to stir at room temperature overnight. Evaporation of the reaction mixture and purification of the residue by flash chromatography using $CHCl_3$:MeOH (8:2) as the eluent gave 0.55g(95%) of 13c as foam; IR: ν 3330-3420 (NH_2,OH)cm^{-1}; UV: λ max (pH1) 235nm (ε12,300); (pH7) 245nm (ε10,700); (pH11) 244nm (ε8600); ^1H NMR (Me_2SO-d_6): δ 5.81-5.87 (m, 3, $C_1'H$+NH_2), 6.28, 6.94, 7.36 (m, 3, C_2H, C_4H and C_5H), 9.19 (br s, 1, NOH). Anal. Calcd for $C_{10}H_{15}N_3O_4.3/4H_2O$ (254.75): C, 47.14; H, 6.47; N, 16.49. Found: C, 47.13; H, 6.18; N, 16.15.

1-(2-Deoxy-β-D-erythro-pentofuranosyl)pyrrole-3-carboxamidine (13d). A mixture of 13c (0.40g, 1.66mmol), Pd/C (10%, 0.50g) and AcOH (0.2ml) in EtOH (35ml) was shaken under hydrogen (50 psi) on a Parr hydrogenator for 2 days at room temperature. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was purified by flash chromatography using $CHCl_3$:MeOH (8:2) as the eluent to yield 0.30g (54%) of 13d as foam; IR:ν 3110-3350 (NH_2,OH)cm^{-1} UV: λ max (pH1) 237nm (ε10,900); (pH7) 236nm (ε10,600); (pH11) 236.5nm (ε11,500); ^1H NMR (Me_2SO-d_6): δ 5.92 (t, 1, J=7.0 Hz, $C_1'H$), 6.58-6.74 (m, 3, NH_2+C_2H), 7.14 and 7.98 (m, 2, C_4H+C_5H), 8.54 (br s, 1, NH). Anal. Calcd for $C_{10}H_{15}N_3O_3.CH_3COOH.H_2O$ (333.31): C, 46.84; H, 6.95; N, 12.60. Found: C, 47.12; H, 6.67; N, 12.47.

2-Ethoxymethyleneamino-5-bromo-1-(2-deoxy-3,5-di-O-p-toluoyl-β-D-erythro-pentofuranosyl)pyrrole-3,4-dicarbonitrile (15a). A mixture of 2-amino-5-bromopyrrole-3,4-dicarbonitrile[58] (7.0g, 33mmol) and diethoxymethylacetate (8.10g, 50mmol) in dry CH_3CN (250ml) was heated under reflux for 3h, cooled and evaporated to dryness. The residue was dissolved in a mixture of dry CH_3CN (50ml) and toluene (50ml), and evaporated to dryness. This process was repeated three times and the residual 2-ethoxymethyleneamino-5-bromopyrrole-3,4-dicarbonitrile (14a, 8.0g, 90%) was used as such for further reactions.

Treatment of the sodium salt of 14a (8.10g, 30.3mmol of 14a and 1.40g, 35mmol of 60% NaH in oil) with 5 (11.70g, 30.5mmol) in CH_3CN (400ml), in the same manner as for 6, gave 14.0g (74.5%) of 15a as foam; IR: ν 1740(C=O), 2210(CN)cm^{-1}; UV: λ max (EtOH) 238nm (ε39,200), 270 (13,400); ^1H NMR ($CDCl_3$): δ 1.42 (t, 3, CH_2CH_3), 2.41 (2s, 6, $2CH_3$), 4.48 (m, 2, CH_2CH_3), 6.39 (t, 1, J=7.0 Hz, $C_1'H$), 7.24-7.90 (m, 8, 2Ph), 8.27 (s, 1, CH). Anal. Calcd for $C_{30}H_{27}BrN_4O_6$ (619.47): C, 58.16; H, 4.39; N, 9.04; Br, 12.89. Found: C, 58.40; H, 4.46; N, 8.95; Br, 13.11.

4-Amino-6-bromo-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]-pyrimidine-5-carbonitrile (16a). A solution of 15a (0.80g, 1.3mmol) in MeOH/NH_3 (50ml) was stirred at room temperature in a pressure bottle for 2 days and then evaporated to dryness. The residue was purified by flash chromatography using $CHCl_3$:MeOH (8:2) as the eluent and crystallized from $CHCl_3$/MeOH mixture to yield 0.35g (76.5%) of 16a; mp >300°C(dec); IR: ν 2215 (CN), 3300-3400 (NH_2,OH)cm^{-1}; UV: λ max (pH1) 233nm (ε15,400), 282 (15,400); (pH7) 218nm (ε17,800), 286 (14,500); (pH11) 286nm (ε16,100); ^1H NMR (Me_2SO-d_6): δ 6.42 (t, 1, J=7.0 Hz, $C_1'H$), 7.04 (br s, 2, NH_2), 8.19 (s, 1, C_2H). Anal. Calcd for $C_{12}H_{12}BrN_5O_3$ (354.17): C, 40.69; H, 3.42; N, 19.76; Br, 22.56. Found: C, 40.45; H, 3.30; N, 19.56; Br, 22.85.

4-Amino-6-bromo-7-(2-deoxy-3,5-di-O-acetyl-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carbonitrile (16b). A mixture of 16a (1.0g, 2.8mmol) and acetic anhydride (1.9ml, 20mmol) in dry pyridine (15ml) was stirred at room temperature for 4h. The reaction mixture was evaporated to dryness and the residue was co-evaporated with dry toluene (3 x 25ml). The yellow residue was dissolved in $CHCl_3$ and passed through a silica gel column (2.5 x 25cm) to get pure compound, which was crystallized from acetone hexane to yield 1.20g (97%) of 16b; mp 166-167°C; IR: ν 1740(C=O), 2210 (CN), 3100-3450 (NH_2)cm^{-1}; UV: λ max (EtOH) 220nm (ε16,400), 286 (13,100); ^1H NMR (Me_2SO-d_6): δ 1.96 and 2.10 (2s, 6, $2COCH_3$), 6.48 (t, 1, J=6.0 Hz, $C_1'H$), 7.03 (br s, 2, NH_2), 8.24 (s, 1, C_2H). Anal. Calcd for $C_{16}H_{16}BrN_5O_5$ (438.24): C, 43.85; H, 3.68; N, 15.97; Br, 18.23. Found: C, 43.94; H, 3.86; N, 15.73; Br, 17.99.

4-Amino-7-(2-deoxy-3,5-di-O-acetyl-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carbonitrile (16d). Dry KF (0.10g, 2mmol) and 18-crown-6 ether (0.028g, 0.1mmol) in anhydrous CH_3CN (30ml) was stirred at room temperature for 0.5h with the exclusion of moisture and then added to a stirred solution of 16b (0.44g, 1mmol) in dry CH_3CN (30ml) containing N,O-bis(trimethylsilyl)acetamide (BSA), 1ml, 4mmol). The reaction mixture was heated under reflux for 12h and evaporated to dryness. The residue was purified by flash chromatography using $CHCl_3$:acetone (8:2) as the eluent. The homogeneous product on crystallization from $CHCl_3$/ether gave 0.20g (56.0%) of 16d; mp>200°C(dec); IR: ν 1720(C=O), 2230(CN)cm^{-1}; UV:λ max (EtOH) 229nm(sh) (ε15,100), 278 (ε19,700); ^1H NMR (Me_2SO-d_6): δ 2.03 and 2.09 (2s, 6, 2 $COCH_3$), 6.51 (t, 1, J=6.0 Hz, $C_1'H$), 6.94 (br s, 2, NH_2), 8.23 (s, 1, C_6H), 8.44 (s, 1, C_2H).

Anal. Calcd for $C_{16}H_{17}N_5O_5$ (359.34): C, 53.48; H, 4.77; N, 19.48. Found: C, 53.53; H, 4.96; N, 19.32.

4-Amino-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carbonitrile(2'-deoxytoyocamycin, 3a) and (4-Amino-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine-5-methylformimidate (22). A solution of 16d (1.60g, 5.0mmol) in CH_3OH/NH_3 (100ml) was stirred in a pressure bottle at room temperature for 12h. The mixture was evaporated to dryness and the residue after purification by column chromatography using acetone:$CHCl_3$ (7:3) as eluent gave 22 (0.13g, 9.5%) as amorphous solid; ^1H NMR (Me_2SO-d_6): δ 3.74 (s, 3, OCH_3), 6.50 (t, 1, J=6.0 Hz, $C_1'H$), 6.90 (br s, 2, NH_2), 8.23 and 8.42 (2s, 2, C_2H and C_6H), 10.03 (br s, 1, NH). Further elution with $CHCl_3$:MeOH (8:2) and crystallization of the homogeneous product from EtOH/ether gave 1.0g (82%) of 3a; mp 205-207°C [lit[34] mp 208-209°C]; IR:ν 2220(CN), 3200-3400 (NH_2,OH)cm^{-1}; UV: λ max (pH1) 234nm (ε26,000), 274 (19,300); (pH7) 230nm (ε17,200), 278 (29,000); (pH11) 230nm (ε17,800), 278 (23,300); ^1H NMR(Me_2SO-d_6): δ 6.51 (t, 1, J=6.0 Hz, $C_1'H$), 6.90 (br s, 2, NH_2), 8.22 (s, 1, C_6H), 8.42 (s, 1, C_2H). Anal. Calcd for $C_{12}H_{13}N_5O_3$ (275.26): C, 52.37; H, 4.77; N, 25.43. Found: C, 52.25; H, 4.75; N, 25.32.

4-Amino-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carboxamide (2'-Deoxysangivamycin, 3b). Method A. In the same manner as for 13a the title compound was prepared by using 3a (0.27g, 1mmol), dioxane (10ml), MeOH (50ml), H_2O (10ml), NH_4OH (20ml) and H_2O_2 (2ml). Yield 0.22g (75%); mp 267-270°C [Lit[34] mp 272-275°C, and all other physicochemical properties of 3b are identical with 2'-deoxysangivamycin reported in literature[39]].

Method B. A mixture of 18 (0.70g, 1.9 mmol), Pd/C (5%, 0.70g) and concentrated NH_4OH (5ml) in EtOH:H_2O (4:1, 200ml) was shaken under hydrogen atmosphere at 40 psi for 24h. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was crystallized from EtOH to yield 0.35g (63%) of 3b; mp 268-270°C, and was identical to 3b prepared by method A.

4-Amino-6-bromo-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carboxamide (18). By following the procedure as described for the preparation of 13a, the title compound was prepared by using 16a (1.30g, 3.67 mmol), MeOH (100ml), dioxane (10ml), H_2O (25ml), NH_4OH (20ml) and H_2O_2 (3ml). The reaction product was purified by flash chromatography using $CHCl_3$:MeOH as the eluent and crystallized from MeOH/$CHCl_3$/ether mixture to yield 1.10g (81%) of 18; mp 163-166°C: IR: ν 1710 ($CONH_2$), 3200-3410 (NH_2,OH)cm^{-1}; UV: λ max (pH1) 231nm (ε27,700), 276 (24,400); (pH7) 231nm (ε19,600), 280 (27,300); (pH11) 228nm (ε20,800), 280 (ε27,900); ^1H NMR (Me_2SO-d_6): δ 6.47 (t, 1, J=6.0 Hz, $C_1'H$), 7.74 (br s, 2, NH_2), 7.99 (br s, 2, $CONH_2$), 8.07 (s, 1, C_2H). Anal. Calcd for $C_{12}H_{14}BrN_5O_4$ (372.13): C, 38.73; H, 3.79; N, 18.81; Br, 21.47. Found: C,38.63; H, 3.80; N, 18.39; Br, 21.41.

4-Amino-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine-5-thiocarboxamide (19a). In the same manner as for 13b, the title compound was prepared by using 3a (0.50g, 1.8 mmol) and crystallized from EtOH to yield 0.35g (62%); mp >230°C (dec); IR: ν 1260 (C=S), 3200-3440 (NH_2,OH)cm^{-1}; UV: λ max (pH1) 241nm (ε16,000), 286 (11,900); (pH7) 246nm (ε11,100), 263 (11,500); (pH11) 235nm (ε12,700), 279 (15,000); ^1H NMR (Me_2SO-d_6): δ 6.54 (t, 1, J=6.0 Hz, $C_1'H$), 7.92 (br s, 3, C_2H+NH_2), 8.11 (s, 1, C_6H), 9.44 and 9.64 (2br s, 2, $CSNH_2$). Anal.Calcd for $C_{12}H_{15}N_5O_3S$ (309.34): C, 46.61; H, 4.89; N, 22.64; S, 10.35. Found: C, 46.41; H, 4.93; N, 22.62; S, 10.45.

4-Amino-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carboxamidine hydrochloride (19b). A mixture of 3a (0.55g, 2mmol) and NH_4Cl (0.11g, 2mmol) in liquid NH_3 (75ml) was heated at 100°C in a steel bomb for 12h after which the NH_3 was evaporated. The residue was crystallized from EtOH containing a drop of HCl to give 0.4g (61%) of 19b; mp 183-185°C; IR: ν 3200-3400 (NH_2,OH)cm^{-1}; UV: λ max (pH1) 283nm (ε6700); (pH7) 284nm (ε6900); (pH11) 275nm (ε4200). Anal. Calcd for $C_{12}H_{17}ClN_6O_3$ (328.76): C, 43.84; H, 5.21; N, 25.55; Cl, 10.79. Found: C, 43.81; H, 5.20; N, 25.56; Cl, 10.91.

4-Amino-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carboxamidoxime (19c). In a similar manner as for 13c, the title compound was prepared by using 3a (0.25g, 0.91mmol) and free NH_2OH (0.30g, 9.1mmol) to yield 0.25g (89%); mp 247-248°C; IR: ν 3200-3400 (NH_2,OH)cm^{-1}; UV: λ max (pH1) 223nm (ε29,500), 275 (20,500); (pH7) 277nm (ε21,700); (pH11) 277nm (ε22,100); ^1H NMR (Me_2SO-d_6): δ 6.02 (br s, 2, NH_2), 6.55 (t, 1, J=6.0 Hz, $C_1'H$), 7.28 and 9.33 (2br s, 2, NH_2), 7.89 and 8.08 (2s, 2, C_2H and C_6H), 9.71 (s, 1, NOH). Anal. Calcd for $C_{12}H_{16}N_6O_4$ (308.29): C, 46.75; H, 5.23; N, 27.25. Found: C, 46.59; H, 5.22; N, 27.07.

2-Ethoxymethyleneamino-5-ethylthio-1-(2-deoxy-3,5-di-O-p-toluoyl-β-D-erythro-pentofuranosyl)-pyrrole-3,4-dicarbonitrile (15b). The title compound was prepared in a similar manner as described for 15a using 2-amino-5-ethylthiopyrrole-3,4-dicarbonitrile[58] (which was converted to 14b by boiling with diethoxymethylacetate), (6.5g, 26mmol), NaH (60%, 1.20g, 30mmol), 5 (11.7g, 30mmol) and dry CH_3CN (300ml). The product was purified by flash chromatography using hexane:acetone (6:4), and crystallized from the same solvent to yield 12.0g (76%); mp 129-131°C; IR: ν 1720 (C=O), 2220 (CN)cm^{-1}; UV: λ max (EtOH) 236nm (ε33,300), 281 (11,200); ^1H NMR ($CDCl_3$): δ 1.27 and 1.43 (2t, 6, $2CH_2CH_3$), 2.39 and 2.43 (2s, 6, $2CH_3$), 4.47 (m, 4, $2CH_2CH_3$), 6.62 (t, 1, J=6.0 Hz, $C_1'H$), 7.22-7.90 (m, 8, 2Ph), 8.27 (s, 1, CH). Anal. Calcd for $C_{32}H_{32}N_4O_6S$ (600.69): C, 63.99; H, 5.37; N, 9.32; S, 5.33. Found: C, 64.13; H, 5.25; N, 9.33; S, 5.50.

4-Amino-6-ethylthio-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carbonitrile (16c). In a similar manner as for 16a, the title compound was prepared by using 15b

(6.5g, 10.1mmol) and MeOH/NH_3 (200ml). The product was crystallized from MeOH:$CHCl_3$:ether mixture to yield 3.60g (91.0%) of 16c; mp 178-179°C; IR: ν 2220 (CN), 3150-3420 (NH_2,OH)cm^{-1}; UV: λ max (pH1) 237nm (ϵ10,800), 292 (9000); (pH7) 221nm (sh) (ϵ13,400), 239 (sh) (8100), 297 (10,200); (pH11) 239nm (ϵ9400), 297(10,700); ^{1}H NMR (Me_2SO-d_6): δ 1.20 (t, 3, CH_2CH_3), 3.0 (q, 2, CH_2CH_3), 6.64 (t, 1, J=6.6 Hz, $C_1'H$), 7.07 (br s, 2, NH_2), 8.22 (s, 1, C_2H). Anal.- Calcd for $C_{14}H_{17}N_5O_3S$ (335.38): C, 50.15; H, 5.11; N, 20.84; S, 9.54. Found: C, 50.06; H, 5.13; N, 20.61; S, 9.56.

4-Amino-6-ethylthio-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carboxamidoxime (19d). In a similar manner as for 19c, the title compound was prepared by using 16c (1.80g, 4.95mmol), NH_2OH (2.50g) and EtOH (100ml) to yield 1.70g (87.0%) as foam; IR: ν 1300 (-SEt), 3000-3400 (NH_2,OH)cm^{-1}; UV: λ max (pH1) 286nm (ϵ12,700); (pH7) 292nm (ϵ14,100); (pH11) 292nm (ϵ14,600); ^{1}H NMR (Me_2SO-d_6): δ 1.22 (t, 3, CH_2CH_3), 2.79 (q, 2, CH_2CH_3), 6.19 (br s, 2, NH_2), 6.76 (t, 1, J=6.0 Hz, $C_1'H$), 7.50-8.20 (m, 2, NH_2), 8.06 (s, 1, C_2H), 9.86 (s, 1, NOH). Anal. Calcd for $C_{14}H_{22}N_6O_4S$ (368.41): C, 45.65; H, 5.47; N, 22.81; S, 8.68. Found: C, 45.88; H, 5.56; N, 22.83; S, 8.45.

2-Ethoxymethyleneamino-5-bromo-1-(2,3,5-tri-O-benzyl-β-D-arabinofuranosyl)pyrrole-3,4-dicarbonitrile (17). The title compound was prepared by following the procedure employed for the preparation of 9a using 14a (14.0g, 52mmol), 8 (24.1g, 55mmol), NaH (60%, 2.4g, 60mmol) and CH_3CN (300ml). The crude product was dissolved in $CHCl_3$, passed through a silica gel column (4 x 40cm) and eluted with $CHCl_3$. The homogeneous fractions were evaporated and the residual oil was used as such for further reactions; yield 28.0g (79.0%).

4-Amino-6-bromo-7-(2,3,5-tri-O-benzyl-β-D-arabinofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carbonitrile (20a). The title compound was prepared by following the procedure employed for the preparation of 16a using 17 (8.5g) and MeOH/NH_3 (400ml). The product was purified by flash chromatography using hexane:acetone (6:4) as the eluent and the homogeneous product was crystallized from the same solvent system to yield 7.5g (89.0%); mp 95-96°C; IR: ν 700 (C-Br), 2220 (CN)cm^{-1}; UV: λ max (EtOH) 288nm (ϵ19,400); ^{1}H NMR ($CDCl_3$): δ 4.53, 4.55 and 4.61 (3s, 6, $3CH_2C_6H_5$), 5.83 (s, 2, NH_2), 6.64 (d, 1, J=6.6 Hz, $C_1'H$), 7.28 (m, 15, 3Ph), 8.22 (s, 1, C_2H). Anal. Calcd for $C_{33}H_{30}BrN_5O_4$ (640.54): C, 61.88; H, 4.72; N, 10.92; Br, 12.48. Found: C, 61.74; H, 4.85; N, 10.91; Br, 12.48.

4-Amino-7-(2,3,5-tri-O-benzyl-β-D-arabinofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carbonitrile (20b). In a similar manner as for 16d, the title compound was prepared by using 20a (2.6g, 4.1mmol), KF (0.44g, 8.2mmol), BSA (4.1 ml, 16.4mmol), 18-crown-6 (0.12g, 0.4mmol) and CH_3CN (150ml). The product after crystallization from ether gave 1.3g (57.0%) of 20b ; mp 98-100°C; IR: ν 700 (C-Br), 2220 (CN)cm^{-1}; UV: λ max (EtOH) 231nm (ϵ10,700), 280 (16,300); ^{1}H NMR ($CDCl_3$): δ 4.51 (m, 6, $3CH_2C_6H_5$), 5.93 (br s, 2, NH_2), 6.68 (d, 1, J=6.6 Hz, $C_1'H$), 7.31 (m, 15, 3Ph), 7.91 (s, 1, C_6H), 8.31 (s, 1, C_2H). Anal. Calcd for $C_{33}H_{31}N_5O_4$ (561.64): C, 70.57; H, 5.56; N, 12.46. Found: C, 70.60; H, 5.67; N, 12.40.

4-Amino-7-(2,3,5-tri-O-benzyl-β-D-arabinofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carboxamide (21a). In a similar manner as for 13a, the title compound was prepared by using 20b (1.45g, 2.58mmol), dioxane (100ml), MeOH (75ml), H_2O (5ml), NH_4OH (25ml) and H_2O_2 (10ml, 5%) to yield 1.20g (80.0%); mp 138-140°C; IR: ν 1620 (C=O) 3180-3480 (NH_2)cm^{-1}; UV: λ max (pH1) 269nm (ϵ5000); (pH7) 269nm (ϵ5100); (pH11) 272nm (ϵ4700); ^{1}H NMR (Me_2SO-d_6): δ 4.36 (m, 6, 3 $CH_2C_6H_5$), 5.35 (br s, 2, NH_2), 6.75 (d, 1, J=6.5 Hz, $C_1'H$), 7.26 (m, 17, 3Ph+$CONH_2$), 7.74 (s, 1, C_6H), 8.23 (s, 1, C_2H). Anal. Calcd for $C_{33}H_{33}N_5O_5$ (579.65): C, 68.38; H, 5.73; N, 12.08. Found: C, 68.17; H, 5.62; N, 12.06.

4-Amino-7-β-D-arabinofuranosylpyrrolo[2,3-d]pyrimidine-5-carboxamide (21b). In a similar manner as for 9b, compound 21b was prepared by using 21a (12.0g, 20.7mmol), $Pd(OH)_2$ (2.5g) and cyclohexene (50ml) in EtOH (200ml) to yield 6.0g (94.0%); mp 250-252°C; [Lit[61] mp 258-260°C]; IR: ν 1670 (C=O), 3140-3420 (NH_2,OH)cm^{-1}; UV: λ max (pH1) 233.5nm (ϵ14,900), 275 (15,200); (pH7) 233 nm (ϵ9400), 245 (8200), 279 (14,400); (pH11) 231nm (ϵ10,100), 280 (14,300); ^{1}H NMR (Me_2SO-d_6): δ 5.49 (br s, 2, NH_2), 6.44 (d, 1, J=5.0 Hz, $C_1'H$), 7.33 and 8.07 (2br s, 4, $CONH_2$, C_2H and C_6H). Anal. Calcd for $C_{12}H_{15}N_5O_5$ (309.28): C, 46.60; H, 4.89; N, 22.63. Found: C, 46.44; H, 4.77; N, 22.51.

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* To whom correspondence should be addressed at Nucleic Acid Research Institute.

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