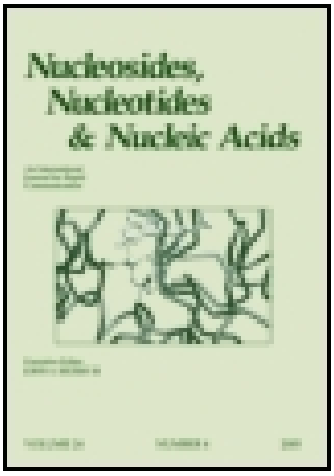

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SYNTHESIS OF 5'-FLUORO-5'-DEOXY- AND 5'-AMINO-5'-DEOXYTOYOCAMYCIN AND SANGIVAMYCIN AND SOME RELATED DERIVATIVES

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Abstract

A series of 5'-substituted analogs of toyocamycin were prepared by condensation of silylated 4-amino-6-bromo-5-cyanopyrrolo[2,3-d]pyrimidine with protected 5-azido-5-deoxy- or 5-fluoro-5-deoxyribofuranose followed by debromination and deblocking. Alternatively, 5'-azido-5'-deoxytoyocamycin was prepared by azidation of toyocamycin. Conversion of the 5-nitrile function of the toyocamycin derivatives into a carboxamide or a thiocarboxamide gave the corresponding analogs of sangivamycin or thiosangivamycin while reduction of the 5'-azido-5'-deoxy nucleosides provided 5'-amino-5'-deoxy derivatives.

Introduction

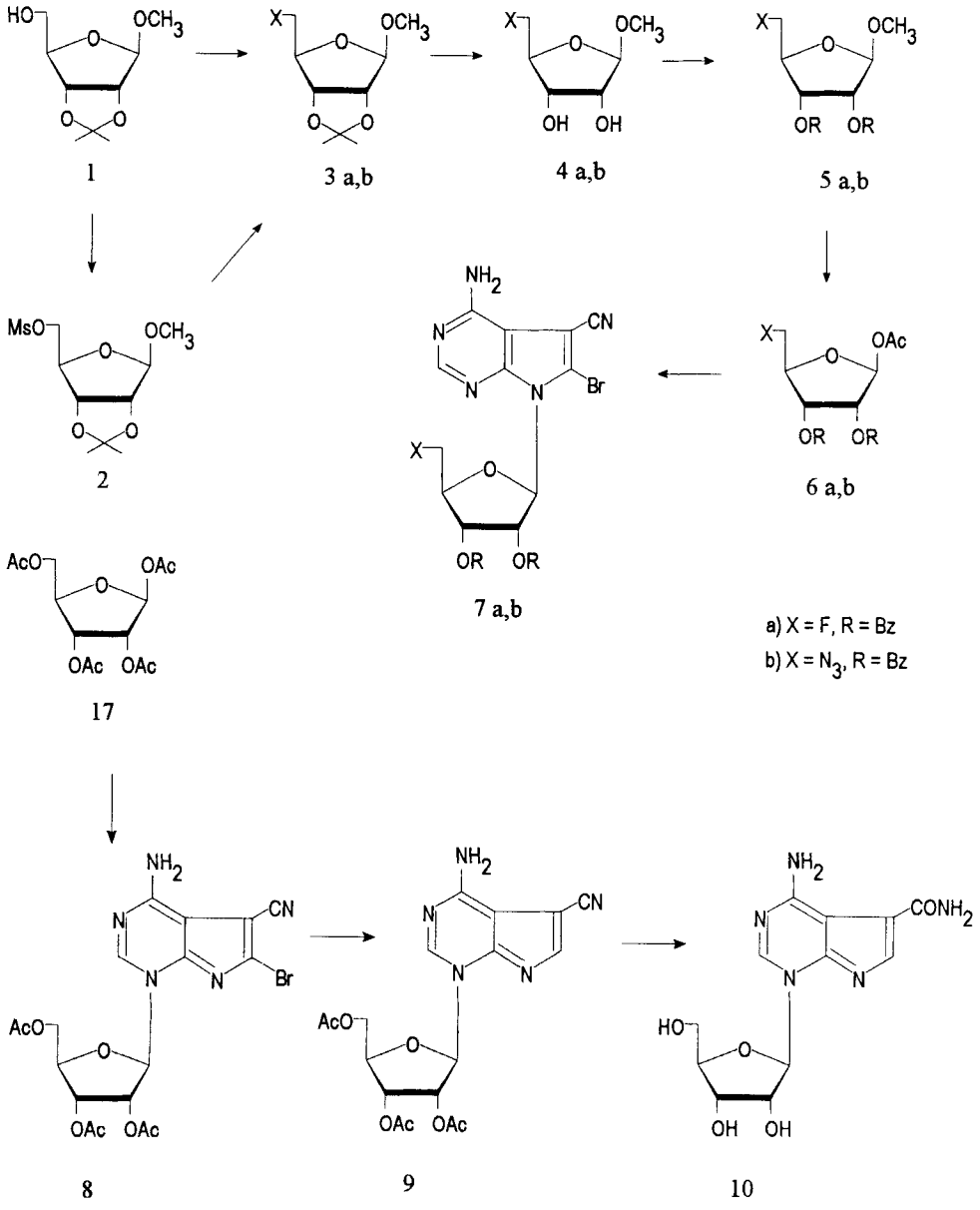
Inhibition of protein kinases involved in intracellular signaling has recently emerged as a potentially promising approach to the development of novel antitumor agents.[1-3] Because of its ability to inhibit[4] such kinases, the nucleoside antibiotic sangivamycin was of interest as a lead compound for the design of potentially more potent and specific analogs. Since in the cell this antibiotic is phosphorylated,[5] and its inhibitory effects then extend to other sites, we prepared a series of sangivamycin analogs modified at their 5'-position to produce agents resistant to phosphorylation.[6] The biological activity of these analogs provided a basis for synthesis of additional toyocamycin and sangivamycin derivatives in an attempt to establish the structure-activity

relationship.[7] The syntheses of some of these nonphosphorylatable pyrrolo[2,3-d]pyrimidine nucleosides are described herein.

Chemistry

We found previously that glycosidation of silylated 4-amino-6-bromo-5-cyanopyrrolo[2,3-d]pyrimidine[8] with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribose in the presence of trimethylsilyl trifluoromethanesulfonate[9] (TMSTF) provided a convenient synthetic approach[10] to toyocamycin. Therefore, we elected this procedure, which involved preparation of the sugar intermediates **6a** and **6b** (Scheme 1), for the synthesis of 5'-fluoro- and 5'-azido-analogs of toyocamycin. While fluorination of methyl 2,3-O-isopropylidene-β-D-ribofuranoside[11] (**1**) with DAST furnished the 5-fluoro derivative **3a**[12] in only a modest yield, displacement of the 5-O-mesyl group in **2**, prepared from **1** and methanesulfonyl chloride in pyridine,[13] with tetrabutylammonium fluoride gave **3a** in a high yield. Hydrolysis of the isopropylidene group in **2a** with aqueous formic acid gave a methyl glycoside **4a** which was benzoylated to afford **5a.** Acetolysis of **5a** furnished an anomeric mixture of 1-O-acetyl derivatives **6a**. Similarly, **2** was converted to **3b** in high yield by treatment with sodium azide in DMF. Hydrolysis of the isopropylidene group in **2b** with methanolic HCl followed by benzoylation furnished **5b**. Acetolysis of **5b** gave an anomeric mixture of **6b** from which the β-anomer was separated by crystallization in an 80% yield.

Reaction of α,β-**6a** with silylated 4-amino-6-bromo-5-cyanopyrrolo[2,3-d]pyrimidine at room temperature and in the presence of TMSTF gave the protected nucleoside **7a** as a single product. In contrast, condensation of β-**6b** with the silylated pyrrolopyrimidine base at room temperature gave a mixture of **7b** and a second nucleoside, presumably an N-1 isomer. Heating the reaction mixture at 70-80 °C resulted in a rearrangement of the isomeric nucleoside to furnish **7b** as a single product. Similar rearrangements of isomeric purine[9] and pyrrolopyrimidine[10] nucleosides in the presence of TMSTF to produce thermodynamically more stable isomers have been reported. Reaction of tetra-O-acetyl-β-D-ribofuranose (**17**, Scheme 1) with the silylated pyrrolopyrimidine

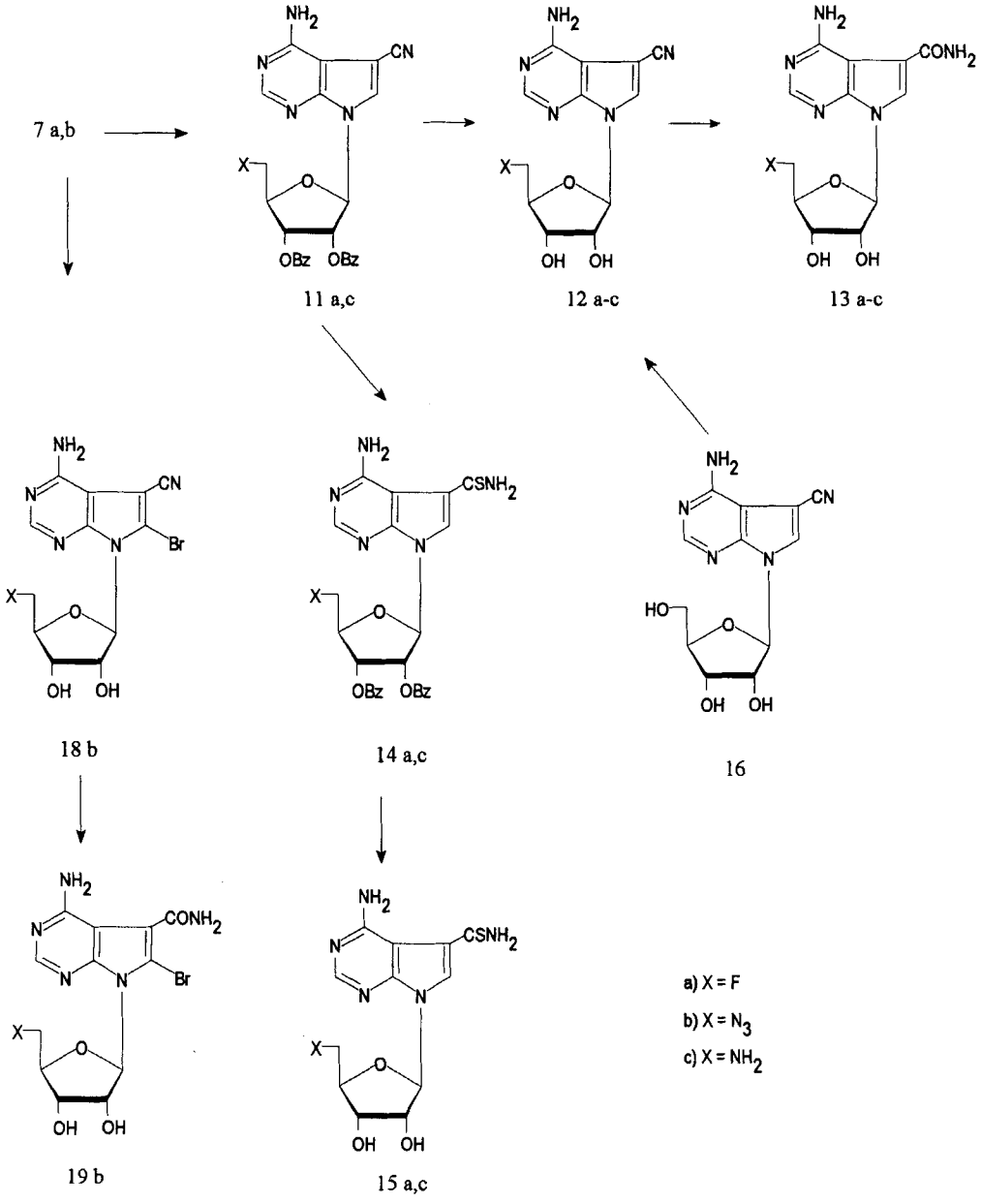


Scheme 1

base at room temperature and in the presence of TMSTF gave only the N-1 isomer **8**. Heating the reaction mixture at 50 °C for 2 hours was not sufficient to effect the isomerization of **8** and heating the mixture at 70-80 °C led to a complex mixture of products, presumably as a result of the poor stability of the protecting acetyl groups under prolonged heating in the presence of a strong Lewis acid.[14]

The assignment of the glycosidation site for **7a,b** and **8** was made on the basis of the UV spectra of **12a,c** (Scheme 2), which were obtained from **7a,b** by catalytic hydrogenation and deblocking, and on the UV spectra of **9**, obtained from **8** by catalytic hydrogenation. Thus, the UV spectra of neutral or basic (pH 12) solutions of **12a** and **12b** showed no change,[8] whereas the UV spectrum of the basic solution of the N-1 isomer **9** showed a new absorption maximum at 259 nm. The structure of **7b** was confirmed by comparing TLC and IR spectra of **13c**, which was obtained from **7b** by sequential hydrogenation, deblocking and hydrolysis (Scheme 2), with those of **13c**, which was prepared from toyocamycin (**16**, Scheme 2) by sequential azidation, hydrolysis, and hydrogenation. The identity of the two products was further confirmed by their undepressed mixture melting point. It is of interest that regioselective azidation of unprotected toyocamycin with triphenylphosphine-carbon tetrabromide-lithium azide,[15] failed. However, substituting sodium azide for lithium azide in this reaction, which was a much less effective method for azidation of the 5'-position of the pyrimidine and purine nucleosides,[15] gave a 40% yield of 5'-azido-5'-deoxytoyocamycin (**12b**). The N-1 glycosidation site of **9** was confirmed by the similar positions of the ^{13}C NMR aglycon signals for **9** and of those for 4-amino-5-cyano-1-[(2-hydroxyethoxy)methyl]pyrrolo[2,3-d]pyrimidine.[16] An upfield shift of C-2 and a downfield shift of C-6 as compared to the signals for the corresponding carbons in the ^{13}C spectrum of toyocamycin[17] were consistent with the assigned site of glycosidation.

Debromination of the protected nucleosides **7a,b** (Scheme 2) and **8** (Scheme 1) was readily accomplished by catalytic hydrogenation, which in the



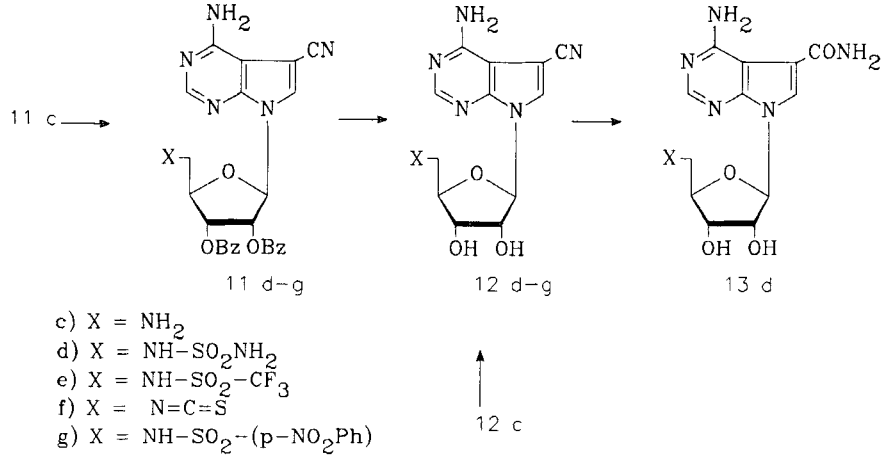
Scheme 2

case of **7b** was accompanied by a reduction of the azido group to an amino function, to afford the protected derivatives **11a,c** and **9**, respectively. Deprotection of **7b** and **11a,c** with methanolic ammonia provided the 5'-azido-6-bromo (**18b**), 5'-fluoro (**12a**) and 5'-amino (**12c**) derivatives of toyocamycin, respectively, which were converted to 5'-azido-6-bromo (**19b**), 5'-fluoro (**13a**) and 5'-amino (**13c**) analogs of sangivamycin by treatment with ammonium hydroxide/hydrogen peroxide[8]. Deprotection of **9** with anhydrous potassium carbonate in methanol followed by treatment with conc. ammonium hydroxide/hydrogen peroxide gave iso-sangivamycin (**10**) which was found to be unstable under acidic conditions. Treatment of **10** with acetone/dimethoxypropane at room temperature and in the presence of perchloric acid, in an attempt to prepare the isopropylidene derivative, resulted in rapid cleavage of the glycosidic bond and in the formation of **1** and 4-amino-5-carboxamidopyrrolo[2,3-d]pyrimidine. At room temperature, TLC of a solution of **10** in 50% aqueous formic acid showed approximately 25% decomposition in 2 h. Treatment of **11a,c** with hydrogen sulfide in pyridine/triethylamine[18] followed by deprotection furnished 5-thiocarboxamide derivatives **15a,c**.

Sulfonylation of **11c** (Scheme 3) with appropriate sulfonyl chlorides followed by deprotection furnished 5'-N-sulfamoylamino (**12d**), 5'-N-trifluoromethanesulfonylamino (**12e**) and 5'-N-p-nitrobenzenesulfonylamino (**12g**) toyocamycin derivatives. Reaction of **11c** with N,N-thiocarbonyl-di-imidazole[19] followed by deblocking provided the 5'-isothiocyano (**12f**) toyocamycin analog, which was also prepared from **12c,** in one step, by treatment with N,N-thiocarbonyl-di-imidazole.

EXPERIMENTAL SECTION

General Procedures. Melting points were determined with a Mel-Temp capillary point block and are uncorrected. Elemental analyses were performed by Robertson Laboratory, Madison, N.J. IR spectra were recorded with Perkin-Elmer Models 457 and 710B spectrophotometers. ^{1}H NMR, ^{19}F and ^{13}C spectra



Scheme 3

were recorded on Varian 390 (90 MHz), Bruker WP-200 (200 MHz) and Bruker AM-450 spectrometers, and chemical shifts are given in ppm using Me_4Si and $CFCl_3$ as internal standards. Thin-layer and column chromatography was performed on EM Science silica gel plates and on silica gel (230-400 mesh) from E. Merck Industries Co., respectively. Evaporations were conducted under diminished pressure at bath temperatures below 40° C.

Methyl 2,3-O-Isopropylidene-5-O-methanesulfonyl-β-D-ribofuranoside (**2**). A cold (0 °C) solution of methyl 2,3-O-isopropylidene-β-D-ribofuranoside (**1**)[11] (20 g, 0.1 mol) in anhydrous pyridine was treated dropwise and with stirring with a solution of methanesulfonyl chloride (60 mL) in pyridine (60 mL). The reaction mixture was kept at 0-5 °C for 24 h, poured into a mixture of ice and water and filtered. The filtered precipitate was washed with cold water and crystallized from ethanol to give 19 g (78%) of **2**: mp 79-80 °C (Lit.[13] mp 78-9 °C); ^{1}H NMR ($CDCl_3$) δ 1.30, (2s, 6H, isopropylidene CH_3), 3.05 (s, 3H, OMs), 3.32 (s, 3H, OCH_3), 4.25 (m, 3H, H-4, H-5), 4.50 (m, 2H, H-2, H-3), 4.95 (s, 1H, H-1).

Methyl 5-Deoxy-5-fluoro-2,3-O-isopropylidene-β-D-ribofuranoside (**3a**). *Method A.* A solution of methyl 2,3-O-isopropylidene-β-D-ribofuranoside (**1**) (2.6

g, 13 mmol) in benzene (7 mL) was added to a solution of DAST (5 mL, 90 mmol) in dry benzene (40 mL) containing anhydrous pyridine (8 mL). The light yellow solution was stirred at 80 °C for 3 h, cooled to 0 °C, and treated with absolute ethanol (5 mL) and with ether (20 mL). The solution was washed with water, dried ($MgSO_4$) and evaporated to give a clear oil which was dissolved in chloroform and applied to a column of silica gel. The column was eluted with ether/pet. ether (1:1) to give, after evaporation of the appropriate fractions, 820 mg (35%) of **3a** as an oil: $[\alpha]_D^{22}$ -27° (c 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.4 (2s, 6H, isopropylidene), 3.25 (s, 3H, OCH_3), 4.1 (m, 1H, H-4), 4.55 (m, 2H, H-2, H-3), 4.85 (d, 1H, $J_{1,2}$=3.1 Hz, H-1); ^{19}F NMR ($CDCl_3$) δ -224.00 (sextet, $J_{F,\ H\text{-}5}$ = 53.2 Hz), $J_{F,H\text{-}4}$ = 13.5 Hz).

Anal. calcd for $C_9H_{15}FO_4$: C, 52.42; H, 7.25; F, 9.22. Found: C, 52.64; H, 6.98; F, 8.96.

Method B. A solution of **2** (18 g, 64 mmol) in anhydrous acetonitrile (250 mL) containing anhydrous tetrabutylammonium fluoride (32 g, 132 mmol) was heated under reflux for 24 h. The reaction mixture was cooled and evaporated to give a residue which was dissolved in chloroform. This solution was washed with water, dried ($MgSO_4$), and evaporated to give **3a** which was purified by chromatography on silica gel eluting with ether/pet. ether (1:6): Yield 11.5 g (90%); $[\alpha]_D^{22}$, ^1H and ^{19}F NMR data of the products obtained by *Method* A and *B* were identical.

Methyl 5-Azido-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside (3b). A mixture of **2** (25 g, 89 mmol) and sodium azide (20 g, 350 mmol) in anhydrous DMF (150 mL) was stirred at 90-100 °C for 1 h, cooled to room temperature and evaporated. The residue was extracted with ether (2 x 100 mL) and the combined solution was washed with water, concentrated to a small volume and applied to a short column of silica gel. The column was eluted with ether/pet. ether (1:1) to give 19 g (94%) of **3b** as an oil: IR (KBr) 2100 cm^{-1} (N_3); ^1H ($CDCl_3$) δ 1.25, 1.35 (2s, 6H, CH_3), 3.30 (s, 3H, OCH_3), 3.35 (m, 2H, H5), 4.15 (m, 1H, H-4), 4.55 (br. s, 2H, H-2 and H-3), 4.90 (s, 1H, H-1).

Anal. calcd for $C_9H_{15}N_3O_4$: C, 47.16, H, 6.55; N, 18.33. Found: 47.42; H, 6.60; N, 18.58.

Methyl 2,3-di-O-Benzoyl-5-deoxy-5-fluoro-β-D-ribofuranoside (5a) A solution of **3a** (4.1 g, 20 mmol) in formic acid (60%, 50 mL) was stirred at room temperature for 20 h, evaporated and the residue was co-evaporated with absolute ethanol repeatedly to give methyl 5-deoxy-5-fluoro-β-D-ribofuranoside (**4a**) as a syrup (3 g): TLC (ethyl acetate), R_f 0.45; ^{1}H NMR (CD_3OD) δ 3.41 (s, 3H, OCH_3), 5.1 (s, 1H, H-1). The syrup was dissolved in anhydrous pyridine (50 mL), cooled to 0 °C, and treated dropwise and with stirring with benzoyl chloride (8 mL). The mixture was kept at room temperature overnight, poured into ice-water and extracted with chloroform. The chloroform solution was washed with water, dried ($MgSO_4$), and evaporated to give **5a** as a colorless semi-solid material which was purified by chromatography on a short column of silica gel eluting with ethyl acetate/pet. ether (1:4): Yield 7.8g (95%); $[\alpha]_D^{22}$ +17.5° (c 1, $CHCl_3$), IR (KBr) 1720 (C=O), 699 cm^{-1} (aromatic); ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 4H, aromatic), 7.25 (m, 6H, aromatic), 5.15 (s, 1H, H-1), 3.40 (s, 3H, OCH_3); ^{19}F NMR ($CDCl_3$) δ 226 (sextet, $J_{F,H-5}$= 49.50 Hz, $J_{F,H-4}$ =23.10 Hz).

Anal. calcd for $C_{20}H_{19}FO_6$: C, 64.17; H, 5.08; F, 5.08. Found: C, 64.32; H, 5.28; F, 4.96.

Methyl 5-Azido-2,3-di-O-benzoyl-5-deoxy-β-D-ribofuranoside (5b). A solution of **3b** (5.5 g, 24 mmol) in anhydrous methanol (200 mL) containing hydrogen chloride (0.2%) was stirred at room temperature for 18 h, neutralized with pyridine, and evaporated to give crude **4b** as a syrup which was purified by chromatography on silica gel eluting with ethyl acetate/pet. ether (1:1): Yield 3.8 g (79%); IR (KBr) 3000 cm^{-1} (OH), 2150 cm^{-1} (N_3); ^{1}H NMR ($CDCl_3$) δ 3.45 (s, 3H, OCH_3), 4.15 (m, 5H), 4.85 (s, 1H, H-1). A cold (0 °C) solution of **4b** (3 g, 16 mmol) in anhydrous pyridine (30 mL) was treated dropwise and with stirring with benzoyl chloride (7 mL, 60 mmol) in 10 min and the mixture was then kept at room temperature overnight, and poured into ice-water. The mixture was extracted with chloroform and the separated chloroform solution was sequentially washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on silica gel eluting first with chloroform and then with ethyl acetate/pet. ether (1:4) to give 5.8 g (88%) of **5b** as a thick syrup:

TLC ethyl acetate/pet. ether 1:9, R_f 0.4; $[\alpha]_D^{22}$ + 6.5° (c 1, $CHCl_3$); IR (N_3), 750 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 3.35 (s, 3H, OCH_3), 3.5 (m, 2H, H-5), 4.50 (m, 1H, H-4), 5.1 (s, 1H, H-1), 5.35 (m, 2H, H-2,H-3), 7.35 (m, 6H, aromatic), 7.90 (m, 4H, aromatic).

Anal. calc for $C_{20}H_{19}N_3O_6$: C, 60.45; H, 4.78; N, 10.57. Found: C, 60.72; H, 4.65; N, 10.80.

1-O-Acetyl-2,3-di-O-benzoyl-5-deoxy-5-fluoro-α,β-D-ribofuranose (6a). A stirred solution of **5a** (10.5g, 28 mmol) in a mixture of acetic acid (100 mL) and acetic anhydride (100 mL) was treated dropwise at 0 °C with concentrated sulfuric acid (0.5 mL). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 22 h. The mixture was neutralized by stirring with anhydrous sodium acetate (5g) and evaporated to give a residue which was dissolved in ethyl acetate. This solution was extracted with water and the aqueous phase was extracted once with ethyl acetate. The combined ethyl acetate solution was washed with water, dried ($MgSO_4$) and evaporated. The residue was co-evaporated with toluene to give 8.78 g (78%) of **6a** as a semi-solid material: $[\alpha]_D^{22}$ + 4.5° (c 1, $CHCl_3$); IR (KBr) 1750 (C=O), 700 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 7.95 (m, 4H, aromatic), 7.40 (m 6H, aromatic), 6.65 (d, $J_{1,2}$=4.50 Hz, α-H-1), 6.45 (s, β-H-1), 2.10, 2.08 (2s, 3H, acetyl); ^{19}F NMR ($CDCl_3$) δ -229.00 (sextet, $J_{F,H-5}$= 49.50 Hz, $J_{F,H-4}$= 29.5 Hz, β-anomer), -232 (sextet, $J_{F,H-5}$= 46.20 Hz, $J_{F,H-4}$= 29.7 Hz, α-anomer).

Anal. calcd for $C_{21}H_{19}FO_7$: C, 62.69; H, 4.70; F, 4.69. Found: C, 62.74; H, 4.56; F 4.82.

1-O-Acetyl-5-azido-2,3-di-O-benzoyl-5-deoxy-β-D-ribofuranose (6b). A cold (0 °C) solution of **5b** (7.9 g, 19.8 mmol) in a mixture of acetic acid and acetic anhydride (100 mL, 1:1) was treated dropwise and with stirring with H_2SO_4 (1 mL). The mixture was stirred at 0-5 °C for 20 h, and then at room temperature for 3 h. The mixture was cooled to 0 °C, neutralized with anhydrous sodium acetate (5 g) and evaporated to give a residue which was partitioned between ethyl acetate and water. The aqueous solution was extracted with ethyl

acetate and the combined ethyl acetate solution was washed with water, dried ($MgSO_4$), and evaporated to give a brown syrup (8 g) which was purified by chromatography on a short column of silica gel eluting with ethyl acetate/pet. ether (1:4). Evaporation of the appropriate fractions furnished a syrupy mixture (7.5 g, 92%) of the α and β anomers of **6b** which was crystallized from ether/pet. ether to give 6.6 g (80%) of β-**6b**: mp 105-6 °C; $[\alpha]_D^{22}$ + 96° (c1, $CHCl_3$); IR (KBr) 2100 (N_3), 1720 (C=O), 700 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 3.35 (qq 2H, H-5), 4.5 (m, 1H, H-4), 5.70 (m, 2H, H-2, H-3), 6.35 (s, 1H, H-1), 7.35 (m, 6H, aromatic), 7.85 (m, 4H, aromatic).

Anal. calc for $C_{21}H_{19}N_3O_7$: C, 59.29; H, 4.50; N, 9.88. Found: C, 59.31; H, 4.60; N, 10.01.

4-Amino-6-bromo-5-cyano-7-(2,3-di-O-benzoyl-5-deoxy-5-fluoro-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (**7a**). A stirred suspension of 4-amino-6-bromo-5-cyanopyrrolo[2,3-d]pyrimidine (5g, 22 mmol) in a mixture of 1,1,1,3,3,3-hexamethyldisilazane (35 mL), chlorotrimethylsilane (0.2 mL) and dry xylene (40 mL) was heated at reflux for 18 h. The dark solution was evaporated and the residual oil was co-evaporated with dry toluene and then dissolved in a solution of **6a** (9.5 g, 21 mmol) in dry 1,2-dichloroethane. The stirred mixture was cooled to 0 °C and treated dropwise with a solution of TMSTF (10 mL, 34 mmol) in anhydrous 1,2-dichloroethane (15 mL). The resulting mixture was sequentially stirred at room temperature overnight, cooled to 0 °C, diluted with dichloromethane (35 mL), poured into ice-water containing sodium hydrogen carbonate (15 g), and filtered. The organic solution was separated, washed with water, dried ($MgSO_4$), and evaporated. The residue was dissolved in chloroform and applied to a short column of silica gel eluting first with ethyl acetate/pet. ether (1:4) to remove the unreacted **6a** (3.5 g), and then eluting with ethyl acetate/ pet. ether (1:1) to give **7a** as a pale yellow foam which was crystallized from chloroform-ether: Yield 6.5 g (77%), mp 154-5 °C, TLC (ethyl acetate:/chloroform 1:4, v/v) R_f 0.5; IR (KBr) 3200 (NH_2), 2205 (CN), 1715 (C=O), 1610 and 710 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 4.65 (m, 3H), 5.85 (br. s, 2H, NH_2), 6.45 (m, 3H), 7.45 (m, 6H aromatic), 7.9 (m, 4H, aromatic), 8.35 (s, 1H, H-

2); ^{19}F NMR ($CDCl_3$) δ -226 (sextet, $J_{F,H-5'} = J_{F,H-5''} = 52.40$ Hz, $J_{F,H-4'} = 21.70$ Hz). Anal. calcd for $C_{26}H_{19}BrFN_5O_5$: C, 53.79; H, 3.27, F, 3.28; N, 12.06. Found: C, 54.01, H, 3.25, F, 3.47; N, 11.90.

4-Amino-6-bromo-5-cyano-7-(5-azido-2,3-di-O-benzoyl-5-deoxy-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (**7b**). To a cold (0 °C) solution of silylated 4-amino-6-bromo-5-cyanopyrrolo[2,3-d]pyrimidine (prepared from 6 g of the base as described for **7a**) and **6b** (6.5 g, 15.8 mmol) in anhydrous 1,2-dichloroethane (300 mL) was added dropwise and with stirring a solution of TMSTF (7 mL) in 1,2-dichloroethane (10 mL) during 15 min. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 22 h, and at 70-80 °C for 3 h. The mixture was cooled to 0 °C, diluted with methylene chloride and poured into a stirred mixture of ice-water-sodium hydrogen carbonate (15 g). The mixture was filtered to recover the unreacted pyrrolopyrimidine base (1.5 g) and the separated aqueous phase was extracted with chloroform. The combined organic solution was washed with water, dried ($MgSO_4$), and evaporated to give a yellow foam which was purified by chromatography on silica gel eluting first with pet. ether and then with ethyl acetate/pet. ether (1:4) to remove the colored impurities. The product was eluted with ethyl acetate/pet. ether (1:1) and obtained as a colorless foam which gave an amorphous solid when triturated with ether/pet. ether: Yield 8.2 g (85%); TLC EtOAc/ $CHCl_3$ 1:4, R_f 0.3; IR (KBr) 3300 (NH), 2175 (CN), 2075 (N_3), 1710 (C=O), 1615, 700 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 3.75 (dd, 2H, H-5'), 4.49 (m, 1H, H-4'), 5.90 (m, 2H H-2', H-3'), 6.35 (d, 1H, $J_{1',2'}$=3.2 Hz, H-1'), 6.5 (br, s, 2H, NH_2), 7.3 (m, 6H, aromatic), 7.80 (m, 4H, aromatic), 8.25 (s, 1H, H-2).
Anal. calc for $C_{26}H_{19}N_8O_5Br$: C, 51.74; H, 3.15; N, 18.57. Found: C, 51.57; H, 3.41; N, 18.39.

4-Amino-6-bromo-5-cyano-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-pyrrolo[2,3-d]pyrimidine (**8**). To a cold (0 °C) solution of silylated 4-amino-6-bromo-5-cyano-pyrrolo[2,3-d]pyrimidine (prepared from 4.76 g, 20 mmol, as described above for **7a**) and **17** (6.37g, 20 mmol) in dry 1,2-dichloroethane (100 mL) was added dropwise and with stirring a solution of TMSTF (6 mL, 31 mmol)

under an argon atmosphere. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 20 h and then at 50 °C for 2.5 h. The mixture was cooled to 0 °C and pyridine (10 mL) followed by chloroform (500 mL) were added. The mixture was washed with a saturated $NaHCO_3$ solution, water and dried ($MgSO_4$). Evaporation of the solution gave a residue which was crystallized from methanol and filtered (6 g, 60.4%, mp 195 °C). The filtrate was evaporated and the residue was purified by chromatography on silica gel eluting with ethyl acetate/toluene (2:1) to give 1g of **8**: Combined yield 70%; IR (KBr) 3200-3500 (NH), 2205 (CN), 1725 (C=O, Ac), 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.35 (s, 1H, H-2), 6.25 (d, 3H, J=3.25 Hz, H-1', NH_2), 5.60 (m, 2H, H-2', H-3'), 4.40 (br, s, 2H, H-5'), 2.1, 2.2 (2s, 9H, Ac).

Anal. Calc for $C_{18}H_{18}N_5O_7Br$: C, 43.54; H, 3.62; N, 14.11. Found: C, 43.44; H, 3.38; N, 14.35.

4-Amino-5-cyano-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (**9**). A solution of **8** (4 g, 8.06 mmol) in anhydrous dioxane (100 mL) containing triethylamine (6 mL) and palladium on charcoal (10%, 1.1g) was stirred under hydrogen at atmospheric pressure and room temperature for 5 h. The mixture was filtered and the catalyst was washed with chloroform. The combined filtrate was evaporated to give a residue which was dissolved in chloroform. This solution was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel, eluting with ethyl acetate/toluene (2:1), followed by crystallization from toluene to give 2.5 g (74.3%) of **9**: mp 126 °C, IR (KBr) 3300-3500 (NH), 2200 (CN), 1725 (C=0, OAc), 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.40 (s, 1H, H-2), 7.80 (s, 1H, H-6), 6.50 (m, 3H, H-1', NH_2), 5.80 (m, 2H, H-2', H-3'), 4.45 (br s, 2H, H-5'), 2.10 (br s, 9H, OAc); ^{13}C NMR (DMSO-d_6) δ 169.9, 169.2, 157.1, 146.2, 145.5, 144.3, 116.9, 102.9, 91.9, 81.8, 79.6; UV (ethanol) λ_{max} 278, 229, 209 nm, (pH 12) 278, 259 nm.

Anal. Calc for $C_{18}H_{19}N_5O_7$: C, 51.80; H, 4.55; N, 16.78. Found: C, 51.01; H, 4.32; N, 16.57.

4-Amino-5-carboxamido-1-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (10). To a stirred solution of **9** (2.09 g, 5 mmol) in anhydrous methanol (50 mL) was added anhydrous potassium carbonate (100 mg) and after stirring at room temperature for 1 h, the mixture was sequentially neutralized with ion exchange resin, (Dowex-50, pyridinium form), diluted with water (50 mL), and heated briefly at reflux. The resin was filtered and washed with hot aqueous methanol (1:1, 100 mL). The combined filtrate was evaporated to give a crystalline solid which was stirred at room temperature with conc. ammonium hydroxide (48 mL) and hydrogen peroxide (30%, 4.8 mL). The suspended solid dissolved in 20 min and a solid product slowly separated from the solution. The mixture was left at 0-5 °C for 18 h, filtered, and the solid was washed with aqueous ethanol (50%), and dried to give 1.3 g (79.4%) of **10**. An analytical sample was obtained by a re-crystallization from water; mp 237 °C dec; IR (KBr) 3000-3300 (NH, OH), 1650, 1625 cm^{-1} (amide and pyrimidine).

Anal. Calc for $C_{12}H_{15}N_5O_5$: C, 46.60; H, 4.89; N, 22.64. Found: C 46.25; H, 4.62; N, 22.51.

4-Amino-5-cyano-7-(2,3-di-O-benzoyl-5-deoxy-5-fluoro-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (11a). A solution of **7a** (5.7 g, 10 mmol) in anhydrous dioxane (150 mL) containing triethylamine (5 mL) was stirred at room temperature under atmospheric pressure H_2 and in the presence of palladium on charcoal (10%, 2 g) for 24 h. The mixture was filtered and the catalyst was washed with chloroform (50 mL). The combined filtrate was evaporated to give a residue which was sequentially dissolved in chloroform, washed with water, dried ($MgSO_4$), evaporated, and dried to a colorless foam (5.2 g, 90%): TLC EtOH/$CHCl_3$ 1:4, R_f 0.3; IR (KBr) 3400 (NH), 2205 (CN), 1715(C=O), 1610 and 700 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 4.55 (m, 2H), 5.95 (br. s, 2H, NH_2), 6.80 (d, 1H, $J_{1',2'}$ =4.55 Hz, H-1'), 7.30 (m, 6H, aromatic), 7.95 (m, 5H, H-6 and 4H-aromatic), 8.35 (s, 1H, H-2); ^{19}F NMR ($CDCl_3$) δ -229.50 (sextet, $J_{F,H-5'} = J_{F,H-5''}$ = 53.50 Hz, $J_{F,H-4}$= 36.60 Hz).

Anal. calc for $C_{26}H_{20}FN_5O_5$: C, 62.29; H, 3.99; F, 3.79; N, 13.97. Found: 62.09; N, 3.97; F, 4.01, N, 13.82.

4-Amino-5-cyano-(5-amino-2,3-di-O-benzoyl-5-deoxy-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (11c). A solution of **7b** (5 g, 8.3 mmol) in anhydrous dioxane (200 mL) and triethylamine (3 mL) was stirred under hydrogen at room temperature and in the presence of palladium on charcoal (10%, 2 g) for 18 h. The solution was filtered and evaporated to give a residue which was dissolved in chloroform. The solution was sequentially washed with water, dried ($MgSO_4$), concentrated to a small volume, and applied to a short column of silica gel. The column was eluted with acetone/pet. ether (1:1) to give 3.7 g (90%) of **11c** as a yellowish foam: TLC acetone/pet. ether 2:3, R_f 0.35; IR (KBr) 3200 (NH), 2200 (CN), 1715 (C=O), 1615, 700 cm^{-1} (aromatic); ^1H NMR ($CDCl_3$) δ 3.5 (m, 2H, H-5'), 4.5 (m, 1H, H-4'), 6.10 (m, 2H, H-2',H-3'), 6.40 (d, 1H, $J_{1',2'}$=4.5 Hz, H-1'), 7.30 (m, 6H, aromatic), 7.90 (m, 5H, H-6 and aromatic), 8.25 (s, 1H, H-2).

Anal. calc for $C_{26}H_{22}N_6O_5$: C, 62.65; H, 4.41; N, 16.86. Found: C, 62.45; H, 4.49; N, 16.96.

4-Amino-5-cyano-7-(5-deoxy-5-fluoro-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (5'-Deoxy-5'-fluorotoyocamycin) (12a). A saturated solution of ammonia in anhydrous methanol (100 mL) was added to **11a** (1.6 g, 3.2 mmol) and the mixture was stirred at room temperature for 24 h. The solution was evaporated to give a residue which was dried and crystallized from hot water to give 850 mg (91%) of **12a**: mp 247-8 °C; IR (KBr) 3300 (OH, NH), 2200 cm^{-1} (CN); UV (ethanol) λ_{max} 279, 231, 209 nm, (pH 12) 278 nm.

Anal. calcd for $C_{12}H_{12}FN_5O_3$ 0.5 H_2O: C, 47.67; H, 4.30; N, 23.19. F, 6.29. Found: C, 47.61; H, 4.33; N, 22.91; F, 6.43.

4-Amino-5-cyano-7-(5-azido-5-deoxy-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (12b). A mixture of toyocamycin (**16**, 291 mg, 1 mmol), triphenylphosphine (320 mg, 1.2 mmol), CBr_4 (500 mg, 1.5 mmol) and sodium azide (650 mg, 10 mmol) in anhydrous DMF (7 mL) was stirred at room temperature for 24 h, filtered and the residue washed with DMF (5 mL) followed by ethanol (10 mL). The combined filtrate was evaporated and the residue was co-evaporated with xylene and then dissolved in methanol. Silica gel (10 g) was

stirred with this solution and the mixture was evaporated and dried, and applied to a short column of silica gel which was then eluted with methanol/chloroform (1:4) to give **12b** contaminated with triphenylphosphine oxide. This residue was dissolved in methylene chloride and crystallized at room temperature to give **12b** which was re-crystallized from water: Yield 125 mg (40 %); mp 190-2 °C; IR (KBr) 3100-3500 (OH, NH), 2210 (CN), 2105 (N_3) cm^{-1}; UV (ethanol) λ_{max} 279, 229, 204 nm, (pH 12) 279 nm.

Anal. Calc for $C_{12}H_{12}N_8O_3$: C, 45.57; H, 3.80; N, 35.44. Found: C, 45.62; H,3.86, N, 35.14.

4-Amino-5-cyano-7-(5-amino-5-deoxy-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (5'-Amino-5'-deoxytoyocamycin) (12c). A solution of **11c** (1.5 g, 3 mmol) in anhydrous methanolic ammonia (100 mL, saturated at 0 °C) was stirred at room temperature for 24 h and evaporated. The residue was sequentially co-evaporated with ethanol, triturated with ether, filtered and crystallized from methanol to give 520 mg (78%) of **12c**: mp 134-7 °C, IR (KBr) 300-3300 (NH_2, OH), 2200 (CN), 1620 cm^{-1}.

Anal. calcd for $C_{12}H_{14}N_6O_3$: C, 49.66; H, 4.82; N, 28.97. Found: C, 49.42; H, 5.04; N, 28.75.

4-Amino-5-cyano-7-(5-deoxy-5-N-sulfamoylamino-β-D-ribofuranosyl)-pyrrolo[2,3-d]pyrimidine (12d). Sulfamoyl chloride (1 g, 8.0 mmol) was added in several portions to a cold (0 °C) and stirred solution of **11c** (2 g, 4.0 mmol) in anhydrous pyridine (25 mL). The reaction mixture was stirred at room temperature for 18 h, cooled to 0 °C and stirred with ice-water. After approximately 15 min, the mixture was evaporated to give a residue which was co-evaporated with toluene and then dissolved in a minimum amount of methanol and precipitated by the addition of cold water. The solid was filtered, washed with cold water, dried and crystallized from methanol/ether to give 2 g (74%) of **11d**: mp 135-37 °C; IR (KBr) 300-3200 (NH), 2200 (CN), 1710 (C=O), 1620 and 700 cm^{-1} (aromatic). A solution of **11d** (1.7g, 2.9 mmol) in methanolic ammonia (100 mL, saturated at 0 °C), was stirred at room temperature for 24 h and evaporated to give a residue which was co-evaporated with absolute

ethanol and crystallized from hot water to give 530 mg (53%) of **12d**: mp 254-7 °C dec; IR (KBr) 3000-3200 (NH_2, OH), 2200 (CN), and 1625 cm^{-1}.

Anal. calc for $C_{12}H_{15}N_7O_5S$: C, 39.02; H, 4.06; N, 26.56. Found: C, 38.87; H, 4.28; N, 26.28.

4-Amino-5-cyano-7-(5-deoxy-5-N-trifluoromethanesulfonylamino-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (**12e**). Trifluoromethanesulfonyl anhydride (60 mg, 0.21 mmol) was added with stirring to a cold (0 °C) solution of **12c** (58 mg, 0.2 mmol) in anhydrous DMF (2 mL). The mixture was stirred at 0-5 °C for 3 hr and then at room temperature for 10 min, re-cooled to 0 °C, and treated with a solution of aqueous triethylamine (~ 2 mL). The mixture was evaporated to give a residue which was co-evaporated with toluene followed by ethanol, washed with ether and then dissolved in methanol. This solution was kept at -20 °C overnight and filtered to give crystalline **12e** which was re-crystallized from methanol/ethanol; yield 35 mg (41%), mp 258-60 °C; IR (KBr) 3000-3400 (NH, OH), 1610, 1420, 1295, 1180 cm^{-1} (SO_2).

Anal. Calc for $C_{13}H_{13}F_3N_6O_5S{\cdot}H_2O$: C, 35.45; H, 3.40; N, 19.09. Found: C, 35.27; H, 3.70; N, 19.25.

4-Amino-5-cyano-7-(5-deoxy-5-isothiocyano-β-D-ribofuranosyl)pyrrolo-[2,3-d]pyrimidine (**12f**). *Method A.* A solution of N,N-thiocarbonyl-di-imidazole (100 mg, 0.56 mmol) in dry chloroform (2 mL) was added to a cold (0 °C) stirred solution of **11c** (250 mg, 0.5 mmol) in dry chloroform (5 mL). Stirring was continued at 0 °C for 15 min and then at room temperature for 90 min and the mixture was evaporated. The residue was washed repeatedly with ether to give 200 mg (77%) of **11f** as a colorless solid: mp 135-8 °C; TLC acetone/pet. ether 2:3, R_f 0.5; IR (KBr) 3200-3100 (NH, OH), 2150 (CN), 2050 (N=C=S), 1710 (C=O), 1620, 1250, 695 cm^{-1} (aromatic). A solution of **11f** in methanolic ammonia was then stirred at 0 °C for 22 hr and evaporated to give a residue which was co-evaporated with ethanol, washed with ether and crystallized from water: Yield 95 mg (58%) of **12f**; mp 250-2 °C dec; IR (KBr) 3100-3400 (OH, NH), 2100 (CN), 2005 cm^{-1} (N=C=S).

Anal. Calc for $C_{13}H_{12}N_6O_3S$: c, 46.98; H, 3.61; N, 25.30. Found: C, 47.01; H, 3.48; N, 25.18.

Method B. A solution of **12c** (100 mg, 0.35 mmol) in anhydrous DMF (4 mL) was treated at 0 °C with N,N-thiocarbonyl-di-imidazole (62 mg, 0.35 mmol) and the mixture was stirred at room temperature for 2 h. The mixture was evaporated to give a residue which was washed with ether followed by ethanol and crystallized from water to furnish 52 mg (46%) of **12f**: mp and IR spectrum were identical with those of the product prepared by *Method A*.

4-Amino-5-cyano-7-(5-deoxy-5-p-nitrobenzenesulfonylamino-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (**12g**). A cold (0 °C) solution of **11c** (500 mg, 1 mmol) in anhydrous pyridine (4 mL) was treated with a solution of p-nitrobenzenesulfonyl chloride (300 mg, 1.4 mmol) in dry pyridine (2 mL). The mixture was stirred at 0 °C for 2 h and then at room temperature for 0.5 h, and poured into ice-water. Chloroform (50 mL) was added to this mixture and, after stirring for 0.5 h, the chloroform solution was separated, washed with water, dried ($MgSO_4$), and evaporated. The residue was dissolved in chloroform and purified by chromatography on silica gel eluting with acetone/pet. ether (2:3) to give 510 mg (74%) of **11g** as an amorphous solid: IR (KBr) 3200 (NH), 2150 (CN), 1710 (C=O), 1615, 1510 NO_2), 1320, 1150 cm^{-1} (SO_2). This intermediate (340 mg, 0.5 mmol) was dissolved in a solution of methanolic ammonia (50 mL, saturated at 0 °C) and kept at room temperature for 20 h. The solution was evaporated and the residue was co-evaporated with ethanol to give a solid which was washed with ether and crystallized from methanol/ethanol: yield 180 mg (71%) of **12g**; mp 195-7 °C; IR (KBr) 3200-3500 (NH, OH), 2050 (CN), 1610, 1510 (NO_2), 1350, 1150 cm^{-1} (SO_2).

Anal. Calc for $C_{18}H_{17}N_7O_7S$: C, 45.47; H, 3.58; N, 20.63. Found: C, 45.19; H, 3.25; N, 20.42.

4-Amino-5-carboxamido-7-(5-deoxy-5-fluoro-β-D-ribofuranosyl)pyrrolo-[2,3-d]pyrimidine (5'-Deoxy-5'-fluorosangivamycin) (**13a**). To a cold (0 °C) solution of **12a** (850 mg, 0.29 mmol) in conc. ammonium hydroxide (30 mL) was added hydrogen peroxide (30%, 3 mL) and the mixture was stirred at room

temperature for 3 h and then kept at 0-5 °C overnight for crystallization. The white solid was filtered, washed with 50% ethanol/water and re-crystallized from hot water to give 750 mg (75%) of **13a**: mp 257-8 °C; TLC methanol/chloroform, 1:4, R_f 0.35; IR (KBr) 3200-3500 (NH, OH), 1610 cm^{-1}.

Anal. calcd for $C_{12}H_{14}FN_5O_4$: C, 46.30; H, 4.50; N, 22.51, F, 6.10. Found: C, 46.23; H, 4.38; N, 22.37, F, 6.13.

4-Amino-5-carboxamido-7-(5-azido-5-deoxy-β-D-ribofuranosyl)pyrrolo-[2,3-d]pyrimidine (13b)[6]. Hydrogen peroxide (30%, 0.5 mL) was added to a cold (0 °C) solution of **12b** (50 mg, 0.14 mmol) in conc. ammonium hydroxide (5 mL) with stirring and the reaction mixture was stirred at 0 °C for 0.5 h and then at room temperature for 3 h. The mixture was evaporated and the residue was co-evaporated with ethanol to give a residue which solidified in methanol/ether: Yield 42 mg (78%); mp 198-200 °C; IR (KBr) 3000-3300 (NH, OH), 2095 (N_3) cm^{-1}.

4-Amino-5-carboxamido-7-(5-amino-5-deoxy-β-D-ribofuranosyl)pyrrolo-[2,3-d]pyrimidine (5'-Amino-5'-deoxysangivamycin) (13c). *Method A*: A solution of **12c** (2.0 g, 6.9 mmol) in conc. ammonium hydroxide (70 mL) and hydrogen peroxide (30%, 7 mL) was stirred at 0-5 °C overnight and filtered. The solid was washed with cold 50% ethanol and crystallized from methanol/ethanol: Yield 1.6 g (79%); mp 245-8 °C; IR (KBr) 3200-3400 (NH_2, OH), 1620 cm^{-1} (C=O).

Anal. calc for $C_{12}H_{16}N_6O_4$: C, 46.75; H, 5.19; N, 27.27. Found: C, 46.68; H, 4.92; N, 27.01.

Method B: A solution of 4-amino-5-carboxamido-7-(5-azido-5-deoxy-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (**13b**) (20 mg, 0.06 mmol) in methanol 10 mL was hydrogenated at room temperature and in the presence of palladium on charcoal (10%, 50 mg) for 5 h. The mixture was filtered and evaporated to give a residue which was crystallized from methanol/ethanol: mp 245-8 °C (undepressed when taken with a mixture of **13c** prepared by *Methods A* and *B*).

4-Amino-5-carboxamido-7-(5-deoxy-5-N-sulfamoylamino-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (13d). Hydrogen peroxide (30%, 0.8

mL) was added to a cold (0 °C) solution of **12d** (220 mg, 0.6 mmol) in conc. ammonium hydroxide (5 mL) and the mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h. The solution was kept at 0-5 °C overnight, and the white solid was filtered, washed with 50% ethanol and dried. Re-crystallization of this material from hot water furnished 190 mg (85%) of pure **13d**: mp 275 °C dec; IR (KBr) 3200-3400 (NH_2, OH), 1610 and 1201 cm^{-1} (SO_2).

Anal. calc for $C_{12}H_{17}N_7O_6S$: C, 37.21; H, 4.39; N, 25.32. Found: C, 36.98; H, 4.42; N, 25.18.

4-Amino-7-(5-deoxy-5-fluoro-β-D-ribofuranosyl)-5-thioamidopyrrolo-[2,3-d]pyrimidine (5'-Deoxy-5'-fluoro-5-thiosangivamycin (15a). A slow stream of hydrogen sulfide was passed through a solution of **11a** (500 mg, 0.17 mmol) in anhydrous pyridine (10 mL) for 1.5 h. The mixture was evaporated to give a residue (**14a**) which was co-evaporated with ethanol and then treated at room temperature with a saturated solution of ammonia in anhydrous methanol (30 mL) for 24 h. The mixture was evaporated to give a residue which was co-evaporated with ethanol and crystallized from methanol/ethanol: Yield 150 mg (27%); mp 235-8 °C dec; TLC EtOAc/ methanol 4:1 R_f 0.65; IR (KBr) 3200-3000 (NH, OH), 1610 cm^{-1}.

Anal. calcd for $C_{12}H_{14}FN_5O_3S$: C, 44.03; H, 4.28; N, 21.40, F, 5.81. Found: C, 47.27; H, 4.01; N, 21.64; F, 5.92.

4-Amino-5-thiocarboxamido-7-(5-amino-5-deoxy-β-D-ribofuranosyl)-pyrrolo[2,3-d]pyrimidine (15c). Hydrogen sulfide was slowly introduced at 0-5 °C into a solution of **11c** (350 mg, 0.71 mmol) in anhydrous pyridine (15 mL) and triethylamine (1.5 mL) for 4 h and then the mixture was stirred at room temperature in a closed vessel for 18 h. Nitrogen was passed through the solution to remove the excess hydrogen sulfide and the solvent was evaporated. The residue was co-evaporated with ethanol to give a yellow semi-solid which showed the absence of CN band in its IR spectrum. This intermediate (**14c**) was treated at room temperature with methanolic ammonia (30 mL, saturated at 0 °C) in a closed flask for 20 h. The mixture was evaporated to give a residue which was co-evaporated with ethanol and crystallized from hot water: Yield 155 mg

(68%); mp 237-40 °C; IR (KBr) 3000-3300 (NH_2, OH), 1620, 1550 cm^{-1} (NH-C=S).

Anal. calc for $C_{12}H_{16}N_6O_3S$: C, 44.44; H, 4.94; N, 25.92. Found: C, 44.56; H, 4.72; N, 25.74.

4-Amino-6-bromo-5-cyano-7-(5-azido-5-deoxy-β-D-ribofuranosyl)-pyrrolo[2,3-d]pyrimidine (**17b**). A solution of **7b** (700 mg, 11.6 mmol) in anhydrous methanolic ammonia (50 mL, saturated at 0 °C) was stirred at room temperature for 20 h and evaporated to give a residue which was co-evaporated with ethanol and washed with pet. ether. The residue was dissolved in ethanol/ether and pet. ether was added slowly to precipitate the product. The solvents were separated and the precipitation step was repeated to give a white powder (370 mg, 81%) which was crystallized from water: mp 175-8 °C, dec; IR (KBr) 3000-3500 (NH, OH), 2200 (CN), 2095 (N_3) cm^{-1}.

Anal. Calcd for $C_{12}H_{11}N_8O_3Br$: C, 36.46; H, 2.78; N,28.35. Found: C, 36.34; H, 3.01; N, 28.28.

4-Amino-6-bromo-5-carboxamido-7-(5-azido-5-deoxy-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (**18b**). To a cold (0 °C) solution of **17b** (350 mg, 0.89 mmol) in conc. ammonium hydroxide (25 mL) was added hydrogen peroxide (30%, 2.5 mL) with stirring. The mixture was stirred at 0-5 °C for 0.5 h and then at room temperature for 4 h and left at 0-5 °C overnight. The white solid which separated was filtered, washed with cold 50% ethanol and dried: Yield 285 mg (78%). An analytical sample was obtained by re-crystallization from water: mp 210-2 °C, dec; IR (KBr) 3000-3500 (NH, OH), 2100 (N_3) cm^{-1}.

Anal. Calcd for $C_{12}H_{13}N_8O_4Br$: C, 34.88; H,3.15; N,27.13. Found: C, 35.05; H, 3.44; N,26.96.

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