Total and Stereospecific Synthesis of Cadeguomycin, 2′-Deoxycadeguomycin, *ara*-Cadeguomycin, and Certain Related Nucleosides[1]

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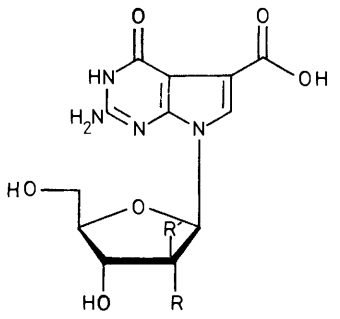
A total and stereospecific synthesis of cadeguomycin (**1**), *ara*-cadeguomycin (**2**), and 2′-deoxycadeguomycin (**3**) has been accomplished from the novel aglycones 2-amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (**11**) or methyl 2-amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxylate (**13**). Ring annulation of 2,6-diaminopyrimidin-4(3*H*)-one (**6**) with methyl chloro(formyl)acetate (**7**) in the presence of NaOAc provided a mixture of two products (**8**) and (**9**), from which the desired methyl 2-amino-3,4-dihydro-4-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxylate (**9**) was separated and converted into the key intermediates (**11**) and (**13**). Reaction of the sodium salt of (**11**) with 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl chloride (**14**) gave the corresponding protected nucleoside (**15**). Deprotection of (**15**) provided (**16**), which on treatment with NH_4OH–H_2O_2, followed by saponification, gave the target nucleoside (**3**) in good yield. Compound (**3**) was also prepared from compounds (**13**) and (**14**) by a similar sequence of reactions. Glycosylation of the sodium salt of (**11**) with 5-*O*-t-butyldimethylsilyl-2,3-*O*-isopropylidene-α-D-ribofuranosyl chloride (**22**) gave protected nucleoside (**23**), which on treatment with 4M-KOH followed by deisopropylidenation afforded cadeguomycin (**1**). Similarly, glycosylation of the sodium salt of (**11**) with 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride (**27**) furnished the corresponding glycosylated product (**28**), which on debenzylation and hydrolysis produced *ara*-cadeguomycin (**2**). Selective functional-group transformations of compound (**16**), (**21**), and (**24**) furnished several 2-amino-4,5-disubstituted pyrrolo[2,3-*d*]pyrimidine nucleosides.

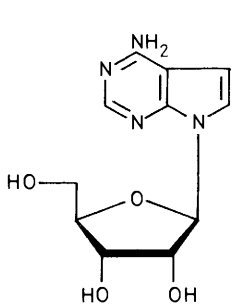
Cadeguomycin (**1**) is one of a family of natural pyrrolo[2,3-*d*]pyrimidine nucleoside antibiotics,[2] isolated[3] from the culture broth of *Streptomyces hygroscopicus* IM7912T as a minor component together with tubercidin (**4**) and characterized as 2-amino-3,4-dihydro-4-oxo-7-β-D-ribofuranosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxylic acid.[4] This interesting antibiotic inhibited the growth of solid IMC carcinoma and pulmonary metastasis of Lewis lung carcinoma in mice with appreciably low toxicity.[5] It also enhanced cell-mediated immunity and macrophage activity.[5] Cadeguomycin displayed a unique property of enhancing uptake of pyrimidine nucleosides into K562 human myelogenous leukaemic cells and YAC-1 murine lymphoma cells, and it potentiated cytotoxicity of *ara*-C,[5–7] as well as 5-fluoro-2′-deoxycytidine[8] both *in vitro* and *in vivo*. This interesting biological activity, coupled with the biogenetic relationship to 7-deazaguanosine (**5**)[9,10] prompted us to synthesize large quantities of cadeguomycin (**1**) and the sugar-modified analogues *ara*-cadeguomycin (**2**) and 2′-deoxycadeguomycin (**3**) to study in detail their biological properties.

Since the isolation of cadeguomycin (**1**) from natural sources, chemical syntheses of (**1**) as well as *ara*-cadeguomycin (**2**) have been reported. Townsend and co-workers[11] have provided a synthesis of compound (**1**) from a preformed nucleoside toyocamycin *via* toyocamycin N^3-oxide. Goto and co-workers[12] have also prepared (**1**), first on a milligram scale, and subsequently they improved[13] the overall yield using 3,7-dihydro-2-methylthio-5-methylpyrrolo[2,3-*d*]pyrimidin-4-one[14] and 2,3-*O*-isopropylidene-5-*O*-triphenylmethyl-D-ribofuranosyl chloride.[15,16] The latter authors have also synthesized[17] *ara*-cadeguomycin (**2**) by utilizing essentially the same sequence of reactions that was applied to the synthesis of cadeguomycin (**1**).[13] However, the synthesis of 2′-deoxycadeguomycin (**3**) has not yet been realized.

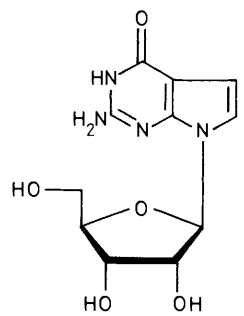
Apart from compounds (**1**), (**2**), and (**3**), several naturally occurring nucleoside antibiotics like nucleoside Q,[18] nucleoside



(**1**) R = OH ; R′ = H , cadeguomycin
(**2**) R = H; R′ = OH , *ara* - cadeguomycin
(**3**) R = R′ = H , 2′ - deoxycadeguomycin



(**4**)



(**5**)

preQ$_0$,[19] and kanagawamicin[20] possess 7-deazaguanine as a common skeleton, with a substituent at the 7-position (purine nomenclature). Since all the above nucleosides contain the common 7-deazaguanine skeleton, it is conceivable that their synthesis can be achieved through a common intermediate. We selected chloro compounds (**11**) and (**13**) as key intermediate aglycones for the synthesis of these nucleosides. In this report we describe the total and stereospecific synthesis of compounds (**1**), (**2**), and (**3**) from the novel aglycones 2-amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (**11**) or methyl 2-amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxylate (**13**).

The synthesis of these 7-deazapurine nucleosides can be achieved using three different synthetic routes. The approach that we elected involves the ring annulation of the substituted pyrimidine (**6**) with methyl chloro(formyl)acetate (**7**) to give the pyrrolo[2,3-*d*]pyrimidine skeleton (**9**), followed by conversion into the intermediates (**11**) or (**13**), and subsequent glycosylation with an appropriate carbohydrate. A similar methodology, which has been used by Secrist and Liu[21] for the synthesis of certain pyrrolo[2,3-*d*]pyrimidines, is similar to the method employed by Noell and Robins.[22] Another strategy that has been used successfully for the synthesis of cadeguomycin was from preformed toyocamycin.[11] A third method could be to ring close an appropriately substituted pyrrole nucleoside, as we described in the case of 2′-deoxytoyocamycin[23] and *ara*-toyocamycin.[24]

Results and Discussion

Our strategy, based on the chloroacetaldehyde precedent,[22] was to generate a substituted 7-deazaguanine ring system directly by forming the pyrrole ring onto a pyrimidine derivative. By employing the appropriate chloroacetaldehyde, substituents might be introduced into the pyrrole ring to give pyrrolo[2,3-*d*]pyrimidine precursor (**9**), which could then be transformed to either (**11**) or (**13**). The key substrate chosen for the synthesis of intermediate (**9**) was methyl chloro(formyl)acetate (**7**), which was prepared as reported.[25] When a solution of 2,6-diaminopyrimidin-4(3*H*)-one (**6**) and ester (**7**) in dimethyl sulphoxide (DMSO) containing anhydrous K_2CO_3 was stirred at ambient temperature for 2 days a mixture of two products was obtained, which after separation were identified as methyl 2,4-diaminofuro[2,3-*d*]pyrimidine-6-carboxylate (**8**) (25% yield) and methyl 2-amino-3,4-dihydro-4-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxylate (**9**) (35% yield) (Scheme 1). However, heating of an aqueous solution of reactants (**6**) and (**7**) with NaOAc for 1 h also gave the same products (**8**) and (**9**) (75% total yield), but increased the yield of the desired major product (**9**) to 50%. Although pure bicycles (**8**) and (**9**) could be separated from the mixture on a small scale (<100 mg) by fractional crystallization [compound (**9**) crystallizes first from MeOH], attempted large-scale separation of (**9**) from (**8**) was found to be rather difficult by the usual chromatographic or crystallization techniques. The problem was, however, resolved by a selective protection * of the pyrrole ring NH-proton in (**9**) with di-t-butyl dicarbonate (DBDC) to give 7-t-butyl 5-methyl 2-amino-3,4-dihydro-4-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidine-5′,7-dicarboxylate (**10**), followed by filtration of compound (**10**) from the insoluble furo pyrimidine (**8**) in boiling EtOAc.

The ^{1}H n.m.r. spectra of both products (**8**) and (**9**) exhibited only one vinyl proton and the absence of the 5-H proton of (**6**), indicating that the products were formed by condensation at C-5 of the pyrimidine ring. Annulation by any other mode would have produced products with two vinyl protons. Besides the vinyl proton, the ^{1}H n.m.r. spectrum of compound (**9**) exhibited two NH protons at δ 10.37 and 11.65, NH_2 protons at δ 6.22, and CO_2Me protons at δ 3.67. The ^{13}C n.m.r. resonances of compound (**9**) were identical with those of natural cadeguomycin (excluding the sugar portion), and also comparable with the reported ^{13}C n.m.r. values of the pyrrolo[2,3-*d*]pyrimidine ring system.[21] Thus, compound (**9**) had ^{1}H and ^{13}C n.m.r. characteristics which readily allowed assignment of the pyrrolo-[2,3-*d*]pyrimidine system to it. However, depending upon the regiospecificity of the reaction, either the 5-methyl carboxylate or 6-methyl carboxylate compound might be produced. This positional assignment was resolved by using ^{13}C n.m.r. data (Table). The signal for C-5 (δ_C 109.80) of compound (**9**) remained as a singlet upon off-resonance decoupling, while that for C-6 (δ_C 124.96) split into a doublet, thus placing the methyl ester function at C-5. That the minor product (**8**) is not the isomeric pyrrolo[2,3-*d*]pyrimidine was also conclusively demonstrated with the help of ^{1}H and ^{13}C n.m.r. spectroscopy. The position of the methyl carboxylate group in (**8**) was readily assigned by ^{13}C n.m.r. spectroscopy where C-5 (δ_C 114.09) split into a doublet upon off-resonance decoupling, while C-6 (δ_C 136.31) remained as a singlet, thus placing the methyl ester group at C-6 in compound (**8**). From heteronuclear two-dimensional chemical-shift correlation techniques,[26] data were obtained to assign the unequivocal structure of compound (**8**). The heteronuclear shift-correlated spectrum (Figure) established the carbon–proton connectivity and the unambiguous assignment of the ^{13}C n.m.r. spectrum.[27] The heteronuclear spectrum also showed that the proton H_d (δ 7.62) is attached to C-5 (δ_C 114.09), which conclusively assigned the chemical shift of C-5.

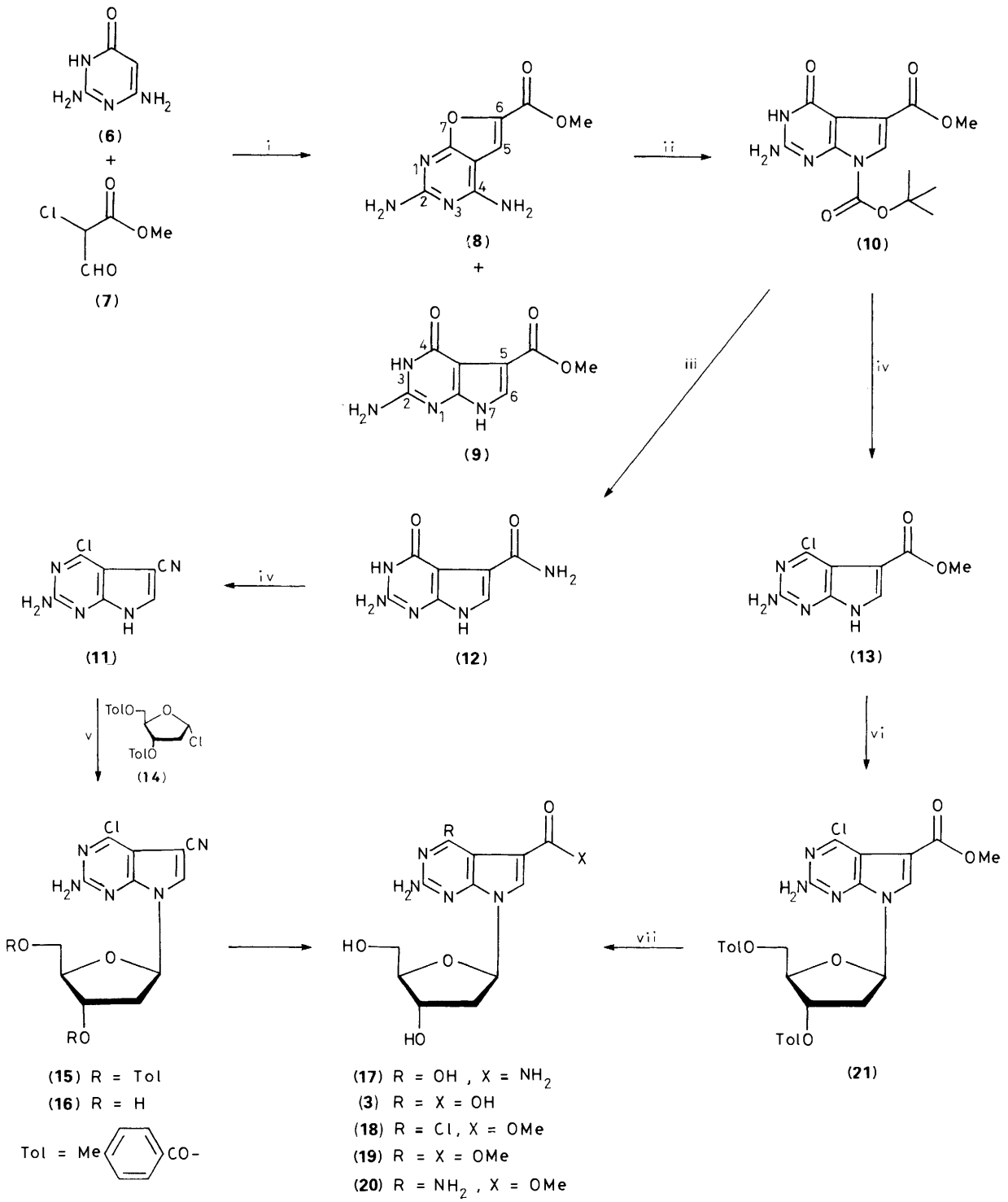
The selective N-7 protection of compound (**9**) by the t-BOC (t-butoxy) group was confirmed by comparison of the proton spectra of compounds (**9**) and (**10**). In the ^{1}H n.m.r. spectrum of (**9**), the 6-H appeared as a doublet by coupling with 7-H of the pyrrole ring. However, in compound (**10**) the 6-H collapsed to a singlet, thus indicating that the 7-H of (**10**) is being blocked and not the 3-H or the exocyclic NH_2 group.

The ring annulation reaction of methyl chloro(formyl)acetate (**7**) with diamine (**6**) occurs in a regiospecific manner. In the formation of pyrrolo[2,3-*d*]pyrimidine, first a carbon–nitrogen bond is being formed between the 6-NH_2 group of (**6**) and the CHO group of compound (**7**), to give an intermediate of type A. The intermediate A on subsequent cyclization and aromatization gives the pyrrolo[2,3-*d*]pyrimidine (**9**). Furo[2,3-*d*]pyrimidine is, however, formed by nucleophilic attack of the 4-oxygen of compound (**6**) at the carbon attached to the halogen of (**7**) to give the intermediate B, followed by cyclization at C-5 of compound (**6**).

After a successful separation and structural assignment of compound (**9**), preparation of the key intermediates 2-amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (**11**) and methyl 2-amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxylate (**13**) required for the preparation of cadeguomycins (**1**), (**2**), and (**3**) was next considered. Thus heating of diester (**10**) with phosphorus trichloride oxide in the presence of *N*,*N*-diethylaniline (DEA) gave a 20% yield of chloro ester (**13**). The low yield of this product (**13**) obtained from (**10**) prompted us to investigate an alternate intermediate (**11**). Reaction of compound (**10**) with MeOH–NH_3 (saturated at 0 °C) at 120 °C for 15 h converted the methyl ester function into an amide group with concomitant deprotection of the t-BOC group to give 2-amino-3,4-dihydro-4-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide (**12**) in 73% yield. Treatment of compound (**12**) with $POCl_3$ in the presence of DEA at reflux temperature for 4 h gave the alternative intermediate (**11**) in 40% yield.

Both intermediates (**11**) and (**13**) are suitable precursors for the stereospecific sodium-salt glycosylation procedure developed recently in our laboratory[28] to obtain the target

* Selective protection was confirmed by ^{1}H n.m.r. spectrum.



Scheme 1. *Reagents and conditions:* i, K_2CO_3 or NaOAc; ii, DBDC, DMF–TEA; iii, MeOH, NH_3, heat; iv, $POCl_3$, DEA; v, NaH; vi, NaH, (**14**); vii, NaOH

nucleosides. Accordingly, the sodium salt of (**11**), generated *in situ* by the treatment of NaH in anhydrous CH_3CN, was treated with 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl chloride[29] (**14**) to give the protected nucleoside (**15**) as crystalline material. No formation of the α-anomer was detected by t.l.c. or h.p.l.c. Deprotection of compound (**15**) with methanolic ammonia at room temperature for 12 h furnished 2-amino-4-chloro-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (**16**) in 88% yield. A solution of compound (**16**) in conc. NH_4OH and H_2O_2 mixture was stirred at room temperature for 2 days to provide a product characterized as 2-amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-3,4-dihydro-4-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide (**17**). The formation of compound (**17**) is of particular interest since base treatment of compound (**16**) under mild reaction conditions, not only converted the nitrile function

Table. ^{13}C N.m.r. data of pyrrolo- and Furo-[2,3-*d*]pyrimidines

Compound	C-2	C-4	C-4a	C-5	C-6	C-7a	Other carbons
(**9**)	153.24	157.39	97.40	109.80	124.96(d)	152.90	50.72 (Me, q) 163.45 (C=O)
(**8**)	159.99	159.02	93.26	114.09(d)	136.31	163.45	51.82 (Me, q) 169.68 (C=O)

All resonances are in p.p.m. downfield from $(CD_3)_2SO$. Letters in parentheses refer to multiplicities in off-resonance decoupled spectra.

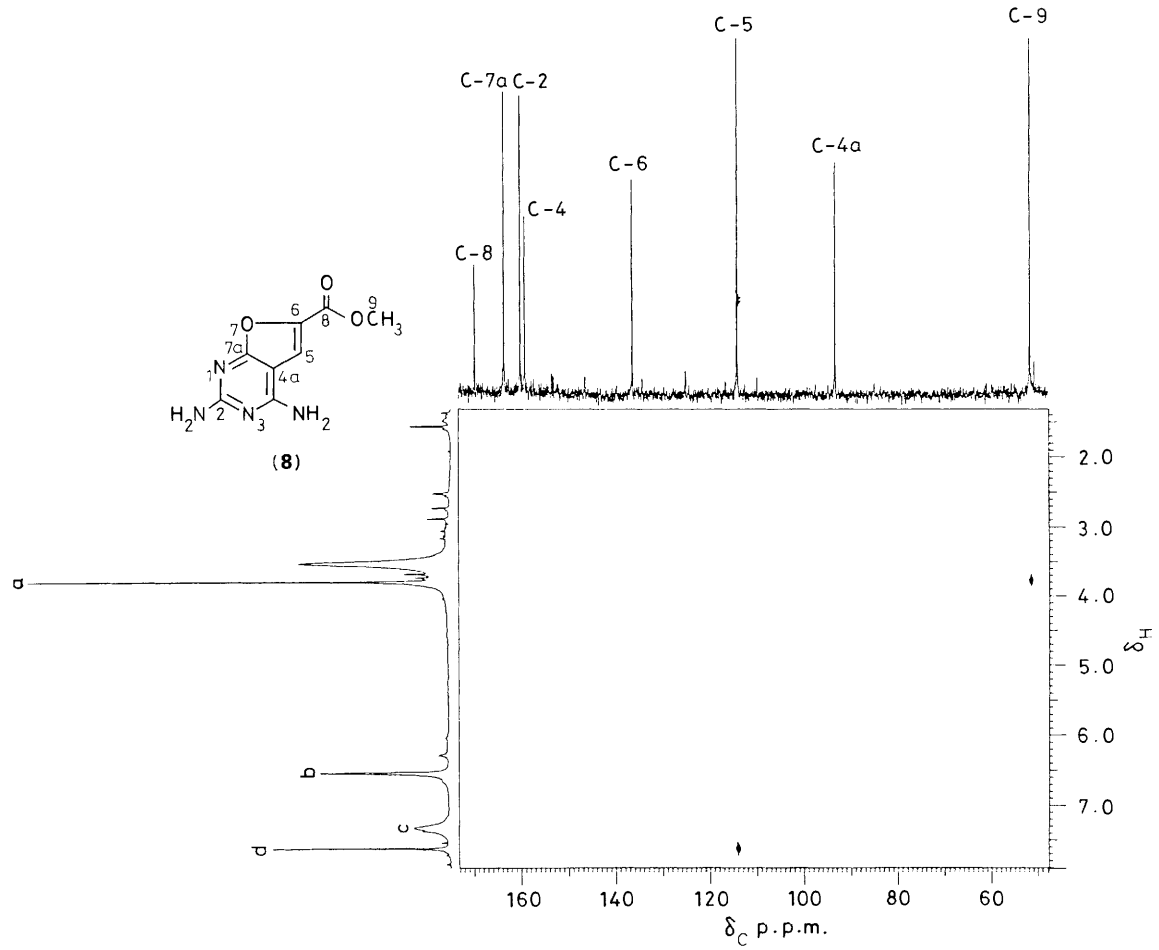
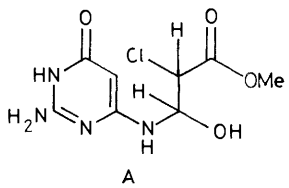
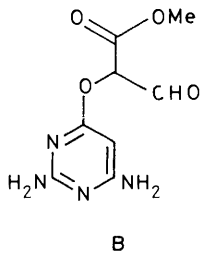


Figure. Two-dimensional heteronuclear shift-correlated spectrum of compound (**8**) in $(CD_3)_2SO$



A

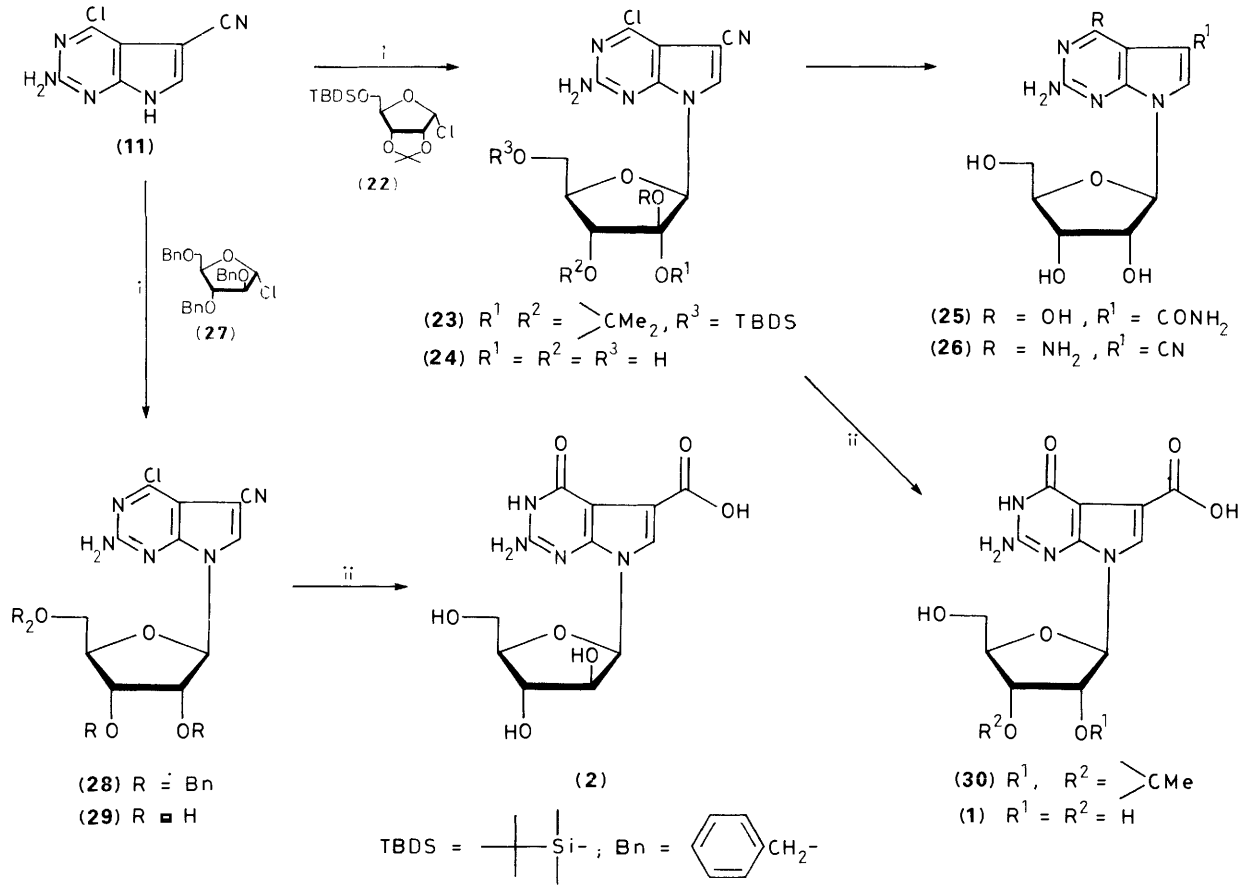


B

into the carboxamide group but also concomitantly hydrolysed the chloro group. Finally the synthesis of the target 2′-deoxycadeguomycin (**3**) was accomplished by heating of the amide (**17**) with 5M-aqueous KOH, followed by acidification.

A similar glycosylation of the sodium salt of ester (**13**) with chloride (**14**) provided the protected nucleoside (**21**) in 87% yield; this product on saponification with 2M-NaOH, followed by neutralization, afforded an alternative route to 2′-deoxycadeguomycin (**3**). After accomplishing the total and stereospecific synthesis of (**3**), we were interested in selective deprotection of the protecting groups, as well as manipulation of the functional groups of compound (**21**) in order to prepare certain selected nucleosides for structure and biological activity relationship studies. Thus, a solution of compound (**21**) in MeOH–NH_3 was stirred at room temperature to furnish the deprotected nucleoside (**18**), in 91% yield. On the other hand, heating of compound (**21**) with MeOH–NH_3 at 80 °C not only deprotected the sugar protecting groups but also selectively converted the chloro group into an amino group to give diamine (**20**) as the major product. It is of interest to note that, even when the above reaction was carried out at >100 °C, the 5-methyl ester function did not convert into an amide group. However, reaction of compound (**21**) with NaOMe in dry MeOH at room temperature readily furnished methyl 2-amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-4-methoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxylate (**19**) in 86% yield.

We next considered the preparation of the natural nucleoside



Scheme 2. *Reagents:* i, NaH; ii, NaOH

antibiotic cadeguomycin (**1**) by using the aglycone (**11**). Since compound (**11**) does not have a C-6 substituent, we anticipated the problem of neighbouring group participation[30] when one uses 2,3,5-tri-*O*-acyl-D-ribofuranosyl halides for glycosylation. However, recently we have found[30] that the problem of neighbouring group participation can be solved by utilizing the halogenose 5-*O*-t-butyldimethylsilyl-2,3-*O*-isopropylidene-α-D-ribofuranosyl chloride[31] (**22**). Accordingly, reaction of the sodium salt of (**11**) and the α-halogenose (**22**) (1 mol equiv. each) gave a 10% yield of the corresponding glycosylated product (**23**), accompanied by recoverable starting aglycone (Scheme 2). Interestingly, reaction of the sodium salt of (**11**) (2 mol equiv.) and compound (**22**) (1 mol equiv.) gave compound (**23**) in 58% yield (based on the sugar used) and the aglycone (**11**) (1 mol equiv.). On the other hand, glycosylation of (**11**) (1 mol equiv.) and NaH (2 mol equiv.) with the α-halogenose (**22**) (1 mol equiv.) gave only a trace amount of the desired product (**23**) and the reactant (**11**) was recovered almost quantitatively. These results indicate that the α-halogenose (**22**) contains a less reactive chlorine, and an excess of the sodium salt of the nucleobase (**11**) has to be employed in order to drive the reaction to completion. Deprotection of the isopropylidene and t-butyldimethylsilyl groups from compound (**23**) with 90% aqueous trifluoroacetic acid (TFA) at 0 °C for 0.5 h furnished 2-amino-4-chloro-7-β-D-ribofuranosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (**24**) in a 96% yield.

The target natural product cadeguomycin (**1**) was prepared in the following manner. When compound (**23**) was heated with 4M-aqueous KOH, 2-amino-3,4-dihydro-7-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-4-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxylic acid (**30**) was obtained in good yield after acidification of the reaction mixture with 2M-HCl to pH 5. Deisopropylidenation of compound (**30**) with aqueous TFA at reflux temperature in an inert atmosphere gave a 75% yield of compound (**1**). The preparation of (**1**) was also accomplished from the nitrile (**24**) by reaction with 4M-aqueous KOH at reflux temperature, followed by acidification. The physiochemical data obtained for the synthetic (**1**) were found to be identical[11–13] with those of natural cadeguomycin, which also corroborates our structural assignment of the intermediate (**9**).

The presence of a nitrile group in compound (**24**) renders the chloro group much more labile for nucleophilic attack. Thus, the chloro group could be selectively displaced without altering the CN function. We were interested in preparing diamino nitrile (**26**) because it can be considered as a 2-amino derivative of the naturally occurring nucleoside antibiotic toyocamycin. Thus, 2,4-diamino-7-β-D-ribofuranosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (**26**) was obtained when compound (**24**) was heated with MeOH–NH_3 at 80 °C for 12 h. Also, treatment of compound (**24**) with conc. NH_4OH and H_2O_2 not only converted the CN group into a carboxamide function but also hydrolysed the chloro group, to give 2-amino-3,4-dihydro-4-oxo-7-β-D-ribofuranosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide (**25**). Selective transformation[32] of the C-4 chloro group of (**24**) into a methoxy function, followed by cleavage of the ether linkage and hydrogenation, should produce nucleosides $PreQ_0$[19] and $PreQ_1$,[33,34] respectively. Thus compound (**24**) lends itself as a potential precursor for the synthesis of diamino nitrile (**26**) and certain related 7-deazaguanosine nucleosides.

Simultaneously, we studied the glycosylation of compound (**11**) with 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride[35] (**27**) to illustrate the potential of the aglycone (**11**) in the nucleoside synthesis. Thus, treatment of molar proportions of

(**11**) with NaH in MeCN, followed by the addition of compound (**27**), and subsequent purification of the reaction product by flash chromatography, provided 2-amino-4-chloro-7-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (**28**) in 58% yield. No formation of the corresponding α-anomer was detected. Debenzylation of compound (**28**) with BCl_3 at −78 °C gave 2-amino-7-β-D-arabinofuranosyl-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (**29**) as a crystalline compound. Finally, *ara*-cadeguomycin (**2**) was prepared by heating of compound (**29**) with 5M-NaOH for 5 h, followed by acidification of the reaction mixture with Dower-50 (H^+) resin. The physicochemical properties of the product (**2**) were identical with those reported previously.[17]

The anomeric configuration of the prepared nucleosides was assigned as β on the basis of ^1H n.m.r. studies. The anomeric proton of compound (**3**) appeared as a triplet centred at δ 6.30 with a peak width of 14.1 Hz, which is similar to that observed for 2′-deoxy-7-deazaguanosine.[9] The ^1H n.m.r. spectra of compounds (**24**) and (**1**) revealed the anomeric doublets centred at δ 5.97 and 5.91, respectively, with a coupling constant of $J_{1',2'}$ 5.7 and 6.3 Hz, respectively, which is comparable for that of β-ribonucleosides.[36,37] Moreover, the ^1H n.m.r. spectrum of compound (**23**) in $(CD_3)_2SO$ exhibited a smaller coupling constant ($J_{1',2'}$ 2.4 Hz) for the anomeric proton and also revealed the difference between the chemical shifts of the two methyl signals of the isopropylidene group as >0.25 p.p.m., a difference characteristic for the β-configuration.[38] The structural assignment of the nucleoside (**28**) was established by comparison of the chemical shift of the anomeric proton in the ^1H n.m.r. spectrum with those of known 7-β-D-arabinofuranosylpyrrolo[2,3-*d*]-pyrimidin-4(3*H*)-one analogues.[39–41] The anomeric proton signal of the β anomer of (**28**) appears at low field (δ 6.42) and has a larger vicinal coupling constant ($J_{1',2'}$ 5.3 Hz), which is in good agreement with that reported[17] for β-D-arabino nucleosides.

In summary, a total and stereospecific synthesis of 2′-deoxycadeguomycin (**3**) was accomplished for the first time using the novel aglycones (**11**) and (**13**). The potential utility of compound (**11**) is further demonstrated by the synthesis of the natural nucleoside antibiotic cadeguomycin (**1**), *ara*-cadeguomycin (**2**), and certain related nucleosides in a simple and straightforward way. The aglycones (**11**) and (**13**) should thus prove to be useful for the synthesis of related natural 7-deazaguanine nucleoside antibiotics.

Experimental

M.p.s were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H and ^{13}C n.m.r. spectra were determined at 300 MHz with an IBM NR/300 spectrometer. The chemical-shift values are expressed in δ-values (p.p.m.) relative to $SiMe_4$ as an internal standard. The presence of solvent as indicated by elemental analysis was verified by ^1H n.m.r. spectroscopy. I.r. spectra ($\nu_{max.}$, in KBr) were recorded with a Perkin-Elmer 1420-spectrophotometer, and u.v. spectra ($\lambda_{max.}$) were recorded on a Beckman DU-50 spectrophotometer. Elemental analyses were performed by Robertson Laboratory, Madison, N.J. T.l.c. was performed on plates of silica gel 60F-254 (EM Reagents). Silica gel (E. Merck; 230—400 mesh) was used for flash column chromatography. All solvents used were reagent grade. Acetonitrile was dried over 3Å molecular sieves. Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl prior to use. Detection of nucleoside components in t.l.c. was by u.v. light and with 10% H_2SO_4 in MeOH spray followed by heating. Evaporations were carried out under reduced pressure with the bath temperature below 30 °C.

Methyl 2-Amino-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-d]pyrimidine-5-carboxylate (**9**) *and Methyl 2,4-Diaminofuro[2,3-d]-pyrimidine-6-carboxylate* (**8**). *Method A.*—2,6-Diaminopyrimidin-4(3*H*)-one* (**6**) (12.6 g, 100 mmol) was suspended in DMSO (55 ml) at room temperature. To this stirred suspension were added methyl chloro(formyl)acetate[25] (**7**), (6.83 g, 50 mmol) and K_2CO_3 (2.30 g, 16.67 mmol) and the mixture was stirred at room temperature. After 1 h and 2 h intervals the same amounts of the aldehyde (**7**) and K_2CO_3 were added and the mixture was stirred at room temperature for an additional 12 h. The reaction mixture was diluted to 500 ml with water and the pH of the solution was adjusted to 6—7 with conc. NH_4OH. After the mixture had been stirred for a further 12 h the solid that precipitated was collected by filtration, washed successively with water (2 × 25 ml) and acetone (25 ml), and dried to give a mixture of the products (**9**) and (**8**) (12.5 g, 60%) in the ratio 1.4:1, respectively.

Method B.—2,6-Diaminopyrimidin-4-(3*H*)-one (**6**) (28.4 g, 225 mmol) was suspended in water (500 ml) and treated with NaOAc (15 g). The mixture was heated to 100 °C and stirred for 0.5 h, when the solution became clear. A suspension of methyl chloro(formyl)acetate[25] (**7**) (43 g, 315.18 mmol) in water (70 ml) was added in one lot, followed by a solution of NaOAc (5 g) in water (30 ml). After the addition, a precipitate started forming within 10 min. The reaction mixture was heated and stirred at 100 °C for 1.5 h, cooled to 0 °C, and filtered. The solid was washed with water (25 ml) followed by acetone (2 × 50 ml) and dried to give a mixture of compounds (**9**) and (**8**) (35 g, 75%) in the ratio 2:1.

The above mixture of (**8**) and (**9**) (*ca.* 100 mg) was boiled with MeOH (100 ml) and the solution was filtered while hot. While the filtrate was cooling, compound (**9**) started to crystallize out. It was immediately filtered off and dried (leaving the crystallization for more than 5 min resulted in co-crystallization of both the compounds).

Compound (**9**). M.p. >295 °C (decomp.); $\nu_{max.}$ 3 350 (NH, NH_2), 1 700, and 1 650 cm^{-1} (C=O); $\lambda_{max.}$(pH 1) 223 (14 700) and 278sh nm (7 300); (pH 7) 228 (18 400) and 294 nm (8 200); (pH 11) 226 (19 400), 252sh (9 400), and 293 nm (7 000); δ_H [$(CD_3)_2SO$] 3.67 (3 H, s, CO_2Me), 6.22 (2 H, s, NH_2), 7.35 (1 H, d, *J* 2.7 Hz, 6-H), 10.37 (1 H, s, 7-H), and 11.65 (1 H, s, 3-H) (Found: C, 46.1; H, 3.8; N, 27.0. $C_8H_8N_4O_3$ requires C, 46.16; H, 3.87; N, 26.91%).

Compound (**9**) was converted into a more soluble form (**10**) and separated from (**8**) on a large scale as described below.

7-t-Butyl-5-Methyl 2-Amino-3,4-dihydro-4-oxo-7H-pyrrolo-[2,3-d]pyrimidine-5,7-dicarboxylate (**10**).—The above mixture of (**8**) and (**9**) (14.5 g, 69.7 mmol) was heated in a mixture of dimethylformamide (400 ml) and triethylamine (10.52 ml, 75 mmol) on a steam-bath for 0.5 h and cooled to room temperature. To this solution was added DBDC (24.0 g, 110 mmol) and the mixture was stirred for 12 h at room temperature. The reaction mixture was evaporated to dryness, the residue was boiled with EtOAc (500 ml), and the solution was filtered. The precipitate was washed again with hot EtOAc (200 ml). The combined EtOAc filtrate and washings were concentrated to 100 ml, and upon cooling deposited crystals, which were collected by filtration. The filtrate was concentrated to 15 ml, diluted with ether, and triturated to give a second crop of crystals. Total yield of *diester* (**10**) was 6.26 g [based on the consumption of (**9**), 50%]; m.p. >250 °C; $\nu_{max.}$ 3 400—3 100 (NH, NH_2), 1 760, 1 720, and 1 620 cm^{-1} (C=O); $\lambda_{max.}$(EtOH)

* Commercially available from Aldrich Chemical Co. Inc., Milwaukee, Wisconsin, U.S.A.

237 (25 500) and 319 nm (2 900); δ_H[$(CD_3)_2SO$] 1.56 (9 H, s, Bu^t), 3.72 (3 H, s, CO_2Me), 6.59 (2 H, br s, NH_2), 7.54 (1 H, s, 6-H), and 10.77 (1 H, br s, 3-H) (Found: C, 50.4; H, 5.3; N, 18.0. $C_{13}H_{16}N_4O_5$ requires C, 50.65; H, 5.23; N, 18.17%).

Sometimes, the above reaction does not go to completion. So the reaction was repeated again to remove all of reactant (**9**) from the mixture in the form of diester (**10**). The remaining solid was crystallized from aqueous DMSO to give compound (**8**) (6.0 g, 31%); m.p. >300 °C; $\nu_{max.}$ 3 350—3 100 (NH_2) and 1 710 cm^{-1} (C=O); $\lambda_{max.}$(pH 1) 285 (16 500) and 306sh nm (13 700); (pH 7) 223sh (24 100) and 306 nm (16 500); (pH 11) 224 (28 700) and 310 nm (20 800); δ_H[$(CD_3)_2SO$] 3.79 (3 H, s, CO_2Me), 6.53 (2 H, s, NH_2), 7.29 (2 H, br s, NH_2), and 7.62 (1 H, s, 5-H) (Found: C, 46.2; H, 3.9; N, 27.0. $C_8H_8N_4O_3$ requires C, 46.16; H, 3.87; N, 26.91).

Methyl 2-Amino-4-Chloro-7H-pyrrolo[2,3-d]*pyrimidine-5-carboxylate* (**13**). *Method A.*—A mixture of compounds (**8**) and (**9**) (7.25 g, 35 mmol) was mixed with benzyltriethylammonium chloride (9 g) and DEA (7 ml) at room temperature. To this was added $POCl_3$ (75 ml) and the mixture was heated at 110—120 °C for 3 h. The excess of $POCl_3$ was distilled off, the residual syrup was poured onto crushed ice (200 g), and the mixture was stirred vigorously for 2 h. The solution was adjusted to pH 3 with conc. NH_4OH and extracted with EtOAc (2 × 350 ml). The organic phase was washed with water (50 ml), followed by saturated brine (30 ml), dried (Na_2SO_4), and evaporated to dryness. The residue was crystallized from a mixture of MeOH–CH_2Cl_2 to give *compound* (**13**) (0.50 g, 6.4%), m.p. >280 °C; $\nu_{max.}$ 3 400—3 100 (NH_2), 1 710 (C=O), and 790 cm^{-1} (C–Cl); $\lambda_{max.}$(pH 1) 232 (27 700) and 319 nm (6 300); (pH 7) 230 (33 000), 260sh (12 400), and 316 nm (7 800); (pH 11) 231 (23 200), 269 (16 700), and 323 nm (6 400); δ_H[$(CD_3)_2SO$] 3.75 (3 H, s, CO_2Me), 6.76 (2 H, s, NH_2), 7.86 (1 H, d, *J* 2.7 Hz, 6-H), and 12.22 (1 H, br s, 7-H) (Found: C, 42.1; H, 2.85; N, 24.4; Cl, 15.4. $C_8H_7ClN_4O_2$ requires C, 42.39; H, 3.11; N, 24.71; Cl, 15.66%).

Method B.—A mixture of compound (**10**) (3.1 g, 10 mmol), DEA (10 ml), and $POCl_3$ (50 ml) was heated at reflux for 2 h. The excess of $POCl_3$ was distilled off from the reaction mixture and the syrup was poured onto stirred, crushed ice (200 g). After being stirred for 2 h the solution was adjusted to pH 3 with conc. NH_4OH and extracted with EtOAc (2 × 300 ml). The extract on work-up as described in method A gave the *title compound* identical with compound (**13**) prepared as above (0.45 g, 20%).

2-Amino-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-d]*pyrimidine-5-carboxamide* (**12**).—A solution of compound (**10**) (13.2 g, 34.74 mmol) in MeOH–NH_3 (500 ml; saturated at 0 °C) was heated at 120 °C in a steel reaction vessel for 16 h. The reaction vessel was cooled to −78 °C, opened carefully, and the precipitated solid was collected by filtration. The solid was washed with cold MeOH (50 ml) and dried to give *compound* (**12**) (6.0 g, 72.5%), m.p. >300 °C (decomp.); $\nu_{max.}$ 3 300—3 120 (NH, NH_2), 1 620, and 1 590 cm^{-1} (C=O); $\lambda_{max.}$(pH 1) 224 (15 800) and 282sh nm (7 900); pH 7) 227 (20 700) and 295 nm (10 000); (pH 11) 225 (21 900), 252sh (11 300), and 292 nm (8 300); δ_H[$(CD_3)_2SO$] 6.34 (2 H, s, NH_2), 7.03 and 9.55 (2 H, 2 s, $CONH_2$), 7.22 (1 H, s, 6-H), 10.83 (1 H, br s, 7-H), and 11.60 (1 H, br s, 3-H) (Found: C, 41.3; H, 3.8; N, 34.6. $C_7H_7N_5O_2 \cdot \frac{1}{2}H_2O$ requires C, 41.58; H, 3.99; N, 34.63%).

2-Amino-4-chloro-7H-pyrrolo[2,3-d]*pyrimidine-5-carbonitrile* (**11**).—The carboxamide (**12**) (10.0 g, 51.8 mmol) and DEA (10 ml) were heated in $POCl_3$ (100 ml) under reflux for 4 h. The excess of $POCl_3$ was distilled off under reduced pressure. The residual syrup was poured over crushed ice (200 g) and the mixture was stirred vigorously for 2 h. The solution was adjusted to pH 3 with conc. NH_4OH and stored in a refrigerator overnight. The precipitated solid was collected by filtration, washed with water (50 ml), and dried. The dry solid was boiled with MeOH (300 ml) for 6 h and the mixture was filtered. The filtrate was concentrated to 50 ml, which on cooling gave *compound* (**11**) (4.1 g, 40%), m.p. >300 °C; $\nu_{max.}$ 3 400—3 150 (NH, NH_2), 2 220 (C≡N), and 800 cm^{-1} (C–Cl); $\lambda_{max.}$(pH 1) 232 (25 000) and 316 nm (7 300); (pH 7) 232 (15 200) and 314 nm (5 100); (pH 11) 234 (21 200), 251 (20 600), 285 (9 100), and 328 nm (5 800); δ_H [$(CD_3)_2SO$] 6.97 (2 H, s, NH_2), 8.13 (1 H, s, 6-H), and 12.50 (1 H, br s, 7-H) (Found: C, 43.3; H, 2.23; N, 34.9; Cl, 17.4. $C_7H_4ClN_5 \cdot \frac{1}{4}CH_3OH$ requires C, 43.18; H, 2.49; N, 34.71; Cl, 17.60%).

2-Amino-4-chloro-7-(2-deoxy-3,5-di-O-p-toluoyl-β-D-erythro-pentofuranosyl)-7H-pyrrolo[2,3-d]*pyrimidine-5-carbonitrile* (**15**).—The aglycone (**11**) (1.2 g, 6.2 mmol) was suspended in dry MeCN (300 ml) at room temperature. To this suspension was added NaH (60% in oil; 0.28 g, 7 mmol) and the mixture was stirred at room temperature for 0.5 h. The mixture became clear in 15 min. 2-Deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl chloride[29] (**14**) (2.72 g, 7 mmol) was added and the mixture was stirred for 10 h, then evaporated to dryness, and the residue on purification by flash chromatography with hexane ⟶ acetone gradient gave compound (**15**) (2.5 g, 74%). An *analytical sample* was prepared by crystallization of the pure material from a mixture of hexane–acetone: m.p. 168—171 °C; $\nu_{max.}$ 3 350—3 100 (NH_2), 2 200 (C≡N), 1 720 (C=O), and 780 cm^{-1} (C–Cl): $\lambda_{max.}$(MeOH) 245 (36 800) and 323 nm (12 000); δ_H [$(CD_3)_2SO$] 2.37 and 2.40 (6 H, 2 s, 2 × Me), 2.75 (1 H, m, 2-H) 3.00 (1 H, m, 2′-H), 4.56 (3 H, m, 4′-H and 5′-H_2), 5.70 (1 H, m, 3′-H), 6.49 (1 H, t, $J_{1',2'}$ 6.36 Hz, 1′-H), 7.21 (2 H, br s, NH_2), 7.31 (4 H, m, ArH), 7.86 (4 H, m, ArH), and 8.38 (1 H, s, 6-H) (Found: C, 61.3; H, 4.5; N, 12.6; Cl, 6.6. $C_{28}H_{24}ClN_5O_5$ requires C, 61.59; H, 4.43; N, 12.82; Cl, 6.50%).

2-Amino-4-chloro-7-(2-dexoy-β-D-erythro-pentofuranosyl)-7H-pyrrolo[2,3-d]*pyrimidine-5-carbonitrile* (**16**).—A solution of the protected nucleoside (**15**) (2.0 g, 3.66 mmol) in MeOH–NH_3 (100 ml; saturated at 0 °C) was stirred at room temperature in a pressure bottle for 12 h. The bottle was cooled (0 °C), opened, and the contents were evaporated to dryness. The residue was triturated with MeOH–CH_2Cl_2 mixture and the precipitated solid was collected and dried. A small amount was crystallized from 95% EtOH to give compound (**16**) as *fine crystals* (1.0 g, 88%); m.p. 246—248 °C; $\nu_{max.}$ 3 400—3 100 (OH, NH_2), 2 220 (C≡N), and 780 cm^{-1} (C–Cl); $\lambda_{max.}$(pH 1) 234 (46 400) and 317 nm (9 700); (pH 7) 234 (44 200) and 317 nm (9 000); (pH 11) 234 (46 300) and 315 nm (9 500); δ_H [$(CD_3)_2SO$] 2.22 and 2.41 (2 H, 2 m, 2′-H_2), 3.53 (2 H, m, 5′-H_2), 3.82 (1 H, m, 4′-H), 4.33 (1 H, m, 3′-H), 4.99 (1 H, t, 5′-OH), 5.31 (1 H, d, 3′-OH), 6.38 (1 H, t, $J_{1',2'}$ 7.0 Hz, 1′-H), 7.17 (2 H, br, s, NH_2), and 8.36 (1 H, s, 6-H) (Found: C, 46.6; H, 4.0; N, 22.4; Cl, 11.6. $C_{12}H_{12}ClN_5O_3$ requires C, 46.53; H, 3.91; N, 22.60; Cl, 11.46%).

Methyl 2-Amino-4-chloro-7-(2-deoxy-3,5-di-O-p-toluoyl-β-D-erythro-pentofuranosyl)-7H-pyrrolo[2,3-d]*pyrimidine-5-carboxylate* (**21**).—To a stirred suspension of compound (**13**) (0.16 g, 0.71 mmol) in dry MeCN (200 ml) was added NaH (60% in oil; 0.032 g, 0.8 mmol) at room temperature. After the addition of NaH, the reaction mixture was stirred at 50 °C for 0.5 h and cooled to room temperature. Compound (**14**) (0.31 g, 0.8 mmol) was added and the mixture was stirred at ambient temperature for 12 h. The reaction mixture was evaporated to dryness and the residue on repeated purification by flash chromatography with hexane ⟶ acetone gradient as the eluant gave the *title*

compound (0.2 g, 49%). A small amount was crystallized from hexane–acetone for analytical purposes: m.p. 191—193 °C; $\nu_{max.}$ 3 350—3 150 (NH_2), 1 710 (C=O), and 800 cm^{-1} (C–Cl); $\lambda_{max.}$(MeOH) 221 (44 500) and 294 nm (20 600); δ_H [$(CD_3)_2SO$] 2.38 and 2.41 (6 H, 2 s, 2 × Me), 2.69 and 3.02 (2 H, 2 m, 2′-H_2), 3.70 (3 H, s, CO_2Me), 4.55 (2 H, m, 5′-H_2), 4.64 (1 H, m, 4′-H), 5.69 (1 H, m, 3′-H), 6.57 (1 H, dd, $J_{1',2'}$ 6.21 and 8.01 Hz, 1′-H), 7.02 (2 H, br s, NH_2), 7.34 (4 H, m, ArH), 7.90 (4 H, m, ArH), and 8.08 (1 H, s, 6-H) (Found: C, 60.0; H, 4.6); N, 9.7; Cl, 6.0. $C_{29}H_{27}ClN_4O_7$ requires C, 60.15; H, 4.70; N, 9.67; Cl, 6.13%).

2-*Amino*-7-(2-*deoxy*-β-D-erythro-*pentofuranosyl*)-3,4-*dihydro*-4-*oxo*-7H-*pyrrolo*[2,3-d]*pyrimidin*-5-*carboxamide* (**17**).—A mixture of compound (**16**) (0.68 g, 2.19 mmol), H_2O_2 (30%; 10 ml), and conc. NH_4OH (100 ml) was stirred at room temperature in a steel reaction vessel for 2 days. The steel vessel was cooled, opened carefully, and the solution was evaporated to dryness. The residue on crystallization from 95% EtOH gave the *title compound* (0.40g 56%): m.p. 257—260 °C; $\nu_{max.}$ 3 400—3 100 (NH, NH_2), 1 680, and 1 640 cm^{-1} (C=O); $\lambda_{max.}$(pH 1) 229 (27 800), 265sh (12 900), and 292 nm (12 400); (pH 7) 230 (32 000), 268sh (13 500), and 294 nm (14 200); (pH 11) 230 (31 100) and 290 nm (11 600); δ_H [$(CD_3)_2SO$] 2.11 and 2.34 (2 H, 2 m, 2′-H_2), 3.52 (2 H, m, 5′-H_2), 3.79 (1 H, m, 4′-H), 4.31 (1 H, m, 3′-H), 4.97 (1 H, m, 5′-OH), 5.26 (1 H, m, 3′-OH), 6.33 (1 H, dd, $J_{1',2'}$ 6.0 and 8.1 Hz, 1′-H), 6.53 (2 H, br s, NH_2), 7.14 and 9.55 (2 H, 2 s, $CONH_2$), 7.55 (1 H, s, 6-H), and 10.98 (1 H, s, 3-H) (Found: C, 45.9; H, 5.0; N, 22.5. $C_{12}H_{15}N_5O_5 \cdot \frac{1}{4}H_2O$ requires C, 45.94; H, 4.98; N, 22.3%).

2-*Amino*-7-(2-*deoxy*-β-D-erythro-*pentofuranosyl*)-3,4-*dihydro*-4-*oxo*-7H-*pyrrolo*[2,3-d]*pyrimidine*-5-*carboxylic Acid* (2′-*Deoxycadeguomycin*) (**3**). *Method A*.—A solution of compound (**17**) (0.50 g, 1.62 mmol) in 5M-KOH (30 ml) was heated under reflux for 3 h. The reaction mixture was cooled to 0 °C and the pH was adjusted to 6 with glacial acetic acid. The precipitated solid was collected by filtration and washed with cold water (10 ml). The solid on crystallization from hot water gave 2′-*deoxycadeguomycin* (**3**) (0.32 g, 64%), m.p. >310 °C (decomp.); $\nu_{max.}$ 3 400—3 000 (NH, NH_2, OH) and 1 650—1 600 cm^{-1} (C=O); $\lambda_{max.}$(pH 1) 232 (25 600), 269 (8 200), and 297 nm (9 300); (pH 7) 226 (20 500), 263 (9 900), and 287 nm (8 500); (pH 11) 223 (23 600), 265 (11 600), and 283sh nm (10 500); δ_H[$(CD_3)_2SO$] 2.16 and 2.38 (2 H, 2 m, 2′-H_2), 3.52 (2 H, m, 5′-H_2), 3.80 (1 H, m, 4′-H), 4.31 (1 H, m, 3′-H), 5.00 (1 H, t, 5′-OH), 5.28 (1 H, d, 3′-OH), 6.30 (1 H, t, $J_{1',2'}$ 7.05 Hz, 1′-H), 6.77 (2 H, s, NH_2), 7.80 (1 H, s, 6-H), 11.61 (1 H, s, 3-H), and 14.13 (1 H, s, CO_2H) (Found: C, 46.5; H, 4.6; N, 18.3. $C_{12}H_{14}N_4O_6$ requires C, 46.46; H, 4.55; N, 18.05).

Method B.—2M-NaOH (10 ml, 20 mmol) was added dropwise to a refluxing solution of compound (**21**) (0.58 g, 1 mmol) in 1,4-dioxane (40 ml) during 10 min. After the addition, the reaction mixture was heated at reflux for 5 h, cooled, and evaporated to dryness. The residue was dissolved in water (15 ml) and the solution was made acidic (pH 2) with 2M-HCl. The precipitated solid was collected and air-dried. The dried material was refluxed with 95% ethanol (3 × 25 ml) and the solution was filtered. The filtrate was evaporated to dryness and the solid residue was crystallized from water to yield the title compound (**3**) (0.21 g, 67%), m.p. >310 °C. This material was found to be identical with compound (**3**) prepared by method A.

Methyl 2-*Amino*-4-*chloro*-7-(2-*deoxy*-β-D-erythro-*pentofuranosyl*)-7H-*pyrrolo*[2,3-d]*pyrimidine*-5-*carboxylate* (**18**).—A solution of compound (**21**) (0.65 g, 1.12 mmol) in MeOH–NH_3 (70 ml) was stirred at room temperature in a pressure bottle for 12 h. The pressure bottle was cooled, opened carefully, and the contents were evaporated to dryness. The residue on purification by flash chromatography with CH_2Cl_2 ⟶ acetone gradient and crystallization from a mixture of acetone–MeOH gave *compound* (**18**) (0.35 g, 91%), m.p. 201—203 °C; $\nu_{max.}$ 3 400—3 100 (OH, NH_2) and 1 630 cm^{-1} (C=O); $\lambda_{max.}$(pH 1) 236 (53 400) and 319 nm (10 600); (pH 7) 234 (50 700), 260sh (13 700), and 317 nm (10 900); (pH 11) 234 (50 000), 260sh (13 700), and 318 nm (10 700); δ_H [$(CD_3)_2SO$] 2.19 and 2.41 (2 H, 2 m, 2′-H_2), 3.55 (2 H, m, 5′-H_2), 3.76 (3 H, s, CO_2Me), 3.82 (1 H, m, 4′-H), 4.32 (1 H, m, 3′-H), 4.99 (1 H, t, 5′-OH), 5.29 (1 H, d, 3′-OH), 6.43 (1 H, t, ($J_{1',2'}$ 6.1 Hz, 1′-H), 6.96 (2 H, s, NH_2), and 8.12 (1 H, s, 6-H) (Found: C, 45.8; H, 4.2; N, 16.3; Cl, 10.6. $C_{13}H_{15}ClN_4O_5$ requires C, 45.56; H, 4.41; N, 16.35; Cl, 10.34%).

Methyl 2-*Amino*-7-(2-*deoxy*-β-D-erythro-*pentofuranosyl*)-4-*methoxy*-7H-*pyrrolo*[2,3-d]*pyrimidine*-5-*carboxylate* (**19**).—A mixture of compound (**21**) (0.20 g, 0.35 mmol) and NaOMe (0.10 g, 1.85 mmol) in dry MeOH (50 ml) was stirred at room temperature for 1 day. The reaction mixture was acidified with Dowex-50 (H^+) resin to pH 3—4. The resin was removed by filtration, and washed with MeOH (2 × 25 ml), and the combined filtrate and washings were evaporated to dryness. The residue was purified by flash chromatography with CH_2Cl_2 ⟶ acetone gradient as eluant. The pure fractions were pooled and evaporated to dryness. The residue after crystallization from a mixture of MeOH–CH_2Cl_2 gave *compound* (**19**) (0.10 g, 86%) as light yellow flakes, m.p. 250—252 °C; $\nu_{max.}$ 3 350—3 100 (OH, NH_2) and 1 600 cm^{-1} (C=O); $\lambda_{max.}$(pH 1) 228 (44 200), 249sh (20 500), and 292 nm (17 200); (pH 7) 229 (26 700), 254sh (11 600), and 294 nm (7 400); (pH 11) 230 (22 100), 254sh (9 300), and 295 nm (6 000); δ_H[$(CD_3)_2SO$] 2.16 and 2.41 (2 H, 2 m 2′-H_2), 3.53 (2 H, m, 5′-H_2), 3.73 and 3.92 (6 H, 2 s, 2 × OMe), 3.81 (1 H, m, 4′-H), 4.32 (1 H, m, 3′-H), 5.00 (1 H, t, 5′-OH), 5.27 (1 H, d, 3′-OH), 6.40 (1 H, t, $J_{1',2'}$ 7.7 Hz, 1′-H), 6.47 (2 H, br s, NH_2), and 7.87 (1 H, s, 6-H) (Found: C, 49.7; H, 5.3; N, 16.5. $C_{14}H_{18}N_4O_6$ requires C, 49.70; H, 5.36; N, 16.55%).

Methyl 2,4-*Diamino*-7-(2-*deoxy*-β-D-erythro-*pentofuranosyl*)-7H-*pyrrolo*[2,3-d]*pyrimidine*-5-*carboxylate* (**20**).—The protected nucleoside (**21**) (0.35 g, 0.60 mmol) in MeOH–NH_3 (saturated at 0 °C; 70 ml) was heated at 80 °C for 1 day in a steel reaction vessel. The steel vessel was cooled, opened, and the contents were evaporated to dryness. The residue was purified by flash chromatography with CH_2Cl_2 ⟶ acetone gradient as eluant. The homogeneous product on crystallization from acetone–MeOH gave *compound* (**20**) (0.12 g, 64%) as crystals, m.p. 255—258 °C; $\nu_{max.}$ 3 400—3 100 (OH, NH_2) and 1 680 cm^{-1} (C=O); $\lambda_{max.}$(pH 1) 238 (32 100) and 307 nm (14 600); (pH 7) 231 (33 700), 254sh (14 600), and 300 nm (12 600); (pH 11) 231 (36 700), 255sh (17 100), and 301 nm (15 300); δ_H[$(CD_3)_2SO$] 2.12 and 2.38 (2 H, 2 m, 2′-H_2), 3.52 (2 H, m, 5′-H_2), 3.78 (4 H, m, 4′-H and OMe), 4.30 (1 H, m, 3′-H), 5.09 (1 H, t, 5′-OH), 5.24 (1 H, d, 3′-OH), 5.87 (2 H, br s, NH_2), 6.36 (1 H, dd, $J_{1',2'}$ 6.1 and 8.1 Hz, 1′-H), 6.67 and 7.57 (2 H, 2 br s, NH_2), and 7.81 (1 H, s, 6′-H) (Found: C, 48.2; H, 5.3; N, 21.4. $C_{13}H_{17}N_5O_5$ requires C, 48.29; H, 5.30; N, 21.65%).

2-*Amino*-7-(5-O-*t*-*butyldimethylsilyl*-2,3-O-*isopropylidene*-β-D-*ribofuranosyl*)-4-*chloro*-7H-*pyrrolo*[2,3-d]*pyrimidine*-5-*carbonitrile* (**23**).—To a stirred suspension of compound (**11**) (1.93 g, 10 mmol) in dry MeCN (300 ml) was added NaH (60% in oil; 0.4 g, 10 mmol) in portions during 15 min. After the addition the mixture was stirred at room temperature for an additional 0.5 h. A solution of 5-*O*-t-butyldimethylsilyl-2,3-*O*-isopropylidene-α-D-ribofuranosyl chloride[31] (**22**) (generated *in situ* from the corresponding lactol; 1.61 g, 5 mmol) in dry THF (20 ml) was added at room temperature and the mixture was

stirred overnight, then evaporated to dryness. The residue was suspended in water (50 ml) and extracted with EtOAc (2 × 75 ml). The combined extract was washed with saturated brine and dried over anhydrous Na_2SO_4. The organic phase was evaporated to dryness. The residue was dissolved in acetone (30 ml), mixed with silica gel (60—100 mesh; 5 g), and the mixture was evaporated to dryness. The dried silica gel was placed on top of a flash silica gel column packed in hexane. The column was eluted with hexane ⟶ EtOAc gradient. The fractions containing the homogeneous product were collected and evaporated to dryness to give *compound* (**23**) (1.3 g, 58%) as an oil, $\nu_{max.}$ 2 220 (C≡N) and 800 cm^{-1} (C–Cl); $\lambda_{max.}$(MeOH) 235 (29 800), 260sh (5 200), and 320 nm (5 900); δ_H[$(CD_3)_2SO$] 0.14 and 0.16 (6 H, 2 s, 2 × Me), 0.95 (9 H, s, Bu^t), 1.41 and 1.66 (6 H, 2 s, CMe_2), 3.90 (2 H, m, 5′-H_2), 4.41 (1 H, m, 4′-H), 4.88 (2 H, m, 2′- and 3′-H), 5.28 (2 H, br s, NH_2), 6.27 (1 H, d, ($J_{1',2'}$ 2.4 Hz, 1′-H), and 7.95 (1 H, s, 6-H) (Found: C, 52.7; H, 6.3; N, 14.4; Cl, 7.5. $C_{21}H_{30}ClN_5O_4Si$ requires C, 52.53; H, 6.29; N, 14.58; Cl, 7.39%).

2-*Amino*-4-*chloro*-7-β-D-*ribofuranosyl*-7H-*pyrrolo*[2,3-d]-*pyrimidine*-5-*carbonitrile* (**24**).—A solution of the protected nucleoside (**23**) (0.20 g, 0.42 mmol) in TFA (9 ml) and water (2 ml) was stirred at 0 °C for 0.5 h, then evaporated to dryness. The residue was dissolved in MeOH (30 ml) and the solution was evaporated to dryness. The white solid was dissolved in acetone (30 ml) and adsorbed onto silica gel (60—100 mesh; 3 g). The dried silica gel was placed on top of a flash silica gel column (3 × 15 cm) packed in CH_2Cl_2. The column was eluted with CH_2Cl_2 ⟶ acetone gradient. The fractions containing homogeneous product were pooled and evaporated to dryness. An analytical sample of *compound* (**24**) was obtained by crystallization of the pure material with hot acetone (0.13 g, 96%); m.p. 214—216 °C; $\nu_{max.}$ 3 350—3 100 (OH, NH_2), 2 240 (C≡N), and 770 (C–Cl); $\lambda_{max.}$(pH 1) 235 (28 500) and 316 nm (4 400); (pH 7) 234 (28 700) and 317 nm (6 000); (pH 11) 234 (29 100) and 319 nm (6 100); δ_H [$(CD_3)_2SO$] 3.57 (2 H, m, 5′-H_2), 3.88 (1 H, m, 4′-H), 4.07 (1 H, m, 3′-H), 4.31 (1 H, m, 2′-H), 5.07 (1 H, t, 5′-OH), 5.19 (1 H, d, 3′-OH), 5.45 (1 H, d, 2′-OH), 5.97 (1 H, d, ($J_{1',2'}$ 5.7 Hz, 1′-H), 7.18 (2 H, br s, NH_2), and 8.40 (1 H, s, 6-H) (Found: C, 44.0; H, 3.65; N, 21.2; Cl, 11.1. $C_{12}H_{12}ClN_5O_4$ requires C, 44.25; H, 3.71; N, 21.50; Cl, 10.88%).

2-*Amino*-3,4-*dihydro* -7-(2,3-O-*isopropylidene*-β-D-*ribofuranosyl*)-4-*oxo*-7H-*pyrrolo*[2,3-d]*pyrimidine*-5-*carboxylic Acid* (**30**). —A solution of the nucleoside (**23**) (0.48 g, 1 mmol) in 1,4-dioxane (5 ml) was treated with M-KOH (10 ml) and heated under reflux at 110 °C for 6 h. The reaction mixture was cooled, diluted with water (10 ml), and extracted with EtOAc (2 × 30 ml). The aqueous alkaline solutions was adjusted to pH 5 with 2M-HCl and the precipitated solid was collected by filtration. The solid was dried over P_2O_5 *in vacuo* and crystallized from aqueous MeOH to yield *compound* (**30**) (0.27 g, 74%), m.p. > 300 °C; $\nu_{max.}$ 3 350—3 100 (NH, NH_2), 1 660, and 1 620 cm^{-1} (C=O); $\lambda_{max.}$(pH 1) 232 (14 200) and 298 nm (5 300); (pH 7) 226 (15 300), 265 (7 800), and 288 nm (6 600); (pH 11) 224 (30 200), 266 (14 900), and 286sh nm (12 800); δ_H[$(CD_3)_2SO$] 1.30 and 1.51 (6 H, 2 s, CMe_2), 3.52 (2 H, m, 5′-H_2), 4.08 (1 H, m, 4′-H), 4.94 (1 H, m, 3′-H), 5.09 (2 H, m, 2′-H and 5′-OH), 6.05 (1 H, d, ($J_{1',2'}$ 2.7 Hz, 1′-H), 6.78 (2 H, br s, NH_2), 7.85 (1 H, s, 6-H), 11.61 (1 H, br s, 3-H), and 14.22 (1 H, s, CO_2H) (Found: C, 47.1; H, 4.9; N, 14.7. $C_{15}H_{18}N_4O_7 \cdot \frac{3}{4}H_2O$ requires C, 47.43; H, 5.17; N, 14.75%).

2-*Amino*-3,4-*dihydro*-4-*oxo*-7-β-D-*ribofuranosylpyrrolo*[2,3-d]*pyrimidine*-5-*carboxylic Acid* (*Cadeguomycin*) (**1**). *Method A*.—A solution of compound (**30**) (0.18 g, 0.5 mmol) in TFA (10 ml) and water (2 ml) was heated under reflux for 4 h in an inert atmosphere. The reaction mixture was filtered and the filtrate was adjusted to pH 7 with conc. NH_4OH. The precipitated solid was collected by filtration and dried over P_2O_5 *in vacuo*. The dried material was boiled with aqueous EtOH for 1 h and filtered. The filtrate on cooling gave cadeguomycin (**1**) (0.12 g, 75%) as a crystalline compound, m.p. > 300 °C (decomp.) [lit.,[11] 327—330 °C (decomp.)]; $\nu_{max.}$ 3 450—3 300 (OH, NH_2), and 1 650 cm^{-1} (C=O); $\lambda_{max.}$(pH 1) 232 (22 700), 265 (7 300), and 298 nm (8 600); (pH 7) 227 (20 000), 265 (9 900), and 287 nm (8 600); (pH 11) 224 (10 100), 266 (5 100), and 288sh nm (4 400); δ_H[$(CD^{13})_2SO$] 3.57 (2 H, m, 5′-H_2), 3.87 (1 H, m, 4′-H), 4.07 (1 H, m, 3′-H), 4.30 (1 H, m, 2′-H), 5.10 (1 H, t, 5′-OH), 5.13 (1 H, d, 3′-OH), 5.37 (1 H, d, 2′-OH), 5.91 (1 H, d, $J_{1',2'}$ 6.3 Hz, 1′-H), 6.79 (2 H, br s, NH_2), 7.85 (1 H, s, 6-H), 11.64 (1 H, br s, 3-H), and 14.17 (1 H, s, CO_2H) (Found: C, 43.9; H, 4.2; N, 16.9 calc. for $C_{12}H_{14}N_4O_7$. C, 44.18; H, 4.33; N, 17.17%).

Method B.—A solution of the nucleoside (**24**) (0.85 g, 2.62 mmol) in 4M-KOH (30 ml) was heated at reflux temperature for 4 h. The reaction mixture was cooled to 0 °C and the pH adjusted to 2 with 2M-HCl. The precipitated solid was collected by filtration and dried. The dried solid was boiled with 95% aqueous EtOH for 1 h and the solution was filtered. The filtrate on cooling gave pure (**1**) (0.55 g, 65%), identical with the sample prepared by method A.

2-*Amino*-3,4-*dihydro*-4-*oxo*-7-β-D-*ribofuranosyl*-7H- *pyrrolo*-[2,3-d]*pyrimidine*-5-*carboxamide* (**25**).—A mixture of (**24**) (0.33 g, 1 mmol), H_2O_2 (10 ml), and conc. NH_4OH (50 ml) was stirred at room temperature in a sealed steel reaction vessel for 2 days. The vessel was cooled, opened carefully, and the contents were evaporated to dryness. The residue on crystallization from 95% aqueous EtOH gave the title compound (0.15 g, 46%), m.p. > 245 °C (decomp.) [lit.,[11] 260.5—261.5 °C (decomp.)]; $\nu_{max.}$ 3 400—3 100 (OH, NH_2) and 1 660 cm^{-1} (C=O); $\lambda_{max.}$(pH 1) 229 (16 100), 269sh (7 400), and 293 nm (7 200); (pH 7) 230 (16 400), 269sh (7 200), and 292 nm (7 500); (pH 11) 230 (17 800), and 288 nm (6 600); δ_H[$(CD_3)_2SO$] 3.53 (2 H, m, 5′-H_2), 3.82 (1 H, m, 4′-H), 4.03 (1 H, m, 3′-H), 4.27 (1 H, m, 2′-H), 5.03 (1 H, t, 5′-OH), 5.10 (1 H, d, 3′-OH), 5.31 (1 H, d, 2′-OH), 5.91 (1 H, d, $J_{1',2'}$ 6.6 Hz, 1′-H), 6.53 (2 H, br s, NH_2), 7.14 and 9.55 (2 H, 2 s, $CONH_2$), 7.59 (1 H, s, 6-H), and 10.98 (1 H, s, 3-H) (Found: C, 44.0; H, 4.7; N, 21.8 calc. for. $C_{12}H_{15}N_5O_6$: C, 44.31; H, 4.65; N, 21.53%).

2,4-*Diamino*-7-β-D-*ribofuranosyl*-7H-*pyrrolo*[2,3-d]*pyrimidine*-5-*carbonitrile* (**26**).—Compound (**24**) (0.33 g, 1 mmol) and $MeOH/NH_3$ (saturated at 0 °C, 70 ml) were heated at 80—90 °C in a sealed steel reaction vessel for 12 h. The vessel was cooled, opened, and the contents were evaporated to dryness. The residue was purified by flash chromatography with CH_2Cl_2–acetone (1:1) as eluant. The pure product on crystallization from a mixture of MeOH–CH_2Cl_2 gave compound (**26**) (0.15 g, 49%), m.p. 233—235 °C; $\nu_{max.}$ 3 400—3 100 (OH, NH_2) and 2 220 cm^{-1} (C≡N); $\lambda_{max.}$(pH 1) 235 (19 000), 269 (4 300), and 305 nm (6 100); (pH 7) 227 (23 700), 257sh (5 800), and 294 nm (7 900); (pH 11) 227 (24 200), 263sh (5 900), and 293 nm (8 100); δ_H [$(CD_3)_2SO$] 3.53 (2 H, m, 5′-H_2), 3.84 (1 H, m, 4′-H), 4.04 (1 H, m, 3′-H), 4.29 (1 H, m, 2′-H), 5.14 (2 H, m, 3′-OH and 5′-OH), 5.36 (1 H, d, 2′-OH), 5.91 (1 H, d, ($J_{1',2'}$ 6.0 Hz, 1′-H), 6.06 (2 H, br s, NH_2), 6.31 (2 H, br s, NH_2), and 8.00 (1 H, s, 6-H) (Found: C, 46.8; H, 4.6; N, 27.2. $C_{12}H_{14}N_6O_4$ requires C, 47.06; H, 4.61; N, 27.44%).

2-*Amino*-4-*chloro*-7-(2,3,5-*tri*-O-*benzyl*-β-D-*arabinofuranosyl*)-7H-*pyrrolo*[2,3-d]*pyrimidine*-5-*carbonitrile* (**28**).—To a solution of compound (**11**) in dry MeCN (100 ml) was added NaH (60% in oil; 0.20 g, 5 mmol) and the mixture was stirred at

room temperature under an argon atmosphere for 1 h. A solution of 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride[35] (**27**), [prepared from 2,3,5-tri-*O*-benzyl-1-*O*-(*p*-nitrobenzoyl)-D-arabinose (2.65 g, 4.6 mmol)] in MeCN (25 ml) was added to the stirred mixture, which was then stirred overnight, evaporated to dryness, and the residue was purified by flash chromatography with hexane–acetone (7:3) as eluant to yield compound (**28**) (1.6 g, 58%) as a foam; $\nu_{max.}$(neat) 3 300—3 100 (NH_2), 2 210 (C≡N), and 780 cm^{-1} (C–Cl); $\lambda_{max.}$(pH 1) 250 nm (8 400); (pH 7) 251 nm (6 800); (pH 11) 244 nm (12 800); δ_H [$(CD_3)_2SO$] 3.69 (2 H, m, 5′-H_2), 3.98—4.64 (9 H, m, 2′-, 3′-, and 4′-H and 3 × CH_2Ph), 6.42 (1 H, d, $J_{1',2'}$ 5.3 Hz, 1′-H), 6.94 (2 H, s, NH_2), 7.15—7.37 (15 H, m, 3 × Ph), and 8.04 (1 H, s, 6-H) (Found: C, 66.5; H, 5.0; N, 11.5; Cl, 6.2. $C_{33}H_{30}ClN_5O_4$ requires C, 66.49; H, 5.07; N, 11.70; Cl, 5.95%).

2-*Amino*-7-β-D-*arabinofuranosyl*-4-*chloro*-7H-*pyrrolo*[2,3-d]*pyrimidine*-5-*carbonitrile* (**29**).—To a stirred solution of the blocked nucleoside (**28**) (2.86 g, 4.8 mmol) in dry CH_2Cl_2 (100 ml) at −78 °C was added BCl_3 (1M solution in CH_2Cl_2; 50 ml, 50 mmol) during 15 min. The reaction mixture was stirred at −78 °C for 2 h and at −20 °C for 3 h. MeOH–CH_2Cl_2 (50 ml, 1:1), was added to the mixture, which was then stirred at −20 °C for 0.5 h and neutralized with conc. NH_4OH at 0 °C. The mixture was filtered and the residual solid was washed with CH_2Cl_2–MeOH (1:1, 50 ml). The combined filtrate and washings were evaporated to dryness. The residue was dissolved in MeOH, adsorbed onto silica gel (10 g), and the mixture was evaporated to dryness. The dried silica gel was placed on top of a flash silica gel column (4 × 40 cm) packed in CH_2Cl_2. The column was eluted with CH_2Cl_2 ⟶ MeOH gradient to give the desired deprotected nucleoside (**29**) as a crystalline compound (0.80 g, 52%), m.p. 265—266 °C (MeOH); $\nu_{max.}$ 3 340—3 200 (OH, NH_2) and 2 240 cm^{-1} (C≡N); $\lambda_{max.}$(pH 1) 235 (34 200) and 317 nm (6 800); (pH 7) 234 (31 200) and 317 nm (6 400); (pH 11) 234 (30 200) and 317 nm (6 200); δ_H [$(CD_3)_2SO$] 3.65 (2 H, m, 5′-H_2), 3.77 (1 H, m, 4′-H), 4.07 (2 H, m, 2′-, and 3′-H), 5.11 (1 H, t, 5′-OH), 5.54 (2 H, m, 2′- and 3′-OH), 6.27 (1 H, d, $J_{1',2'}$ 4.7 Hz, 1′-H), 7.14 (2 H, s, NH_2), and 8.19 (1 H, s, 6-H) (Found: C, 44.1; H, 3.7; N, 21.4; Cl, 10.7. $C_{12}H_{12}ClN_5O_4$ requires C, 44.20; H, 3.72; N, 21.50; Cl, 10.80%).

2-*Amino*-7-β-D-*arabinofuranosyl*-3,4-*dihydro*-4-*oxo*-7H-*pyrrolo*[2,3-d]*pyrimidine*-5-*carboxylic Acid*(*ara-Cadeguomycin*) (**2**).—A solution of compound (**29**) (0.11 g, 0.33 mmol) was heated under reflux with 5M-NaOH (10 ml) for 5 h. The reaction mixture was poured onto crushed ice (100 g). The resulting solution was adjusted to pH 6 with Dowex-50 (H^+) resin. The precipitated solid was decanted and washed with cold water (10 ml). The dried product was crystallized from aqueous EtOH to give the *title compound* (0.56 g, 56%), m.p. >300 °C; [lit.,[17] 240—250 °C (decomp); the difference in m.p. may be due to decomposition]; $\nu_{max.}$ 3 500—3 000 (OH, NH_2, CO_2H), and 1680—1 620 cm^{-1} (C=O); $\lambda_{max.}$(pH 1) 232 (8 300), 272 (2 900), and 297 nm (3 400); (pH 7) 227 (19 300), 264 (9 200), and 288 nm (7 900); (pH 11) 225 (22 500) and 265 nm (11 000); δ_H [$(CD_3)_2SO$] 3.61 (2 H, m, 5′-H_2), 3.75 (1 H, m, 4′-H), 4.04 (2 H, m, 2′- and 3′-H), 5.16 (1 H, t, 5′-OH), 5.52 and 5.57 (2 H, 2 d, 2′- and 3′-OH), 6.18 (1 H, d, $J_{1',2'}$ 4.2 Hz, 1′-H), 6.70 (2 H, s, NH_2), 7.65 (1 H, s, 6-H), 11.58 (1 H, s, 3-H), and 14.08 (1 H, s, CO_2H) (Found: C, 44.12; H, 4.0; N, 16.9. $C_{12}H_{14}N_4O_7$ requires C, 44.18; H, 4.32; N, 17.17%).

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