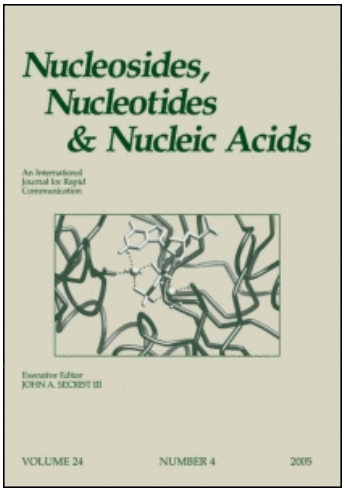

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USE OF THE SODIUM SALT GLYCOSYLATION METHOD IN NUCLEOSIDE SYNTHESIS

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ABSTRACT: A general and stereospecific method has been developed for the direct preparation of β-D-ribofuranosyl, β-D-arabinofuranosyl and 2-deoxy-β-D-erythro-pentofuranosyl derivatives of a number of nitrogen heterocycles. The azoles thus far employed include appropriately substituted pyrrole, pyrazole, imidazole, 1,2,4-triazole, indole, imidazo-[4,5-c]pyridine, pyrrolo[2,3-d]pyrimidine, pyrrolo[3,2-c]pyridine, pyrrolo[3,2-c]pyrimidine, purine, pyrazolo[3,4-b]pyridine and pyrazolo-[3,4-d]pyrimidine. This simple high-yield methodology provided a facile route to the large-scale preparation of biologically significant nucleosides, such as 2'-deoxyribavirin, 2-chloro-2'-deoxyadenosine, tubercidin, 2'-deoxytubercidin, ara-sangivamycin, 2'-deoxytoyocamycin, cadeguomycin, 2'-deoxycadeguomycin, ara-cadeguomycin, kanagawamicin, 2'-deoxy-3-deazaguanosine, araG, brunfelsamidine ribonucleoside and 2'-deoxyribofuranosyl derivative of the antibiotic SF-2140. This procedure appears to be considerably superior to the previously reported glycosylation methods.

2'-Deoxyribonucleosides of 2-haloadenine (2-fluoro, 2-chloro and 2-bromo) are a relatively new group of compounds of current clinical interest due to their potent anticancer activity.[1] The substitution of a halogen at the 2-position of adenine moiety rendered these nucleosides resistant to deamination by the catabolic enzyme adenosine deaminase[1] and thus, they are capable of exerting a more prolonged biochemical effect than the parent 2'-deoxyadenosine. As a consequence these nucleosides are highly toxic to cells in culture.[2-9] It has been found[4] that 2-chloro-2'-deoxyadenosine, given on a frequent schedule, produced 60% survivors of mice bearing L1210 leukemia. Thus, the potential use

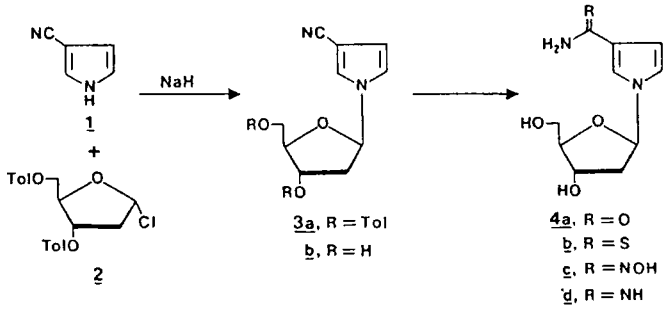
of 2-halo-2′-deoxyadenosines as anticancer agents has prompted a need for a convenient and facile method for the large-scale synthesis of these and related nucleosides. We have developed a simple and stereospecific sodium salt glycosylation method for the preparation of certain 2′-deoxy as well as arabinosyl and ribofuranosyl nucleosides. This procedure appears to be of general utility, overcomes many of the limitations found in earlier glycosylation procedures, and can be adapted to large-scale syntheses.

Some of the inherent disadvantages of the prior glycosylation procedures reported by us[10-13] and by others[14-17] for introducing the 2-deoxy-β-D-ribofuranosyl moiety onto an azole are that they invariably provide anomeric mixtures as well as positional isomers resulting in a tedious separation, and consequently low yields of the desired 2′-deoxy nucleoside. In view of these difficulties, a four-step deoxygenation procedure using phenoxythiocarbonylation[18-20] or imidazolylthiocarbonylation[21,22] of the 2′-hydroxy group of the corresponding 3′,5′-protected β-D-ribofuranoside has been developed to provide the requisite 2′-deoxynucleoside. These later procedures, however, require the availability of the preformed ribonucleoside and are not generally applicable in the presence of halogen substituted aglycons,[1] which are most useful for further nucleophilic displacement reactions. Recently, a phase-transfer glycosylation procedure under strongly alkaline conditions has been used to prepare certain 2′-deoxyribonucleosides.[23] A highly reactive aglycon is often a basic requirement for an effective phase-transfer glycosylation since the halogenose gradually decomposes under the strong alkaline reaction conditions.[23]

In order to investigate the feasibility of our procedure, we first considered the glycosylation of a simple substituted pyrrole. We selected pyrrole-3-carbonitrile[24] (1) for glycosylation studies, since brunfelsamidine, a novel convulsant isolated recently from the roots and bark of Brunfelsia grandiflora is identified[25] as pyrrole-3-carboxamidine. The water extracts of Brunfelsia grandiflora is a widely used remedy against rheumatism, arthritis, fevers and snakebite.[26] The ribonucleoside of pyrrole-3-carbonitrile would also provide a "dideaza" analog of the broad spectrum antiviral agent ribavirin.[27]

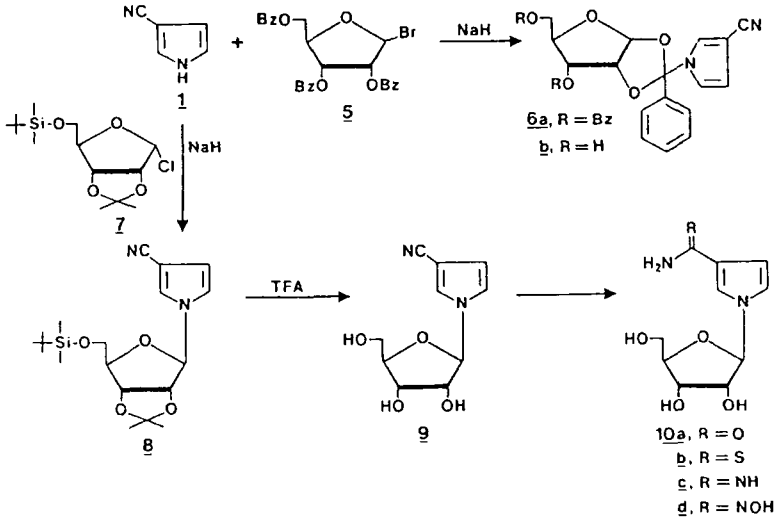
Reported procedures for the preparation of pyrrole nucleosides[28-30] are neither straightforward nor simple. Kawana and Emoto[28] utilized partially hydrogenated pyrroles in the glycosylation reaction using the

"indoline-indole" method.[30] Subsequent photodehydrogenation of Δ^3-pyrroline nucleoside intermediates gave the pyrrole nucleosides. However, our synthetic pathway involved the direct attachment of a glycon moiety to a preformed fully aromatic pyrrole derivative. Thus, reaction of 1-chloro-2-deoxy-3,5-di-O-p-toluoyl-α-D-erythro-pentofuranose[31] (2) with the sodium salt of 1 gave a 65% yield of the corresponding protected nucleoside (3a). No formation of the α-anomer of 3a was detected in this reaction. Deprotection of the glycon moiety of 3a was accomplished by the treatment with $MeOH/NH_3$ to yield 1-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrole-3-carbonitrile (3b), in which the nitrile function was available for further transformation reactions to afford 4a-d.[32]



In an effort to prepare a ribofuranosyl derivative of 1, freshly prepared 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide[33] (5) was reacted with the sodium salt of 1 in dioxane. A nucleoside product (6a) was formed and was isolated in 85% yield. Debenzoylation of 6a with $MeOH/NH_3$ afforded a compound for which a phenylmethylidene structure (6b) was assigned. The formation of 6a was presumably due to the participation of the neighboring benzoyl group and resulted from the attack of the anion of 1 on the carbonyl carbon of the protecting group rather than the C_1 carbon of the carbohydrate moiety.[34]

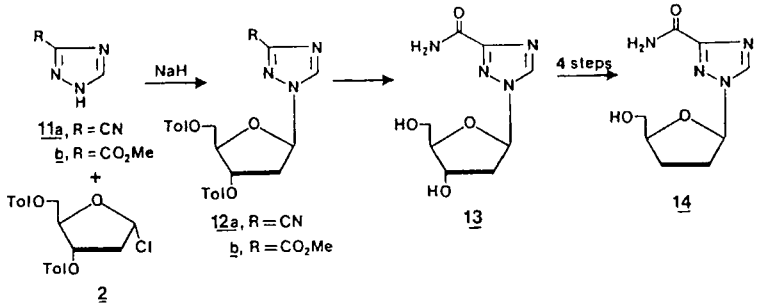
In order to prepare the target β-D-ribofuranosyl derivative of brunfelsamidine (10c), the recently reported[35] 1-chloro-2,3-O-isopropylidene-5-O-(t-butyl)dimethylsilyl-α-D-ribofuranose (7) was prepared and coupled with the sodium salt of 1 in anhydrous CH_3CN. A clean reaction was observed and the desired product 8 was isolated in over 66% yield.



Treatment of 8 with aqueous trifluoroacetic acid (TFA) gave 1-β-D-ribofuranosylpyrrole-3-carbonitrile (9) in almost quantitative yield, in which the carbonitrile function was available for further transformation reactions. Thus, treatment of 9 with NH_4OH/H_2O_2 gave 2,4-dideazaribavirin (10a), whereas reaction with NH_2OH in EtOH gave the corresponding 3-carboxamidoxime (10d), which on catalytic (Raney Ni) hydrogenation furnished brunfelsamidine ribonucleoside (10c).[36] Our attempt to convert 9 directly to 10c with liquid NH_3/NH_4Cl was not successful.

The experimental methodology is relatively simple. In general, a 10 mmolar solution (or suspension) of the substrate in 100 ml of anhydrous CH_3CN or dioxane is treated with a 11 mmolar quantity of NaH (50% in oil) and the mixture is stirred at room temperature in an inert atmosphere for 30 min. An appropriate α-halogenose (10 mmol) is added portionwise. After stirring for 2-3 h, the reaction mixture is filtered, the filtrate is evaporated and the residue purified by flash silica gel column chromatography using, normally, hexane:acetone (7:3) or hexane:ethyl acetate (8:2) as the eluent.

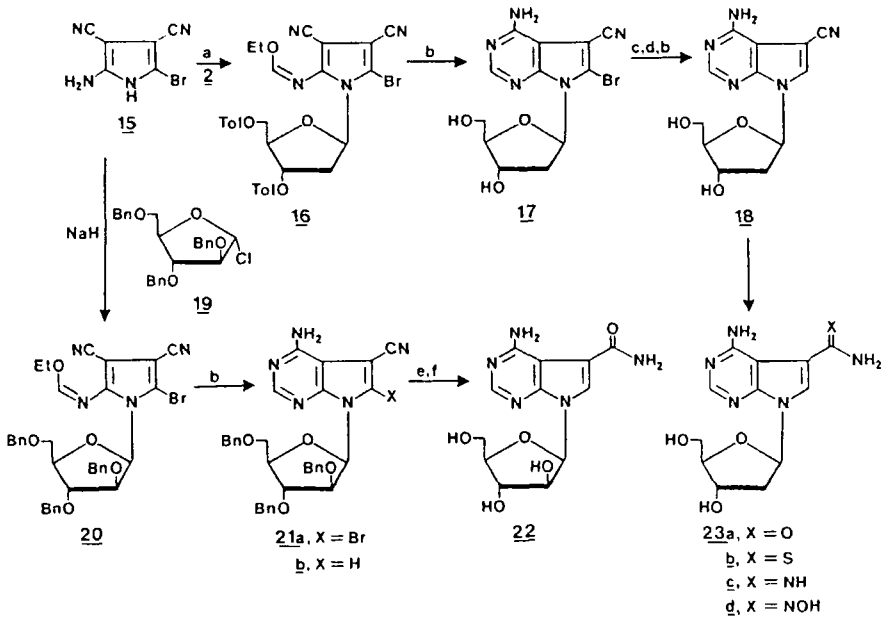
Under this experimental condition only the nucleosides with β-anomeric configuration were isolated. No formation of the α-anomer was detected by usual chromatographic (TLC or HPLC) techniques. Since the starting halogenose has the α-configuration, the exclusive formation



of the blocked β-nucleosides in our study is presumed to be due to a direct Walden inversion (S_N2) at the C_1-carbon of the carbohydrate moiety by the anionic heterocyclic nitrogen.

This simple methodology furnished a route to the preparation of 2′,3′-dideoxyribavirin (14). Certain 2′,3′-dideoxynucleosides inhibit the *in vitro* replication of HIV retrovirus,[37] the etiologic agent of the Acquired Immune Deficiency syndrome (AIDS).[38,39] Glycosylation of the sodium salt of either 1,2,4-triazole-3-carbonitrile[40] (11a) or methyl 1,2,4-triazole-3-carboxylate[41] (11b) with the α-halogenose 2 in CH_3CN gave the corresponding N-1 glycosylated products 12a and 12b in 35% and 28% yield, respectively, along with minor amounts of N-2 glycosyl isomers with β-anomeric configuration. Ammonolysis of either 12a or 12b gave an excellent yield of 2′-deoxyribavirin (13). The four-step deoxygenation of 13, *via* the 3′-O-methoxythiocarbonyl intermediate, furnished the desired 2′,3′-dideoxyribavirin[42] (14), which in a preliminary study was found to be inactive against HIV retrovirus in culture.

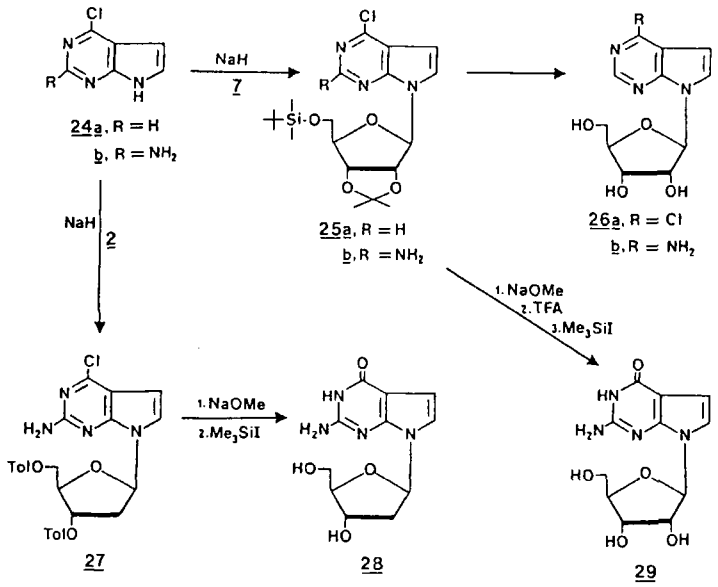
This versatile procedure provided a stereospecific method for the synthesis of tubercidin (26b), 7-deazaguanosine (29), cadeguomycin (44), kanagawamicin (51), 2′-deoxytoyocamycin (18), *ara*-sangivamycin (22) and a host of other pyrrolo[2,3-*d*]pyrimidine nucleosides of biological significance. For the synthesis of 2′-deoxytoyocamycin (18) and *ara*-sangivamycin (22), 2-amino-5-bromopyrrole-3,4-dicarbonitrile[43] (15) served as a useful starting material. The protection of the amino group was effected by the treatment of 15 with diethoxymethylacetate in CH_3CN to give the 2-ethoxymethyleneamino compound, which on treatment with 2 in the presence of NaH gave a 75% yield of the corresponding blocked



a. $HC(OEt)_2COOMe$; b. MeOH/NH_3; c. Ac_2O/Py; d. KF/18Crown-6; e. NH_4OH/H_2O_2; f. $Pd(OH)_2$

nucleoside 16. Compound 16 cleanly cyclized to 4-amino-6-bromo-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carbonitrile (17) on treatment with MeOH/NH_3. Selective acetylation of 17 with Ac_2O in pyridine, followed by reductive debromination[44] with N,O-bis(trimethylsilyl)acetamide (BSA) in the presence of 'naked' fluoride ion and deacetylation gave 2'-deoxytoyocamycin[32] (18), in which the nitrile function was available for further transformation reactions to give 23.

The 2-ethoxymethyleneaminopyrrole was also used in the glycosylation studies to obtain ara-sangivamycin (22) and certain related compounds. Thus, treatment of the sodium salt of the pyrrole with 1-chloro-2,3,5-tri-O-benzyl-α-D-arabinofuranose[45] (19) gave the corresponding benzyl blocked nucleoside 20, which was readily ring closed in the presence of MeOH/NH_3 to yield 4-amino-6-bromo-7-(2,3,5-tri-O-benzyl-β-D-arabinofuranosyl)pyrrolo[2,3-d]pyrimidine-5-carbonitrile (21a). Reductive debromination with BSA gave 21b, which on oxidative hydration by the treatment with NH_4OH/H_2O_2, followed by debenzylation with $Pd(OH)_2$ in the presence of cyclohexene gave ara-sangivamycin (22). Compound 21b could be used for further transformation reactions[46] to obtain potent antiviral[47] nucleosides which are

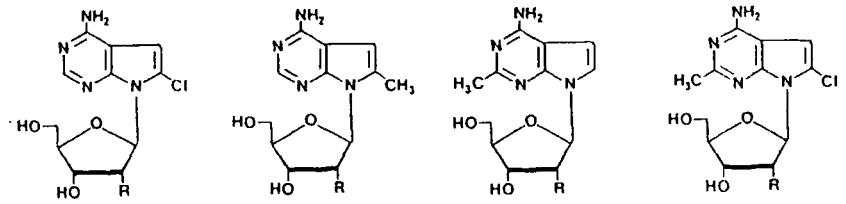


totally free of contamination with the ribonucleoside antibiotics toyocamycin or sangivamycin.

The naturally occurring cytotoxic[48,49] nucleoside antibiotic tubercidin (26b) was prepared by the direct glycosylation of the sodium salt of 4-chloropyrrolo[2,3-d]pyrimidine[50] (24a). Reaction of 24a with 7 in CH_3CN gave a 67% yield of the blocked nucleoside 25a, which on deprotection with TFA furnished 4-chloro-7-β-D-ribofuranosylpyrrolo-[2,3-d]pyrimidine (26a) in almost quantitative yield. Treatment of 26a with $MeOH/NH_3$ gave tubercidin in 81% yield. A similar glycosylation of the sodium salt of 2-amino-4-chloropyrrolo[2,3-d]pyrimidine[51] (24b) with 7 gave the blocked nucleoside 25b, which on sequential conversion of the C-4 chloro group into a methoxy, deisopropylidenation of the glycon moiety and cleavage of the ether linkage without affecting the glycosidic cleavage gave the desired 7-deazaguanosine (29) in good yield. In a like manner, condensation of the sodium salt of 24b with 2 and subsequent treatment of the condensation product (27) with NaOMe, followed by Me_3SiI treatment provided a straightforward route to the preparation of 2'-deoxy-7-deazaguanosine (28).

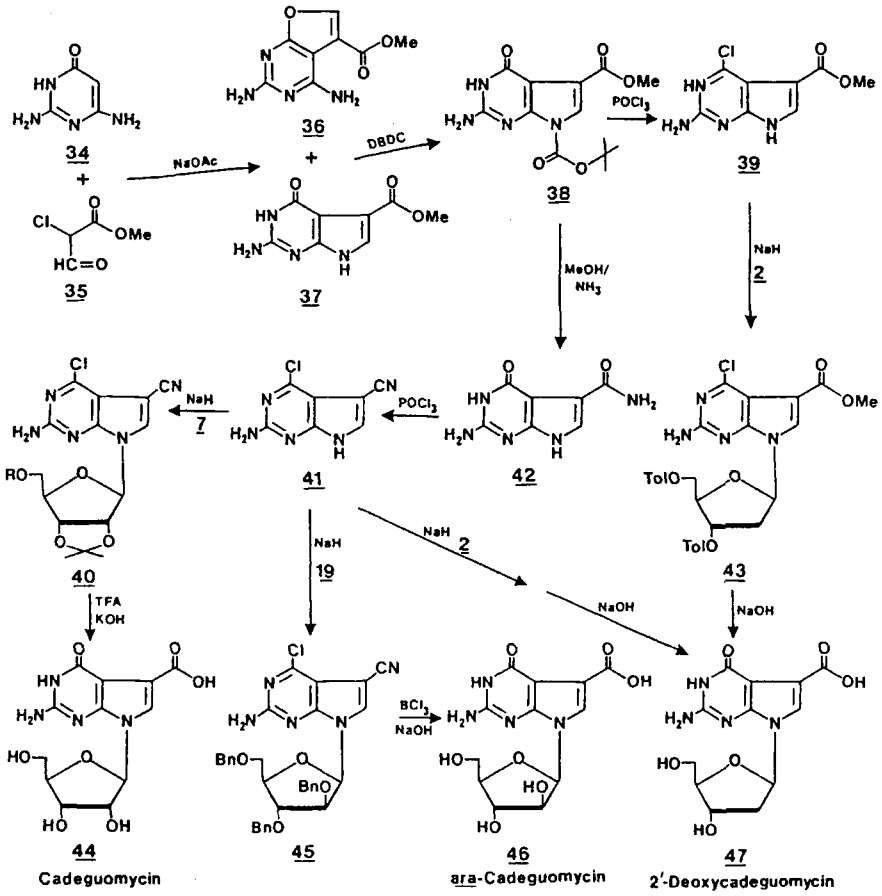
The syntheses of 6-chloro- (30, R=OH)[52], 6-methyl- (31, R=OH),[52] 2-methyl- (32, R=OH)[52] and 2-methyl-6-chloro-tubercidins (33, R=OH),[52]

as well as the corresponding 2′-deoxynucleosides (30-33, R=H)[53] have also been accomplished by this procedure in good yields.



Cadeguomycin (44) is a novel pyrrolo[2,3-d]pyrimidine nucleoside antibiotic, isolated recently[54] from the culture broth of Streptomyces hygroscopicus IM7912T as a minor component together with tubercidin, and characterized as 2-amino-4(3H)-oxo-7-β-D-ribofuranosylpyrrolo[2,3-d]-pyrimidine-5-carboxylic acid.[55] This interesting antibiotic inhibited the growth of solid IMC carcinoma and pulmonary metastasis of Lewis lung carcinoma in mice with appreciably low toxicity.[56] It also enhanced cell-mediated immunity and macrophage activity.[56] Cadeguomycin displayed a unique property of enhancing uptake of pyrimidine nucleosides into K562 human myelogenous leukemic cells and YAC-1 murine lymphoma cells, and it potentiated cytotoxicity of ara-C[56-58] as well as 5-fluoro-2′-deoxycytidine[59] both in vitro and in vivo. This interesting and potent activity resulted in the multistep synthesis of cadeguomycin[60-62] and ara-cadeguomycin.[63] However, the synthesis of 2′-deoxycadeguomycin (47) has not yet been realized. Utilization of our sodium salt glycosylation method is found to be remarkably successful not only for the synthesis of 2′-deoxycadeguomycin, but also for the preparation of cadeguomycin (44), ara-cadeguomycin (46) and the unusual nucleoside antibiotic kanagawamicin (51).

As a base moiety for the synthesis of 47, we elected to use the hitherto inaccessible methyl 2-amino-4-chloropyrrolo[2,3-d]pyrimidine-5-carboxylate (39) or 2-amino-4-chloropyrrolo[2,3-d]pyrimidine-5-carbonitrile (41) for the glycosylation studies. Our approach was to build the substituted pyrrole ring onto a preformed pyrimidine ring so that the pyrrolo[2,3-d]pyrimidine precursor (37) thus generated could be transformed to either 39 or 41. When a mixture of 2,6-diaminopyrimidin-4-(3H)-one (34) was heated with methyl formylchloroacetate[64] (35) in



water containing NaOAc, a mixture of two products was formed. The separation of these products was found to be rather difficult by usual chromatographic or crystallization techniques. This problem was, however, resolved by selective protection of the pyrrole ring NH-proton in 37 by allowing the mixture to react with di-tert-butyl dicarbonate (DBDC) in the presence of Et_3N to give methyl 2-amino-4(3H)-oxo-7-tert-butyloxycarbonylpyrrolo[2,3-d]pyrimidine-5-carboxylate (38). Compound 38 was readily separated by dissolving in boiling EtOAc and filtration from the insoluble furo[2,3-d]pyrimidine compound 36.

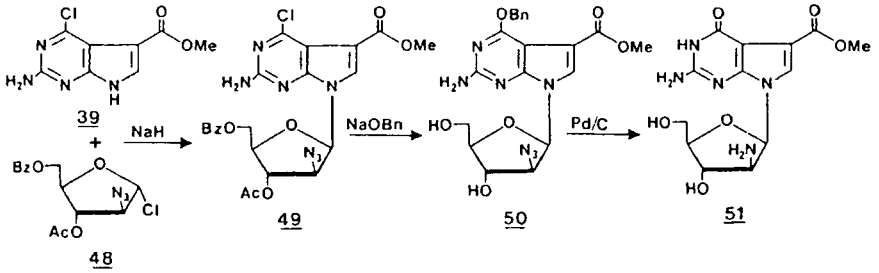
Conversion of 38 into 39 was accomplished by refluxing a solution of 38 in $POCl_3$ in the presence of N,N-diethylaniline (DEA). Reaction of 38 with $MeOH/NH_3$ at elevated temperature converted the methyl ester

function to an amide group with concomitant removal of the BOC group to give 2-amino-4(3H, 7H)-oxopyrrolo[2,3-d]pyrimidine-5-carboxamide (42) in 73% yield. Treatment of 42 with $POCl_3$ in the presence of DEA at reflux temperature produced the other building block 2-amino-4-chloropyrrolo-[2,3-d]pyrimidine-5-carbonitrile (41). Both 39 and 41 are suitable precursors for the stereospecific synthesis of cadeguomycins.

The sodium salt of 39, generated in situ by the treatment with NaH in CH_3CN, was reacted with the α-halogenose 2 in an inert atmosphere to give a 87% yield of the corresponding blocked nucleoside 43. Saponification of 43 with 2N NaOH in dioxane, followed by neutralization afforded 2'-deoxycadeguomycin (47). A similar glycosylation of the sodium salt of 41 with 2, and further functional group manipulation of the nucleoside intermediate furnished a second route to 2'-deoxycadeguomycin.

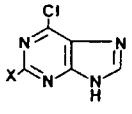
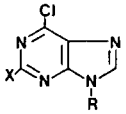
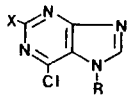
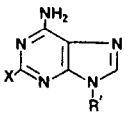
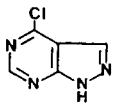
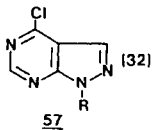
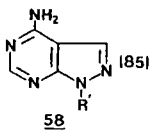
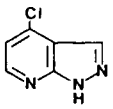
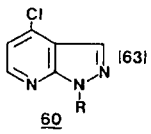
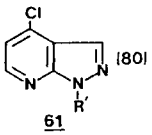
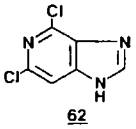
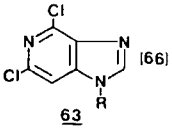
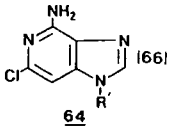
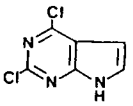
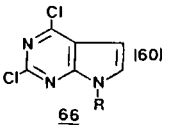
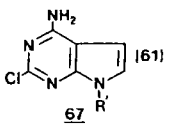
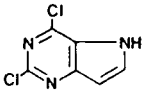
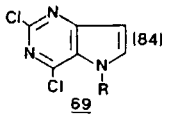
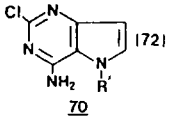
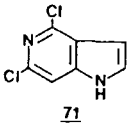
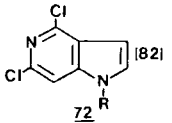
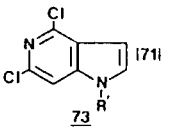
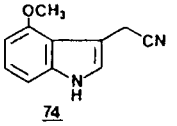
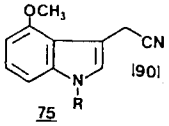
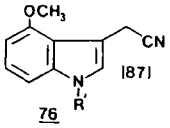
A total synthesis of cadeguomycin (44) and ara-cadeguomycin (46) has also been accomplished by reacting the appropriate α-halogenoses (7 and 19, respectively) with the sodium salt of 41, and subsequent deprotection of the glycon moiety, followed by saponification. By using this methodology, we have recently prepared several grams of cadeguomycin, ara-cadeguomycin and 2'-deoxycadeguomycin for detail biological evaluation.

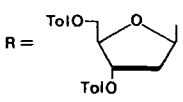
The ready availability of the aglycon methyl 2-amino-4-chloropyrrolo[2,3-d]pyrimidine-5-carboxylate (39) provided a simple route for the preparation of the aminonucleoside antibiotic kanagawamicin (51). Kanagawamicin was isolated by Tanaka and coworkers[65] in 1983. This antibiotic showed antitumor activity and also exhibited antibacterial

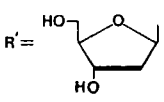


activity against Gram-negative bacteria.[65] Glycosylation of the sodium salt of 39 with 3-O-acetyl-2-azido-2-deoxy-5-O-benzoyl-α-D-arabino-furanosyl chloride[66] (48) under standard experimental conditions gave

Table I. Condensation of the Sodium Salt of Various Chloropurines and Chloropurine Analogues with 1-Chloro-2-deoxy-3,5-di-O-p-toluoyl-α-D-erythro-pentofuranose (2)

starting heterocycle	intermediate (% yield)		final product (% yield)
	 +		
52a, X = H	53a, X = H (61)	54a, X = H (13)	55a, X = H (80)
b, X = Cl	b, X = Cl (59)	b, X = Cl (11)	b, X = Cl (75)
c, X = NH_2	c, X = NH_2 (55)	c, X = NH_2 (9)	c, X = NH_2 (85)
 56	 (32) 57		 (85) 58
 59	 (63) 60		 (80) 61
 62	 (66) 63		 (66) 64
 65	 (60) 66		 (61) 67
 68	 (84) 69		 (72) 70
 71	 (82) 72		 (71) 73
 74	 (90) 75		 (87) 76

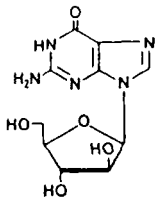
R = 

R' = 

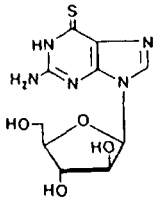
the corresponding protected nucleoside (49), which on treatment with sodium benzyloxide and catalytic hydrogenation gave kanagawamicin (51) in respectable yield.

Use of this simple glycosylation procedure for the preparation of 2'-deoxyribonucleosides of various chloropurines and chloropurine analogs has been found to be very successful. Table I shows the condensation products of these purines and purine analogs with 2. The isolated yields of the condensation products are generally good. This method also provided a facile and convenient route to the large-scale preparation[67] of the biologically significant araG (77) and ara-6-thioguanine (78).

3-Deazaguanine is a structural analog of guanine in which the pyrimidine ring nitrogen in the 3-position is replaced by CH and was first reported by us[68] in 1976. Since that report, the broad-spectrum antiviral activity against a variety of DNA and RNA viruses,[69] as well as the potent antitumor activity against L1210 leukemia and mammary adenocarcinomas in mice[70-72] of 3-deazaguanine and its metabolite 3-deazaguanosine have been confirmed independently in a number of laboratories. The antitumor mode of action of 3-deazaguanine has been postulated to be due to the consequence of its incorporation into tumor cell DNA.[72,73] To evaluate this hypothesis we undertook the synthesis of the 2'-deoxy derivatives of 3-deazaguanosine. Again, the sodium salt glycosylation method was found to be very successful. Glycosylation of the sodium salt of methyl 5-cyanomethylimidazole-4-carboxylate[68] (79)

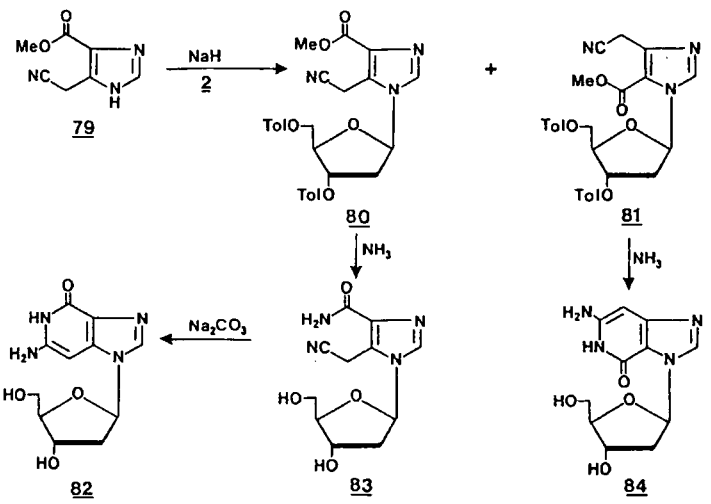


77

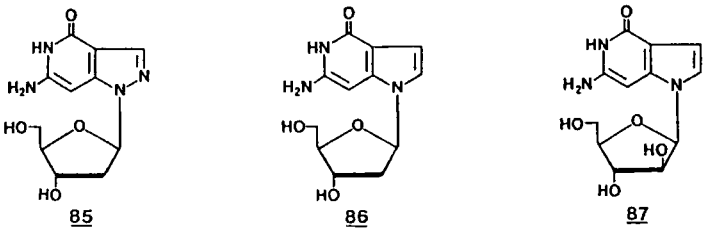


78

with 2 gave a mixture of two nucleoside products (80 and 81) in 49% and 45% yield, respectively. No formation of the α-anomer was detected. Subsequent treatment of each of the blocked nucleosides with liquid NH_3 provided 2'-deoxy-3-deazaguanosine (82) and the corresponding N-7 glycosyl isomer (84).[74] 2'-Deoxy-3-deazaguanosine exhibited significant broad-spectrum antiviral and antitumor activity in vitro.[74]



Making use of this sodium salt glycosylation method and ring closure of the azole nucleoside precursors, we have recently prepared 2-deoxy-β-D-ribofuranosyl derivatives of 6-aminopyrazolo[4,3-c]pyridin-4(5H)-one[75] (85) and 3,7-dideazaguanosine[76] (86).



Besides ourselves, a number of other laboratories[77-82] have recently recognized the simplicity and stereospecificity of our sodium salt glycosylation method in nucleoside synthesis. Although the use of a sodium salt of heterocyclic base (generated either by NaH[83,84] or by NaOMe[85]) in glycosylation studies has to date been sparsely documented, we believe the present improved technique is a valuable addition to the synthetic methodology for a variety of nucleosides. This simple procedure is quite general in nature and appears to be considerably superior to the previously reported glycosylation methods.

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