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A FACILE SYNTHESIS OF TUBERCIDIN AND RELATED 7-DEAZAPURINE NUCLEOSIDES VIA THE STEREOSPECIFIC SODIUM SALT GLYCOSYLATION PROCEDURE

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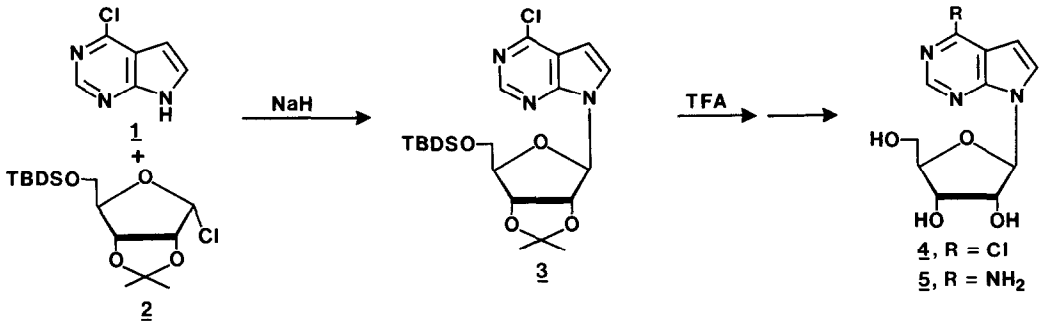
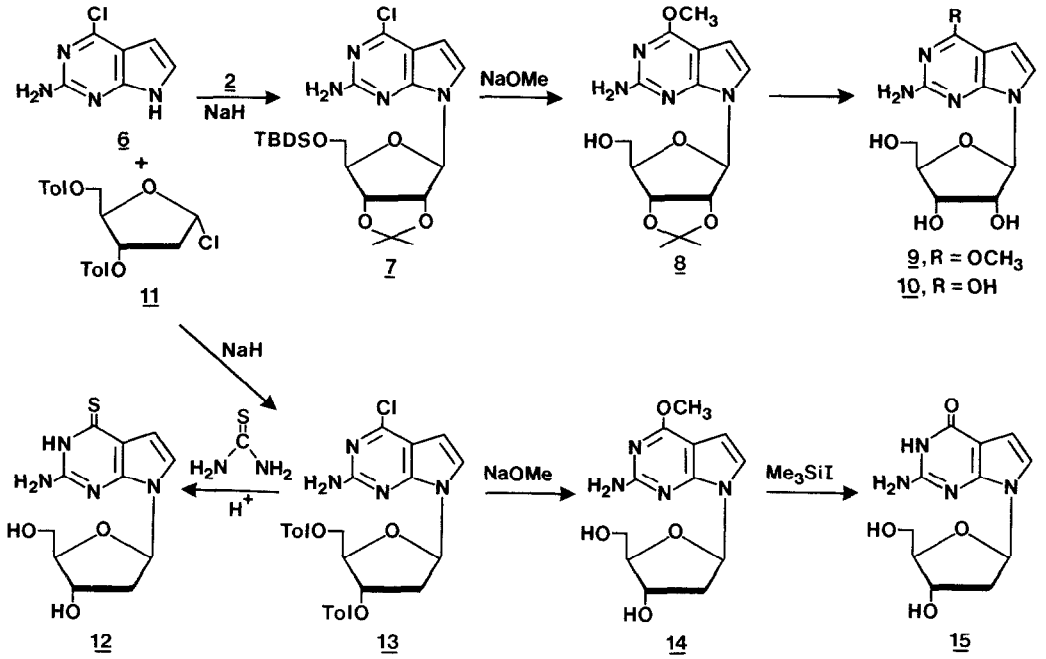
Summary. A facile high-yield synthesis of 7-deazaadenosine (tubercidin, 5), 7-deazaguanosine (10), 2'-deoxy-7-deaza-6-thioguanosine (12) and 2'-deoxy-7-deazaguanosine (15) by the regioselective and stereospecific sodium salt glycosylation procedure is described.

Since the isolation[1-3] and structural elucidation[4] of the naturally occurring pyrrolo-[2,3-d]pyrimidine nucleoside antibiotics tubercidin (5), toyocamycin and sangivamycin derived from Streptomyces species, a number of reports have appeared in the literature describing their biological (antiviral, antineoplastic and antiparasitic) and physicochemical properties.[5-8] In addition, the base- as well as the sugar-modified analogues of these natural nucleosides have been prepared and evaluated for their antiviral and antitumor activities.[9-11] Notwithstanding the several multistep synthesis of 5 and related compounds reported so far,[4,12] there is still a need for a simple and straightforward large-scale preparation of these antibiotics and their derivatives. We now report a facile and high-yield route to tubercidin (5) by the sodium salt glycosylation procedure[13] and also demonstrate the potential of this procedure for the improved synthesis of 7-deazaguanosine (10) as well as 2'-deoxy-7-deazaguanosine (15).



Our strategy was to accomplish the regiocontrolled and stereospecific glycosylation of the sodium salt of 4-chloro- and 2-amino-4-chloropyrrolo[2,3-d]pyrimidine (1 or 6, respectively) with an appropriate halogenose to obtain the protected nucleoside intermediate, which could then be converted to the desired 5, 10 or 15. As a representative example, the sodium salt of 4-chloropyrrolo[2,3-d]pyrimidine[14] (1, 20 mmol), generated in situ by the treatment with sodium hydride (60% in oil, 20 mmol), in anhydrous acetonitrile, was reacted with 1-chloro-2,3-O-isopropylidene-5-O-t-butyldimethylsilyl-α-D-ribofuranose[15] (2, 10 mmol), at ambient temperature for 1 hour in a dry inert atmosphere. The reaction mixture was filtered to remove

a small amount of insoluble material. Evaporation of the filtrate and purification of the residue on a flash silica gel column using hexane:ethyl acetate (9:1, v/v) as the solvent, gave syrupy 4-chloro-7-(2,3-O-isopropylidene-5-O-t-butyldimethylsilyl-β-D-ribofuranosyl)-pyrrolo[2,3-d]pyrimidine[16] (3, 67% yield). Compound 3 was the only nucleoside product which could be detected by TLC or column chromatography procedures. Deprotection of 3 with 90% aqueous trifluoroacetic acid at room temperature for 1 hour furnished 4-chloro-7-β-D-ribofuranosylpyrrolo[2,3-d]pyrimidine (4) [98.5% yield; mp 161-163°C (Lit.[17] mp 161-163°C)]. Treatment of 4 with methanolic ammonia (saturated at 0°C) at 120°C for 15 hours resulted in the displacement of the chloro group to provide 4-amino-7-β-D-ribofuranosylpyrrolo[2,3-d]-pyrimidine (tubercidin, 5; 81% yield) with mp 248-250°C [Lit.[5] mp 247-248°C].[18] There was no depression observed by mixture melting point of an authentic sample.[19]



Extrapolation of this regioselective and stereospecific glycosylation procedure also makes it an eminently attractive method for the synthesis of guanosine analogues in the 7-deazapurine ring system. Thus, treatment of 2-amino-4-chloro-7H-pyrrolo[2,3-d]pyrimidine[20] (6, 6 mmol) with sodium hydride (6 mmol) in acetonitrile, followed by the addition of 2 (6 mmol) and subsequent purification of the reaction product by flash chromatography on a column of silica gel (hexane:ethyl acetate, 9:1, v/v) provided syrupy 7 (53% yield).[16] Further treatment of 7 with 1N sodium methoxide in methanol at reflux temperature for 8 hours gave a 83% yield of 2-amino-4-methoxy-7-(2,3-O-isopropylidene-β-D-ribofuranosyl)pyrrolo[2,3-d]-pyrimidine (8),[16] which on deisopropylidenation with aqueous trifluoroacetic acid at ambient temperature for 0.5 hour and purification of the product on a column of silica gel (dichloromethane:acetone, 1:1, v/v) furnished 2-amino-4-methoxy-7-β-D-ribofuranosylpyrrolo[2,3-d]-pyrimidine [9, 92% yield, mp 247-250°C]. Cleavage of the ether-linkage of 9 with trimethylsilyl iodide[21] in anhydrous acetonitrile at reflux temperature for 9 hours gave 2-amino-7-β-D-ribofuranosylpyrrolo[2,3-d]pyrimidin-4(3H)-one (10, mp 312-314°C, 90 % yield), which was shown to be identical with 7-deazaguanosine as previously reported.[22]

This general procedure was also utilized to prepare 2'-deoxy-7-deazaguanosine (15). The sodium salt of 6 (3 mmol), produced in situ by sodium hydride in acetonitrile, was treated with 1-chloro-2-deoxy-3,5-di-O-p-toluoyl-α-D-erythro-pentofuranose[23] (11, 3.3 mmol) at ambient temperature for 16 hours. After purification of the reaction product on a silica gel column (chloroform:ethyl acetate, 9:1, v/v), a 75% yield of 13 was obtained (mp 162-164°C), which is significantly superior to the 45% yield reported by the strongly alkaline conditions of phase-transfer procedure.[20] No formation of the α-anomer of 13 in this reaction was detected. When 13 was treated with 0.5N sodium methoxide in methanol at reflux temperature for 1 hour, deprotection of the sugar moiety with concomitant nucleophilic displacement of the 4-chloro function to a methoxy group occurred to give 2-amino-4-methoxy-7-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[2,3-d]pyrimidine [14, yield 92%, mp 152-154°C (Lit.[24] mp 152-154°C)]. Treatment of 14 with trimethylsilyl iodide gave a 92% yield of 7-deaza-2'-deoxyguanosine [15, mp 264-266°C, (Lit.[24] mp 262-265°C)]. Compound 15 was also obtained, in 15% yield, from 2'-deoxy-7-deaza-6-thioguanosine (12) by oxidative hydrolysis (ammonium hydroxide/hydrogen peroxide). 2'-Deoxy-7-deaza-6-thioguanosine [mp 196-201°C, dec; 72% yield, (Lit.[20] mp >200°C)] was, in turn, prepared from 13 by treatment with thiourea in the presence of formic acid, followed by deprotection with sodium methoxide in methanol.

The anomeric configuration of the isolated pyrrolo[2,3-d]pyrimidine nucleosides was assigned as β on the basis of ^{1}H NMR studies. The ^{1}H NMR spectra of 4 and 9 in Me_2SO-d_6 revealed the anomeric doublets centered at δ 6.20 and 5.96, respectively, with a coupling constant $J_{1,2}$ = 6.0 Hz, which is within the acceptable limits for β-ribonucleosides.[25,26] Moreover, the ^{1}H NMR spectra of 3 and 8 in Me_2SO-d_6 exhibited much smaller coupling constants ($J_{1,2}$ = 3.0 Hz) and also revealed the difference between the chemical shift of the two methyl signals of the isopropylidene group as >0.20 ppm, a difference characteristic of the β-configuration.[27] The anomeric configuration of 13 was also assigned as β by ^{1}H NMR studies, where the anomeric proton was observed as dd at δ 6.58 with a peak width of 14 Hz. This pattern is similar to that observed for the anomeric proton of 2'-deoxy-7-deazaguanosine.[24] Since the starting halogenose 11 has the α-configuration[28] in the solid state, the exclusive formation of 13 is presumed to be due to a direct Walden inversion (S_N2) at the C_1 carbon by the anionic heterocyclic nitrogen.

Thus, the facile synthetic pathway we have developed for the total synthesis of tubercidin, 7-deazaguanosine and 2'-deoxy-7-deazaguanosine can now be used for gram-scale preparation of these nucleoside derivatives. This procedure, starting with an appropriate aglycon and a suitable halogenose, appears to be superior to the previously reported glycosylations of this ring system[4,29,30] including the phase-transfer procedure.[20,22]

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