A Facile and Improved Synthesis of Tubercidin and Certain Related Pyrrolo[2,3-*d*]pyrimidine Nucleosides by the Stereospecific Sodium Salt Glycosylation Procedure [1]

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

Department of Medicinal Chemistry, Nucleic Acid Research Institute, 3300 Hyland Avenue, Costa Mesa, California 92626

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A simple synthesis of tubercidin (**1**), 7-deazaguanosine (**2**) and 2'-deoxy-7-deazaguanosine (**14**) has been accomplished using the sodium salt glycosylation procedure. Reaction of the sodium salt of 4-chloro- and 2-amino-4-chloro-pyrrolo[2,3-*d*]pyrimidine, **3** and **4**, respectively, with 1-chloro-2,3-*O*-isopropylidene-5-*O*-(*t*-butyl)dimethylsilyl-α-D-ribofuranose (**5**) gave the corresponding protected nucleosides **6** and **7** with β-anomeric configuration. Deprotection of **6** provided **8**, which on heating with methanolic ammonia gave tubercidin (**1**) in excellent yield. Functional group transformation of **7**, followed by deisopropylidenation gave 2-aminotubercidin (**10**) and 2-amino-7-β-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidine-4(3*H*)-thione (**11**). Treatment of **7** with 1*N* sodium methoxide followed by exposure to aqueous trifluoroacetic acid, and ether cleavage furnished 7-deazaguanosine (**2**). 2'-Deoxy-7-deazaguanosine (**14**) and 2'-deoxy-7-deaza-6-thioguanosine (**18**) were also prepared by using similar sequence of reactions employing **4** and 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose (**15**).

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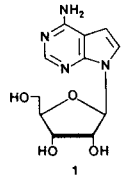
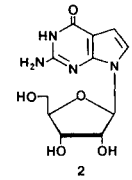
The pyrrolo[2,3-*d*]pyrimidine nucleosides such as tubercidin (4-amino-7-β-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidine, **1**) and 7-deazaguanosine (2-amino-7-β-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one, **2**) are of interest not only from chemical but also from biological view-point [2,3]. Tubercidin (**1**) is a naturally occurring cytotoxic [4,5] nucleoside antibiotic, structurally related to adenosine. The natural occurrence of nucleoside antibiotics related to 7-deazaguanosine, *e.g.* nucleoside Q [6-9], nucleoside preQ$_0$ [10,11], cadeguomycin [12-18] and kanagawamicin [19-20], and their multifaceted physiological properties stimulated considerable interest in the large-scale synthesis of certain pyrrolo[2,3-*d*]pyrimidine nucleosides for biological evaluation. Since the isolation [21,22] of **1** from the natural sources, a number of reports have appeared in the literature describing its biological and physicochemical properties[3,5,23,24]. Besides **2**, several base- as well as the sugar-modified analogs of **1** have also been prepared by multistep synthesis and evaluated for their biological properties [25-29].



1
Tubercidin



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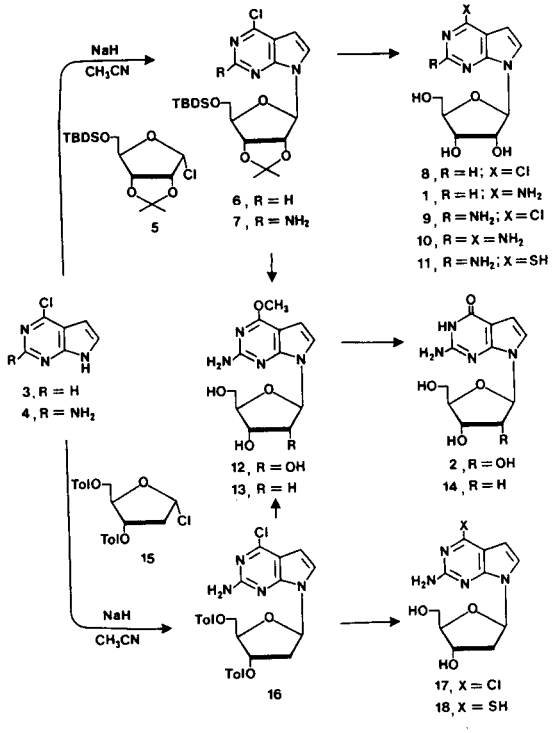
Considerable effort has been expended in the development of methods for the synthesis of tubercidin (**1**) and 7-deazaguanosine (**2**). The first method involved the direct fusion of an appropriate pyrrolo[2,3-*d*]pyrimidine with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose in the presence of an acid catalyst producing a low yield of the corresponding nucleoside product [30,31]. The second route utilized a silylated aglycon and an acylated sugar halide [32]. A phase-transfer glycosylation procedure has also been used for the preparation of pyrrolo[2,3-*d*]pyrimidine nucleosides, including 7-deazaguanosine [33,34] and 2'-deoxy-7-deazaguanosine. However, the availability of **1** and **2** in quantity was restricted by the moderate yield obtained by these procedures. Moreover, these methods generally afford a mixture of positional isomers and anomers. Therefore, a simple and direct method for large-scale preparation of **1**, **2** and certain related compounds was sought in our laboratory. We now report a facile and total synthesis of tubercidin (**1**) by the stereospecific sodium salt glycosylation procedure [35,36] and also demonstrate the potential of this procedure for the preparation of 7-deazaguanosine (**2**) as well as 2'-deoxy-7-deazaguanosine (**14**).

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, **3** and **4**, respectively, with an appropriate α-halogenose to obtain the protected nucleoside intermediate, which could then be converted to the desired **1**, **2** or **14**. Although we were quite successful in the preparation of 2'-deoxyribonucleosides by the sodium salt glycosylation procedure [25,35], the problem of neighboring group participation [37] still remains when one uses 2,3,5-tri-*O*-acyl-D-ribofuranosyl halide and a pyrrolo[2,3-*d*]pyrimidine without C-6 substituent. However, the use of recently reported [38] 1-chloro-2,3-*O*-isopropylidene-5-*O*-(*t*-butyl)dimethylsilyl-α-D-ribofuranose (**5**) was found to be very successful for the prepa-

ration of anomerically pure ribonucleosides without the problem of neighboring group participation. Thus, reaction of 2 equivalents of the sodium salt of 4-chloropyrrolo-[2,3-*d*]pyrimidine (**3**) [39], generated *in situ* by the treatment with sodium hydride in anhydrous acetonitrile, with 1 equivalent of **5** at room temperature, followed by purification of the reaction product by flash silica gel column chromatography gave 4-chloro-7-[2,3-*O*-isopropylidene-5-*O*-(*t*-butyl)dimethylsilyl-β-D-ribofuranosyl]pyrrolo[2,3-*d*]-pyrimidine (**6**) as an oily syrup in 67% yield based on the sugar used. However, when the glycosylation was carried out with 1 equivalent each of the sodium salt of **3** and **5** gave a 15% yield of the glycosylated product **6** accompanied by recoverable starting aglycon **3**. Compound **6** was the only nucleoside product which could be detected

Scheme I



by tlc or column chromatography procedures. Deprotection of **6** with 90% aqueous trifluoroacetic acid at room temperature for an hour furnished 4-chloro-7-β-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidine (**8**) in a 99% yield. Compound **8** was found to be identical in all respects (mp, uv, ir, ^{1}H nmr and tlc) with the one reported earlier (40). Treatment of **8** with methanolic ammonia (saturated at °0) at 120° for 15 hours resulted in the displacement of the chloro group to provide tubercidine (**1**) in 81% yield. There was no depression observed by mixture melting point of **1** with an authentic sample of tubercidin [40] and was found to posses the same uv, ir, ^{1}H nmr and identical R_f values in three different chromatographic solvent systems as naturally occurring tubercidin [41].

To illustrate the potential of this procedure we next studied the glycosylation of 2-amino-4-chloropyrrolo-[2,3-*d*]pyrimidine (**4**) [42]. Thus, treatment of **4** with equimolar quantities of sodium hydride in acetonitrile, followed by the addition of **5** and subsequent purification of the reaction product by flash chromatography on a column of silica gel provided syrupy 2-amino-4-chloro-7-[2,3-*O*-isopropylidene-5-*O*-(*t*-butyl)dimethylsilyl-β-D-ribofuranosyl]-pyrrolo[2,3-*d*]pyrimidine (**7**) in a 53% yield. Deisopropylidenation of **7** with 80% aqueous acetic acid at reflux temperature gave a low yield (30%) of 2-amino-4-chloro-7-β-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidine (**9**). 2-Aminotubercidin (2,4-diamino-7-β-D-ribofuranosylpyrrolo[2,3-*d*]-pyrimidine, **10**) was obtained in an overall yield of 81% by heating **7** with methanolic ammonia (saturated at 0°) at 110-120° for 24 hours, followed by deisopropylidenation with 90% aqueous trifluoroacetic acid.

In view of the potent antitumor properties of 6-thioguanosine [43], the synthesis of 7-deaza-6-thioguanosine (2-amino-7-β-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidine-4(3*H*)-thione, **11**) is of particular interest. The synthesis of **11** was accomplished by the treatment of **7** with thiourea in ethanol at reflux temperature, followed by the exposure with 90% aqueous trifluoroacetic acid at room temperature for an hour. The preparation of 7-deazaguanosine (**2**) could be accomplished from **9** by transformation of the C-4 chloro group. However, the low yield of **9** obtained from **7**, made us look for an alternative procedure.

The synthetic approach to **2**, thus involved the conversion of C-4 chloro group into a methoxy group, deisopropylidenation and subsequent cleavage of the ether linkage without affecting the glycosidic bond. Thus, treatment of **7** with 1*N* sodium methoxide in methanol at reflux temperature for 6 hours, followed by stirring with aqueous trifluoroacetic acid at 0-5° for 0.5 hour furnished a 77% yield of 2-amino-4-methoxy-7-β-D-ribofuranosylpyrrolo[2,3-*d*]-pyrimidine (**12**). Cleavage of the ether linkage of **12** was accomplished with trimethylsilyl iodide [44] in anhydrous acetonitrile at reflux temperature for 4 hours to give an excellent yield of 2-amino-7-β-D-ribofuranosylpyrrolo[2,3-*d*]-pyrimidin-4(3*H*)-one (**2**), which was found to be identical with 7-deazaguanosine as previously reported [34].

Utilization of this general procedure to prepare 2'-deoxy-7-deazaguanosine (**14**) also found to be remarkably successful. The sodium salt of **4**, 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 (**15**) [45] at ambient temperature for 2 hours. After purification of the reaction product on a flash silica gel column, a 78% yield of 2-amino-4-chloro-7-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**16**) was obtained, which is significantly superior to the 45% yield reported by the strongly alkaline conditions of phase-

transfer procedure [42]. As in the case of **6**, no formation of the α-anomer of **16** in this reaction was detected. When **16** was treated with 0.5*N* sodium methoxide in methanol at reflux temperature for an hour, deprotection of the sugar moiety with concomitant nucleophilic displacement of the C-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 (**13**) in 86% yield. Compound **13** was identical with that described by Winkeler and Seela [46]. Treatment of **13** with trimethylsilyl iodide gave a 92% yield of 2-amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (7-deaza-2'-deoxyguanosine, **14**) [46]. Removal of the protecting toluoyl groups in **16** without affecting the C-4 chloro group was accomplished with methanolic ammonia at room temperature to afford 2-amino-4-chloro-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**17**) [42]. Finally, 2'-deoxy-7-deaza-6-thioguanosine (2-amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine-4(3*H*)-thione, **18**) [42] was prepared from **16** by the treatment with thiourea in the presence of formic acid, followed by deprotection with 1*N* sodium methoxide in methanol, in an overall yield of 76%.

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 **8** and **12** in DMSO-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 [48,49]. Moreover, the ^{1}H nmr spectrum of **6** in DMSO-d_6 exhibited much smaller coupling constant ($J_{1',2'}$ = 2.97 Hz) for the anomeric proton 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 [50]. The anomeric configuration of **16** was also assigned as β by ^{1}H nmr studies, where the anomeric proton was observed as dd at 6.54 with a peak width of 14.5 Hz. This pattern is similar to that observed for the anomeric proton of 2'-deoxy-7-deazaguanosine [46]. Since the starting halogenose **15** has the α-configuration in the solid state [51], the exclusive formation of **16** is presumed to be due to a direct Walden inversion (S_N2) at the C_1 carbon by the anionic heterocyclic nitrogen.

In summary, we have developed a simple synthetic pathway to tubercidin, 7-deazaguanosine and 2'-deoxy-7-deazaguanosine, which can be extended to other 7-deazapurine nucleosides. This procedure, starting with an appropriate preformed aglycon and a suitable α-halogenose, appears to be superior to the previously reported glycosylations of this ring system [30,32,34,42].

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H nmr) spectra were determined at 300 MHz with an IBM NR/300 spectrometer. The chemical-shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. The signals are described as s (singlet), d (doublet), and m (multiplet). The presence of solvent as indicated by elemental analysis was verified by ^{1}H nmr. Infrared spectra (ir, in potassium bromide) were recorded with a Perkin-Elmer 1420-spectrophotometer and ultraviolet spectra (uv, sh = shoulder) were recorded on a Beckman DU-50 spectrophotometer. Elemental analyses were performed by Robertson Laboratory, Madison, NJ. Thin-layer chromatography (tlc) 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 3A molecular sieves. Tetrahydrofuran was distilled over sodium/benzophenone ketyl prior to use. Detection of nucleoside components in tlc was by uv light and with 10% sulfuric acid in methanol spray followed by heating. Evaporations were carried out under reduced pressure with the bath temperature below 30°.

4-Chloro-7-[2,3-*O*-isopropylidene-5-*O*-(*t*-butyl)dimethylsilyl-β-D-ribofuranosyl]pyrrolo[2,3-*d*]pyrimidine (**6**).

To a stirred solution of 4-chloropyrrolo[2,3-*d*]pyrimidine (**3**, 3.06 g, 20 mmoles) [39] in dry acetonitrile (200 ml) was added sodium hydride (60% in oil, 0.8 g, 20 mmoles) in small portions during 15 minutes period. The stirring was continued for another 0.5 hour. A solution of 1-chloro-2,3-*O*-isopropylidene-5-*O*-(*t*-butyl)dimethylsilyl-α-D-ribofuranose (**5**, generated *in situ* from the corresponding lactol, 3.04 g , 10 mmoles) [38] in dry tetrahydrofuran (30 ml) was added at room temperature and the mixture was stirred overnight. The reaction mixture was evaporated to dryness. The residue was suspended in water (40 ml) and extracted with ethyl acetate (2 x 15 ml). The ethyl acetate extract was washed with water (40 ml), followed by saturated brine solution (25 ml), dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography over silica gel using hexane → ethyl acetate as the eluent. The fractions containing the pure product were collected and evaporated to give 2.7 g (67%) of **6** as an oil; ir: ν 3400 (NH_2) cm^{-1}; uv (methanol): λ max 258 nm (ε 14,200); ^{1}H nmr (deuteriochloroform): δ 0.09 (s, 6, 2CH_3), 0.91 (s, 9, *t*-butyl), 1.41 and 1.67 (2s, 6, isopropylidene CH_3), 6.43 (d, 1, J = 2.97 Hz, C_1-*H*), 6.65 (d, 1, C_5*H*), 7.59 (d, 1, C_6*H*), 8.69 (s, 1, C_2*H*) and other sugar protons.

Anal. Calcd. for $C_{20}H_{30}ClN_3O_4Si$: C, 54.58; H, 6.87; N, 9.54; Cl, 8.06. Found: C, 54.61; H, 6.86; N, 9.38; Cl, 8.33.

The column on further elution with hexane:acetone (1:1, v/v) gave the crude unreacted base **3** (1.50 g), which was crystallized and reused again.

2-Amino-4-chloro-7-[2,3-*O*-isopropylidene-5-*O*-(*t*-butyl)dimethylsilyl-β-D-ribofuranosyl]pyrrolo[2,3-*d*]pyrimidine (**7**).

In a similar manner as for **6**, the title compound was prepared by using 2-amino-4-chloropyrrolo[2,3-*d*]pyrimidine (**4**, 3.36 g, 20 mmoles) [42], sodium hydride (0.80 g, 20 mmoles), acetonitrile (500 ml), and **5** (3.22 g, 10 mmoles). The crude product was purified by flash chromatography using hexane → ethyl acetate as the eluent to give 2.41 g (53%) of **7** as an oil; ir: ν 3400 (NH_2) cm^{-1}; uv (methanol): λ max 235 nm (ε 36,000), 259 (8,700), 314 (9,700); ^{1}H nmr (deuteriochloroform): δ 0.07 (s, 6, 2CH_3), 0.91 (s, 9, *t*-butyl), 1.37 and 1.63 (2s, 6, isopropylidene CH_3), 5.03 (s, 2, NH_2), 6.24 (d, 1, J = 2.91, C_1-*H*), 6.41 (d, 1, C_5*H*), 7.13 (d, 1, C_6*H*) and other sugar protons.

Anal. Calcd. for $C_{20}H_{31}ClN_4O_4Si$: C, 52.78; H, 6.86; N, 12.31; Cl, 7.80. Found: C, 53.01; H, 6.97; N, 12.11; Cl, 7.89.

The column on further elution with acetone gave 1.7 g of crude unreacted base **4** which was purified and reused again.

4-Chloro-7-β-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidine (**8**).

The protected nucleoside **6** (0.50 g, 1.14 mmoles) was treated with trifluoroacetic acid (9 ml) and water (1 ml) at 0°. The reaction mixture was stirred at room temperature for 1 hour and evaporated to dryness. The

residue was dissolved in methanol (20 ml) and evaporated to dryness. This process was repeated three times to remove traces of trifluoroacetic acid. The residue on purification by flash chromatography using dichloromethane → acetone as the eluent and further crystallization from acetone gave **8** (0.32 g, 99%), mp 161-163° (lit [40] mp 161-163°); ir: ν 800 (C-Cl), 3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 222 nm (sh) (ϵ 10,200), 269 (3,800); (*p*H 7): λ max 222 nm (sh) (ϵ 12,800), 274 (3,400); (*p*H 11): λ max 221 nm (ϵ14,000), 275 (3,300); ^{1}H nmr (DMSO-d_6): δ 6.20 (d, 1, J = 6.0 Hz, $C_1'H$), 6.75 (d, 1, C_5H), 8.0 (d, 1, C_6H), 8.66 (s, 1, C_2H) and other sugar protons.

Anal. Calcd. for $C_{11}H_{12}ClN_3O_4$: C, 46.24; H, 4.23; N, 14.70; Cl, 12.43. Found: C, 46.15; H, 4.06; N, 14.58; Cl, 12.70.

4-Amino-7-β-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidine (Tubercidin, **1**).

Compound **8** (0.8 g, 2.8 mmoles) was dissolved in methanolic ammonia (saturated at 0°, 100 ml) and placed in a steel bomb. The bomb was heated at 120-130° for overnight, cooled and opened carefully. The solution was evaporated to dryness. The residue on crystallization from water gave 0.60 g of **1** as light yellow crystals (81%), mp 248-250° (lit [40] mp 247-248°); ir: ν 3200-3400 cm^{-1}; uv (*p*H 1): λ max 226 nm (ϵ 23,600), 269 (11, 500); (*p*H 7): λ max 270 nm (ϵ 11,900); (*p*H 11): λ max 269 nm (ϵ 12,100); ^{1}H nmr (DMSO-d_6): δ 5.98 (d, 1, J = 6.3 Hz, $C_1'H$), 6.58 (d, 1, C_5H), 7.06 (s, 2, NH_2), 7.33 (d, 1, C_6H), 8.04 (s, 1, C_2H) and other sugar protons.

Anal. Calcd. for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.51; H, 5.06; N, 20.85.

2-Amino-4-chloro-7-β-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidine (**9**).

The protected nucleoside **7** (0.35 g, 0.77 mmole) in 80% acetic acid (20 ml) was heated at 80-100° for 4 hours. The reaction mixture was cooled to 0°, neutralized with ammonium hydroxide and evaporated to dryness. The residue was purified by flash chromatography over silica gel using dichloromethane → methanol as the eluent. The fractions containing the pure product were pooled and evaporated to dryness to give **9** as a foam 0.07 g (30%); ir: ν 3300-3400 cm^{-1}; uv (*p*H 1): λ max 236 nm (ϵ 31,900), 262 (sh) (4,900), 315 (5,200); (*p*H 7): λ max 234 nm (ϵ 28,300), 257 (sh) (4,700), 313 (5,700); (*p*H 11): λ max 234 nm (ϵ 27,900), 257 (sh) (4,700), 310 (5,700); ^{1}H nmr (DMSO-d_6): δ 5.99 (d, 1, J = 6.3 Hz, $C_1'H$), 6.37 (d, 1, C_5H) 6.72 (s, 2, NH_2), 7.38 (d, 1, C_6H) and other sugar protons.

Anal. Calcd. for $C_{11}H_{13}ClN_4O_4$: C, 43.93; H, 4.36; N, 18.62; Cl, 11.81. Found: C, 43.69; H, 4.21; N, 18.32; Cl, 11.63.

2,4-Diamino-7-β-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidine (2-Aminotubercidin, **10**).

The nucleoside **7** (1.0 g, 2.19 mmoles) in methanolic ammonia (saturated at 0°, 70 ml) was heated at 110-120° in a steel bomb for 24 hours. The steel bomb was cooled to −78°, opened carefully and evaporated to dryness. The residue was dissolved in dichloromethane:acetone (1:1, 100 ml) and passed through a silica gel column (5 x 15 cm). The column was eluted with the same solvent system (200 ml). The eluent on evaporation gave a foam which was used as such for deisopropylidenation without characterization.

The above foam was dissolved in trifluoroacetic acid:water (9:1, 25 ml) and stirred at room temperature for 1 hour. The reaction mixture was evaporated to dryness. The residue was dissolved in methanol (20 ml), adjusted to *p*H 6-7 with ammonium hydroxide and evaporated to dryness. The residue was triturated with acetone:methanol (1:1, 10 ml) and filtered. The precipitate on crystallization from methanol/acetone gave pure **10** (0.50 g, 81%), mp 219-221°; ir: ν 3200-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 229 nm (ϵ 17,900), 262 (6,600), 297 (4,800); (*p*H 7): λ max 221 nm (ϵ 17,200), 262 (6,800), 289 (sh) (5,000); (*p*H 11): λ max 220 nm (ϵ 17,000), 262 (6,300), 287 (sh) (5,300); ^{1}H nmr (DMSO-d_6): 5.89 (d, 1, J = 6.2 Hz, $C_1'H$), 6.66 (d, 1, C_5H), 7.23 (d, 3, C_6H and NH_2), 8.50 (br s, 2, NH_2) and other sugar protons.

Anal. Calcd. for $C_{11}H_{15}N_5O_4 \cdot CF_3COOH$: C, 39.50: H, 4.08; N, 17.71. Found: C, 39.12; H, 3.80; N, 17.73.

2-Amino-7-β-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidine-4(3*H*)-thione (**11**).

A mixture of **7** (3.80 g, 8.35 mmoles) and thiourea (1.08 g, 16.7 mmoles) in ethanol (150 ml) was heated at reflux for 1 hour. The reaction mixture was evaporated to dryness. The residue was treated with trifluoroacetic acid:water (9:1, 30 ml) and stirred at room temperature for 1 hour. The solvent was removed under reduced pressure. The residue was dissolved in methanol (50 ml), cooled to 0° and adjusted to *p*H 6-7 with concentrated ammonium hydroxide. The solution was evaporated to dryness and the residue crystallized from aqueous methanol, yield 2.2 g (88%), mp 255-257°; ir: ν 1380 (C=S), 3300-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 235 nm (ϵ 26,800), 266 (16,400), 342 (22,000); (*p*H 7): λ max 235 nm (ϵ 27,800), 266 (16,800), 341 (21,200); (*p*H 11): λ max 236 nm (ϵ 27,200), 260 (sh) (13,900), 320 (17,800); ^{1}H nmr (DMSO-d_6): δ 5.85 (d, 1, J = 6.3 Hz, $C_1'H$), 6.41 (d, 1, C_5H), 6.61 (s, 2, NH_2), 7.13 (d, 1, C_6H), 11.78 (s, 1, N*H*) and other sugar protons.

Anal. Calcd. for $C_{11}H_{14}N_4O_4S \cdot ½\ H_2O$: C, 43.00; H, 4.92; N, 18.22; S, 10.42. Found: C, 43.22; H, 4.84; N, 18.21; S, 10.45.

2-Amino-4-methoxy-7-β-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidine (**12**).

A solution of **7** (1.6 g, 3.52 mmoles) in 1*N* sodium methoxide in methanol (100 ml) was heated at reflux for 6 hours. The reaction mixture was cooled to 0° and neutralized to *p*H 6 with dilute acetic acid. Then, it was evaporated to dryness, the residue was boiled with acetone (2 x 150 ml) and filtered. The filtrate was evaporated to dryness and the residue was purified by flash chromatography using dichloromethane → acetone as the eluent. The pure fractions were pooled and evaporated to give a foam.

The above foam (1 g) wa dissolved in trifluoroacetic acid:water (9:1, 25 ml) and stirred at 0-5° for 0.5 hour. The reaction mixture was evaporated to dryness. The residue was dissolved in methanol (30 ml) and evaporated to dryness. This process was repeated for three times to remove last traces of trifluoroacetic acid. The residue was purified by flash chromatography using dichloromethane → methanol as the eluent. The pure product was crystallized from a mixture of acetone/methanol/dichloromethane (5/2/4) to give 0.80 g (77%) of **12**, mp 247-250°; ir: ν 3200-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 224 nm (ϵ 14,400), 259 (5,500), 284 (4,400); (*p*H 7): λ max 224 nm (ϵ 12,500), 259 (5,000), 284 (3,900); (*p*H 11): λ max 224 nm (ϵ 13,200), 259 (5,000), 282 (3,900); ^{1}H nmr (DMSO-d_6): δ 3.91 (s, 3, OCH_3), 5.96 (d, 1, J = 6.0 Hz, $C_1'H$), 6.19 (s, 2, NH_2), 6.27 (d, 1, C_5H), 7.11 (d, 1, C_6H) and other sugar protons.

Anal. Calcd. for $C_{12}H_{16}N_4O_5$: C, 48.65; H, 5.44; N, 18.90. Found: C, 48.68; H, 5.43; N, 18.63.

2-Amino-7-β-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (7-Deazaguanosine **2**).

A solution of **12** (0.40 g, 1.35 mmoles) in dry acetonitrile (50 ml) was treated with sodium iodide (dried prior to use, 0.21 g, 1.40 mmoles) and chlorotrimethylsilane (freshly distilled, 0.15 g, 1.40 mmoles) at room temperature under argon atmosphere. The reaction mixture was stirred at room temperature for 1 hour, heated at reflux for 4 hours and cooled to 0°. The precipitated solid was collected by filtration and crystallized from aqueous methanol as light yellow needles, yield 0.35 g (92%), mp 320-322° (lit [34] mp 310-312°); ir: ν 1630 (C=O), 3200-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 220 nm (ϵ 18,600), 259 (13,00); (*p*H 7): λ max 217 nm (ϵ 24,000), 258 (14,500), 284 (sh) (8,400); (*p*H 11): λ max 261 nm (ϵ 13,700); ^{1}H nmr (DMSO-d_6): δ 5.85 (d, 1, J = 6.30 Hz, $C_1'H$), 6.22 (s, 2, NH_2), 6.25 (d, 1, C_5H), 6.91 (d, 1, C_6H), 10.35 (s, 1, N*H*) and other sugar protons.

Anal. Calcd. for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.84. Found: C, 46.60; H, 4.86; N, 19.69.

2-Amino-4-chloro-7-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**16**).

To a suspension of **4** (0.48 g, 3 mmoles) in dry acetonitrile (100 ml) was added sodium hydride (60% in oil, 0.125 g, 3.13 mmoles) at room temperature and stirred for 0.5 hour. 1-Chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose [45] (**15**, 1.2 g, 3.1 mmoles) was added and

stirred at room temperature for 2 hours. The reaction mixture was filtered and the filtrate evaporated to dryness. The residue was purified by flash chromatography using hexane → acetone as the eluent. The pure fractions were pooled and evaporated to give 1.15 g (78%) of **16** as a foam. A small portion was crystallized from a mixture of acetone/hexane as colorless crystals, mp 160-163° (lit [47] mp 168°); ir: ν 760 (C-Cl), 1705 (C=O), 3400 (NH_2) cm^{-1}; uv (methanol): λ max 236 nm (ϵ 41,900), 315 (4,100); ^1H nmr (DMSO-d_6): δ 2.37 and 2.40 (2s, 6, 2 CH_3), 6.38 (d, 1, C_5H), 6.54 (dd, J = 5.8, 8.7 Hz, $C_1'H$), 6.79 (s, 2, NH_2), 7.35 (m, 5, C_6H and aromatic H's), 7.90 (2d, 4, aromatic H's) and other sugar protons.

Anal. Calcd. for $C_{27}H_{25}ClN_4O_5$: C, 63.67; H, 4.98; N, 10.24; Cl, 6.48. Found: C, 63.51; H, 4.78; N, 10.34; Cl, 6.52.

2-Amino-4-methoxy-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]-pyrimidine (**13**).

A solution of **16** (2.0 g, 3.66 mmoles) in 0.5*N* sodium methoxide in methanol (20 ml) was heated at reflux for 1 hour. The reaction mixture was cooled in ice-water bath and neutralized with 6*N* hydrochloric acid. The solvent was removed *in vacuo* to give a thick slurry. The slurry was treated with 2-propanol (30 ml) and evaporated to dryness. The residue was boiled with methanol (75 ml), filtered and the filtrate evaporated to dryness. The residue on purification by flash chromatography using dichloromethane → methanol as the eluent gave 0.92 g (86%) of **13**. An analytical sample was prepared by crystallization of the pure compound from a mixture of acetone/hexane, mp 152-154°; ir: ν 3300-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 229 nm (ϵ 44,400), 291 (15,000); (*p*H 7): λ max 224 nm (ϵ 39,900), 259 (14,700), 284 (11,700); (*p*H 11): λ max 224 nm (ϵ 40,600), 259 (15,000), 284 (12,000); ^1H nmr (DMSO-d_6): δ 3.91 (s, 3, OCH_3), 6.21 (s, 2, NH_2), 6.26 (d, 1, C_5H), 6.41 (dd, 1, J = 8.4 and 5.76 Hz, $C_1'H$), 7.10 (d, 1, C_6H) and other sugar protons.

Anal. Calcd. for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.29; H, 5.59; H, 19.73.

2-Amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidin-4-(3*H*)-one (2'-Deoxy-7-deazaguanosine, **14**).

The title compound was prepared in a similar manner as described for **2**, using **13** (0.48 g, 1.7 mmoles), sodium iodide (0.27 g, 1.8 mmoles), chlorotrimethylsilane (0.19 g, 1.8 mmoles) and dry acetonitrile (100 ml). The product on crystallization from water gave 0.42 g (92%) of pure **14**, mp 258-260° (lit [46] mp 262-265° dec); ir: ν 1650 (C=O), 3250-3450 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 222 nm (ϵ 13,300), 259 (9,400); (*p*H 7): λ max 218 nm (ϵ 18,500), 259 (11,100), 282 (sh) (6,500); (*p*H 11): λ max 261 nm (ϵ 9,900); ^1H nmr (DMSO-d_6): δ 6.23-6.31 (m, 4, $C_1'H$, C_5H and NH_2), 6.91 (d, 1, C_6H), 10.35 (s, 1, N*H*) and other sugar protons.

Anal. Calcd. for $C_{11}H_{14}N_4O_4 \cdot ½\ H_2O$: C, 47.99; H, 5.49; N, 20.35. Found: C, 47.99; H, 5.27; N, 20.28.

2-Amino-4-chloro-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]-pyrimidine (**17**).

A solution of **16** (1.4 g, 2.7 mmoles) in methanolic ammonia (70 ml) was stirred at room temperature in a pressure bottle for 12 hours. The bottle was cooled, opened and evaporated to dryness. The residue on purification by flash chromatography using dichloromethane → acetone gave 0.7 g (91%) of **17**, mp 169-172° (lit [42] mp 168°); ir: ν 780 (C-Cl), 3200-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 237 nm (ϵ 29,300), 264 (sh) (4,000), 319 (4,700); (*p*H 7): λ max 234 nm (ϵ 29,800), 260 (sh) (4,400), 313 (6,000); (*p*H 11): λ max 234 nm (ϵ 29,100), 260 (sh) (4,200), 313 (6,000); ^1H nmr (DMSO-d_6): 6.35 (d, 1, C_5H), 6.41 (dd, 1, J = 6.0 and 8.1 Hz, $C_1'H$), 6.72 (s, 2, NH_2), 7.36 (d, 1, C_6H) and other sugar protons.

Anal. Calcd. for $C_{11}H_{13}ClN_4O_3$: C, 46.40; H, 4.60; N, 19.67; Cl, 12.47. Found: C, 46.67; H, 4.65; N, 19.24; Cl, 12.22.

2-Amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine-4-(3*H*)-thione (**18**).

A mixture of **16** (0.85 g, 1.63 mmoles) and thiourea (0.5 g) in ethanol (100 ml) containing two drops of formic acid was heated at reflux for 1 hour. The solution was evaporated to dryness. The residue was partitioned between water/dichloromethane (50 ml and 100 ml, respectively) and extracted with dichloromethane (2 x 100 ml). The organic layer was washed with water (30 ml), followed by saturated brine solution (20 ml), dried over anhydrous sodium sulfate and evaporated to dryness. The residue was suspended in toluene (50 ml) and evaporated again. The material obtained was dried over phosphorus pentoxide for 2 hours and used for the next reaction.

The above residue in dry methanol (40 ml) was stirred with 1*N* sodium methoxide in methanol (10 ml) for 2 hours at room temperature. The *p*H of the solution was adjusted to 7 with amberlite 50 (H^+) resin and filtered. The filtrate was evaporated to dryness and the residue purified by flash chromatography using dichloromethane → methanol as the eluent to give 0.35 g (76%) of **18** which was crystallized from aqueous methanol, mp 196-201° dec (lit [42] mp 200°); ir: ν 1260 (C=S), 3200-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 235 nm (ϵ 18,600), 266 (10,900), 342 (15,100); (*p*H 7): λ max 235 nm (ϵ 19,200), 266 (11,400), 341 (14,700); (*p*H 11): λ max 235 nm (ϵ 18,700), 258 (9,600), 321 (12,800); ^1H nmr (DMSO-d_6): δ 6.28 (dd, 1, J = 5.9 and 8.1 Hz, $C_1'H$), 6.38 (d, 1, C_5H), 6.65 (s, 2, NH_2), 7.12 (d, 1, C_6H), 11.62 (br s , 1, N*H*) and other sugar protons.

Anal. Calcd. for $C_{11}H_{14}N_4O_3S \cdot ⅓\ H_2O$: C, 45.82; H, 5.12; N, 19.43; S, 11.12. Found: C, 46.06; H, 5.00; N, 19.22; S, 10.92.

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