Direct Synthesis of Pyrrole Nucleosides by the Stereospecific Sodium Salt Glycosylation Procedure [1]

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A stereospecific high-yield glycosylation of preformed fully aromatic pyrroles has been accomplished for the first time. Reaction of the sodium salt of pyrrole-2-carbonitrile (**1a**) and pyrrole-2,4-dicarbonitrile (**1b**) with 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose (**2**) gave exclusively the corresponding blocked nucleosides with β-anomeric configuration **3a** and **3b**, which on deprotection gave 1-(2-deoxy-β-D-*erythro*-pentofuranosyl) derivatives of **1a** (**3c**) and **1b** (**3d**). Functional group transformation of **3c** and **3d** provided a number of 2-monosubstituted **4a-c** and 2,4-disubstituted **4d-f** derivatives of 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrole. Similar glycosylation of the sodium salt of **1a** and **1b** with 1-chloro-2,3,5-tri-*O*-benzyl-α-D-arabinofuranose (**5**) and further functional group transformation of the intermediate blocked nucleosides **6a** and **6b** provided 1-β-D-arabinofuranosyl derivatives of pyrrole-2-carboxamide (**7b**) and pyrrole-2,4-dicarboxamide (**7d**). The synthetic utility of this glycosylation procedure for the preparation of 1-β-D-ribofuranosylpyrrole-2-carbonitrile (**12**) has also been demonstrated by reacting the sodium salt of **1a** with 1-chloro-2,3-*O*-isopropylidene-5-*O*-(*t*-butyl)dimethylsilyl-α-D-ribofuranose (**10**) and subsequent deprotection of the blocked intermediate **11**. This study provided a convenient route to the preparation of aromatic pyrrole nucleosides.

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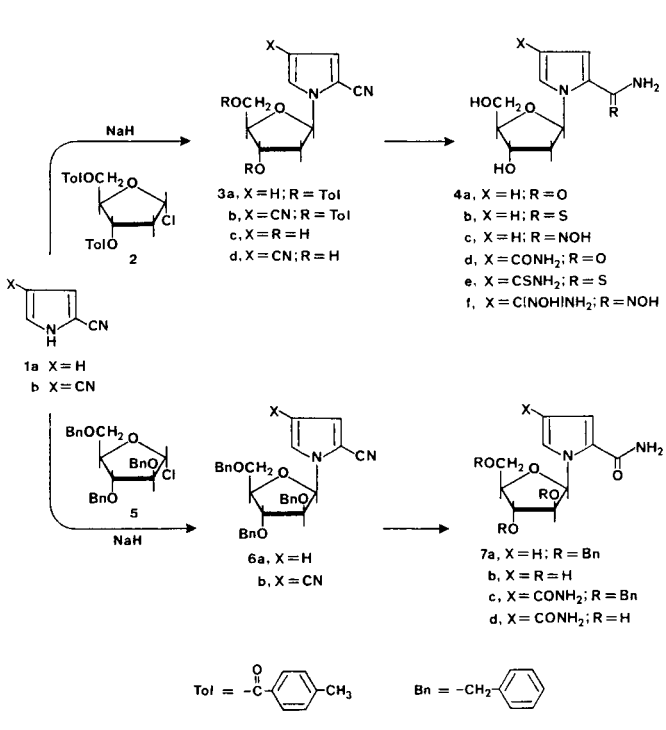
The stereospecific sodium salt glycosylation procedure for the preparation of 2'-deoxyribonucleosides (2'-deoxy-β-D-*erythro*-pentofuranosyl) with β-anomeric configuration has been a part of our ongoing research program [2-8]. Application of this simple single-phase procedure for the synthesis of pyrrole nucleosides has now been found to be remarkably successful. Prior procedure for the preparation of pyrrole *N*-nucleosides [9-11] utilized partially hydrogenated pyrroles in the glycosylation reaction using the "indoline-indole" method [12,13], *e.g.* the synthesis of 1-D-glucopyranosyl-3-pyrroline [9], which on subsequent photodehydrogenation gave 1-β-D-glucopyranosylpyrrole [10]. However, our synthetic pathway involves the direct attachment of a glycon moiety (2'-deoxy-β-D-*erythro*-pentofuranosyl, β-D-arabinofuranosyl, as well as β-D-ribofuranosyl) to a preformed fully aromatic pyrrole derivative.

Scheme I



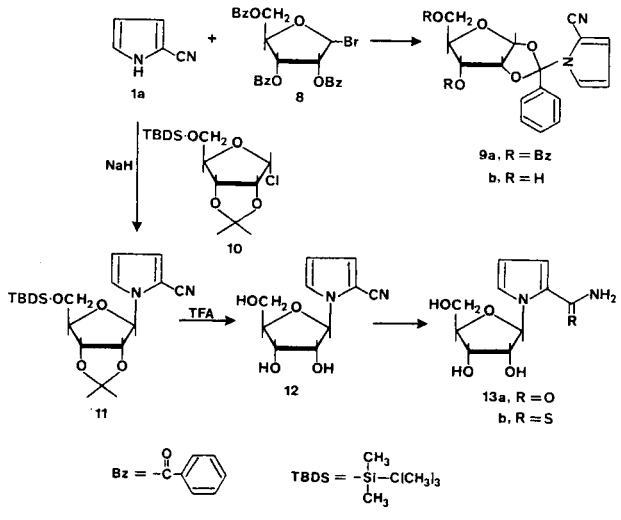
In the present work we first selected pyrrole-2-carbonitrile [14] (**1a**) for glycosylation studies. The sodium salt of **1a**, generated *in situ* by the treatment of sodium hydride in acetonitrile, was reacted with readily available 1-chloro-2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranose [15] (**2**). A clean reaction was observed at room temperature, and the desired 1-(2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl)pyrrole-2-carbonitrile (**3a**) was isolated in 67% yield (Scheme I). No formation of the α-anomer was detected. When **3a** was treated with methanolic ammonia (saturated at 0°) at room temperature, deprotection of the glycon moiety occurred to give almost quantitative yield of 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrole-2-carbonitrile (**3c**). The presence of the carbonitrile function in **3c** was evident as confirmed by the infrared spectrum, which revealed a sharp absorption band at 2215 cm^{-1}. The carbonitrile group of **3c** was available for further transformation reactions to obtain a number of 2-substituted-pyrrole-2'-deoxyribonucleosides. Thus, treatment of **3c** with ammonium hydroxide containing hydrogen peroxide (30%), and purification of the reaction product by chromatography on silica gel furnished 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrole-2-carboxamide (**4a**) in ex-

cellent yield. Reaction of **3c** with hydrogen sulfide in pyridine containing triethylamine at room temperature gave the corresponding 3-thiocarboxamide derivative **4b** in 86% yield. When **3c** was allowed to react with free hydroxylamine in ethanol at reflux temperature, 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrole-3-carboxamidoxime (**4c**) was formed and was isolated in 86% yield.

The other heterocycle that was employed for the glycosylation reaction was pyrrole-2,4-dicarbonitrile (**1b**). Compound **1b** was prepared as reported [14] and converted to the sodium salt by the treatment with sodium hydride in acetonitrile. Reaction of the protected halogenose **2** with the sodium salt of **1b** gave a 68% yield of 1-(2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl)pyrrole-2,4-dicarbonitrile (**3b**) (Scheme I). As in the case of **3a**, no formation of the α-anomer of **3b** in this reaction was also detected. Deprotection of the blocking groups of the glycon moiety of **3b** was accomplished by the treatment with methanolic ammonia at room temperature to yield 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrole-2,4-dicarbonitrile (**3d**), in which the carbonitrile functions were available for further transformation reactions. Oxidative hydration of **3d** with ammoniacal hydrogen peroxide gave the corresponding 2,4-dicarboxamide derivative (**4d**) in high yield. Reaction of **3d** with hydrogen sulfide in pyridine at ambient temperature afforded 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrole-2,4-bisthiocarboxamide (**4e**). Similarly, when **3d** was allowed to react with free hydroxylamine in ethanol at reflux temperature, 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrole-2,4-dicarboxamidoxime (**4f**) was formed and was isolated in 70% yield after flash chromatography.

The preparation of the β-D-arabinofuranosyl derivatives of **1a** and **1b** were also accomplished in a manner similar to that of **3a**. Glycosylation of the sodium salt of **1a** with 1-chloro-2,3,5-tri-*O*-benzyl-α-D-arabinofuranose [16] (**5**) in anhydrous acetonitrile at ambient temperature and purification of the reaction product by flash chromatography on silica gel gave a 74% yield of 1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)pyrrole-2-carbonitrile (**6a**). Treatment of **6a** with aqueous ammonium hydroxide containing hydrogen peroxide (30%), readily gave the corresponding 2-carboxamide derivative **7a**. Debenzylation of **7a** with palladium hydroxide in ethanol in the presence of cyclohexene (as hydrogen source) at reflux temperature gave the desired 1-β-D-arabinofuranosylpyrrole-2-carboxamide (**7b**) in 71% yield. Similar glycosylation of the sodium salt of **1b** with **5** gave an 87% yield of 1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)pyrrole-2,4-dicarbonitrile (**6b**), which on sequential hydration and debenzylation furnished 1-β-D-arabinofuranosylpyrrole-2,4-dicarboxamide (**7d**).

Scheme II



This general glycosylation procedure has been found to be applicable equally well for the preparation of β-D-ribofuranosyl derivatives of **1a**. In an effort to prepare such a ribofuranosyl analog, freshly prepared 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide [17] (**8**) was reacted with the sodium salt of **1a** in dioxane. A nucleoside product **9a** was formed and was isolated in 84% yield after silica gel column chromatography of the reaction product (Scheme II). The benzoyl blocking groups of **9a** were removed by the treatment with methanolic ammonia to afford **9b**. The ^{1}H nmr spectrum (phenyl protons at δ 7.37-7.47) and the elemental analysis of **9b** indicated the presence of a benzoyl type group, however the ir spectrum failed to show any carbonyl stretching band. On the basis of this evidence 1,2-[phenyl(2-cyanopyrrolyl)methylidene]-α-D-ribofuranose structure was assigned to **9b**. The formation of **9a** was presumably due to the participation of the neighboring benzoyl group and resulted by the attack of the anion of **1a** on the carbonyl carbon of the protection group rather than the C_1 carbon of the glycon.

In order to prepare the target β-D-ribofuranosyl derivative of **1a**, the recently reported [18] 1-chloro-2,3-*O*-isopropylidene-5-*O*-(*t*-butyl)dimethylsilyl-α-D-ribofuranose (**10**) was prepared and coupled with the sodium salt of **1a** in anhydrous acetonitrile at room temperature. A relatively clean reaction was observed and the product was purified on an open bed silica gel column to give 1-(2,3-*O*-isopropylidene-5-*O*-(*t*-butyl)dimethylsilyl-β-D-ribofuranosyl)pyrrole-2-carbonitrile (**11**) in over 61% yield, as the major product. No attempt was made to isolate the minor product. Compound **11** was found to be rather sensitive to moisture and our attempts to crystallize it failed. Deprotection of **11** with aqueous trifluoroacetic acid at room temperature gave the desired 1-β-D-ribofuranosyl-

pyrrole-2-carbonitrile (**12**) in 87% yield. Further functional group transformation reactions with **12** by standard procedures gave 1-β-D-ribofuranosylpyrrole-2-carboxamide (**13a**) and the corresponding 2-thiocarboxamide (**13b**).

The anomeric configuration of the isolated pyrrole-2′-deoxyribonucleosides **3c** and **3d** was assigned as β on the basis of ^{1}H nmr data, where the characteristic triplet for the anomeric proton was observed at δ 6.05-6.12 with a peak width of 13.0 Hz. This pattern is similar to that observed for the anomeric proton of other 2′-deoxy-β-D-ribonucleosides [5,19]. Since the starting halogenose **2** has the α-configuration [20] in the solid state, the exclusive formation of the blocked 2′-deoxy-β-D-ribonucleosides in this study is presumed to be due to a direct Walden inversion (S_N2) at the C_1 carbon by the anionic heterocyclic nitrogen. The anomeric configuration of **7b** and **7d** was again assigned as β on the basis of $J_{1',2'}$ coupling constant (6.0 Hz) observed for the anomeric proton in the ^{1}H nmr spectra, which is within the region of 3.5-8.0 Hz expected for a vicinal, *cis* arrangement of the $C_{1'}$ and $C_{2'}$ protons [21]. The anomeric configuration of **12** was also assigned as β on the basis of ^{1}H nmr studies. The ^{1}H nmr spectrum of **12** in DMSO-d_6 revealed the anomeric doublet centered at δ 5.57 with a small coupling constant ($J_{1,2}$ = 4.7 Hz), which is within the acceptable limits for β-ribonucleosides [22,23]. Moreover, the ^{1}H nmr spectrum of **11** in DMSO-d_6 exhibited a much smaller coupling constant ($J_{1,2}$ = 3.5 Hz) and also revealed the difference between the chemical shift of the two methyl signals of the isopropylidene group to be 0.26 ppm, a difference characteristic of the β-configuration [24,25].

Thus, the synthesis of these pyrrole nucleosides by the stereospecific sodium salt glycosylation procedure represents the first report of a direct attachment of a glycon moiety to a fully aromatic preformed pyrrole. We believe that this constitutes a very convenient and straightforward route to the preparation of a wide variety of pyrrole nucleosides.

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 IBM NR/300 spectrometer. The chemical-shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. The presence of solvent as indicated by elemental analysis was verified by ^{1}H nmr. Infrared spectra (ir in potassium bromide) were obtained on a Beckman Acculab 2 spectrometer and ultraviolet spectra (uv, sh = shoulder) were recorded on a Cary Model 15 spectrophotometer. Elemental analyses were performed by Robertson Laboratory, Florham Park, N. J. Thin-layer chromatography (tlc) was run on silica gel 60 F-254 plates (EM Reagents). E. Merck silica gel (230-400 mesh) was used for flash column chromatography. All solvents used were reagent grade. Detection of nucleoside components on 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°.

1-(2-Deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl)pyrrole-2-carbonitrile (**3a**).

To a solution of pyrrole-2-carbonitrile [14] (**1a**, 0.92 g, 10 mmoles) in dry acetonitrile (35 ml) was added sodium hydride (60% in oil, 0.48 g, 12 mmoles) and the mixture was stirred at room temperature under a nitrogen atmosphere for 30 minutes. 1-Chloro-2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranose [15] (**2**, 3.88 g, 10 mmoles) was added portionwise with stirring. The reaction mixture was stirred at room temperature for 30 minutes, at 50° for 30 minutes, cooled and then filtered to remove a small amount of insoluble material. Evaporation of the filtrate gave a crude product, which was purified by flash chromatography using hexane:acetone (7:3, v/v) as the eluent. Crystallization of the homogeneous product from hexane/acetone gave **3a** as needles, yield 3.0 g (67%); mp 126-128°; ir: ν 1710 (C=O), 2210 (C≡N) cm^{-1}; uv (methanol): λ max 242 nm (ε 32,900); ^{1}H nmr (deuteriochloroform): δ 2.41 (s, 3, CH_3), 2.43 (s, 3, CH_3), 6.21 (t, 1, J = 6.0 Hz, C_1′H), 6.28 (dd, 1, J = 3.5 Hz, C_4H), 6.84 (dd, 1, J = 3.5 Hz, C_5H), 7.11 (dd, 1, J = 3.0 Hz, C_3H), 7.25 (m, 4, Ph) and 7.93 (m, 4, Ph).

Anal. Calcd. for $C_{26}H_{24}N_2O_5$: C, 70.26; H, 5.44; N, 6.29. Found: C, 69.98; H, 5.43; N, 6.20.

1-(2-Deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl)pyrrole-2,4-dicarbonitrile (**3b**).

In the same manner as for **3a**, the title compound was prepared by using pyrrole-2,4-dicarbonitrile [14] (**1b**, 1.17 g, 10 mmoles), sodium hydride (60% in oil, 0.48 g, 12 mmoles), acetonitrile (50 ml) and **2** (3.88 g, 10 mmoles). Purification of the reaction product by flash chromatography using hexane:acetone (7:3, v/v) as eluent and crystallization of the homogeneous product from hexane/acetone gave 3.2 g (68%) of **3b**, mp 120-121°; ir: ν 1720 (C=O), 2220 (C≡N) cm^{-1}; uv (methanol): λ max 240 nm (ε 37,700); ^{1}H nmr (deuteriochloroform): δ 2.42 (s, 3, CH_3), 2.43 (s, 3, CH_3), 6.25 (t, 1, J = 6.0 Hz, C_1′H), 7.05 (d, 1, J = 4.0 Hz, C_5H), 7.28 (m, 4, Ph), 7.58 (d, 1, J = 3.5 Hz, C_3H), and 7.93 (m, 4, Ph).

Anal. Calcd. for $C_{27}H_{23}N_3O_5$: C, 69.07; H, 4.94; N, 8.95. Found: C, 69.22; H, 4.95; N, 9.04.

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)pyrrole-2-carbonitrile (**3c**).

A solution of **3a** (11.0 g, 24.8 mmoles) in methanolic ammonia (saturated at 0°, 250 ml) was stirred at room temperature in a pressure bottle for 12 hours and then evaporated to dryness. The residue was purified by flash chromatography using chloroform:acetone (8:2, v/v) as the eluent and crystallized from ether to yield 5.0 g (97%) of **3c**, mp 78-79°; ir: ν 2215 (C≡N), 3380 (OH) cm^{-1}; uv (ethanol): λ max 227 nm (ε 6,000), 250 (7,200); ^{1}H nmr (DMSO-d_6): δ 6.05 (t, 1, J = 6.5 Hz, C_1′H), 6.26 (dd, 1, J = 3.0 Hz, C_4H), 6.98 (dd, 1, J = 3.0 Hz, C_5H) and 7.48 (s, 1, C_3H).

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.54; H, 5.70; N, 13.34.

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)pyrrole-2,4-dicarbonitrile (**3d**).

The title compound was prepared in a similar manner as described for **3c**, using **3b** (13.5 g, 28.7 mmoles) and methanolic ammonia (300 ml). The product was isolated as amphorous solid in 74% (5.0 g) yield; ir: ν 2220 (C≡N), 3300-3350 (OH) cm^{-1}; uv (ethanol): λ max 230 nm (ε 7,300), 247 (7,000); ^{1}H nmr (DMSO-d_6): δ 6.12 (t, 1, J = 6.5 Hz, C_1′H), 7.56 (s, 1, C_5H) and 8.30 (s, 1, C_3H).

Anal. Calcd. for $C_{11}H_{11}N_3O_3 \cdot \frac{1}{2}CH_3OH$: C, 55.41; H, 5.25; N, 16.86. Found: C, 55.64; H, 4.96; N, 16.82.

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)pyrrole-2-carboxamide (**4a**).

A solution of **3c** (3.2 g, 15.4 mmoles) in water (10 ml) was treated with ammonium hydroxide and hydrogen peroxide (30%, 5 ml) and the mixture was stirred at room temperature for 12 hour. The reaction mixture was evaporated to dryness. The residue was dissolved in methanol (50 ml) and adsorbed onto silica gel (10 g). The excess solvent was evaporated. Co-evaporation with toluene (3 x 50 ml) from the solid mass gave dry

residue, which was loaded onto a silica gel column (4 x 40 cm) packed in chloroform. The column was eluted with chloroform:methanol (9:1, v/v). The homogeneous fractions were pooled and the solvents evaporated to yield 2.8 g (81%) of **4a** as amphorous solid; ir: ν 1660 (C=O), 3200-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 264 nm (ϵ 13,100); (*p*H 7): λ max 264 nm (ϵ 12,300); (*p*H 11): λ max 264 nm (ϵ 15,600); ^{1}H nmr (DMSO-d_6): δ 6.05 (t, 1, J = 6.0 Hz, C_1H), 6.78 (d, 1, J = 3.0 Hz, C_4H), 6.94 (d, 1, J = 3.0 Hz, C_5H), 6.91 and 7.52 (2s, 2, $CONH_2$) and 7.34 (s, 1, C_3H).

Anal. Calcd. for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.14; H, 6.61; N, 12.46.

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)pyrrole-2-thiocarboxamide (**4b**).

A solution of **3c** (1.5 g, 7.2 mmoles) in anhydrous pyridine (150 ml) containing triethylamine (5 ml) was saturated with hydrogen sulfide gas at room temperature. After stirring the reaction mixture in a sealed vessel at room temperature for 12 hours, it was evaporated to dryness. The residue was purified by flash chromatography using chloroform:acetone (8:2, v/v) as the eluent, and crystallized from chloroform/acetone to give 1.5 g (86%) of **4b**, mp 127-128°; ir: ν 1260 (C=S), 3200-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 279.5 nm (ϵ 11,200), 314.5 (15,800); (*p*H 7): λ max 280 nm (ϵ 11,900), 313.5 (16,700); (*p*H 11): λ max 279 nm (ϵ 12,200), 313.5 (16,800); ^{1}H nmr (DMSO-d_6): δ 6.08 (t, 1, J = 6.0 Hz, C_1H), 6.58 (d, 1, J = 3.0 Hz, C_4H), 7.20 (d, 1, J = 3.0 Hz, C_5H), 7.43 (s, 1, C_3H), 9.01 and 9.26 (2s, 2, $CSNH_2$).

Anal. Calcd. for $C_{10}H_{14}N_2O_3S$: C, 49.59; H, 5.83; N, 11.56; S, 13.21. Found: C, 49.59; H, 5.88; N, 11.37; S, 13.45.

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)pyrrole-2-carboxamidoxime (**4c**).

A solution of **3c** (2.2 g, 10.5 mmoles) and free hydroxylamine (2.7 g, 82 mmoles) in absolute ethanol (200 ml) was heated under reflux for 2 hours and allowed to stir at room temperature overnight. Evaporation of the reaction mixture and purification of the residue by flash chromatography using chloroform:methanol (8:2, v/v) as the eluent gave 2.2 g (86%) of **4c** as gum; ir: ν 3300-3400 (NH_2, OH) cm^{-1}; uv (ethanol): λ max 250 nm (ϵ 31,300); ^{1}H nmr (DMSO-d_6): δ 5.60 (s, 2, NH_2), 6.06 (t, 1, J = 6.0 Hz, C_1H), 6.34 (dd, 1, J = 3.0 Hz, C_4H), 6.67 (m, 1, C_3H), 7.16 (dd, 1, J = 3.0 Hz, C_5H) and 9.50 (s, 1, NO*H*).

Anal. Calcd. for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.27; N, 17.41. Found: C, 49.50; H, 6.25; N, 17.28.

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)pyrrole-2,4-dicarboxamide (**4d**).

In a similar manner as for **4a**, the title compound was prepared by using **3d** (4.2 g, 18.0 mmoles), ammonium hydroxide (150 ml) and 30% hydrogen peroxide (10 ml) in water (15 ml). The reaction product was purified by flash chromatography using chloroform:methanol (8:2, v/v) as the eluent to yield 4.0 g (83%) of **4d** as amorphous solid which was crystallized from methanol/dichloromethane/ether, mp 99-102°; ir: ν 1670 (C=O), 3200-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 260 nm (ϵ 12,000); (*p*H 7): λ max 260 nm (ϵ 12,700); (*p*H 11): λ max 261 nm (ϵ 11,700); ^{1}H nmr (DMSO-d_6): δ 6.83 (t, 1, J = 6.0 Hz, C_1H), 6.91 and 7.12 (2s, 2, $CONH_2$), 7.11 (s, 1, C_5H), 7.44 and 7.67 (2s, 2, $CONH_2$) and 7.84 (s, 1, C_3H).

Anal. Calcd. for $C_{11}H_{15}N_3O_5$: C, 48.88; H, 5.97; N, 15.54. Found: C, 48.79; H, 5.88; N, 15.51.

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)pyrrole-2,4-bisthiocarboxamide (**4e**).

In a similar manner as for **4b**, the title compound was prepared by using **3d** (2.0 g, 8.6 mmoles), triethylamine (5 ml) and pyridine (150 ml) saturated with hydrogen sulfide gas. The crude product was purified by flash chromatography using chloroform:methanol (8:2, v/v) as the eluent, and crystallized from chloroform/methanol to yield 1.60 g (62%), mp 186-187°; ir: ν 1230 (C=S), 3200-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 256 nm (ϵ 5,800), 267 (5,900), 314 (6,200); (*p*H 7): λ max 251 nm (ϵ 7,100), 290 (6,000), 315 (6,900); (*p*H 11): λ max 248 nm (ϵ 4,600), 270 (4,600), 276 (4,500), 313 (4,300); ^{1}H nmr (DMSO-d_6): δ 6.99 (s, 1, C_5H), 7.01 (t, 1, J = 6.5 Hz, C_1H), 7.95 (s, 1, C_3H), 8.99 and 9.22 (2s, 2, $CSNH_2$), 9.31 and 9.56 (2s, 2, $CSNH_2$).

Anal. Calcd. for $C_{11}H_{15}N_3O_3S_2$: C, 43.85; H, 5.02; N, 13.94; S, 21.24. Found: C, 43.99; H, 5.10; N, 13.80; S, 21.04.

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)pyrrole-2,4-dicarboxamidoxime (**4f**).

In the same manner as for **4c**, reaction of **3d** (2.0 g, 8.6 mmoles) with free hydroxylamine (3.0 g, 90.8 mmoles) in absolute ethanol (200 ml) gave 1.80 g (70%) of **4f** after flash chromatography using chloroform:methanol (1:1), v/v) as the eluent; hygroscopic foam; ir: ν 3300-3450 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 218.5 (ϵ 24,700), 258 sh (10,500); ^{1}H nmr (DMSO-d_6): δ 5.48 (s, 2, NH_2), 5.65 (s, 2, NH_2), 6.54 (s, 1, C_5H), 6.63 (t, 1, J = 6.0 Hz, C_1H), 7.45 (s, 1, C_3H), 9.06 and 9.58 (2s, 2, 2NO*H*).

Anal. Calcd. for $C_{11}H_{17}N_5O_5$: C, 44.15; H, 5.73; N, 23.39. Found: C, 44.01; H, 5.88; N, 23.25.

1-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)pyrrole-2-carbonitrile (**6a**).

To a stirred solution of **1a** (2.76 g, 30 mmoles) in dry acetonitrile (200 ml) was added sodium hydride (60% in oil, 1.40 g, 35 mmoles) in small portions at room temperature. After the addition of sodium hydride, the mixture was stirred for 30 minutes, and then 1-chloro-2,3,5-tri-*O*-benzyl-α-D-arabinofuranose [16] (**5**, 13.14 g, 30 mmoles) in dry acetonitrile (200 ml) was added. The reaction mixture was stirred at room temperature for 12 hours under a nitrogen atmosphere, and filtered to remove a small amount of insoluble material. Evaporation of the filtrate gave crude product, which was purified by flash chromatography using toluene:ethyl acetate (1:25, v/v) as the eluent to yield 11.0 g (74%) of **6a** as syrup; ir (neat): ν 2210 (C$\equiv$N) cm^{-1}; uv (ethanol): λ max 251 nm (ϵ 30,300); ^{1}H nmr (deuteriochloroform): δ 4.22, 4.55 and 4.59 (3s, 6, $3CH_2C_6H_5$), 6.14 (d, 1, J = 4.5 Hz, C_1H), 6.21 (dd, 1, J = 3.5 Hz, C_4H), 6.86 (dd, 1, J = 3.5 Hz, C_5H), 7.07 (dd, 1, J = 3.0 Hz, C_3H) and 7.27-7.38 (m, 15, $3CH_2C_6H_5$).

Anal. Calcd. for $C_{31}H_{30}N_2O_4$: C, 75.28; H, 6.11; N, 5.66. Found: C, 75.20; H, 5.99; N, 5.89.

1-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)pyrrole-2,4-dicarbonitrile (**6b**).

In a similar manner as for **6a**, the title compound was prepared by using **1b** (1.17 g, 10 mmoles), sodium hydride (60% in oil, 0.48 g, 12 mmoles), acetonitrile (150 ml) and **5** (4.40 g, 10 mmoles). The crude product was purified by repetitive column chromatography over silica gel using toluene:ethyl acetate (1.25, v/v) as the eluent. The major product was again purified on a silica gel column using a gradient of hexane-ethyl acetate to yield 4.5 g (87%) of **6b** as oil; ir (neat): ν 2220 (C$\equiv$N) cm^{-1}; uv (ethanol): λ max 214 nm (ϵ 39,300), 249 (13,200); ^{1}H nmr (deuteriochloroform): δ 4.47, 4.51 and 4.59 (3s, 6, $3CH_2C_6H_5$), 6.21 (d, 1, J = 4.5 Hz, C_1H), 7.06 (m, 2, C_5H and C_3H) and 7.30 (m, 15, $3CH_2C_6H_5$).

Anal. Calcd. for $C_{32}H_{29}N_3O_4$: C, 73.97; H, 5.63; N, 8.08. Found: C, 73.69; H, 5.63; N, 7.98.

1-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)pyrrole-2-carboxamide (**7a**).

A solution of **6a** (0.49 g, 1 mmole) in dioxane/methanol (30 ml and 100 ml each) was diluted with water (20 ml) and the *p*H of the solution was adjusted to 9 with ammonium hydroxide (~15 ml). To the solution was added hydrogen peroxide (30%, 10 ml) and stirred at room temperature for 15 hours. The reaction mixture was evaporated to dryness. The residue was purified by flash chromatography using hexane:acetone (6:4, v/v) as the eluent to yield 0.45 g (88%) of **7a** as hygroscopic gum; ir: ν 1640 (C=O), 3340 (NH_2) cm^{-1}; uv (ethanol): λ max 212 nm (ϵ 33,200), 265 (20,900); ^{1}H nmr (deuteriochloroform): δ 4.40, 4.54 and 4.55 (3s, 6, $3CH_2C_6H_5$), 5.72 (br s, 2, $CONH_2$), 6.15 (dd, 1, J = 3.5 Hz, C_4H), 6.64 (dd, 1, J = 3.5 Hz, C_5H), 6.97 (d, 1, J = 4.5 Hz, C_1H), 7.03 (m, 1, C_3H) and 7.28 (m, 15, $3CH_2C_6H_5$).

Anal. Calcd. for $C_{31}H_{32}N_2O_5.\frac{1}{2}H_2O$: C, 71.94; H, 6.42; N, 5.41. Found: C, 72.21; H, 6.15; N, 5.26.

1-β-D-Arabinofuranosylpyrrole-2-carboxamide (**7b**).

A mixture of **7a** (5.50 g, 10.7 mmoles), cyclohexene (15 ml) and palladium hydroxide (3.0 g) in ethanol (150 ml) was heated under reflux for 15 hours. The cooled reaction mixture was filtered and the filtrate

evaporated to dryness. The residue was again dissolved in a mixture of ethanol (150 ml), cyclohexene (15 ml) and palladium hydroxide (3.0 g), and refluxed for 15 hours. The catalyst was removed by filtration, the filtrate evaporated to dryness and the residue was purified by flash chromatography using chloroform:methanol (9:1, v/v) as the eluent to give 2.2 g (71%) of **7b** as amphorous solid; ir: ν 1650 (C=O), 3200-3400 (NH_2, OH) cm^{-1}; uv (ethanol): λ max 267 nm (ϵ 24,000); ^1H nmr (DMSO-d_6): δ 6.0 (dd, 1, J = 3.0 Hz, C_4H), 6.76 (d, 1, J = 6.0 Hz, $C_1'H$), 6.79 (dd, 1, J = 3.0 Hz, C_5H), 6.91 and 7.53 (2 br s, 2, $CONH_2$), and 7.31 (m, 1, C_3H).

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.56; H, 5.39; N, 12.49. Found: C, 53.51; H, 5.40; N, 12.29.

1-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)pyrrole-2,4-dicarboxamide (**7c**).

In a similar manner as for **7a**, compound **7c** was prepared by using **6b** (15.0 g, 29 mmoles) in dioxane:methanol (1:1, 400 ml) and ammonium hydroxide (40 ml), water (10 ml), and hydrogen peroxide (30%, 25 ml) to yield, after crystallization from acetone/hexane, 12.0 g (75%); mp 154-155°; ir: ν 1640 (C=O), 3340 (NH_2) cm^{-1}; uv (ethanol): λ max 249.5 nm (ϵ 11,700), 264 (12,400); ^1H nmr (DMSO-d_6): δ 4.55 (m, 6, $3CH_2C_6H_5$), 6.88 and 7.11 (2 br s, 2, $CONH_2$), 6.92 (d, 1, J = 4.5 Hz, $C_1'H$), 7.00 (dd, 1, J = 3.5 Hz, C_5H), 7.23-7.54 (m, 17, $3CH_2C_6H_5$ and $CONH_2$), 7.77 (s, 1, C_3H).

Anal. Calcd. for $C_{32}H_{33}N_3O_6$: C, 69.17; H, 5.98; N, 7.56. Found: C, 69.18; H, 5.99; N, 7.50.

1-β-Arabinofuranosylpyrrole-2,4-dicarboxamide (**7d**).

In a similar manner as for **7b**, the title compound was prepared by using **7c** (6.0 g, 10.9 mmoles), palladium hydroxide (3.0 g), cyclohexene (20 ml) and ethanol (250 ml). Crystallization of the product from aqueous ethanol gave 2.0 g (65%) of **7d**, mp 207-208°; ir: ν 1650 (C=O), 3200-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 220 nm (ϵ 14,800), 243 (7,100), 261 (7,500); (*p*H 7): λ max 213 nm (ϵ 32,900), 246 (14,800), 262 (14,800); (*p*H 11): λ max 262 (ϵ 17,100); ^1H nmr (DMSO-d_6): δ 6.70 (d, 1, J = 6.0 Hz, $C_1'H$), 6.83 and 7.39 (2 br s, 2, $CONH_2$), 7.04 and 7.65 (2 br s, 2, $CONH_2$), 7.13 (s, 1, C_5H) and 7.75 (s, 1, C_3H).

Anal. Calcd. for $C_{11}H_{15}N_3O_6$: C, 46.32; H, 5.31; N, 14.72. Found: C, 46.25; H, 5.38; N, 14.60.

3,5-Di-*O*-benzoyl-1,2-[phenyl(2-cyanopyrrolyl)methylidene]-α-D-ribofuranose (**9a**).

To a solution of **1a** (1.84 g, 20 mmoles) in dry dioxane (50 ml) was added sodium hydride (60% in oil, 0.9 g, 22 mmoles) and the mixture was stirred under nitrogen at room temperature for 0.5 hours. A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide [17] (**8**, prepared from 10.5 g of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose) in dioxane (100 ml) was added dropwise with stirring. After the addition of **8**, the reaction mixture was stirred at room temperature for 30 minutes and at 50° for 1 hour, filtered and the filtrate evaporated to dryness. The residue was dissolved in methanol (25 ml), adsorbed on silica gel (10 g) and placed on top of a silica gel column (5 x 20 cm). The column was eluted with hexane:acetone (8:2, v/v), the fractions having R_f = 0.33 were pooled and evaporated to yield 9.0 g (84%) of **9a** as amphorous solid; ir: ν 1710 (C=O), 2220 (C≡N) cm^{-1}; uv (ethanol): λ max 230 nm (ϵ 38,000); ^1H nmr (deuteriochloroform): δ 6.06 (dd, 1, J = 3.5 Hz, C_4H), 6.37 (d, 1, J = 4.2 Hz, $C_1'H$), 6.43 (dd, 1, J = 3.5 Hz, C_5H), 6.90 (dd, 1, J = 3.0 Hz, C_3H), and 7.36-8.11 (m, 15, 3, Ph).

Anal. Calcd. for $C_{31}H_{24}N_2O_7$: C, 69.39; H, 4.51; N, 5.22. Found: C, 69.41; H, 4.72; N, 5.18.

1,2-[Phenyl(2-cyanopyrrolyl)methylidene]-α-D-ribofuranose (**9b**).

In a similar manner as for **3c**, debenzoylation of **9a** (6.9 g, 12.5 mmoles) with methanolic ammonia (200 ml), and purification of the reaction product by flash chromatography using chloroform:acetone (7:3) as eluent gave 2.5 g (61%) of **9b** as needles (from acetone/ether); mp 136-138°; ir: ν 2210 (C≡N) cm^{-1}; uv (*p*H 1): λ max 225 nm (ϵ 4,300), 249 (5,200); (*p*H 7): λ max 225 nm (ϵ 5,400), 246 (5,700); (*p*H 11): λ max 251 nm (ϵ 5,500); ^1H nmr (DMSO-d_6): δ 6.11 (d, 1, J = 4.0 Hz, $C_1'H$), 6.30 (m, 1, C_4H), 6.30 (m, 1, C_4H), 7.08 (m, 1, C_5H), 7.31 (m, 1, C_3H) and 7.37-7.47 (m, 5, Ph).

Anal. Calcd. for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 61.91; H, 4.87; N, 8.32.

1-(2,3-*O*-Isopropylidene-5-*O*-(*t*-butyl)dimethylsilyl-β-D-ribofuranosyl)-pyrrole-2-carbonitrile (**11**).

To a stirred solution of **1a** (1.84 g, 20 mmoles) in dry acetonitrile (50 ml) was added sodium hydride (60% in oil, 0.8 g, 20 mmoles) in small portions. After the addition of sodium hydride, the reaction mixture was stirred at ambient temperature for 30 minutes. 1-Chloro-2,3-*O*-isopropylidene-5-*O*-(*t*-butyl)dimethylsilyl-α-D-ribofuranose [18] (**10**, 3.22 g, 10 mmoles, in dry THF at −78°) was added and the stirring was continued at room temperature overnight. The reaction mixture was evaporated to dryness and the residue was suspended in water (50 ml). The aqueous solution was extracted with ethyl acetate (2 x 50 ml) and the organic phase was washed successively with water (50 ml), saturated brine solution (50 ml), and dried over anhydrous sodium sulfate. The solvent was evaporated to give an oil, which was purified on a silica gel column (2.5 x 40 cm) using hexane:ethyl acetate (9:1, v/v) as eluent to yield 2.3 g (61%) of **11** as colorless gum; ir (neat): ν 2210 (C≡N) cm^{-1}; uv (ethanol): λ max 229 nm (ϵ 10,400), 250 (13,100); ^1H nmr (deuteriochloroform): δ 0.09 (s, 6, 2, CH_3), 0.91 (s, 9, *t*-butyl), 1.35 and 1.61 (2s, 6, isopropylidene CH_3), 5.86 (d, 1, J = 3.5 Hz, $C_1'H$), 6.21 (dd, 1, J = 3.5 Hz, C_4H), 6.83 (dd, 1, J = 3.5 Hz, C_5H), and 7.17 (m, 1, C_3H).

Anal. Calcd. for $C_{19}H_{30}N_2O_4Si$: C, 60.28; H, 7.99; N, 7.39. Found: C, 60.56; H, 8.19; N, 7.19.

1-β-D-Ribofuranosylpyrrole-2-carbonitrile (**12**).

Compound **11** (1.85 g, 4.9 mmoles) was combined with trifluoroacetic acid (10 ml) and water (1 ml), and the mixture was stirred at room temperature for 30 minutes. After evaporation of the solvents, the residue was dissolved in methanol (10 ml) and again evaporated to dryness. This process was repeated for 3 times to remove the last traces of trifluoroacetic acid. The crude product was purified by flash chromatography over silica gel using dichloromethane:acetone (7:3, v/v) as eluent to yield 0.95 g (87%) of **12** as amphorous solid; ir (neat): ν 2210 (C≡N) cm^{-1}; uv (ethanol): λ max 230 nm (ϵ 9,300), 251 (12,200); ^1H nmr (DMSO-d_6): δ 5.57 (d, 1, J = 4.7 Hz, $C_1'H$), 6.30 (m, 1, C_4H), 7.01 (m, 1, C_5H) and 7.51 (m, 1, C_3H).

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.56; H, 5.39; N, 12.48. Found: C, 53.42; H, 5.55; N, 12.20.

1-β-D-Ribofuranosylpyrrole-2-carboxamide (**13a**).

In a similar manner as for **4a**, the title compound was prepared by using **12** (0.20 g, 0.89 mmole), methanol (20 ml), dioxane (15 ml), water (1 ml), ammonium hydroxide (5 ml) and 30% hydrogen peroxide (5 ml). The reaction product was purified by flash chromatography using dichloromethane:methanol (9:1, v/v) as the eluent to yield 0.15 g (69%) of **13a** as a foam which was crystallized from ether, mp 131-134°; ir: ν 1650 (C=O) cm^{-1}; uv (ethanol): λ max 265 nm (ϵ 11,000); ^1H nmr (DMSO-d_6): δ 6.06 (m, 1, C_4H), 6.60 (d, 1, J = 3.8 Hz, $C_1'H$), 6.79 (m, 1, C_5H), 7.37 (m, 1, C_3H), 6.96 and 7.53 (2 br s, 2, $CONH_2$).

Anal. Calcd. for $C_{10}H_{14}N_2O_5 \cdot \frac{1}{2}H_2O$: C, 47.81; H, 6.02; N, 11.15. Found: C, 47.99; H, 5.85; N, 11.27.

1-β-D-Ribofuranosylpyrrole-2-thiocarboxamide (**13b**).

In a similar manner as for **4b**, compound **13b** was prepared by saturating a solution of **12** (0.30 g, 1.33 mmole) in dry pyridine (30 ml) containing triethylamine (5 ml) with hydrogen sulfide gas at room temperature. The reaction product was purified by flash chromatography using dichloromethane:acetone (8:2, v/v) as the eluent to yield 0.25 g (72%); ir: ν 1260 (C=S), 3230-3400 (NH_2, OH) cm^{-1}; uv (ethanol): λ max 284 nm (ϵ 7,000), 317 (10,300); ^1H nmr (DMSO-d_6): δ 6.09 (m, 1, C_4H), 6.62 (m, 1, C_5H), 6.75 (d, 1, J = 4.1 Hz, $C_1'H$), 7.44 (m, 1, C_3H), 8.91 and 9.33 (2 br s, 2, $CSNH_2$).

Anal. Calcd. for $C_{10}H_{14}N_2O_4S.\frac{1}{2}H_2O$: C, 44.93; H, 5.65; N, 10.48; S, 11.99. Found: C, 45.21; H, 5.58; N, 10.18; S, 11.76.

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