C-Nucleosides. 7. Preparation and Utility of 6-Hydroxy-6-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2*H*-pyran-3(6*H*)-one as a Key Intermediate of C-Nucleoside Synthesis

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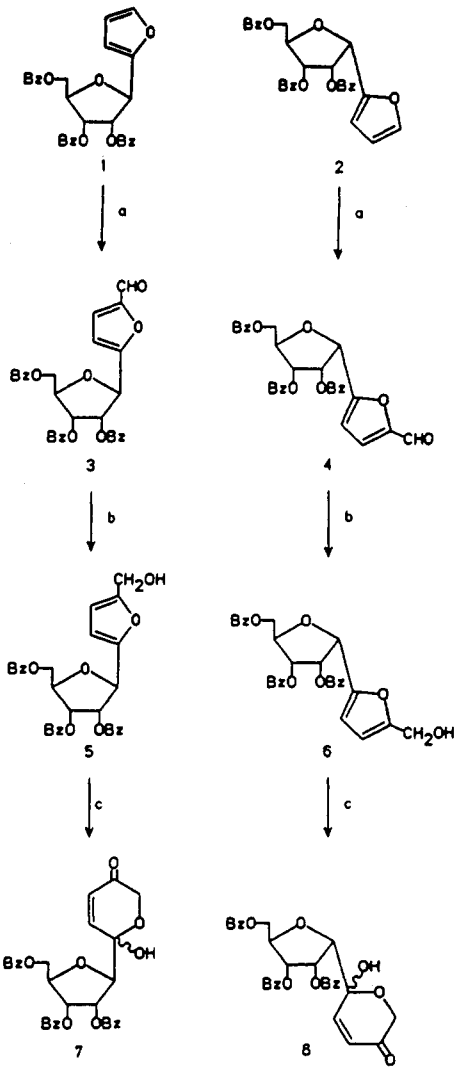
The novel ring transformation of pyranulose glycoside **7** which was obtained by oxidation of furfuryl alcohol **5** is described. Treatment of **7** with appropriate monoamines afforded the pyrrole-2-carboxaldehydes **11a–c**. With ethylenediamine, **7** reacts to give pyrrolo[1,2-*a*]pyrazine **14**, whereas the reaction of **7** with *o*-phenylenediamine leads to two products, pyrrolo[1,2-*a*]quinoxaline **17** and quinoxaline **18** in 16% and 43% yield, respectively. A possible mechanism for this reaction is proposed.

For several years, we have been studying the transformation of 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)furan (**1**) into a variety of C-nucleosides.[1] In this paper, we describe the preparation of a pyranulose glycoside, 6-hydroxy-6-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2*H*-pyran-3(6*H*)-one (**7**) and demonstrate the novel ring transformation of **7** to pyrrole-2-carboxaldehydes, pyrrolo[1,2-*a*]pyrazine, quinoxaline, and pyrrolo[1,2-*a*]-quinoxaline C-nucleosides.

A variety of methods have been reported for the synthesis of pyranones from 2-furfuryl alcohol derivatives based either on an 1,4 halogen addition[2] to the furan ring and subsequent hydrolysis in mild acid followed by an immediate rearrangement to the six-membered 2*H*-pyran-3(6*H*)-one ring or an oxidation procedure using *m*-chloroperbenzoic acid (MCPBA)[3] or pyridinium chlorochromate.[4] Other methods have also been reported.[5] For the application of these procedures to **7**, 5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-furfuryl alcohol (**5**) was obtained by reduction of furfural **3**[6] with $NaBH_4$ in 88% yield. Treatment of **5** with MCPBA in dichloromethane at room temperature afforded a mixture of diastereomeric pyranulose **7** (differing in configuration only at C-6) in yield of 72% with no trace of the other anomer. In an attemp to synthesize the corresponding 2,3-*O*-isopropylidene derivative to settle the anomeric configuration, deprotection of pyranulose **7** was attempted, but basic conditions led to the formation of a number of unidentified products. To confirm this, we prepared the corresponding α anomer **8** from **2** by the method used for the preparation of the β anomer (Scheme I). The assignments of the anomeric configuration at C-1′ to **5–8** were based on comparison of their ^1H NMR spectra. The chemical shift of the anomeric proton in compound **6** and **8** (δ 5.56 and 4.49) appeared downfield from that of compound **5** and **7** (δ 5.28 and 4.40) since the β face location of this anomeric proton placed it out of the shielding influence of the 2′-oxygen. This is in agreement with the general trend seen for most nucleoside anomeric pairs.[7] The observation of the H-1′ signal of **7** was found at higher field at δ 4.40 compared with that of H-5′ at δ 4.51–4.94. The assignment may be attributed to the shielding effect of the hydroxy group adjacent to the anomeric proton.[6] Treatment of **7** with hydrochloric acid in methanol did not afford the meth-

Scheme I[a]



[a] Reagents: (a) DMF, $POCl_3$; (b) $NaBH_4$, MeOH; (c) MCPBA, CH_2Cl_2.

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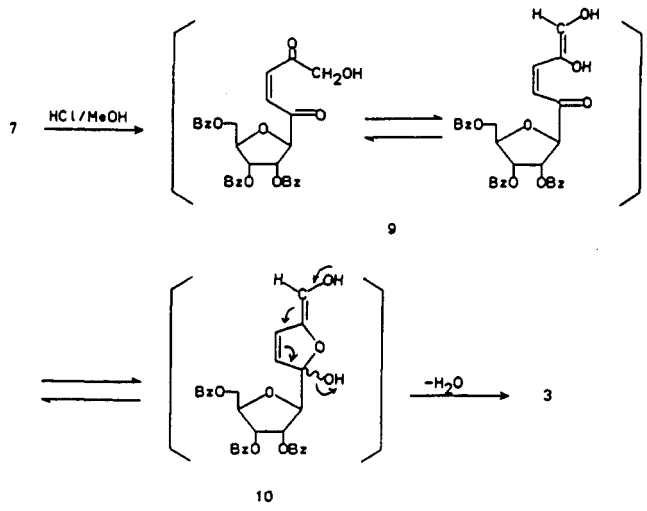
Scheme II

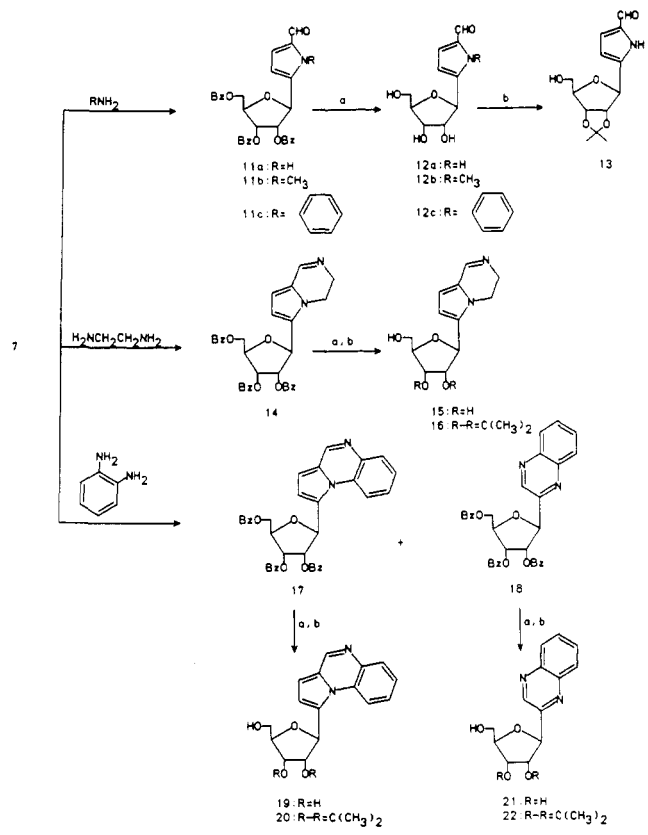


oxylated pyranulose but instead gave furfural **3** in 51% yield. We proposed that the mechanism of this ring transformation involves the formation of intermediate γ-diketone **9** which undergoes ring closure to the five-membered aldehyde enol **10** (Scheme II).[8] Pyranulose **7** was found to be sensitive to strong acid or alkaline media.

The pyranulose **7** was reacted with 36% aqueous ammonia in dioxane at room temperature for 4 h. The reaction gave a single major product together with a small amounts of polar byproducts. Purification of the crude product by low pressure liquid column chromatography using benzene gave the pyrrole-2-carboxaldehyde **11a** in an overall yield of 41% from the glycosylfuran **1** in 4 steps. The ^{1}H NMR spectrum of this substance clearly showed the disappearance of the methylene group and the presence of a single aldehyde proton at δ 9.49 and a vinyl proton at δ 6.37 and 6.90. In the mass spectrum, the molecular ion peak was found at *m/e* 539 (M^+). When the same reactions of **7** with primary monoamines are performed, the corresponding pyrrole-2-carboxaldehydes **11b,c** are obtained (Scheme III). Deprotection of **11a–c** with sodium methoxide in methanol afforded **12a–c** in appropriate yields. In order to determine the anomeric configuration, the isopropylidene acetal **13** was synthesized by using ethyl orthoformate and acetone in the presence of *p*-toluenesulfonic acid. Its ^{1}H NMR spectrum showed two singlets at δ 1.36 and 1.60 with a difference in shift value of 0.24 ppm: a value of less than 0.10 ppm should be expected in the case of an α anomer.[9] The proton at C-4′ showed a quartet, and the absorption of H-3′ was well-resolved, the coupling of H-3′ and H-4′ was about 3.0 Hz. In α anomers this coupling constant should be zero, resulting in an apparent triplet for H-4′.[10] This demonstrates that the β ribofuranoside configuration was preserved during the reaction sequence. The novel ring transformation of furfural **3** to pyrrole-2-carboxaldehydes **11a–c** is a simple procedure and **11a** is a useful intermediate for the preparation of new C-nucleosides.

Next, treatment of **7** with ethylenediamine in chloroform at room temperature afforded the expected 3,4-dihydro-6-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[1,2-*a*]-pyrazine (**14**) in 40% yield. Debenzoylation of **14** with

Scheme III[a]



[a] Reagents: (a) CH_3ONa, MeOH; (b) TsOH, $CH(OEt)_3$, acetone.

sodium methoxide in methanol at room temperature afforded the deblocked compound **15**.

Compound **7** and *o*-phenylenediamine in chloroform were heated under reflux for 2 h, giving a 16% yield of 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[1,2-*a*]-quinoxaline (**17**) and a 43% yield of 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)quinoxaline (**18**) (Scheme III). Structural assignments of **17** and **18** were largely based on mass spectral data which, in addition to the parent peaks, typically showed peaks for B + 30 that are characteristic of C-nucleosides. A plausible explanation for the formation of **17** involves nucleophilic attack by *o*-phenylenediamine on the carbonyl carbon of the pyranulose moiety of **7** with subsequent formation of Schiff's base I which is then opend to give imino ketone II. II cyclizes to aldehyde enol III.[11] Dehydration of III yields pyrrole aldehyde IV which is converted to tricyclic compound **17** by ring formation (path a).[12] In path b, Michael addition of *o*-phenylenediamine to **7** and ring opening produce diketo diamine VI which then undergoes cyclization to dihydroquinoxaline VII. Loss of hydroxy acetone from VII leads to the compound **18** (Scheme IV).[13] The ^{1}H NMR spectrum of the reaction mixture indicates the presence of a hydroxy acetone (δ 4.26 and 2.19, each singlet).

Deprotection of **17** and **18** with sodium methoxide in methanol afforded **19** and **21**. The assignments of anomeric configurations of **15**, **19**, and **21** were made on the basis of the difference in the chemical shifts of the two methyl signals of the corresponding 2,3-*O*-isopropylidene derivatives **16**, **20**, and **22** (see Experimental Section).

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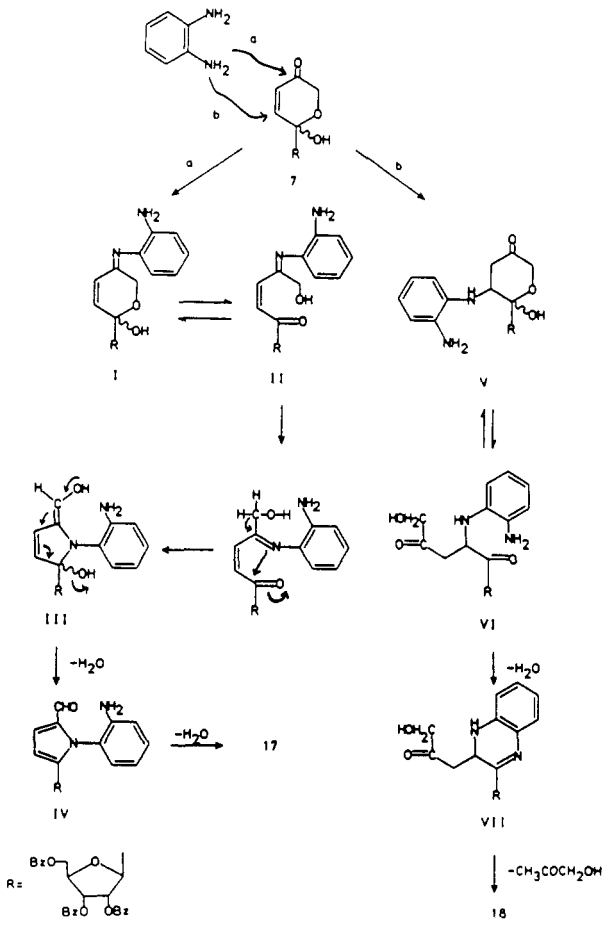
Scheme IV



Experimental Section

Melting points were determined on a Yanagimoto apparatus and are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. ^{1}H NMR spectra were measured with a JNM-GX-270 spectrometer, with tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded on a JEOL JNM-FX-100 Fourier transform spectrometer operating at 25.00 MHz, with tetramethylsilane as an internal standard. Optical rotation was determined on a JASCO DIP 181 digital polarimeter with a 10 cm, 1 mL microcell. Mass spectra were obtained on Hitachi M-52 or M-80 spectrometers. Elemental analyses were determined by the analytical center of this faculty. Analytical thin-layer chromatography was performed on glass plates coated with a 0.5-mm layer of silica gel GF_{254} (Merck). The compounds were detected with a UV light (254 nm). Column chromatography was performed on silica gel C-200 (74–149 μm, Wakogel).

5-(2,3,5-Tri-*O*-benzoyl-β- and -α-D-ribofuranosyl)-2-furfuryl Alcohol (5 and 6). To a solution of **3** (576 mg, 1.1 mmol) in methanol (5 mL) was slowly added $NaBH_4$ (120 mg, 3.2 mmol) in methanol (5 mL) at 0 °C for 15 min. Acetone was added, and then water was added and the mixture was extracted with chloroform (3 × 30 mL). The extracts were combined, washed with water, dried over magnesium sulfate, and evaporated to a syrup. This syrup was chromatographed over a column of silica gel with chloroform as the eluent. This afforded 509 mg (88.1%) of **5** as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 4.47 (s, 2, CH_2OH), 4.59 (dd, 1, H-5′a, $J_{4',5'a}$ = 4.0 Hz, $J_{5'a,5'b}$ = 11.7 Hz), 4.66–4.70 (m, 1, H-4′), 4.81 (dd, 1, H-5′b, $J_{4',5'b}$ = 3.4 Hz), 5.28 (d, 1, H-1′, $J_{1',2'}$ = 5.7 Hz), 5.89 (t, 1, H-3′), 5.97 (t, 1, H-2′), 6.22 (d, 1, H-4, $J_{3,4}$ = 3.0 Hz), 6.40 (d, 1, H-3), 7.33–8.16 (m, 15, Ar H); IR ($CHCl_3$) 3600 cm^{-1} (OH), 1730 cm^{-1} (C=O).

Anal. Calcd for $C_{31}H_{26}O_9 \cdot H_2O$: C, 66.42; H, 5.04. Found: C, 66.52; H, 4.76.

In the same manner (reaction solvent was used dimethylformamide), 107 mg (73%) of **6** was obtained as a colorless syrup from 145 mg of **4**: ^{1}H NMR ($CDCl_3$) δ 4.43 (s, 2, CH_2OH), 4.60 (dd, 1, H-5′a, $J_{4',5'a}$ = 4.5 Hz, $J_{5'a,5'b}$ = 11.9 Hz), 4.74 (dd, 1, H-5′b, $J_{4',5'b}$ = 3.7 Hz), 4.85 (m, 1, H-4′), 5.56 (d, 1, H-1′, $J_{1',2'}$ = 4.7 Hz), 5.87 (t, 1, H-3′), 6.03 (t, 1, H-2′), 6.21 (d, 1, H-4, $J_{3,4}$ = 3.4 Hz), 6.40 (d, 1, H-3), 7.31–8.09 (m, 15, Ar H); IR ($CHCl_3$) 3610 cm^{-1} (OH), 1730 cm^{-1} (C=O).

Anal. Calcd for $C_{31}H_{26}O_9$: C, 68.63; H, 4.83. Found: C, 68.28; H, 5.12.

(6*R*)- and (6*S*)-6-Hydroxy-6-(2,3,5-tri-*O*-benzoyl-β- and -α-D-ribofuranosyl)-2*H*-pyran-3(6*H*)-one (7 and 8). To a solution of **5** (660 mg, 1 mmol) in dichloromethane (20 mL) was slowly added 80% MCPBA (300 mg, 1.2 mmol) at 0–5 °C, and the mixture was allowed to stand at room temperature for 3 h. Solvent was removed under reduced pressure and the residue was chromatographed over silica gel with chloroform–benzene (1:1) as the eluent. This afforded 488 mg (72%) of **7** as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 3.85, 4.03, 4.34 (each d, $^1/_2$ each, H-2, J = 16.8 Hz), 4.40 (apparent s, 1, H-1′), 4.51–4.94 (m, $^7/_2$, H-2, H-4′, H-5′), 5.50 (dd, $^1/_2$, H-3′, $J_{2',3'}$ = 6.4 Hz, $J_{3',4'}$ = 1.7 Hz), 5.67 (dd, $^1/_2$, H-2′, $J_{1',2'}$ = 1.0 Hz, $J_{2',3'}$ = 5.4 Hz), 5.79 (dd, $^1/_2$, H-3′, $J_{2',3'}$ = 5.4 Hz, $J_{3',4'}$ = 3.0 Hz), 5.86 (dd, $^1/_2$, H-2′, $J_{1',2'}$ = 3.0 Hz, $J_{2',3'}$ = 6.4 Hz), 6.13, 6.23 (each d, $^1/_2$ each, H-4, $J_{4,5}$ = 10.4 Hz), 6.92, 6.95 (each d, $^1/_2$ each, H-5), 7.26–8.11 (m, 15, Ar H); ^{13}C NMR ($CDCl_3$) δ 62.54, 63.18 (C-5′), 66.05, 66.58 (C-2), 72.02, 72.95, 79.10, 79.62, 86.82, 87.40 (C-1′, C-2′, C-3′, C-4′), 92.32, 92.90 (C-6), 128.06–133.50 (Ar C, C-4), 144.91, 145.44 (C-5), 165.27, 166.73 (C=O), 194.05 (C-3).

Anal. Calcd for $C_{31}H_{26}O_{10}$: C, 66.66; H, 4.69. Found: C, 66.99; H, 5.04.

In the same manner, 14 mg (94%) of **8** was obtained as a colorless foam from 15 mg of **6**: ^{1}H NMR ($CDCl_3$) δ 4.02, 4.10 (each d, $^1/_2$ each, H-2, J = 17.0 Hz), 4.49 (d, $^1/_2$, H-1′, $J_{1',2'}$ = 5.0 Hz), 4.51 (d, 1, H-2), 4.53 (d, $^1/_2$, H-1′, $J_{1',2'}$ = 4.5 Hz), 4.55–4.76 (m, 2, H-5′), 4.83 (m, 1, H-4′), 5.78 (dd, $^1/_2$, H-3′, $J_{2',3'}$ = 5.0 Hz, $J_{3',4'}$ = 8.4 Hz), 5.81 (dd, $^1/_2$, H-3′, $J_{2',3'}$ = 2.9 Hz, $J_{3',4'}$ = 5.2 Hz), 6.04, 6.09 (each d, $^1/_2$ each, H-4, $J_{4,5}$ = 10.4 Hz), 6.13 (dd, $^1/_2$, H-2′, $J_{1',2'}$ = 4.5 Hz, $J_{2',3'}$ = 2.9 Hz), 6.24 (t, $^1/_2$, H-2′, $J_{1',2'}$ = $J_{2',3'}$ = 5.0 Hz), 7.03, 7.07 (each d, $^1/_2$ each, H-5), 7.29–8.07 (m, 15, Ar H); ^{13}C NMR ($CDCl_3$) δ 63.94 (C-5′), 66.23, 66.52 (C-2), 71.72, 72.54, 72.95, 79.33, 81.32, 83.37 (C-1′, C-2′, C-3′, C-4′), 93.02, 93.78 (C-6), 126.95–133.85 (Ar C, C-4), 145.26, 145.61 (C-5), 165.33, 166.21 (C=O), 194.05 (C-3).

Anal. Calcd for $C_{31}H_{26}O_{10}$: C, 66.66; H, 4.69. Found: C, 66.29; H, 4.94.

Reaction of 7 with HCl–MeOH. A solution of **7** (12 mg, 0.02 mmol) in methanol (2 mL) containing 4 drops of concentrated hydrochloric acid was allowed to stir at room temperature for 5 days. The reaction mixture was neutralized with a saturated sodium bicarbonate solution and then extracted with chloroform (3 × 10 mL). The extracts were combined, washed with water, dried over magnesium sulfate, and evaporated in vacuo to a syrup. This syrup was purified by preparative TLC with chloroform–methanol (99:1) as eluent. This afforded 6 mg (51%) of **3** as a colorless syrup. Identity was confirmed by comparing IR and ^{1}H NMR spectra with the product previously prepared by the reported procedure.

5-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrole-2-carboxaldehyde (11a). To a solution of **7** (200 mg, 0.35 mmol) in dioxane (10 mL) was added 36% ammonia (90 mg, 0.9 mmol) at 0–5 °C. The reaction mixture was stirred for 4 h at room temperature. The reaction mixture was neutralized with acetic acid and then extracted with chloroform (3 × 50 mL). The extracts were combined, washed with water, dried over magnesium sulfate, and evaporated in vacuo to a syrup. This syrup was chromatographed over a column of silica gel with benzene as the eluent. This afforded 142 mg (72%) of **11a** as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 4.69–4.83 (m, 3, H-4′, H-5′), 5.39 (d, 1, H-1′, $J_{1',2'}$ = 4.4 Hz), 5.60–5.64 (m, 2, H-2′, H-3′), 6.37 (dd, 1, H-3, $J_{1,3}$ = 2.2 Hz, $J_{3,4}$ = 3.7 Hz), 6.90 (dd, 1, H-4, $J_{1,4}$ = 2.7 Hz), 7.37–8.07 (m, 15, Ar H), 9.49 (s, 1, CHO), 9.85 (br, 1, NH); ^{13}C NMR ($CDCl_3$) δ 63.71 (C-5′), 72.13, 75.76, 78.28, 80.03 (C-1′, C-2′, C-3′, C-4′), 108.76 (C-4), 121.39 (C-3), 128.41–133.56 (Ar C, C-5), 137.01 (C-2), 165.27, 165.44, 166.44 (C=O), 178.96 (CHO).

Anal. Calcd for $C_{31}H_{25}NO_8$: C, 69.01; H, 4.67; N, 2.60. Found: C, 68.75; H, 4.81; N, 2.43.

1-Methyl-5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-pyrrole-2-carboxaldehyde (11b). This compound was prepared from **7** and 25% methylamine as described above for **11a**: colorless

foam, 39%; MS, m/e 553 (M^+); ^1H NMR ($CDCl_3$) δ 4.04 (s, 3, CH_3), 4.55 (dd, 1, H-5'a, $J_{4',5'a}$ = 3.4 Hz, $J_{5'a,5'b}$ = 11.8 Hz), 4.71 (m, 1, H-4'), 4.78 (dd, 1, H-5'b, $J_{4',5'b}$ = 3.4 Hz), 5.36 (d, 1, H-1', $J_{1',2'}$ = 6.4 Hz), 5.85 (t, 1, H-3'), 5.97 (t, 1, H-2'), 6.35 (d, 1, H-4, $J_{3,4}$ = 4.4 Hz), 6.80 (d, 1, H-3), 7.34–8.04 (m, 15, Ar H), 9.49 (s, 1, CHO); ^{13}C NMR ($CDCl_3$) δ 33.17 (CH_3), 63.65 (C-5'), 74.43, 77.05, 78.34, 80.38 (C-1', C-2', C-3', C-4'), 108.64 (C-4), 123.56 (C-3), 128.41–133.56 (Ar-C, C-5), 138.42 (C-2), 165.39, 166.03 (C=O), 179.90 (CHO).

Anal. Calcd for $C_{32}H_{27}NO_8$: C, 69.43; H, 4.92, N, 2.53. Found: C, 69.21; H, 5.27; N, 2.23.

1-Phenyl-5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrole-2-carboxaldehyde (11c). A solution of **7** (106 mg, 0.19 mmol) and aniline (18 mg, 0.19 mmol) in benzene (4 mL) was heated under reflux for 4 h. Benzene was removed under reduced pressure and the residue was purified by preparative TLC to afford **11c** as a colorless syrup: 36%; MS, m/e 615 (M^+); ^1H NMR ($CDCl_3$) δ 4.47–4.53 (m, 2, H-4', H-5'a), 4.73 (dd, 1, H-5'b, $J_{4',5'b}$ = 4.71, $J_{5'a,5'b}$ = 13.1 Hz), 4.98 (d, 1, H-1', $J_{1',2'}$ = 5.7 Hz), 5.72 (t, 1, H-3'), 5.87 (t, 1, H-2'), 6.52 (d, 1, H-4, $J_{3,4}$ = 4.4 Hz), 7.04 (d, 1, H-3), 7.28–8.08 (m, 20, Ar H), 9.36 (s, 1, CHO); ^{13}C NMR ($CDCl_3$) δ 63.71 (C-5'), 72.19, 75.12, 79.74 (C-1', C-2', C-3', C-4'), 109.69 (C-4), 120.05 (C-3), 128.36–136.37 (Ar C, C-5), 138.36 (C-2), 164.92, 165.27, 166.09 (C=O), 179.14 (CHO).

Anal. Calcd for $C_{37}H_{29}NO_8$: C, 72.18; H, 4.75; N, 2.28. Found: C, 71.82; H, 4.81; N, 2.18.

3,4-Dihydro-6-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[1,2-*a*]pyrazine (14). This compound was prepared from **7** and ethylenediamine as described above for **11a**: light yellow syrup, 40%; ^1H NMR ($CDCl_3$) δ 3.72–4.02 (m, 4, H-3, H-4), 4.54 (dd, 1, H-5'a, $J_{4',5'a}$ = 3.7 Hz, $J_{5'a,5'b}$ = 12.1 Hz), 4.68 (m, 1, H-4'), 4.81 (dd, 1, H-5'b, $J_{4',5'b}$ = 3.0 Hz), 5.34 (d, 1, H-1', $J_{1',2'}$ = 6.1 Hz), 5.86 (t, 1, H-3'), 5.94 (t, 1, H-2'), 6.30, 6.34 (each d, 1 each, H-7, H-8, $J_{1,2}$ = 4.0 Hz), 7.31–8.05 (m, 15, Ar H), 8.14 (s, 1, H-1); ^{13}C NMR ($CDCl_3$) δ 40.48, 47.04 (C-3, C-4), 63.65 (C-5'), 72.49, 74.24, 75.53, 80.32 (C-1', C-2', C-3', C-4'), 108.87, 111.56 (C-7, C-8), 128.47–133.27 (Ar C, C-8a, C-6), 152.20 (C-1), 165.21–166.09 (C=O).

Anal. Calcd for $C_{33}H_{28}N_2O_7$: C, 70.20; H, 5.00; N, 4.96. Found: C, 69.80; H, 5.21; N, 4.67.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[1,2-*a*]quinoxaline (17) and 2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)quinoxaline (18). A solution of **7** (318 mg, 0.57 mmol) and *o*-phenylenediamine (70 mg, 0.6 mmol) in chloroform (5 mL) was heated under reflux for 2 h. The reaction mixture was evaporated to dryness in vacuo. TLC (chloroform–methanol, 99:1) showed that the light yellow syrup contained two major components (R_f 0.23 and 0.21). The mixture were separated by preparative TLC with chloroform–methanol (99:1) as the eluent after three elutions.

Compound **17**: R_f 0.21; colorless foam, 16%; MS, m/e 612 (M^+); ^1H NMR ($CDCl_3$) δ 4.63 (dd, 1, H-5'a, $J_{4'5'a}$ = 3.7 Hz, $J_{5'a,5'b}$ = 12.1 Hz), 4.76 (dd, 1, H-5'b, $J_{4',5'b}$ = 2.0 Hz), 4.85 (m, 1, H-4'), 5.87–6.02 (m, 2, H-1', H-3'), 6.35 (t, 1, H-2', $J_{1',2'}$ = $J_{2',3'}$ = 5.7 Hz), 6.85, 7.02 (each d, 1 each, H-2, H-3, $J_{2,3}$ = 4.4 Hz), 7.31–8.12 (m, 18, Ar H), 8.48 (dd, 1, H-6), 8.77 (s, 1, H-4); ^{13}C NMR ($CDCl_3$) δ 64.00 (C-5'), 72.72, 73.66, 75.35, 80.56 (C-1', C-2', C-3', C-4'), 107.12, 114.08, 116.89, (C-2, C-3, C-9), 125.43–137.25 (Ar C), 145.85 (C-4), 165.21, 165.56, 166.09 (C=O).

Anal. Calcd for $C_{37}H_{28}N_2O_7$: C, 72.54; H, 4.61; N, 4.57. Found: C, 72.34; H, 4.90; N, 4.43.

Compound **18**: R_f 0.23; colorless foam, 43%; MS, m/e 574 (M^+); ^1H NMR ($CDCl_3$) δ 4.66 (dd, 1, H-5'a, $J_{4',5'a}$ = 5.0 Hz, $J_{5'a,5'b}$ = 12.8 Hz), 4.88 (m, 2, H-4', H-5'b), 5.65 (d, 1, H-1', $J_{1',2'}$ = 5.4 Hz), 6.01 (t, 1, H-3'), 6.22 (t, 1, H-2'), 7.26–8.12 (m, 19, Ar H), 9.08 (s, 1, H-3); ^{13}C NMR ($CDCl_3$) δ 63.94 (C-5'), 72.72, 75.70, 80.62, 82.61 (C-1', C-2', C-3', C-4'), 128.30–133.39 (Ar C), 141.64, 142.45 (C-4a, C-8a), 143.92 (C-3), 152.17 (C-2), 165.33, 166.09 (C=O).

Anal. Calcd for $C_{34}H_{26}N_2O_7$: C, 71.07; H, 4.56; N, 4.88. Found: C, 70.87, H, 4.86; N, 4.63.

General Deprotection Procedure. Sufficient methanolic sodium methoxide (0.9 mmol) was added to the protected C-nucleoside (0.15 mmol) in absolute methanol (2 mL). The mixture was allowed to stand at room temperature for 5 h, rendered neutral with acetic acid, and evaporated. The residue was purified by preparative TLC to afford the free C-nucleosides.

5-(β-D-Ribofuranosyl)pyrrole-2-carboxaldehyde (12a): colorless foam, 62%; $[\alpha]^{22.5}_D$ −82.8° (*c* 0.25, methanol); ^1H NMR (CD_3OD) δ 3.72 (dd, 1, H-5'a, $J_{4',5'a}$ = 3.7 Hz, $J_{5'a,5'b}$ = 12.1 Hz), 3.85 (dd, 1, H-5'b, $J_{4',5'b}$ = 3.0 Hz), 3.95 (m, 1, H-4'), 4.00 (t, H-2', $J_{1',2'}$ = $J_{2',3'}$ = 6.1 Hz), 4.14 (t, 1, H-3'), 4.82 (d, 1, H-1'), 6.30 (d, 1, H-4, $J_{3,4}$ = 3.7 Hz), 6.97 (d, 1, H-3), 9.37 (s, 1, CHO); ^{13}C NMR (CD_3OD) δ 62.83 (C-5'), 72.25, 77.93, 80.09, 86.18 (C-1', C-2', C-3', C-4'), 110.04 (C-4), 134.09 (C-3), 142.34 (C-5), 151.72 (C-2), 180.54 (CHO); high resolution mass spectrum, m/e 227.0798 ($C_{10}H_{13}NO_5$ requires 227.0792).

1-Methyl-5-(β-D-ribofuranosyl)pyrrole-2-carboxaldehyde (12b): syrup, 63%; $[\alpha]^{22.5}_D$ −118.0° (*c* 0.05, methanol); ^1H NMR (CD_3OD) δ 3.63 (dd, 1, H-5'a, $J_{4',5'a}$ = 4.7 Hz, $J_{5'a,5'b}$ = 12.1 Hz), 3.71 (dd, 1, H-5'b), 3.93–3.98 (m, 1, H-4'), 3.99 (s, 3, CH_3), 4.06 (t, 1, H-3', $J_{2',3'}$ = $J_{3',4'}$ = 5.0 Hz), 4.20 (t, 1, H-2'), 4.,0 (d, 1, H-1'), 6.38 (d, 1, H-4, $J_{3,4}$ = 4.0 Hz), 6.97 (d, 1, H-3), 9.43 (s, 1, CHO); ^{13}C NMR (CD_3OD) δ 33.58 (CH_3), 63.48 (C-5'), 72.84, 76.40, 77.63, 86.70 (C-1', C-2', C-3', C-4'), 109.87 (C-4), 125.21 (C-3), 134.21 (C-5), 143.98 (C-2), 181.30 (CHO); high resolution mass spectrum, m/e 241.0972 ($C_{11}H_{15}NO_5$ requires 241.0949).

1-Phenyl-5-(β-D-ribofuranosyl)pyrrole-2-carboxaldehyde (12c): syrup, 57%; $[\alpha]^{22.5}_D$ −46.31° (*c* 0.25, methanol); ^1H NMR (CD_3OD) δ 3.57 (dd, 1, H-5'a, $J_{4',5'a}$ = 4.7 Hz, $J_{5'a,5'b}$ = 11.8 Hz), 3.65 (dd, 1, H-5'b, $J_{4',5'b}$ = 3.7 Hz), 3.75 (m, 1, H-4'), 3.98 (t, 1, H-3', $J_{2',3'}$ = $J_{3',4'}$ = 5.4 Hz), 4.20 (t, 1, H-2'), 4.41 (d, 1, H-1'), 6.59 (d, 1, H-4, $J_{3,4}$ = 4.0 Hz), 7.16 (d, 1, H-3), 7.38–7.52 (m, 5, Ar H), 9.26 (s, 1, CHO); ^{13}C NMR (CD_3OD) δ 63.43 (C-5'), 72.84, 76.87, 77.11, 86.41 (C-1', C-2', C-3', C-4'), 110.92 (C-4), 121.75 (C-3), 129.76, 130.11, 135.55, 137.89 (Ar C, C-5), 143.33 (C-2), 180.77 (CHO); high resolution mass spectrum, m/e 303.1086 ($C_{16}H_{17}NO_5$ requires 303.1105).

3,4-Dihydro-6-(β-D-ribofuranosyl)pyrrolo[1,2-*a*]pyrazine (15): colorless foam, 53%; $[\alpha]^{22.5}_D$ −37.33° (*c* 0.15, methanol); ^1H NMR (CD_3OD) δ 3.62 (dd, H-5'a, $J_{4',5'a}$ = 5.1 Hz, $J_{5'a,5'b}$ = 12.1 Hz), 3.70 (dd, 1, H-5'b, $J_{4',5'b}$ = 3.7 Hz), 3.78 (m, 2, H-3 or H-4), 3.91 (m, 1,H-4'), 4.02–4.08 (m, 3, H-3', H-3, or H-4), 4.19 (t, 1, H-2', $J_{1',2'}$ = $J_{2',3'}$ = 7.1 Hz), 4.80 (d, 1, H-1'), 6.29, 6.49 (each d, 1 each, H-7 and H-8, $J_{7,8}$ = 4.0 Hz), 8.09 (br s, 1, H-1); ^{13}C NMR (CD_3OD) δ 41.48 (C-3 or C-4), 63.53 (C-5'), 72.84, 76.11, 77.75, 86.76 (C-1', C-2', C-3', C-4'), 109.58, 113.55 (C-7, C-8), 129.35, 136.19 (C-6, C-8a), 153.92 (C-1); high resolution mass specrum, m/e 252.1116 ($C_{12}H_{16}N_2O_4$ requires 252.1109).

1-(β-D-Ribofuranosyl)pyrrolo[1,2-*a*]quinoxaline (19): 66%; colorless foam; $[\alpha]^{22.5}_D$ −125.6 (*c* 0.025, methanol); ^1H NMR (CD_3OD) δ 3.65–3.78 (m, 2, H-5'), 4.12 (m, 1, H-4'), 4.16 (t, 1, H-3', $J_{2',3'}$ = $J_{3',4'}$ = 5.4 Hz), 4.57 (t, 1, H-2'), 5.43 (d, 1, H-1'), 7.07, 7.15 (each d, 1 each, H-2, H-3, $J_{2,3}$ = 4.0 Hz), 7.50 (t, 1, H-8, $J_{7,8}$ = $J_{8,9}$ = 7.1 Hz), 7.59 (t, 1, H-7), 7.88 (d, 1, H-9), 8.57 (d, 1, H-6), 8.75 (s, 1, H-4); ^{13}C NMR (CD_3OD) δ 63.48 (C-5'), 72.89, 75.53, 77.93, 86.53 (C-1', C-2', C-3', C-4'), 109.43, 115.66 (C-2, C-3), 118.99 (C-9), 126.54–132.80 (C-1, C-3a, C-5a, C-6, C-7, C-8), 146.78 (C-4); high resolution mass spectrum, m/e 300.1138 ($C_{16}H_{16}N_2O_4$ requires 300.1109).

2-(β-D-Ribofuranosyl)quinoxaline (21): 75%; mp 107–108 °C; $[\alpha]^{22.5}_D$ −13.50° (*c* 0.02, methanol); ^1H NMR (CD_3OD) δ 3.78 (dd, 1, H-5'a, $J_{4',5'a}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.1 Hz), 3.92 (dd, H-5'b, $J_{4',5'b}$ = 3.0 Hz), 4.14 (m, 1, H-4'), 4.21 (t, 1, H-3', $J_{2',3'}$ = $J_{3',4'}$ = 5.0 Hz), 4.32 (t, 1, H-2'), 5.11 (d, 1, H-1'), 7.81–7.89 (m, 2, H-6, H-7), 8.07–8.12 (m, 2, H-5, H-8), 9.12 (s, 1, H-3); ^{13}C NMR (C-D_3OD) δ 63.30 (C-5'), 72.84, 78.21, 85.41, 86.88 (C-1', C-3', C-3', C-4'), 129.82, 131.28, 131.67 (C-5, C-6, C-7, C-8), 142.63, 143.00 (C-4a, C-8a), 145.44 (C-3), 156.79 (C-2); high resolution mass spectrum, m/e 262.0968 ($C_{13}H_{14}N_2O_4$ requires 262.0952).

General Acetonization Procedure. Ethyl orthoformate was added to a well-stirred suspension of deprotected C-nucleosides in acetone containing *p*-toluenesulfonic acid monohydrate and the mixture was allowed to stand at room temperature for 24 h. The sodium bicarbonate was added, and the mixture was stirred for 15 min. The solid was collected by filtration and thoroughly washed with acetone. The filtrate were combined and evaporated in vacuo to a syrup which was purified by preparative TLC with chloroform–methanol (50:1) as the eluent.

5-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)pyrrole-2-carboxaldehyde (13): colorless foam, 69%; ^1H NMR ($CDCl_3$) δ 1.36 (s, 3, CH_3), 1.60 (s, 3, CH_3), 3.78 (dd, 1, H-5'a, $J_{4',5'a}$ = 3.0 Hz, $J_{5'a,5'b}$ = 11.8 Hz), 3.98 (dd, 1, H-5'b, $J_{4',5'b}$ = 2.4 Hz), 4.28 (q,

1, H-4'), 4.66 (dd, 1, H-2', $J_{1',2'}$ = 4.4 Hz, $J_{2',3'}$ = 6.4 Hz), 4.88 (dd, 1, H-3', $J_{3',4'}$ = 3.0 Hz), 5.06 (d, 1, H-1'), 6.27 (d, 1, H-4, $J_{3,4}$ = 4.0 Hz), 6.94 (d, 1, H-3), 9.43 (s, 1, CHO), 10.74 (br, 1, NH).

3,4-Dihydro-6-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-pyrrolo[1,2-*a*]pyrazine (16): colorless foam, 75%; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 3, CH_3), 1.59 (s, 3, CH_3), 3.68 (dd, 1, H-5'a, $J_{4',5'a}$ = 4.0 Hz, $J_{5'a,5'b}$ = 12.1 Hz), 3.80 (dd, 1, H-5'b), 3.89–3.97 (m, 4, H-3, H-4), 4.18 (q, 1, H-4'), 4.85 (d, 1, H-1', $J_{1',2'}$ = 5.3 Hz), 4.79, 4.89 (each t, 1 each, H-2', H-3'), 6.22, 6.37 (each d, 1 each, H-7, H-8, $J_{1,2}$ = 4.0 Hz), 8.13 (apparent s, 1, H-1).

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)pyrrolo[1,2-*a*]quinoxaline (20): colorless foam, 81%; ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 3, CH_3), 1.61 (s, 3, CH_3), 3.78 (dd, 1, H-5', $J_{4',5'a}$ = 3.4 Hz, $J_{5'a,5'b}$ = 12.1 Hz), 3.91 (dd, 1, H-5'b, $J_{4',5'b}$ = 3.4 Hz), 4.41 (q, 1, H-4'), 4.93 (dd, 1, H-3', $J_{2',3'}$ = 5.7 Hz, $J_{3',4'}$ = 3.4 Hz), 5.17 (t, 1, H-2'), 5.50 (d, 1, H-1'), 6.90, 7.03 (each d, 2 each, H-2, H-3, J = 4.4 Hz), 7.45–7.58 (m, 2, H-7, H-8), 7.98 (d, 1, H-9, J = 8.0 Hz), 8.40 (d, 1, H-6, J = 8.4 Hz).

2-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)quinoxaline (22): colorless foam, 87%; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3, CH_3), 1.68 (s, 3, CH_3), 3.69–3.80 (br, 1, H-5'a), 4.04 (dd, 1, H-5'b, $J_{4',5'b}$ = 2.4 Hz, $J_{5'a,5'b}$ = 12.4 Hz), 4.57 (q, 1, H-4'), 4.95–5.03 (m, 2, H-2', H-3'), 5.22 (br, 1, OH), 5.38 (d, 1, H-1', $J_{1',2'}$ = 3.7 Hz), 7.26–7.85 (m, 2, H-6, H-7), 8.05–8.18 (m, 2, H-5, H-8), 8.91 (s, 1, H-3).

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Total Synthesis of Prodigiosin, Prodigiosene, and Desmethoxyprodigiosin: Diels–Alder Reactions of Heterocyclic Azadienes and Development of an Effective Palladium(II)-Promoted 2,2'-Bipyrrole Coupling Procedure

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The total synthesis of prodigiosin (1), a red pigment first isolated from *Serratia marcescens*, possessing the characteristic pyrrolylpyrromethene skeleton of a class of naturally occurring polypyrroles exhibiting antimicrobial and cytotoxic properties, is detailed. The approach is based on the application of an inverse electron demand Diels–Alder reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate in a 1,2,4,5-tetrazine → 1,2-diazine → pyrrole strategy for preparation of prodigiosin pyrrole ring B and the subsequent implementation of an effective intramolecular palladium(II)-promoted 2,2'-diaryl coupling for construction of the prodigiosin 2,2'-bipyrrole AB ring system. In situ generated activated ester derivatives of pyrrole-1-carboxylic acid or the use of pyrrole-1-carboxylic acid anhydride proved suitable for the generation of *mixed* 1,1'-carbonyldipyrrole compounds for use in the palladium(II)-promoted mixed, 2,2'-bipyrrole coupling. Extensions of this approach to the preparation of the naturally occurring parent pyrrolylpyrromethene, prodigiosene (**2a**), and 2-methyl-3-pentylprodigiosene (**2e**, desmethoxyprodigiosin) are detailed. A comparison of the in vitro cytotoxic properties of prodigiosin (1), prodigiosene (**2a**), and 2-methyl-3-pentylprodigiosene (**2e**) are reported and reveal exceptional cytotoxic potency (3.7×10^{-4} μg/mL ≡ 3.7×10^{-10} g/mL) for prodigiosin against 9PS (P388) mouse leukemia which may be attributed to the presence of the prodigiosin C-6 methoxy substituent.

Prodigiosin (1), a red pigment first isolated from *Serratia marcescens*,[1] was the initial member of a class of naturally occurring polypyrroles possessing a common, characteristic pyrrolylpyrromethene skeleton[2] which now include prodigiosene (**2a**), norprodigiosin (**2b**), undecylprodigiosin (**2c**), nonylprodigiosin (**2d**), cyclic nonylprodigiosin (**3**), cycloprodigiosin (**4**), metacycloprodigiosin (**5**), and **6**, which have been shown to possess potent antimicrobial and cytotoxic properties.[3] Extensive past efforts utilized in the preparation and structural confirmation of the naturally occurring[1,4] and synthetic[5] pro-

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