

Synthesis of 5-Hydroxy-2-( $\beta$ -D-ribofuranosyl)pyridine

Isamu Maeba, Makoto Suzuki, Naoko Takahashi,

Takashi Iijima and Hiroshi Furukawa\*

Faculty of Pharmacy, Meijo University, Tempaku,  
Nagoya 468 Japan

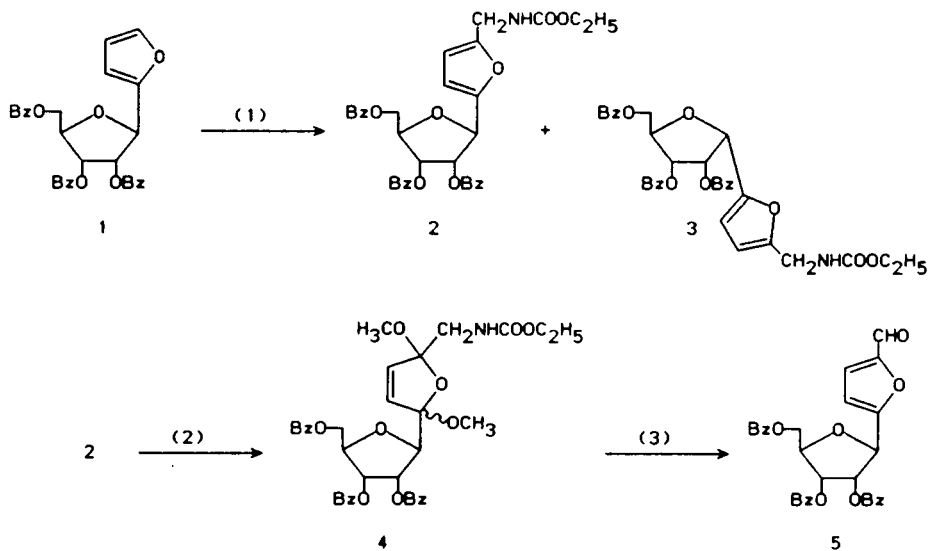
Received March 23, 1987

The synthesis of 5-hydroxy-2-( $\beta$ -D-ribofuranosyl)pyridine (**12**) from 2-(2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)furan (**1**) is described. Treatment of **1** with  $\alpha$ -methoxycarbamate in the presence of *p*-toluenesulfonic acid in benzene at reflux temperature afforded furfurylcarbamate (**2**) and its  $\alpha$ -isomer in a 5/1 ratio. The anomerization was circumvented by treatment of **1** with  $\alpha$ -methoxycarbamate in the presence of boron trifluoride in benzene at room temperature. Compound **2** was electrochemically oxidized to give dihydrofuran **4**. However, conversion of **4** into **11** was unsuccessful. Treatment of azide **8** with bromine and methanol afforded **9**. Reduction of **9** with zinc powder gave dihydrofurfurylamine **10**, in 80% yield. Treatment of this with concentrated hydrochloric acid in methanol yielded **11**, which on deblocking with 5% sodium hydroxide aqueous solution gave **12**.

*J. Heterocyclic Chem.*, **25**, 503 (1988).

Since discoveries that several of the naturally occurring C-nucleosides [1] have interesting biological properties, considerable effort has been directed toward the synthesis of many structural analogues. During our efforts to develop a general synthetic method for C-nucleosides, we have prepared an extremely useful intermediate 2-(2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)furan (**1**) from which pyridazine, phthalimide, phthalazine and pyrrolinone C-nucleosides [2-5] have been synthesized. As a continuation of our efforts to utilize intermediate **1** in C-nucleosides, we report a synthesis of 5-hydroxy-2-( $\beta$ -D-ribofuranosyl)pyridine (**12**) from **1**.

A few reports have dealt with the preparation of pyridine C-nucleosides [6]. Shono *et al.* [7] reported that the facile synthesis of pyridoxine from electrochemical oxidation of  $\alpha$ -aminoalkylfuran followed by ring transformation. At the beginning, we attempted to apply this method for the preparation of **12** from **1**. Treatment of **1** with  $\alpha$ -methoxycarbamate in the presence of *p*-toluenesulfonic acid in benzene at reflux temperature afforded two major products only. These were readily separable by preparative tlc and identified as ethyl 5-(2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)-2-furfurylcarbamate (**2**) and its  $\alpha$  isomer **3** in a combined yield of 47% and in a 5/1 ratio, respectively.

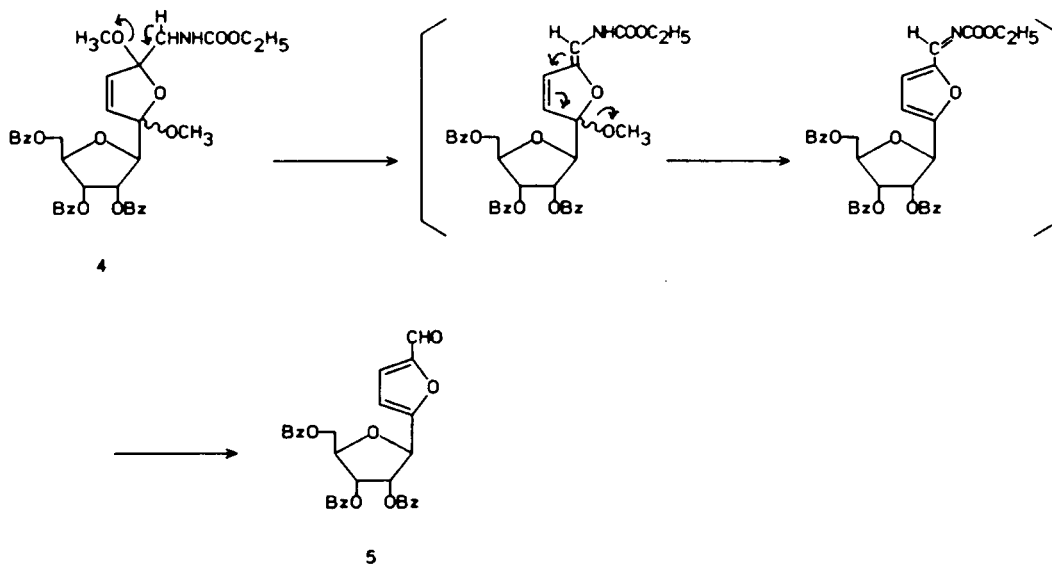


(1) CH<sub>3</sub>OCH<sub>2</sub>NHCOOC<sub>2</sub>H<sub>5</sub>, TsOH; (2) anodic oxidn. in MeOH; (3) H<sup>+</sup>.

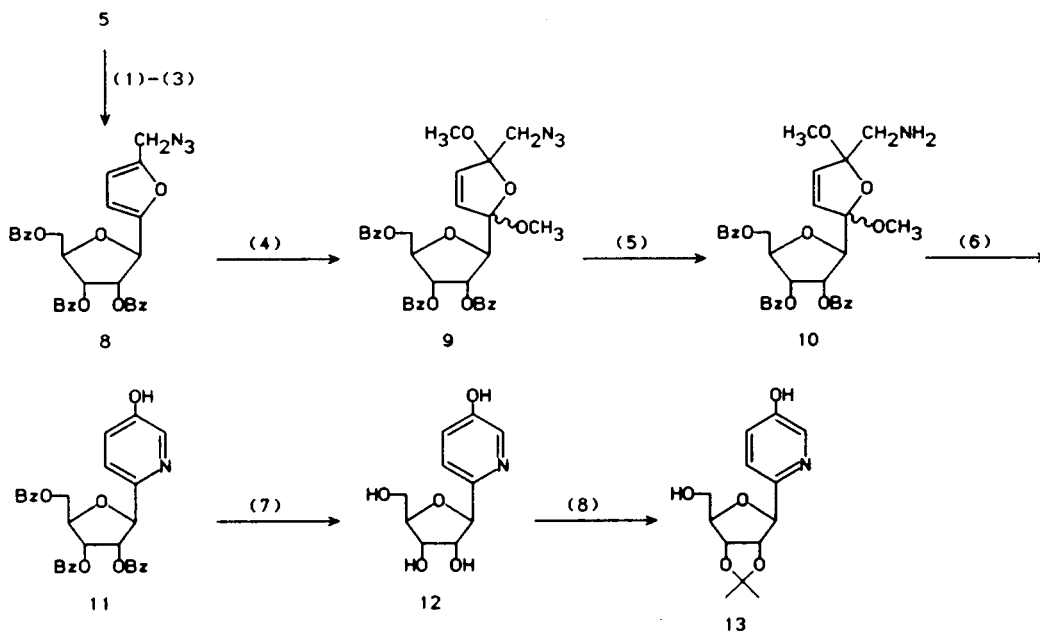
Scheme 1

The assignments of the anomeric configuration at C-1' to **2** and **3** were based on comparison of their  $^1\text{H}$  nmr spectra. The chemical shift of the anomeric proton in compound **3** ( $\delta$  5.53) appeared downfield from that of compound **2** ( $\delta$  5.26) since the  $\beta$  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 the most nucleoside anomeric pairs [8]. The anomerization was circumvented by treatment of **1** with  $\alpha$ -methoxycarbamate in the presence of boron trifluoride in benzene at

room temperature. The isolated yield of **2** was routinely 80-90% after purification by silica gel column chromatography, with no trace of the  $\alpha$  isomer. Compound **2** was electrochemically oxidized in methanol to afford as a mixture of dihydrofurfurylcarbamate **4** which could not be separated, even by preparative tlc. Attempted ring transformation of **4** into pyridine under a variety of acidic conditions, proved unsuccessful, leading to glycosylfuran-2-aldehyde **5** [5]. The mechanism of this transformation is proposed as shown in Scheme 2.



Scheme 2



(1)  $\text{NaBH}_4/\text{MeOH}$ ; (2)  $\text{SOCl}_2$ , pyridine; (3)  $\text{NaN}_3$ , 18-crown-6; (4) bromine, MeOH; (5) Zn, HCl/acetone; (6) HCl/MeOH; (7) 5% NaOH; (8) *p*-TsOH,  $\text{HC}(\text{OC}_2\text{H}_5)_3/\text{acetone}$

Scheme 3

Next, ring transformation of dihydrofurfurylamine **10** which was synthesized in six steps from **1**, was examined. Formylation of **1** with dimethylformamide and phosphorus oxychloride afforded aldehyde **5** in 96% yield [5]. Compound **5** was efficiently reduced with sodium borohydride in methanol. Alcohol **6** was chlorinated with thionyl chloride in benzene, and the chloromethyl compound **7**, without isolation, was treated with sodium azide in dioxane. The resulting azide **8** was obtained in an overall yield of 69% from **5**. Treatment of azide **8** with bromine and methanol afforded **9** as a mixture of geometric isomers in 92% yield. These isomers could not be separated by preparative tlc, but the mixture was entirely satisfactory for the next step. Reduction of **9** with zinc powder and concentrated hydrochloric acid in acetone gave an inseparable diastomeric mixture of furfurylamine **10** in 80% yield. Brief treatment of the furfurylamine **10** with hydrochloric acid gave two products, protected hydroxypyridine **11** and glycosylfuran-2-aldehyde **5** in yields of 78% and 6%, respectively. We anticipated that the difference of propensity of carbamate **4** and amine **10** to undergo elimination of methanol leading to **5** might depend on their acidity. The acidity of the carbamate proton in **4** is the dominant influence to the elimination reaction. Deprotection of **11** with 5% sodium hydroxide solution at room temperature afforded 5-hydroxy-2-( $\beta$ -D-ribofuranosyl)pyridine (**12**) in 64% yield, the structure of which was confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  nmr and mass spectrum.

In order to determine the anomeric configuration, the isopropylidene acetal **13** was synthesized by using ethyl orthoformate in the presence of *p*-toluenesulfonic acid. The  $^1\text{H}$  nmr spectrum showed two singlets at  $\delta$  1.35 and 1.62 with  $\Delta\delta = 0.27$  ppm: a value of less than 0.10 ppm would be expected in the case of an  $\alpha$  anomer [9]. This showed that the  $\beta$  ribofuranoside configuration had been preserved during the reaction sequence.

## EXPERIMENTAL

Melting points were determined on a Yanagimoto apparatus and are uncorrected. Infrared (ir) spectra were measured with a JASCO IRA-1 spectrometer. The  $^1\text{H}$  nmr spectra were measured with a JNM-GX-270 spectrometer, with tetramethylsilane as an internal standard. The  $^{13}\text{C}$  nmr spectra were recorded on a JEOL JNM-FX-100 Fourier transform spectrometer operating at 25.00 MHz, with tetramethylsilane as an internal standard. The uv spectra were obtained on a JASCO UVIDE-610 Spectrophotometer. Optical rotation was determined using a JASCO DIP 181 Digital Polarimeter with a 10 cm, 1 ml microcell. Elemental analysis 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<sub>254</sub> (Merck). The compounds were detected with a uv light (254 nm). Column chromatography was performed on silica gel C-200 (74-149  $\mu\text{m}$ , Wakogel).

Ethyl 5-(2,3,5-Tri-*O*-benzoyl- $\beta$ - and - $\alpha$ -D-ribofuranosyl)-2-furfurylcarbamate (**2** and **3**).

Method A.

A solution of **1** (384 mg, 0.75 mmole) and ethyl methoxymethylcarbamate 300 mg (2.7 mmoles) in benzene (10 ml) containing *p*-toluenesulfonic acid (71 mg, 0.38 mmole) was heated under reflux for 3 hours. The reaction mixture was neutralized with a saturated sodium bicarbonate solution and then extracted with chloroform (3  $\times$  50 ml). The extracts were combined, washed with water, dried over magnesium sulfate, and evaporated *in vacuo* to a syrup. Tlc (chloroform-methanol 100:1) showed that the syrup contained two major components (Rf 0.42 and 0.38). The mixture was chromatographed over a column of silica gel with chloroform-benzene (1:1) as the eluent. The first compound eluted, **2** (164 mg, 39%, corresponding to Rf 0.42 on tlc), was obtained as a colorless syrup;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.24 (t, 3,  $\text{CH}_2\text{CH}_3$ ,  $J = 7.1$  Hz), 4.11 (q, 2,  $\text{CH}_2\text{CH}_3$ ,  $J = 7.1$  Hz), 4.19 (d, 2,  $\text{CH}_2\text{N}$ ,  $J = 5.7$  Hz), 4.57 (dd, 1, H-5'a,  $J_{4,5'a} = 4.0$  Hz,  $J_{5'a,5'b} = 11.7$  Hz), 4.65-4.68 (m, 1, H-4'), 4.82 (dd, 1, H-5'b,  $J_{4,5'b} = 3.0$  Hz,  $J_{5'a,5'b} = 11.7$  Hz), 4.88-4.94 (br, 1, NH), 5.26 (d, 1, H-1',  $J_{1',2'} = 5.7$  Hz), 5.88 (t, 1, H-3',  $J_{2',3'} = J_{3',4'} = 5.7$  Hz), 5.95 (t, 1, H-2',  $J_{1',2'} = 5.7$  Hz), 6.16 (d, 1, H-3,  $J_{3,4} = 3.0$  Hz), 6.38 (d, 1, H-4,  $J_{3,4} = 3.0$  Hz), 7.34-8.15 (m, 15, Ar H);  $^{13}\text{C}$  nmr (deuteriochloroform):  $\delta$  14.51 ( $\text{CH}_3$ ), 37.91 ( $\text{CH}_2\text{N}$ ), 60.90 ( $\text{CH}_2\text{O}$ ), 64.18 (C-5'), 72.89, 73.95, 77.46, 79.97 (C-1', C-2', C-3', C-4), 107.82, 110.51 (C-3, C-4), 128.36-133.39 (Ar-C), 149.47, 153.10 (C-2, C-5), 156.32, 165.15, 165.33, 166.09 (C=O).

Anal. Calcd. for  $\text{C}_{34}\text{H}_{35}\text{NO}_{10} \cdot 1/2\text{H}_2\text{O}$ : C, 65.59; H, 5.18; N, 2.25. Found: C, 65.60; H, 5.12; N, 2.19.

Compound **3** was eluted as the second fraction (30 mg, 7.8%, corresponding to Rf 0.38 on tlc) as a colorless syrup. Due to the unstable and hygroscopic nature of this compound good elemental analysis could not be obtained;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.22 (t, 3,  $\text{CH}_2\text{CH}_3$ ,  $J = 7.0$  Hz), 4.03-4.23 (m, 4, 2  $\times$   $\text{CH}_2$ ), 4.56-4.85 (m, 4, H-4', H-5', NH), 5.53 (d, 1, H-1',  $J_{1',2'} = 4.7$  Hz), 5.86 (t, 1, H-3',  $J_{2',3'} = J_{3',4'} = 4.7$  Hz), 6.00 (t, 1, H-2',  $J_{1',2'} = J_{2',3'} = 4.7$  Hz), 6.15 (d, 1, H-4,  $J_{3,4} = 3.0$  Hz), 6.38 (d, 1, H-3,  $J_{3,4} = 3.0$  Hz), 7.29-8.12 (m, 15, Ar-H).

Method B.

To a solution of **1** (2.00 g, 3.9 mmoles) in benzene (50 ml) was cautiously added 2 ml of boron trifluoride etherate at 0.5°. Ethyl methoxymethyl carbamate (529 mg, 3.9 mmoles) in benzene (5 ml) was then added dropwise with stirring. The reaction mixture was stirred for 30 minutes at room temperature. The reaction mixture was neutralized with a saturated sodium bicarbonate solution and then extracted with chloroform (3  $\times$  100 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 chloroform-benzene (1:1) as the eluent. This afforded 2.0 g of **2** (91%) as a colorless syrup. Identification was confirmed by comparing ir and  $^1\text{H}$  nmr spectrum.

Electrolysis of (**2**).

Electrolysis Apparatus.

The electrolysis cell was a glassy carbon beaker (cathode electrode), 7.2 cm long in diameter and 6.5 cm high, fitted with a thermometer, and a magnetic stirrer. Anode electrode was platinum wire. Current was controlled by manually adjusting the applied voltage as required.

A solution of **2** (98 mg, 0.16 mmole) and ammonium bromide (50 mg) in methanol (20 ml) was electrolyzed at 20-25° for 50 minutes under a current of 0.01 amp at 14 V. The reaction mixture was neutralized with a saturated sodium bicarbonate solution and then extracted with chloroform (3  $\times$  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 silica gel column with chloroform as the eluent. This afforded 108 mg of ethyl 5-(2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)-2,5-dimethoxy-2,5-dihydro-2-furfurylcarbamate (**4**) (100%) as a colorless syrup;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.00-1.30 (m, 3,  $\text{CH}_3$ ), 3.00-3.36 (m, 6,  $\text{OCH}_3$ ), 3.38-3.36 (m, 2,  $\text{CH}_2\text{N}$ ), 3.78-4.20 (m, 2,  $\text{CH}_2\text{O}$ ), 4.28-4.80 (m, 5, H-1', H-4', H-5', NH), 5.50-6.20 (m, 4, H-3, H-4, H-2', H-3'), 7.00-8.00 (m, 15, Ar-H);  $^{13}\text{C}$  nmr (deuteriochloroform):  $\delta$  14.63 ( $\text{CH}_3$ ), 50.01, 50.14 ( $\text{CH}_2\text{N}$ ), 60.96 ( $\text{CH}_2\text{O}$ ), 63.89, 64.12 (C-5'), 72.49, 72.60; 72.72, 72.84, 78.80, 79.39 (C-1', C-2', C-3', C-4'), 108.99, 109.28, 109.58,

110.57 (C-3, C-4), 128.41-133.39 (C-2, C-5, Ar-C), 156.73, 165.00, 165.21, 166.09 (C=O).

*Anal.* Calcd. for  $C_{36}H_{37}NO_{12}$ : C, 63.99; H, 5.52; N, 2.07. Found: 63.57; H, 5.56; N, 2.43.

#### Reaction of **4** with Trifluoroacetic Acid.

To a solution of 120 mg of **4** in 5 ml of dichloromethane was added 0.1 ml of trifluoroacetic acid, and the resulting solution was stirred at room temperature for 10 minutes. The reaction mixture was neutralized with a saturated sodium bicarbonate solution and then extracted with chloroform (3 × 30 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 chloroform as the eluent. This afforded 90 mg of **5** (86.9%) as a colorless crystals: mp 90-91°. Identification was confirmed by comparing ir and <sup>1</sup>H nmr spectra with the product previously prepared by the reported procedure [4].

#### 5-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2-furfuryl alcohol (**6**).

To a solution of **5** (576 mg, 1.1 mmoles) in methanol (5 ml) was slowly added sodium borohydride (120 mg, 3.2 mmoles) in THF (5 ml) at 0° for 15 minutes. 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 of **6** (88%) as a colorless syrup; <sup>1</sup>H nmr (deuteriochloroform): δ 4.47 (s, 2, CH<sub>2</sub>OH), 4.59 (dd, 1, H-5'a, J<sub>4,5'a</sub> = 4.0 Hz, J<sub>5'a,5'b</sub> = 11.7 Hz), 4.66-4.70 (m, 1, H-4'), 4.81 (dd, 1, H-5'b, J<sub>4,5'b</sub> = 3.4 Hz, J<sub>5'a,5'b</sub> = 11.7 Hz), 5.28 (d, 1, H-1', J<sub>1,2'</sub> = 5.7 Hz), 5.89 (t, 1, H-3, J<sub>2,3'</sub> = J<sub>3,4'</sub> = 5.7 Hz), 5.97 (t, 1, H-2', J<sub>1,2'</sub> = J<sub>2,3'</sub> = 5.7 Hz), 6.22 (d, 1, H-4, J<sub>3,4</sub> = 3.0 Hz), 6.40 (d, 1, H-3, J<sub>3,4</sub> = 3.0 Hz), 7.33-8.16 (m, 15, Ar-H); ir (chloroform): 3600 cm<sup>-1</sup> (OH), 1730 cm<sup>-1</sup> (C=O).

*Anal.* Calcd. for  $C_{31}H_{26}O_8 \cdot H_2O$ : C, 66.42; H, 5.04. Found: C, 66.52; H, 4.76.

#### 5-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2-furfuryl chloride (**7**).

A solution of **6** (241 mg, 0.44 mmole), pyridine (0.1 ml) and thionyl chloride (210 mg, 10 mmoles) in dry benzene (10 ml) was heated at 40° for 3 hours. Water was added, and the mixture was extracted with chloroform (3 × 50 ml). The extracts were combined, 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 217 mg of **7** (87%) as a colorless syrup; <sup>1</sup>H nmr (deuteriochloroform): δ 4.45 (s, 2, CH<sub>2</sub>Cl), 4.59 (dd, 1, H-5'a, J<sub>4,5'a</sub> = 4.0 Hz, J<sub>5'a,5'b</sub> = 11.7 Hz), 4.66-4.70 (m, 1, H-4'), 4.89 (dd, 1, H-5'b, J<sub>4,5'b</sub> = 3.2 Hz, J<sub>5'a,5'b</sub> = 11.7 Hz), 5.29 (d, 1, H-1', J<sub>1,2'</sub> = 5.7 Hz), 5.88 (t, 1, H-3', J<sub>2,3'</sub> = J<sub>3,4'</sub> = 5.7 Hz), 5.95 (t, 1, H-2', J<sub>1,2'</sub> = J<sub>2,3'</sub> = 5.7 Hz), 6.31 (d, 1, H-4, J<sub>3,4</sub> = 3.3 Hz), 6.41 (d, 1, H-3, J<sub>3,4</sub> = 3.3 Hz), 7.33-8.14 (m, 15, Ar-H). Although this compound was homogeneous by tlc, we were unable to obtain proper microanalytical data.

#### 5-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2-furfuryl azide (**8**).

To a stirred solution of **7** (850 mg, 1.5 mmoles) in THF (20 ml) and 18-crown-6 (21 mg) was added sodium azide (300 mg, 4.6 mmoles) in water (3 ml). The mixture was stirred for 12 hours at room temperature and then was heated at 65° for 3 hours. Water was added, and then the mixture was extracted with chloroform (3 × 30 ml). The dried chloroform solution on evaporation afforded a syrup. The syrup was chromatographed over a column of silica gel with benzene as the eluent. This afforded 778 mg of **8** (90%) as a white solid, mp 99-100°; <sup>1</sup>H nmr (deuteriochloroform): δ 4.17 (s, 2, CH<sub>2</sub>N<sub>3</sub>), 4.58 (dd, 1, H-5', J<sub>4,5'a</sub> = 4.0, J<sub>5'a,5'b</sub> = 11.8 Hz), 4.66-4.70 (m, 1, H-4'), 4.79 (dd, 1, H-5'b, J<sub>4,5'b</sub> = 3.4 Hz, J<sub>5'a,5'b</sub> = 11.8 Hz), 5.29 (d, 1, H-1', J<sub>1,2'</sub> = 5.7 Hz), 5.88 (t, 1, H-3', J<sub>2,3'</sub> = J<sub>3,4'</sub> = 5.7 Hz), 5.95 (t, 1, H-2', J<sub>1,2'</sub> = J<sub>2,3'</sub> = 5.7 Hz), 6.28 (d, 1, H-4, J<sub>3,4</sub> = 3.4 Hz), 6.34 (d, 1, H-3, J<sub>3,4</sub> = 3.4 Hz), 7.33-8.13 (m, 15, Ar-H); ir (chloroform): 2080 cm<sup>-1</sup> (N<sub>3</sub>), 1730 cm<sup>-1</sup> (C=O).

*Anal.* Calcd. for  $C_{31}H_{25}N_3O_8$ : C, 65.60; H, 4.44; N, 7.40. Found: C, 65.66; H, 4.51; N, 7.28.

#### 5-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2,5-dimethoxy-2,5-dihydro-2-furfuryl azide (**9**).

To a solution of **3** (262 mg, 0.46 mmole) in methanol (40 ml) was added 3.0 g of sodium bicarbonate. The suspension was cooled in an ice bath, and bromine in methanol was added dropwise with stirring. The bromine had disappeared after 20-30 seconds, and the reaction mixture was perfectly white. When the color no longer disappeared and tlc analysis indicated complete disappearance of starting material, the mixture was poured into water and extracted with chloroform (3 × 50 ml), and the extracts were combined, washed with water, dried over magnesium sulfate, and evaporated. The yield of the crude isomeric mixture **9**, was 266 mg (92%) of a colorless foam which was chromatographically inseparable; <sup>1</sup>H nmr (deuteriochloroform): δ 3.13-3.85 (m, 8, CH<sub>2</sub>N<sub>3</sub>, 2 × OCH<sub>3</sub>), 4.34-4.80 (m, 4, H-1', H-4', H-5'), 5.63-5.97 (m, 2, H-2', H-3'), 6.00-6.29 (m, 2, H-3, H-4), 7.25-8.12 (m, 15, Ar-H); ir (chloroform): 2100 cm<sup>-1</sup> (N<sub>3</sub>), 1730 cm<sup>-1</sup> (C=O).

*Anal.* Calcd. for  $C_{33}H_{31}N_3O_{10}$ : C, 62.95; H, 4.96; N, 6.67. Found: C, 63.06; H, 5.03; N, 6.48.

#### 5-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2,5-dimethoxy-2,5-dihydro-2-furfurylamine (**10**).

To a solution of **9** (264 mg, 0.42 mmole) in acetone (10 ml) was slowly added concentrated hydrochloric acid (0.5 ml) and zinc dust (320 mg) at 0°. The reaction mixture was stirred at room temperature for 1 hour. The resulting mixture was filtered, and the filtrate was extracted with chloroform (3 × 10 ml). The combined chloroform solution was dried over magnesium sulfate and evaporated *in vacuo* to a syrup which was purified by preparative tlc with chloroform-methanol (25:1) as the eluent after three elutions. This afforded 182 mg (80.4%) of **10** as a colorless syrup; <sup>1</sup>H nmr (deuteriochloroform): δ 3.10-3.38 (m, 8, CH<sub>2</sub>N, 2 × OCH<sub>3</sub>), 4.32-4.79 (m, 4, H-1', H-4', H-5'), 5.63-6.40 (m, 4, H-3, H-4, H-2', H-3'), 7.24-8.11 (m, 15, Ar-H); ir (chloroform): 3600, 3550-3300 cm<sup>-1</sup> (NH<sub>2</sub>), 1720 cm<sup>-1</sup> (C=O).

*Anal.* Calcd. for  $C_{33}H_{33}NO_{10} \cdot 5/4H_2O$ : C, 63.30; H, 5.72; N, 2.24. Found: C, 63.23; H, 5.38; N, 2.27.

#### 5-Hydroxy-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridine (**11**).

To a solution of **10** (739 mg, 1.2 mmoles) in methanol (15 ml) was added 0.5 ml of concentrated hydrochloric acid at 0° for 1 hour. The reaction mixture was neutralized with a saturated sodium bicarbonate solution and then extracted with chloroform 3 × 30 ml). The extracts were combined, washed with water, dried over magnesium sulfate, and evaporated *in vacuo* to a syrup. Tlc (chloroform-methanol, 100:3) showed that the syrup contained two major components (Rf 0.69 and 0.24), the mixture was chromatographed over a column of silica gel with chloroform-methanol (9:1) as the eluent. The first compound eluted, **5** (27 mg, 6.3%, corresponding to Rf 0.69 on tlc) was obtained as a syrup. Identity was confirmed by comparing ir and <sup>1</sup>H nmr spectra with the product previously prepared by the reported procedure [4].

Compound **11** was eluted as the second fraction (331 mg, 78%, corresponding to Rf 0.24 on tlc) as a colorless syrup; <sup>1</sup>H nmr (deuteriochloroform): δ 4.64 (dd, 1, H-5'a, J<sub>4,5'a</sub> = 4.4 Hz, J<sub>5'a,5'b</sub> = 11.8 Hz), 4.73-4.78 (m, 1, H-4'), 4.84 (dd, 1, H-5'b, J<sub>4,5'b</sub> = 3.4 Hz, J<sub>5'a,5'b</sub> = 11.8 Hz), 5.36 (d, 1, H-1', J<sub>1,2'</sub> = 4.0 Hz), 5.85-5.93 (m, 2, H-2', H-3'), 7.07 (dd, 1, H-4, J<sub>3,4</sub> = 8.1 Hz, J<sub>4,6</sub> = 1.7 Hz), 7.31-8.07 (m, 16, H-3, Ar-H), 8.15 (d, 1, H-6, J<sub>4,6</sub> = 1.7 Hz); <sup>13</sup>C nmr (deuteriochloroform): δ 64.35 (C-5'), 72.60, 76.58, 79.97, 83.43 (C-1', C-2', C-3', C-4'), 122.45 (C-4), 124.26 (C-3), 128.53-133.44 (Ar-C), 137.19 (C-6), 148.07 (C-2), 153.80 (C-5), 165.68, 166.62 (C=O); ms: m/e 539 (M<sup>+</sup>); ir (chloroform): 3300-3200 cm<sup>-1</sup> (OH), 1720 cm<sup>-1</sup> (C=O).

*Anal.* Calcd. for  $C_{31}H_{25}NO_8 \cdot 1/4H_2O$ : C, 68.44; H, 4.72; N, 2.57. Found: C, 68.49; H, 5.03; N, 2.50.

#### 5-Hydroxy-2-(β-D-ribofuranosyl)pyridine (**12**).

To a solution of **11** (35 mg, 0.065 mmole) in methanol (10 ml) was added 1.5 ml of 5% sodium hydroxide aqueous solution at 0° for 1 hour,

rendered neutral with acetic acid, and evaporated. The residue was chromatographed over a column of silica gel with chloroform-methanol (4:1) as the eluent. This afforded 9.4 mg of **12** (64%) as a colorless syrup;  $^1\text{H}$  nmr (perdeuteriomethanol):  $\delta$  3.70 (dd, 1, H-5'a,  $J_{4',5'a} = 3.8$  Hz,  $J_{5'a,5'b} = 12.3$  Hz), 3.85 (dd, 1, H-5'b,  $J_{4',5'b} = 3.0$  Hz,  $J_{5'a,5'b} = 12.3$  Hz), 3.98-4.02 (m, 1, H-4'), 4.04 (t, 1, H-2',  $J_{1',2'} = J_{2',3'} = 5.7$  Hz), 4.12 (t, 1, H-3',  $J_{2',3'} = J_{3',4'} = 5.7$  Hz), 4.74 (d, 1, H-1',  $J_{1',2'} = 5.7$  Hz), 7.21 (dd, 1, H-4,  $J_{3,4} = 8.4$  Hz,  $J_{4,6} = 2.7$  Hz), 7.37 (d, 1, H-3,  $J_{3,4} = 8.4$  Hz), 8.08 (br s, 1, H-6);  $^{13}\text{C}$  nmr (perdeuteriomethanol):  $\delta$  63.42 (C-5'), 72.54, 78.26; 85.82; 86.53 (C-1', C-2', C-3', C-4'), 124.38, 124.85 (C-3, C-4), 137.06 (C-6), 151.00 (C-2), 155.21 (C-5); ms:  $m/e$  227 ( $\text{M}^+$ );  $[\alpha]_D^{25} = -21.5^\circ$  (c 0.33, methanol).

Anal. Calcd. for  $\text{C}_{10}\text{H}_{13}\text{NO}_5 \cdot 9/10\text{H}_2\text{O}$ ; C, 49.34; H, 6.13; N, 5.75. Found: C, 49.68; H, 6.00; N, 5.24.

#### 5-Hydroxy-2-(2,3-O-isopropylidene- $\beta$ -D-ribofuranosyl)pyridine (**13**).

Ethyl orthoformate (0.1 ml, 0.6 mmole) was added to a well-stirred suspension of **12** (9.4 mg, 0.041 mmole) in acetone (1 ml) containing *p*-toluenesulfonic acid monohydrate (10 mg) and the mixture was allowed to stand at room temperature for 18 hours. The reaction mixture was neutralized with a sodium bicarbonate and the mixture was stirred for 15 minutes. The solid was collected by filtration and thoroughly washed with acetone. The filtrate was combined and evaporated *in vacuo* to a syrup which was purified by preparative tlc with chloroform-methanol (24:1) as the eluent, yield 86%, colorless syrup;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.35, 1.62 (each s, 3 each, isopropylidene  $\text{CH}_3$ ), 3.82 (dd, 1, H-5'a,  $J_{4',5'a} = 1.0$  Hz,  $J_{5'a,5'b} = 12.1$  Hz), 4.90 (dd, 1, H-5'b,  $J_{4',5'b} = 1.7$  Hz,  $J_{5'a,5'b} = 12.1$  Hz), 4.54 (apparent s, 1, H-4'), 4.71 (dd, 1, H-2',  $J_{1',2'} = 3.4$

Hz,  $J_{2',3'} = 6.1$  Hz), 5.00 (dd, 1, H-3',  $J_{2',3'} = 6.1$  Hz,  $J_{3',4'} = 1.7$  Hz), 5.06 (d, 1, H-1',  $J_{1',2'} = 3.4$  Hz), 7.16-7.12 (m, 2, H-3, H-4), 8.30 (br s, 1, H-6).

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