C-Nucleosides. Part 13.† Synthesis of 5-Nitro-2-(β-D-ribofuranosyl)furan

Isamu Maeba,* Kazuya Osaka, and Chihiro Ito
Faculty of Pharmacy, Meijo University, Tempaku-ku, Nagoya 468, Japan

The synthesis of 5-nitro-2-(β-D-ribofuranosyl)furan (**4**) from the glycosylfuran (**1**) is described. Treatment of compound (**1**) with acetyl nitrate in acetonitrile afforded compound (**2**) in quantitative yield. When compound (**2**) was treated with pyridine, acetic acid was lost from the molecule to afford the protected nitrofuran (**3**) in 95% yield. Deprotection of compound (**3**) with methanolic sodium hydroxide afforded three products, nitrofuran (**4**) and the unexpected spiro compounds (**5a, b**) in 29, 4, and 9% yield, respectively. The configuration of the spiro-carbon in (**5a**) and (**5b**) was established by NOE experiments.

A variety of nitroheterocyclic systems have been demonstrated to possess useful therapeutic properties. Nitrofurans, for example, have been extensively investigated and several are of clinical use in man.[1] These reports prompted us to investigate the synthesis of nitrofuran substituted *C*-nucleosides in an effort to obtain pharmacologically useful agents.

Nitration of 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)furan (**1**)[2] with acetyl nitrate in acetonitrile 0 °C gave compound (**2**) as a mixture of isomers in quantitative yield. These isomers could not be separated by preparative TLC (PLC), but the mixture was entirely satisfactory for the next step. Thus, treatment of compound (**2**) with pyridine in methanol at 50 °C led to loss of acetic acid to afford 5-nitro-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)furan (**3**) in 95% yield. The removal of the sugar protecting groups in compound (**3**) was readily accomplished with methanolic sodium hydroxide to afford 5-nitro-2-(β-D-ribofuranosyl)furan (**4**) in 29% yield, accompanied by the unexpected (1*R*,2*R*,5*R*,6*R*,7*R*)- and (1*R*,2*S*,5*R*,6*R*,7*R*)-6,7-dihydroxy-3,8-dioxabicyclo[3.2.1]-octane-2-spiro-5′-furan-2′-ones (**5a**) and (**5b**) in 4% and 9% yield, respectively. Extending the reaction time decreased the yield of the spiro compounds (**5a, b**). On the other hand, treatment of compound (**3**) with sodium carbonate in dimethyl sulphoxide at room temperature afforded the furan derivative (**6**) resulting from the elimination of two benzoyloxy groups.

In order to determine the anomeric configuration of the nitrofuran (**4**), the isopropylidene acetal (**7**) was synthesized using *p*-toluenesulphonic acid (PTSA) in acetone. Its ^{1}H NMR spectrum showed two singlets at δ 1.38 and 1.60 (Δδ = 0.22 ppm: a value of less than 0.10 ppm would be expected in the case of an α anomer[3]). The proton on C-4′ showed a quartet, and the absorption of 3′-H was well resolved, the coupling of 3′-H and 4′-H being 4.7 Hz. In α anomers this coupling constant should be zero, resulting in an apparent triplet for 4′-H.[4] From the ^{13}C NMR spectrum, it was observed that the shifts for the three carbons of the 2,3-*O*-isopropylidene group of (**7**) at 25.39, 27.38, and 115.08 ppm clearly appear in the range expected for the β anomer (25.5 ± 0.2, 27.5 ± 0.2, and 114.5 ± 0.6).[5] This showed that the β-ribofuranoside configuration had been preserved during the reaction sequence. The spiro structures of (**5a**) and (**5b**) were established by the ^{1}H NMR splitting pattern[6] shown by the hydrogens at positions 1, 7, 5, and 6. A model indicates that the dihedral angle between the vicinal hydrogens at positions 1 and 7 and at positions 5 and 6 is approximately 90°. The observed values, $J_{1,7} = J_{5,6} = 0$ Hz, provide definite evidence for the *trans* configuration. The configuration at C-2 was also established by nuclear Overhauser effect (NOE) experiments. Irradiation of the olefinic proton (δ 7.47, 4′-H) in (**5a**) gave a 4.0% enhancement of the signal at δ 4.51 assignable to 7-H. Irradiation of the olefinic proton (δ 8.09, 4′-H) in (**5b**) gave a 4.0% enhancement of the signal at δ 4.03 assignable to 4-H$_a$. These data indicate that the configurations of (**5a**) and (**5b**) are 2*R* and 2*S*, respectively. The 4′-H signal of (**5b**) at δ 8.09 occurs at lower field than that of (**5a**) at δ 7.47. This chemical shift difference can be attributed to the deshielding effect of a sugar oxygen atom in the chair conformation (dioxane ring) of the 2*S*-isomer (**5b**). The ratio of spiro compounds (**5a**) and (**5b**) was approximately 1:2. Attempted epimerization of the 2*R* spiro compound (**5a**) to the 2*S* isomer with 90% trifluoroacetic acid[7] failed. Treatment of compound (**4**) with methanolic sodium hydroxide did not afford the spiro compounds (**5a, b**). However, treatment of the acetonide (**7**) with methanolic sodium hydroxide afforded the corresponding spiro compounds (**8a**) and (**8b**). A plausible explanation for the formation of (**5a**) and (**5b**) involves nucleophilic attack by 5′-OH on the carbon atom at position 2 of the partially benzoylated form of (**4**) with subsequent formation of spiro ring (**I**) which is then attacked by hydroxide to give (**II**). Proton transfer from a hydroxy group of (**II**) and loss of $HN(OH)_2$ would give the spiro compounds (**5a, b**) (Scheme 2).

Treatment of (**5a**) with ammonia in dioxane at room temperature gave a mixture of the epimers of pyrrolinone (**9**), found to be identical with the product prepared previously by the reported procedure.[7]

Experimental

M.p.s were determined on a Yanagimoto apparatus and are uncorrected. Mass spectra were obtained on Hitachi M-52 or M-80 spectrometers. ^{1}H NMR spectra were measured with a JNM-GX-270 spectrometer, with tetramethylsilane as an 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. Elemental analyses were determined by the analytical center of this faculty. Analytical thin-layer chromatography (TLC) was performed on glass plates coated with a 0.5 mm layer of silica gel GF_{254} (Merck). The compounds were detected by UV light (254 nm). Column chromatography was performed on silica gel C-200 (74–149 μm, Wakogel).

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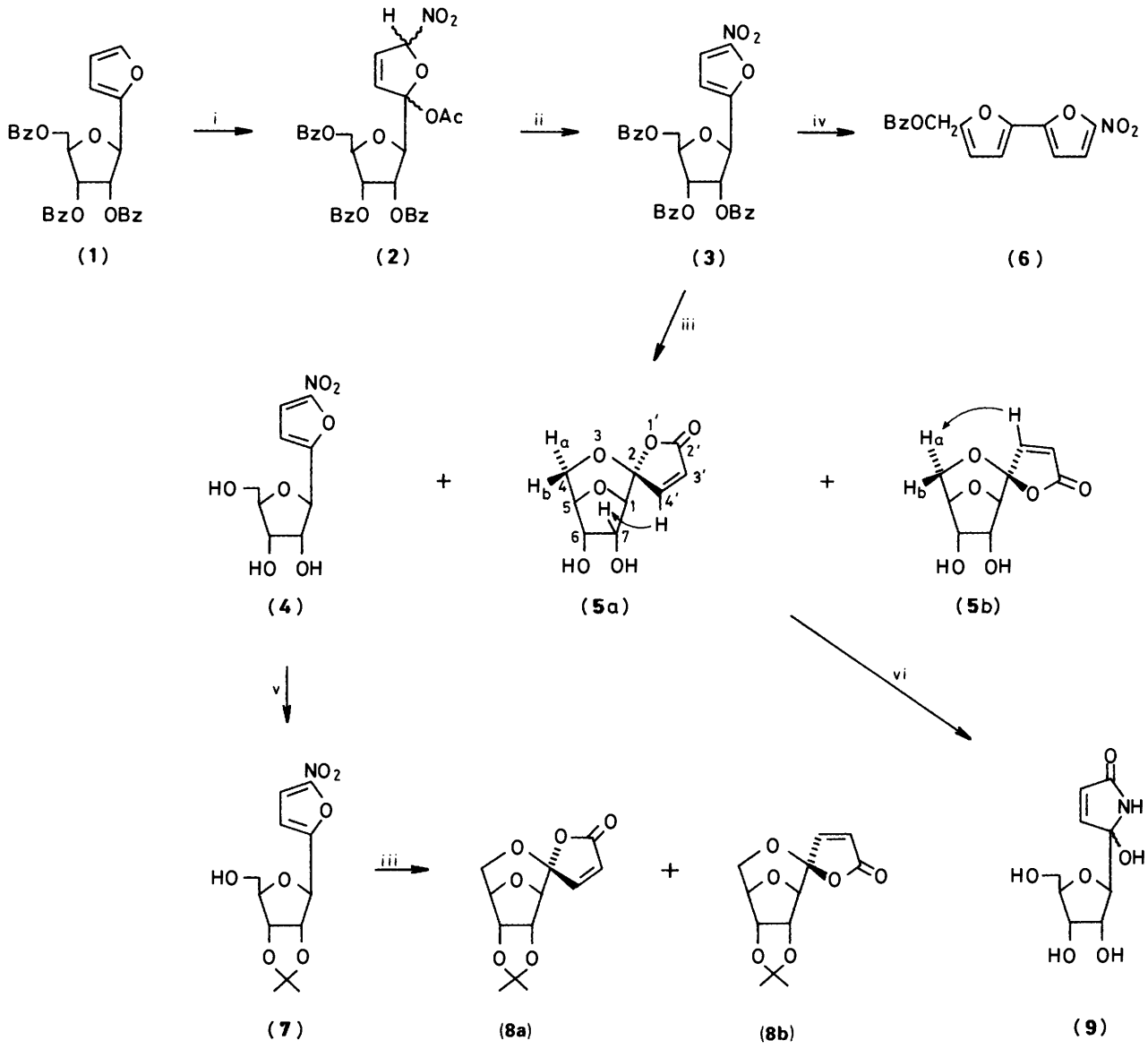
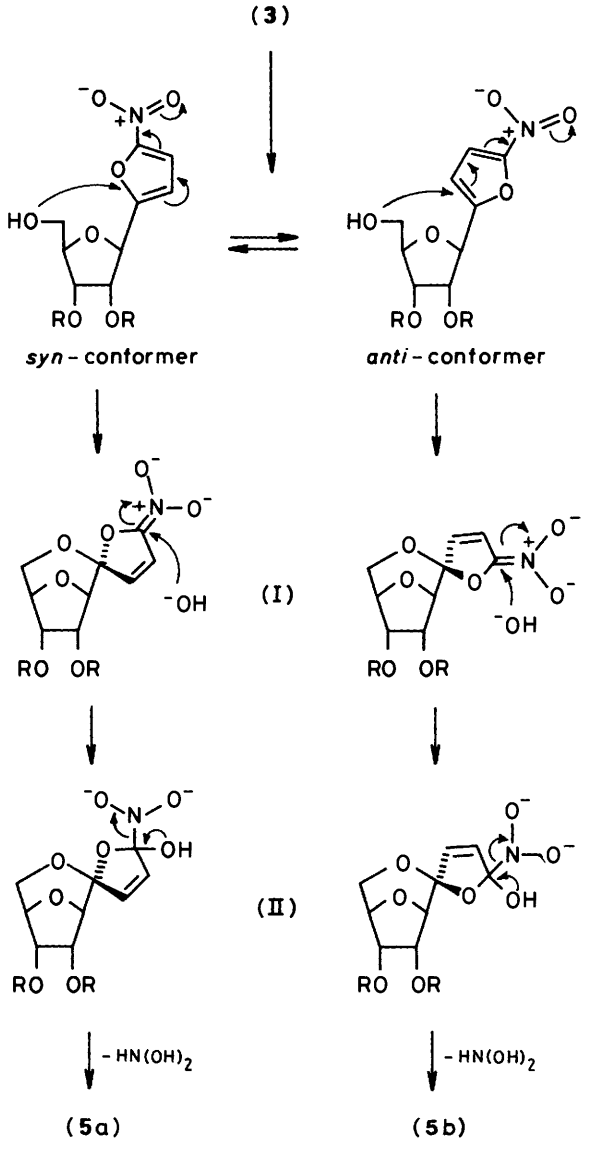


Scheme 1. *Reagents:* i, acetyl nitrate, acetonitrile; ii, pyridine, MeOH; iii, 5% NaOH–MeOH; iv, Na_2CO_3, DMSO; v, PTSA, acetone; vi, NH_3, dioxane.

2-*Acetoxy*-5-*nitro*-2-(2,3,5-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)-2,5-*dihydrofuran* (**2**).—Acetyl nitrate [prepared from Ac_2O (10 ml) and conc. HNO_3 (sp. gr. 1.50, 1 ml) at 0 °C] was added to a solution of the glycosylfuran (**1**) (594 mg, 1.2 mmol) in acetonitrile (10 ml) at 0 °C. After 3 h, the reaction mixture was poured into ice water, then neutralized with aqueous sodium hydrogen carbonate and extracted with chloroform (3 × 30 ml). The extracts were combined, washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to afford a syrup, which was chromatographed over a column of silica gel with chloroform as eluant to give the β-*isomeric mixture* (**2**) (715 mg, quantitative yield) as a yellow syrup; the isomers were chromatographically inseparable. Due to the unstable nature of this compound, good analysis could not be obtained; $\delta_H(CDCl_3$, partial) 1.93, 1.99, 2.02, 2.04 (3 H each, s, Me).

5-*Nitro*-2-(2,3,5-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)*furan* (**3**).—To a solution of compound (**2**) (471 mg, 0.8 mmol) in methanol (20 ml) at 0 °C was added pyridine (3 ml) during 10 min. The mixture was stirred at 50 °C for 5 h, and then the solvent was evaporated under reduced pressure. The resulting syrup was chromatographed over a column of silica gel with chloroform as eluant, to give the *title compound* (**3**) (402 mg, 95%) as a yellow syrup (Found: C, 64.14; H, 4.34; N, 2.39. $C_{30}H_{23}NO_{10}\cdot 0.2H_2O$ requires C, 64.21; H, 4.20, N, 2.50%); $\delta_H(CDCl_3)$ 4.64 (1 H, dd, *J* 3.7 and 11.8 Hz, 5′-H_a), 4.77 (1 H, q, 4′-H), 4.80 (1 H, dd, *J* 3.0 and 11.8 Hz, 5′-H_b), 5.33 (1 H, d, *J* 5.7 Hz, 1′-H), 5.86 (1 H, t, *J* 5.7 Hz, 2′-H or 3′-H), 5.91 (1 H, t, 2′-H or 3′-H), 6.66 (1 H, d, *J* 3.7 Hz, 3-H), 7.23 (1 H, d, *J* 3.7 Hz, 4-H), and 7.35–8.13 (15 H, m, ArH); δ_C ($CDCl_3$) 63.65 (C-5′), 72.54, 74.47, 76.46, 80.79 (C-1′, -2′, -3′, and -4′), 105.36, 111.85 (C-3 and -4), 128.53–133.68 (Ar-C), 152.50, 153.80 (C-2 and -5), 165.15, 165.32, and 166.21 (C=O); *m/z* 557 (M^+, 58%).

5-*Nitro*-2-(β-D-*ribofuranosyl*)*furan* (**4**) *and* (1R,2R,5R,6R,-7R)- *and* (1R,2S,5R,6R,7R)-6,7-*Dihydroxy*-3,8-*dioxabicyclo*-[3.2.1]*octane*-2-*spiro*-5′-*furan*-2′-*one* (**5a**) *and* (**5b**).—To a solution of the nitrofuran (**3**) (466 mg, 0.8 mmol) in methanol (11 ml) was added 5% aqueous NaOH (4 ml) at 0 °C during 35 min, then the mixture was rendered neutral with acetic acid and evaporated. TLC (chloroform–methanol, 9:1) showed that the light yellow syrup contained three major



Scheme 2. R = Bz or H.

components (R_F 0.24, 0.30, and 0.40). The mixture was separated by preparative TLC (PLC) with chloroform–methanol as developer (× 3).

Compound (**4**) (59 mg, 29%); R_F 0.24; yellow syrup (Found: M^+, 245.0507. $C_9H_{11}NO_7$ requires M, 245.0504); $\delta_H(CD_3OD)$ 3.66 (1 H, dd, J 4.9 and 12 Hz, 5′-H_a), 3.76 (1 H, dd, J 3.7 and 12 Hz, 5′-H_b), 3.98 (1 H, q, 4′-H), 4.11 (1 H, t, J 5.3 Hz, 2′-H or 3′-H), 4.25 (1 H, t, 2′-H or 3′-H), 4.81 (1 H, d, J 5.3 Hz, 1′-H), 6.77 (1 H, d, J 3.7 Hz, 3-H), and 7.41 (1 H, d, J 3.7 Hz, 4-H); $\delta_C(CD_3OD)$ 63.30 (C-5′), 72.78, 76.23, 79.21, 86.47 (C-1′, -2′, -3′, and -4′), 112.38, 113.38 (C-3 and -4), and 153.57, 158.31 (C-2 and -5); m/z 245 (M^+, 39%).

Compound (**5a**) (7 mg, 4%); R_F 0.30; m.p. 178–179 °C (Found: C, 50.62; H, 4.55. $C_9H_{10}O_6$ requires C, 50.47; H, 4.71%); $\delta_H(CD_3OD)$ 3.73 (1 H, d, J 11.1 Hz, 4-H_b), 3.93 (1 H, s, 1-H), 4.13, (1 H, dd, J 2.0 and 11.1 Hz, 4-H_a), 4.18 (1 H, apparent s, 5-H), 4.45 (1 H, d, J 6.4 Hz, 6-H), 4.51 (1 H, d, J 6.4 Hz, 7-H), 6.34 (1 H, d, J 5.7 Hz, 3′-H), and 7.47 (1 H, d, J 5.7 Hz, 4′-H); $\delta_C(CD_3OD)$ 67.75 (C-4) 72.72, 73.83, 83.95, 89.05 (C-1, -5, -6, and -7), 106.30 (C-2), 126.66 (C-3′), 152.34 (C-4′), and 171.53 (C=O).

Compound (**5b**) (16 mg, 9%); R_F 0.40; m.p. 213–215 °C (Found: C, 50.53; H, 4.66%); $\delta_H(CD_3OD)$ 3.82 (1 H, d, J 11.1 Hz, 4-H_b), 3.92 (1 H, s, 1-H), 4.03 (1 H, dd, J 2.4 and 11.1 Hz, 4-H_a), 4.18 (1 H, apparent s, 5-H), 4.39 (1 H, d, J 6.4 Hz, 6-H), 4.59 (1 H, d, J 6.4 Hz, 7-H), 6.30 (1 H, d, J 5.7 Hz, 3′-H), and 8.09 (1 H, d, J 5.7 Hz, 4′-H); $\delta_C(CD_3OD)$ 68.62 (C-4), 73.07, 74.42, 84.01, 86.17 (C-1, -5, -6, and -7), 104.66 (C-2), 129.17 (C-3′), 153.75 (C-4′), and 171.00 (C=O).

5-Nitro-2-[5′-(benzoyloxymethyl)furan-2′-yl]furan (**6**).—A solution of the protected nitrofuran (**3**) (20 mg, 0.04 mmol) in dimethylsulphoxide (2 ml) containing sodium carbonate (25 mg) was stirred at room temperature for 3 days. Water was added, and the mixture was extracted with ethyl acetate (3 × 10 ml). The dried extracts, on evaporation, afforded a yellow oil which was purified by PLC with chloroform–methanol (97:3) as developer, to give the *title compound* (**6**) (10 mg, 88%) as a yellow oil (Found: C, 61.26; H, 3.84; N, 4.39. $C_{16}H_{11}NO_6$ requires C, 61.34; H, 3.54; N, 4.47%) $\delta_H(CDCl_3)$ 5.36 (2 H, s, CH_2), 6.65 (1 H, d, J 3.5 Hz, 4′-H), 6.77 (1 H, d, J 3.9 Hz, 4-H), 6.94 (1 H, d, J 3.5 Hz, 3′-H), 7.41 (1 H, d, J 3.9 Hz, 3-H), and 7.42–8.08 (5 H, m, ArH); $\delta_C(CDCl_3)$ 107.93, 111.33, 113.20, 113.85 (C-3, -4, -3′, and -4′), 128.47–129.82 (Ar-C), 143.86, 144.15, 148.13, 152.11 (C-2, -5, -2′, and -5′), and 166.09 (C=O).

2-(2,3-O-Isopropylidene-β-D-ribofuranosyl)-5-nitrofuran (**7**).—To a solution of compound (**4**) (18 mg, 0.07 mmol) in acetone (1 ml) was added acetone containing PTSA monohydrate (12 mg) and the mixture was allowed to stand at room temperature for 2 h. The reaction mixture was neutralized with sodium hydrogen carbonate and stirred for 15 min. The solid was collected by filtration and thoroughly washed with acetone. The filtrate and washings were combined and evaporated under reduced pressure to give a syrup, which was purified by PLC with chloroform–methanol (97:3) as developer to give the *acetonide* (**7**) (12 mg, 57%) as a yellow syrup; $\delta_H(CDCl_3)$ 1.38, 1.60 (6 H, each s, isopropylidene Me), 3.75 (1 H, dd, J 4.2 and 12.1 Hz, 5′-H_a), 3.88 (1 H, dd, J 3.2 and 12.1 Hz, 5′-H_b), 4.27 (1 H, q, 4′-H), 4.83 (1 H, t, J 4.7 Hz, 3′-H), 4.89 (1 H, d, J 4.7 Hz, 1′-H), 4.94 (1 H, t, J 4.7 Hz, 2′-H), 6.62 (1 H, d, J 3.7 Hz, 3-H), and 7.28 (1 H, d, J 3.7 Hz, 4-H); $\delta_C(CDCl_3)$ 25.39, 27.38 (CH_3), 62.77 (C-5′), 77.05, 78.34, 81.85, 83.89 (C-1′, -2′, -3′, and -4′), 111.45, 111.97 (C-3 and -4), 115.08 (isopropylidene CMe_2), and 155.27 (C-2 and -5).

(1R,2R,5R,6R,7R)- and (1R,2S,5R,6R,7R)-6,7-(Isopropylidenedioxy)-3,8-dioxabicyclo[3.2.1]octane-2-spiro-5′-furan-2′-one (**8a**) *and* (**8b**).—The same procedure was used as for the reaction of (**3**) with methanolic sodium hydroxide.

Compound (**8a**) (16%); R_F 0.30 (chloroform–methanol, 99:1); m.p. 167–169 °C (Found: M^+, 254.0815. $C_{12}H_{14}O_6$ requires M, 254.0789); $\delta_H(CDCl_3)$ 1.37, 1.51 (6 H, each s, isopropylidene Me), 3.67, (1 H, d, J 11.1 Hz, 4-H), 4.06 (1 H, s, 1-H), 4.29 (1 H, dd, J 11.1 and 2.0 Hz, 4-H), 4.31 (1 H, d, J 2.0 Hz, 5-H), 4.85, 4.89 (2 H, each d, J 6.1 Hz, 6-H and 7-H), 6.28 (1 H, d, J 5.7 Hz, 3′-H), and 7.13 (1 H, d, J 5.7 Hz, 4′-H). The structure was confirmed by comparison with the IR and ^{1}H NMR spectra of the product prepared by the acetonization of (**5a**).

Compound (**8b**) (26%); R_F 0.36 (chloroform–methanol, 99:1); m.p. 181–182 °C (Found: M^+, 254.0787); $\delta_H(CDCl_3)$ 1.36, 1.49 (6 H, each s, isopropylidene Me), 3.83 (1 H, d, J 11.1 Hz, 4-H), 4.01 (1 H, dd, J 2.0 and 11.1 Hz, 4-H), 4.03 (1 H, s, 1-H), 4.29 (1 H, d, J 2.0 Hz, 5-H), 4.86, 5.11 (2 H, d, J 5.7 Hz, 6- and 7-H), 6.25 (1 H, d, J 5.7 Hz, 3′-H), and 7.87 (1 H, d, J 5.7 Hz, 4′-H).

(5R)- and (5S)-5-Hydroxy-5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-3-pyrrolin-2-one (**9**).—To a solution of spiro compound (**5a**) (50 mg, 0.2 mmol) in dioxane (10 ml) was added ammonia (2 ml) at 0 °C, and the mixture was allowed to stand at

room temperature for 2 h. Water was added, and the resultant mixture was neutralized with acetic acid. The mixture was extracted with chloroform (3 × 10 ml), washed with water, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed over a column of silica gel with chloroform–methanol (95:5) as the eluant to afford the *pyrrolinone* (**9**) (30 mg, 61%) as a colourless syrup; the structure was confirmed by comparing the IR and ^1H NMR spectra with the spectra of the products previously prepared by the reported procedure.

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