C-Nucleosides. Part 14.† Synthesis of (6*S*)- and (6*R*)-6-Methoxy-6-(β-D-ribofuranosyl)pyran-3(2*H*,6*H*)-one. Potential Chiral Synthons, and 6-(β-D-Ribofuranosyl)pyridazine-3-carboxamide, a 2-Azanicotinamide *C*-Nucleoside, from 6-Hydroxy-6-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyran-3(2*H*,6*H*)-one

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The synthesis of (6*S*)- and (6*R*)-6-methoxy-6-(β-D-ribofuranosyl)pyran-3(2*H*,6*H*)-one **5a** and **5b** is described. Acetonization of 6*S*-compound **5a** afforded two products, unexpected spiro compounds **6a** and **6b** in a 2:1 ratio. The configuration of the spiro-carbon in compounds **6a** and **6b** was established by NOE experiments. However, acetonization of the 6*R*-isomer **5b** afforded compounds **6a** and **6b** in a 7:1 ratio. On the basis of the ratio of spiro compounds, the stereochemistry of compounds **5a** and **5b** was assigned as 6*S* and 6*R*, respectively. Treatment of compound **1** with hydrazine in dioxane afforded the 6-hydroxymethylpyridazine **7**, a 2-azanicotinamide *C*-nucleoside, in 58% yield by a novel ring transformation. Krohnke oxidation converted the bromomethylpyridazine **8** into the aldehyde **10**. Oxidation of aldehyde **10** in ethanolic potassium hydroxide at −78 °C with ozone afforded the ester **13** in 65% yield. The ester reacted with aq. ammonia in methanol to produce the 2-azanicotinamide *C*-nucleoside **14**, the stereochemistry of which was determined by NOE experiments.

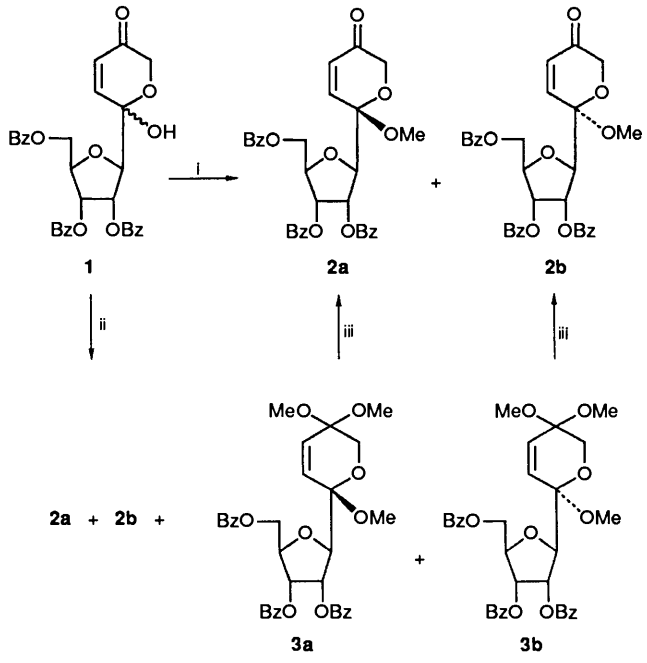
In the last decade, the direct formation of C–C bonds at the anomeric centre of carbohydrates has attracted considerable attention. One reason for such efforts is the biological importance of *C*-nucleosides.[1] Secondly, synthetic *C*-glycosyl compounds represent interesting chiral synthons, suitable for the synthesis of complex molecules, as they contain a large number of chiral centres and functional groups.[2] In a recent report from our laboratory, we described the preparation of a functionalized *C*-glycoside, 6-hydroxy-6-(2,3,5,-tri-*O*-benzoyl-β-D-ribofuranosyl)pyran-3(2*H*,6*H*)-one **1**, and its utilization in the synthesis of *C*-nucleosides.[3] One of the distinctive features of the synthesis of compound **1** involves stereocontrolled formation of a bis-cyclic ether skeleton. Since our interest in compound **1** continues, we now describe the synthesis of (6*S*)- and (6*R*)-6-methoxy-6-(β-D-ribofuranosyl)pyran-3(2*H*,6*H*)-one **5a** and **5b** and the assignment of stereochemistry at C-6, and the synthesis of 2-azanicotinamide *C*-nucleoside **14**, by a novel ring transformation of compound **1**.

Hemiacetal **1** was treated with trimethyl orthoformate in the presence of BF_3–diethyl ether at room temperature for 2 h. The reaction gave four products, (6*S*)- and (6*R*)-6-methoxy-6-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyran-3(2*H*,6*H*)-one **2a** and **2b** and (2*S*)- and (2*R*)-2,5,5-trimethoxy-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5,6-dihydro-2*H*-pyran **3a** and **3b**, in 3, 3, 25 and 39% yield, respectively. Two of these compounds **2a** and **2b** were faster moving on TLC than were **3a** and **3b**. Treatment of compound **1** with methyl iodide in the presence of silver(I) oxide afforded the epimeric mixture **2a** and **2b** in 93% yield and 1:1 ratio. Treatment of compounds **2a** and **2b** with trimethyl orthoformate in the presence of BF_3–diethyl ether afforded an epimeric mixture of compounds **3a** and **3b** in 61 and 65% yield, respectively. However, treatment of compounds **3a** and **3b** with toluene-*p*-sulphonic acid (PTSA) in 1,4-dioxane afforded the ketones **2a** and **2b** in 89 and 94% yield, respectively. Epimerization was not observed in this deacetalization experiment. Debenzoylation of compounds **1** and **2** could not be employed because of the sensitivity and ease of decomposition of the enone on contact with alkaline solution. Debenzoylation of compounds **3a** and **3b** with 5% aq. NaOH gave the deblocked compounds (2*S*)- and (2*R*)-2,5,5-trimethoxy-2-(β-D-ribofuranosyl)-5,6-dihydro-2*H*-pyran **4a** and **4b** in 93 and 90% yield, respectively. Deacetalization of compounds **4a** and **4b** with PTSA in 1,4-dioxane gave the desired compounds **5a** and **5b** in 91 and 88% yield, respectively.

In order to determine the anomeric configuration, we attempted to prepare the acetonide from compounds **5a** and **5b** with acetone–PTSA; however, acetonization of compound **5a** afforded unexpectedly (1*R*,2*S*,5*R*,6*R*,7*R*)- and (1*R*,2*R*,5*R*,6*R*,7*R*)-6,7-(isopropylidenedioxy)-3,8-dioxabicyclo-[3.2.1]octane-2-spiro-2′-pyran-5′(2′H,6′H)-one **6a** and **6b** in 37 and 19% yield, respectively. The ratio **6a**:**6b** was 2:1 by ^{1}H NMR spectroscopy. Acetonization of compound **5b** afforded the same two products, **6a** and **6b** in 42 and 7% yield, respectively. The ratio of products **6a** and **6b** was 7:1 by ^{1}H NMR spectroscopy. The spiro compounds **6a** and **6b** were not interconvertible by treatment with PTSA in acetone for 48 h. The formation of spiro compounds **6a** and **6b** showed that the β-ribofuranoside configuration had been preserved during the reaction sequence.

The spiro structure of compounds **6a** and **6b** was established by the ^{1}H NMR splitting pattern[4] shown by the hydrogens at positions 1, 7, 5 and 6. Molecular models indicated that the dihedral angle between the vicinal hydrogens at positions 1 and 7 and at positions 5 and 6 was *ca.* 90°. The observed values, $J_{1,7} = J_{5,6} = 0$ Hz, provided definite evidence for the *trans* configuration. The configuration at C-2 was established by nuclear Overhauser effect experiments. Irradiation of the olefinic proton (δ 7.63, 3′-H) in compound **6a** gave a 4% enhancement of the signal at δ 3.66 assignable to 4-H^a. Irradiation of the olefinic proton (δ 6.85, 3′-H) in compound **6b** gave 16% enhancement of the signal at δ 4.93 assignable to 7-H. These data indicated that the configuration of compounds **6a** and **6b** is 2*S* and 2*R*, respectively. The 3′-H signal of compound **6a** at δ 7.63 occurs at lower field than that of its isomer **6b** (δ 6.85). This chemical-shift difference can be attributed to the deshielding effect of a

† Part 13, J. Maeba, K. Osaka and C. Ito, *J. Chem. Soc., Perkin Trans. 1*, 1990, 515.



Scheme 1 *Reagents:* i, acetone, MeI, Ag_2O; ii, $HC(OMe)_3$, $BF_3{\cdot}Et_2O$; iii, 1,4-dioxane, PTSA

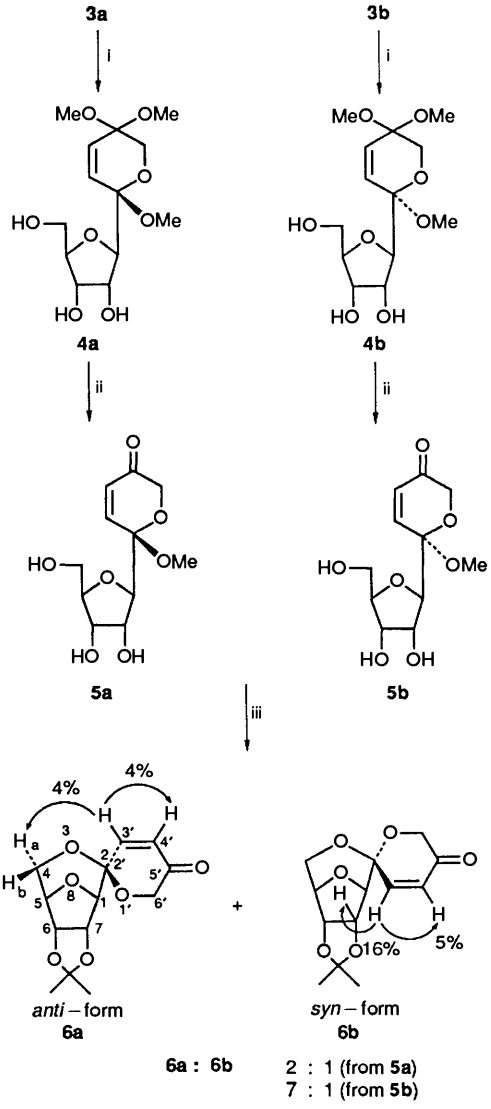
sugar oxygen atom in the chair conformation (dioxane ring) of the 2*S*-isomer **6a**.

Although Schemes 1 and 2 depict compounds **2a** and **b**, **3a** and **b**, **4a** and **b** and **5a** and **b** as each possessing an absolute configuration about the hydroxy carbon (pyran C) that connects the pyran and sugar moieties, this is merely illustrative since the actual stereochemical assignment (*S* or *R*) was not readily obtainable from available spectra data. Attempts to determine the configuration at the pyran glycosidic position by X-ray analysis were frustrated by our inability to obtain suitable crystals.

On the basis of the ratio of products **6a** and **6b**, the stereochemistry is assumed to be as follows: formation of the stable *anti*-form **6a** involves back-side attack by 5′-OH on the carbon atom bearing the leaving group at position 6 of compound **5b** with subsequent formation of the spiro ring and loss of methanol from substrate **5b**. However, the formation of spiro compound **6a** from substrate **5a** requires that a carboxonium ion be initially formed by loss of the OMe group at position 6, followed by attack of the 5′-OH group. Therefore, the stereochemistry of compounds **2a**, **3a**, **4a**, **5a** and **2b**, **3b**, **4b**, **5b** was assumed to be 6*S* and 6*R*, respectively.

Next, treatment of compound **1** with anhydrous hydrazine (1.5 mol equiv.) in 1,4-dioxane at room temperature for 30 min afforded 3-hydroxymethyl-6-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazine **7** in 58% yield. The structure assignment of product **7** was supported by the ^1H NMR spectrum, which exhibited a methylene proton singlet at δ 4.93. The ^{13}C NMR and mass spectra were consistent with structure **7**. Variation in the reaction temperature, reaction time and solvent did not improve the above yield. In order to change the hydroxymethyl group to a carboxamide group, we initially attempted oxidation of alcohol **7** to the corresponding aldehyde or carboxylic acid by a number of general methods. These attempts proved unsuccessful, leading to the formation of a large number of products. The ^1H NMR spectra of the products indicated loss of the ribose moiety.

In an alternative approach to aldehyde **10**, 3-bromomethyl-6-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazine **8** served as the starting material. Treatment of alcohol **7** with thionyl bromide in benzene at room temperature afforded the

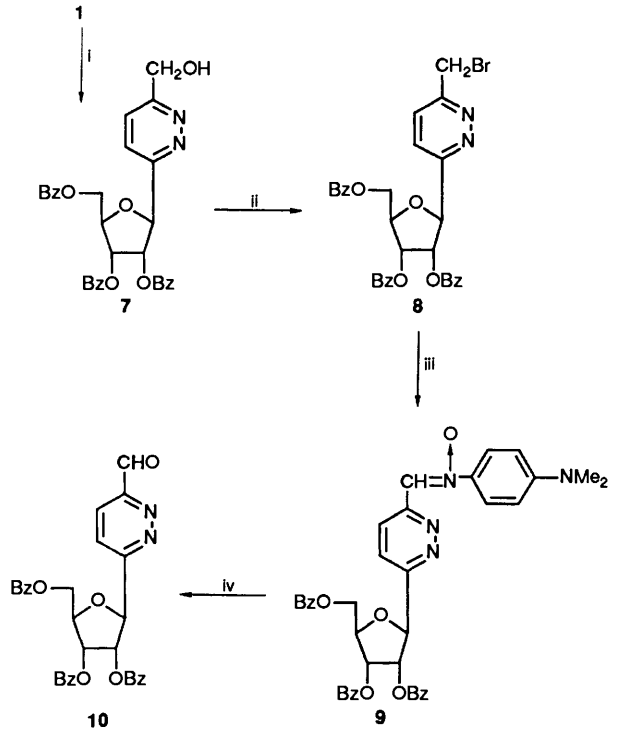


Scheme 2 *Reagents:* i, MeOH, NaOH; ii, 1,4-dioxane, PTSA; iii, acetone, PTSA

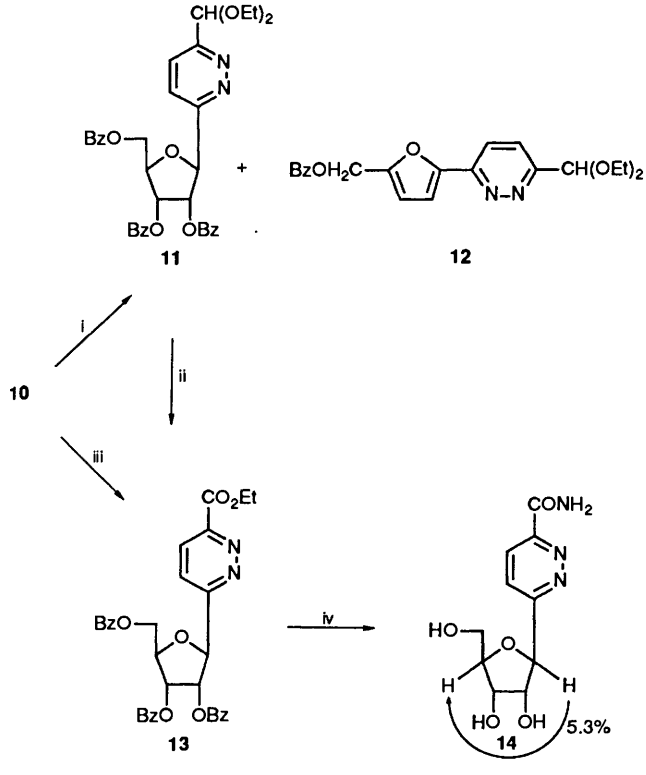
bromomethyl derivative **8** in 74% yield. While compound **8** gave satisfactory ^1H and ^{13}C NMR spectra, it appeared to be unstable. The Sommelet method[5] was unsuccessful for the conversion of bromide **8** into aldehyde **10**. Finally, we succeeded in the preparation of target aldehyde **10** by the method of Krohnke and Borner.[6] Reaction of the bromide **8** with pyridine gave the pyridinium salt, which was subsequently treated with *N*,*N*-dimethyl-*p*-nitrosoaniline and sodium carbonate to produce the nitrone **9** in 48% yield. Hydrolysis of compound **9** with 2.5 mol dm^{-3} sulphuric acid gave the 6-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazine-3-carboxaldehyde **10** in 79% yield (Scheme 3).

Deslongchamps *et al.* reported the oxidation of acetals by ozone at neutral pH to give the corresponding esters.[7] We attempted to apply this method to convert aldehyde **10** into an ester. The aldehyde **10** was treated with hydrochloric acid in ethanol to obtain two products, the desired acetal **11** (41%) and the furan derivative **12** (17% yield) resulting from elimination of two benzoyloxy groups. Oxidation of acetal **11** with ozone in methylene dichloride at −78 °C gave ethyl 6-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazine-3-carboxylate **13** in 8% yield. This low yield prompted us to investigate a second approach to ester **13**.

Djerassi and co-workers reported a one-step conversion of aldehydes into esters by oxidation with ozone in base.[8]



Scheme 3 *Reagents:* i, NH_2NH_2, 1,4-dioxane; ii, benzene, $SOBr_2$; iii, pyridine; then *N,N*-dimethyl-*p*-nitrosoaniline, Na_2CO_3; iv, 2.5 mol dm^{-3} H_2SO_4



Scheme 4 *Reagents:* i, HCl, EtOH; ii, CH_2Cl_2, ozone; iii, 10% KOH–EtOH, ozone; iv, NH_4OH

Compound **10** was dissolved in 10% ethanolic potassium hydroxide and cooled to −78 °C. Ozone was passed through the solution for 8 h to yield protected ester **13** (65% yield). The ester **13** reacted readily with aq. ammonia in methanol at room temperature to produce the desired 6-(β-D-ribofuranosyl)pyridazine-3-carboxamide **14** in 29% yield (Scheme 4). The stereochemistry of compound **14** was determined by an NOE experiment. Irradiation of the anomeric proton (δ 5.03, 1′-H) gave a 5.3% enhancement of the signal at δ 3.93 assignable to 4′-H. This showed that the β-ribofuranoside configuration had been preserved during the reaction sequence. Studies to evaluate the biological activity of the azanicotinamide **14** will be reported elsewhere.

Experimental

M.p.s were determined on a Yanagimoto apparatus and are uncorrected. Mass spectra were taken at low resolution on a Hitachi M-80 instrument by direct insertion at 70 eV, and at high resolution on a JMS-HX 110 instrument. ^1H NMR spectra were measured with a JNM-GX-270 or a GX-400 (JEOL) spectrometer, with tetramethylsilane as internal standard; *J*-values are given in Hz. ^{13}C NMR spectra were recorded on a JEOL JNM-FX-100 Fourier transform spectrometer operating at 25.00 MHz, with tetramethylsilane as internal standard. Elemental analyses were determined by the analytical centre of this faculty. Analytical TLC was performed on glass plates coated with a 0.5 mm layer of silica gel GF_{254} (Merck). The compounds were detected with UV light (254 nm). Column chromatography was performed on silica gel C-200 (74–149 μm, Wakogel).

(6S)- *and* (6R)-6-*Methoxy*-6-(2′,3′,5′-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)*pyran*-3(2H,6H)-*one* **2a** *and* **2b**.—To a suspension of Ag_2O (200 mg) and methyl iodide (1 cm^3) in acetone (1 cm^3) was added a solution of compound **1** (100 mg, 0.18 mmol) in acetone (2 cm^3) and the mixture was stirred at room temperature for 2 days. After the catalyst was removed by filtration, the solvent was evaporated off under reduced pressure. TLC [hexane–ethyl acetate (3:1)] showed that the syrup contained two major components (R_f 0.28 and 0.25). The mixture was separated by preparative TLC (PLC) with hexane–ethyl acetate (4:1) as developer (× 3).

Compound **2a**: (48 mg, 47%); R_f 0.28; foam (Found: C, 66.3; H, 5.3. $C_{32}H_{28}O_{10}\cdot 0.5H_2O$ requires C, 66.09; H, 5.03%); $\delta_H(CDCl_3)$ 3.32 (3 H, s, OMe), 4.32 (1 H, d, *J* 17.5, 2-H^a), 4.40 (1 H, d, 2-H^b), 4.49 (1 H, dd, *J* 5.0 and 12.1, 5′-H^a), 4.57 (1 H, d, *J* 3.0, 1′-H), 4.63 (1 H, m, 4′-H), 4.81 (1 H, dd, *J* 3.4 and 12.1, 5′-H^b), 5.78 (1 H, dd, *J* 5.4 and 7.4, 3′-H), 5.96 (1 H, dd, *J* 3.0 and 5.4, 2′-H), 6.28 (1 H, d, *J* 10.8, 4-H), 7.02 (1 H, d, *J* 10.8, 5-H) and 7.29–8.10 (15 H, m, ArH); $\delta_C(CDCl_3)$ 52.18 (OMe), 63.53 and 68.74 (C-2 and -5′), 72.31, 72.84, 79.62 and 85.41 (C-1′, -2′, -3′ and -4′), 96.24 (C-6), 128.47–133.39 (Ar-C and C-4), 146.37 (C-5), 165.21 and 166.09 (C=O) and 193.06 (C-3).

Compound **2b**: (47 mg, 46%); R_f 0.25; foam (Found: C, 66.7; H, 5.3. $C_{32}H_{28}O_{10}\cdot\frac{1}{3}H_2O$ requires C, 66.43; H, 5.00%); $\delta_H(CDCl_3)$ 3.46 (3 H, s, OMe), 4.14 (1 H, d, *J* 17.0, 2-H^a), 4.42 (1 H, d, 2-H^b), 4.52–4.63 (3 H, m, 1′- and 4′-H and 5′-H^a), 4.76 (1 H, dd, *J* 2.7 and 11.8, 5′-H^b), 5.74 (1 H, t, *J* 5.7, 3′-H), 5.86 (1 H, t, *J* 5.7, 2′-H), 6.15 (1 H, d, *J* 10.4, 4-H), 6.98 (1 H, d, *J* 10.4, 5-H) and 7.31–8.09 (15 H, m, ArH); $\delta_C(CDCl_3)$ 50.90 (OMe), 63.71 and 67.57 (C-2 and -5′), 71.67, 72.37, 80.09 and 81.49 (C-1′, -2′, -3′ and -4′), 96.35 (C-6), 128.41–133.37 (Ar–C and C-4), 144.03 (C-5), 164.92, 165.27 and 166.09 (C=O) and 193.23 (C-3).

Treatment of Compound **1** *with Trimethyl Orthoformate. The Formation of Compounds* **2a** *and* **b** *and* (2S)- *and* (2R)-2,5,5-*Trimethoxy*-2-(2′,3′,5′-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)-5,6-*dihydro*-2H-*pyran* **3a** *and* **3b**.—To a solution of compound **1** (314.7 mg, 0.56 mmol) in trimethyl orthoformate (2 cm^3) at 0 °C was added one drop of $BF_3\cdot Et_2O$. The reaction mixture was stirred at room temperature for 2 h, and then it was neutralized with aq. sodium hydrogen carbonate and extracted with chloroform (3 × 10 cm^3). The mixture was separated by PLC with chloroform as developer (× 3) to give compounds **2a** and **b**

(16.9 mg, 5.8%) [R_f 0.27; chloroform–methanol (99.1)] and the acetals **3a** and **b** (271.7 mg, 77.8%) [R_f 0.22; chloroform–methanol (99:1)]. Compounds **3a** and **3b** were separated by PLC with hexane–ethyl acetate (4:1) as developer (× 3).

Compound **3a**: (85.4 mg, 24.5%); R_f 0.27; foam (Found: C, 65.1; H, 5.6. $C_{34}H_{34}O_{11}$·0.5H_2O requires C, 65.06; H, 5.62%); $\delta_H(CDCl_3)$ 3.28 (6 H, s, OMe), 3.29 (3 H, s, OMe), 3.89 (2 H, br, 6-H), 4.39 (1 H, d, *J* 2.4, 1′-H), 4.49–4.63 (2 H, m, 4′-H and 5′-H^a), 4.74 (1 H, dd, *J* 3.4 and 11.1, 5′-H^b), 5.81 (1 H, dd, *J* 5.4 and 7.4, 3′-H), 5.93–5.96 (2 H, m, 2′- and 3-H), 6.23 (1 H, d, *J* 10.8, 4-H) and 7.25–8.08 (15 H, m, ArH); $\delta_C(CDCl_3)$ 49.00 and 51.48 (OMe), 64.09 and 67.10 (C-6 and -5′), 72.66, 73.48, 79.15 and 86.35 (C-1′, -2′, -3′ and -4′), 92.67 and 96.82 (C-5 and -2), 128.30–133.15 (Ar–C, C-4 and -3) and 165.15 (C=O).

Compound **3b**: (134.7 mg, 38.7%); R_f 0.23; foam (Found: C, 65.9; H, 5.5. $C_{34}H_{34}O_{11}$ requires C, 66.01; H, 5.54%); $\delta_H(CDCl_3)$ 3.21, 3.24 and 3.40 (9 H, each s, OMe), 3.81 (1 H, d, *J* 11.1, 6-H^a), 3.93 (1 H, d, *J* 11.1, 6-H^b), 4.51–4.58 (3 H, m, 1′- and 4′-H and 5′-H^a), 4.72 (1 H, dd, *J* 5.0 and 13.4, 5′-H^b), 5.70 (1 H, t, *J* 6.1, 3′-H), 5.82 (1 H, dd, *J* 4.0 and 6.1, 2′-H), 5.93 (1 H, d, *J* 10.8, 3-H), 6.16 (1 H, d, *J* 10.8, 4-H) and 7.22–8.08 (15 H, m, ArH); $\delta_C(CDCl_3)$ 48.79, 49.20 and 50.25 (OMe), 63.94 and 65.99 (C-6 and -5′), 72.08, 72.84, 79.10 and 82.96 (C-1′, -2′, -3′ and -4′), 92.73 and 97.00 (C-5 and -2), 127.71–133.21 (Ar–C, C-4 and -3) and 165.15 and 166.15 (C=O).

Treatment of Compounds **2a** *and* **2b** *with Trimethyl Orthoformate.*—The same procedure was used as for the reaction of compound **1** with trimethyl orthoformate containing BF_3·Et_2O. This afforded an epimeric mixture of **3a** and **3b** (33 mg, 61%) from substrate **2a** (50 mg). Identity was confirmed by comparison of ^{1}H NMR spectrum. In the same manner, compounds **3a** and **3b** (29.5 mg, 64.5%) were obtained as a foam from substrate **2b** (42.3 mg).

Treatment of Acetals **3a** *and* **3b** *with PTSA.*—A solution of compound **3a** (45.6 mg, 0.07 mmol) in 1,4-dioxane (1 cm^3) containing PTSA (7 mg) was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, and the residue was chromatographed over a column of silica gel with chloroform as eluent. This afforded compound **2a** (37.7 mg, 89.3%) as a foam. Identity was confirmed by comparison of ^{1}H NMR spectrum. In the same manner, compound **2b** (18.5 mg, 93.8%) was obtained as a foam from the acetal **3b** (21.3 mg).

(2S)- *and* (2R)-2,5,5-*Trimethoxy*-2-(β-D-*ribofuranosyl*)-5,6-*dihydro*-2H-*pyran* **4a** *and* **4b**.—To a solution of compound **3a** (75.7 mg, 0.12 mmol) in methanol (2 cm^3) at 0 °C was added 5% aq. NaOH (0.6 cm^3) during 15 min, and the mixture was kept at room temperature for 30 min and evaporated. The residue was chromatographed over a column of silica gel with chloroform–methanol (9:1) as eluent. This afforded compound **4a** (34.6 mg, 92.6%) as a foam.

Compound **4a**: $\delta_H(CDCl_3)$ 3.27, 3.28 and 3.32 (9 H, each s, OMe), 3.56 (1 H, dd, *J* 5.4 and 11.8, 5′-H^a), 3.73 (1 H, dd, *J* 3.0 and 11.8, 5′-H^b), 3.80–3.86 (2 H, m, 3′- and 4′-H), 3.88 (2 H, s, 6-H_2), 3.93 (1 H, d, *J* 2.7, 1′-H), 4.18 (1 H, dd, *J* 2.7 and 5.4, 2′-H), 5.92 (1 H, d, *J* 10.8, 3-H) and 6.24 (1 H, d, *J* 10.8, 4-H); $\delta_C(CDCl_3)$ 49.32, 49.84 and 51.72 (OMe), 63.94 and 67.80 (C-6 and -5′), 71.84, 72.85, 84.51 and 89.10 (C-1′, -2′, -3′ and -4′), 94.07 and 98.69 (C-5 and -2) and 130.64 and 131.57 (C-4 and -3) [Found: (M^+ + H − OCH_3), 276.1224. $C_{12}H_{20}O_7$ requires (M + H − OCH_3), 276.1208].

In the same manner, compound **4b** (47.4 mg, 89.7%) was obtained as a foam from substrate **3b** (106.7 mg).

Compound **4b**: $\delta_H(CDCl_3)$ 3.27, 3.28 and 3.33 (9 H, each s, OMe), 3.56–4.05 (8 H, m, 1′-, 2′-, 3′-, 4′-H, 5′-H_2 and 6-H_2), 5.90 (1 H, d, *J* 10.4, 3-H) and 6.17 (1 H, d, *J* 10.4, 4-H); $\delta_C(CDCl_3)$ 49.20, 49.55 and 50.20 (OMe), 62.48 and 66.23 (C-6 and -5′), 71.78, 73.19, 84.19 and 86.12 (C-1′, -2′, -3′ and -4′), 94.25 and 98.52 (C-5 and -2) and 129.76 and 131.16 (C-4 and -3) [Found: (M^+ + H − OCH_3), 276.1208. $C_{12}H_{20}O_7$ requires (M + H − OCH_3), 276.1208].

(6S)- *and* (6R)-6-*Methoxy*-6-(β-D-*ribofuranosyl*)*pyran*-3(2H,6H)-*one* **5a** *and* **5b**.—A solution of compound **4a** (14.4 mg, 0.05 mmol) in 1,4-dioxane (1 cm^3) containing PTSA (7 mg) was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, and the residue was chromatographed over a column of silica gel with chloroform–methanol (4:1) as eluent. This afforded compound **5a** (11.1 mg, 90.7%) as a foam.

Compound **5a**: $\delta_H(CD_3OD)$ 3.42 (3 H, s, OMe), 3.55 (1 H, dd, *J* 5.4 and 11.7, 5′-H^a), 3.72 (1 H, dd, *J* 3.0 and 11.7, 5′-H^b), 3.79–3.89 (2 H, m, 3′- and 4′-H), 4.12 (1 H, d, *J* 3.7, 1′-H), 4.21 (1 H, t, *J* 3.7, 2′-H), 4.36 (1 H, s, 2-H^a), 4.37 (1 H, s, 2-H^b), 6.25 (1 H, d, *J* 10.8, 4-H) and 7.07 (1 H, d, *J* 10.8, 5-H); $\delta_C(CD_3OD)$ 52.48 (OMe), 63.77 (C-5′), 69.21 (C-2), 72.72, 72.89, 85.18 and 88.51 (C-1′, -2′, -3′ and -4′), 98.17 (C-6), 130.17 (C-4), 148.89 (C-5) and 195.69 (C-3) [Found: (M^+ − OCH_3), 229.0734. $C_{10}H_{13}O_6$ requires (M − OCH_3), 229.0711].

In the same manner, compound **5b** (11.7 mg, 87.7%) was obtained as a foam from substrate **4b** (15.7 mg).

Compound **5b**: $\delta_H(CD_3OD)$ 3.42 (3 H, s, OMe), 3.63 (1 H, dd, *J* 5.0 and 12.8, 5′-H^a), 3.77–3.82 (2 H, m, 4′-H and 5′-H^b), 3.90 (1 H, t, *J* 4.0, 3′-H), 4.01 (1 H, t, *J* 4.0, 2′-H), 4.15 (1 H, d, *J* 4.0, 1′-H), 4.24 (1 H, d, *J* 16.8, 2-H^a), 4.39 (1 H, d, *J* 16.8, 2-H^b), 6.21 (1 H, d, *J* 10.4, 4-H) and 7.00 (1 H, d, *J* 10.4, 5-H); $\delta_C(CD_3OD)$ 62.60 (C-5′), 68.10 (C-2), 72.19, 73.07, 84.83 and 85.00 (C-1′, -2′, -3′ and -4′), 98.05 (C-6), 129.70 (C-4), 147.37 (C-5) and 196.10 (C-3) [Found: (M^+ − OCH_3), 229.0718. $C_{10}H_{13}O_6$ requires (M − OCH_3), 229.0711].

(1R,2S,5R,6R,7R)- *and* (1R,2R,5R,6R,7R)-6,7-(*Isopropylidenedioxy*)-3,8-*dioxabicyclo*[3.2.1]*octane*-2-*spiro*-2′-*pyran*-5′(2′H,6′H)-*one* **6a** *and* **6b**.—To a solution of compound **5a** (49 mg, 0.02 mmol) in acetone (5 cm^3) was added PTSA (10 mg), and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was neutralized with sodium hydrogen carbonate and the solid was collected by filtration and thoroughly washed with acetone. The solvent was evaporated off under reduced pressure. TLC [chloroform–methanol (197:3)] showed that the syrup contained two major components (R_f 0.24 and 0.21). The ratio of products **6a**:**6b** was 2:1 by ^{1}H NMR spectroscopy. The mixture was separated by PLC with chloroform–methanol (49:1) as developer (× 3), to afford the spiro compounds **6a** (19.5 mg, 36.6%) and **6b** (10.5 mg, 19.3%). In the same manner, compounds **6a** (21.5 mg, 41.3%) and **6b** (3.5 mg, 6.7%) were obtained from substrate **5b** (50.5 mg).

Compound **6a**: R_f 0.24; m.p. 196–198 °C; $\delta_H(CDCl_3)$ 1.36 and 1.51 (6 H, each s, Me), 3.66 (1 H, d, *J* 12.1, 4-H^a), 3.83 (1 H, dd, *J* 2.0 and 12.1, 4-H^b), 4.03 (1 H, s, 1-H), 4.16 (1 H, d, *J* 17.1, 6′-H^a), 4.26 (1 H, d, *J* 2.0, 5-H), 4.57 (1 H, d, *J* 17.1, 6′-H^b), 4.81 (1 H, d, *J* 6.1, 6-H), 5.11 (1 H, d, *J* 6.1, 7-H), 6.22 (1 H, d, *J* 10.4, 4′-H) and 7.63 (1 H, d, *J* 10.4, 3′-H); $\delta_C(CDCl_3)$ 24.51 and 25.98 (Me), 65.46 and 66.69 (C-4 and -6′), 79.97, 80.15, 82.61 and 82.90 (C-1, -5, -6 and -7), 91.09 (C-2), 112.15 (isopropylidene CMe_2), 128.00 (C-4′), 143.80 (C-3′) and 193.76 (C=O) (Found: M^+, 268.0936. $C_{13}H_{16}O_6$ requires M, 268.0946).

Compound **6b**: R_f 0.21; $\delta_H(CDCl_3)$ 1.38 and 1.52 (6 H, each s, Me), 3.54 (1 H, d, *J* 11.4, 4-H^a), 4.13–4.17 (2 H, m, 1-H and 4-H^a), 4.24–4.30 (2 H, m, 6′-H^a and 5-H), 4.43 (1 H, d, *J* 17.1, 6′-H^b), 4.85 (1 H, d, *J* 5.7, 6-H), 4.93 (1 H, d, *J* 5.7, 7-H), 6.20 (1 H, d, *J* 10.4, 4′-H) and 6.85 (1 H, d, *J* 10.4, 3′-H); $\delta_C(CDCl_3)$ 24.69 and 25.98 (Me), 63.89 and 66.34 (C-4 and -6′), 79.51, 80.32, 82.08 and 82.78 (C-1, -5, -6 and -7), 91.62 (C-2), 112.73

(isopropylidene CMe_2), 129.76 (C-4'), 142.63 (C-3') and 194.00 (C=O) (Found: M^+, 268.0948).

3-Hydroxymethyl-6-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)pyridazine **7**.—To a solution of compound **1** (606.8 mg, 1.09 mmol) in 1,4-dioxane (2 cm^3) was added anhydrous hydrazine (52.3 mg, 1.63 mmol). The mixture was stirred for 30 min at room temperature. Solvent was removed under reduced pressure and the residue was chromatographed over silica gel with hexane–ethyl acetate (3:2) as eluent. This afforded the *alcohol* **7** (351.4 mg, 58.3%) as a yellow foam; $\delta_H(CDCl_3)$ 2.50 (1 H, br, OH, exchanges with D_2O), 4.63 (1 H, dd, *J* 3.7 and 12.1, 5'-H^a), 4.78–4.89 (2 H, m, 4'-H and 5'-H^b), 4.93 (2 H, s, CH_2OH), 5.66 (1 H, apparent d, 2'-H), 5.91–5.94 (1 H, m, 3'-H), 5.93 (1 H, d, *J* 4.7, 1'-H) and 7.35–8.05 (17 H, m, ArH, 4- and 5-H); $\delta_C(CDCl_3)$ 63.42 (CH_2OH), 64.00 (C-5'), 72.60, 76.00, 80.85 and 82.08 (C-1', -2', -3' and -4'), 125.31 and 125.61 (C-5 and C-4), 128.48–133.50 (Ar–C), 159.60 and 161.58 (C-6 and -3) and 165.45 and 166.21 (C=O) (Found: M^+, 554.1677. $C_{31}H_{26}N_2O_8$ requires M, 554.1686).

3-Bromomethyl-6-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)-pyridazine **8**.—To a solution of compound **7** (101.4 mg, 0.18 mmol) in benzene (2 cm^3) at 0–5 °C was added thionyl bromide (152.2 mg, 0.73 mmol), and the mixture was stirred for 1 h at room temperature before being neutralized with saturated aq. sodium hydrogen carbonate and extracted with chloroform (3 × 10 cm^3). The extracts were combined, washed with water, dried over magnesium sulphate and evaporated to give a brown syrup. The residual syrup was chromatographed over silica gel with hexane–ethyl acetate (4:1) as eluent. This afforded compound **8** (83.0 mg, 73.5%) as a brown syrup. Owing to the unstable and hygroscopic nature of this compound, good elemental analyses could not be obtained; $\delta_H(CDCl_3)$ 4.64 (1 H, dd, *J* 3.9 and 12.1, 5'-H^a), 4.69 (2 H, s, CH_2Br), 4.81 (1 H, q, 4'-H), 4.90 (1 H, dd, *J* 3.2, 5'-H^b), 5.67 (1 H, apparent d, 2'-H), 5.89–5.95 (1 H, m, 3'-H), 5.92 (1 H, d, *J* 5.0, 1'-H) and 7.34–8.07 (17 H, m, ArH, 4- and 5-H); $\delta_C(CDCl_3)$ 30.59 (CH_2Br), 64.00 (C-5'), 72.54, 76.00 80.80 and 81.96 (C-1', -2', -3' and -4'), 125.66 (C-4 or -5), 127.95–133.44 (Ar–C), 159.48 and 159.71 (C-6 and -3) and 165.27 and 166.03 (C=O).

N-[4-(Dimethylamino)phenyl]-α-[6-(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)pyridazin-3-yl]nitrone **9**.—A solution of compound **8** (78.0 mg, 0.13 mmol) in pyridine (1 cm^3) was stirred at room temperature for 1 h. Pyridazine was removed under reduced pressure, and a solution of *N,N'*-dimethyl-*p*-nitrosoaniline (28.8 mg, 0.19 mmol) in methanol (3 cm^3) was added. After 10 min, saturated aq. sodium carbonate was added during 5 min and the mixture was stirred for an additional 1 h. Water was added, and the mixture was extracted with chloroform (3 × 10 cm^3). The extracts were combined, washed with water, dried over magnesium sulphate and evaporated to give a brown syrup. The residual syrup was chromatographed over silica gel with hexane–chloroform (1:1) as eluent. This afforded the nitrone **9** (41.8 mg, 48.2%) as a yellow foam; $\delta_H(CDCl_3)$ 3.06 (6 H, s, Me), 4.66 (1 H, dd, *J* 3.0, 5'-H^b), 4.82 (1 H, q, 4'-H), 5.70–5.98 (2 H, m, 2'- and 3'-H), 5.95 (1 H, d, *J* 4.7, 1'-H), 6.71–8.80 (20 H, m, ArH and 5-H), 8.54 (1 H, s, CH=N) and 9.33 (1 H, d, *J* 9.1, 4-H); $\delta_C(CDCl_3)$ 40.13 (Me), 63.89 (C-5'), 72.60, 75.94, 80.85 and 82.08 (C-1', -2', -3' and -4'), 111.21 (CH=N), 122.45–133.33 (Ar–C), 137.31, 151.76, 154.62 and 158.72 (benzene Cquat, C-6 and -3) and 165.27 and 166.09 (C=O) (Found: M^+, 686.2368. $C_{39}H_{34}N_4O_8$ requires M, 686.2373).

6-(2',3',5'-Tri-O-benzoyl-β-D-ribofuranosyl)pyridazine-3-carbaldehyde **10**.—To a solution of nitrone **9** (61.1 mg, 0.09 mmol) in benzene (2 cm^3) at 0–5 °C was added 2.5 mol dm^{-3} sulphuric acid (0.1 cm^3) and the mixture was stirred for 3 h at room temperature. Water was added, and the mixture was extracted with benzene (3 × 10 cm^3). The extracts were combined, washed with water, dried over magnesium sulphate and evaporated to give a brown syrup. The residual syrup was chromatographed over silica gel with chloroform–methanol (99:1) as eluent. This afforded the *aldehyde* **10** (38.6 mg, 78.5%) as a syrup; $\delta_H(CDCl_3)$ 4.63 (1 H, dd, *J* 3.7 and 12.1, 5'-H^a), 4.84 (1 H, q, 4'-H), 4.95 (1 H, dd, *J* 3.2, 5'-H^b), 5.75 (1 H, apparent d, 2'-H), 5.93 (2 H, m, 1'- and 3'-H), 7.36–8.04 (17 H, m, ArH, 4- and 5-H) and 10.34 (1 H, s, CHO); $\delta_C(CDCl_3)$ 63.89 (C-5'), 72.72, 75.88, 81.38 and 82.02 (C-1', -2', -3' and -4'), 125.02 and 125.61 (C-5 and -4), 128.59–133.62 (Ar–C), 155.15 and 163.34 (C-6 and -3), 165.39, 165.58 and 166.21 (C=O) and 192.12 (CHO) (Found: M^+, 552.1507. $C_{31}H_{24}N_2O_8$ requires M, 552.1530).

6-(2',3',5'-Tri-O-benzoyl-β-D-ribofuranosyl)pyridazine-3-carbaldehyde Diethyl Acetal **11** *and 6-{5-[(Benzoyloxy)-methyl]furan-2-yl}pyridazine-3-carbaldehyde Diethyl Acetal* **12**.—A solution of compound **10** (53.8 mg, 0.10 mmol) in ethanol (2 cm^3) containing one drop of conc. hydrochloric acid was heated at 55 °C for 10 h. After this time, two new compounds were detected (TLC) in the reaction mixture, with R_f-values of 0.31 and 0.37 [hexane–ethyl acetate (2:1)]. The solvent was removed under reduced pressure. The mixture was separated by PLC with hexane–ethyl acetate (2:1) as eluent after three elutions.

Compound **11**: yield 40.6%; R_f 0.31; $\delta_H(CDCl_3)$ 1.21–1.28 (6 H, m, CH_2Me), 3.56–3.69 (4 H, m, CH_2Me), 4.67 (1 H, dd, *J* 3.7 and 11.8, 5'-H^a), 4.80 (1 H, m, 4'-H), 4.89 (1 H, dd, *J* 3.0, 5'-H^b), 5.68 (1 H, s, CH), 5.68 (1 H, d, *J* 5.7, 1'-H), 5.88–5.95 (2 H, m, 2'- and 3'-H) and 7.37–8.11 (17 H, m, ArH, 5- and 4-H); $\delta_C(CDCl_3)$ 15.15 (Me), 63.12 and 64.12 (CH_2, C-5'), 72.60, 76.11, 80.85 and 82.09 (C-1', -2', -3' and -4'), 101.91 (CH), 125.48–133.27 (Ar–C), 160.41 and 161.13 (C-6 and -3) and 166.20 and 167.11 (C=O) (Found: M^+, 626.2327. $C_{35}H_{34}N_2O_9$ requires M, 626.2262).

Compound **12**: yield 16.7%; R_f 0.37; $\delta_H(CDCl_3)$ 1.26 (6 H, t, *J* 6.1, CH_2Me), 3.65 and 3.81 (4 H, each q, CH_2Me), 5.40 (2 H, s, CH_2O), 5.70 (1 H, s, CH), 6.68 and 7.35 (2 H, each d, *J* 3.4, 3- and 4-H furan), 7.41–7.57 (3 H, m, benzene), 7.77 and 7.91 (2 H, each d, *J* 8.4, 5- and 4-H pyridazine) and 8.08 (2 H, d, benzene) (Found: M^+, 382.1465. $C_{21}H_{22}N_2O_5$ requires M, 382.1527).

Ethyl 6-(2',3',5'-Tri-O-benzoyl-β-D-ribofuranosyl)pyridazine-3-carboxylate **13**.—Acetal **11** (24.8 mg, 0.04 mmol) was dissolved in methylene dichloride (1.5 cm^3), the solution was cooled to −78 °C, and ozone was passed through the solution for 3 h at −78 °C. The solvent was removed under reduced pressure. The residue was purified by PLC with hexane–ethyl acetate (3:1) as eluent after three elutions. This afforded *ester* **13** (1.7 mg, 8%) as a syrup; $\delta_H(CDCl_3)$ 1.46 (3 H, t, *J* 7.1, CH_2Me), 4.52 (2 H, q, CH_2Me), 4.64 (1 H, dd, *J* 3.7 and 12.1, 5'-H^a), 4.83 (1 H, q, 4'-H), 4.92 (1 H, dd, *J* 3.0, 5'-H^b), 5.75 (1 H, d, *J* 6.0, 1'-H), 5.87–5.96 (2 H, m, 2'- and 3'-H) and 7.35–8.11 (17 H, m, ArH, 4- and 5-H); $\delta_C(CD_3OD)$ 14.22 (Me), 62.60 and 63.94 (CH_2Me and C-5'), 72.78, 76.05, 81.32 and 81.73 (C-1', -2', -3' and -4'), 125.02 (C-4 or C-5), 128.24–133.50 (Ar–C), 151.52, 162.46, 163.87, 165.27, 165.39 and 166.15 (C-6, -3 and C=O) (Found: M^+, 596.1803. $C_{33}H_{28}N_2O_9$ requires M, 596.1793).

Oxidation of Aldehyde **10**.—Aldehyde **10** (52.2 mg, 0.09 mmol) was dissolved in ethanol (3 cm^3), the solution was cooled to −78 °C, and 10% ethanolic potassium hydroxide (0.4 cm^3) was added, and ozone was passed through the solution for 7 h

at −78 °C. The reaction mixture was neutralized with acetic acid. The solvent was removed under reduced pressure. The residue was purified by PLC, with chloroform as eluent, after three elutions. This afforded ester **13** (29.5 mg, 65%) as a syrup. Identity was confirmed by comparison of IR and ^{1}H NMR spectra.

6-(β-D-*Ribosuranosyl*)*pyridazine*-3-*carboxamide* **14**.—To a solution of ester **13** (29.5 mg, 0.05 mmol) in methanol (3 cm^3) was added 28% aq. ammonia (0.2 cm^3) at room temperature and the mixture was kept for 19 h, then evaporated, and the residue was chromatographed over a column of silica gel with chloroform–methanol (9:1) as eluent. This afforded the *amide* **14** (3.6 mg, 28.6%) as needles; m.p. 182–185 °C; $\delta_H[(CD_3)_2SO]$ 3.57 (1 H, br d, *J* 11.9, 5′-H^a), 3.66 (1 H, br d, 5′-H^b), 3.93 (1 H, q, 4′-H), 3.97 (1 H, t, 3′-H), 4.07 (1 H, t, 2′-H), 4.83, 4.93 and 5.17 (3 H, each br s, OH, exchanges with D_2O), 5.03 (1 H, d, *J* 5.9, 1′-H), 7.82 and 8.42 (2 H, each br s, NH_2, exchanges with D_2O), 8.04 (1 H, d, *J* 8.8, 5-H) and 8.18 (1 H, d, 4-H); $\delta_C[(CD_3)_2SO]$ 61.38 (C-5′), 71.04, 76.73, 83.24 and 85.04 (C-1′, -2′, -3′ and -4′), 125.73 and 125.93 (C-5 and -4), 152.47 (C-6) and 164.41 and 164.44 (C-3, C=O) (Found: M^+, 255.0838. $C_{10}H_{13}N_3O_5$ requires M, 255.0854).

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