C-Nucleosides. 1. Synthesis of 3-(β-D-Ribofuranosyl)pyridazines

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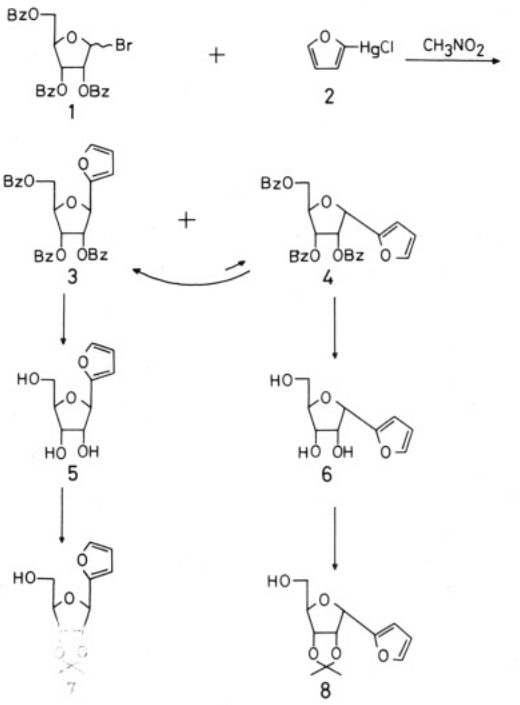
A synthesis of the versatile and stable *C*-nucleoside precursors 2-(2,3,5-tri-*O*-benzoyl-β- and -α-D-ribofuranosyl)furan (**3** and **4**) is described. Compound **4** can be epimerized effectively to **3** in dichloromethane with trifluoroacetic acid so that a high yield of the desired isomer **3** from **4** is readily achieved. The conversion of the furan ring of **3** into a pyridazine ring was performed by the Clauson-Kaas method to give 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazine (**11**) and 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-4,5-dihydro-6(1*H*)-pyridazinone (**12**). Deblocking of **11** gave 3-(β-D-ribofuranosyl)pyridazine (**13**). Finally, treatment of **11** with *m*-chloroperbenzoic acid in $CHCl_3$ gave 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazine 1-oxide (**20**) and 2-oxide (**21**) in 61% and 17% yields, respectively. Deblocking of **20** and **21** gave 3-(β-D-ribofuranosyl)pyridazine 1-oxide (**22**) and 2-oxide (**23**).

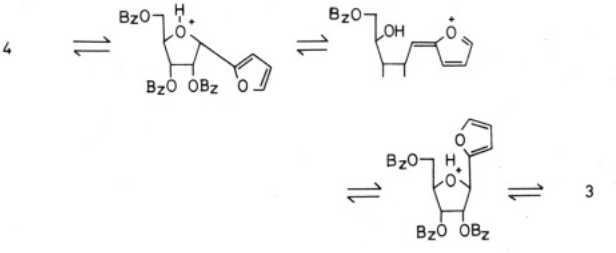
The *C*-nucleosides are a group of molecules containing ribose bound to the carbon atom of a heterocyclic aglycon, some of which are known to exhibit significant antibacterial, antiviral, and antitumor activities. The biological activities[1] of these compounds encouraged us to prepare a new class of *C*-nucleosides. As a part of our general program on the synthesis of *C*-nucleosides, we have developed a convenient preparation of 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)furan (**3**) as a key intermediate for *C*-nucleoside synthesis. It has been known for a considerable time that furan derivatives can be converted into a large number of other heterocyclic systems.[2] We present herein the details of the synthesis of **3** and then demonstrate the utility of **3** through the construction of a pyridazine *C*-nucleoside by the Clauson-Kaas method.[3]

The hitherto unknown *C*-glycosyl furans **3** and **4**, which were the starting material in our synthesis of pyridazine *C*-nucleosides, were obtained in 58% yield as an anomeric mixture by the reaction of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**1**)[4] with 2-(chloromercuri)furan (**2**)[5] in nitromethane at room temperature (Scheme I). For the assignment of the anomeric configuration of *C*-glycosyl furans **3** and **4**, which were readily separable chromatographically, the ^1H NMR and ^{13}C NMR data obtained from the corresponding 2′,3′-*O*-isopropylidene derivatives **7** and **8** were used. The following were noted in the ^1H NMR spectra: (a) The difference in the chemical shifts of the two methyl signals of the 2′,3′-*O*-isopropylidene group for **7** (δ 1.37 and 1.59, $\Delta\delta = 0.22$) is larger than that for **8** (δ 1.34 and 1.50, $\Delta\delta = 0.16$).[6] (b) The H-4′ signal in **7** is observed as a quartet at δ 4.18 ($J_{3',4'} = J_{4',5'} = 4$ Hz) and in **8** as a triplet at δ 4.22 ($J_{3',4'} = 0$ Hz).[7] (c) An 8.6% NOE enhancement of the signal of H-1′ of **8** was observed upon irradiation of H-5′. This enhancement was not observed for **7**. (d) The H-1′ of **8** (δ 5.05) resonated in higher field than that of **7** (δ 4.90).[8] From the ^{13}C NMR spectra, it was observed that the shifts for the three carbons of the 2′,3′-*O*-isopropylidene group of **7** at 25.39, 27.37 and 114.49 ppm clearly show in the β range (25.5 ± 0.2, 27.5 ± 0.2, and 114.5 ± 0.6), while those of **8** at 25.03, 26.20, and 113.08 ppm clearly are in the α range (24.9 ± 0.3, 26.3 ± 0.2, and 112.7 ± 0.6).[9] These indicate that **7** and **8** are the β- and α-glycoside, respectively.

Scheme I



Scheme II



In contrast to the general properties[10] of the predominant formation of the β anomer by substitution of **1** through a heavy metal process, the present process with

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Table I. ^{1}H NMR Data[a] for H-1′ of C-Nucleoside Analogues

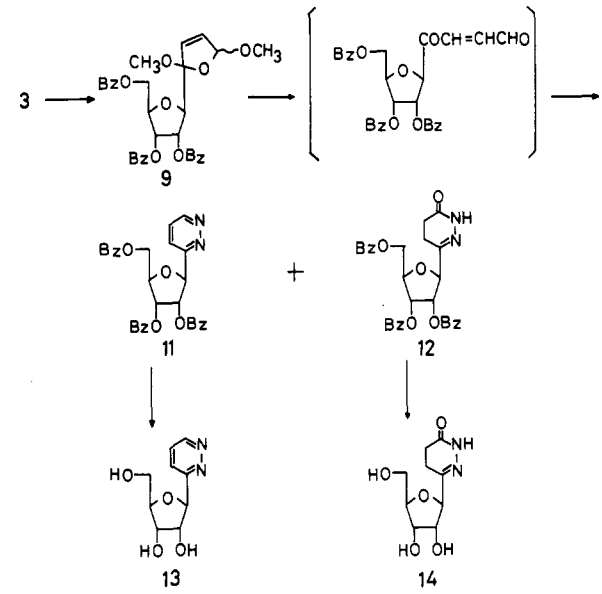
compd	δ(H-1′)	$J_{1',2'}$, Hz	solvent[b]	compd	δ(H-1′)	$J_{1',2'}$, Hz	solvent[b]
3	5.28	5.0	A	15	5.86	4.0	A
4	5.56	5.0	A	16	5.11	4.0	A
5	4.56	5.5	B	17	5.36	4.0	C
6	5.03	4.0	B	18	4.43	4.0	C
7	4.90	5.5	A	20	5.32	5.5	A
8	5.05	4.5	A	21	c		A
11	5.66	6.0	A	22	4.68	5.0	C
12	c		A	23	5.06	0	C
13	5.05	6.0	C	24	5.53	5.0	A
14	4.14	5.0	C	25	5.80	4.0	A

[a] Chemical shifts in parts million downfield from Me_4Si. [b] A = $CDCl_3$; B = CD_3OD; C = Me_2SO-d_6. [c] Obscured by overlapping with the signals of the ribofuranosyl moiety.

2 produced the α anomer as the major product (ca. 6:1 α/β). Since the majority of naturally occurring and bioactive C-nucleosides possess the β configuration, variations in temperature, concentration, and reactant proportions were examined in order to obtain the β isomer exclusively. These attempts were uniformly unsuccessful, and mixtures of 3 and 4 were obtained, with the α isomer 4 predominating in all cases, as judged by the ^{1}H NMR spectra. Attention was then turned to the epimerization of 4. Fox et al.[11] have described the epimerization to β-pseudoisocytidine in methanolic hydrogen chloride from the corresponding α isomer. Application of this procedure to 4 was unsuccessful. However, when the α isomer 4 was stirred in dichloromethane with trifluoroacetic acid, equilibration did occur and afforded the desired isomer 3 in an excellent yield (85%). Thus it seems, as shown in Scheme II, that the combination of protonation of the oxygen of furan ring and then protonation of the furanose ring oxygen by the acid allows opening and reclosure to take place. Also, pure 3 epimerized to 4 under the same conditions, but the rate of epimerization was significantly lower than that of 4 to 3. At the equilibrium point the β/α ratio was approximately 9:1. The formation of pyranosyl isomers, as found in the case of pseudouridine,[12] was not observed.

Clauson-Kaas et al. have described the conversion of furans into pyridazines by a series of reactions involving oxidation of the furans with bromine and methanol into 2,5-dimethoxy-2,5-dihydrofurans and then ring opening with acid to give the enediones which are ring closed by hydrazine.[13] Application of this procedure to 3 afforded 2-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,5-dimethoxy-2,5-dihydrofuran (9) as a mixture of geometric isomers in 98% yield. These isomers could not be separated by preparative TLC, but the mixture was entirely satisfactory for the next step. Compound 9, hydrazine hydrochloride, and trifluoroacetic acid in acetone solution reacted slowly at room temperature over 3 days, giving a 51% yield of 3-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyridazine (11) and a 7% yield of 3-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4,5-dihydro-6(1H)-pyridazinone (12). The structure of the unexpected product dihydropyridazinone 12 was presumed by the presence of an A_2B_2 pattern corresponding to a CH_2CH_2 moiety, in addition to the signal of the NH group in the ^{1}H NMR spectrum, and by the presence of an absorption band in the IR spectrum at 1680 cm^{-1} ascribed to the amide carbonyl group distinct from the ester band at 1720 cm^{-1}. On the other hand, treatment of 9 with hydrazine hydrochloride in tetrahydrofuran at reflux afforded a mixture of dihydropyridazinone 12 and the furan derivative 19 resulting from the elimination of two benzoyloxy groups. Similar base-catalyzed eliminations of these protecting groups have been already reported.[14] Debenzoylation of 11 and 12 with sodium methoxide gave the deblocked compounds 13 and 14, respectively (Scheme III).

Scheme III



It is reasonable to assume that the compounds 9 and 11–14 have the β configuration, the same as the synthetically related precursor 3, because complete inversion to the other isomer (i.e., from β to α) would be highly unlikely. To further confirm these considerations, we also attempted to prepare the corresponding α isomers from 4 by procedures analogous to those for the preparation of the β isomers. An attempt to cyclize 2-(2,3,5-tri-O-benzoyl-α-D-ribofuranosyl)-2,5-dimethoxy-2,5-dihydrofuran (10) with the same procedure as for the preparation of 11 was unsuccessful. By the reaction of 10 with hydrazine hydrochloride in tetrahydrofuran at room temperature, the pyridazine 15 was isolated only in 1% yield and gave the dihydropyridazinone 16 as the major product (58%). We can offer no convincing argument as to the mechanistic origin of the dihydropyridazinone, and the formation of this type of product does not appear to have been previously observed. The α isomers can be differentiated from their β counterparts on the basis of their ^{1}H NMR data. The chemical shifts for H-1′ are consistently further

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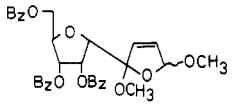
Chart I



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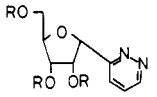
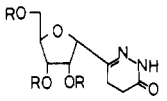
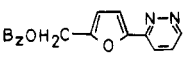


15 R = COC_6H_5
17 R = H



16 R = COC_6H_5
18 R = H



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Scheme IV

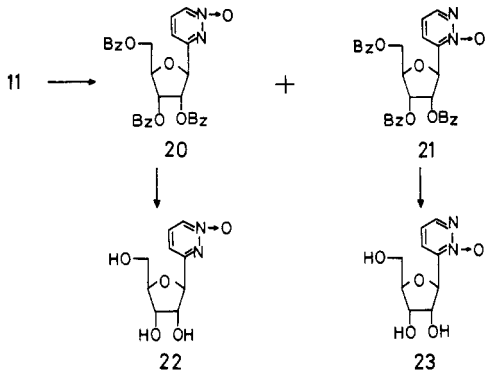

Table II. ^{13}C NMR[a] Results for the Pyridazine Moiety of C-Nucleoside Analogues

	β-D-ribofuranosyl			
compd	C-3	C-4	C-5	C-6
13	162	125	127	151
1-oxide 22	163	114	135	132
2-oxide 23	145	132	116	149

[a] Spectra were recorded in Me_2SO-d_6 with tetramethylsilane as an internal standard. The chemical shift values of the ^{13}C spectra are in parts million downfield from Me_4Si.

downfield for the α isomers (10 and 15–18, Chart I) than for the corresponding β isomers (9 and 11–14) (Table I). This relationship has been observed also in the cases of the isomers of pseudouridine,[15] pyrazofurin,[16] and some purine-like C-nucleosides.[17] The β-3-pyridazine compound 11 was used as the starting material for preparation of other members of the series.

Since photochemical transformations[18] to pyrroles are accomplished with pyridazine N-oxides, N-oxidation of 11 was undertaken. Reaction of the pyridazine 11 with a small excess of m-chloroperbenzoic acid afforded the isomeric mono N-oxides, i.e., 3-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyridazine 1-oxide (20) in 61% yield and the 2-oxide (21) in 17% yield. The position of the N–O group in these N-oxides was determined by analysis of the ^1H NMR and ^{13}C NMR spectra of the corresponding deblocked N-oxides 22 and 23. In ^1H NMR spectra, the hydrogen atoms ortho and para to the N–O function undergo a shielding effect, while the meta hydrogen atoms undergo a deshielding effect.[19] The signal of H-4 (para) of 1-oxide 22 at δ 7.50 occurs at higher field than that of 13 at δ 7.93, and H-4 (meta) of 2-oxide 23 at δ 8.30 occurs at lower field than that of 13 (see Scheme IV and Table II). In the ^{13}C NMR spectra, N-oxidation of pyridazines resulted in a higher field signal for resonances assigned to C-α (carbon atoms bonded to an N-oxide group) and in smaller low-field ones for C-β (carbon atoms bonded to C-α).[20] Spectra assignment of ^{13}C resonances in the pyridazine derivatives was performed by measuring the selectively proton-decoupled ^{13}C NMR spectrum. The signal of the C-α (C-6) of 1-oxide 22 at 132 ppm shows a higher field than that of 13 at 151 ppm, and C-β (C-5) of 1-oxide 22 at 135 ppm shows at lower field than that of 13 at 127 ppm. The signal of the C-α (C-3) of 2-oxide 23 at 145 ppm shows at higher field than that of 13 at 162 ppm, and C-β (C-4) of 2-oxide 23 at 132 ppm shows at lower field than that of 13 at 125 ppm. These data indicate that 22 and 23 are the 1-oxide and 2-oxide, respectively. To established the anomeric configuration of the pyridazine N-oxides 22 and 23, we also prepared the α isomers (1-oxide 24 and 2-oxide 25), starting from the α-pyridazine 15 by the same procedure. Anomerization was not observed in the N-oxidation experiment. Photochemical conversions of 20 and 21 are now being undertaken in our laboratory.

Experimental Section

Melting points were determined on a Yanagimoto apparatus and are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. Mass spectra were measured with Hitachi M-52 spectrophotometer and ^1H NMR spectra with a JEOL JNM-PS-100 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. Analytical thin-layer chromatography was performed on glass plates coated with a 0.25-mm layer of silica gel GF_{254} (Merk). The compounds were detected with a UV light (254 nm). Column chromatography was performed on silica gel C-200 (74–149 μm, Wakogel). Nitromethane and benzene were stored over 4A molecular sieves. All reactions were repeated at least once to check for reproducibility.

2-(2,3,5-Tri-O-benzoyl-β- and -α-D-ribofuranosyl)furan (3 and 4). A solution of 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose (5.04 g, 10 mmol) in dry benzene (20 mL) was saturated under ice cooling with gaseous dry hydrogen bromide in the course of 1 h. The reaction mixture was allowed to stand at room temperature for additional 1 h, the benzene solution was evaporated in vacuo (bath temperature 40 °C), and the residue was coevaporated with 20 mL of dry benzene. The syrupy residue was dissolved in 15 mL of dry nitromethane, the solution was treated with 3.0 g (10 mmol) of powdered 2-(chloromercuri)furan (2), and the whole reaction mixture was stirred at room temperature for 5 h. The resulting brown solution was allowed to stand overnight. The insoluble portion was filtered off and washed with benzene. The filtrates were combined and evaporated in vacuo to a brown syrup. TLC (benzene–AcOEt, 20:1) showed that the brown syrup contained two major components (R_f 0.36 and 0.33). The mixture was chromatographed over a column of silica gel with benzene as the eluent. The first compound eluted, 3 (0.5 g, 5%; corresponding to R_f 0.36 on TLC), was obtained as a syrup: MS, m/e

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512 (M^+); ^1H NMR ($CDCl_3$) δ 4.44–4.90 (m, 3, H-4′, H-5′), 5.80–6.00 (m, 2, H-2′, H-3′), 6.26 (dd, 1, H-4 furan, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.5 Hz), 6.43 (d, 1, H-3 furan, $J_{3,4}$ = 3.5 Hz), 7.15–8.12 (m, 16, Ar H and H-5 furan); ^{13}C NMR ($CDCl_3$) δ 64.11 (C-5′), 72.71, 74.35, 76.69, 79.62 (C-1′, C-2′, C-3′, C-4′), 109.45, 110.45 (C-3, C-4 furan), 128.41–133.38 (Ar C), 143.39 (C-5 furan), 150.23 (C-2 furan), 165.21, 165.32, 166.14 (C=O).

Compound **4** was eluted as the second fraction (2.7 g, 53% corresponding to R_f 0.33 on TLC) as colorless crystals: mp 96–97 °C; MS m/e 512 (M^+); ^1H NMR ($CDCl_3$) δ 4.45–4.90 (m, 3, H-4′, H-5′), 5.76–6.04 (m, 2, H-2′, H-3′), 6.26 (dd, 1, H-4 furan, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.5 Hz), 6.40 (d, 1, H-3 furan, $J_{3,4}$ = 3.5 Hz), 7.10–8.10 (m, 16, Ar H and H-5 furan); ^{13}C NMR ($CDCl_3$) δ 64.29 (C-5′), 72.77, 73.07, 75.70, 78.62 (C-1′, C-2′, C-3′, C-4′), 109.51, 110.39 (C-3, C-4 furan), 128.35–133.21 (Ar C), 142.74 (C-5 furan), 149.59 (C-2 furan), 165.09, 165.44, 166.14 (C=O). Anal. Calcd for $C_{30}H_{24}O_8$: C, 70.30; H, 4.72. Found for **3**: C, 70.41; H, 4.57. Found for **4**: C, 70.17; H, 4.63.

Epimerization of 4 by Trifluoroacetic Acid. To a solution of 100 mg of **4** in 3 mL of dichloromethane was added 0.3 mL of trifluoroacetic acid, and the resulting solution was stored at room temperature for 24 h. Sodium bicarbonate was added, and the mixture was stirred to 1 h. The solid was collected by filtration, throughly washed with dichloromethane, and dried over magnesium sulfate. Evaporation of the solvent in vacuo gave a syrup (95 mg) which was shown by ^1H NMR spectrum to consist of **3** and **4** in a ratio of 9:1.

2-(2,3-*O*-Isopropylidene-β- and -α-D-ribofuranosyl)furan (7 and 8). Ethyl orthoformate (0.65 mL, 4 mmol) was added during 10–20 min at room temperature to a well-stirred suspension of **5** (320 mg, 1.6 mmol) in acetone (6.5 mL) containing *p*-toluenesulfonic acid monohydrate (30 mg, 0.16 mmol), and the mixture was allowed to stand at room temperature for 12 h. Then sodium bicarbonate (140 mg, 1.7 mmol) was added, and the mixture was stirred for 15 min. The solid was collected by filtration and throughly washed with acetone. The filtrates were combined and evaporated in vacuo to a syrup which was purified on a silica gel column with $CHCl_3$ as the eluent, affording 194 mg of **7** (50.6%) as a colorless foam: MS, m/e 240 (M^+); ^1H NMR ($CDCl_3$) δ 1.37 (s, 3, isopropylidene CH_3), 1.59 (s, 3, isopropylidene CH_3), 2.32 (br s, 1, OH), 3.71 (m, 2, H-5′), 4.18 (q, 1, H-4′, $J_{3',4'}$ = $J_{4',5'}$ = 4 Hz), 4.71–4.83 (m, 2, H-2′, H-3′), 6.40 (apparent s, 2, H-3, H-4 furan), 7.45 (apparent s, 1, H-5 furan); ^{13}C NMR ($CDCl_3$) δ 25.39, 27.37 (CH_3), 62.59 (C-5′), 79.73, 81.78, 83.54, 85.00 (C-1′, C-2′, C-3′, C-4′), 108.69, 110.45 (C-3, C-4 furan), 114.49 (isopropylidene C_{quat}), 143.09 (C-5 furan), 151.58 (C-2 furan).

In the same manner 80 mg (20.9%) of the α isomer **8** was obtained as a colorless foam from 320 mg of **6**: MS, m/e 240 (M^+); ^1H NMR ($CDCl_3$) δ 1.34 (s, 3, isopropylidene CH_3), 1.50 (s, 3, isopropylidene CH_3), 2.58 (br s, 1, OH), 3.64 (d, 2, H-5′, $J_{4',5'}$ = 5.5 Hz), 4.22 (t, 1, H-4′, $J_{4',5'}$ = 5.5 Hz, $J_{3',4'}$ = 0 Hz), 4.66–4.90 (m, 2, H-2′, H-3′), 6.35 (dd, 1, H-4 furan, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.5 Hz), 6.48 (d, 1, H-3 furan, $J_{3,4}$ = 3.5 Hz), 7.39 (d, 1, H-5 furan, $J_{4,5}$ = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 25.03, 26.20 (CH_3), 62.18 (C-5′), 77.28, 81.72, 82.54, 84.12 (C-1′, C-2′, C-3′, C-4′), 109.40, 110.51 (C-3, C-4 furan), 113.08 (isopropylidene C_{quat}), 142.16 (C-5 furan), 149.76 (C-2 furan). Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found for **7**: C, 60.14; H, 6.55. Found for **8**: C, 60.05; H, 6.86.

2-(2,3,5-Tri-*O*-benzoyl-β- and -α-D-ribofuranosyl)-2,5-dimethoxy-2,5-dihydrofuran (9 and 10). To a solution of **3** (800 mg, 1.6 mmol) in methanol (10 mL) was added 1.0 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 s, 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 $CHCl_3$ (3 × 50 mL), and the extracts were combined, washed with water, dried over magnesium sulfate, and evaporated. The residual syrup showed no furan ring signals at δ 6.26 and 6.43 in the ^1H NMR spectrum. The yield of the crude isomeric mixture **9** was 850 mg (98%) of a colorless foam which was chromatographically inseparable: R_f 0.54 ($CHCl_3$–EtOH, 25:1); MS, m/e 574 (M^+); ^1H NMR ($CDCl_3$ partial) δ 3.16, 3.25, 3.40, 3.47 (each s, 3 each, OCH_3).

In the same manner 850 mg (98%) of the isomer **10** was obtained as a colorless foam from 800 mg of **4**: R_f 0.38 ($CHCl_3$–EtOH, 25:1); MS, m/e 574 (M^+); ^1H NMR ($CDCl_3$ partial) δ 3.02, 3.06, 3.31, 3.43 (each s, 3 each, OCH_3).

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazine (11) and 3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4,5-dihydro-6(1*H*)-pyridazinone (12). A solution of **9** (2.8 g, 50 mmol) in acetone (40 mL) was added to 3.0 g of hydrazine hydrochloride. The suspension was cooled in an ice bath, and 8 mL of 50% trifluoroacetic acid was added dropwise with stirring. The reaction mixture was stirred at room temperature for 3 days. Water was added, and the mixture was extracted with chloroform (3 × 30 mL). The extracts were combined, washed with saturated sodium bicarbonate solution and water, dried over magnesum sulfate, and evaporated to a syrup. TLC ($CHCl_3$–EtOH, 25:1) showed that the brown syrup contained two major components (R_f 0.47 and 0.37). The mixture was chromatographed over a column of silica gel with $CHCl_3$ as the eluent. The first compound eluted, **11** (1.3 g, 51%; corresponding to R_f 0.47 on TLC), was obtained as a colorless foam: MS, m/e 524 (M^+); ^1H NMR ($CDCl_3$) δ 4.60–4.95 (m, 3, H-4′, H-5′), 5.88–6.05 (m, 2, H-2′, H-3′), 7.20–8.10 (m, 17, Ar H and H-4, H-5 pyridazine), 9.04 (dd, 1, H-6 pyridazine, $J_{5,6}$ = 6 Hz, $J_{4,6}$ = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 64.00 (C-5′), 72.54, 76.05, 80.67, 82.25 (C-1′, C-2′, C-3′, C-4′), 124.66, 127.12 (C-4, C-5 pyridazine), 128.41–133.44 (Ar C), 151.22 (C-6 pyridazine), 160.35 (C-3 pyridazine), 165.27, 166.03 (C=O). Anal. Calcd for $C_{30}H_{24}N_2O_7$: C, 68.69; H, 4.61; N, 5.34. Found: C, 68.52; H, 4.74; N; 5.21.

Compound **12** was eluted as the second fraction (200 mg, 7%; corresponding to R_f 0.37 on TLC) as a colorless foam: MS, m/e 542 (M^+); IR ($CHCl_3$) 3410, 3000, 1720, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.49 (m in A_2B_2 pattern, 4, H-4, H-5 pyridazine), 4.40–4.85 (m, 4, H-1′, H-4′, H-5′), 5.70–5.95 (m, 2, H-2′, H-3′), 7.20–8.15 (m, 15, Ar H), 8.42 (s, 1, NH); ^{13}C NMR ($CDCl_3$) δ 20.71, 25.79 (C-4, C-5 pyridazine), 63.88 (C-5′), 72.54, 72.71, 80.61, 82.19 (C-1′, C-2′, C-3′, C-4′), 128.41–133.50 (Ar C), 150.87 (C-3 pyridazine), 165.27, 165.38, 166.03, 167.40 (C=O). Anal. Calcd for $C_{30}H_{26}N_2O_8$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.27; H, 4.65; N, 5.29.

3-(2,3,5-Tri-*O*-benzoyl-α-D-ribofuranosyl)pyridazine (15) and 3-(2,3,5-Tri-*O*-benzoyl-α-D-ribofuranosyl)-4,5-dihydro-6(1*H*)-pyridazinone (16). A solution of **10** (2.8 g, 50 mmol), hydrazine hydrochloride (3 g) in THF (40 mL), and water (6 mL) was allowed to stir at room temperature for 24 h. Water was added, and the mixture was extracted with chloroform (3 × 30 mL). The extracts were combined, washed with saturated sodium bicarbonate solution and water, dried over magnesium sulfate, and evaporated to a brown syrup. TLC ($CHCl_3$–EtOH, 25:1) showed that the brown syrup contained two major components (R_f 0.24 and 0.22). The mixture was chromatographed over a column of silica gel with $CHCl_3$ as the eluent. The first compound eluted, **15** (30 mg, 1%; corresponding to R_f 0.24 on TLC), was obtained as colorless crystals: mp 147–148 °C; MS, m/e 524 (M^+); ^1H NMR ($CDCl_3$) δ 4.50–4.90 (m, 3, H-4′, H-5′), 5.95 (dd, 1, H-3′, $J_{2',3'}$ = 4 Hz, $J_{3',4'}$ = 7 Hz), 6.23 (t, 1, H-2′, $J_{1',2'}$ = $J_{2',3'}$ = 4 Hz), 7.05–8.00 (m, 17, Ar H and H-4, H-5 pyridazine), 8.95 (dd, 1, H-6 pyridazine, $J_{5,6}$ = 5 Hz, $J_{4,6}$ = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 64.35 (C-5′), 73.77, 74.41, 79.21, 81.08 (C-1′, C-2′, C-3′, C-4′), 125.25, 126.36 (C-4, C-5 pyridazine), 128.29–133.38 (Ar C), 150.82 (C-6 pyridazine), 159.77 (C-3 pyridazine), 164.56, 165.21, 166.08 (C=O). Anal. Calcd for $C_{30}H_{24}N_2O_7$: C, 68.69; H, 4.61; N, 5.34. Found: C, 68.46; H, 4.63; N, 5.54.

Compound **16** was eluted as the second fraction (1.5 g, 58%; corresponding to R_f 0.22 on TLC) as colorless crystals: mp 153–154 °C; MS, m/e 542 (M^+); ^1H NMR ($CDCl_3$) δ 2.49 (m in A_2B_2 pattern, 4, H-4, H-5 pyridazine), 4.50–4.90 (m, 3, H-4′, H-5′), 5.83 (dd, 1, H-3′, $J_{2',3'}$ = 4 Hz, $H_{3',4'}$ = 7 Hz), 6.12 (t, 1, H-2′, $J_{1',2'}$ = $J_{2',3'}$ = 4 Hz), 7.20–8.10 (m, 15, Ar H), 8.85 (s, 1, NH); ^{13}C NMR ($CDCl_3$) δ 22.28, 25.97 (C-4, C-5 pyridazine), 64.06 (C-5′), 73.07, 74.12, 78.97, 81.02 (C-1′, C-2′, C-3′, C-4′), 128.41–133.85 (Ar C), 151.28 (C-3 pyridazine), 165.03, 165.27, 166.14, 167.55 (C=O). Anal. Calcd for $C_{30}H_{26}N_2O_8$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.64; H, 4.99; N, 5.22.

3-[5-[(Benzoyloxy)methyl]furan-2-yl]pyridazine (19) and 12. A solution of **9** (2.8 g, 50 mmol) and hydrazine hydrochloride (3 g) in THF (40 mL) and water (6 mL) was heated under reflux for 5 h and then worked up as above for **15** and **16**. For compound **16**: 760 mg (28%). For compound **19**: 140 mg (9%); mp 119.5–120

°C; MS, m/e 280 (M^+); IR ($CHCl_3$) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.39 (s, 2, CH_2), 6.69 (d, 1, H-4 furan, $J_{3,4}$ = 4 Hz), 7.20–8.16 (m, 8, Ar H, H-3 furan and H-4, H-5 pyridazine), 9.05 (dd, 1, H-6 pyridazine, $J_{5,6}$ = 5 Hz, $J_{4,6}$ = 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 58.44 (CH_2), 111.38, 113.49 (C-3, C-4 furan), 121.86, 126.60 (C-4, C-5 pyridazine), 128.41, 129.75, 133.21 (Ar C), 149.65 (C-6 pyridazine), 151.22, 151.69, 152.16 (C-2, C-5 furan and C-3 pyridazine), 166.08 (C=O). Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 10.00. Found: C, 68.73, H, 4.59; N, 9.82.

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazine 1-Oxide (20) and 2-Oxide (21). Compound **11** (2.6 g, 50 mmol) and *m*-chloroperbenzoic acid (950 mg, 55 mmol) in 50 mL of $CHCl_3$ were stirred at room temperature for 24 h. Water was added, and the mixture was neutralized with $NaHCO_3$ and then extracted with $CHCl_3$ (3 × 30 mL). The dried $CHCl_3$ solution on evaporation afforded a syrup. TLC ($CHCl_3$–EtOH, 25:1) showed that the colorless syrup contained two major components (R_f 0.31 and 0.29). The mixture was chromatographed over a column of silica gel with $CHCl_3$ as the eluent. The first compound eluted, **21** (460 mg, 17%; corresponding to R_f 0.31 on TLC), was obtained as a colorless foam: MS, m/e 540 (M^+); ^1H NMR ($CDCl_3$) δ 4.50–4.95 (m, 3, H-4′, H-5′), 5.66–5.98 (m, 3, H-1′, H-2′, H-3′), 6.94 (dd, 1, H-5 pyridazine, $J_{4,5}$ = 8 Hz, $J_{5,6}$ = 5 Hz), 7.15–8.10 (m, 16, Ar H and H-4 pyridazine), 8.33 (dd, 1, H-6 pyridazine, $J_{5,6}$ = 5 Hz, $J_{4,6}$ = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 63.18 (C-5′), 71.31, 73.83, 77.34, 78.80 (C-1′, C-2′, C-3′, C-4′), 116.24 (C-5 pyridazine), 128.29–133.32 (Ar C and C-4 pyridazine), 149.59 (C-3 pyridazine), 157.48 (C-6 pyridazine), 164.97, 165.15, 166.03 (C=O).

Compound **20** was eluted as the second fraction (1.6 g, 61%; corresponding to R_f 0.29 on TLC) as a colorless foam: MS, m/e 540 (M^+); ^1H NMR ($CDCl_3$) δ 4.50–4.95 (m, 3, H-4′, H-5′), 5.80–5.95 (m, 2, H-2′, H-3′), 7.00–8.20 (m, 18, Ar H and H-4, H-5, H-6 pyridazine); ^{13}C NMR ($CDCl_3$) δ 63.70 (C-5′), 72.19, 75.81, 80.68, 81.08 (C-1′, C-2′, C-3′, C-4′), 113.84 (C-4 pyridazine), 128.41–134.43 (Ar C and C-5, C-6 pyridazine), 160.64 (C-3 pyridazine), 165.15, 166.03 (C=O). Anal. Calcd for $C_{30}H_{24}N_2O_8$: C, 66.66; H, 4.48; N, 5.18. Found for **20**: C, 66.75; H, 4.32; N, 4.94. Found for **21**: C, 66.83; H, 4.55; N, 5.36.

3-(2,3,5-Tri-*O*-benzoyl-α-D-ribofuranosyl)pyridazine 1-Oxide (24) and 2-Oxide (25). The same procedure was used as for the reaction of **11** with *m*-chloroperbenzoic acid. For compound **24**: 59%; mp 176–177.5 °C; R_f 0.36 ($CHCl_3$–EtOH, 25:1); MS, m/e 540 (M^+); ^1H NMR ($CDCl_3$) δ 4.45–4.90 (m, 3, H-4′, H-5′), 5.90 (dd, 1, H-3′, $J_{2',3'}$ = 5 Hz, $J_{3',4'}$ = 7 Hz), 6.17 (t, 1, H-2′, $J_{1',2'} = J_{2',3'}$ = 5 Hz), 7.05–8.10 (m, 18, Ar H and H-4, H-5, H-6 pyridazine). For compound **25**: 20%; mp 178–179 °C; R_f 0.4 ($CHCl_3$–EtOH, 25:1); MS, m/e 540 (M^+); ^1H NMR ($CDCl_3$) δ 4.50–4.90 (m, 3, H-4′, H-5′), 5.95 (dd, 1, H-3′, $J_{2',3'}$ = 4 Hz, $J_{3',4'}$ = 7 Hz), 6.52 (t, 1, H-2′, $J_{1',2'} = J_{2',3'}$ = 4 Hz), 7.03–8.10 (m, 17, Ar H and H-4, H-5 pyridazine), 8.35 (dd, 1, H-6 pyridazine, $J_{5,6}$ = 5 Hz, $J_{4,6}$ = 1.5 Hz). Anal. Calcd for $C_{30}H_{24}N_2O_8$: C, 66.66; H, 4.48; N, 5.18. Found for **24**: C, 66.71; H, 4.38; N, 4.96. Found for **25**: C, 66.41; H, 4.65; N, 5.03.

General Deprotection Procedure. Sufficient methanolic sodium methoxide was added to the protected *C*-nucleoside in absolute methanol. 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*-nucleoside.

2-(β-D-Ribofuranosyl)furan (5): mp 56–57 °C; 95%; MS, m/e 200 (M^+); ^1H NMR (CD_3OD) δ 3.45–3.71 (m, 2, H-5′), 3.80–4.30 (m, 3, H-2′, H-3′, H-4′), 4.76 (s, 3, OH), 6.28 (apparent s, 2, H-3, H-4 furan), 7.45 (d, 1, H-5 furan, $J_{4,5}$ = 1.8 Hz); ^{13}C NMR (CD_3OD) δ 63.65 (C-5′), 72.89, 75.46, 79.32, 85.76 (C-1′, C-2′, C-3′, C-4′), 109.51, 111.27 (C-3, C-4 furan), 143.91 (C-5 furan), 153.92 (C-2 furan).

2-(α-D-Ribofuranosyl)furan (6): colorless foam; 94%; MS, m/e 200 (M^+); ^1H NMR (CD_3OD) δ 3.48–3.78 (m, 2, H-5′), 3.82–4.07 (m, 1, H-4′), 4.19 (m, 2, H-2′, H-3′), 4.73 (s, 3, OH), 6.28–6.52 (m, 2, H-3, H-4 furan), 7.45 (d, 1, H-5 furan, $J_{4,5}$ = 1.5 Hz); ^{13}C NMR (CD_3OD) δ 62.83 (C-5′), 73.24, 73.88, 78.04, 83.18 (C-1′, C-2′, C-3′, C-4′), 109.63, 111.15 (C-3, C-4 furan), 143.03 (C-5 furan), 152.51 (C-2 furan). Anal. Calcd for $C_9H_{12}O_5$: C, 53.99; H, 6.04. Found for **5**: C, 54.17; H, 6.13. Found for **6**: C, 53.74, H, 5.83.

3-(β-D-Ribofuranosyl)pyridazine (13): mp 112–113 °C; 79%; MS, m/e 212 (M^+); ^1H NMR (Me_2SO-d_6) δ 3.70 (m, 2, H-5′), 3.95–4.22 (m, 3, H-2′, H-3′, H-4′), 4.20 (br, 3, OH), 7.77 (dd, 1, H-5 pyridazine $J_{4,5}$ = 8 Hz, $J_{5,6}$ = 5 Hz), 7.93 (d, 1, H-4 pyridazine, $J_{4,5}$ = 8 Hz), 9.17 (d, 1, H-6 pyridazine, $J_{5,6}$ = 5 Hz); ^{13}C NMR (Me_2SO-d_6) δ 61.48 (C-5′), 71.08, 76.69, 83.54, 84.94 (C-1′, C-2′, C-3′, C-4′).

3-(α-D-Ribofuranosyl)pyridazine (17): colorless foam; 55%; MS, m/e 212 (M^+); ^1H NMR (CD_3OD) δ 3.62–4.0 (m, 2, H-5′), 4.1–4.45 (m, 3, H-2′, H-3′, H-4′), 4.88 (s, 3, OH), 7.72 (dd, 1, H-5 pyridazine, $J_{4,5}$ = 8 Hz, $J_{5,6}$ = 5 Hz), 7.85 (dd, 1, H-4 pyridazine, $J_{4,5}$ = 8 Hz, $J_{4,6}$ = 2 Hz), 9.03 (dd, 1, H-6 pyridazine, $J_{5,6}$ = 5 Hz, $J_{4,6}$ = 2 Hz). Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.74; N, 13.20. Found for **13**: C, 51.15; H, 5.87; N, 13.41. Found for **17**: C, 51.21; H, 5.59; N, 13.06.

3-(β-D-Ribofuranosyl)-4,5-dihydro-6(1*H*)-pyridazinone (14): colorless foam; 71%; MS, m/e 230 (M^+); ^1H NMR (Me_2SO-d_6) δ 2.38 (m, 4, H-4, H-5 pyridazine), 3.20–3.58 (m, 3, H-4′, H-5′), 3.70–4.05 (m, 2, H-2′, H-3′), 4.80 (br, 3, OH), 10.60 (s, 1, NH).

3-(α-D-Ribofuranosyl)-4,5-dihydro-6(1*H*)-pyridazinone (18): mp 167–168.5 °C; 68%; MS, m/e 230 (M^+); ^1H NMR (Me_2SO-d_6) δ 2.35 (m, 4, H-4, H-5 pyridazine), 3.20–4.10 (m, 5, H-2′, H-3′, H-4′, H-5′), 4.70 (br, 3, OH), 10.48 (s, 1, NH). Anal. Calcd for $C_9H_{14}N_2O_5$: C, 46.95; H, 6.13; N, 12.17. Found for **14**: C, 47.18; H, 6.24; N, 11.93. Found for **18**: C, 46.72; H, 5.98; N, 12.34.

3-(β-D-Ribofuranosyl)pyridazine 1-Oxide (22): mp 176–177 °C; 83%; MS, m/e 228 (M^+); ^1H NMR (Me_2SO-d_6) δ 3.66 (apparent s, 2, H-5′), 4.01 (apparent s, 3, H-2′, H-3′, H-4′), 5.00 (br, 3, OH), 7.50 (d, 1, H-4 pyridazine, $J_{4,5}$ = 8 Hz), 7.91 (t, 1, H-5 pyridazine, $J_{4,5} = J_{5,6}$ = 8 Hz), 8.30 (d, 1, H-6 pyridazine, $J_{5,6}$ = 8 Hz); ^{13}C NMR (Me_2SO-d_6) δ 61.36 (C-5′), 70.90, 76.52, 82.43, 84.94 (C-1′, C-2′, C-3′, C-4′).

3-(β-D-Ribofuranosyl)pyridazine 2-Oxide (23): mp 63–64.5 °C; 75%; MS, m/e 228 (M^+); ^1H NMR (Me_2SO-d_6) δ 3.40–4.03 (m, 5, H-2′, H-3′, H-4′, H-5′), 5.00 (br, 3, OH), 7.37 (dd, 1, H-5 pyridazine, $J_{4,5}$ = 8 Hz, $J_{5,6}$ = 6 Hz), 8.30 (dd, 1, H-4 pyridazine, $J_{4,5}$ = 8 Hz, $J_{4,6}$ = 2 Hz), 8.56 (dd, 1, H-6 pyridazine, $J_{5,6}$ = 6 Hz, $J_{4,6}$ = 2 Hz). ^{13}C NMR (Me_2SO-d_6) δ 59.73 (C-5′), 69.44, 73.53, 80.09, 82.13 (C-1′, C-2′, C-3′, C-4′). Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.28. Found for **22**: C, 47.61; H, 5.17; N, 12.43. Found for **23**: C, 47.53; H, 5.42; N, 12.07.

Registry No. **1**, 22860-91-9; **2**, 5857-37-4; **3**, 86528-49-6; **4**, 86528-50-9; **5**, 86528-51-0; **6**, 86528-64-5; **7**, 86528-52-1; **8**, 86528-53-2; **9** (isomer 1), 86528-54-3; **9** (isomer 2), 86561-48-0; **10** (isomer 1), 86561-47-9; **10** (isomer 2), 86561-49-1; **11**, 86528-55-4; **12**, 86528-56-5; **13**, 86528-65-6; **14**, 86528-67-8; **15**, 86528-57-6; **16**, 86528-58-7; **17**, 86528-66-7; **18**, 86528-68-9; **19**, 86528-59-8; **20**, 86528-60-1; **21**, 86528-61-2; **22**, 86528-69-0; **23**, 86528-70-3; **24**, 86528-62-3; **25**, 86528-63-4; 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose, 14215-97-5; hydrazine hydrochloride, 14011-37-1.