C-Nucleosides. 5. Synthesis of 5-Hydroxy-5-(β-D-ribofuranosyl)-3-pyrrolin-2-one from Glycosylfuran

Isamu Maeba, Osamu Hara, Makoto Suzuki, and Hiroshi Furukawa*

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

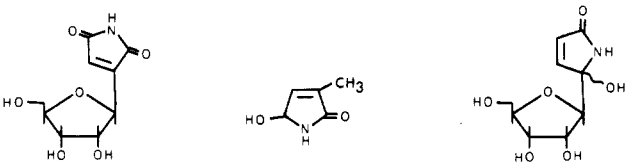
Received February 26, 1986

Synthesis of 5-hydroxy-5-(β-D-ribofuranosyl)-3-pyrrolin-2-one (**18**) from 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)furan (**3**) is described. Treatment of β- and α-azido compounds **9** and **10** with *tert*-butyl alcohol in benzene afforded only *tert*-butyl *N*-[5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-furyl]carbamate (**11**). Autoxidation of carbamate **11** afforded pyrrolinone **14** in 47% yield. Cleavage of the *N*-*tert*-butoxycarbonyl group of **14** was performed by treatment with trifluoroacetic acid in chloroform to give 5-hydroxy-5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-3-pyrrolin-2-one (**15**). Deblocking of **15** with 5% sodium hydroxide solution gave **18**. Treatment of **18** with trifluoroacetic acid gave the spiro pyrrolinone **21** in 71% yield. The configuration of the spiro position in **21** was established by NOE experiments. The spiro compound underwent the ring opening with methanolic hydrochloric acid to give **19**, which was also obtained on treatment of **18** with methanolic hydrochloric acid.

The *C*-glycosyl nucleoside showdomycin, 3-(β-D-ribofuranosyl)maleimide (**1**), was first isolated from *Streptomyces showdoensis* by Nishimura et al.,[1] and as the compound shows significant antibacterial and antitumor activities, it has been the subject of numerous biochemical studies that have been reviewed.[2] The activity of showdomycin is based upon its ability to act as an alkylating agent for sulfhydryl groups of enzymes,[3] wherein the sulfhydryl groups add to the maleimide double bond. Jatropham, 5-hydroxy-3-methyl-3-pyrrolin-2-one (**2**), is an alkaloid isolated from *Jatropha macrorhiza* (Euphorbiaceae) and had inhibitor activity toward the P-388 lymphocytic leukemia test system.[4] These findings prompted us to synthesize pyrrolinone *C*-nucleoside **18**, which is structurally related to **1** and **2**. During the course of our research, we developed a preparative procedure for the versatile *C*-nucleoside precursor 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)furan (**3**)[5] and its utilization in the synthesis of pyridazine,[5] phthalimide,[6] and phthalazine[7] *C*-nucleosides. We report herein the synthesis of **18** from **3**. The procedure for conversion of the furan ring of **3** into a pyrrole ring utilized the propensity of aminofuran **11** to undergo autoxidation[8] (Chart I).

Glycosylfuran **3** was efficiently formylated with dimethylformamide and $POCl_3$. Aldehyde **5** was oxidized with Jones reagent at 0 °C to afford the carboxylic acid **7** in 93% yield. The carboxylic acid **7** was chlorinated with thionyl chloride, and the acid chloride, without isolation, was treated with sodium azide in dioxane. The resulting acyl azide **9** was obtained in an overall yield of 77% from **3**. It is reasonable to assume that **5**, **7**, and **9** have the β configuration as does the precursor **3**. To confirm this, we prepared the corresponding α anomers (**6**, **8**, **10**) from **4** by the method used for the preparation of the β anomers. The assignments of the anomeric configuration at C-1′ to **5**–**10** were based on comparison of their ^1H NMR spectra. In the β isomers the H-1′ signal is consistently found at higher field than in the corresponding α isomer.[9] Thus,

Chart I



1 **2** **18**

5, **7**, and **9** exhibited the H-1′ signal upfield (δ 5.38, 5.37, 5.35) of **6**, **8**, and **10** (δ 5.62, 5.56, 5.66). This showed that the β-ribofuranoside configuration had been preserved during the reaction sequence. Treatment of β-acyl azide **9** with *tert*-butyl alcohol in benzene at reflux for 10 h afforded the desired relatively unstable carbamate **11** in 86% yield as a syrup after purification by silica gel column chromatography (Scheme I). On the other hand, treatment of α-acyl azide **10** under the same reaction conditions also afforded a 31% yield of carbamate **11** with no trace of the other anomer. The unavailability of the other carbamate **11** anomer made interfered with assignment of anomeric configuration on the basis of its NMR spectrum. In an attempt to synthesize the corresponding 2,3-*O*-isopropylidene derivative to settle this point unequivocally, debenzoylation of **11** which because of its instability was used immediately after workup was attempted, but basic or acidic conditions alike led to the formation of a number of unidentified products. It is reasonable, however, to assume that carbamate **11** has the β configuration, because complete inversion in high yield from β to α would be highly unlikely. A plausible mechanism for the conversion of acyl azide to carbamate is shown on Scheme II.[10] It is noteworthy that the spiro ring structure **12** is essential for this mechanism. Subsequent cyclization yields the thermodynamically more stable isomer,[11] whose stereochemistry was therefore assumed to be β.

The formation of pyrroles by photoxidation or autoxidation of 2-furylcarbamates has been described in the literature.[8] Unsensitized photoxygenation of **11** with a 400-W high-pressure mercury lamp in chloroform afforded *N*-(*tert*-butoxycarbonyl)pyrrolinone **14** in only 13% yield, but yields in other solvents such as benzene, ether, acetone, dichloromethane, and tetrahydrofuran were lower. These

(1) Nishimura, H.; Mayama, M.; Komatsu, Y.; Kato, H.; Simaoka, N.; Tanaka, Y. *J. Antibiot., Ser. A* **1964**, *17*, 148.
(2) Suhandolnik, R. J. *Nucleoside Antibiotics*; Wiley-Interscience: New York, 1970; p 193.
(3) Kalman, T. I. *Biochem. Biophys. Res. Commun.* **1972**, *49*, 1007.
(4) Wiedhopf, R. M.; Trumbull, E. R.; Cole, J. R. *J. Pharm. Sci.* **1973**, *62*, 1206.
(5) Maeba, I.; Iwata, K.; Usami, F.; Furukawa, H. *J. Org. Chem.* **1983**, *48*, 2998.
(6) Maeba, I.; Usami, F.; Furukawa, H. *J. Org. Chem.* **1984**, *49*, 1534.
(7) Maeba, I.; Ishikawa, T.; Furukawa, H. *Carbohydr. Res.* **1985**, *140*, 332.
(8) Yakushijin, K.; Kozuka, M.; Ito, Y.; Suzuki, R.; Furukawa, H.; *Heterocycles* **1980**, *14*, 1073.
(9) Chu, C. K.; El-Kabbani, F. M.; Thompson, B. B. *Nucleosides Nucleotides* **1984**, *3*, 1.
(10) Patai, S. *The Chemistry of the Azido Group*; Wiley-Interscience: New York, 1971; p 215.
(11) Hanessian, S.; Ogawa, T.; Guidon, Y. *Carbohydr. Res.* **1974**, *38*, C12.

0022-3263/87/1952-2368$01.50/0

Table I. 270-MHz Proton Magnetic Resonance Spectra[a] of Certain *C*-Nucleosides

compd	H-1′	H-2′	H-3′	H-4′	Ha-5′	Hb-5′	H-3	H-4	others
18	3.79 (d)	3.95–4.11 (m)					6.03 (d)	7.11 (d)	
	3.84 (d)			3.87 (m)	3.71–3.78 (m)	3.57–3.65 (m)	6.03 (d)	7.11 (d)	
19a		3.84–3.91 (m)			3.72 (dd)	3.58 (dd)	6.18 (d)	7.04 (d)	3.17 (s, OCH_3)
19b		3.83–4.08 (m)			3.71 (dd)	3.54 (dd)	6.20 (d)	7.02 (d)	3.17 (s, OCH_3)
22a	4.10 (d)	4.34 (t)	4.77 (dd)	4.23 (m)	3.94 (dd)	3.69 (dd)	6.28 (dd)	6.91 (dd)	3.22 (s, OCH_3) 1.52 1.32 (s, $C(CH_3)_2$) 7.66 (br s, NH), 1.30 (br, OH)
22b	3.98 (d)	4.84 (dd)	4.73 (dd)	4.29 (q)[b]	3.80 (dd)	3.65 (dd)	6.28 (dd)	6.85 (m)[c]	3.22 (s, OCH_3) 1.51 1.35 (s, $C(CH_3)_2$) 6.85 (m, NH), 1.75 (br, OH)

compd	H-1	H-7	H-6	H-5	Ha-4	Hb-4	H-3′	H-4′	others
20a	4.00 (s)	4.85 (s)		4.26 (d)	3.99 (dd)	3.73 (dd)	6.18 (dd)	7.58 (dd)	1.49 1.37 (s, $C(CH_3)_2$) 7.17 (br s, NH)
20b	3.99 (s)	4.90 (d)	4.88 (d)	4.29 (d)	3.96 (dd)	3.68 (dd)	6.22 (dd)	6.83 (dd)	1.49 1.38 (s, $C(CH_3)_2$) 7.36 (br s, NH)
21a	3.81 (br s)	4.51 (d)[d]	4.36 (d)[d]	4.12 (br s)	3.97 (dd)	3.71 (dt)	6.11 (d)	7.71 (d)	
21b	3.81 (br s)	4.51 (d)[d]	4.41 (d)[d]	4.12 (br s)	3.94 (dd)	3.66 (dt)	6.14 (d)	7.03 (d)	

[a] Spectra were obtained in deuteriated methanol (**18**, **19a**, **19b**, **21a**, **21b**) and deuteriated chloroform (**20a**, **20b**, **22a**, **22b**) with tetramethylsilane as internal standard. The chemical shift values (δ) are downfield from Me_4Si. [b] Apparent quartet. [c] NH and H-4 peaks overlapped. [d] Tentative assignment.

Table II. ^1H Coupling Constants (J, Hz) of Certain *C*-Nucleosides

compd	1′,2′	2′,3′	3′,4′	4′,5′a	4′,5′b	5′a,5′b	3,4	3,NH	4,NH
18	4.8						6.0		
	4.4	*a*	*a*	*a*	*a*	*a*	6.0		
19a	*a*	*a*	*a*	3.0	5.0	11.9	6.0		
19b	*a*	*a*	*a*	3.0	5.3	11.7	6.0		
22a	5.3	6.3	3.0	2.3	2.0	12.4	5.8	1.6	1.6
22b	4.3	6.0	2.3	2.6	3.6	12.1	6.0	1.3	*a*

compd	1,7	7,6	6,5	5,4a	5,4b	4a,4b	1,5	1,4a	1,4b	3′,4′	3′,NH	4′,NH
20a	0	0	0	2.0	1.0	11.0	0	0	0	5.8	1.6	1.6
20b	0	6.0	0	2.0	1.0	11.0	0	0	0	5.8	1.6	1.6
21a	0	6.3	0	2.2	1.0	11.7	~0	~0	1.0	6.0		
21b	0	6.3	0	2.2	1.0	11.7	~0	~0	1.0	6.0		

[a] Unresolved.

reactions were accompanied by formation of side products observed by thin-layer chromatography that could not be identified due to their instability. However, on stirring at room temperature in daylight for 30 h, **11** underwent autoxidation to pyrrolinone **14** in 47% yield (Scheme III).

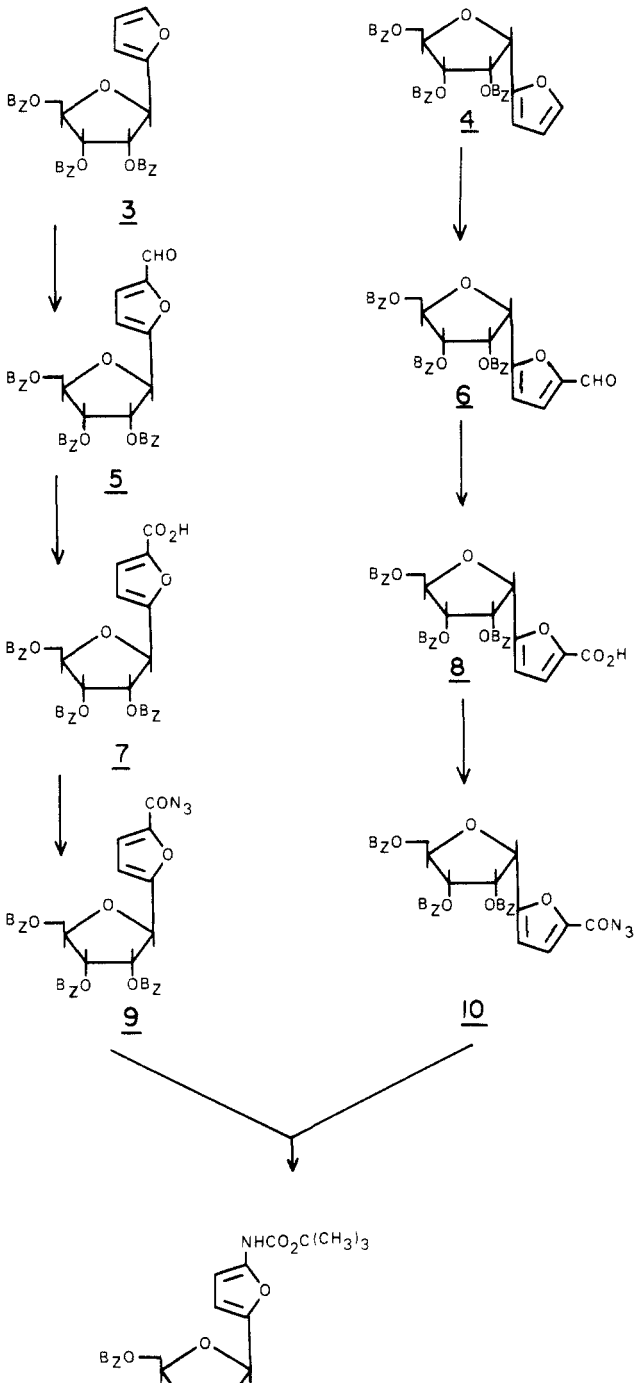
Removal of the *N-tert*-butoxycarbonyl group of **14** by treatment with trifluoroacetic acid in chloroform at 0–5 °C for 1 h gave in 55% yield the protected hydroxypyrrolinone **15** as a 1:1 mixture of two diastereoisomers that could be separated by preparative TLC. The similar chemical shifts of the anomeric protons in the NMR spectra of the individual isomers indicated that both had the β configuration and thus were diastereomeric only at the carbon bearing the hydroxy group. The occurrence of ring–chain tautomerism in systems related to that present in compounds of type **15** is well-known.[12] However, the ^{13}C NMR and ^1H NMR spectral data in the Experimental Section support the hydroxy lactam structure for both in the solvent used and show that the contribution of the tautomeric open-chain keto amide form **16** is not important. Of interest was the observation of the H-1′ signal at unexpectedly higher field at δ 4.22 compared with that of H-5′ at δ 4.64. The assignment was confirmed by double irradiation and may be attributed to the shielding effect of the hydroxy group adjacent to the anomeric proton. Attempt to determine the configuration at the 5-position by X-ray analysis were frustrated by our inability to obtain suitable crystals. The hydroxypyrrolinones **15** react with methanol in the presence of a catalytic amount of acid to give the separable diastereomeric mixture of methoxypyrrolinones **17** in 93% yield.

Debenzoylation of **15** with 5% sodium hydroxide solution at room temperature afforded a mixture of diastereomic 5-hydroxy-5-(β-D-ribofuranosyl)-3-pyrrolin-2-ones (**18**) in 1:1 ratio, which could not be resolved, even by preparative TLC. The mixture **18** reacted smoothly with methanol in the presence of a catalytic amount of acid to give the separable deprotected methoxypyrrolinones **19**, which could also be prepared by debenzoylation of **17**. In order to determine the anomeric configuration, we attempted to prepare the diastereomeric acetonides from **18** with ethyl orthoformate/*p*-toluenesulfonic acid; however, instead compounds **20a** and **20b** were formed in a ratio of 1:3 (Scheme IV). The spiro structure was established by the ^1H NMR splitting pattern[13] 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 value, $J_{1,7} = J_{5,6} = 0$ Hz, provides definite evidence for the trans configuration. The configuration at C-2 was also established by nuclear Overhauser effect

(12) Flitsch, W. *Chem. Ber.* **1970**, *103*, 3205.

(13) Nakagawa, Y.; Kano, H.; Tsukuda, Y.; Koyama, H. *Tetrahedron Lett.* **1967**, *42*, 4105.

Scheme I



(NOE) experiments. Irradiation of the NH (δ 7.58) and overlapping olefinic proton (δ 7.58, H-4′) in **20a** gave a 12.9% enhancement of the signal at δ 4.85 assignable to H-7, a 15.1% enhancement of the signal at δ 6.18 assignable to H-3′, and 10.8% enhancement of the signal at δ 3.99 assignable to Ha-4. On addition of deuterium oxide, the enhancement of the signal at δ 4.85 due to H-7 disappeared. Irradiation of the olefinic proton (δ 6.83, H-4′) in **20b** gave a 12.1% enhancement of the signal at δ 4.90 assignable to H-7 and 15.4% enhancement of the signal at δ 6.22 assignable to H-3′. These data indicate that **20a** and **20b** are 2*R* and 2*S*, respectively. The H-4′ signal of **20a** at δ 7.58 occurs at lower field than that of **20b** at δ 6.83. The difference of chemical shift can be attributed to the deshielding effect of a sugar oxygen atom. Another technique utilized for assignment of anomeric configuration is an application of spin–lattice relaxation time (T_1) for the anomeric proton.[14] The T_1 for β anomers was found to be about 2.5 times longer (3.25–4.18 s) than for the α anomers (1.35–1.06 s). The configuration of **18** was also supported by its T_1 (3.11 s) for anomeric proton. Deprotection of **20a** with 90% trifluoroacetic acid also gave a mixture of diastereomers **21a** and **21b** in 75% yield that could be separated. Treatment of **18** with 90% trifluoroacetic acid also gave **21a** and **21b**. Stirring of **21a** with 90% trifluoroacetic acid afforded **21b**, while pure **21b** epimerized to **21a** under the same conditions. At the equilibrium point the *R*:*S* ratio was approximately 1:3. Thus, shown in Scheme V, protonation of the O-3 of the dioxane ring results in opening and reclosure to take place the preponderant product, 2*S* (**20b**, **21b**), resulting from attack by the 5′-OH on the syn conformer, as expected. Treatment of mixture **21** with hydrochloric acid in methanol afforded a mixture of diastereomers **19** in 64% yield.

The configuration of **19** was established as β on the basis of ^{13}C and ^{1}H NMR chemical shift data. Treatment of **19** with ethyl orthoformate in the presence of *p*-toluenesulfonic acid gave predominantly the isopropylidene derivatives **22a,b**, whereas prolonged treatment afforded **20a,b** predominantly. Now the ^{13}C NMR signals of the isopropylidene methyl in acetonides of nucleosides occur at chemical shift values of 25.5 ± 0.2 and 27.5 ± 0.2 ppm in the β anomers and at 24.9 ± 0.3 and 26.3 ± 0.2 ppm in the α anomers.[15] The acetonides **22a,b** exhibit chemical shifts at 25.45 and 27.44 ppm consistent with a β assignment. The ^{1}H NMR spectra showed two singlets at δ 1.52 and 1.32 for **22a** and at δ 1.51 and 1.35 for **22b** with Δδ = 0.2 and 0.16 ppm; a value of less than 0.10 ppm would be expected in the case of an α anomer.[16] The actual stereochemical assignment (*R*, *S*) of **22** was not readily obtainable from available spectral data. Studies to evaluate the biological activity of these pyrrolinone *C*-nucleosides will be reported elsewhere.

Experimental Section

Melting points were determined on a Yanagimoto apparatus and are uncorrected. Infrared (IR) spectra were measured with a Jasco IRA-1 spectrometer. ^{1}H NMR spectra were measured with a JEOL JNM-PS-100 and 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. Analytical thin-layer chromatography was performed on glass plates coated with a 0.5-mm layer of silica gel GF_{254} (Merck). The compounds were detected with a UV light (254 nm). Column chromatography was performed on silica gel C-200 (74–149 μm, Wakogel).

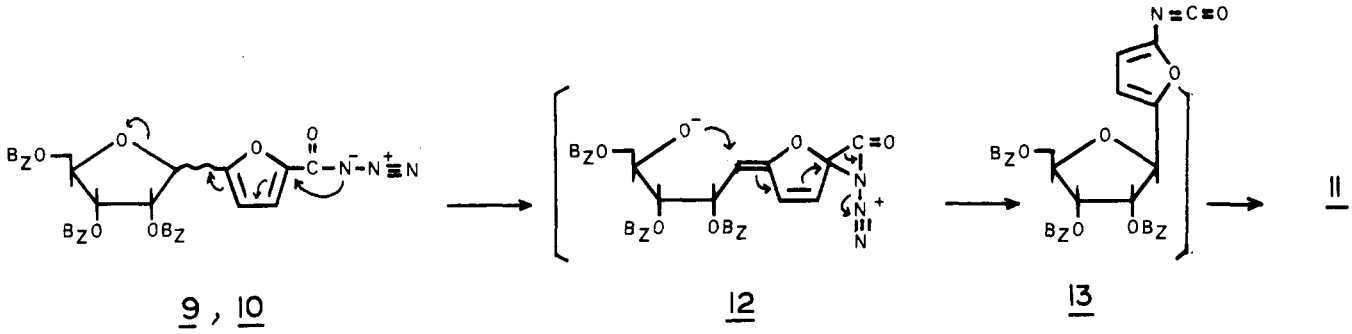
5-(2,3,5-Tri-*O*-benzoyl-β- and -α-D-ribofuranosyl)-2-furancarboxaldehyde (5 and 6). To a mixture of 286 mg (4 mmol) of dimethylformamide and 600 mg (4 mmol) of phosphorus oxychloride, which was kept at 0–5 °C for 20 min, was added 2.0 g (3.9 mmol) of **3** in 2 mL of dimethylformamide under stirring at such a rate that the temperature of reaction mixture did not rise about 20 °C. After the addition of **3**, the mixture was kept at 80 °C for 40 min. The reaction mixture was poured into 100 mL of cracked ice and water and neutralized with sodium bicarbonate, and the mixture was extracted with ethyl acetate (3 × 30 mL). The extracts were combined, washed with water, dried

(14) Tran-Dinh, S.; Newmann, J. M.; Thiery, J. M.; Huynh-Dihn, J.; Igolen, J.; Guschlbauer, W. *J. Am. Chem. Soc.* **1977**, *99*, 3267. Legraverend, M.; Bisagni, E.; Lhoste, J.-M. *J. Heterocycl. Chem.* **1981**, *18*, 893.

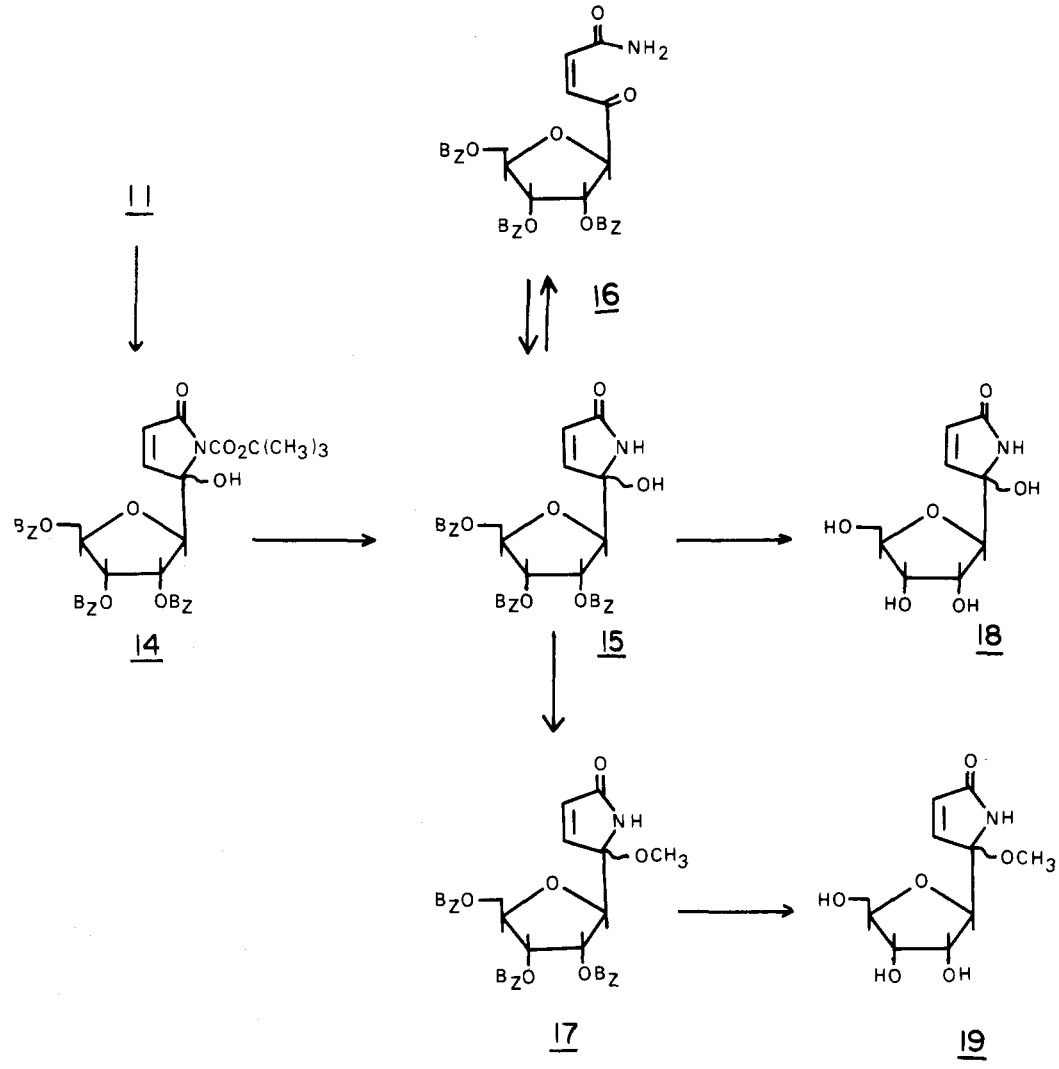
(15) Ohrui, H.; Jones, G. H.; Moffatt, J. G.; Maddox, M. L.; Christensen, A. T.; Bryam, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4602.

(16) Imbach, J. L.; Kam, B. L. *J. Carbohydr., Nucleosides, Nucleotides* **1974**, *1*, 271.

Scheme II



Scheme III



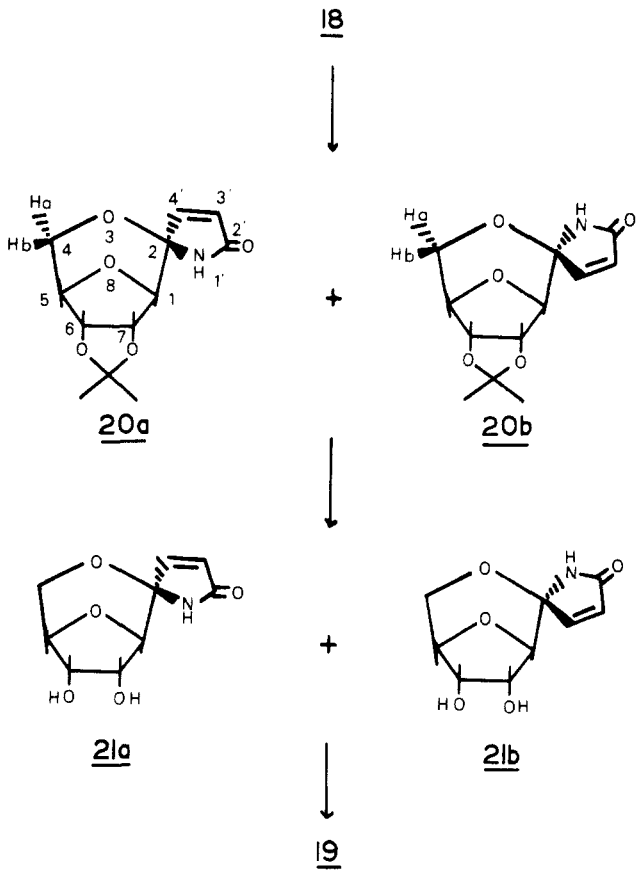
over magnesium sulfate, and evaporated in vacuo to a brown syrup. The residue was chromatographed over a column of silica gel with chloroform as the eluent. This afforded 2.1 g (96%) of **5** as a colorless crystals: mp 90–91 °C; ^{1}H NMR ($CDCl_3$) δ 4.40–4.96 (m, 3, H-4′, H-5′), 5.38 (d, 1, H-1′, $J_{1',2'}$ = 6 Hz), 5.78–6.00 (m, 2, H-2′, H-3′), 6.60 (d, 1, H-4, $J_{3,4}$ = 4 Hz), 7.16 (d, 1, H-3, $J_{3,4}$ = 4 Hz), 7.28–8.18 (m, 15, Ar H), 9.48 (s, 1, CHO). Anal. Calcd for $C_{31}H_{24}O_9 \cdot H_2O$: C, 66.66; H, 4.69. Found: C, 66.68; H, 4.47.

In the same manner 1.4 g (64%) of α anomer **6** was obtained as a colorless foam from 2.0 g of **4**: ^{1}H NMR ($CDCl_3$) δ 4.40–5.00 (m, 3, H-4′, H-5′), 5.62 (d, 1, H-1′, $J_{1',2'}$ = 6 Hz), 5.86 (t, 1, H-3′, $J_{2',3'} = J_{3',4'}$ = 6 Hz), 6.02 (t, 1, H-2′, $J_{1',2'} = J_{2',3'}$ = 6 Hz), 6.60 (d, 1, H-4, $J_{3,4}$ = 4 Hz), 7.08 (d, 1, H-3, $J_{3,4}$ = 4 Hz), 7.12–8.20 (m, 15, Ar H), 9.44 (s, 1, CHO). Anal. Calcd for $C_{31}H_{24}O_9$: C, 68.80; H, 4.44. Found: C, 68.61; H, 4.40.

5-(2,3,5-Tri-*O*-benzoyl-β- and -α-D-ribofuranosyl)-2-furoic Acid (7 and 8). A solution of chromium trioxide (10 g) in concentrated sulfuric acid (11 mL) and water (50 mL) was cautiously added to a stirred solution of **5** (886 mg, 1.6 mmol) in acetone (10 mL) at 0 °C until an orange–yellow color persisted. The solution was stirred for an additional 1 h at 0 °C. 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. The residue was chromatographed over a column of silica gel with chloroform as the eluent. This afforded 800 mg (93%) of **7** as a colorless crystals: mp 64–65 °C; ^{1}H NMR ($CDCl_3$) δ 4.82 (s, 3, H-4′, H-5′), 5.37 (d, 1, H-1′, $J_{1',2'}$ = 6 Hz), 5.60–6.04 (br s, 2, H-2′, H-3′), 6.70 (br s, 1, H-4), 7.20–8.30 (m, 16, Ar H, H-3).

In the same manner, 160 mg (62%) of α anomer **8** was obtained as a colorless foam from 270 mg of **6**: ^{1}H NMR ($CDCl_3$) δ 4.20–5.00 (m, 3, H-4′, H-5′), 5.40 (br, 1, COOH), 5.56 (d, 1, H-1′, $J_{1',2'}$ = 6 Hz), 5.62–6.12 (m, 2, H-2′, H-3′), 6.36 (d, 1, H-4, $J_{3,4}$ = 4 Hz), 6.86 (d, 1, H-3, $J_{3,4}$ = 4 Hz), 7.00–8.00 (m, 15, Ar H). Anal. Calcd for

Scheme IV



$C_{31}H_{24}O_{10}\cdot 3H_2O$: C, 60.98; H, 4.95. Found for **7**: C, 60.79; H, 5.03. Found for **8**: C, 61.17; H, 4.82.

5-(2,3,5-Tri-*O*-benzoyl-β- and -α-D-ribofuranosyl)-2-furoyl Azide (9 and 10). A solution of **7** (1.05 g, 1.9 mmol) and thionyl chloride (339 mg, 2.85 mmol) in benzene (40 ml) was refluxed under stirring for 2 h. Evaportion of excess of thionyl chloride and benzene gave a brownish oil, to which was added 4 mL of dioxane. To the cooled solution was added 185 mg (2.85 mmol) of sodium azide in 1 mL of water. The mixture was stirred for 1 h at room temperature, poured into 50 mL of cracked ice and water, and extracted with chloroform (3 × 10 mL). The extracts were combined, washed with water, dried over magnesium sulfate, and evaporated to a syrup. The residue was chromatographed over a column of silica gel with chloroform as the eluent. This afforded 950 mg (84%) of **9** as a syrup: IR ($CHCl_3$) 2150 cm^{-1} (N_3); ^1H NMR ($CDCl_3$) δ 4.56–4.93 (m, 3, H-4′, H-5′), 5.35 (d, 1, H-1′, $J_{1',2'}$ = 6 Hz), 5.76–6.06 (m, 2, H-2′, H-3′), 6.57 (d, 1, H-4, $J_{3,4}$ = 4 Hz), 7.12–8.18 (m, 16, Ar H, H-3).

In the same manner 620 mg (75%) of α anomer **10** was obtained as a colorless foam from 800 mg of **8**: IR ($CHCl_3$) 2150 cm^{-1} (N_3); ^1H NMR ($CDCl_3$) δ 4.44–5.00 (m, 3, H-4′, H-5′), 5.66 (d, 1, H-1′, $J_{1',2'}$ = 6 Hz), 5.92 (t, 1, H-3′, $J_{2',3'} = J_{3',4'}$ = 6 Hz), 6.08 (t, 1, H-2′, $J_{1',2'} = J_{2',3'}$ = 6 Hz), 6.62 (d, 1, H-4, $J_{3,4}$ = 4 Hz), 7.18–8.20 (m, 16, Ar H, H-3). Anal. Calcd for $C_{31}H_{23}N_3O_9$: C, 64.03; H, 3.99; N, 7.23. Found for **9**: C, 64.25; H, 4.06; N, 6.93. Found for **10**: C, 63.75; H, 4.13; N, 7.05.

***tert*-Butyl *N*-[5-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2-furyl]carbamate (11).** A solution of **9** (831 mg, 1.43 mmol) in benzene (32 mL) and *tert*-butyl alcohol (14.5 mL) was refluxed under stirring for 10 h. Excess of reagent and benzene were removed by evaporation in vacuo. This residue was chromatographed over a column of silica gel with chloroform as the eluent. This afforded 750 mg (86%) of **11** as a syrup: ^1H NMR ($CDCl_3$) δ 1.50 (s, 9, $C(CH_3)_3$), 4.30–4.85 (m, 3, H-4′, H-5′), 5.19 (d, 1, H-1′, $J_{1',2'}$ = 5 Hz), 5.88–6.00 (m, 3, H-2′, H-3′, H-3), 6.24 (br s, 1, NH), 6.41 (d, 1, H-4, $J_{3,4}$ = 4 Hz), 7.14–8.24 (m, 15, Ar H).

In the same manner 49 mg (31%) of **11** was obtained as a syrup from 150 mg of **10**. Identity was confirmed by comparing IR and ^1H NMR spectra. Although this compound was homogeneous by TLC, we were unable to obtain proper microanalytical data for it.

(5*R*)- or (5*S*)-*N*-(*tert*-Butoxycarbonyl)-5-hydroxy-5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-3-pyrrolin-2-one (14). A solution of **11** (630 mg, 1.0 mmol) in chloroform (10 mL) was stirred at room temperature in aggregate daylight for 30 h. The solvent were removed under reduced pressure, and the residue was purified by preparative TLC with chloroform as the eluent. This afforded 280 mg (47%) of **14** as a colorless needles: mp 137–139 °C; ^1H NMR ($CDCl_3$) δ 1.34 (s, 9, $C(CH_3)_3$), 4.45–4.94 (m, 3, H-4′, H-5′), 5.05 (d, 1, H-1′, $J_{1',2'}$ = 8 Hz), 5.48 (t, 1, H-2′, $J_{1',2'} = J_{2',3'}$ = 8 Hz), 5.75 (dd, 1, H-3′, $J_{2',3'}$ = 8 Hz, $J_{3',4'}$ = 4 Hz), 6.04 (d, 1, H-3, $J_{3,4}$ = 7 Hz), 7.22 (d, 1, H-4, $J_{3,4}$ = 7 Hz), 7.28–8.26 (m, 15, Ar H). Anal. Calcd for $C_{35}H_{33}NO_{11}$: C, 65.32; H, 5.13; N, 2.17. Found: C, 65.18; H, 5.09; N, 2.02.

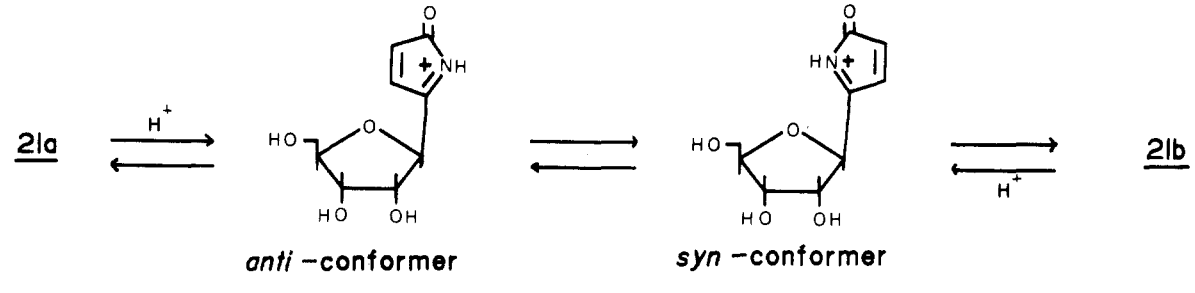
Photooxidation of 11. A solution of **11** (370 mg, 0.6 mmol) in chloroform (10 mL) was irradiated in the presence of oxygen at room temperature for 30 min. The solvent were removed under reduced pressure, and the residue was chromatographed on silica gel with chloroform as the eluent. This afforded 45 mg of **14** (13%) as a colorless needles, mp 137–139 °C. Identity was confirmed by comparing IR and ^1H NMR spectra.

(5*R*)- and (5*S*)-5-Hydroxy-5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-3-pyrrolin-2-one (15a and 15b). A solution of **14** (230 mg, 0.35 mmol) in chloroform (4 mL) was cooled in an ice bath, and 1.1 g of trifluoroacetic acid was added dropwise with stirring. The reaction mixture was stirred at 0–5 °C for 1 h. Sodium bicarbonate was added, and the mixture was stirred for 1 h. The solid was collected by filtration, thoroughly washed with chloroform, and dried over magnesium sulfate. Evaporation of the solvent in vacuo gave a syrup that was chromatograph over a column of silica gel with chloroform as the eluent. This afforded 107 mg (55%) of the two isomers of **15** as a colorless foam. The isomers were separable by preparative TLC with benzene–ethyl acetate (2:1) as the eluent after four elutions.

Faster Isomer 15a: colorless crystals; mp 65–67 °C; R_f 0.48 (benzene–ethyl acetate, 1:2); ^1H NMR ($CDCl_3$) δ 4.22 (d, 1, H-1′, $J_{1',2'}$ = 4 Hz), 4.64 (br s, 3, H-4′, H-5′), 5.63 (t, 1, H-3′, $J_{2',3'} = J_{3',4'}$ = 6 Hz), 5.82 (dd, 1, H-2′, becomes a doublet when the H-1′ is irradiated, $J_{1',2'}$ = 4 Hz, $J_{2',3'}$ = 6 Hz), 6.04 (d, 1, H-3, $J_{3,4}$ = 6 Hz), 7.06 (d, 1, H-4, $J_{3,4}$ = 6 Hz), 7.24–8.12 (m, 15, Ar H), 3.65, 6.98 (each br s, 1 each, OH, NH); ^{13}C NMR ($CDCl_3$) δ 64.06 (C-5′), 72.42, 72.89, 79.68, 86.58 (C-1′, C-2′, C-3′, C-4′), 88.69 (C-5), 127.59–133.56 (Ar C, C-3), 149.29 (C-4), 165.38, 165.62, 172.34 (C=O).

Slower Isomer 15b: Colorless needles; mp 154–156 °C; R_f 0.42 (benzene–ethyl acetate, 1:2); ^1H NMR ($CDCl_3$) δ 4.21 (d, 1, H-1′, $J_{1',2'}$ = 4 Hz), 4.68 (br s, 3, H-4′, H-5′), 5.65–5.90 (m, 2, H-2′, H-3′),

Scheme V



6.06 (d, 1, H-3, $J_{3,4}$ = 6 Hz), 7.08 (d, 1, H-4, $J_{3,4}$ = 6 Hz), 7.30–8.14 (m, 15, Ar H), 4.18, 6.76 (each s, 1 each, OH, NH); ^{13}C NMR ($CDCl_3$) δ 64.35 (C-5′), 72.60, 72.95, 79.62, 86.23 (C-1′, C-2′, C-3′, C-4′), 88.98 (C-5), 128.35–133.38 (Ar C, C-3), 148.36 (C-4), 165.38, 166.61, 171.88 (C=O).

Anal. Calcd for $C_{30}H_{25}NO_9$ (mixture): C, 66.30; H, 4.62; N, 2.58. Found: C, 65.97; H, 4.54; N, 2.38.

(5*R*)- and (5*S*)-5-Methoxy-5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-3-pyrrolin-2-one (17a and 17b). A solution of **15** (500 mg, 1 mmol) in methanol (10 mL) containing 4 drops of concentrated hydrochloric acid was allowed to stir at room temperature for 24 h. The reaction mixture was neutralized with anhydrous sodium bicarbonate. The solid was collected by filtration and thoroughly washed with methanol. The filtrates were combined and evaporated in vacuo to a syrup, which was separated by preparative TLC with benzene–ethyl acetate (4:1) as the eluent after three elutions. This afforded 475 mg (93%) of **17** as a colorless foam.

Faster Isomer 17a: colorless foam; R_f 0.38 (benzene–ethyl acetate, 4:1); ^{1}H NMR ($CDCl_3$) δ 3.10 (s, 3, OCH_3), 4.18 (d, 1, H-1′, $J_{1',2'}$ = 4 Hz), 4.44–4.95 (m, 3, H-4′, H-5′), 5.61 (t, 1, H-3′, $J_{2',3'} = J_{3',4'}$ = 6 Hz), 5.82 (dd, 1, H-2′, $J_{1',2'}$ = 4 Hz, $J_{2',3'}$ = 6 Hz), 6.19 (d, 1, H-3, $J_{3,4}$ = 6 Hz), 6.70 (br s, 1, NH), 6.98 (d, 1, H-4, $J_{3,4}$ = 6 Hz), 7.10–8.20 (m, 15, Ar H); ^{13}C NMR ($CDCl_3$) δ 50.66 (CH_3), 63.30 (C-5), 72.42, 79.38, 87.58 (C-1′, C-2′, C-3′, C-4′), 92.61 (C-5), 128.41–133.50 (Ar C, C-3), 147.49 (C-4), 165.33, 165.68, 166.21, 171.65 (C=O).

Slower Isomer 17b: colorless foam; R_f 0.33 (benzene–ethyl acetate, 4:1); ^{1}H NMR ($CDCl_3$) δ 3.08 (s, 3, OCH_3), 4.21 (d, 1, H-1′, $J_{1',2'}$ = 3 Hz), 4.44–4.92 (m, 3, H-4′, H-5′), 5.74 (t, 1, H-3′, $J_{2',3'} = J_{3',4'}$ = 6 Hz), 5.88 (dd, 1, H-2′, $J_{1',2'}$ = 3 Hz, $J_{2',3'}$ = 6 Hz), 6.24 (d, 1, H-3, $J_{3,4}$ = 6 Hz), 6.45 (br s, 1, NH), 7.05 (d, 1, H-4, $J_{3,4}$ = 6 Hz), 7.14–8.20 (m, 15, Ar H); ^{13}C NMR ($CDCl_3$) δ 50.54 (CH_3), 63.60 (C-5′), 72.60, 78.39, 79.21, 86.70 (C-1′, C-2′, C-3′, C-4′), 92.84 (C-5), 128.35–133.44 (Ar C, C-3), 146.37 (C-4), 165.38, 166.20, 170.95 (C=O).

Anal. Calcd for $C_{31}H_{27}NO_9$ (mixture): C, 66.78; H, 4.88; N, 2.51. Found: C, 66.80; H, 5.01; N, 2.34.

(5*R*)- and (5*S*)-5-Hydroxy-5-(β-D-ribofuranosyl)-3-pyrrolin-2-one (18). To a solution of **15** (598 mg, 1.1 mmol) in methanol (20 mL) was added 5 mL of 5% NaOH solution at 0 °C for 30 min, and the mixture was allowed to stand at room temperature for 30 min, rendered neutral with acetic acid, and evaporated. The residue was chromatographed over a column of silica gel with chloroform–methanol (2:1) as the eluent. This afforded 148 mg (58%) of **18** as a colorless foam. Despite multiple elutions, the diastereomers were not separated: ^{13}C NMR (C_D3OD) δ 63.18, 63.41 (C-5′), 72.71, 72.89, 85.70, 88.22, 88.63 (C-1′, C-2′, C-3′, C-4′), 90.74 (C-5), 127.54, 128.47 (C-3), 150.64, 151.99 (C-4), 174.22, 174.69 (C=O). Anal. Calcd for $C_9H_{13}NO_6 \cdot H_2O$: C, 43.37; H, 6.07; N, 5.62. Found: C, 43.43; H, 5.95; N, 5.37.

(5*R*)- and (5*S*)-5-Methoxy-5-(β-D-ribofuranosyl)-3-pyrrolin-2-one (19a and 19b). The same procedure was used as the reaction of **15** with methanol containing concentrated hydrochloric acid. Compound **19** (72% from **18**, 64% from **21**) was separated by preparative TLC with chloroform–methanol (8:1) as the eluent after three elutions.

Faster Isomer 19a: colorless foam; R_f 0.51 (chloroform–methanol, 4:1); ^{13}C NMR (CD_3OD) δ 50.95 (OCH_3), 63.35 (C-5′), 72.71, 85.64, 88.16 (C-1′, C-2′, C-3′, C-4′), 95.41 (C-5), 130.22 (C-3), 149.94 (C-4), 174.51 (C=O).

Slower Isomer 19b: colorless foam; R_f 0.48 (chloroform–methanol, 4:1); ^{13}C NMR (CD_3OD) δ 50.83 (OCH_3), 63.59 (C-5′), 72.77, 72.95, 85.18, 88.33 (C-1′, C-2′, C-3′, C-4′), 95.35 (C-5), 130.98 (C-3), 149.18 (C-4), 174.16 (C=O).

Anal. Calcd for $C_{10}H_{15}NO_6 \cdot H_2O$ (mixture): C, 45.62; H, 6.51; N, 5.32. Found: C, 45.35; H, 6.51; N, 5.71.

Debenzoylation of **17** with 5% NaOH solution gave **19**, which was confirmed by comparing IR and ^{1}H NMR spectra.

(1*R*,2*R*)- and (2*S*,5*R*,6*R*,7*R*)-6,7-(Isopropylidenedioxy)-3,8-dioxabicyclo[3.2.1]octane-2-spiro-5′-pyrrolin-2′-one (20a and 20b). Ethyl orthoformate (0.1 mL, 0.5 mmol) was added to a well-stirred suspension of **18** (50 mg, 0.2 mmol) in acetone (1 mL) containing *p*-toluenesulfonic acid monohydrate (4 mg), and the mixture was allowed to stand at room temperature for 12 h. The sodium bicarbonate was added, and the mixture was stirred for 15 min. The solid was collected by filtration and thoroughly washed with acetone. The filtrates were combined and evaporated in vacuo to a syrup that was purified by preparative TLC with benzene–acetone (4:1) as the eluent.

Compound 20a: mp 166–168 °C; 18%; R_f 0.37 (benzene–acetone, 4:1); ^{13}C NMR ($CDCl_3$) δ 24.68, 25.97 (CH_3), 66.34 (C-4), 79.68, 81.26, 82.31, 83.48 (C-1, C-5, C-6, C-7), 88.74 (C-2), 112.44 (isopropylidene C_{quat}), 128.35 (C-3′), 146.08 (C-4′), 172.87 (C=O).

Compound 20b: colorless foam; 55%; R_f 0.32 (benzene–acetone, 4:1); ^{13}C NMR ($CDCl_3$) δ 24.68, 25.97 (CH_3), 65.58 (C-4), 79.97, 80.79, 82.02, 84.53 (C-1, C-5, C-6, C-7), 89.27 (C-2), 112.67 (isopropylidene C_{quat}), 130.51 (C-3′), 144.79 (C-4′), 171.99 (C=O).

Anal. Calcd for $C_{12}H_{15}NO_5$ (mixture): C, 56.91; H, 5.97; N, 5.53. Found: C, 56.62; H, 6.12; N, 5.32.

(1*R*,2*R*)- and (2*S*,5*R*,6*R*,7*R*)-6,7-Dihydroxy-3,8-dioxabicyclo[3.2.1]octane-2-spiro-5′-pyrrolin-2′-one (21a and 21b). A solution of **18** (45 mg, 0.1 mmol) in 90% trifluoroacetic acid was allowed to stir at room temperature for 30 min. Evaporation of the solvent in vacuo gave a syrup that was chromatograph over a column of silica gel with chloroform–methanol (2:1) as the eluent. This afforded 33 mg (71%) of the two isomers of **21** as a colorless foam. The isomers were separable by preparative TLC with chloroform–methanol (20:1) as the eluent after five elutions.

Compound 21a: 14%; colorless foam; R_f 0.53 (chloroform–methanol, 5:1); ^{13}C NMR (CD_3OD) δ 68.15 (C-4), 73.42, 74.59, 84.06, 87.63 (C-1, C-5, C-6, C-7), 90.85 (C-2), 128.53 (C-3′), 148.59 (C-4′), 174.57 (C=O).

Compound 21b: 57%; colorless foam; R_f 0.48 (chloroform–methanol, 5:1); ^{13}C NMR (CD_3OD) δ 67.39 (C-4), 73.07, 74.12, 84.36, 88.69 (C-1, C-5, C-6, C-7), 91.55 (C-2), 130.57 (C-3′), 147.77 (C-4′), 174.16 (C=O).

Anal. Calcd for $C_9H_{11}NO_5$ (mixture): C, 50.70; H, 5.20; N, 6.57. Found: C, 50.65; H, 5.11; N, 6.85.

Treatment of **20a** with 90% trifluoroacetic acid gave **21**, which was confirmed by comparing IR and ^{1}H NMR spectra.

Epimerization of 21 by Trifluoroacetic Acid. To a solution of 10 mg of **21a** was added 0.5 mL of 90% trifluoroacetic acid, and the resulting solution was stored at room temperature for 12 h. Evaporation of the acid in vacuo gave a syrup shown by ^{1}H NMR to consist of **21a** and **21b** in a ratio of 1:3. Also, **21b** epimerized to **21a** under the same conditions. The ratio of **21a** to **21b** was 1:3 by ^{1}H NMR.

5-Methoxy-5-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-pyrrolin-2-one (22a and 22b). The same procedure was used as the reaction of **18** with ethyl orthoformate and acetone containing *p*-toluenesulfonic acid for 30 min. Compound **22** was separated by preparative TLC with chloroform–methanol (19:1) as the eluent after three elutions.

Faster Isomer 22a: 31%; colorless foam; R_f 0.37 (chloroform–methanol, 19:1); ^{13}C NMR ($CDCl_3$) δ 25.44, 27.43 (CH_3), 50.83 (OCH_3), 62.48 (C-5′), 80.79, 81.26, 85.70, 87.05 (C-1′, C-2′, C-3′, C-4′), 94.13 (C-5), 114.43 (isopropylidene C_{quat}), 130.28 (C-3), 147.48 (C-4), 173.40 (C=O).

Slower Isomer 22b: 38%; colorless foam; R_f 0.33 (chloroform–methanol, 19:1); ^{13}C NMR ($CDCl_3$) δ 25.44, 27.43 (CH_3), 50.78 (OCH_3), 63.65 (C-5′), 81.14, 82.43, 86.11, 88.51 (C-1′, C-2′, C-3′, C-4′), 93.78 (C-5), 113.61 (isopropylidene C_{quat}), 131.22 (C-3), 146.31 (C-4), 172.11 (C=O).