

Synthesis of 1,2,3-Triazole Nucleosides *via* the Acid-catalyzed Fusion Procedure

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The acid-catalyzed fusion of methyl 1,2,3-triazole-4-carboxylate, 4-cyano-1,2,3-triazole, and 4-nitro-1,2,3-triazole with an acylated ribofuranose provided the corresponding 2- β -D-ribofuranosyl-4-substituted-1,2,3-triazoles along with the isomeric 1- β -D-ribofuranosyl-4-substituted-1,2,3-triazoles. The structures of these nucleosides were assigned on the basis of their nmr spectra. The synthesis of 2- β -D-ribofuranosyl-1,2,3-triazole-4-carboxamide from both the corresponding methyl ester and cyano nucleosides is described. The cyano nucleosides were utilized to prepare 2- β -D-ribofuranosyl-1,2,3-triazole-4-thiocarboxamide and 1- β -D-ribofuranosyl-1,2,3-triazole-4-thiocarboxamide. Reduction of the 4-nitro-1,2,3-triazole nucleosides provided 4-amino-2- β -D-ribofuranosyl-1,2,3-triazole and the isomeric 4-amino-1- β -D-ribofuranosyl-1,2,3-triazole. The acid-catalyzed fusion procedure with 1,2,3-triazole afforded 1- β -D-ribofuranosyl-1,2,3-triazole and 2- β -D-ribofuranosyl-1,2,3-triazole.

The cycloaddition of various glycosyl azides with substituted acetylenes has provided numerous examples of 1(3)-glycosyl-1,2,3-triazoles (1-9). The isomeric 2-glycosyl-1,2,3-triazoles, however, are not accessible from azido sugars. In the present work the synthesis of 1,2,3-triazole nucleosides by methods other than cycloaddition was investigated. It was found that the acid-catalyzed fusion procedure (10) with 4-substituted-1,2,3-triazoles provided 2-glycosyl-4-substituted-1,2,3-triazoles along with the isomeric 1-glycosyl-4-substituted-1,2,3-triazoles.

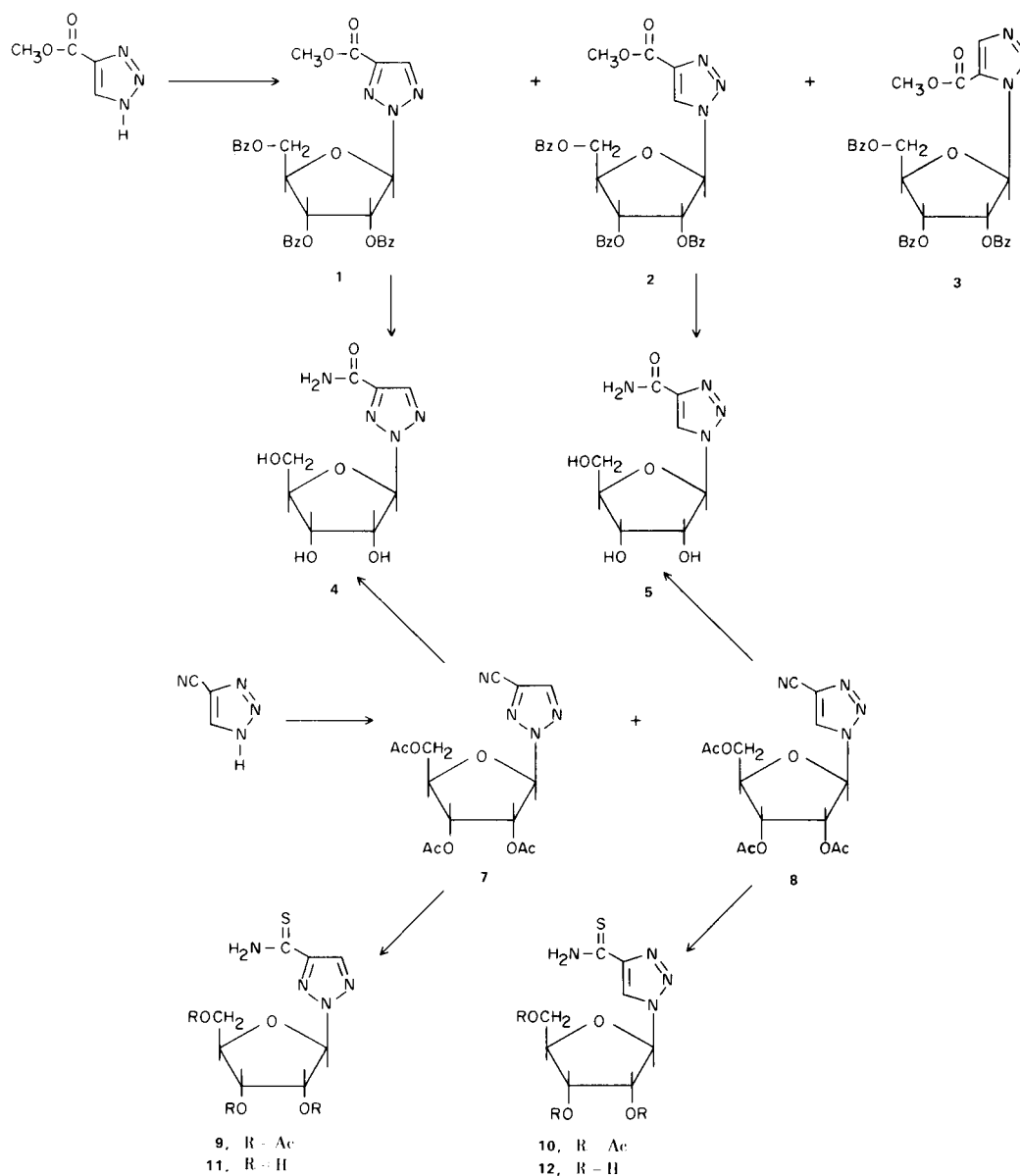
Nucleosides of 1,2,3-triazole-4-carboxamide are of interest as structural isomers of the broad spectrum antiviral nucleoside 1- β -D-ribofuranosyl-1,2,4-triazole-3-carboxamide recently reported by our laboratories (11,12). The synthesis of the corresponding 1,2,3-triazole nucleosides was approached as follows.

Fusion of methyl 1,2,3-triazole-4-carboxylate (13) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- β -D-ribofuranose in the presence of an acidic catalyst provided a mixture of two major nucleosides **1** and **2** in a ratio of approximately 2:1 and a small amount of a third isomer **3** (see Scheme 1). These products were separated and compared with the two isomers [1-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)-1,2,3-triazole-4-carboxylic acid methyl ester and 1-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)-1,2,3-triazole-5-

carboxylic acid methyl ester] obtained by cycloaddition of methyl propiolate with 2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl azide as recently reported by Alonso, *et al.* (6). The major nucleoside (**1**) from the fusion procedure was different from both of these isomers and was therefore assigned the structure 2-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)-1,2,3-triazole-5-carboxylic acid methyl ester. The second major product (**2**) was identical with an authentic sample of 1-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)-1,2,3-triazole-4-carboxylic acid methyl ester, and the very minor isomer **3** was similarly identified as 1-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)-1,2,3-triazole-5-carboxylic acid methyl ester. Treatment of isomers **1** and **2** with methanolic ammonia provided 2- β -D-ribofuranosyl-1,2,3-triazole-4-carboxamide (**4**) and 1- β -D-ribofuranosyl-1,2,3-triazole-4-carboxamide (**5**), respectively. The isomeric 1- β -ribofuranosyl-1,2,3-triazole-5-carboxamide (**6**) was similarly obtained from the minor isomer (**3**) of the cycloaddition procedure.

The fusion procedure with 4-cyano-1,2,3-triazole (14) and 1,2,3,5-tetra-*O*-acetyl- β -D-ribofuranose afforded two nucleosides in a 1:1 ratio, which were identified as 4-cyano-2-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,3-triazole (**7**) and 4-cyano-1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,3-triazole (**8**) by conversion of these products with ammonia and hydrogen peroxide to the nucleoside

SCHEME 1



carboxamides **4** and **5** respectively (see Scheme 1). The corresponding thiocarboxamide nucleosides were prepared by treatment of each cyano nucleoside (**7** and **8**) with hydrogen sulfide and triethylamine to provide, after deacylation, 2-β-D-ribofuranosyl-1,2,3-triazole-4-thiocarboxamide (**11**) and 1-β-D-ribofuranosyl-1,2,3-triazole-4-thiocarboxamide (**12**), respectively.

The fusion of certain purines (**15**, **16**) and 1,2,4-triazoles (**17**) in the absence of catalyst has been reported to provide good yields of the β-D-ribofuranosyl nucleosides. When 4-nitro-1,2,3-triazole (**18**) was subjected to the fusion procedure with 1,2,3,5-tetra-O-acetyl-β-D-ribofur-

anose without an acidic catalyst, two nucleosides **13** and **14** were obtained in a 2.4:1 ratio (see Scheme 2). The structures of these products were assigned on the basis of their nmr spectra as 4-nitro-2-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-1,2,3-triazole (**13**) and 4-nitro-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-1,2,3-triazole (**14**). The nmr spectra of various substituted 1,2,3-triazoles have been studied (**19**) and the H-5 signals of 1-substituted-1,2,3-triazoles were found to occur at lower field than the H-4 resonance. In addition, the signal for H-5 showed a larger solvent shift (DMSO-d₆ vs. deuteriochloroform) than did the H-4 signal. These criteria were recently

SCHEME 2

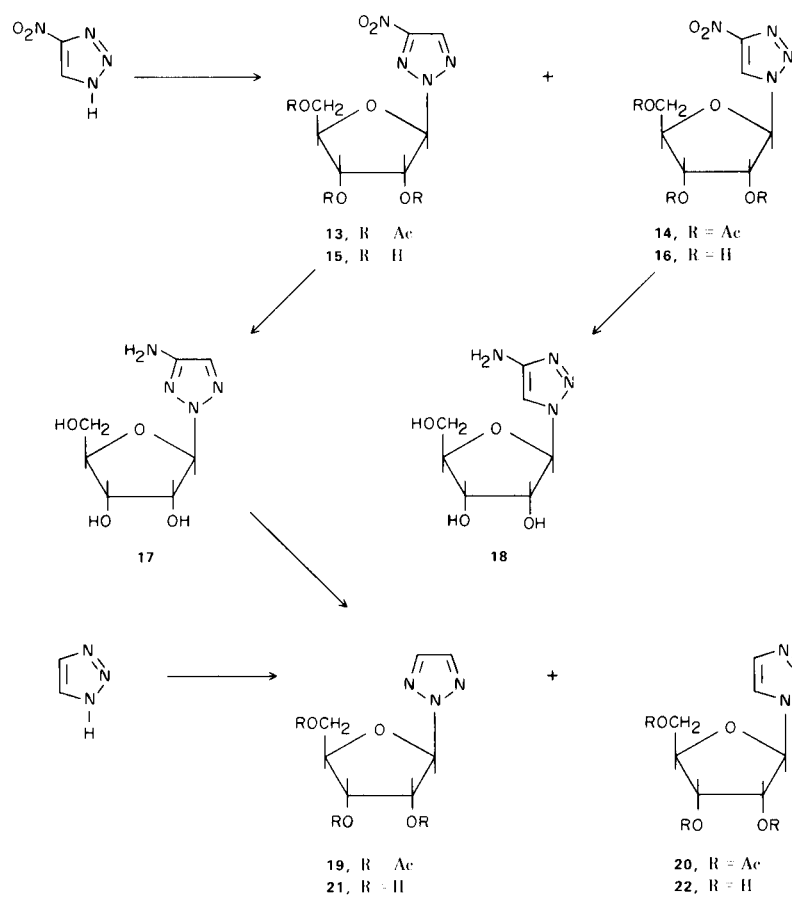


TABLE I

Chemical Shifts for H-4 and H-5 Protons



R	R'	δ (ppm)			δ (ppm)		
		DMSO-d ₆	CDCl ₃	$\Delta \delta$	DMSO-d ₆	CDCl ₃	$\Delta \delta$
CO ₂ CH ₃	Bz	8.50	8.12	0.38	9.15	8.35	0.80
CN	Ac	8.81	8.10	0.71	9.33	8.46	0.87
NO ₂	Ac	8.93	8.27	0.66	9.57	8.68	0.89
H	Ac	8.01	7.68	0.33	7.86, 8.37	7.75, 7.77	0.11, 0.60

Bz = C₆H₅CO; Ac = CH₃CO.

TABLE II
Ultraviolet Spectral Data of 1,2,3-Triazole Nucleosides

Compound	$\lambda_{\text{max, pH 1}}$ m μ	ϵ	$\lambda_{\text{max, EtOH}}$ m μ	ϵ	$\lambda_{\text{max, pH 11}}$ m μ	ϵ
4	228	11,350	226	11,450	231	10,200
5	209	12,800	213	10,600	223	5,500
6	214	9,400	217	9,800	228	6,450
7			228	8,900		
8			211	5,100		
11	245	7,350	243	7,650	240	7,500
	298	7,350	303	7,550	295	5,200
12	238	9,950	239	9,900	209	9,000
	294	9,800	299	9,550	294	9,600
13	254	7,400	250	7,550	258	6,750
14	256	7,650	255	7,650	260	7,400
15	256	8,050	258	7,550	258	8,050
16	258	7,900	256	7,250	258	7,900
17	218	5,100	254	5,700	249	6,100
	249	2,550				
18	210	3,750	254	2,300	249	3,000
	259	650				
21	218	8,400	219	6,600	222	4,950
22	212	4,550	214	2,550	225	600

utilized for assignment of the structures of certain 1,2,3-triazole nucleosides prepared by cycloaddition of glycosyl azides with methyl propiolate (6). The data in Table I show a consistently larger δ value for H-5 in the 1,4-substituted-1,2,3-triazoles compared with H-5 of the 2,4-substituted isomers. The solvent-induced shifts of the 1,4-substituted isomers also are larger than in the 2,4-substituted-1,2,3-triazoles in agreement with previously reported data (6,19). These data (Table I) for the 4-nitro-1,2,3-triazole nucleosides (13 and 14) correlate closely with the δ values and solvent-induced shifts observed for the nucleosides described above.

Treatment of 13 and 14 with sodium methoxide in methanol provided the corresponding deacylated nucleosides, 4-nitro-2- β -D-ribofuranosyl-1,2,3-triazole (15) and 4-nitro-1- β -D-ribofuranosyl-1,2,3-triazole (16). Reduction (20), of the 4-nitro-1,2,3-triazole nucleosides (15 and 16) with hydrazine in the presence of a palladium catalyst provided 4-amino-2- β -D-ribofuranosyl-1,2,3-triazole (17) and 4-amino-1- β -D-ribofuranosyl-1,2,3-triazole (18), respectively. The structure of 15 was further confirmed by reductive deamination of the 4-amino-1,2,3-triazole nucleoside (17) with sodium nitrite and hypophosphorus acid which provided 2- β -D-ribofuranosyl-1,2,3-triazole (21). This nucleoside (21) was also obtained along with 1- β -D-

ribofuranosyl-1,2,3-triazole (22) directly from 1,2,3-triazole (13) via the acid-catalyzed fusion procedure after deacylation of the blocked intermediates 19 and 20, which were formed in a 1:5 ratio.

The nmr spectrum of 21 exhibited a singlet (2-protons) at δ 7.89 for the 4,5-protons, whereas two doublets (J ca. 1 Hz) were observed at δ 7.80 and δ 8.35 for the 4 and 5 protons of 22. Similar spectra have been reported for 2-methyl-1,2,3-triazole and 1-methyl-1,2,3-triazole (19).

The β -configuration of 2, 6, 8 and 12 follows from the known configuration (21) of 2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl azide. Since only one anomer was detected in each of the above fusion reactions, the small coupling constants ($J_{1',2'}$ = 1.3 to 3.0 Hz for the acyl derivatives) are evidence (22,23) for the β -configuration of the remaining nucleosides.

The ultraviolet spectra data of these nucleosides are reported in Table II.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Evaporations were accomplished with a Buchler rotating evaporator under reduced pressure with a bath temperature of 35°. The nmr spectra were recorded at 60 MHz on

a Perkin-Elmer Hitachi R20A spectrometer and chemical shifts are reported in parts per million (δ) with DDS or TMS as an internal reference. Specific rotations were determined with a Perkin-Elmer Model 141 Polarimeter. Ultraviolet spectra were determined with a Cary 15 spectrophotometer. Merck silica gel (0.05-0.2 mm) was used for chromatographic separations. Analytical results were determined by MHW Laboratories, Garden City, Michigan and Heterocyclic Chemical Corp., Harrisonville, Missouri.

2-(2,3,5-Tri-*O*-benzoyl- β -D-ribofuranosyl)-1,2,3-triazole-4-carboxylic Acid Methyl Ester (**1**), 1-(2,3,5-Tri-*O*-benzoyl- β -D-ribofuranosyl)-1,2,3-triazole-4-carboxylic Acid Methyl Ester (**2**) and 1-(2,3,5-Tri-*O*-benzoyl- β -D-ribofuranosyl)-1,2,3-triazole-5-carboxylic Acid Methyl Ester (**3**).

Methyl 1,2,3-triazole-4-carboxylate (2.54 g., 0.020 mole) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- β -D-ribofuranose (10.1 g., 0.020 mole) were thoroughly mixed in a mortar, then heated in an oil bath at 160° until a melt was achieved. *Bis*-(*p*-nitrophenyl)phosphate (5 mg.) was added and heating *in vacuo* at 160-165° was continued for 10 minutes. The residue was triturated with benzene and the insoluble product was collected and recrystallized from benzene to yield 3.00 g. of **2**, m.p. 189-190°, which was identical with an authentic sample prepared by cycloaddition of the azido sugar with methyl propiolate as reported by Alonso, *et al.* (6). The filtrate was evaporated to a syrup and the residue was crystallized from methanol to provide 3.83 g. of **1**; m.p. 112-113°; $[\alpha]_D^{25}$ -57.6° (*c* 1.00, chloroform); nmr (DMSO- d_6) δ 6.87 (d, 1, $J_{1',2'}$ 2.2 Hz, 1'-H), 8.50 (s, 1, 5-H); (deuteriochloroform) δ 6.59 (d, 1, $J_{1',2'}$ 1.3 Hz, 1'-H), 8.12 (s, 1, 5-H).

Anal. Calcd. for $C_{30}H_{25}N_3O_9$: C, 63.04; H, 4.41; N, 7.35. Found: C, 63.00; H, 4.46; N, 7.12.

The filtrates were combined and the solvent was removed by evaporation to leave a syrup. The syrup was dissolved in a minimum of benzene and applied to a silica gel column (5 x 70 cm.) packed in benzene. The column was eluted with benzene-ether (9:1, 6 liters) and fractions of 20 ml. were collected. Fractions 80-120 provided an additional 2.62 g. of **1**, fractions 150-180 provided 200 mg. of **3** which was identified by comparison with an authentic sample (6), and fractions 213-250 provided 0.40 g. of **2**. Total yields of **1** and **2** were 57% and 30% respectively.

2- β -D-Ribofuranosyl-1,2,3-triazole-4-carboxamide (**4**).

Method 1.

Methanol saturated with ammonia at 0° (ca. 150 ml.) was added to 5.71 g. (0.010 mole) of **1** in a pressure bottle and kept at room temperature for 4 days. After removal of the solvent, water (30 ml.) was added and the mixture was extracted with ether (six 20 ml. portions). The solvent was removed and the compound crystallized from ethanol to give 2.25 g. (92%) of **4**: m.p. 150-151°; $[\alpha]_D^{25}$ -59.4° (*c* 1.00, water); nmr (DMSO- d_6) δ 5.97 (d, 1, $J_{1',2'}$ 4.0 Hz, 1'-H), 8.28 (s, 1, 5-H).

Anal. Calcd. for $C_8H_{12}N_4O_5$: C, 39.34; H, 4.95; N, 22.94. Found: C, 39.14; H, 4.90; N, 22.99.

Method 2.

4-Cyano-2-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,3-triazole (**7**) (0.35 g., 0.001 mole) was added to 15% aqueous ammonia (30 ml.) and 30% hydrogen peroxide (3 ml.). After stirring at room temperature for 6 hours an additional 3 ml. of 30% hydrogen peroxide was added and stirring was continued for 20 hours. Platinum black was added to destroy the excess peroxide, the solution was filtered, and the filtrate was evaporated to

dryness. The residue was dissolved in a minimum of methanol and applied to a 20 x 20 cm. silica gel preparative plate which was developed in ethyl acetate-methanol (9:1). The band containing **4** was removed and the compound was extracted with ethyl acetate-methanol (1:1). The solvent, along with acetamide, was removed *in vacuo*. The compound was dissolved in hot 2-propanol; cooling of the solution and filtering provided 14 mg. of **4**.

1- β -D-Ribofuranosyl-1,2,3-triazole-4-carboxamide (**5**).

4-Cyano-1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,3-triazole (**8**). (0.35 g., 0.001 mole) was added to 15% aqueous ammonia (30 ml.) and 30% hydrogen peroxide (3 ml.). The solution was stirred 4 hours before additional hydrogen peroxide was added. The procedure and product isolation was identical to that used in method 2 for compound **4**. The compound was dissolved in hot 2-propanol; cooling of the solution and filtering provided 30 mg. of crystalline **5** which was identical to an authentic sample prepared by the procedure of Alonso, *et al.* (6).

1- β -D-Ribofuranosyl-1,2,3-triazole-5-carboxamide (**6**).

Methanol (100 ml.) saturated with ammonia at 0° was added to 2.05 g. of 1-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)-1,2,3-triazole-5-carboxylic acid methyl ester (**6**) in a glass pressure bottle. After 4 days at room temperature the solvent was removed and the residue dissolved in water (50 ml.). The solution was extracted with ethyl acetate (4 x 50 ml.). The water was removed *in vacuo* to leave a syrup which was dissolved in ethanol. After standing for several days the compound crystallized to provide 680 mg. (75%) of **6**: m.p. 86-88°; $[\alpha]_D^{25}$ -59.4° (*c* 1.00, water); nmr (DMSO- d_6) δ 6.76 (d, 1, $J_{1',2'}$ 3.0 Hz, 1'-H), 8.30 (s, 1, 4-H).

Anal. Calcd. for $C_8H_{12}N_4O_5 \cdot 0.5H_2O$: C, 37.94; H, 5.17; N, 22.12. Found: C, 37.88; H, 5.09; N, 22.33.

4-Cyano-2-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,3-triazole (**7**) and 4-Cyano-1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,3-triazole (**8**).

4-Cyano-1,2,3-triazole (0.95 g., 0.010 mole) and 1,2,3,5-tetra-*O*-acetyl- β -D-ribofuranose (3.18 g., 0.010 mole) were thoroughly mixed in a mortar, then heated in an oil bath at 155° until a melt was achieved. *Bis*-(*p*-nitrophenyl)phosphate (15 mg.) was added and heating *in vacuo* at 155° was continued for 10 minutes. Separation of the isomers was accomplished by chromatography of the resultant syrup on a silica gel column (4.5 x 53 cm.) packed in chloroform. The column was eluted with chloroform-ether (1:1, 2 liters) and fractions of 20 ml. were collected. Fractions 39-52 provided 1.39 g. (39%) of **7**, crystallized from ethanol: m.p. 77-79°; $[\alpha]_D^{25}$ -44.5° (*c* 1.00, chloroform); nmr (DMSO- d_6) δ 6.53 (d, 1, $J_{1',2'}$ 2.5 Hz, 1'-H), 8.81 (s, 1, 5-H); (deuteriochloroform) δ 6.32 (d, 1, $J_{1',2'}$ 3.0 Hz, 1'-H), 8.10 (s, 1, 5-H).

Anal. Calcd. for $C_{14}H_{16}N_4O_7$: C, 47.73; H, 4.58; N, 15.90. Found: C, 47.78; H, 4.51; N, 15.98.

Fractions 65-95 provided 1.36 g. (39%) of **8**, crystallized from ethanol: m.p. 90.5-92°; $[\alpha]_D^{25}$ -57.2° (*c* 1.00, chloroform); nmr (DMSO- d_6) δ 6.55 (d, 1, $J_{1',2'}$ 3.5 Hz, 1'-H), 9.33 (s, 1, 5-H); (deuteriochloroform) δ 6.23 (d, 1, $J_{1',2'}$ 4.0 Hz, 1'-H), 8.46 (s, 1, 5-H).

Anal. Calcd. for $C_{14}H_{16}N_4O_7$: C, 47.73; H, 4.58; N, 15.90. Found: C, 47.73; H, 4.55; N, 16.04.

2-(2,3,5-Tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,3-triazole-4-thiocarboxamide (**9**).

Hydrogen sulfide was passed through a suspension of 2.0 g. of **7** in ethanol (60 ml.) to which 3.5 ml. of triethylamine had been added. After 2½ hours passage of hydrogen sulfide was

ceased and the solvent was removed. The resultant syrup was dissolved in a minimum of chloroform and added to a silica gel column (2 x 38 cm.) packed in chloroform. The column was eluted with chloroform (0.25 liter) and chloroform-ethyl acetate (9:1, 0.5 liter); 20 ml. fractions were collected. Fractions 19-34 provided 2.6 g. (98%) of **9** as a syrup: nmr (DMSO- d_6) δ 6.36 (d, 1, $J_{1',2'}$ 2.0 Hz, 1'-H), 8.39 (s, 1, 5-H); (deuteriochloroform) δ 6.24 (d, 1, $J_{1',2'}$ 3.0 Hz, 1'-H), 8.32 (s, 1, 5-H).

1-(2,3,5-Tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,3-triazole-4-thiocarboxamide (**10**).

Hydrogen sulfide was passed through a suspension of 2.0 g. of **8** in ethanol (60 ml.) to which 3.5 ml. of triethylamine had been added. After 3 hours the passage of hydrogen sulfide gas was ceased and the solvent was removed. The product was crystallized from ethanol to give 1.90 g. (86%) of **10**; m.p. 110-112°; $[\alpha]_D^{25}$ -120.6° (c 1.00, chloroform); nmr (DMSO- d_6) δ 6.48 (d, 1, $J_{1',2'}$ 3.5 Hz, 1'-H), 8.92 (s, 1, 5-H); (deuteriochloroform) δ 6.23 (d, 1, $J_{1',2'}$ 4.0 Hz, 1'-H), 8.58 (s, 1, 5-H).

Anal. Calcd. for $C_{14}H_{18}N_4O_7S$: C, 43.52; H, 4.69; N, 14.50; S, 8.29. Found: C, 43.66; H, 4.92; N, 14.42; S, 8.35.

2- β -D-Ribofuranosyl-1,2,3-triazole-4-thiocarboxamide (**11**).

Sodium methoxide in methanol (60 mg. of sodium in 30 ml. of methanol) was added to 1.0 g. of **9** and the resulting solution was stirred at room temperature for 4 hours. After neutralization with Amberlite IRC 50, the solution was filtered, and the filtrate was evaporated to dryness. Methanol and silica gel (2.5 g.) were added to the syrup, and the mixture was evaporated to dryness. The silica gel mixture was added to a dry-packed silica gel column (1 x 18 cm) and the column was eluted with chloroform (0.1 liter), ethyl acetate-chloroform (1:1, 0.1 liter) and ethyl acetate (0.4 liter); 20 ml. fractions were collected. Fractions 14-28 provided 0.61 g. (91%) of **11** as a syrup: nmr (DMSO- d_6) δ 5.95 (d, 1, $J_{1',2'}$ 4.0 Hz, 1'-H), 8.32 (s, 1, 5-H).

Anal. Calcd. for $C_8H_{12}N_4O_4S$: C, 36.93; H, 4.65; N, 21.53; S, 12.30. Found: C, 37.04; H, 4.48; N, 21.24; S, 12.00.

1- β -D-Ribofuranosyl-1,2,3-triazole-4-thiocarboxamide (**12**).

1-(2,3,5-Tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,3-triazole-4-thiocarboxamide (1.0 g.) was added to sodium methoxide in methanol (60 mg. of sodium in 30 ml. of methanol) and the resulting solution was stirred at room temperature for 4 hours. After neutralization of the solution with Amberlite IRC 50, the solution was filtered, and the filtrate was evaporated to dryness. The product was crystallized from ethanol to give 0.55 g. (82%) of **12**: m.p. 152-154°; $[\alpha]_D^{25}$ -85.2° (c 1.00, water); nmr (DMSO- d_6) δ 6.04 (d, 1, $J_{1',2'}$ 4.8 Hz, 1'-H), 8.90 (s, 1, 5-H).

Anal. Calcd. for $C_8H_{12}N_4O_4S$: C, 36.93; H, 4.65; N, 21.53; S, 12.30. Found: C, 37.09; H, 4.69; N, 21.41; S, 12.16.

4-Nitro-2-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,3-triazole (**13**) and 4-Nitro-1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,3-triazole (**14**).

4-Nitro-1,2,3-triazole (8.55 g., 0.075 mole) and 1,2,3,5-tetra-*O*-acetyl- β -D-ribofuranose (23.85 g., 0.075 mole) were mixed in a mortar, then heated *in vacuo* (ca. 20 mm.) in an oil bath at 175° for 45 minutes. The syrup was dissolved in a minimum of chloroform and applied to a silica gel column (5.5 x 88 cm.) packed in chloroform. The column was eluted with chloroform-ethyl acetate (9:1, 7 liters) and fractions of 20 ml. were collected. Fractions 104-160 provided 16.15 g. (58%) of **13** as a syrup: $[\alpha]_D^{25}$ -37.3° (c 1.13, chloroform); nmr (DMSO- d_6) δ 6.52 (d, 1, $J_{1',2'}$ 2.4 Hz, 1'-H), 8.93 (s, 1, 5-H); (deuteriochloroform) δ 6.24 (d, 1,

$J_{1',2'}$ 3.5 Hz, 1'-H), 8.27 (s, 1, 5-H).

Anal. Calcd. for $C_{13}H_{16}N_4O_9$: C, 41.97; H, 4.34; N, 15.06. Found: C, 41.75; H, 4.51; N, 14.94.

Fractions 225-300 provided 6.81 g. (24%) of **14** which was crystallized from ethanol: m.p. 100-102°; $[\alpha]_D^{25}$ -59.1° (c 1.00, chloroform); nmr (DMSO- d_6) δ 6.52 (d, 1, $J_{1',2'}$ 3.0 Hz, 1'-H), 9.57 (s, 1, 5-H); (deuteriochloroform) δ 6.27 (d, 1, $J_{1',2'}$ 1'-H), 8.68 (s, 1, 5-H).

Anal. Calcd. for $C_{13}H_{16}N_4O_9$: C, 41.97; H, 4.34; N, 15.06. Found: C, 42.02; H, 4.38; N, 15.29.

4-Nitro-2- β -D-ribofuranosyl-1,2,3-triazole (**15**).

A solution of sodium methoxide (from 200 mg. of sodium) in methanol (150 ml.) was added to **13** (11.16 g., 0.03 mole). The solution was stirred at room temperature for 15 hours and then was neutralized with Bio-Rad AG 50W X-2 (H). The resin was removed by filtration and the solvent was removed by evaporation *in vacuo*. Crystallization of the product from 2-propanol-ethanol (4:1) provided 6.2 g. (84%) of **15**: m.p. 147-148° $[\alpha]_D^{25}$ -59.8° (c 1.00, water); nmr (DMSO- d_6) δ 5.96 (d, 1, $J_{1',2'}$ 3.5 Hz, 1'-H), 8.75 (s, 1, 5-H).

Anal. Calcd. for $C_7H_{10}N_4O_6$: C, 34.15; H, 4.09; N, 22.76. Found: C, 34.18; H, 4.08; N, 22.78.

4-Nitro-1- β -D-ribofuranosyl-1,2,3-triazole (**16**).

A solution of **14** (3.72 g., 0.01 mole) and sodium methoxide (from 150 mg. of sodium) in methanol (50 ml.) was stirred at room temperature for 4 hours. The solution was neutralized with Bio-Rad AG 50W X-2 (H) and the resin removed by filtration. The solvent was removed and the compound was crystallized from ethanol-ethyl acetate (1:4) to give 2.1 g. (85%) of **16**: m.p. 172-174°; $[\alpha]_D^{25}$ -66.3° (c 1.00, water); nmr (DMSO- d_6) δ 6.03 (d, 1, $J_{1',2'}$ 3.5 Hz, 1'-H), 9.44 (s, 1, 5-H).

Anal. Calcd. for $C_7H_{10}N_4O_6$: C, 34.15; H, 4.09; N, 22.76. Found: C, 33.95; H, 4.35; N, 22.78.

4-Amino-2- β -D-ribofuranosyl-1,2,3-triazole (**17**).

A solution of **15** (2.46 g., 0.01 mole) in methanol (50 ml.) and 5% palladium-on-carbon catalyst (500 mg.) was stirred at room temperature while a solution of 99% hydrazine hydrate in methanol (1:3, v/v) was added dropwise until evolution of nitrogen ceased. The catalyst was removed by filtration through Celite and the solvent was removed by evaporation *in vacuo* to give 2.30 g. of syrup. The syrup was dissolved in methanol and absorbed on 5 g. of silica gel. The methanol was removed and the mixture was added to a dry packed silica gel column (2.5 x 28 cm.). The column was eluted with chloroform (0.2 liter), chloroform-ethyl acetate (1:1, 0.2 liter), ethyl acetate (0.2 liter), and ethyl acetate-methanol (9:1, 0.5 liter); 20 ml. fractions were collected. Fractions 30-35 provided 2.0 g. (93%) of **17** as a syrup; nmr (DMSO- d_6) δ 5.62 (d, 1, $J_{1',2'}$ 4.0 Hz, 1'-H), 7.03 (s, 1, 5-H).

Anal. Calcd. for $C_7H_{12}N_4O_4$: C, 38.89; H, 5.59; N, 25.92. Found: C, 38.64; H, 5.81; N, 25.71.

4-Amino-1- β -D-ribofuranosyl-1,2,3-triazole (**18**).

A solution of **16** (1.23 g., 0.005 mole) in methanol (25 ml.) and 5% palladium-on-carbon catalyst (250 mg.) was stirred at room temperature while a solution of 99% hydrazine hydrate in methanol (1:3, v/v) was added dropwise until evolution of nitrogen ceased. The catalyst was removed by filtration through Celite and the solvent was removed. The product was crystallized from ethyl acetate-methanol (3:1) to give 1.0 g. (92%) of **18**, m.p. 102-104°. The nmr spectrum indicated the presence of ethyl acetate. After heating at 100° *in vacuo* overnight **18** had a melting point of 141-

143°; $[\alpha]_D^{25}$ -65.8° (c 1.00, water); nmr (DMSO- d_6) δ 5.77 (d, 1, $J_{1',2'}$ 4.0 Hz, 1'-H), 7.34 (s, 1, 5-H).

Anal. Calcd. for $C_7H_{12}N_4O_4$: C, 38.89; H, 5.59; N, 25.92. Found: C, 38.67; H, 5.51; N, 26.04.

2-(2,3,5-Tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,3-triazole (**19**) and 1-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,3-triazole (**20**).

A mixture of 1,2,3-triazole (1.66 g., 0.024 mole) and 1,2,3,5-tetra-*O*-acetyl- β -D-ribofuranose (6.36 g., 0.020 mole) was heated in an oil bath at 145° until a melt was achieved. Bis-(*p*-nitrophenyl)phosphate (20 mg.) was added and heating was continued for 2 hours. The syrup was cooled, dissolved in chloroform (75 ml.) and washed with aqueous 5% sodium bicarbonate (25 ml.). The chloroform layer was separated and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the solvent was removed. The syrup was applied to a silica gel column (2.5 x 80 cm.) packed in methylene chloride. Elution was with methylene chloride-ethyl acetate (9:1, 4 liters) and fractions of 20 ml. were collected.

Fractions 50-62 provided 0.68 g. of syrup which was shown by nmr to be **19** with a small amount of unreacted sugar: nmr (DMSO- d_6) δ 6.34 (d, 1, $J_{1',2'}$ 3.0 Hz, 1'-H), 8.01 (s, 2; 4,5-H); (deuteriochloroform) δ 6.25 (d, 1, $J_{1',2'}$ 2.0 Hz, 1'-H), 7.68 (s, 2; 4,5-H).

Fractions 82-160 provided 3.5 g. (53%) of **20** as a syrup: nmr (DMSO- d_6) δ 6.42 (d, 1, $J_{1',2'}$ 3.3 Hz, 1'-H), 7.86 (d, 1, $J_{4,5}$ ca. 1, 4-H), 8.37 (d, 1, $J_{4,5}$ ca. 1, 5-H); (deuteriochloroform) δ 6.20 (d, 1, $J_{1',2'}$ 3.0 Hz, 1'-H), 7.75 (d, 1, $J_{4,5}$ ca. 1, 4-H), 7.77 (d, 1, $J_{4,5}$ ca. 1, 5-H).

Anal. Calcd. for $C_{13}H_{17}N_3O_7$: C, 47.71; H, 5.23; N, 12.84. Found: C, 47.53; H, 5.21; N, 12.63.

2- β -D-Ribofuranosyl-1,2,3-triazole (**21**).

Method 1.

A solution of **17** (0.43 g., 0.002 mole) and 50% hypophosphorous acid (1.31 g., 0.01 mole) in water (5 ml.) was kept at 35-40° while sodium nitrite (150 mg.) in water (3 ml.) was added dropwise. The reaction was kept at 35° for 30 minutes and the solvent was removed. The syrup was dissolved in methanol and absorbed on silica gel (3 g.). The methanol was removed and the mixture was applied to a silica gel column (1.5 x 32 cm.) packed in chloroform. Elution was with chloroform (0.1 liter), chloroform ethyl acetate (1:1, 0.2 liter) and ethyl acetate (0.5 liter) and fractions of 20 ml. were collected. Fractions 20-27 provided 200 mg. (50%) of **21** as a syrup: nmr (DMSO- d_6) δ 5.93 (d, 1, $J_{1',2'}$ 3.8 Hz, 1'-H), 7.89 (s, 2; 4,5-H).

Anal. Calcd. for $C_7H_{11}N_3O_4$: C, 41.79; H, 5.51; N, 20.89. Found: C, 41.89; H, 5.43; N, 20.65.

Method 2.

A solution of sodium methoxide (from 50 mg. of sodium) in methanol (60 ml.) was added to **19** (630 mg.) and the solution was stirred at room temperature for 3 hours. The solution was neutralized with Amberlite IRC 50; the resin was removed by filtration. The syrup obtained upon removal of the solvent was dissolved in methanol and absorbed on silica gel (2 g.). The methanol was removed and the mixture was added to a silica gel column (1 x 20 cm.) packed in chloroform. Elution was with chloroform (0.1 liter), chloroform-ethyl acetate (1:1, 0.1 liter), and ethyl acetate-methanol (9:1, 0.2 liter); fractions of 20 ml. were collected. Fractions 11-14 provided 330 mg. (85%) of **21** which was identical to that prepared by Method 1.

1- β -D-Ribofuranosyl-1,2,3-triazole (**22**).

A solution of sodium methoxide (from 120 mg. of sodium)

in methanol (50 ml.) was added to **20** (1.0 g.). The solution was stirred at room temperature for 4 hours and then neutralized with Bio-Rad AG 50W X-2 (H). The solution was filtered and the solvent was removed. The syrup was dissolved in methanol and absorbed on silica gel (3 g.). After removal of the methanol the mixture was added to a silica gel column (1 x 20 cm.) packed in chloroform. Elution was with chloroform (20 ml.), chloroform-ethyl acetate (1:1, 40 ml.), ethyl acetate (40 ml.), and ethyl acetate-methanol (9:1, 100 ml.); fractions of 20 ml. were collected. Fractions 8-12 contained the product which was crystallized from ethyl acetate-ethanol (3:1) to provide 200 mg. (33%) of **22**: m.p. 123-125°; $[\alpha]_D^{25}$ -48.9° (c 1.00, water); nmr (DMSO- d_6) δ 6.00 (d, 1, $J_{1',2'}$ 4.2 Hz, 1'-H), 7.80 (d, 1, $J_{4,5}$ ca. 1 Hz, 4-H), 8.35 (d, 1, $J_{4,5}$ ca. 1 Hz, 5-H).

Anal. Calcd. for $C_7H_{11}N_3O_4$: C, 41.79; H, 5.51; N, 20.89. Found: C, 41.71; H, 5.32; N, 20.98.

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