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CARBOHYDRATE RESEARCH

Note

Cyclization reactions of N^1-(glycopyranosylamino)guanidines [1,2]

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Abstract

Acetylation of N^1-(aldopyranosylamino)guanidines **2–4** with D-*gluco*, D-*galacto*, and L-*arabino* configuration gives rise to N^1-per(*O*-acetylglycopyranosylamino)-N^1,N^2,N^3-triacetylguanidines **5–7** in good yields, as already stated by Feather and coworkers [*Carbohydr. Res.*, 267 (1995) 17–25] for the *gluco* compound. The acylaminoguanidines prepared have been cyclized under mild conditions (boiling in ethanol or treatment with cold 0.1 M sodium methylate solution) to afford 3-amino-N^1-glycopyranosyl-5-methyl-1*H*-1,2,4-triazoles. The structure of these pyranosyl nucleosides **9**, **10**, **12–14** is discussed using ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. © 1997 Elsevier Science Ltd.

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We have been interested in studying the reactions of monosaccharides and aldehydo-sugar derivatives with aminoguanidinium salts **1** [2]. The condensation products of aldoses with **1** exist in aqueous solution (pH 6) as cyclic pyranosylaminoguanidines (**2**) with the protonated aminoguanidine substituent at C-1 equatorial, and at pH 12 and in deuteriodimethyl sulfoxide solution as acyclic (*E*)-carboximide-amide-hydrazones. Both types of compounds are also preparatively accessible. The cyclic isomers **2–4** are present exclusively when mineral acid salts of the condensation products are dissolved in dimethyl sulfoxide, and we proposed a mechanism of the ring-chain interconversion between glycosylaminoguanidine and carboximide-amide forms [2]. Hirsch and Feather elaborated a more complicated procedure to obtain the trifluoroacetic acid salt of the D-*gluco* compound **2c** ($HX=CF_3CO_2H$) [3]. This material gave an interesting crystalline heptaacetate **5** upon acetylation, the structure of which is unique: **5** exists in solution in two different conformational forms and its crystal structure also includes two conformers. The crystallographically independent molecules have the common $^4C_1$ conformation (β anomer) with the

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[1] Heterocyclic compounds from sugars, Part XVI. For Part XV see ref. [1].

[2] Dedicated with best wishes to Professor Hans Paulsen on the occasion of his 75th birthday.

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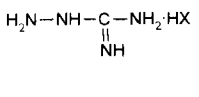
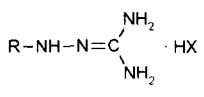
acetylated aminoguanidine substituent occupying (*E*) and (*Z*) isomeric forms.





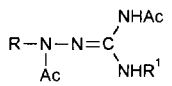
1 a X = Cl
b X = NO_3
c X = CF_3CO_2

2 R = β-D-Glc*p*
3 R = β-D-Gal*p*
4 R = α-L-Ara*p*

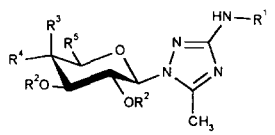
Since the interaction between the aminoguanidine salts **1** and carbohydrates is of particular biochemical and medicinal importance—it is known that **1** inhibits the formation of advanced glycosylation end products that have been implicated in the etiology of diabetic complications, an activity which is, however, disputed by several authors [4]—we have investigated the chemical transformations of the condensation products **2–4**, prepared previously by us [2]. In the course of our previous studies, experiences have been gained on the synthesis of different acylated aromatic and heterocyclic carbaldehyde carboximide-amide-hydrazones and their structural assignments, particularly with respect to the configuration of the C=N double bond [5]. Treatment of aromatic carboximide-amide-hydrazones with hot acetic anhydride or benzoyl chloride afforded 1,4-diacyl-3-acylamino-5-aryl-4,5-dihydro-1*H*-1,2,4-triazoles [6]. In contrast, acylation of (*E*) and (*Z*) isatin carboximide-amide-hydrazones gave rise to the corresponding N^3,N^4-diacyl derivatives [7].

Conventional acetylation of either the hydrochloride or nitrate of **2** in cold pyridine and triethylamine with acetic anhydride resulted in the (*E*,*Z*) heptaacetate **5** in moderate yields (see ref. [3]). The preparation of the educt **3a** from **1a** and D-galactose demonstrates that the lengthy, low yielding procedure already described for the preparation of **2c** [3] could be improved as shown in the Experimental. Acetylation of compounds **3a** and **4a** similarly allows the conversion to the peracetates **6** and **7**. In the latter reaction, the *O*,*N*-pentaacetyl compound **11** was isolated in moderate yield, too. The resulting *O*,*N*-acetyl derivative showed IR bands characteristic for NH, amide, and acetyl groups (for **6**: 3398, 3324, 2940, 1755, 1699, and 1660 cm^{-1}). The characteristic mass spectral fragmentation pattern of N^1-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosylamino)-N^1,N^2,N^3-triacetylguanidine (**7**) upon electron impact is shown in Fig. 1.

Deacetylation of the above (*E*,*Z*)-*O*,*N*-acetylated N^1-glycosylamino(guanidines) results in the cyclized products **8–10**. Upon action of catalytic amounts of sodium methylate, the intermediary *O*-deacetylated compounds cyclized to the corresponding 3-aminotriazole nucleosides. These are closely related to the valuable synthetic 1,2,4-triazole nucleoside, 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide (Virazole, Ribavirin®), a broad spectrum antiviral agent which also displays antitumor activity in mice. This attracted considerable attention because of the peculiar mechanism of action, i.e. the reduction of guanosine triphosphate pool as a consequence of inosine monophosphate dehydrogenase inhibition [8]. Treatment of the free 1*H*-1,2,4-triazole nucleoside **8** with acetic anhydride gave rise to the *O*,*N*-peracetyl derivative **12**, which could also be obtained through thermal cyclization of **5** in good yield. Moreover, acetylation of **2** in hot acetic anhydride–sodium acetate resulted in the same nucleoside, 3-acetamido-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-5-methyl-1*H*-1,2,4-triazole (**12**), which crystallized as monohydrate. The present regioselective reaction allows the formation of 1,2,4-triazole-N^1-nucleosides. In fact, it helps to overcome the difficulties arising from the classical silylation and glycosylation steps in the synthesis of basic 1,2,4-triazole nucleosides [9], in which the preformed heterocycle had to be coupled with an activated and protected glycosyl compound.



5 R = 2,3,4,6-tetra-*O*-acetyl-β-D-Glc*p* R^1 = Ac
6 R = 2,3,4,6-tetra-*O*-acetyl-β-D-Gal*p* R^1 = Ac
7 R = 2,3,4-tri-*O*-acetyl-α-L-Ara*p* R^1 = Ac
11 R = 2,3,4-tri-*O*-acetyl-α-L-Ara*p* R^1 = H



	R^1	R^2	R^3	R^4	R^5
8	H	H	H	OH	CH_2OH
9	H	H	OH	H	CH_2OH
10	H	H	OH	H	H
12	Ac	Ac	H	OAc	CH_2OAc
13	Ac	H	H	OAc	CH_2OAc
14	H	Ac	OAc	H	H

The ^1H and ^{13}C NMR spectra of aminoguanidine derivatives **5–7**, in dimethylsulfoxide solution, are

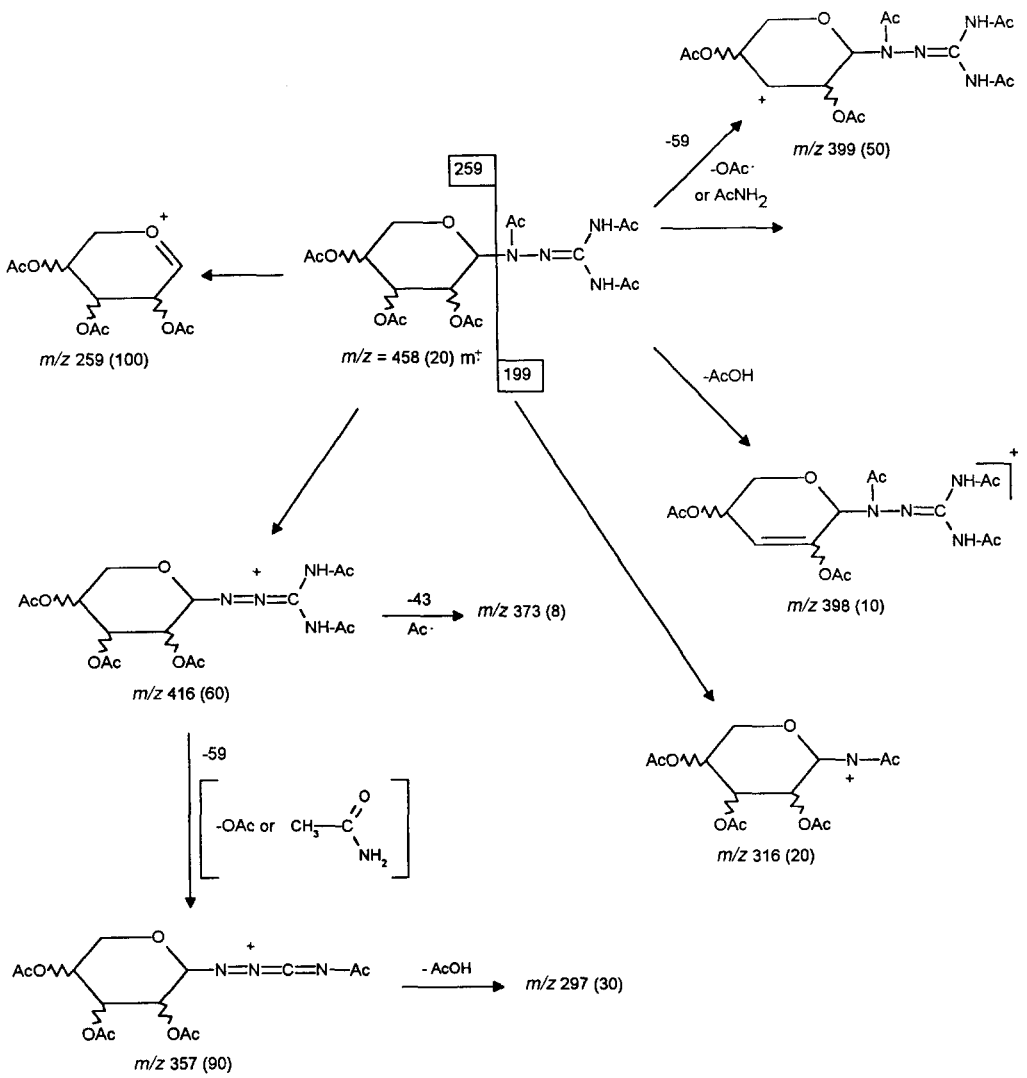


Fig. 1. EI mass spectral fragmentation pattern for **7**.

Table 1
^{1}H NMR chemical shifts (δ, ppm) and coupling constants (J, Hz) for 3-amino-5-methyl-N^1-pyranosyl-1*H*-1,2,4-triazole derivatives in $(CD_3)_2SO$

Compound	Pyranosyl C–H						Pyranosyl O–R (OH, OAc)				5-Me	Other H
	H-1′ ($J_{1',2'}$)	H-2′ ($J_{2',3'}$)	H-3′ ($J_{3',4'}$)	H-4′ ($J_{4',5'}$)	H-5′ (^2J)	5′-CH_2 (^2J)	2′-OR (^3J)	3′-OR (^3J)	4′-OR (^3J)	5′-CH_2OR (^3J)		
8	4.97 (9.0)	3.67 (8.9)	3.30 (9.0)	3.11 (9.0)	3.34	3.65, 3.41	5.11 (5.7)	5.10 (5.1)	5.04 (5.4)	4.58 (5.8)	2.24	5.12 (NH_2)
9	4.90 (9.0)	4.00 (9.0)	3.44	3.71	3.57	3.49, 3.46	4.91 (5.4)	4.84 (5.7)	4.48 (3.5)	4.63 (5.6)	2.23	5.08 (NH_2)
10	4.85 (8.7)	4.00	3.45	3.70	3.72, 3.62 (11.7)	– –	4.95 (5.7)	4.87 (6.0)	4.63 (3.3)	– –	2.23	5.09 (NH_2)
12	6.06 (9.0)	5.47 (9.6)	5.41 (9.6)	5.06 (9.6)	4.29	4.18, 4.05 (11.7)	1.82	1.94	2.01	2.00	2.43	10.22 (NH); 2.00 (NAc)
13	5.17 (9.0)	3.72 (9.0)	3.34 (9.0)	3.15 (9.0)	3.40	3.67, 3.42	5.20	5.20	5.20	4.60	2.37	10.19 (NH); 2.01 (NAc)
14	5.82 (9.1)	5.57 (9.9)	5.33 (3.7)	5.28	4.13, 3.97 (13.2)	–	1.84	1.94	2.13	–	2.43	10.19 (NH); 2.00 (NAc)

Table 2
^{13}C NMR chemical shifts (δ, ppm) for 3-amino-5-methyl-N^1-pyranosyl-1H-1,2,4-triazole derivatives in $(CD_3)_2SO$

Compound	Pyranosyl C						Triazole C			Other C
	C-1′	C-2′	C-3′	C-4′	C-5′	5′-CH_2	C-3	C-5	5-Me	
8	84.5	71.3	77.3	69.8	79.2	61.0	162.1	152.3	11.4	–
9	85.3	68.4	74.0	68.3	77.5	60.6	162.0	152.0	11.4	–
10	85.5	68.5	73.5	68.3	68.4	–	162.0	152.0	11.4	–
12	81.6	72.5	69.4	67.5	73.0	61.5	155.4	153.7	11.4	168.4, 20.0 (2′-Ac); 169.6, 20.2 (3′-Ac); 169.2, 20.3 (4′-Ac); 170.0, 20.5 (5′-CH_2*OAc*); 23.1 (3-Ac) [a]
13	84.9	71.4	77.2	69.8	79.5	60.9	154.8	153.0	11.5	167.6, 23.2 (3-Ac)
14	82.9	67.4	70.5	68.1	66.1	–	155.2	153.3	11.5	168.4, 20.1 (2′-Ac); 169.6, 20.4 (3′-Ac); 169.8, 20.7 (4′-Ac); 23.1 (3-Ac) [a]

[a] C=O of 3-Ac not observed.

characterized by several sets of signals as well as by broad lines which may result from a dynamic equilibrium between different forms. Although ^{1}H NMR spectra show a clear temperature dependence, recordings at elevated temperatures (up to 60 °C) did not result into a collapse to a single set of signals. Accordingly, a complete interpretation of these spectra was not possible. Nevertheless, NH signals in the region 10.6–9.2 ppm were assigned to NH groups: signals between 6.2 and 3.6 ppm to pyranose ring protons, and the resonances between 2.3 and 1.8 ppm to acetyl groups. The spectrum of di-*N*-acetyl compound **11** shows a single set of signals, although also in this case distinct line broadening occurred. In contrast, confirmation of structure as well as complete and unambiguous assignment of all proton and carbon signals for N^1-pyranosyl-1,2,3-triazole derivatives **8–10** and **12–14** could be achieved from APT, COSY, HMQC [10] and NOE-difference, 1D-HETCOR [11], and long-range INEPT experiments [12]. ^{1}H NMR data are collected in Table 1; ^{13}C chemical shifts in Table 2. The obtained data are in fairly good agreement with those reported for similar compounds [3,13–16], however, it should be emphasized that complete and unequivocal assignment is not possible only on the basis of comparison with literature data.

1. Experimental

Materials and methods.—Melting points were determined on a Boëtius heating-stage microscope. All NMR spectra were recorded on a Varian Unity*PLus* 300 spectrometer (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) from $(CD_3)_2SO$ solns at 28 °C. The solvent multiplet was used as an internal standard which was related to Me_4Si with δ 2.49 ppm (^{1}H) and δ 39.5 ppm (^{13}C), respectively. Optical rotations were measured with a Schmidt–Haënsch polarimeter. TLC was performed on Kieselgel GF_{254} (E. Merck), using A, 7:3 toluene–EtOAc; B, 3:2 toluene–acetone; C, 1:1 benzene–acetone; D, MeOH, and spots were detected by spraying with H_2SO_4 in EtOH followed by heating. Silica gel (40–63 μm) was used for column chromatography. High resolution MS measurements were performed with VG7035 instrument by peak matching technique (EI 70 eV, resolution 10,000, ion source temp 150 °C).

General procedure.—A) *Synthesis of* O,N-*acetylated* N^1-*(aldopyranosylamino)guanidines* **5–7**. The magnetically stirred and ice-cooled suspension of **2–4** [2] (12 g, 40 mmol), in dry pyridine (165 mL) and Et_3N (6 mL), was treated with Ac_2O (110 mL), and after 15 h the resulting clear mixture was evaporated under reduced pressure. The resulting syrupy residue was extracted with $CHCl_3$ (3 × 140 mL), washed successively with water, $KHSO_4$ soln (until no pyridine is detectable), and water. After drying ($MgSO_4$) and evaporation of the solvent, a slightly yellow syrup was obtained. Recrystallization from EtOAc–hexane gave the chromatographically pure compound (TLC, A). The mother liquor contained some minor compounds.

B) *General procedure for the Zemplén deacetylation of the* O,N-*acetylated* N^1-*(aldopyranosylamino)-guanidines* **5–7**. The corresponding acetylated glycopyranosylaminoguanidines **5–7** (0.5 mmol) dissolved in abs MeOH (3.8 mL) was treated with NaOMe [0.05 mL (1 N)] for 32 h. The precipitated product (cooling is necessary to achieve reasonable yields) was recrystallized from MeOH or water–EtOH (TLC, D).

N^1-*(β-*D-*Galactopyranosylamino)guanidine·hydrochloride* (**3a**).—A soln of D-galactose (5.4 g, 30 mmol) and **1a** (3.24 g, 30 mmol) in water (12 mL) was held at room temp for 16 h. The water was distilled off and the crystalline residue recrystallized from water–EtOH to give 7.03 g (86%) of **3a**; mp 160 °C, lit. 160 °C [2]; $[\alpha]_D^{25}$ +7.1° (*c* 1.39, H_2O), lit. $[\alpha]_D^{24}$ +7° (*c* 1, H_2O) [2].

N^1-*(2,3,4-Tetra-*O-*acetyl-β-*D-*glucopyranosylamino)-*N^1, N^2, N^3-*triacetylguanidine* (**5**).—The corresponding N^1-(β-D-glucopyranosylamino)guanidine salt (**2a** or **b**) [2] was treated as described in the general procedure A. The crystalline product (17 g, 80%) melted at 178–180 °C, lit. 166–167 °C [3]; $[\alpha]_D^{20}$ −2.5° (*c* 1.54, $CHCl_3$), lit. $[\alpha]_D^{24}$ −2.1° (*c* 1.17, $CHCl_3$) [3]. Anal. Calcd for $C_{21}H_{30}N_4O_{12}$ (530.5): C, 47.54; H, 5.70; N, 10.56. Found C, 47.50; H, 5.78; N, 10.80.

N^1-*(2,3,4,6-Tetra-*O-*acetyl-β-*D-*galactopyranosylamino)-*N^1,N^2,N^3-*triacetylguanidine* (**6**).—N^1-(β-D-Galactopyranosylamino)guanidine (**3a** or **b**) [2] was treated as described in the general procedure A. The crystalline product (14.9 g, 70%) melted at 179–180 °C; $[\alpha]_D^{24}$ −13° (*c* 1.17, $CHCl_3$). Anal. Calcd for $C_{21}H_{30}N_4O_{12}$ (530.5): C, 47.54; H, 5.70; N, 10.56. Found C, 47.39; H, 6.00; N, 10.53.

N^1-*(2,3,4-Tri-*O-*acetyl-α-*L-*arabinopyranosylamino)-* N^1, N^2, N^3 - *triacetylguanidine* (**7**).—N^1-(α-L-Arabinopyranosylamino)guanidine (**4a** or **b**) [2] was treated as described in the general procedure A. The crystalline product (10.54 g, 58%) melted at 171–172

°C; $[\alpha]_D^{24}$ −2° (*c* 1.97, $CHCl_3$). Anal. Calcd for $C_{18}H_{26}N_4O_{10}$ (458.4): C, 47.18; H, 5.72; N, 12.22. Found C, 47.45; H, 5.68; N, 12.08.

The mother liquor of **7** deposited after standing 1.96 g (11%) of N^1-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosylamino)-N^1,N^3-diacetylguanidine (**11**); mp 203–205 °C; $[\alpha]_D^{21}$ +48° (*c* 1, H_2O), +1° (*c* 1.1, $CHCl_3$) (Tlc, B). Compound **11**: ^{1}H NMR [$(CD_3)_2SO$]: δ 10.54 (br s, 1 H, NH), 7.81 (br s, 1 H, HN), 6.96 (br s, 1 H, NH), 5.70 (m, 1 H, H-1′), 5.23 (m, 1 H, H-2′), 5.18 (m, 1 H, H-3′), 5.12 (m, 1 H, H-4′), 3.75–3.90 (m, 2 H, H-5′a, H-5′b), 2.07, 2.00, 1.90, 1.88, 1.86 (each s, COMe); ^{13}C NMR [$(CD_3)_2SO$]: δ 172.5, 169.9, 169.5, 168.6 (each *C*OMe), 158.4 (C=N), 82.4 (C-1′), 71.8 (C-3′), 68.5 (C-4′), 65.9 (C-2′), 65.6 (C-5′), 23.8, 21.1, 20.8, 20.6, 20.4 (each CO*Me*). Anal. Calcd for $C_{16}H_{24}N_4O_9$ (416.4): C, 46.15; H, 5.81; N, 13.45. Found C, 46.16; H, 5.75; N, 13.47.

3-Amino-1-(β-D-glucopyranosyl)-5-methyl-1H-1,2,4-triazole (**8**).—N^1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylamino)-N^1,N^2,N^3-triacetylguanidine (**5**) was treated as described in the general procedure B. The crystalline product (0.10 g, 72%) melted at 280–281 °C; $[\alpha]_D^{20}$ +10° (*c* 1.4, H_2O). Anal. Calcd for $C_9H_{18}N_4O_6$ (278.3): C, 38.85; H, 6.52; N, 20.14. Found C, 38.83; H, 6.48; N, 20.14.

3-Amino-1-(β-D-galactopyranosyl)-5-methyl-1H-1,2,4-triazole (**9**).—N^1-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosylamino)-N^1,N^2,N^3-triacetylguanidine (**6**) was treated as described in the general procedure B. The crystalline product (0.089 g, 64%) melted at 285–287 °C; $[\alpha]_D^{21}$ +43° (*c* 1.3, H_2O). Anal. Calcd for $C_9H_{18}N_4O_6$ (260.3): C, 41.53; H, 6.20; N, 21.53. Found C, 41.68; H, 6.36; N, 21.29.

3-Amino-1-(α-L-arabinopyranosyl)-5-methyl-1H-1,2,4-triazole (**10**).—N^1-(2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosylamino)-N^1,N^2,N^3-triacetylguanidine (**7**) was treated as described in the general procedure B. The crystalline product (0.10 g, 91%) melted at 276–279 °C; $[\alpha]_D^{22}$ +36° (*c* 1.2, H_2O). The compound, precipitated after 5 min from the reaction, is the partial acetylation product **11**; mp and mixed mp 203–205 °C; $[\alpha]_D^{21}$ +18.1° (*c* 0.9, DMF), +49° (*c* 0.9, H_2O). Deacetylation of **11** according to the general procedure B leads also to **10**; yield 65%, mp and mixed mp 278 °C (dec).

3-Acetamido-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-5-methyl-1H-1,2,4-triazole (**12**).—a) A soln of **8** (0.28 g, 1 mmol), in dry pyridine (2.5 mL), was treated with Ac_2O (0.8 mL) for 2 h. After removal of the volatiles, the chromatographically homogenous (TLC, A) product was recrystallized from water to give **12** (0.45 g, 92%); mp 95–96 °C; $[\alpha]_D^{27}$ −16° (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{19}H_{24}N_4O_9 \cdot H_2O$ (488.4): C, 46.72; H, 5.78; N, 11.47. Found C, 46.81; H, 5.60; N, 11.28.

b) A suspension of **2b** (6 g, 20 mmol) and anhyd NaOAc (5.5 g) in Ac_2O (12 mL) was refluxed for 15 min. The cooled mixture was dild with ice–water (130 mL), and after 2 h the soln was extracted with $CHCl_3$ (3 × 60 mL), then with $NaHCO_3$ soln and water, dried ($MgSO_4$), and evaporated under reduced pressure. The amorphous product (11 g) was recrystallized from water (45 mL) to give 2.63 g (27%) hydrated product with mp 98–99 °C; $[\alpha]_D^{20}$ −15° (*c* 1.46, $CHCl_3$).

c) A soln of **5** (0.53 g, 1 mmol) in EtOH (3.5 mL) was heated in EtOH for 6 h. The reaction mixture was evaporated and the residue chromatographed in system C. The first fractions contained some educt. Further elution gave amorphous **12** (0.40 g 81%). Recrystallization gave an analytical sample with mp 98–100 °C; $[\alpha]_D^{20}$ −15° (*c* 1.8, $CHCl_3$). Anal. Calcd for $C_{19}H_{26}N_4O_{10}$ (488.4): C, 46.72; H, 5.78; N, 11.47. Found C, 46.54; H, 5.56; N, 11.54.

3-Acetamido-1-(β-D-glucopyranosyl)-5-methyl-1H-1,2,4-triazole (**13**).—The foregoing dried (0.8 kPa) compound **12** was treated as described in the general procedure B. The syrupy compound was dissolved in EtOH and precipitated with gradual addition of ether to yield an amorphous substance. Anal. Calcd for $C_{11}H_{18}N_4O_6$ (302.3): C, 43.70; H, 6.00; N, 18.54. Found C, 43.60; H, 5.91; N, 18.54.

3-Acetamido-1-(2,3,4-tri-O-acetyl-α-L-arabinopyranosyl)-5-methyl-1H-1,2,4-triazole (**14**).—3-Acetamido-1-(α-L-arabinopyranosyl)-5-methyl-1,2,4-triazole (**13**) was treated as described in the general procedure A. The resulting syrupy compound was chromatographed using system C to yield **14** (11.4 g, 72%) as an amorphous substance; $[\alpha]_D^{24}$ +13.9° (*c* 3.16, $CHCl_3$). Anal. Calcd for $C_{16}H_{22}N_4O_8$ (398.4): C, 48.23; H, 5.57; N, 14.06. Found C, 48.48; H, 5.56; N, 13.93.

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