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Synthesis and reactions of 1,5- and 1,3-dialkyl-(D-*manno*-pentitol-1-yl)-1*H*-1,2,4-triazole nucleosides derived from 1-(chloroalkyl)-1-aza-2-azoniaallene salts

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Abstract

1-(Chloroalkyl)1-aza-2-azoniaallene salts underwent cycloaddition with penta-*O*-benzoyl-D-mannonic acid nitrile to give several intermediates. The salts of these rearranged spontaneously to the protonated 1,2,4-triazoles, which hydrolysed, in situ, to the acyclic 1,2,4-triazole C-nucleosides. Deblocking of the latter afforded the free nucleosides. Analogous treatment of 1,1-*tert*-butylmethyl derivatives of 1-aza-2-azoniaaallene salts with penta-*O*-benzoyl-D-mannonic acid nitrile gave, after rearrangment and hydrolysis, acyclic C-nucleosides which on deblocking furnished the free nucleosides. Acetalation of 1-ethyl-3-(D-*manno*-pentitol-1-yl)-5-methyl-1*H*-1,2,4-triazole and 5-(D-*manno*-pentitol-1-yl)-3-methyl-1-(1,2,4-trichlorophenyl)-1*H*-1,2,4-triazole with acetone and dimethoxypropane in the presence of acid afforded their 2,3:4,5-diacetal derivatives

Keywords: Acetalation; Acyclic C-nucleosides; Cycloadditions; Cumulenes; Sugar nitrile

1. Introduction

In the 1970s, a considerable number of C-glycosyl nucleosides were isolated from natural products [1,2], but only a few 1,2,4-triazole C-ribofuranosides were documented [3–8]. These compounds were prepared as analogues [9] of the potent antiviral *N*-nucleoside ribavirin [10–14] because of their broad spectrum of action against RNA and DNA viruses. The antiviral properties of some acyclic 1,2,4-triazole C-nucleosides [15] against herpes simplex viruses (HSV 1 and 2) prompted us to study synthetic approaches [16,17] to prepare new 1,2,4-triazole C-nucleoside analogues as promising potentially biological active candidates. Some of these nucleosides have been selected recently for biological study as potential herbisides, fungisides or insectisides [18]. A recent review on C-nucleosides contained more than 1000 references [19].

We describe here the synthesis of some acyclic D-*manno*-pentitol of 1,2,4-triazole C-nucleosides via cycloaddition of 1-(chloroalkyl)-1-aza-2-azoniaallene salts (**3**) [20–24] with the penta-*O*-benzoyl-D-mannonic acid nitrile (**5**) [25].

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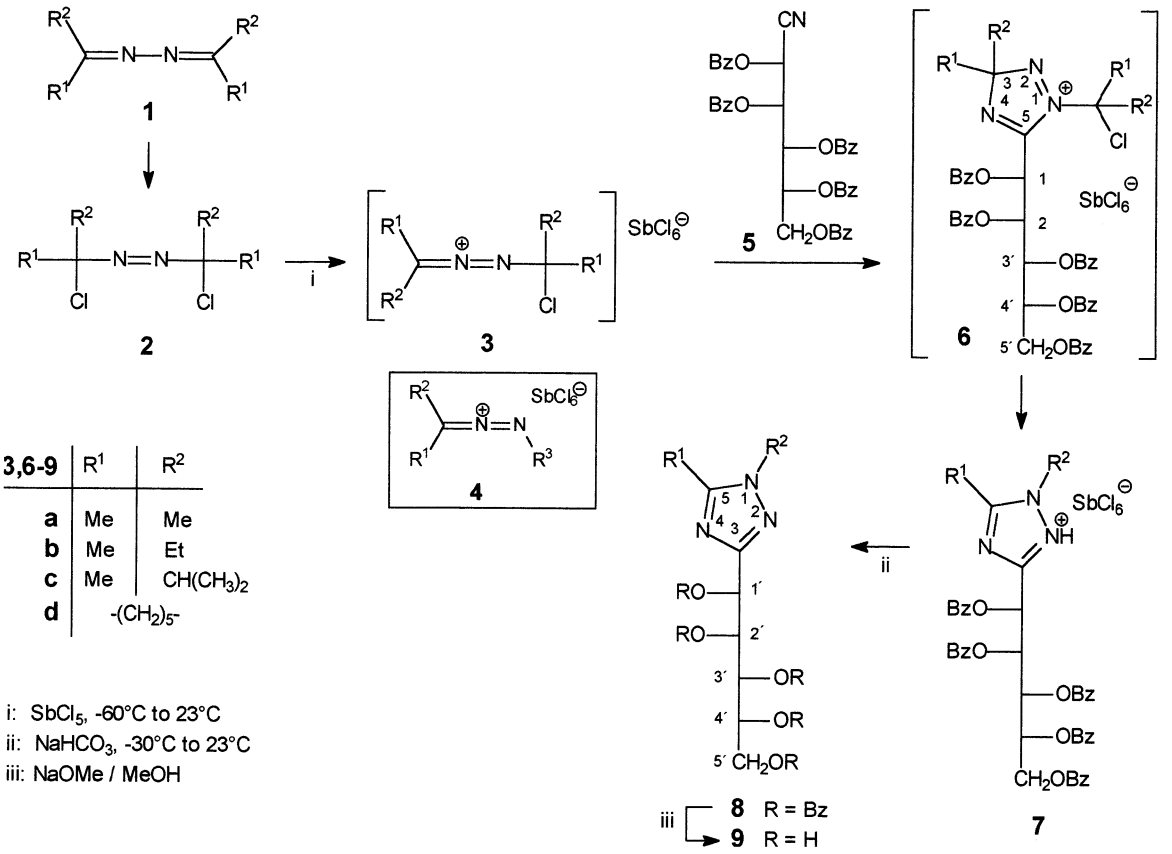
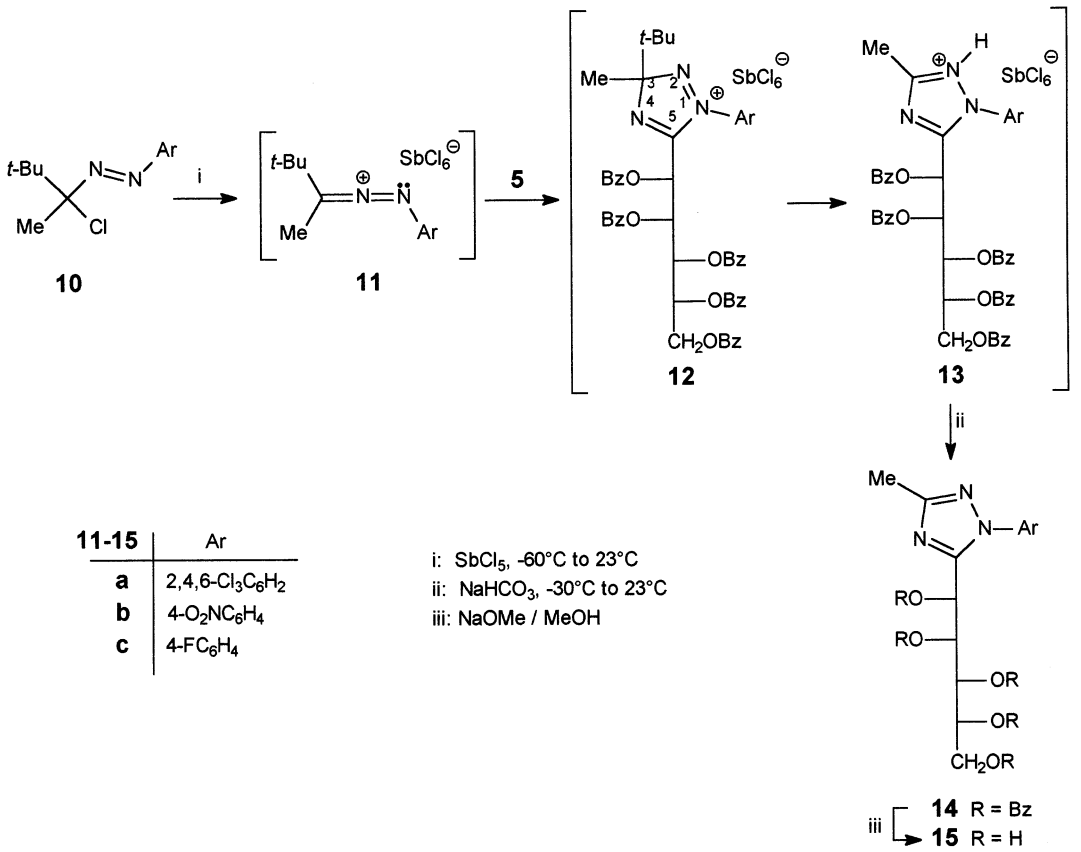
2. Results and discussion

In our recent work [16–18], various 1,2,4-triazole C-nucleosides were synthesized from cycloaddition of the short-lived reactive intermediates 1-(chloroalky)-1-aza-2-azoniaallenes (**3**) and 1-aza-2-azoniaallenes (**4**) (R^1, R^2 = alkyl, $R^3 = CO_2Et$ or aryl) with the glycosyl and the acyclic (2-hydroxyethoxy)alkyl cyanides. In the present study, the reactive intermediates **3** and 1,2,3,4,5-penta-*O*-benzoyl-D-mannonic acid nitrile (**5**) have been selected for the synthesis of some new 1,2,4-triazole C-nucleosides. The sugar nitrile **5** was prepared from hydroxylamination of D-mannose followed by benzoylation at 50 °C, then at room temperature for 24 h. Chlorination of the hydrazones **1** afforded the dichlorides **2**, which were converted, at approximately −60 °C, to the salts **3** in the presence of $SbCl_5$. At approximately −30 °C the color changed from orange to brown, indicating that **3** underwent cycloaddition reaction with sugar nitrile **5** to give the unseparable 5-(D-*manno*-pentitol-1-yl)-3*H*-1,2,4-triazolium hexachloroantimonates **6**. When the temperature was raised above −30 °C, **6** furnished the protonated triazoles **7** by [1,2] migration [26,27] of the alkyl group (R^2) from C-3 to N-2 and elimination of the ($CClR^1R^2$) group from N-1. The C-nucleosides **8a–d** were obtained from hydrolysis of the triazolium salts **7a–d**, in situ, with aqueous $NaHCO_3$ [26,28] in good yields. Treatment of **8a–d** with NaOMe in MeOH afforded the free nucleosides **9a–d** in 81–90% yields (Scheme 1).

The heterocumulenes **11** with *tert*-butyl group were used to synthesize electrically neutral 2-unsubstituted 1,2,4-triazoles [26,28]. Thus, 1-aza-2-azoniaallene salts **11,** formed at low temperature from the 1-chloroalkyl azo compounds **10** [16–18,20–30] on treatment with a Lewis acid such as $SbCl_5$, was reacted with the nitrile **5** to give the inseparable salts **12**. The formation of the intermediate **13**, resulting from elimination of the bulky *tert*-butyl group and [1,2] H-shift, proves that sterically electron-withdrawing substituents



Scheme 1.



Scheme 2.

forming stable carbonium ions can escape during the [1,2] shift [28]. Hydrolysis of **13**, in situ, with aqueous $NaHCO_3$ gave the nucleosides **14a–c** in good yields. Successful removal of the benzoyl groups of **14a–c** with NaOMe in MeOH which afforded the free nucleosides **15a–c** in 89, 80, 95% yields, respectively (Scheme 2).

Acetalation of **9b** and **15a** with acetone and 2,2-dimethoxypropane in the presence of *p*-toluenesulphonic acid at room temperature for 0.5 h afforded, after chromatographic purification, the 2,3:4,5-diacetal derivatives **16** as oil (FABMS *m/z* 342 $[MH]^+$; 364 $[MNa]^+$) in 65% yield and **17** as oil (FABMS *m/z* 493 $[MH]^+$; 515 $[MNa]^+$) in 78% yield (Scheme 3).

The structures of the nucleosides were determined by homo and heteronuclear NMR spectroscopic methods and by mass spectra. The ^1H NMR spectra of **8a–d** and **14a–c** showed a similar pattern, since H-1′, H-2′ and H-3′ appeared, mostly, as multiplets, doublets or a doublet of doublets in the region δ 6.23–6.70. The doublet of doublets of doublets appeared in the region δ 5.78–5.90 with *J* couplings between 3.2 and 3.7 Hz being attributed to H-4′. The doublet of doublets at δ 4.86, 4.82, 4.84, 4.90, 4.85 and 4.82 with *J* couplings 5.8, 5.4, 5.5, 6.3, 5.2, 5.3 and 5.3 Hz, respectively, were assigned to H-5′. The H-5 appeared as a doublet of doublets in the region δ 4.49–4.63 with geminal coupling $\sim$ 12.0 Hz. The alkyl groups at N-1 and C-5 were assigned. The free nucleosides **8a–d** and **15a–c** were characterized by two-dimensional NMR spectroscopy. The procedures are already described [17,31].

The structures of **14** and **15** were characterized from their HMQC NMR spectroscopic study. The quaternary C-atoms of the diacetal groups of compound **14** at δ 109.9 and 109.8 showed a $^{2/3}J_{CH}$ correlation to H-2′, H-3′ and H-4′, H-5′ at δ 4.29, 4.03 and 4.07, 3.93, respectively. Moreover, the ^{13}C NMR of **14** showed a large difference in the chemical shift ($\sim$ 11.0 ppm) between C-2′, C-3′ and those of the adduct **9a**. The coupling constants in the

^{1}H NMR spectra of the diacetals **14** and **15** between H-1′, H-2′, H-3′ and H-4′ are in the range 7.0–8.0 Hz, confirming the expected *cis*-configuration of these protons. These data are in agreement with the results obtained from the acetalation of the D-*manno* series [32].

3. Experimental

General methods.—Melting points are uncorrected. NMR spectra were measured with Bruker AC-250, WM-250 and 600 MHz (^{1}H) and at 62.9 MHz (^{13}C) with TMS as internal standard and on a δ scale in ppm. EI and FAB mass spectra were recorded on a MAT 312 mass spectrometer using 3-nitrobenzylalcohol (NBOH) or glycerol as matrix. Some molecular ions were detected by doping the samples with Na^+ ion. Column chromatography was performed on SiO_2 (for flash chromatography, Merck). The cycloadditions were carried with exclusion of moisture.

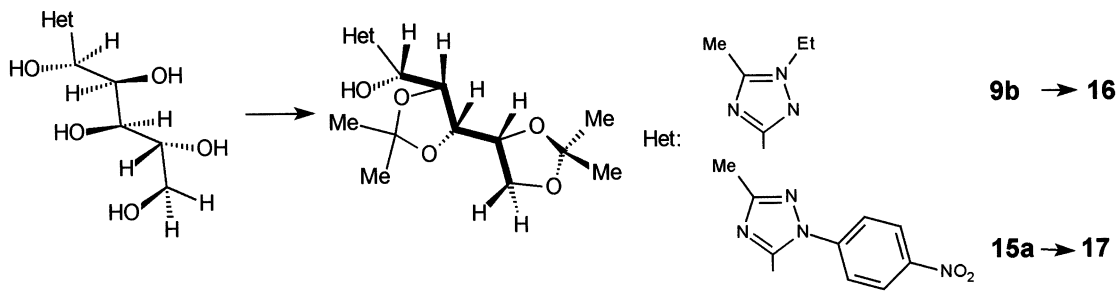
Preparation of acylated D-*glycosyl-1*H-*1,2,4-triazole nucleosides* **8** *and* **14**

General procedure. A solution of $SbCl_5$ (3.0 mmol) in CH_2Cl_2 (30 mL) was added dropwise to a stirred, cooled (-60 °C) solution of the sugar nitrile **5** (2.0 mmol) and the required 1-(chloroalkyl)azo compounds **3** (3.0 mmol) in dry CH_2Cl_2 (20 mL). After stirring at -60 °C for 1 h, then at 0 °C for 1 h and finally at 23 °C for 10 min, pentane (50 mL) was added. The residue was dissolved in CH_3CN (40 mL). After cooling to 0 °C, an aq solution of $NaHCO_3$ (2.52 g, 30 mmol in 30 mL of H_2O) was added and the mixture was stirred at room temperature for 2 h. The organic solvent was evaporated and the residue was extracted with $CHCl_3$ (3×20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to dryness. The amorphous residue was purified by column chromatography using first $CHCl_3$ and then $CHCl_3$/MeOH (19:1) as eluent.

1,5-Dimethyl-3-(1,2,3,4,5-penta-O-*benzoyl-*D-manno-*pentitol-1-yl)-1*H-*1,2,4-triazole* (**8a**). From **3a** (0.55 g, 3.0 mmol). Yield: 1.19 g, 78%; mp 70–77 °C (amorphous). δ_H (250 MHz, $CDCl_3$, 303 K): 8.12–7.84 (m, 10 H, ArH); 7.64–7.22 (m, 15 H, ArH); 6.45–6.36 (m, 3 H, H-1′, H-2′, H-3′); 5.85 (m, 1 H, $J_{4',5''}$ 5.8 Hz, H-4′); 4.86 (dd, 1 H, $J_{4',5'}$ 3.3 Hz, H-5′); 4.61 (dd, 1 H, $J_{5',5''}$ 12.0 Hz, H-5″); 3.49, 2.18 (2s, 6 H, $2CH_3$). Anal. Calcd for $C_{44}H_{37}N_3O_{10}$: 68.83; H, 4.86; N, 5.47; Found: C, 68.59; H, 4.69; N, 5.31. *m/z* (FAB > 0) 768 [MH^+]; 790 [MNa^+].

1-Ethyl-5-methyl-3-(1,2,3,4,5-penta-O-*benzoyl-*D-manno-*pentitol-1-yl)-1*H-*1,2,4-triazole* (**8b**). From **3b** (0.66 g, 3.0 mmol). Yield: 1.2 9 g, 83%; mp 66–72 °C (amorphous). δ_H (250 MHz, $CDCl_3$, 303 K): 8.06–7.93 (m, 10 H, ArH); 7.54–7.25 (m, 15 H, ArH); 6.44 (dd, 1 H, $J_{3',4'}$ 8.9 Hz, H-3′); 6.39 (dd, 1 H, $J_{2',3'}$ 1.2 Hz, H-2′); 6.35 (d, 1 H, $J_{1',2'}$ 9.0 Hz, H-1′); 5.89 (ddd, 1 H, $J_{4',5''}$ 5.4 Hz, H-4′); 4.82 (dd, 1 H, $J_{4',5'}$ 3.5 Hz, H-5′); 4.55 (dd, 1 H, $J_{5',5''}$ 12.0 Hz, H-5″); 3.82 (q, 2 H, *J* 7.0 Hz, CH_2CH_3); 2.22 (s, 3 H, CH_3); 1.09 (t, 3 H, CH_2CH_3). Anal. Calcd for $C_{45}H_{39}N_3O_{10}$: 69.13; H, 5.03; N, 5.37. Found: C, 68.74; H, 4.89; N, 5.28; *m/z* (FAB > 0) 782 [MH^+]; 804 [MNa^+].

1-Isopropyl-5-methyl-3-(1,2,3,4,5-penta-O-*benzoyl-*D-manno-*pentitol-1-yl)-1*H-*1,2,4-triazole* (**8c**). From **3c** (0.72 g, 3.0 mmol). Yield: 1.2 g, 81%. mp 54–61 °C (amorphous). δ_H ($CDCl_3$, 303 K): 8.12–7.84 (m, 10 H, ArH); 7.61–7.24 (m, 15 H, ArH); 6.39–6.23 (m, 3 H,



Scheme 3.

H-1′, H-2′, H-3′); 5.90 (ddd, 1 H, $J_{4',5''}$ 5.5 Hz, H-4′); 4.88 (dd, 1 H, $J_{4',5'}$ 3.7 Hz, H-5′); 4.62 (dd, 1 H, $J_{5',5''}$ 11.5 Hz, H-5″); 4.52 [d, 1 H, C*H*$(CH_3)_2$]; 2.23 (s, 3 H, CH_3); 1.13 [d, 6 H, *J* 6.9 Hz, CH$(CH_3)_2$]. Anal. Calcd for $C_{46}H_{41}N_3O_{10}$: C, 69.42; H, 5.19; N, 5.28. Found: C, 69.08; H, 4.92; N, 5.12; *m*/*z* (FAB > 0) 796 [MH^+]; 818 [MNa^+].

6,7,8,9-Tetrahydro-2-(1,2,3,4,5-penta-O-*benzoyl*-D-manno-*pentitol*-*1*-*yl)*-*5*H-*1,2,4-triazolo-[1,5-a]azepine* (**8d**). From **3d** (0.79 g, 3.0 mmol). Yield: 1.14 g, 71%. mp 55–62 °C (amorphous). δ_H ($CDCl_3$, 600 MHz, HMQC, ROSEY, 303 K): 8.0–7.94 (m, 10 H, ArH); 7.49–7.30 (m, 15 H, ArH); 6.42 (dd, 1 H, $J_{3',4'}$ 8.0 Hz, H-3′); 6.38 (d, 1 H, $J_{2',3'}$ 1.3 Hz, H-2′); 6.38 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1′); 5.87 (ddd, 1 H, $H_{4',5''}$ 6.3 Hz, H-4′); 4.84 (dd, 1 H, $J_{4',5''}$ 3.7 Hz, H-5′), 4.55 (dd, 1 H, $J_{5',5'}$ 12.2 Hz, H-5″); 3.97 (dt, 2 H, H-10a, H-10b); 2.72 (dt, 2 H, H-6a, H-6b); 1.69 (m, 2 H, H-8a, H-8b); 1.54, 1.42 (m, 2 H, H-9a, H-9b); 1.44 (m, 2 H, H-7a, H-7b). δ_C ($CDCl_3$): 165.3, 165.2, 165.0, 164.9, 164.8 (C=O); 157.6 (C-3); 156.6 (C-5); 133.3, 133.0, 132.9, 130.0, 129.9, 129.8, 129.7, 129.5, 129.4, 129.2, 128.4, 128.3, 128.2, 128.1 (Ar); 70.9 (C-1′); 70.0 (C-4′); 69.3 (C-3′); 68.2 (C-2′); 62.8 (C-5′), 50.9 (C-10); 30.1 (C-8); 27.0 (C-9); 27.0 (C-6); 24.5 (C-7). Anal. Calcd for $C_{47}H_{41}N_3O_{10}$: C, 69.88; H, 5.12; N, 5.20. Found: C, 69.71; H, 5.06; N, 5.29; *m*/*z* (FAB > 0) 808 [MH^+].

3-*Methyl*-*5*-*(1,2,3,4,5-penta*-O-*benzoyl*-D-manno-*pentitol*-*1*-*yl)*-*1*-*(2,4,6-trichlorophenyl)*-*1*H-*1,2,4-traizole* (**14a**). From **10a** (0.98 g, 3.0 mmol). Yield: 1.18 g, 63%; mp 62–69 °C (amorphous). δ_H (600 MHz, $CDCl_3$, 303 K): 8.0–7.91 (m, 8 H, ArH); 7.56–7.25 (m, 19 H, ArH); 6.70 (dd, 1 H, $J_{2',3'}$ 1.2 Hz, H-2′); 6.60 (m, 2 H, H-3′, H-1′); 5.89 (dd, 1 H, $J_{4',5''}$ 5.2 Hz, H-4′); 4.90 (dd, 1 H, $J_{4',5'}$ 3.5 Hz, H-5′); 4.63 (dd, 1 H, $J_{5',5''}$ 12.0 Hz, H-5″); 2.38 (s, 3 H, CH_3). Anal. Calcd for $C_{49}H_{36}Cl_3N_3O_{10}$: C, 63.07; H, 3.89; N, 4.50. Found: C, 62.91; H, 3.82; N, 4.69; *m*/*z* (FAB > 0) 932/934 [MH^+]; 954/956 [MNa^+].

3-*Methyl*-*1*-*(4-nitrophenyl)*-*5*-*(1,2,3,4,5-penta*-O-*benzoyl*-D-manno-*pentitol*-*1*-*yl)*-*1*H-*1,2,4-triazole* (**14b**). From **10b** (0.81 g, 3.0 mmol). Yield: 1.26 g, 72%; mp 65–72 °C (amorphous). δ_H (600 MHz, $CDCl_3$, 303 K): 8.22–7.24 (m, 29 H, ArH); 6.40 (dd, 1 H, $J_{2',3'} = 1.0$ Hz, H-2′); 6.35 (dd, $J_{3',4'}$ 8.2 Hz, H-3′); 6.33 (d, 1 H, $J_{1',2'}$ 8.8 Hz, H-1′); 5.80 (ddd, 1 H, $J_{4',5''}$ 5.2 Hz, H-4′); 4.85 (dd, 1 H, $J_{4',5'}$ 3.5 Hz, H-5′); 4.50 (dd, 1 H, $J_{5',5''}$ 12.3 Hz, H-5″); 2.30 (s, 3 H, CH_3). δ_C ($CDCl_3$): 165.2 (C-3); 151.4 (C-5); 133.9, 133.1, 130.1, 129.9, 128.4, 125.6, 124.5 (Ar); 70.7 (C-1′); 69.1 (C-4′); 68.9 (C-3′); 65.4 (C-2′); 62.6 (C-5′). Anal Calcd for $C_{49}H_{38}N_4O_{12}$: C, 67.27; H, 4.38; N, 6.40. Found: C, 66.92; H, 4.25; N, 6.19; *m*/*z* (FAB < 0) 875 [MH^+]; 931 [MNa^+].

1-*(4*-*Fluorophenyl)*-*3*-*methyl*-*5*-*(1,2,3,4,5-penta*-O-*benzoyl*-D-manno-*pentitol*-*1*-*yl)*-*1*H-*1,2,4-triazole* (**14c**). From **10c** (0.73 g, 3.0 mmol). Yield: 1.16 g, 68%; mp 60–67 °C (amorphous). δ_H ($CDCl_3$, 303 K): 8.02–7.26 (m, 29 H, Ar); 6.40 (dd, 1 H, $J_{2',3'}$ 1.3 Hz, H-2′); 6.33 (dd, 1 H, $J_{3',4'}$ 7.9 Hz, H-3′); 6.31 (d, 1 H, $J_{1',2'}$ 8.6 Hz, H-1′), 5.78 (ddd, 1 H, $J_{4',5''}$ 5.3 Hz, H-4′); 4.82 (dd, 1 H, $J_{4',5'}$ 3.4 Hz, H-5′); 4.49 (dd, 1 H, $J_{5',5''}$ 12.3 Hz, H-5″); 2.38 (s, 3 H, CH_3). Anal. Calcd for $C_{49}H_{38}NFN_3O_{10}$: C, 69.44; H, 4.52; N, 4.96. Found: C, 69.07; H, 4.43; N, 4.82; *m*/*z* (FAB > 0) 848 (MH^+); 870 (MNa^+).

Preparation of free nucleosides (**9**) *and* (**15**)

General procedure. A solution of acylated nucleosides **8** and **14** (1.13 mmol) in 0.3 M NaOMe (25 mL) was stirred at 23 °C for 18 h. The solution was neutralized with 0.1 M HCl and filtered. The filtrate was evaporated to dryness and the residue was partitioned between water (30 mL) and Et_2O (3 × 20 mL). The aqeous layer was evaporated to dryness and afterwards co-evaporated with EtOH (3 × 20 mL). The residue was purified on SiO_2 column using MeOH, in gradient (0–20%) and $CHCl_3$ as eluent. Evaporation of the appropriate fractions afforded the pure nucleosides **9** and **15**.

1,5-*Dimethyl*-*3*-*(*D-manno-*pentitol*-*1*-*yl)*-*1*-H*1,2,4-triazole* (**9a**). From **8a** (0.87 g). Yield: 0.23 g, 82%; mp 136–140 °C dec. δ_H (600 MHz, D_2O): 4.04 (d, 1 H, $J_{1',2'}$ 9.1 Hz, H-1′); 4.02 (dd, 1 H, $J_{2',3'}$ 1.2 Hz, H-2′); 3.80 (dd, 1 H, $J_{3',4'}$ 6.2 Hz, H-3′); 3.78 (ddd, 1 H, $J_{4',5'}$ 3.0 Hz, H-5′); 3.69 (s, 3 H, *N*–Me); 3.68 (dd, 1 H, $J_{4',5''}$ 5.8 Hz, H-4′); 3.59 (dd, 1 H, $J_{5',5''}$ 12.1 Hz, H-5″); 2.33 (s, 3 H, C_5–*Me*). δ_C (D_2O): 161.5 (C-3); 154.4 (C-5); 70.6 (C-2′, C-4′); 68.7 (C-3′); 66.4 (C-1′); 63.0 (C-5′); 34.6

(*N*–Me); 10.6 (C_5–*Me*). Anal. Calcd. for $C_9H_{17}N_3O_5$: C, 43.72; H, 6.93; N, 16.99. Found: C, 43.52; H, 6.84; N, 16.86; *m/z* (FAB > 0) 248 $[M+H]^+$; 270 $[MNa]^+$.

*1-Ethyl-5-methyl-3-(*D-manno-*pentitol-1-yl)--1*H-*1,2,4-triazole* (**9b**). From **8b** (0.88 g). Yield: 0.24 g, 81%.; mp 101–111 °C dec. δ_H (600 MHz, D_2O): 4.87 (d, 1 H, $J_{1',2'}$ 8.7 Hz, H-1′); 4.20 (q, 2 H, *J* 7.0 Hz, CH_2CH_3); 4.02 (dd, 1 H, $J_{2',3'}$ 1.2 Hz, H-2′); 3.77 (dd, 1 H, $J_{3',4'}$ 8.6 Hz, H-3′); 3.74 (dd, 1 H, $J_{4',5'}$ 2.8 Hz, H-5′); 3.67 (ddd, 1 H, $J_{4',5''}$ 6.2 Hz, H-4′); 3.59 (dd, 1 H, $J_{5',5''}$ 11.8 Hz, H-5″); 2.63 (s, 3 H, C_5–Me); 1.37 (t, 3 H, CH_2CH_3). δ_C (D_2O): 155.9 (C-3); 151.3 (C-5); 70.6 (C-2′); 70.5 (C-4′); 68.7 (C-3′); 65.5 (C-5′); 63.1 (C-1′); 45.0 (CH_2CH_3); 13.1, 9.3 (2Me). Anal. Calcd. for $C_{10}H_{19}N_3O_5$: C, 45.97; H, 7.33; N, 16.08. Found: C, 45.72; H, 7.19; N, 16.19; *m/z* (FAB > 0) 262 $[MH]^+$; 284 $[MNa]^+$.

*1-Isopropyl-3-(*D-manno-*pentitol-1-yl)-5-methyl-1*H-*1,2,4-triazole* (**9c**). From **8c** (0.28 g); mp 125–132 °C. δ_H (600 MHz, D_2O): 4.74 (d, 1 H, $J_{1',2'}$ 9.0 Hz, H-1′); 4.08 (dd, 1 H, $J_{2',3'}$ 1.2 Hz, H-2′); 3.79 (dd, 1 H, $J_{3',4'}$ 6.0 Hz, H-3′); 3.78 (dd, 1 H, $J_{4',5'}$ 3.0 Hz, H-5′); 3.69 (ddd, 1 H, $J_{4',5''}$ 6.4 Hz, H-4′); 3.58 (dd, 1 H, $J_{5',5''}$ 11.6 Hz, H-5″); 2.37 (s, 3 H, C_5–Me); 1.35 [d, 1 H, $CH(Me)_2$]; 1.08 [t, 1 H, $CH(Me)_2$]. δ_C (D_2O): 161.4 (C-3); 152.8 (C-5); 70.7 (C-2′); 70.6 (C-4′); 68.8 (C-3′); 66.1 (C-1′); 63.1 (C-5′); 50.3 [$CH(Me)_2$]; 13.3 (C_5–*Me*); 10.8, 10.6 [$CH(Me)_2$]. Anal. Calcd. for $C_{11}H_{21}N_3O_5$: C, 47.99; H, 7.69; N, 15.26. Found; C, 47.72; H, 7.61; N, 15.45; *m/z* (FAB > 0) 276 $[MH]^+$; 298 $[MNa]^+$.

*6,7,8,9-Tetrahydro-2-(*D-manno-*pentitol-1-yl)-5*H-*1,2,4-triazolo[1,5-a]azepine* (**9d**). From **8d** (0.79 g). Yield: 0.28 g, 90%; mp 78–82 °C. δ_H (600 MHz, DMSO-d_6): 5.09 (d, $J_{1,OH}$ 6.0 Hz, $C_{1'}$–OH); 4.44 (d, $J_{4',OH}$ 7.6 Hz, $C_{4'}$–OH); 4.40 (dd, 1 H, $J_{1',2'}$ 8.8 Hz, H-1′); 4.33 (t, $J_{5',OH}$ 5.8 Hz, $C_{5'}$–OH); 4.22 (d, $J_{3',OH}$ 5.7 Hz, $C_{3'}$–OH); 4.16 (pt, 2 H, *J* 5.0 Hz, H-10a, H-10b); 3.99 (ddd, 1 H, $J_{2',3'}$ 1.2 Hz, H-2′); 3.96 (d, $J_{2',OH}$ 7.4 Hz, $C_{2'}$–OH); 3.65 (t, 1 H, $J_{3',4'}$ 8.1 Hz, H-3′); 3.61 (dd, 1 H, $J_{4',5'}$ 3.4 Hz, H-5′); 3.45 (m, 1 H, $J_{4',5''}$ 5.7 Hz, H-4′); 3.38 (ddd, 1 H, $J_{5',5'}$ 11.8 Hz, H-5″); 2.84 (pt, 2 H, *J* 3.0 Hz, H-6a, H-6b); 1.81 (pt, 2 H, *J* 5.6 Hz, H-8a, H-8b); 1.68 (dt, 2 H, *J* 5.2 Hz, H-9a, H-9b); 1.59 (dt, 2 H, *J* 5.4 Hz; H-7a, H-7b). δ_C (D_2O): 161.0 (C-3); 159.2 (C-5); 71.6 (C-4′); 71.1 (C-2′); 69.2 (C-3′); 66.7 (C-1′); 63.1 (C-5′); 50.9 (C-10); 29.1 (C-8); 26.4 (C-9); 26.1 (C-6), 23.9 (C-7). Anal. Calcd for $C_{12}H_{21}N_3O_5$: C, 50.17; H, 7.37; N, 14.63. Found: C, 49.82; H, 7.29; N, 14.78; *m/z* (FAB > 0) 288 $[MH]^+$.

*5-(*D-manno-*Pentitol-1-yl)-3-methyl-1-(2,4,-6-trichlorophenyl)-1*H-*1,2,4-triazole* (**15a**). From **14a** (0.9 g). Yield: 0.35 g; 89%; mp 92–96 °C. δ_H (600 MHz, D_2O): 7.92, 7.91 (AA′BB′, 2 H, ArH); 4.34 (dd, 1 H, $J_{1',2'}$ 9.2 Hz, H-1′); 4.02 (dd, 1 H, $J_{2',3'}$ 1.0 Hz, H-2′); 3.58 (dd, 1 H, $J_{3',4'}$ 9.2 Hz, H-3′); 3.56 (dd, 1 H, $J_{4',5'}$ 3.2 Hz, H-5′); 3.44 (dd, 1 H, $J_{4',5''}$ 6.0 Hz, H-4′); 3.36 (dd, 1 H $J_{5',5''}$ 11.1 Hz, H-5″); 2.33 (s, 3 H, Me). δ_C (D_2O): 159.6 (C-3); 159.4 (C-5); 135.8, 134.8, 134.4, 132.2, 125.9, 128.7 (Ar); 70.9 (C-4′), 70.8 (C-2′); 69.0 (C-3′); 65.0 (C-1′); 63.7 (C-5′); 13.5 (Me). Anal. Calcd for $C_{14}H_{16}Cl_3N_3O_5$: C, 40.75; H, 3.912; N, 10.18. Found: C, 40.52; H, 3.83; N, 10.32; *m/z* (FAB > 0) 412/414 $[MH]^+$; 434/436 $[MNa]^+$.

*5-(*D-manno-*Pentitol-1-yl)-3-methyl-1-(4-nitrophenyl))-1*H-*1,2,4-triazole* (**15b**). From **14b** (0.9 g). Yield: 0.29 g; 80%; mp 121–125 °C dec. δ_H (600 MHz, D_2O): 7.47, 7.35 (AA′BB′, 4 H, ArH); 4.34 (d, 1 H, $J_{1',2'}$ 9.1 Hz, H-1′); 4.07 (dd, 1 H, $J_{2',3'}$ 1.2 Hz, H-2′); 3.73 (dd, 1 H, $J_{3',4'}$ 9.1 Hz, H-3′); 3.70 (dd, 1 H, $J_{4',5'}$ 3.9 Hz, H-5′); 3.68 (ddd, 1 H, $J_{4',5''}$ 5.9 Hz, H-4′); 3.63 (dd, 1 H, $J_{5',5''}$ 11.2 Hz, H-5″); 2.29 (s, 3 H, Me). δ_C (D_2O): 160.7 (C-3); 154.5 (C-5); 147.0, 141.5, 125.4, 125. (Ar); 70.5 (C-4′); 70.2 (C-2′); 68.5 (C-3′); 64.7 (C-1′); 63.9 (C-5′); 13.9 (Me). Anal. Calcd for $C_{14}H_{18}N_4O_7$: C, 47.46; H, 5.12; N, 15.81. Found: C, 47.09; H, 4.96; N, 15.92; *m/z* (FAB > 0) 355 $[MH]^+$; 377 $[MNa]^+$.

*1-(4-Fluorophenyl)-5-(*D-manno-*pentitol-1-yl)-3-methyl-1*H-*1,2,4-triazole* (**15c**). From **14c** (0.53 g). Yield: 0.19 g, 95%; mp 166–170 °C dec. δ_H (600 MHz, D_2O): 7.59, 7.33 (AA′BB′, 4 H, ArH); 4.97 (d, 1 H, $J_{1',2'}$ 8.7 Hz, H-1′); 4.16 (dd, 1 H, $J_{2',3'}$ 1.1 Hz, H-2′); 3.72 (dd, 1 H, $J_{3',4'}$ 9.1 Hz, H-3′), 3.70 (dd, 1 H, $J_{4',5'}$ 6.0 Hz, H-5′), 3.68 (ddd, 1 H, $J_{4',5''}$ 2.7 Hz, H-4′); 3.61 (dd, 1 H, $J_{5',5''}$ 11.0 Hz, H-5″); 2.45 (s, 3 H, Me). δ_C (D_2O): 163.4 (d, *J* 246 Hz, *p*-C); 156.6 (C-3); 155.7 (C-5); 116.8 (d, *J* 23 Hz, *m*-C); 128.1 (d, *J* 9.0 Hz, *o*-C); 131.0 (d, *J*

3.0 Hz, *i*-C); 71.2 (C-4′); 70.4 (C-2′); 68.6 (C-3′); 63.8 (C-1′), 63.0 (C-5′); 11.2 (Me). Anal. Calcd. for $C_{14}H_{18}FN_3O_5$: C, 51.37; H, 5.54; N, 12.84. Found: C, 51.26; H, 5.49; N, 21.76; *m/z* (FAB > 0) 328 $[MH]^+$; 350 $[MNa]^+$.

*1-Ethyl-3-(1,2:4,5-di-O-isopropylidene-*D-manno-*pentitol-1-yl)-5-methyl-1*H-*1,2,4-triazole* (**16**).—To a stirred solution of **9b** (100 mg, 0.40 mmol) in dry DMF (2 mL), dry acetone (5 mL), dimethoxypropane (2 mL) and *p*-toluenesulphonic acid (10 mg) were added. The solution was stirred at room temperature for 30 min, neutralized with Na_2CO_3 and then evaporated to dryness. The residue was partitioned between $CHCl_3$ (2 × 10 mL) and H_2O (10 mL). The combined organic extracts was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was purified on short column of SiO_2. Elution with $CHCl_3$–MeOH (95:5) afforded the pure acetal **16** (90 mg, 65%) as oil. δ_H (600 MHz, $CDCl_3$): 4.71 (d, 1 H, H $J_{1',2'}$ 7.0 Hz, H-1′); 4.29 (t, 1 H, $J_{2',3'}$ 7.0 Hz, H-2′); 4.10 (dd, 1 H, $J_{5',5''}$ 13.5 Hz, H-5″); 4.07 (dd, 1 H, $J_{4',5''}$ 5.0 Hz, H-4′); 4.03 (dd, 1 H, $J_{3',4'}$ 7.0 Hz, H-3′); 4.02 (q, 2 H, *J* 7.0 Hz, CH_2CH_3); 3.93 (dd, 1 H, $J_{4',5'}$ 7.0 Hz, H-5′); 2.38 (s, 3 H, C_5–Me); 1.38 (t, 3 H, CH_2CH_3); 136, 1.30, 1.28, 1.27 [s, 12 H, $C(Me)_2$]. δ_C ($CDCl_3$): 161.4 (C-3); 151.4 (C-5); 109.9, 109.8 (2quat-C); 81.2 (C-2′); 79.6 (C-3′); 76.4 (C-4′); 69.2 (C-1′); 67.1 (C-5′); 26.3, 27.1, 26.1, 25.1 [2C(*Me*)$_2$)]; 11.1 (Me). Mass spectrum: *m/z* 341.4056 ($C_{16}H_{27}N_3O_5$ Anal. Calcd *m/z* 341.4063 for M^+).

*5-(1,2:4,5-Di-*O*-isopropylidene-*D-manno-*pentitol-1-yl)-3-methyl-1-(2,4,6-trichlorophenyl)--1*H-*1,2,4-triazole* (**17**).—To a stirred solution of **15a** (100 mg, 0.20 mmol) in dry DMF (2 mL), dry acetone (5 mL), dimethoxypropane (2 mL) and *p*-toluenesulphonic acid (10 mg) was stirred at room temperature for 30 min. The solution was worked-up as in the previous experiment to give **17** (90 mg, 75%) as oil. δ_H (250 MHz $CDCl_3$): 7.49, 7.48 (4.32 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1′); 4.27 (t, 1 H, $J_{2',3'}$ 8.0 Hz, H-2′); 4.09 (ddd, 1 H, $J_{4',5''}$ 5.1 Hz, H-4′); 4.06 (t, 1 H, $J_{3',4'}$ 8.0 Hz, H-3′); 3.94 (dd, 1 H, $J_{4',5'}$ 6.7 Hz, H-5′); 3.86 (dd, 1 H, $J_{5',5''}$ 12.5. Hz, H-5″); 2.50 (s, 3 H, Me); 1.40, 1.35, 1.31, 1.13 [s, 12 H, $C(Me)_2$]. Mass spectrum *m/z* 492.7850 ($C_{20}H_{24}Cl_3N_3O_5$ Anal. Calcd *m/z* 492.7857 for M^+).

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