A Simple One Pot Synthesis of 1-(*s*-Triazolo[4,3-*x*]azinyl-3)-substituted Polyols

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Open-chain *C*-nucleosides, 1-(*s*-triazolo[4,3-*x*]azinyl-3)polyols **13-18** were prepared by one-pot synthesis from hydrazinoazines **20a,c** and various *D*-aldoses **1-6**. No protective groups were required for these transformations. 1-(*s*-Triazolo[4,3-*b*]pyridazinyl-3)-*D*-*xylo*-tetritol (**15a**) was isolated and characterised in the form of its 4-*O*-triphenylmethyl derivative **19**. Reaction of hydrazinopyridazines **20a,b** with methyl 2,3-di-*O*-acetyl-*L*-threuronate (**22**), followed by treatment with bromine, gave the corresponding (2*R*,3*S*)-2,3-diacetoxy-3-(*s*-triazolo[4,3-*b*]pyridazinyl-3)propanoic acid methyl esters **24a,b**. Acetonisation of 1-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D*-*gluco*-pentitol (**17a**) gave a mixture of isomeric bis-acetonides **25** and **26**, while acetonisation of 1-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D*-*manno*-pentitol (**18a**) gave acetonide **27** as a single isomer.

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Due to strong antiviral, antibiotic and antitumor activities associated with various *C*-nucleosides, much attention has been payed on the synthesis of this class of compounds [1-7]. Our interest in *C*-nucleoside chemistry first resulted in the synthesis of azolopyridazinyl substituted polyolols by 1,3-dipolar cycloaddition of methyl acrylate to protected and unprotected aldose-azomethinimines [8-10].

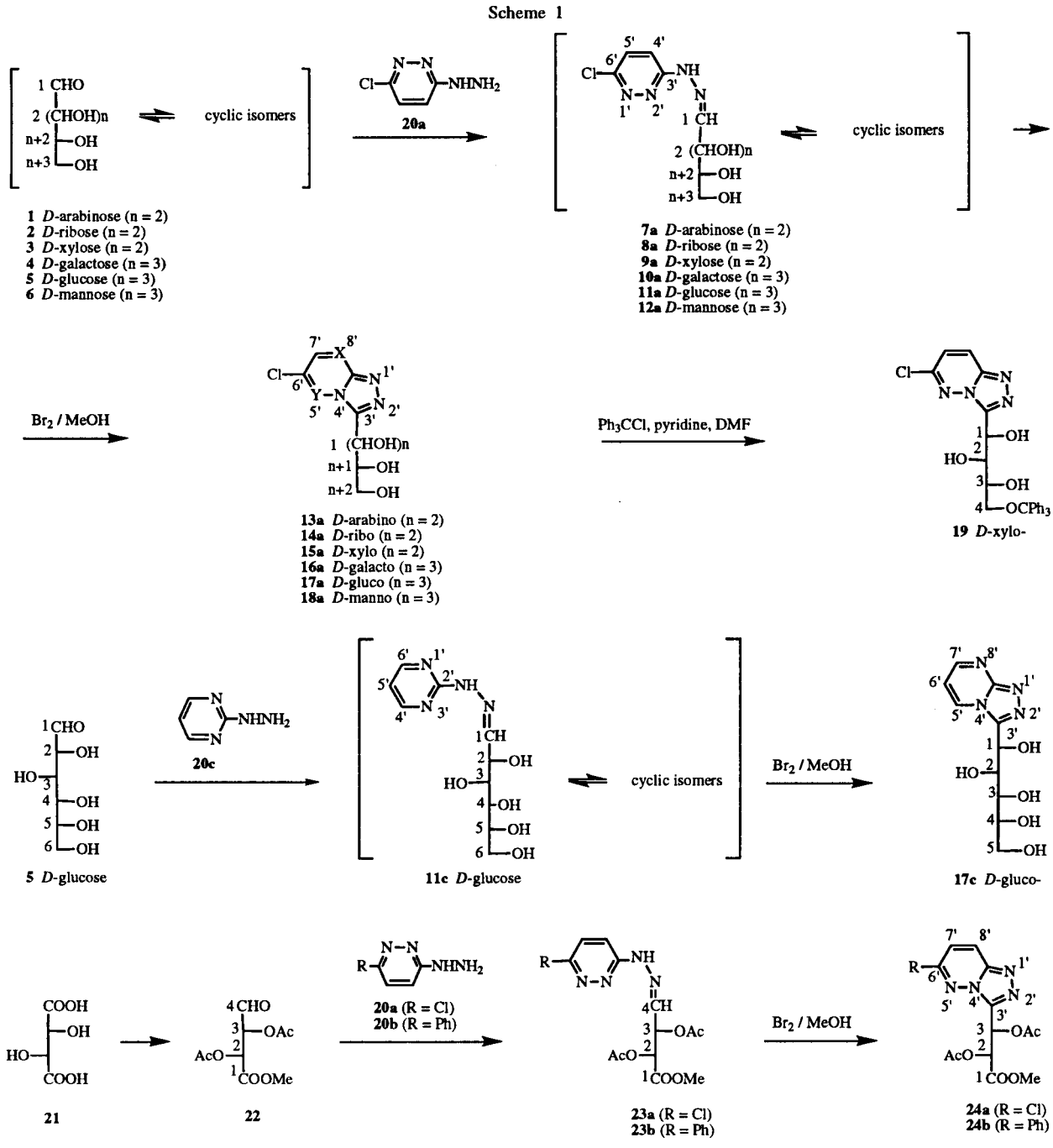
We report now a novel simple synthesis of 1-(*s*-triazolo[4,3-*x*]azinyl-3)-substituted polyols **13-18a,c** which starts from commercially available aldoses **1-6** and does not require any protective, and consequently, deprotective steps. Since the formation of aldose heteroarylhydrazones from aldoses and heteroarylhydrazines has been previously reported in the literature [11]. Since, according to our earlier observation, that aldehydeazinylhydrazones, with the hydrazono group attached at α-position in respect to the ring nitrogen atom, can be oxidatively cyclized into the corresponding *s*-triazolo[4,3-*x*]azines [12-14], we decided to apply this synthesis also on the preparation of 1-(*s*-triazolo[4,3-*x*]azinyl-3)-substituted polyols. For this purpose *D*-arabinose (**1**), *D*-ribose (**2**), *D*-xylose (**3**), *D*-galactose (**4**), *D*-glucose (**5**), and *D*-mannose (**6**), were chosen as representative aldoses, and 6-chloro-3-hydrazinopyridazine (**20a**), 6-phenyl-3-hydrazinopyridazine (**20b**), and 2-hydrazinopyrimidine (**20c**) were chosen as heteroarylhydrazines. Acid-catalysed reaction of aldoses **1-6** with 3-chloro-6-hydrazinopyridazine (**20a**) and 2-hydrazinopyrimidine (**20c**) in refluxing methanol or ethanol resulted in the formation of the corresponding hydrazones **7-12a,c** [15]. Cyclization of aldosehydrazones **7-12a,c** into the corresponding 1-(*s*-triazolo[4,3-*x*]azinyl-3)polyols **13-18a,c** was achieved by the addition of methanolic bromine to the reaction mixture. 1-(6-Chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D*-*xylo*-pentitol (**15a**) was isolated and characterised in the form of its 4-*O*-triphenylmethyl derivative **19**. The synthesis of 1-(*s*-triazolo[4,3-*x*]azinyl-3)polyols was also applied to *aldo*-tetrose derivative methyl 2,3-di-*O*-acetyl-*L*-threuronate (**22**), which was prepared in four steps from *L*-tartaric acid **21** [16]. Thus, reaction of methyl 2,3-di-*O*-acetyl-*L*-threuronate (**22**) with 6-chloro-3-hydrazinopyridazine (**20a**) and 3-hydrazino-6-phenylpyridazine (**20b**) gave the corresponding hydrazones **23a,b**. Treatment of hydrazones **23a,b** with methanolic bromine afforded the corresponding (2*R*,3*S*)-3-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-2,3-diacetoxypropanoic acid methyl ester (**24a**) and (2*R*,3*S*)-2,3-diacetoxy-3-(6-phenyl-*s*-triazolo[4,3-*b*]pyridazinyl-3)propanoic acid methyl ester **24b** (Scheme 1).

Treatment of 1-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D*-*gluco*-pentitol (**17a**) with acetone in the presence of catalytic amounts of sulphuric acid gave a 2:3 mixture of isomeric 2:3,4:5-bis-*O*-(1-methylethylidene-1)-1-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D*-*gluco*-pentitol (**25**) and 1:2,4:5-bis-*O*-(1-methylethylidene-1)-1-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D*-*gluco*-pentitol (**26**), which were separated by crystallisation. On the other hand, acid-catalysed treatment of 1-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D*-*manno*-pentitol (**18a**) with acetone resulted in the formation of 2:3,4:5-bis-*O*-(1-methylethylidene-1)-1-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D*-*manno*-pentitol (**27**) as a single isomer. (Scheme 2).

The structures of 1-(*s*-triazolo[4,3-*x*]azinyl-3) polyols **13-18** and their derivatives **19**, **24-28** were confirmed by ^{1}H nmr spectra, C,H,N analyses, and X-ray structural analyses [17]. The ^{1}H nmr spectra of 1-(*s*-triazolo-[4,3-*b*]azinyl-3) polyols **13-19** and **24-27** are in agreement with those found in other azolopyridazinyl polyols [8-10] and 3-substituted-*s*-triazolo[4,3-*x*]azines and [12-14].

Generally, this synthesis offers an easy and efficient access to 1-(*s*-triazolo[4,3-*x*]azinyl-3) polyols and their

Scheme 1



Compounds 7-12, 20, 23	R	Heterocycle
a	Cl	6-chloropyridazinyl-3
b	Ph	6-phenylpyridazinyl-3
c	H	pyrimidinyl-2

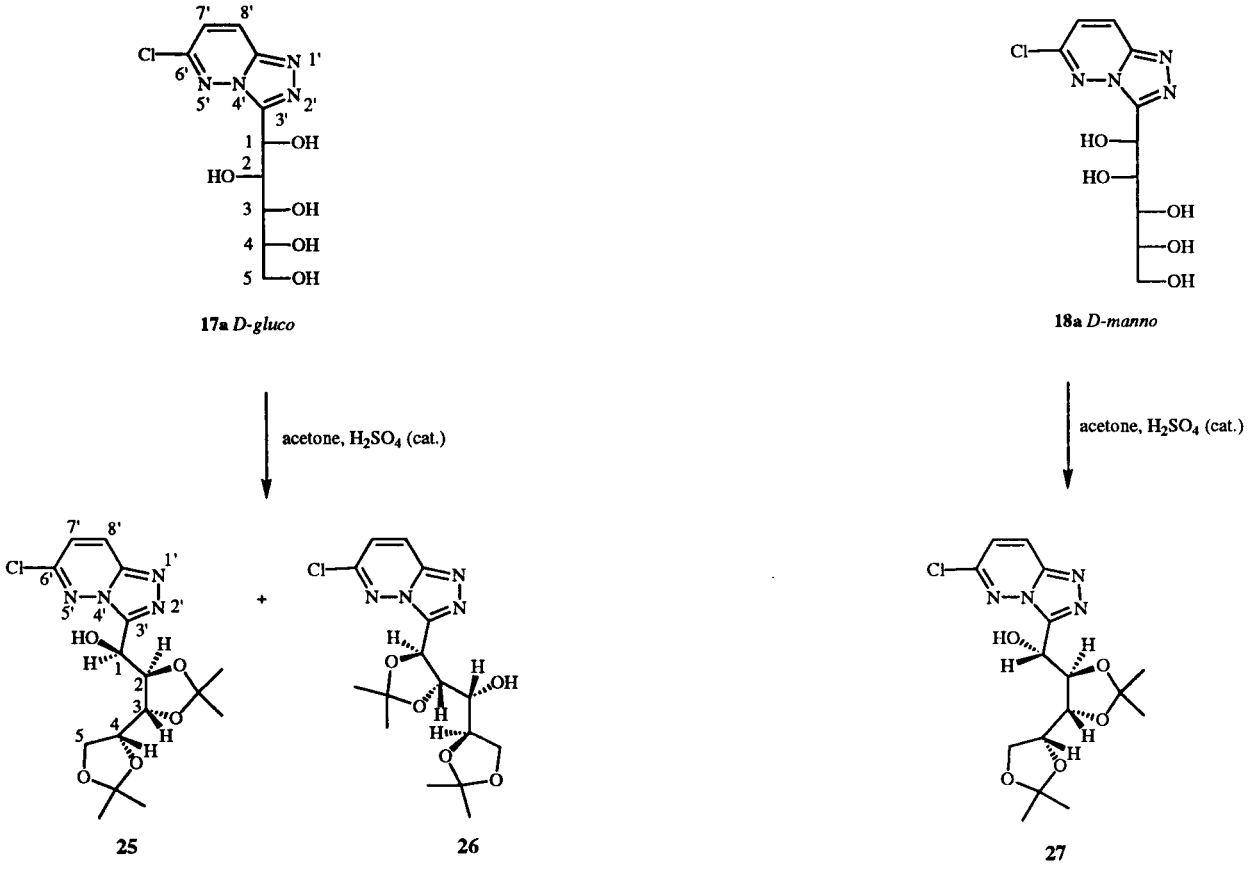
Compounds 13-19, 24	R	Heterocycle
a	Cl	6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3
b	Ph	6-phenyl-*s*-triazolo[4,3-*b*]pyridazinyl-3
c	H	*s*-triazolo[4,3-*a*]pyrimidinyl-3

derivatives. Since polyols **13-19** and **24-27** could be used as precursors for the preparation of cyclic 1-(*s*-triazolo[4,3-*x*]aziyl-3) substituted *C*-nucleosides and iminopolyols, further research in this field is in progress.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage and on a Büchi 535 melting point apparatus. The ^{1}H nmr spectra were obtained on a Varian EM60L (60 MHz) spectrometer and on a

Scheme 2



Bruker AVANCE DPX 300 (300 MHz) spectrometer with DMSO-d_6 or deuteriochloroform ($CDCl_3$) as solvents and TMS as internal standard. The elemental analyses for C, H, and N were obtained on a Perkin-Elmer CHN Analyser 2400. The optical rotations were measured on a Perkin-Elmer 241 MC Polarimeter.

D-Aldose *N*-Azinylhydrazones **7-12a,c**. General Procedure.

A mixture of aldose **1-6** (0.005 mole), hydrazinoazine **20a,c** (0.005 mole), ethanol (95%, 20 ml), and hydrochloric acid (36%, one drop) was stirred at reflux temperature for 1 hour, cooled to 20°, and the precipitate collected by filtration to give a hydrazone **7-12a,c**. Experimental and analytical data for hydrazones **7-12a,c** are given in Tables 1 and 2.

1-(*s*-Triazolo[4,3-*x*]azinyl-3) Polyols **13-18a,c**. General Procedure.

A mixture of aldose **1-6** (0.005 mole), hydrazinoazine **20a,c** (0.005 mole), methanol (20 ml), and hydrochloric acid (36%, one drop) was stirred at reflux temperature for 2 hours, cooled to 20°, and to this mixture a solution of bromine (0.26 ml, 0.005 mole) in methanol (5 ml) was added dropwise while stirring. Stirring was continued for 1 hour, then ethanol (5 ml) and pyridine (1 ml) were added, and volatile components evaporated *in vacuo* at 50°. The residue was dissolved in ethanol (95%, 10 ml) and evaporated *in vacuo* at 60°. Ethanol (95%, 5 ml) was added to the residue and the solution was left at 20°, with occasional scratching, for one day. The precipitate was collected by filtration to give a polyol **13-18a,c**. Experimental and analytical data for compounds **13-18a,c** are given in Tables 1 and 2.

1-(6-Chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-4-*O*-triphenylmethyl-*D*-*xylo*-tetritol (**19**).

Crude 1-(*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D*-*xylo*-tetritol (**15a**) was prepared from *D*-xylose (**3**; 0.005 mole) and 3-chloro-6-hydrazinopyridazine (**20a**, 0.723 g, 0.005 mole) according to the procedure described above for the preparation of 1-(*s*-triazolo[4,3-*x*]azinyl-3) polyols **13-18a,c**. The residue, containing crude 1-(*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D*-*xylo*-tetritol (**15a**), was dissolved in anhydrous *N*,*N*-dimethylformamide (5 ml), then pyridine (0.8 ml) and triphenylmethyl chloride (2 g, 0.075 mole) were added, and the mixture was stirred at room temperature for 24 hours. The reaction mixture was diluted with chloroform (50 ml) and the resulting solution washed with water (3 x 25 ml). Organic phase was dried over anhydrous magnesium sulphate, filtered and the filtrate evaporated *in vacuo*. The residue was subjected to flash chromatography (Kieselgel 60, FLUKA, 20 g) under the following conditions: first, elution with a mixture of chloroform and methanol (25:1, 100 ml) in order to wash out side products, followed by the elution of the product with a mixture of chloroform and methanol (10:1). Fractions containing the product were combined, and volatile components evaporated *in vacuo* to give **19** as an amorphous solid. Experimental and analytical data for compound **19** are given in Tables 1 and 2.

Methyl 2,3-Di-*O*-acetyl-*L*-threuronate (**22**).

This compound was prepared from *L*-tartaric acid (**21**) according to the procedure described in the literature [16].

Table 1

Experimental and Analytical Data

Compound	Yield (%)	mp °C Specific Rotation	Molecular Formula Analyses
7a	84	176-177 (washed with ethanol) $[\alpha]_D^{22}$ -26.8° (c = 1.51, DMSO)	$C_9H_{13}ClN_4O_4$ Calcd: C, 39.12; H, 4.75; N, 20.29 Found: C, 38.96; H, 4.71; N, 20.28
8a	84	157-159 (washed with ethanol) $[\alpha]_D^{22}$ +22.9° (c = 1.20, DMSO)	$C_9H_{13}ClN_4O_4$ Calcd: C, 39.12; H, 4.75; N, 20.29 Found: C, 38.93; H, 4.71; N, 20.16
9a [19]	85	154-156 (washed with ethanol) $[\alpha]_D^{22}$ +6.9° (c = 2.08, DMSO)	$C_9H_{13}ClN_4O_4$ Calcd: C, 39.12; H, 4.75; N, 20.29 Found: C, 39.33; H, 5.05; N, 19.81
10a	73	147-150 (washed with ethanol) $[\alpha]_D^{22}$ +22.1° (c = 2.26, DMSO)	$C_{10}H_{15}ClN_4O_5$ Calcd: C, 39.21; H, 4.94; N, 18.30 Found: C, 38.93; H, 5.11; N, 18.37
11a	87	184-189 (from 60% ethanol) $[\alpha]_D^{21}$ +13.3° (c = 1.47, DMSO)	$C_{10}H_{15}ClN_4O_5$ Calcd: C, 39.21; H, 4.94; N, 18.30 Found: C, 39.19; H, 4.98; N, 18.05
11c	75	184-186 (dec.) (washed with ethanol) $[\alpha]_D^{22}$ -4.5° (c = 1.10, H_2O)	$C_{10}H_{16}N_4O_5$ Calcd: C, 44.10; H, 5.93; N, 20.58 Found: C, 43.92; H, 5.88; N, 20.55
12a	87	186 (dec.) (from 60% ethanol) $[\alpha]_D^{21}$ +8.9° (c = 1.13, DMSO)	$C_{10}H_{15}ClN_4O_5$ Calcd: C, 39.21; H, 4.94; N, 18.30 Found: C, 39.20; H, 4.64; N, 18.02
13a	51	137-139 (from 90% ethanol) $[\alpha]_D^{23}$ -57.9° (c = 0.70, H_2O)	$C_9H_{11}ClN_4O_4$ Calcd: C, 39.41; H, 4.05; N, 20.44 Found: C, 39.03; H, 3.94; N, 20.07
14a	44	174-176 (from 90% ethanol) $[\alpha]_D^{23}$ +24.6° (c = 1.22, H_2O)	$C_9H_{11}ClN_4O_4$ Calcd: C, 39.41; H, 4.05; N, 20.44 Found: C, 39.19, H, 3.83, N, 20.31
16a	58	206-207 (from 90% ethanol) $[\alpha]_D^{21}$ +8.7° (c = 2.24, H_2O)	$C_{10}H_{13}ClN_4O_5$ Calcd: C, 39.47; H, 4.31; N, 18.42 Found: C, 39.24; H, 4.10; N, 18.27
17a	79	182-183 (from 90% ethanol) $[\alpha]_D^{21}$ -8.8° (c = 2.54, H_2O)	$C_{10}H_{13}ClN_4O_5$ Calcd: C, 39.47; H, 4.31; N, 18.42 Found: C, 39.43; H, 4.37; N, 18.27
17c	60	151-152 (from 90% ethanol) $[\alpha]_D^{23}$ +13.5° (c = 1.00, H_2O)	$C_{10}H_{14}N_4O_5$ Calcd: C, 44.43; H, 5.22; N, 20.74 Found: C, 44.16; H, 5.18; N, 20.84
18a	81	185-186 (from 90% ethanol) $[\alpha]_D^{21}$ -8.78° (c = 2.54, H_2O)	$C_{10}H_{13}ClN_4O_5$ Calcd: C, 39.47; H, 4.31; N, 18.42 Found: C, 39.43; H, 4.24; N, 18.21
19	60	70-120 (amorphous solid) (washed with ether) $[\alpha]_D^{22}$ +15.1° (c = 1.27, $CHCl_3$)	$C_{28}H_{25}ClN_4O_4$ Calcd: C, 65.10; H, 4.88; N, 10.85 Found: C, 64.83; H, 4.71; N, 10.55
23a	71	146-147 (dec.) (from methanol) $[\alpha]_D^{20}$ +40.5° (c = 1.21, $CHCl_3$)	$C_{13}H_{15}ClN_4O_6$ Calcd: C, 43.57; H, 4.22; N, 15.64 Found: C, 43.49; H, 3.99; N, 15.50
23b	91	166-167 (dec.) (from methanol) $[\alpha]_D^{20}$ +27.3°(c = 1.20, $CHCl_3$)	$C_{19}H_{20}N_4O_6$ Calcd: C, 56.98; H, 5.04; N, 14.00 Found: C, 56.96; H, 4.79; N, 14.12
24a	62	122-123 (from ethyl acetate/n-hexane) $[\alpha]_D^{25}$ -33.0° (c = 1.29, $CHCl_3$)	$C_{13}H_{13}ClN_4O_6$ Calcd: C, 43.81; H, 3.68; N, 15.73 Found: C, 43.63; H, 3.44; N, 15.47
24b	84	146-147 (from ethyl acetate/n-hexane) $[\alpha]_D^{25}$ -45.4° (c = 0.94, $CHCl_3$)	$C_{19}H_{18}N_4O_6$ Calcd: C, 57.27; H, 4.56; N, 14.07 Found: C, 56.95; H, 4.32; N, 13.98
25	26	186-187 (from ethanol) $[\alpha]_D^{22}$ +14.8° (c = 1.43, $CHCl_3$)	$C_{16}H_{21}ClN_4O_5$ Calcd: C, 49.98; H, 5.51; N, 14.58 Found: C, 49.90; H, 5.38; N, 14.85
26	39	208-209 (from ethanol) $[\alpha]_D^{22}$ -38.1° (c = 1.30, $CHCl_3$)	$C_{16}H_{21}ClN_4O_5$ Calcd: C, 49.98; H, 5.51; N, 14.58 Found: C, 49.80; H, 5.47; N, 14.40

Table 1 (continued)
Experimental and Analytical Data

Compound	Yield (%)	mp °C Specific Rotation	Molecular Formula Analyses
27	78	155-156 (from ethanol) $[\alpha]_D^{25}$ -11.4° (c = 1.52, $CHCl_3$)	$C_{16}H_{21}ClN_4O_5$ Calcd: C, 49.98; H, 5.51; N, 14.58 Found: C, 49.59; H, 5.36; N, 14.49

Table 2
^{1}H NMR Data

Compound	MHz Solvent	(TMS)
7a	300 DMSO-d_6	3.35-3.47 (2H, m, 2C*H*OH), 3.48-3.56 (1H, m, C*H*OH), 3.56-3.65 (1H, m, C*H*OH), 4.30-4.36 (2H, m, CH and OH), 4.56 (1H, d, J = 5.4 Hz, OH), 4.57 (1H, d, J = 7.4 Hz, OH), 4.92 (1H, d, J = 6.2 Hz, OH), 7.45 (1H, d, $H_{5'}$), 7.50 (1H, d, H_1), 7.59 (1H, d, $H_{4'}$), 11.26 (1H, s, N*H*-Het), J_{H1H2} = 5.9 Hz Hz, $J_{H4'H5'}$ = 9.4 Hz.
8a	300 DMSO-d_6	3.35-3.65 (4H, m, 4C*H*OH), 4.24 (1H, br t, C*H*OH), 4.33 (1H, broad peak, OH), 4.56 (1H, broad peak, OH), 4.82 (1H, br s, OH), 5.12 (1H, br s, OH), 7.46 (1H, d, $H_{5'}$), 7.47 (1H, s, H_1), 7.61 (1H, d, $H_{4'}$), 11.26 (1H, s, N*H*-Het), J_{H1H2} = 7.3 Hz, $J_{H4'H5'}$ = 9.4 Hz.
9a	300 DMSO-d_6	3.35-3.60 (4H, m, 4C*H*OH), 4.17 (1H, m, C*H*OH), 4.30-4.55 (3H, br m, 3OH), 5.09 (1H, d, J = 4.7 Hz, OH), 7.46 (1H, d, $H_{5'}$), 7.46 (1H, d, H_1), 7.60 (1H, d, $H_{4'}$), 11.27 (1H, s, N*H*-Het), J_{H1H2} = 7 Hz, $J_{H4'H5'}$ = 9.4 Hz
10a	300 DMSO-d_6	3.30-3.60 (4H, m, 4C*H*OH), 3.73 (1H, br t, J = 6.5 Hz, C*H*OH), 4.18 (2H, broad peak, 2OH), 4.37 (1H, br d, C*H*OH), 4.47 (2H, broad peak, 2OH), 4.85 (1H, broad peak, OH), 7.46 (1H, d, $H_{5'}$), 7.53 (1H, d, H_1), 7.59 (1H, d, $H_{4'}$), 11.26 (1H, br s, N*H*-Het), J_{H1H2} = 5.8 Hz, $J_{H4'H5'}$ = 9.4 Hz.
11a	300 DMSO-d_6	3.34-3.43 (2H, m, 2C*H*OH), 3.44-3.53 (1H, m, C*H*OH), 3.54-3.62 (1H, m, C*H*OH), 3.76 (1H, dt, J = 6.3 Hz and 1.4 Hz, C*H*OH), 4.18 (1H, m, C*H*OH), 4.25 (1H, d, J = 7.0 Hz, OH), 4.31 (1H, t, J = 5.6 Hz, 6-OH), 4.44 (1H, d, J = 6.3 Hz, OH), 4.49 (1H, d, J = 5.4 Hz, OH), 5.13 (1H, d, J = 4.7 Hz, OH), 7.43 (1H, d, H_1), 7.46 (1H, d, $H_{5'}$), 7.60 (1H, d, $H_{4'}$), 11.27 (s, 1H, N*H*-Het), J_{H1H2} = 7.5 Hz, Hz, $J_{H4'H5'}$ = 9.5 Hz.
11c	300 DMSO-d_6	2.90-3.27 (4H, m, 4C*H*OH), 3.40-3.52 (1H, m, C*H*OH), 3.62-3.72 (1H, m, C*H*OH), 3.85 (1H, dd, H_1), 4.34 (1H, t, 6-OH), 4.85 (1H, d, J = 4.9 Hz, OH), 4.88 (1H, d, J = 5.2 Hz, OH), 5.26 (1H, br s, OH), 5.68 (1H, br t, N*H*CH), 6.67 (1H, t, $H_{5'}$), 8.32 (1H, br d, N*H*-Het), 8.34 (2H, d, $H_{4'}$ and $H_{6'}$), J_{H1H2} = 8.7 Hz, J_{H1NH} = 3.4 Hz, J_{NHNH} = 2.3 Hz, $J_{H4'H5'}$ = $J_{H5'H6'}$ = 4.8 Hz.
12a	300 DMSO-d_6	3.35-3.53 (2H, m, 2C*H*OH), 3.54-3.73 (3H, m, 3C*H*OH), 4.00-4.12 (1H, m, C*H*OH), 4.24 (1H, d, J = 7.5 Hz, OH), 4.27-4.37 (2H, m, 2OH), 4.44 (1H, d, J = 4.9 Hz, OH), 5.11 (1H, d, J = 5.5 Hz, OH), 7.47 (2H, br d, $H_{1'}$ and $H_{5'}$), 7.60 (1H, d, $H_{4'}$), $J_{H4'H5'}$ = 9.4 Hz.
13a	300 DMSO-d_6	3.35-3.41 (1H, m, C*H*OH), 3.54-3.62 (2H, m, 2C*H*OH), 3.95 (1H, dd, H_2), 4.00-7.00 (4H, broad peak, 4OH), 5.35 (1H, d, H_1), 7.50 (1H, d, $H_{7'}$), 8.45 (1H, d, $H_{8'}$), J_{H1H2} = 4.2 Hz, J_{H2H3} = 7.8 Hz, $J_{H7'H8'}$ = 9.7 Hz
14a	300 DMSO-d_6	3.51 (1H, dd, H_{4a}), 3.67 (1H, dd, H_{4b}), 3.78 (1H, dt, H_3), 4.25 (1H, dd, H_2), 3.80-5.00 (4H, broad peak, 4OH), 5.25 (1H, d, H_1), 7.50 (1H, d, $H_{7'}$), 8.46 (1H, d, $H_{8'}$), J_{H1H2} = 8.5 Hz, J_{H2H3} = 4.3 Hz, J_{H3H4a} = 6.4 Hz, J_{H3H4b} = 4.0 Hz, J_{H4aH4b} = 11.1Hz, $J_{H7'H8'}$ = 9.7 Hz.
16a	300 DMSO-d_6	3.33-3.46 (2H, m, CH_2), 3.63 (1H, dt, H_3), 3.73 (1H, dq, H_4), 4.05 (ddd, 1H, H_2), 4.167 (d, 1H, 3-OH), 4.20 (d, 1H, 4-OH), 4.42 (t, 1H, 5-OH), 4.69 (d, 1H, 2-OH), 5.38 (dd, 1H, H_1), 5.45 (d, 1H, 1-OH), 7.48 (d, 1H, $H_{7'}$), 8.44 (d, 1H, $H_{8'}$), J_{H1OH} = 7.6 Hz, J_{H1H2} = 3.3 Hz, J_{H2H3} = 9.1 Hz, J_{H2OH} = 6.5 Hz, J_{H3H4} = 1.1 Hz, J_{H3OH} = 6.8 Hz, J_{H4OH} = 7.7 Hz, J_{CH2OH} = 5.6 Hz.
17a	300 DMSO-d_6	3.01 (1H, dd, H_3), 3.29 (1H, dd, H_{5a}), 3.45-3.55 (2H, m, H_{5b} and H_4), 3.50-3.75 (5H, broad peak, 5OH), 4.49 (1H, dd, H_2), 5.26 (1H, d, H_1), 7.51 (1H, d, $H_{7'}$), 8.48 (1H, d, $H_{8'}$), J_{H1H2} = 8.7 Hz, J_{H2H3} = 1.3 Hz, J_{H3H4} = 8.1 Hz, J_{H4H5a} = 6.6 Hz, J_{H5aH5b} = 11.9 Hz.
17c	300 DMSO-d_6	3.13 (1H, m, C*H*OH), 3.28-3.36 (1H, m, C*H*OH), 3.45-3.58 (2H, m, 2C*H*OH), 4.15-4.24 (2H, m, 2OH), 4.28 (1H, d, H_2), 4.38 (1H, d, J = 5.5 Hz, OH), 4.48 (1H, d, J = 6.2 Hz, OH), 4.89 (1H, dd, H_1), 5.42 (1H, d, 1-OH), 7.34 (1H, dd, $H_{6'}$), 8.87 (1H, dd, $H_{7'}$), 9.37 (1H, dd, $H_{5'}$), J_{H1H2} = 7.3 Hz, J_{H1OH} = 5.4 Hz, $J_{H5'H6'}$ = 6.8 Hz, $J_{H5'H7'}$ = 1.9 Hz, $J_{H6'H7'}$ = 4.3 Hz.
18a	300 DMSO-d_6	3.43-3.55 (2H, m, 2C*H*OH), 3.68 (1H, br dd, J = 10.1 Hz and 2.4 Hz, C*H*OH), 3.76 (1H, br d, J = 8.3 Hz, C*H*OH), 4.34 (4H, broad peak, 4OH), 4.49 (1H, d, H_2), 5.22 (1H, d, H_1), 5.80 (1H, br s, 1-OH), 7.49 (1H, d, $H_{7'}$), 8.45 (1H, d, $H_{8'}$), J_{H1H2} = 9.7 Hz, $J_{H7'H8'}$ = 9.7 Hz.
19	300 DMSO-d_6	2.97 (1H, dd, H_{4a}), 3.06 (1H, dd, H_{4b}), 3.37 (1H, m, H_3), 4.40 (1H, ddd, H_2), 4.56 (1H, d, 3-OH), 4.90 (1H, d, 2-OH), 5.22 (1H, dd, H_1), 5.78 (1H, d, 1-OH), 7.20-7.40 (15H, m, CPh_3), 7.53 (1H, d, $H_{7'}$), 8.49 (1H, d, $H_{8'}$), J_{H1H2} = 8.4 Hz, J_{H1OH} = 5.8 Hz, J_{H2H3} = 2.0 Hz, J_{H2OH} = 6.1 Hz, J_{H3H4a} = 6.5 Hz, J_{H3H4b} = 6.1 Hz, J_{H3OH} = 6.8 Hz, J_{H4aH4b} = 8.8 Hz.
23a	60 $CDCl_3$	2.16 (3H, s, MeCO), 2.22 (3H, s, MeCO), 3.83 (3H, s, OMe), 5.63 (1H, d, H_2), 6.06 (1H, dd, H_3), 7.43 (1H, d, $H_{5'}$), 7.64 (1H, d, $H_{4'}$), 7.70 (1H, d, H_4), 12.22 (1H, br s, NH), J_{H2H3} = 3.3 Hz, J_{H3H4} = 5.2 Hz, $J_{H4'H5'}$ = 9.5 Hz.
23b	60 $CDCl_3$	2.09 (3H, s, MeCO), 2.20 (3H, s, MeCO), 3.85 (3H, s, OMe), 5.77 (1H, d, H_2), 6.19 (1H, dd, H_3), 7.53-8.23 (8H, m, 5H-Ph, H_4, $H_{4'}$, and $H_{5'}$), 12.93 (1H, br s, NH), J_{H2H3} = 3.5 Hz, J_{H3H4} = 4.5 Hz.
24a	60 $CDCl_3$	2.16 (3H, s, MeCO), 2.23 (3H, s, MeCO), 3.82 (3H, s, OMe), 5.99 (1H, d, H_2), 6.93 (1H, d, H_3), 7.20 (1H, d, $H_{7'}$), 8.17 (1H, d, $H_{8'}$), J_{H2H3} = 4.0 Hz, $J_{H7'H8'}$ = 9.8 Hz.

Table 2 (continued)

^{1}H NMR Data

Compound	MHz Solvent	(TMS)
24b	60 $CDCl_3$	2.15 (3H, *s*, MeCO), 2.22 (3H, *s*,MeCO), 3.81 (3H, *s*, OMe), 6.12 (1H, d, H_2), 7.13 (1H, d, H_3), 7.58-7.81 (4H, m, 3H-Ph and $H_{7'}$), 8.00-8.17 (2H, m, 2H-Ph), 8.29 (1H, d, $H_{8'}$), J_{H2H3} = 4.0 Hz, $J_{H7'H8'}$ = 10.0 Hz.
25	300 DMSO-d_6	0.95 (3H, *s*, Me), 1.04 (3H, *s*, Me), 1.30 (3H, *s*, Me), 1.34 (3H, *s*, Me), 3.65 (1H, m, C*H*-O-), 3.87 (1H, t, H_3), 3.93-3.99 (2H, m, 2C*H*-O-), 4.61 (1H, t, H_2), 5.25 (1H, t, H_1), 6.19 (1H, d, OH), 7.53 (1H, d, $H_{7'}$), 8.49 (d, 1H, $H_{8'}$), J_{H1H2} = J_{H2H3} = J_{H3H4} = 6.4 Hz, J_{H1OH} = 5.9 Hz, $J_{H7'H8'}$ = 9.6 Hz.
26	60 DMSO-d_6	0.97 (3H, *s*, Me), 1.22 (3H, *s*, Me), 1.46 (6H, *s*, 2 Me), 3.23-4.02 (4H, m, H_3, H_4, and CH_2), 5.07 (1H, dd, H_2), 5.42 (1H, d, OH), 5.53 (1H, d, H_1) 7.60 (1H, d, $H_{7'}$), 8.57 (1H, d, $H_{8'}$), J_{H1H2} = 8 Hz, J_{H2H3} = 4 Hz, J_{H3OH} = 7 Hz, $J_{H7'H8'}$ = 10 Hz.
27	60 DMSO-d_6	1.27 and 1.33 (12H, 2*s*, 4Me), 3.70-4.68 (5H, m, H_2, H_3, H_4, and CH_2), 5.23 (1H, dd, H_1), 6.34 (1H, d, OH), 7.54 (1H, d, $H_{7'}$), 8.53 (1H, d, $H_{8'}$), J_{H1H2} = 8.0 Hz, J_{H1OH} = 6.0 Hz, $J_{H7'H8'}$ = 10.0 Hz.

Methyl 2,3-Di-*O*-acetyl-*L*-threuronate *N*-(3-Chloropyridazinyl-6)hydrazone (**23a**) and Methyl 2,3-Di-*O*-acetyl-*L*-threuronate *N*-(6-Phenylpyridazinyl-3)hydrazone (**23b**). General Procedure.

A mixture of hydrazinopyridazine **20a,b** (0.01 mole), water (50 ml), acetic acid (100%, 1 ml), anhydrous sodium acetate (1.5 g) and methyl 2,3-di-*O*-acetyl-*L*-threuronate (**22**, 2.32 g, 0.01 mole) was stirred at 25° for 1 hour, the precipitate collected by filtration, and washed with water (20 ml) to give a hydrazone **23a,b**. Experimental and analytical data for compounds **23a,b** are given in Tables 1 and 2.

(2*R*,3*S*)-3-(6-Chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-2,3-diacetoxypropanoic Acid Methyl Ester (**24a**) and (2*R*,3*S*)-2,3-Diacetoxy-3-(6-Phenyl-*s*-triazolo[4,3-*b*]pyridazinyl-3)propanoic Acid Methyl Ester (**24b**). General Procedure.

Bromine (0.0052 ml, 0.001 mole) was added to a stirred mixture of methyl 2,3-di-*O*-acetyl-*L*-threuronate *N*-pyridazinylhydrazone **23a,b** (0.001 mole), methanol (4 ml), and anhydrous sodium acetate (300 mg). The mixture was stirred at 20° for 1 hour. Volatile components were evaporated *in vacuo* at 30-40°, saturated aqueous sodium bicarbonate (5 ml) was added to the residue, and the product was extracted with chloroform (20 ml). Organic phase was dried over anhydrous magnesium sulphate, filtered, and the filtrate evaporated *in vacuo*. The residue was triturated with diisopropyl ether (5 ml) and the precipitate collected by filtration to give **24a,b**. Experimental and analytical data for compounds **24a,b** are given in Tables 1 and 2.

2:3,4:5-Bis-*O*-(1-methylethylidene-1)-1-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D-gluco*-pentitol (**25**) and 1:2,4:5-Bis-*O*-(1-methylethylidene-1)-1-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D-gluco*-pentitol (**26**).

A mixture of anhydrous acetone (40 ml), sulphuric acid (98%, 1.6 ml), and 1-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D-gluco*-pentitol (**17a**, 3.045 g, 0.01 mole) was stirred at 20° for 2 hours. Saturated aqueous sodium bicarbonate (50 ml) was added to the reaction mixture and one half of the solvent was evaporated *in vacuo* at 35-40°. The precipitate was collected by filtration, washed with water, and dried *in vacuo* over sodium hydroxide pellets to give a 2:3 mixture of **25** and **26** in 79% yield, mp 170-171° (from ethyl acetate).

Anal. Calcd. for $C_{16}H_{21}ClN_4O_5$: C, 49.98; H, 5.51; N, 14.58. Found: C, 49.64; H, 5.31; N, 14.58.

A mixture of **25** and **26** was dissolved in boiling anhydrous ethanol. Upon cooling to 20° two different types of crystals precipitated, large compact crystals of 2:3,4:5-bis-*O*-(1-methylethylidene-1)-1-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D-gluco*-pentitol (**25**) and cotton-like crystals of 1:2,4:5-bis-*O*-(1-methylethylidene-1)-1-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D-gluco*-pentitol (**26**). In order to separate compounds **25** and **26** efficiently, this mixture was, with occasional stirring, carefully warmed up to 40° [18]. Compact crystals of **25**, which remained undissolved, were collected by filtration to give 2:3,4:5-bis-*O*-(1-methylethylidene-1)-1-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D-gluco*-pentitol (**25**). The filtrate was cooled to 0° and the precipitate collected by filtration to give 1:2,4:5-bis-*O*-(1-methylethylidene-1)-1-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D-gluco*-pentitol (**26**). Experimental and analytical data for compounds **25** and **26** are given in Tables 1 and 2.

2:3,4:5-Bis-*O*-(1-methylethylidene-1)-1-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D-manno*-pentitol (**27**).

A mixture of anhydrous acetone (40 ml), sulphuric acid (98%, 1.6 ml), and 1-(6-chloro-*s*-triazolo[4,3-*b*]pyridazinyl-3)-*D-manno*-pentitol (**18a**, 3.045 g, 0.01 mole) was stirred at 20° for 2 hours. Saturated aqueous sodium bicarbonate (50 ml) was added to the reaction mixture, one half of the solvent evaporated *in vacuo* at 35-40°, and the product extracted with dichloromethane (3 x 30 ml). Organic phases were combined, dried over anhydrous sodium sulphate, filtered and the filtrate evaporated *in vacuo*. The residue was triturated with petroleum ether (10 ml), and the precipitate collected by filtration to give **27**. Experimental and analytical data for compound **27** are given in Tables 1 and 2.

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[17] The structures of compounds **16a**, **25**, and **28** were also confirmed by X-ray structural analyses.

[18] Crystals of **25** and **26**, which precipitate from ethanol, can also be separated manually.

[19] For hydrazone **9a** could not be obtained better analysis for C, H, and N. It was cyclised into *s*-triazolo[4,3-*b*]pyridazine derivative **15a** and characterised as triphenylmethyl derivative **19**.