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Synthesis and conformational analysis of *seco* C-nucleosides and their *diseco* double-headed analogues of the 1,2,4-triazole, 1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazole[1]

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Abstract

Reaction of D-glucono- (**1**) or D-galactono- (**2**) 1,5-lactones and D-*glycero*-D-guloheptonic-1,4-lactone (**11**) with thiocarbohydrazide (**3**) afforded the *seco* C-nucleosides 4-amino-3-(D-gluco- (**4**) or D-*galacto*- (**5**) pentitol-1-yl)-5-mercapto-1,2,4-triazoles and 4-amino-3-(D-*glycero*-D-*gulo*-hexitol-1-yl)-5-mercapto-1,2,4-triazole (**12**). Their conversions to the 3-(1,2,3,4,5-penta-*O*-acyl-D-*gluco*- (**7** and **9**) or the D-*galacto* (**8** and **10**) pentitol-1-yl)-6-substituted 1,2,4-triazolo[3,4-b]1,3,4-thiadiazole and 3-(1,2,3,4,5,6-hexa-*O*-acetyl-D-*glycero*-D-*gulo*hexitol-1-yl)-6-methyl-1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazole (**13**) were achieved under acylative conditions. Reaction of diethyl galactrate (**17**) with **3** gave 1,4-bis (4-amino-5-mercapto-1,2,4-triazol-3-yl)-*galacto*-tetritol (**18**), which upon reaction with acetic anhydride gave 1,4-bis(6-methyl-1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazol-3-yl)-1,2,3,4-tetra-*O*-acetyl-*galacto*-tetritol (**19**). When the tetra-*O*-acetylgalactaric acid (**15**) was used instead of **17**, the attack of **3** had taken place on the ester group rather than the carboxylic group, whereby **16** was obtained rather than the tetra-*O*-acetyl derivative of **18**. The structures were confirmed by using ^{1}H,^{13}C and 2D NMR spectra (DQFCOSY and HMQC) experiments. The vicinal coupling constants were used to deduce the favored conformations.

Keywords: *seco* C-nucleoside; *diseco* C-nucleoside; 1,2,4-Triazole; 1,2,4-Triazolo[3,4-*b*]1,3,4-thiadiazole; Conformation

1. Introduction

Many important advances have occurred in the field of acyclonucleosides [1–3] and C-nucleosides [4–11]. The discovery of new C-nucleoside antibiotics has led to the development of new synthetic strategies and the preparation of synthetic C-nucleosides, some of which possess important anticancer and antiviral activities. Some acyclo C-nucleosides have been found to be naturally occurring with various biological activities [12–14]. A number of acyclo C-nucleosides can be readily transformed to the C-nucleoside analogues by the anhydro ring formation of the suitable acyclic polyol residue.

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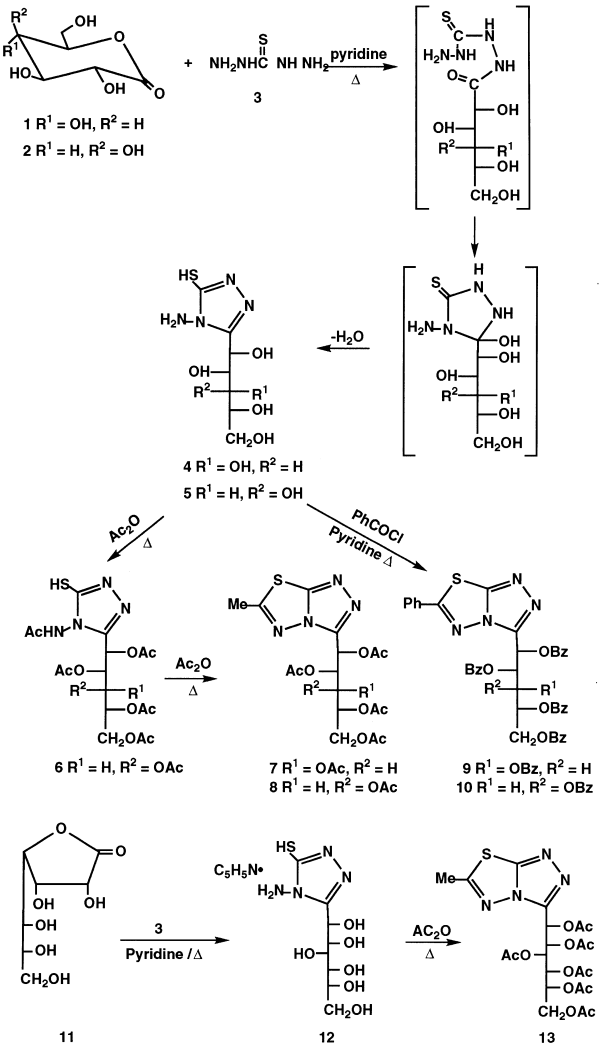
The antifungal, antiinflammatory and antitubercular properties exhibited by 4-amino-5-mercapto-3-substituted-1,2,4-triazoles [15–18] have made them important chemotherapeutic agents. The incorporation of various substituents into the 1,2,4-triazole ring and its fusion with various heterocyclic systems yield compounds with enhanced biological activities [19–23]. Some 3,6-disubstituted 1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazole derivatives showed anti-HIV-1 activity at concentrations slightly below cytotoxic levels [24]. Others possess significant to mild antiinflammatory activity [25,26], antibacterial and antifungal properties [15,27,28]. Substitution at the 3- and 6- positions seemed to be important in lowering the cytotoxicity of the compounds. Consequently, the attachment of an alditolyl moiety at position-3 and an alkyl or aromatic substituent at position-6 of the 1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazole may lead to an improvement in their biological activity as a consequence of the hydrophilic nature of the alditolyl residue that may increase their transportation into biological systems. Therefore, the goal in the present work is to develop a novel synthetic approach to the acyclo C-nucleosides of the 4-amino-5-mercapto-1,2,4-triazoles and then construct the 1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazole via inserting the carbon-3 with the required substituent. Their double-headed analogues were also prepared. The prepared acyclo C-nucleosides are termed as *seco* and *diseco* C-nucleosides according to our recently developed method for classification of acyclonucleosides.

2. Results and discussion

The synthesis of 4-amino-5-mercapto-1,2,4-triazoles can be achieved by the cyclization of an acylthiocarbazinic acid or a thiocarbohydrazide (**3**) [29–39]. In order to approach the synthesis of the target compounds, the C-3 in the skeleton of 4-amino-3-(D-*gluco*- (**4**) or D-*galacto*- (**5**) pentitol-1-yl)-5-mercapto-1,2,4-triazole can be generated from the C-1 of an aldonolactone or the respective acid. Thus, the dehydrative cyclization of equimolar amounts of D-glucono- (**1**) and D-galactono- (**2**) 1,5-lactone with thiocarbohydrazide (**3**) in pyridine gave **4** and **5**, respectively . The reaction proceeds through a nucleophilic attack of N-1 of the thiocarbohydrazide (**3**) on the lactone carbonyl carbon, which led to a lactone ring opening that followed by further nucleophilic attack of the N-3 to the carbonyl carbon and subsequent dehydration of the cyclized intermediate to give **4** and **5**, respectively (Scheme 1). The combustion analysis and the FAB mass spectrum of **4** (which showed a peak at *m*/*z* 267 (12%) that is characteristic for the protonated molecular ion) are in agreement with the molecular formula $C_7H_{14}N_4O_5S$. The low relative intensity of MH^+ is mainly attributed to the instability [40] of **4** caused by the presence of the sugar part in its structure. The fragment at *m*/*z* 232 (7%) can be attributed to the loss of hydrogen sulfide from the molecular ion. Loss of the sugar moiety was also observed to give ion at *m*/*z* 107 (30%). The ^{1}H NMR spectra of **4** and **5** showed eight exchangable protons. The five hydroxyl protons of the sugar residue resonated at higher field than that of the NH_2 and SH protons, which were



Scheme 1.

assigned to the singlets at δ 5.51–5.53 and 13.62 [34], respectively. The 2D NMR spectra of **4** confirmed the assigned structure. The ^1H–^1H DQFCOSY technique facilitated the correlation of protons with each other (Table 1). At the highest frequency, H-1 was assigned, and it was shown to be coupled with H-2, which was the starting point of the vertical dashed line meeting the diagonal at the signal of the proton coupled to H-1 (Fig. 1). At a lower frequency H-3 resonates and is coupled with both of H-2 and H-4 that was found to resonate between both of H-5 and H-5′. The ^{13}C NMR spectrum of **4** (Table 2) showed two types of signals. In the downfield region only two signals at δ_c 153.66 and 167.25 were assigned for the heterocyclic ring carbon atoms, C-3 and C-5, respectively. In the upfield region five signals of the sugar carbon atoms resonated. The ^1H and ^{13}C signals are correlated in the ^1H–^{13}C HMQC experiment of **4**, which helped in identifying the carbon atoms of the sugar moiety. Similarly, the spectra of the D-galacto analogue was assigned.

The various methods that have been applied for the synthesis of 1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazole involve mainly the construction of the fused ring from functionalized derivatives of either 1,3,4-thiadiazole [31,41,42] or 1,2,4-triazole [31,32,42–44]. Thus, treatment of **4** and **5** with boiling acetic anhydride caused a ring closure to form the thiadiazole ring, as well as acetylation of the sugar moiety to give 3-(1,2,3,4,5-penta-*O*-acetyl-D-*gluco*-(**7**) and D-*galacto*-(**8**)-pentitol-1-yl)-6-methyl-1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazoles. The reaction involves an amino group acetylation as the first step that has been indicated from the successful isolation of the 4-acetylamino-3-(1,2,3,4,5-penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-5-mercapto-1,2,4-triazole (**6**) as a byproduct in the case of the D-galacto analogue. Moreover, the later can be converted to **8** in a quantitative yield under dehydrative cyclization conditions. The structures were deduced from the respective spectral data. The IR spectra of **6** showed characteristic absorption bands due to the NH (3174 cm^{-1}), OAc (1755 cm^{-1}) and NAc (1688 cm^{-1}), whereas those of **7** and **8** showed the disappearance of the NAc and HN absorptions and retained only the acetoxy carbonyl absorption. The elemental analysis and

Table 1
^1H NMR spectra[a] of compounds **4** and **5** in DMSO-d_6 and **6–10** and **13** in $CDCl_3$

Compd no.	Chemical shifts in δ values (multiplicity, integration)							
Assignment	**4**	**5**	**6**	**7**	**8**	**9**[b]	**10**[b]	**13**
H-1	4.88(d,1 H)	4.99(d,1 H)	5.90(d,1 H)	6.26(d,1 H)	6.33(d,1 H)	6.90(d,1 H)	7.02(d,1 H)	6.28(d,1 H)
H-2	4.16(d,1 H)	3.86(m,1 H)	5.69(d,1 H)	6.03(dd,1 H)	↑ 5.57 (q,2 H)	6.83 (dd,1 H)	6.55 (dd, 1 H)	5.83 (dd, 1 H)
H-3	3.20 (d, 1H)	3.74 (dd, 1H)	5.37 (d,1 H)	5.18(dd,1 H)	↓	6.00(dd,1 H)	6.29(dd,1 H)	5.64(dd,1 H)
H-4	3.56(m,1 H)	3.57(t,1 H)	5.29(t,1 H)	5.08(m,1 H)	5.35(t,1 H)	5.84(m,1 H)	5.95(m,1 H)	5.53(t,1 H)
H-5	3.58(dd,1 H)	↑ 3.42(t,2 H)	4.26(dd,1 H)	4.12(dd,1 H)	4.28(dd,1 H)	4.68(dd,1 H)	4.66(dd,1 H)	4.98(q,1 H)
H-5′	3.39(dd,1 H)	↓	3.87(dd,1 H)	3.96(dd,1 H)	3.90(dd,1 H)	4.39(dd,1 H)	4.57(dd,1 H)	—
H-6								4.18(dd,1 H)
H-6′								4.30(dd,1 H)
Me				2.70(s,3 H)	2.71(s,3 H)			2.73(s,3 H)
OAc & NAc			2.22(s,3 H)	1.94(s,3 H)	1.96(s,3 H)			1.99(s,3 H)
			2.02(s,3 H)	2.04(s,6 H)	2.01(s,6 H)			2.08(s,3 H)
			2.09(s,6 H)	2.05(s,3 H)	2.14(s,3 H)			2.10(s,3 H)
			2.10(s,6 H)	2.06(s,3 H)	2.17(s,3 H)			2.13(s,3 H)
								2.16(s,3 H)
								2.18(s,3 H)
NH_2	5.53(s, 2 H)	5.51(s,2 H)	—					
NH			8.84(s,1 H)					
OH	4.34(m,3 H)	4.18(m,2 H)						
	4.64(d,1 H)	4.38(dd,1 H)						
	5.53(s,1 H)	4.7(d,1 H)						
		5.24(d,1 H)						
SH	13.62(s,1 H)	13.6(s,1 H)	11.45(s,1 H)					
H_2O			3.47(s,2 H)					

[a] Compounds **5** and **13** were measured at 200 MHz. Compounds **4** and **6–10** were measured on 600 MHz.
[b] The Ar–H were assigned as multiplets at δ: 7.23–7.35, 7.46–7.48, 7.87–7.88 and 7.97–8.01.

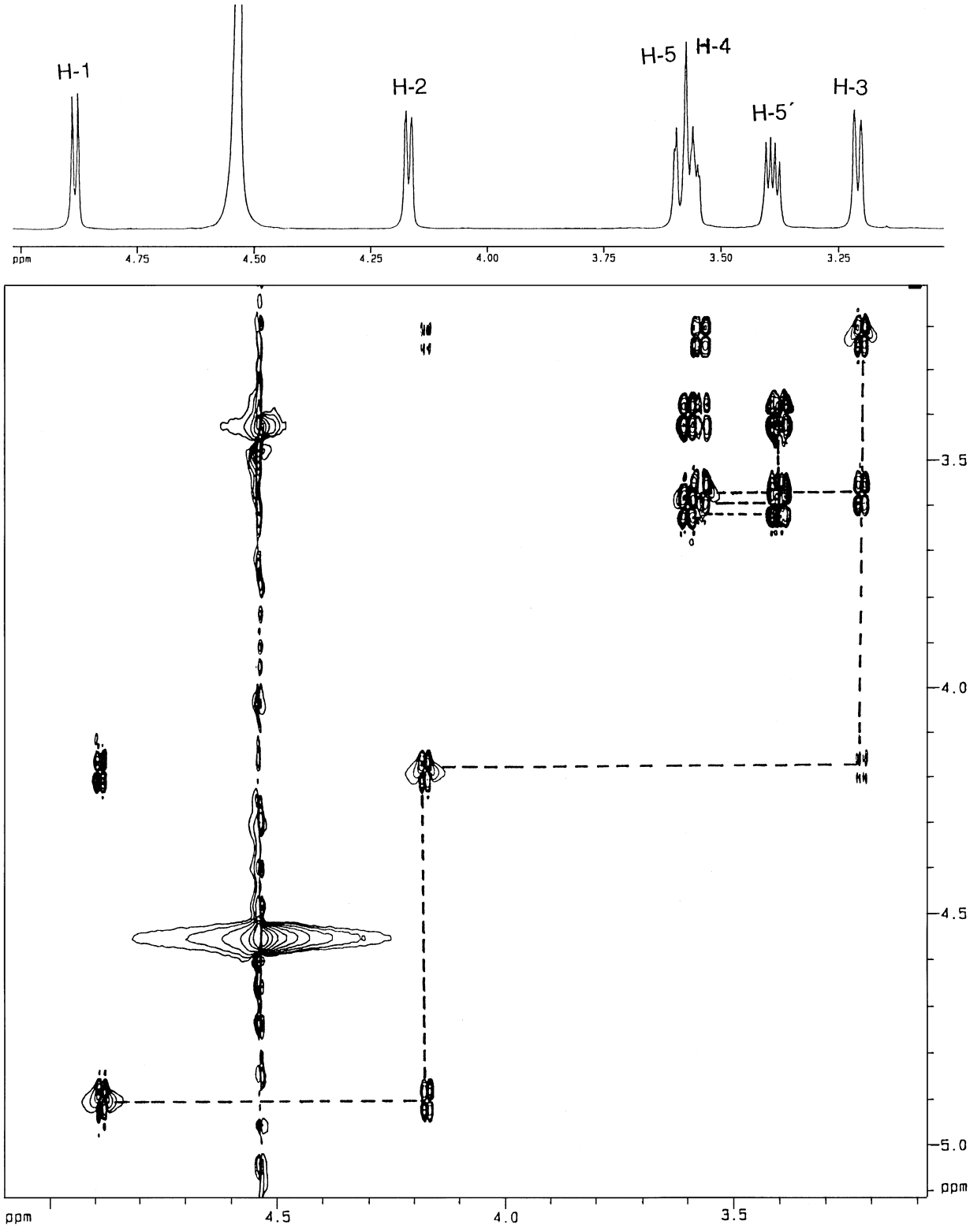


Fig. 1. DQFCOSY spectrum of **4**.

the mass spectral data of **6**, which showed a molecular ion peak at *m*/*z* 518 as the base peak, led to the assignment of the molecular formula $C_{19}H_{26}N_4O_{11}S$, whereas the spectra of **7** and **8** showed molecular ion peaks at *m*/*z* 500 agreeing with the molecular formula $C_{19}H_{24}N_4O_{10}S$. Moreover, they showed a typical acetoxyalkyl chain fission [45] (Scheme 2), whereby the loss of AcOH,

Table 2
^{13}C NMR spectra of compounds **4** in DMSO-d_6 and **6–10** in $CDCl_3$

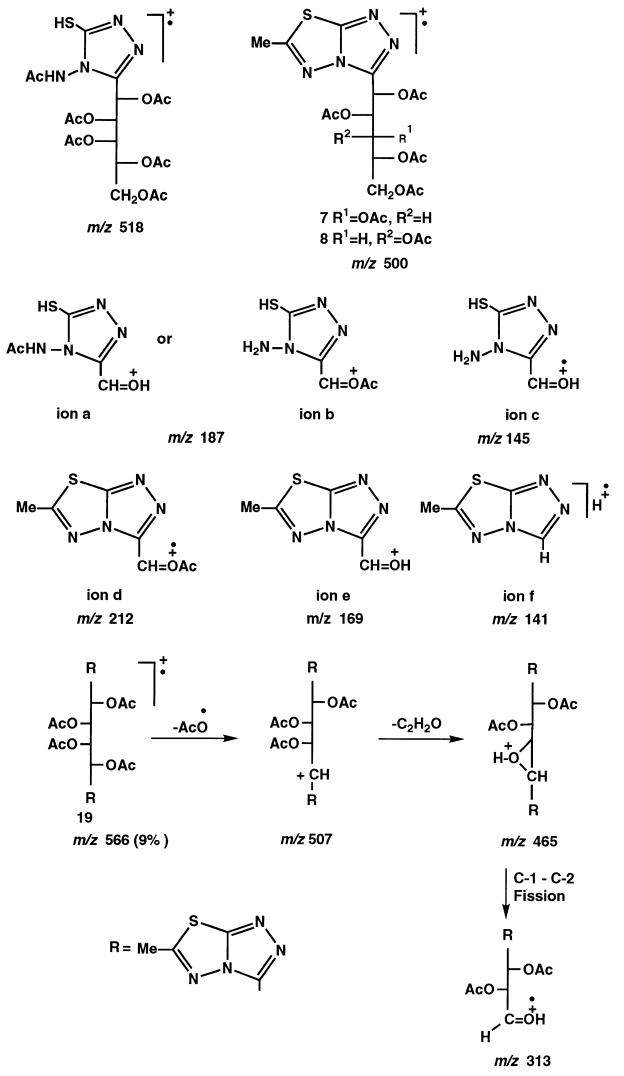
Compd no.	Chemical shifts (δ_c)					
Assignment	**4**	**6**	**7**	**8**	**9**[a]	**10**[b]
Sugar carbons						
C-1	67.60	61.82	64.67	65.64	65.85	66.00
C-2	71.88	68.08	69.18	69.07	70.51	70.26
C-3	71.62	67.74	67.96	69.44	69.28	69.77
C-4	72.29	67.58	67.91	69.11	69.03	69.18
C-5	64.25	62.06	61.49	63.26	62.66	62.88
Heterocyclic carbons						
C-3	153.66	154.94	154.83	154.70	154.18	154.19
C-5	167.25	165.88	—			
C-6			142.43	142.94	143.08	143.45
C-7a			165.9	166.97	167.49	167.25
Others						
Me			18.24	19.66		
Ac		20.28	20.41	21.66		
		20.56	20.47	21.87		
		20.63	20.59	21.91		
		20.77	20.61	21.96		
			20.78			

[a] The aromatic carbon signals were assigned at δ_c: 127.16, 128.29, 128.32, 128.38, 128.55, 129.14, 129.27, 129.34, 129.72, 129.88, 129.93, 129.98, 132.61, 133.00, 133.27, 133.33, 133.48 and 133.56.
[b] The aromatic carbon signals were assigned at δ_c: 127.07, 128.19, 128.25, 128.31, 128.35, 128.50, 129.20, 129.64, 129.73, 129.82,

$CH_2=C=O$ and Ac, as well as the fission of the chain is a general feature in their spectra. The stability of the triazole as well as the 1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazole rings towards electron bombardment has been reflected from the presence of the corresponding ions at *m*/*z* 187 (ion a or b) and 212 (ion d) resulting from the fission of C-1–C-2 bond of the alditolyl part of **6, 7** and **8**, respectively, which subsequently loses an acetyl radical to give ions at *m*/*z* 145 (ion c) and 169 (ion e) for **6** and **7** and **8**, respectively, which in the later case was the base peak.

The ^1H NMR spectrum of **6** showed only two exchangable protons; an NH resonance appeared in a downfield region (δ 8.84) compared with that of **5**, indicating its attachment to the acetyl group. The singlet of the SH proton was shifted to the upfield region at δ 11.45. The singlet of the N-acetyl group was assigned to the signal at δ 2.22. The presence of the five acetyl group protons, and the downfield shift of the sugar protons as well as the study of their 2D NMR (H, H DQFCOSY and ^1H–^{13}C HMQC) spectra confirmed the assignment of the structure of **6**. The absorption at the lower frequency is due to H-5′ which is coupled with both of the H-5 and H-4, while the signal at the highest field was assigned to H-1 that coupled with H-2 which in turn coupled with H-3 and the later coupled with H-4. The ^{13}C NMR spectrum of **6** showed only two signals at the downfield region at δ_c 154.94 and 165.88 corresponding to the C-3 and C-5 of the triazole ring, respectively, which confirmed the uncyclized nature of **6**. The resonance of the alditolyl carbons were assigned by using the cross peaks with those of the protons, which led to the assignment shown in Table 1. The ^1H NMR spectra of compounds **7** and **8** showed characteristic singlets at δ 2.70–2.71 corresponding to the 6-methyl group and the disappearance of the signals of the NH_2, NH, N-acetyl and SH protons of their precursors which confirmed the cyclization process. Their 2D NMR spectra (^1H–^1H DQFCOSY and ^1H–^{13}C HMQC), facilitated the spectral assignment of **7** and **8**. Their ^{13}C NMR spectra showed new signals compared with those of **4—6**. The signals at δ_c 142.43–142.94 and 165.90–166.97 were assigned for the respective C-6 and C-7a of the thiadiazole ring, while the signal at δ_c 18.24–19.66 was assigned for the methyl group of the heterocyclic ring.

Treatment of compounds **4** and **5** with benzoyl chloride in pyridine under reflux afforded the cyclized products 3-(1,2,3,4,5-penta-*O*-benzoyl)-6-phenyl-1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazoles **9** and **10**, respectively. The FAB mass spectra of **9** and **10** showed the protonated molecular ion peak at *m*/*z*



Scheme 2.

873 (24%). A cleavage of a benzoic acid molecule led to a peak of low intensity at *m*/*z* 751, whereas the rupture of the C-1–C-2 bond as well as the loss of the benzoyloxy alkyl chain gave a fragment of low relative intensity at *m*/*z* 231. No peak for the phenyl group was found, but a peak at *m*/*z* 105 corresponding to the benzoyl group was observed as the base peak. Their ^{1}H NMR spectra showed a downfield shift of the sugar protons compared with the acetyl derivatives **7** and **8**, which was due to the deshielding effect of the benzoyloxy group (Table 1).

The ^{1}H–^{13}C HMQC experiment of **9** and **10** showed a similar correlation of the sugar protons with their carbon atoms as for **7** and **8** (Tables 1 and 2). The three signals of the heterocyclic ring carbons were assigned [δ_c 154.18–154.19 (C–3), 143.08–143.45 (C-6) and 167.49–167.25 (C-7a)].

In order to prepare analogues with a longer alditolyl residue, the reactions have been extended to the D-*glycero*-D-*gulo*-heptonic-1,4-lactone (**11**), which upon reaction with thiocarbohydrazide (**3**) afforded 4-amino-3-(D-*glycero*-D-*gulo*-hexitol-1-yl)-5-mercapto-1,2,4-triazole (**12**). Its ^{1}H NMR spectrum showed exchangable protons agreeing with the assigned structure, particularly the singlets at δ 5.48 (NH_2) and 13.56 (SH). The spectrum showed signals at a lower field (δ 7.39, 7.8, and 8.5) that are characteristic of the pyridine nucleus, indicating that the product was cocrystallized with pyridine. Trials to get rid of the pyridine from the product by coevaporation with toluene and extended drying of the solid sample did not improve the situation. However, the pyridine was not a part of the molecule as it was readily realized from its disappearance in the spectrum of the corresponding acetyl derivative 3-(1,2,3,4,5,6-hexa-*O*-acetyl-D-*glycero*-D-*gulo*-hexitol-1-yl)-6-methyl-1,2,4-triazolo-[3,4-*b*]1,3,4-thiadiazole (**13**) that was readily formed from **12** by boiling with acetic anhydride. The spectra of **13** confirmed the assigned structure (Table 1).

Furthermore, this investigation has been extended to the synthesis of a double headed *diseco* C-nucleoside analogue. The thiocarbohydrazide (**3**) can be successfully reacted with aliphatic acids or their substituted derivatives in one step either under reflux or by fusion at 165–168 °C [37,39] to give the triazole ring. However, fusion of galactaric acid (**14**) or 2,3,4,5-tetra-*O*-acetyl galactaric acid (**15**) [46] with **3** under the later reaction conditions, did not go to completion, and a mixture of products was obtained that could not be separated in the former case because of the insolubility in most of the solvents, whereas the mixture from **15** could be separated by fractional crystallization to give, in addition to the starting material **15**, galactaric acid **14** and a product that can be identified as **16**. The IR spectrum of **16** showed absorption bands characteristic for the NH_2 (3272–3115 cm^{-1}) and C = N (1629 cm^{-1}) and the absence of a carbonyl absorption that can be argued to the presence of *O*-acetyl groups. The ^{1}H NMR spectrum of **16** did not show any characteristic signals for the sugar moiety, but shows only three singlets at δ 2.25, 5.54, and 13.43 attributed to a methyl, NH_2, and SH groups, respectively. Moreover, the elemental analysis, as well as the mass spectrum of **16**, which showed a molecular ion peak at *m*/*z* 130 (100%), agreed with the

molecular formula $C_3H_6N_4S$. These data led to the conclusion that the structure is 4-amino-5-mercapto-3-methyl-1,2,4-triazole (**16**), which can be directly prepared by the reaction of acetic acid with **3** [29,37]. The formation of **16** from **15** may be attributed to the greater electrophilicity of the carbonyl ester group of **15**, which can be readily attacked by the thiocarbohydrazide rather than its attacking the carboxylic group. Thus the *N*-acetylthiocarbohydrazide intermediate is formed, which then undergoes cyclization to the triazole **16** under the dehydrative conditions of the reaction. Meantime, the attack on the ester group, rather than on the carboxylic acid group, resulted in the deacetylation of **15** to **14**. Consequently, the diethyl galactarate (**17**) [46] was selected to react with **3** in pyridine to afford the target double headed *diseco* C-nucleoside 1,4-bis-(4-amino-5-mercapto-1,2,4-triazol-3-yl)-*galacto*-tetritol (**18**), but in low yield. However, the yield was improved by carrying out the reaction by fusion at 165–168 °C for 1 h to give **18** in a better yield, without the formation of any undesired products. The success of the later procedure may be attributed to the lower melting point of **17** compared to that of **14**, accompanied with the higher electrophilicity of the carbonyl group in **17**. The ^{1}H NMR spectrum of **18** showed a singlet with an intensity of two protons assigned for the two SH protons, whereas the two NH_2 protons were resonated at higher field as a singlet at δ 5.52.

Treatment of **18** with acetic anhydride afforded the 1,2,3,4-tetra-*O*-acetyl-1,4-bis(6-methyl-1,2,4-triazol-3-yl[3,4-*b*]1,3,4-thiadiazole)-*galacto*-tetritol (**19**), whose IR spectrum showed a characteristic band at 1750 cm^{-1} for the OAc groups. Its ^{1}H NMR spectrum showed only two singlets at δ 6.47 and 5.87 corresponding to H-1, H-4 and H-2, H-3, respectively. The two singlets that appeared at δ 2.04 and 2.15 were assigned to the four acetyl groups. The two methyl groups on the ring were assigned to the singlet of six protons intensity at δ 2.75. The pattern of the ^{1}H NMR spectra of **18** and **19** indicated the existence of a center of symmetry. The mass spectrum of **19** showed a molecular ion peak at *m*/*z* 566 (9%). The spectrum also showed similar ions to that resulting from **7** and **8** at *m*/*z* 212 (63%, ion d) and *m*/*z* 169 (100%, ion e). Loss of a carbon monoxide molecule led to the formation of a protonated 6-methyl-1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazole ion fragment at *m*/*z* 141 (24%, ion f) (Scheme 2).

3. Conformational analysis of the *seco* C-nucleosides analogues

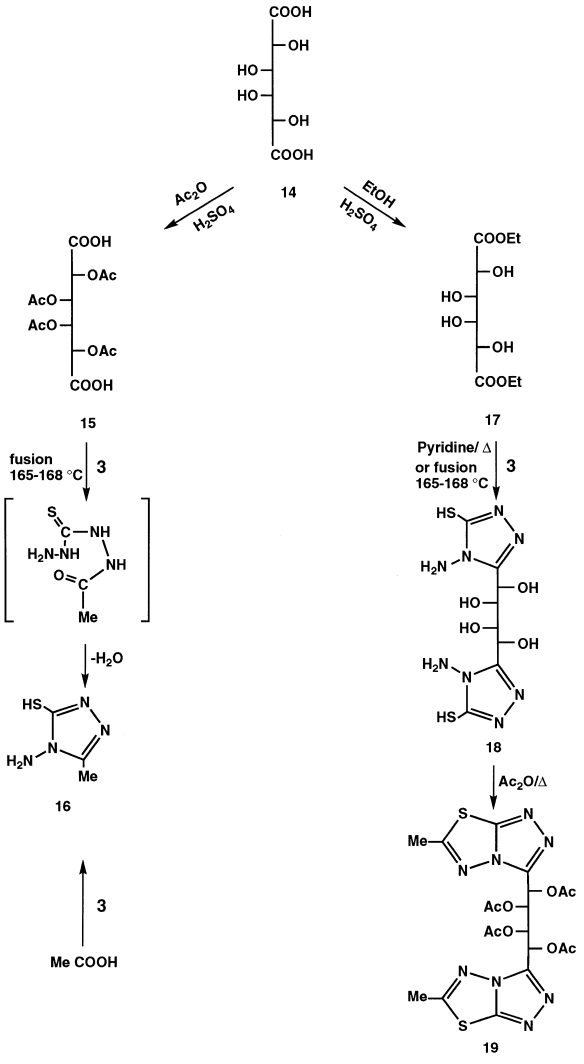
The studies on the conformation of acylated and nonacylated carbohydrate derivatives [47–52] have contributed to the conclusion that the favored conformation is that having an extended, planar, zig-zag arrangement of carbon atoms, corresponding to the maximum staggering of small–medium–large sets of groups along each carbon–carbon bond. This could be deduced from the vicinal proton–proton coupling constants [48,49,52–54]. If such an arrangement generates a parallel 1,3-interaction of a pair of substituents along the chain, the molecule would prefer an alternative conformation having the carbon chain in a bent or "sickle" conformation formed by rotation about one carbon–carbon bond to alleviate the interaction. Using the above considerations, the conformation of the acylated *seco* C–nucleoside analogues **6–10**, **13** and *diseco* analogue **19** were deduced from the vicinal proton–proton coupling constants (Table 3) from their ^{1}H NMR analyses.

The coupling constants of the vicinal protons of the acetyl and benzoyl derivatives of the D-gluco isomers **7** and **9** were found to be almost identical (Table 3), which indicated that they adopt a similar conformation in their solutions in the deuterated chloroform. It would be anticipated that the extended planar zig-zag conformation **20** represents an unfavorable situation because of the 1,3-interaction of the acyloxy groups on positions 1 and 3 (Fig. 2). This expectation is verified by the high values of $J_{1,2}$ (8.34–8.49 Hz) which requires that H-1 and H-2 be in antiparallel dispositions; otherwise $J_{1,2}$ should be <4 Hz in order to verify the gauche arrangement of H–1 and H-2 in the conformer **20**. Rotation of the C-1–C-2 bond will lead to the required orientation of H-1 and H-2, with the result of the sickle conformation **21**. The H-2–H-3 and H-4–H-5 are in a gauche arrangement as confirmed by the observed values of $J_{2,3}$ 2.35–2.21 and $J_{4,5}$ 2.83–3.47 Hz. The high values of $J_{3,4}$ (8.62–8.12 Hz) are in agreement with the antiparallel dispositions of H-3 and H-4. The value of $J_{4,5'}$ (5.06 Hz) is rather small in order to agree with an antiparallel arrangement of H-4 and H-5′ as in the conformer **21** and indicated that a contribution in the population state from a rotamer other than that of **21**, which has H-5′ disposed with H-4 in a gauche manner, must exist. A rotation about the

C-4–C-5 bond generates such a conformer **22** which has H-4 and H-5′ in a gauche relation.

The small values of $J_{1,2}$ (2.2–1.25) and $J_{3,4}$ (1.36–1.19) of the D-galacto derivatives **6** and **8** indicate a gauche arrangement of H-1 and H-2 as well as H-3 and H-4 (Fig. 3). The high value of $J_{2,3}$ (8.62–8.88 Hz) is due to the antiparallel relation of H-2 and H-3 as in **23**. The $J_{4,5'}$ values (7.34–7.44) of both **6** and **8** indicate an anti relation between H-4 and H-5′, whereas that of H-4 and H-5 is of intermediate magnitude (5.02–5.16). This can be readily achieved by the existence of a population of the rotamer **24** which can result by rotation about the C-4–C-5 bond so that H-4 and H-5′ assume an antiparallel relationship. Therefore these compounds exist practically entirely in the favored extended planar zig-zag conformation **23** and **24** and these results are compatible with other acyclic chains having the D-galacto configuration [45,51].

A deviation from the expected gauche relation of H-1 and H-2 in the conformer **25** of the benzoyl derivative of the D-galacto analogue **10** has been deduced from the intermediate value of the observed $J_{1,2}$ (5.15 Hz), which is inconsistent with planar zig-zag conformation **25** (Fig. 4) that would require the $J_{1,2}$ value to be less than 4.0 Hz.



Scheme 3.

Table 3
Coupling constants of **4, 6–10** and **13**

Compd no.	Coupling constants (Hz)						
Assignment	**4**	**6**	**7**	**8**	**9**	**10**	**13**
$J_{1,2}$	7.42	2.20	8.34	1.25	8.49	5.15	7.40
$J_{2,3}$	0.00	8.62	2.35	8.88	2.21	7.70	3.50
$J_{3,4}$	8.28	1.36	8.62	1.19	8.12	2.69	6.70
$J_{4,5}$	2.52	5.02	2.83	5.16	3.47	4.62	4.60
$J_{4,5'}$	5.78	7.34	5.06	7.44	5.59	6.99	
$J_{5,5'}$	11.36	11.66	12.50	11.61	12.35	11.85	
$J_{5,6}$							5.60
$J_{5,6'}$							5.60
$J_{6,6'}$							11.80

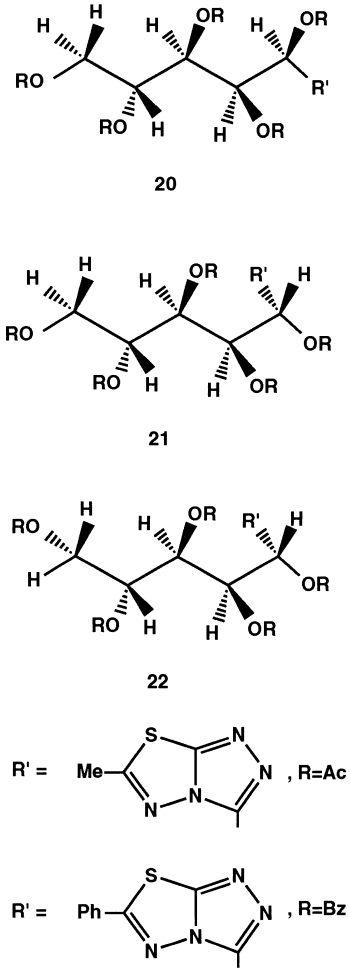


Fig. 2. Conformers of D-gluco compounds **7** and **9**.

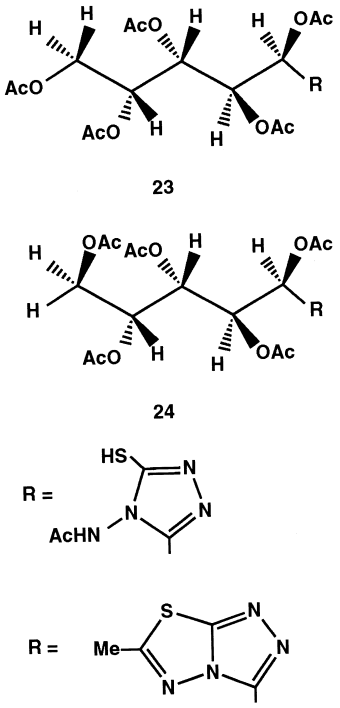


Fig. 3. Conformations of the acetyl derivatives of the D-galacto compounds **6** and **8**.

Rotation around the C-1–C-2 bond would generate either the conformer **26**, which has H-1 and H-2 in an antiparallel disposition and requires a much higher value for $J_{1,2}$ (7–9 Hz) than the observed value, or the conformer **27**, which is suffering from a 1,3-interaction of the benzoyloxy groups at positions 1 and 3. The intermediate value of $J_{1,2}$ suggested a substantial contribution of the conformers **25** and **26**. The conformer **25** has the four bulky groups in gauche relationships with each other, whereas in the conformer **26**, they are separated into two sets as represented by the Newman projections in Fig. 4. However, **26** has a 1,3-interaction between the heterocyclic ring on C-1 and the benzoyloxy group on C-3. But it seems that this situation is a comparable one to that of the presence of the four bulky substituents in a gauche arrangement. This creates a somewhat unfavorable situation that leads to a population of conformer **25** and **26** and explains the intermediate value observed for $J_{1,2}$. On the other hand, the two above unfavorable factors are existing in the energetically unfavorable conformer **27** because of the 1,3-interaction of the two benzoyloxy groups as well as the presence of the four bulky groups in a gauche arrangement. On the other hand, when the rotation of C-2–C-3 was considered, in order to have an arrangement of H-1–H-2 which agreed

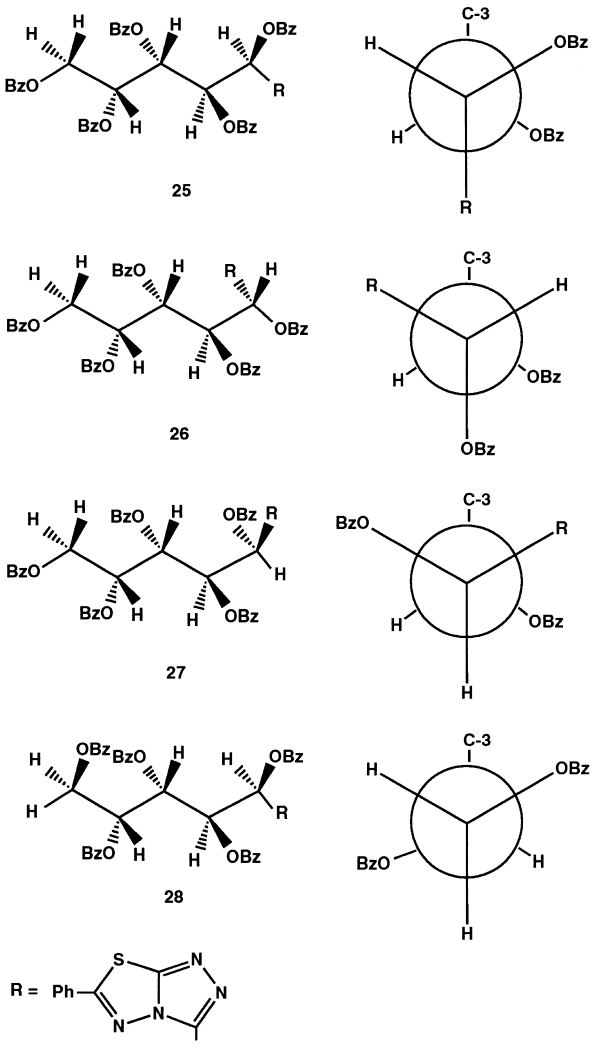


Fig. 4. Conformations of the benzoyl derivative of the D-galacto compound **10**.

with $J_{1,2}$ value, the situation did not improve as it would result in a 2,4-interaction of two benzoyloxy groups. This deviation compared to the respective acetyl derivative can be attributed to the bulkiness of the benzoyloxy groups. The coupling constants $J_{2,3}$ (7.70 Hz) and $J_{3,4}$ (2.69 Hz) are corresponding to an anti relation of H-2 and H-3, and a gauche relation of H-3 and H-4. The intermediate magnitude of both $J_{4,5}$ (4.62 Hz) and $J_{4,5'}$ (6.99 Hz) indicates that rotameric state other than those of **25** and **26** around the C-4–C-5 bond must be significantly populated and can be introduced by rotation of the latter bond. Therefore, the conformer **28** may be contributed to the population as the other possible rotamer would suffer from a 1,3-interaction of the benzoyloxy groups at the 3 and 5 positions.

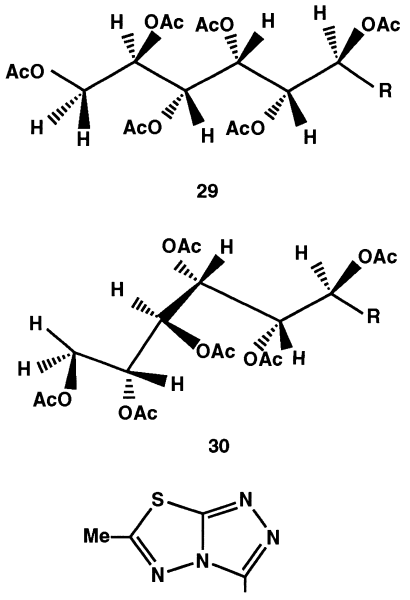


Fig. 5. Conformations of the D-glycero-D-gulo compound **13**.

From these results it is clear that the acetylated and benzoylated derivatives **6, 8** and **10** having the D-galacto configuration do not possess the same conformation. This can be attributed to both electronic and steric factors.

The observed values of $J_{1,2}$ (7.4 Hz) and $J_{2,3}$ (3.5 Hz) of the acetyl derivative **13** having the D-*glycero*-D-*gulo* configuration indicated an anti orientation of H-1 and H-2 and a gauche arrangement of H-2 and H-3, which agreed with the planar zig-zag conformation **29** (Fig. 5). However, this conformation has a 2,4-interaction of the two acetoxy groups, and this has been readily realized from the values of $J_{3,4}$ (6.7 Hz) and $J_{4,5}$ (4.6 Hz) that are inconsistent with it, as it requires both values to be in agreement with the gauche and anti arrangement of H-3–H-4 and H-4–H-5, respectively. This unfavorable interaction can be relieved by rotation of the C-3–C-4 bond to afford **30** in which the arrangement of H-3–H-4 and H-4–H-5 can agree with the observed coupling constants.

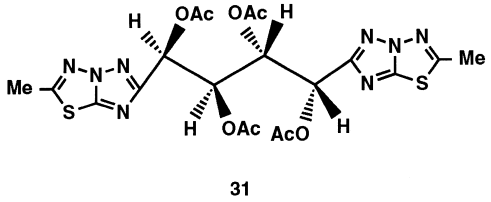


Fig. 6. Conformation of the symmetrical galacto-tetritol derivative **19**.

The value of $J_{5,6}$ (5.6 Hz) and $J_{5,6'}$ (5.6 Hz) are of intermediate magnitude, indicating that other rotameric states about C-5–C-6 bond must be significantly populated.

The ^{1}H NMR spectrum of **19** showed the sugar protons as two singlets with zero coupling constants, indicating that the molecule exhibits a conformation **31** having a center of symmetry (Fig. 6).

4. Experimental

Melting points were determined on a Mel-Temp apparatus and are uncorrected. IR spectra were recorded with a Unicam SP1025 spectrometer. Mass spectra were recorded using electron ionization (EI) on a Finnigan MAT 312 Spectrometer and fast-atom-bombardment (FAB) on a Kratos MS 50 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AC 250 MHz or a Bruker Avance DRX 600 MHz spectrometers. The chemical shifts are expressed on the δ scale using Me_4Si as a standard. *J*-values are given in Hz. The assignment of ^{1}H NMR spectra was based on chemical-shift correlation (DQFCOSY) spectra. The assignment of ^{13}C NMR spectra were based on carbon–proton shift-correlation spectra (HMQC). TLC was performed on Merck Silica Gel 60 F254 with detection by charring in sulfuric acid and by UV light. Microanalyses were performed in the unit of Microanalysis at the Faculty of Science, Alexandria University.

*3-(*D*-Alditol-1-yl)-4-amino-5-mercapto-1,2,4-triazole*.—General procedure: A solution of **1**, **2** or **11** (0.028 mol) in dry pyridine (3.0 mL) was treated with thiocarbohydrazide **3** (0.028 mol). The reaction mixture was heated under reflux for 1.5–2.0 h whereby a solid product formed. It was left to cool, filtered, washed with alcohol, and crystallized.

*4-Amino-3-(*D-gluco-*pentitol-1-yl)-5-mercapto-1,2,4-triazole* (**4**).—The compound was crystallized from MeOH–H_2O in white needles (81% yield); mp 201–202 °C; IR ν_{max}^{KBr} 3440 (OH); 3375–3135 (NH_2) and 1613 cm^{-1} (C=N); ^{1}H NMR and ^{13}CNMR (DMSO-d_6, Tables 1 and 2); FABMS (DMSO, NBOH): *m/z* 267 (MH^+, 12%), 232 (7% M^+-H_2S). Anal. Calcd for $C_7H_{14}N_4O_5S$ (266.27): C, 31.57; H, 5.29; N, 21.04. Found: C, 31.58; H, 5.49; N, 21.27.

*4-Amino-3-(*D-galacto-*pentitol-1-yl)-5-mercapto-1,2,4-triazole* (**5**).—The compound was crystallized

from H_2O (68% yield); mp 214–215 °C; IR ν_{max}^{KBr} 3456 (OH); 3347–3260 (NH_2) and 1622 cm^{-1} (C=N); ^1H NMR (DMSO-d_6, Table 1). Anal. Calcd for $C_7H_{14}N_4O_5S$ (266.27): C, 31.57; H, 5.29; N, 21.04. Found: C, 31.50; H, 5.52; N, 20.82.

*4-Amino-3-(*D-glycero-D-gulo-*hexitol-1-yl)-5-mercapto-1,2,4-triazole* (**12**).—The compound was crystallized from EtOH (71% yield); mp 176–178 °C; IR ν_{max}^{KBr}: 3470 (OH); 3300–3180 (NH_2); and 1620 cm^{-1} (C=N); ^1H NMR (DMSO-d_6): δ 4.71–4.82 (m, 2 H, H-1 and H-2), 3.98–4.08 (m, 2 H, H-3 and H-4); 3.5–3.6 (m, 3 H, H-5, 6, 6′) 4.34, 4.55, 5.71 (m, s, d, 6 H, D_2O exchangable 6 OH), 5.48 (s, 2 H, D_2O exchangable NH_2) and 13.56 (s, 1 H, D_2O exchangable SH). Anal. Calcd for $C_8H_{16}N_4O_6S{\cdot}0.75C_5H_5N$ (355.63): C, 39.68; H, 5.59; N, 18.70. Found: C, 39.59; H, 5.81; N, 18.87.

*3-(Penta- and hexa-*O*-acetyl-*D*-alditol-1-yl)-6-methyl-1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazoles.*—General procedure: A suspension of compounds **4, 5** or **12** (0.3 g) in an excess of acetic anhydride (20 mL) was heated under reflux. The solid compounds were dissolved within 30 mins. The reflux was continued for a further 4.0–5.0 h. The reaction mixture was then evaporated under reduced pressure, and the residue thus obtained was then crystallized.

*3-(1,2,3,4-5-Penta-*O*-acetyl-*D*-gluco-pentitol)-6-methyl-1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazole* (**7**).—The compound was crystallized from EtOH as white prisms (63% yield); mp 123–125 °C; IR ν_{max}^{KBr}: 1756 (OCO) and 1642 cm^{-1} (C=N); ^1H NMR, and ^{13}C NMR ($CDCl_3$, Tables 1 and 2); MS: *m/z* 500 (4%, M^+), 457 (14%, $M^+ - Ac$), 440 (15%, $M^+ - AcOH$), 398 (51%, $M^+ - AcOH - CH_2=C=O$), 339 (32%, $M^+ - AcOH - CH_2=C=O - AcO$), 295 (26%, $M^+ - AcOH - CH_2=C=O - AcO - Ac$), 253 (51%, $M^+ - AcOH - 2Ac - CH_2=C=O$), 212 [17%, $M^+ - H(CHOAc)_4$], 169 [35%, $M^+ - H(CHOAc)_4 - Ac$]. Anal. Calcd for $C_{19}H_{24}N_4O_{10}S$ (500.47): C, 45.59; H, 4.83; N, 11.19. Found: C, 45.13; H, 4.38; N, 11.05.

*4-Acetylamino-3-(1,2,3,4,5-penta-*O*-acetyl-*D*-galacto-pentitol-1-yl)-5-mercapto-1,2,4-triazole* (**6**) *and 3-(1,2,3,4,5-penta-*O*-acetyl-*D*-galacto-pentitol-1-yl)-6-methyl-1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazole* (**8**).—The residue obtained from **5** was triturated with MeOH, whereby a crystalline product **6** was obtained immediately. It was filtered and recrystallized from MeOH (25% yield); mp 148–150 °C; IR ν_{max}^{KBr}: 3174 (NH); 1755 (OCO); 1688 (NCO) and 1622 cm^{-1} (C=N); ^1H NMR and ^{13}C NMR ($CDCl_3$, Tables 1 and 2); MS: *m/z* 518 (M^+, 100%), 476 (40%, $M^+ - CH_2=C=O$), 458 (8%, $M^+ - AcOH$), 434 (20%, $M^+ - 2CH_2=C=O$), 416(9%, $M^+ - AcOH - CH_2=C=O$), 356 (20%, $M^+ - 2AcOH - CH_2=C=O$), 271 (21%, 356 − Ac), 230 (30%, 271 − $CH_2=C=O$), 187 [35%, $M^+ - H(C{\cdot}HOAc)_4$], 145 [35%, $M^+ - H$ $(CHOAc)_4 - Ac$]. Anal. Calcd for $C_{19}H_{26}N_4O_{11}S.\ H_2O$ (536.58): C, 42.53; H, 5.25; N, 10.44. Found: C, 42.62; H, 5.06; N, 10.27.

From the mother liquor compound **8** was separated and recrystallized from EtOH as white needles (51% yield); mp 140 °C; IR 1755 (OCO) and 1642 cm^{-1} (C=N); ^1H NMR, and ^{13}C NMR ($CDCl_3$, Tables 1 and 2). MS: *m/z* 500 (14%, M^+), 457 (45%, $M^+ - Ac$), 440 (33%, $M^+ - AcOH$), 398 (35%, $M^+ - AcOH - CH_2=C=O$), 339 (20%, $M^+ - AcOH - CH_2=C=O - AcO$), 295 (16%, $M^+ - AcOH - CH_2=C=O - AcO - Ac$), 253 (38%, $M^+ - AcOH - 2CH_2=C=O - AcO - Ac$), 212 [52%, $M^+ - H(CHOAc)_4$], 169 [100%, $M^+ - H(CHOAc)_4 - Ac$]. Anal. Calcd for $C_{19}H_{24}N_4O_{10}S$. (500.47): C, 45.59; H, 4.83; N, 11.19. Found: C, 44.82; H, 4.56; N, 11.10.

Conversion of **6** *to* **8**. A solution of **6** (0.1 g) in acetic anhydride (10 mL) was heated under reflux for 2 h. The solution was evaporated to dryness under reduced pressure, and the product thus obtained was crystallized from EtOH (0.85 g, 94% yield). It was found to be identical with the product from the previous experiment.

*3-(1,2,3,4,5,6-Hexa-*O*-acetyl-*D*-glycero-D-gulo-hexitol-1-yl)-1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazole* (**13**).—The residue obtained was chromatographed on silica gel. Elution with 2:1 EtOAc–petroleum ether gave a colorless syrup (70% yield); IR ν_{max}^{KBr}: 1756 (OCO) and 1644 cm^{-1} (C=N), ^1H NMR ($CDCl_3$, Table 1). Anal Calcd. for $C_{22}H_{28}N_4O_{12}S$. (572.53): C, 46.14; H, 4.92; N, 9.78. Found: C, 46.36; H, 4.72; N, 9.50.

*3-(1,2,3,4,5-Penta-*O*-benzoyl-*D*-alditol-1-yl)-6-phenyl-1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazoles.*—General procedure. A suspension of compounds **4** or **5** (1.0 mmol) in dry pyridine (10.0 mL) was treated with benzoyl chloride (7.0 mmol). The reaction mixture was heated under reflux for 6 h, then left to cool and poured on ice-cold water with stirring. The solid obtained was filtered, washed well with water, and dried.

*3-(1,2,3,4,5-Penta-*O*-benzoyl-*D*-gluco-pentitol-1-yl)-6-phenyl-1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazole* (**9**).—The compound was crystallized from EtOH

as white needles (63% yield); mp 158–160 °C; IR ν_{max}^{KBr}: 1732 (OCO) and 1629 cm^{-1} (C = N); ^1H NMR and ^{13}C NMR ($CDCl_3$, Tables 1 and 2); FABMS: *m/z* 873 (25%, $M^+ + 1$), 751 (5%, $M^+ - HOCOPh$], 231 [3%, $M^+ - H(CHOCOPh)_4 - COPh$] and 105 [100%, $COPh^+$]. Anal. Calcd for $C_{49}H_{36}N_4O_{10}S$. (872.87): C, 67.42; H, 4.15; N, 6.41. Found: C, 67.00; H, 4.20; N, 7.00.

3-(1,2,3,4,5-Penta-O-*benzoyl*-D-galacto-*alditol-1-yl)-6-phenyl-1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazole* (**10**).—The compound was crystallized from $CHCl_3$–MeOH as pellets (82% yield); mp 215° C; IR ν_{max}^{KBr}: 1725 (OCO) and 1602 cm^{-1} (C = N); ^1H NMR, and ^{13}C NMR ($CDCl_3$, Tables 1 and 2). FABMS: *m/z* 873 (24%, $M^+ + 1$), 751 (5%, $M^+ - HOCOPh$), 231 [3%, $M^+ - H(CHOCOPh)_4 - COPh$] and 105 [100%, COPh]. Anal. Calcd for $C_{49}H_{36}N_4O_{10}S$. (872.87): C, 67.42; H, 4.15; N, 6.41. Found: C, 67.77; H, 3.67; N, 6.34.

4-Amino-5-mercapto-3-methyl-1,2,4-triazole (**16**).—A well-mixed mixture of thiocarbohydrazide (**3**) (1.4 g, 13.2 mmol) and tetra-*O*-acetylgalactaric acid (**15**) (2.5 g, 6.6 mmole) was heated in an oil bath for 1 h at 165–168 °C, whereby it melted and became pale brown and then solidified. The solid obtained was boiled with methanol and filtered. The solid was identical with galactaric acid (**14**). Then, compound **16** was separated from the filtrate as plates (13% yield); mp 208–210 °C; lit. mp 204–205 °C [29]. The starting material was recovered from the mother liquor.

1,4-Bis-(4-amino-5-mercapto-1,2,4-triazol-3-yl)-galacto-*tetritol* (**18**).—Method (a). A solution of diethyl galactrate (**17**) (0.6 g, 2.25 mol) in pyridine (7.0 mL) was treated with **3** (0.47 g, 4.43 mmol). The reaction mixture was heated under reflux for 4 h, whereby a solid material precipitated. The mixture was left to cool, and a solid was filtered, washed with EtOH and recrystallized from H_2O to give **18** (0.3 g, 39% yield); mp 300–302 °C; IR ν_{max}^{KBr}: 3420 (OH); 3360–3130 (NH_2) and 1630 cm^{-1} (C = N). ^1H NMR (DMSO-d_6): δ 3.95 (d, 2 H, H-2 and H–3), 4.89 (d, 2 H, H-1 and H-4), 4.88, 4.91 and 5.32 (d, s and d, 4 H, D_2O exchangable, 4 OH), 5.52 (s, 4 H, D_2O exchangable, 2 NH_2) and 13.52 (s, 2 H, D_2O exchangable, 2 SH). Anal. Calcd for $C_8H_{14}N_8O_4S_2 \cdot H_2O$ (368.39): C, 26.08; H, 4.37; N, 30.42. Found: C, 26.28; H, 4.03; N, 30.71.

Method (b). A mixture of **17** (0.6 g, 2.25 mmol) and **3** (0.47 g, 4.43 mmol) was heated in an oil bath for 1 h at 165–168 °C. The residue was cooled and the product was crystallized from H_2O (0.5 g, 64% yield). It was identical with the product from method (a).

2,3,4,5-Tetra-O-*acetyl-1,4-bis-(1,2,4-triazol-3-yl-[3,4-*b*]1,3,4-thiadiazole)*-galacto-*tetritol* (**19**).—A suspension of **18** (0.3 g) in acetic anhydride (20 mL) was heated under reflux for 6–8 h. The solution was evaporated under reduced pressure and the residue was crystallized from EtOH (0.3 g, 63.5% yield); mp 285 °C; IR ν_{max}^{KBr}: 1750 (OCO) and 1640 cm^{-1} (C = N). ^1H NMR ($CDCl_3$): δ 2.04 (s, 6 H, 2 $OCOCH_3$), 2.15(s, 6 H, 2 $OCOCH_3$) 2.75 (s, 6 H, $2CH_3$) 5.87 (s, 2 H, H-2 and H-3) and 6.47 (s, 2 H, H-1 and H-4). MS: *m/z* 566 (9%, M^+), 523 (40%, $M^+ - Ac$), 507 (15%, $M^+ - AcO$), 483 (20% $M^+ - Ac - CH_2 = C = O$), 465 (53%, $M^+ - AcO - CH_2 = C = O$), 405 (21% $M^+ - Ac - CH_2 = C = O - AcOH$), 345 (30% $M^+ - AcO - CH_2 = C = O - 2$ AcOH), 313 (42%, C-1–C-2 fission), 254 (26%, 313 − Ac), 212 [63%, $M^+ - R\text{-}(CHOAc)_3$], 169 [100%, $M^+ - R(CHOAc)_3 - CH_2 = C = O$], 141 (24%, RH^+). Anal. Calcd for $C_{20}H_{22}N_8O_8S_2$. (566.36): C, 42.39; H, 3.91; N, 19.78. Found: C, 41.90; H, 3.55; N, 19.52.

Acknowledgements

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