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4-Thiopyranoside and 4-thiofuranoside derivatives of D-galactosamine

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Abstract

Methyl 2-benzamido-2-deoxy-4-thio-α-D-galactopyranoside (**7**) was prepared in different ways starting from methyl 2-benzamido-3,6-di-*O*-benzoyl-2-deoxy-α-D-glucopyranoside (**1**). A 4,6-epidithiogalactopyranoside was obtained from the 4-*O*-mesyl derivative of **1**. The transformations of **7** into 2-benzamido-2-deoxy-4-thio-D-galactofuranose and into the corresponding methyl α- and β-4-thio-D-galactofuranosides are reported. The $^2T_3$ conformation is proposed for the α anomers of the prepared furanoid compounds. © 1998 Elsevier Science Ltd.

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1. Introduction

Thiosugars are interesting compounds from both chemical and pharmaceutical points of view [1,2]. Thus, 3-thio and 6-thio derivatives of D-glucose have therapeutic effects in autoimmune disorders [3]. Thiosugars in which the ring oxygen is replaced by a sulfur atom exhibit interesting biological activities. Thus, 5-thio-D-glucopyranose inhibits the transport of D-glucose and the release of insulin [1], 5-thio-L-fucose is a potent enzyme inhibitor [4], and some glycosides of 5-thio-D-xylopyranose have significant antithrombotic activity [5]. The syntheses of several 5-thioaldopyranosides have been described recently [6].

Syntheses of 5-thiohexosamine derivatives have been described [7]. However, as far as we are aware, the preparation of 2-amino-4-thiosugars has not been reported although, among other, 2-amino-2-deoxy-D-galactose is a sugar fragment present in many natural oligosaccharides that are part in the structure of glycopeptides [8] and glycolipids [9]. Additionally, the interest in the syntheses of furanosides, and particularly galactofuranosides, is growing due primarily to the widespread occurrence of this cyclic form in lower organisms [10].

The syntheses of 4-thio-D-galactofuranose [11] and 6-deoxy-4-thio-D-galactose [12] have been described. In this paper, we report on the preparation of the first 2-amino-4-thiosugar derivative, 2-benzamido-2-deoxy-4-thio-D-galactofuranose (**10**) and also of its methyl α- and β-glycosides (**15** and **16**). To intro-

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duce the sulfur atom at C-4 of the sugar ring, we have used a synthetic approach that involves a nucleophilic displacement of a sulfonyloxy group by potassium thiocyanate [13] or potassium thioacetate [1].

2. Results and discussion

The key intermediate for the syntheses of the D-galactofuranose derivatives **10–16** was methyl 2-benzamido-4-thio-α-D-galactopyranoside **7** which was obtained by four different pathways (Scheme 1) starting in all cases from methyl 2-benzamido-3,6-di-*O*-benzoyl-2-deoxy-α-D-glucopyranoside (**1**) [14]. Reaction of **1** with either 4-bromobenzenesulfonyl chloride or trifluoromethanesulfonic anhydride gave the corresponding 4-sulfonyloxy derivative **2** or **5** in high yield.

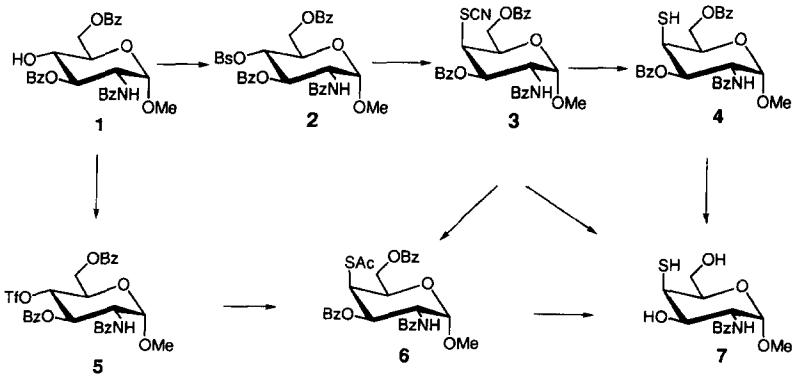
The NMR data (Tables 1 and 2) of **2** and **5** supported the esterification of HO-4. Nucleophilic displacement of the sulfonyloxy group of **2** and **5** by potassium thiocyanate or potassium thioacetate respectively gave the corresponding methyl galactosides **3** and **6** having a substituent precursor of the thiol group at C-4. The yield was higher in the case of the transformation **2** → **3** than in the case of **5** → **6** but, in the latter, the reaction time was shorter and the reaction could be conducted under milder conditions. Compound **6** was also obtained by reaction of the thiocyanate group of **3** with zinc dust under acetylating conditions. Thermal rearrangement of the thiocyanate group to the isothiocyanate group is a well known reaction [15], which has been applied to

Table 1
^{1}H-NMR data (δ in ppm, J in Hz)

Comp	H-1	H-2	H-3	H-4	H-5	H-6	H-6′	NH
2[a]	4.90	4.71	5.72	5.23	4.24	4.76	4.47	6.39
3[a]	4.95	4.95	5.76	4.31	4.68	4.72	4.57	6.47
4[a]	4.95	5.09	5.56	3.79	4.58	4.63	4.58	6.44
5[a]	4.94	4.74	5.88	5.40	4.37	4.84	4.47	6.51
6[a]	4.94	4.78	5.74	4.60	4.67	4.59	4.37	6.44
7[b]	4.71	4.32	4.10	3.51	3.93	3.51	3.51	8.09
9c[a]	4.93	4.70	4.45	4.24	4.80	3.96	3.40	6.57
10α[c]	5.21	4.46	4.38	3.38	3.88	3.54	3.54	
10β[c]	5.28	4.56	4.22	3.75	3.94	3.49	3.49	
11[a]	5.99	4.92	5.52	3.77	5.23	4.27	4.08	6.76
12[a]	5.91	5.00	5.24	3.92	5.36	4.31	4.08	6.88
13[a]	4.85	4.92	5.58	3.77	5.21	4.26	4.11	6.76
14[a]	4.92	4.82	5.19	3.86	5.44	4.28	4.12	6.66
15[c]	4.86	4.57	4.36	3.38	3.80	3.56	3.56	
16[c]	5.00	4.63	4.23	3.66	3.98	3.54	3.49	

	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{2,NH}$
2[a]	3.5	10.8	9.5	9.9	2.2	4.1	12.4	9.5
3[a]	3.8	10.3	3.8	1.2	6.8	4.9	10.6	8.8
4[a]	3.7	11.0	4.3	1.4	8.8		12.4	9.4
5[a]	3.5	10.7	9.6	9.8	1.9	3.6	12.7	9.4
6[a]	3.7	11.1	4.3	1.6	7.3	4.7	11.2	9.4
7[b]	3.7	10.7	4.0	2.1				8.1
9c[a]	3.6	10.2	5.2	2.4	3.6	1.6	12.0	7.9
10α[c]	4.3	10.5	7.9	4.5	6.0	6.2	11.2	
10β[c]	5.7	7.6	6.9	3.6	6.2	6.1	11.2	
11[a]	4.5	10.9	8.8	5.7	3.8	5.7	12.1	8.3
12[a]	4.2	7.5	7.7	5.1	3.8	6.1	12.1	8.2
13[a]	4.1	10.5	8.3	5.8	3.9	5.9	12.0	8.8
14[a]	3.3	6.1	7.7	4.5	4.1	6.5	11.9	8.0
15[c]	4.3	10.7	8.2	5.0				
16[c]	4.6	6.6	6.7	3.4	6.1	6.2	10.9	

[a] In $CDCl_3$.
[b] In Me_2SO-d_6.
[c] In CD_3OD.



Scheme 1.

Table 2
^{13}C-NMR data (δ in ppm)

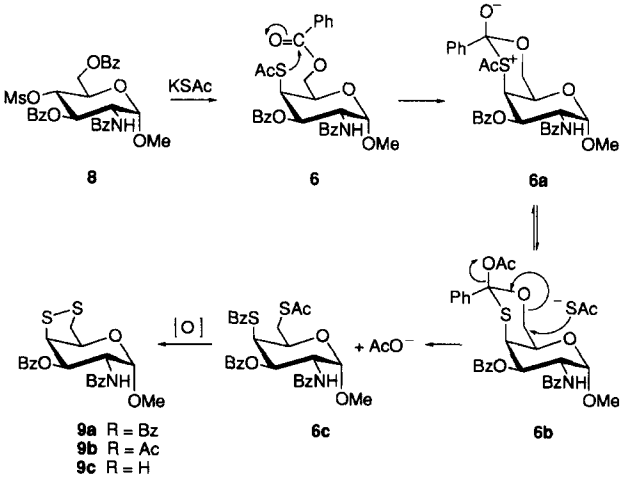
Compd	C-1	C-2	C-3	C-4	C-5	C-6
2[a]	98.05	52.71	70.74	75.87	67.74	62.15
3[a]	98.54	49.17	69.70	54.38	66.58	63.50
4[a]	98.62	48.16	70.76	42.25	67.32	64.77
5[a]	98.13	53.08	70.30	79.07	67.02	61.55
6[a]	98.68	50.28	69.49	46.71	67.20	64.19
7[b]	98.03	50.74	69.80	45.18	66.04	61.80
9c[a]	99.24	51.16	69.36	63.87	73.83	43.71
10α[c]	75.47	63.86	75.58	52.93	73.13	66.39
10β[c]	81.61	66.60	77.55	55.55	72.44	66.28
11[a]	74.92	58.22	74.28	45.04	70.36	63.14
12[a]	80.36	60.82	76.42	49.05	68.69	63.63
13[a]	84.45	59.84	75.30	44.98	70.89	63.15
14[a]	90.90	62.54	77.58	49.21	69.04	63.84
15[c]	85.70	62.89	75.65	52.61	73.66	66.26
16[c]	91.95	64.99	78.61	55.79	72.35	66.28

[a]In $CDCl_3$.
[b]In Me_2SO-d_6.
[c]In CD_3OD.

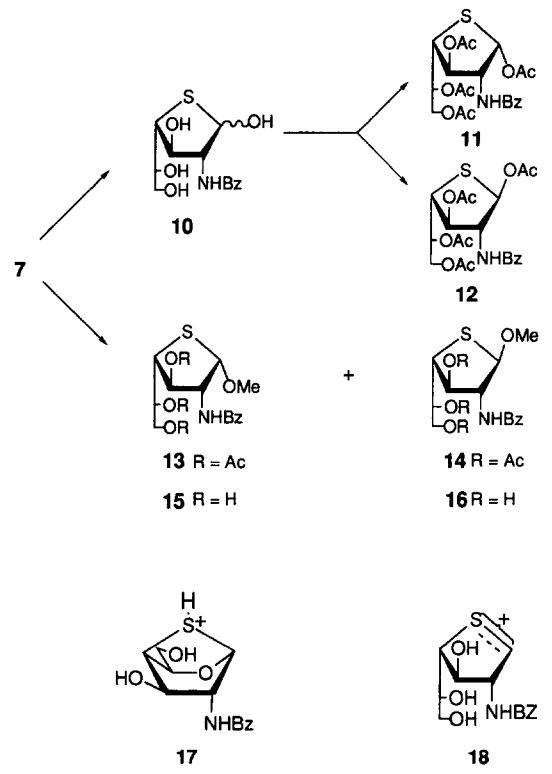
the transformation of sugar thiocyanates into the corresponding isothiocyanates [13]. However, we have not observed formation of the isomeric isothiocyanate during the synthesis of **3**, although the reaction was conducted at 110 °C. Compound **3** showed a ^{13}C-NMR signal at δ 111.1 ppm and an IR absorption at 2158 cm^{-1} characteristic of the thiocyanate group, and not the corresponding signals at δ ca. 144 ppm and ν ca. 2025 cm^{-1} described for sugar isothiocyanates [13,16]. The NMR data of the sugar rings of **3** and **6** were consistent with the replacement of the sulfonyloxy group by an SCN (SAc) group and the change from the D-*gluco* to the D-*galacto* configuration. Thus, the spectra of **3** and **6** showed strong upfield shifts in the resonances of H-4 and C-4 and the $J_{4,5}$ value was ca. 1.5 Hz as described for related galactopyranosides [11].

The reduction of the thiocyanate group of **3** gave the 4-thiol derivative **4** whose ^{1}H-NMR spectrum had a doublet at δ 1.82 ppm for the SH group. The presence of this group was also confirmed by an IR absorption at 2575 cm^{-1}. The O-deprotected 2-amino-4-thio-D-galactoside **7** was obtained on treatment with sodium methoxide of either **3**, **4** or **6**. The transformation **3** → **7** (25%), which could be interpreted as a nucleophilic displacement on the CN group [17], gave a yield lower than in the other two cases due to the formation of sugar disulfide. The best routes for the transformation **1** → **7** (Scheme 1) are **1** → **5** → **6** → **7** (overall yield 60%) and **1** → **2** → **3** → **4** → **7** (overall yield 66%).

The attempted preparation of **6** by nucleophilic displacement of the mesyloxy group of the methyl 4-*O*-mesylglucoside **8** with potassium thioacetate was not successful. When the reaction was performed in butanone, under the same conditions used for the transformation **5** → **6**, there was no progress, and when the reaction was carried out at 140 °C in dimethylsulfoxide a complex mixture of products was formed in 30 min, as evidenced by ^{1}H-NMR spectroscopy. Progress of the reaction was monitored in deuterated dimethylsulfoxide by analysing the resonance for H-3 in the 5.25–6.00 ppm region where more than six different compounds, including **6** as the main one, were detected. After 5 h, signals for **9a** and **9b** in a 1:1 ratio were observed as the two main components. Deacylation of the reaction mixture with sodium methoxide gave **9c** in 41% yield. A possible mechanism to explain the formation of **9a** is depicted in Scheme 2. The 4-thioacetate **6**, initially formed, evolves to the dithioester **6c** via the oxathiane **6b**. The acetoxydimethylsulfonium ion, formed from potassium thioacetate and dimethylsulfoxide [18], could act as an oxidizing agent in the formation of **9a** and participate in the transesterification reaction that leads to the equilibrium between **9a** and **9b**. The FAB–mass spectrum of an aliquot of the reaction mixture after 2 h in deuterated dimethylsulfoxide showed signals that may correspond to $[M+23]^+$ for **6c**, **6**, **9a** and **9b** [*m/z* 602 (11%), 586 (32), 454 (7) and 392 (7), respectively]. Other signals [*m/z* 540 (37%) and 524 (64)] account for transacylation products from **6c** and **6**, respectively. The formation of a bicyclic compound similar to **9c** starting from a 4,6-di-*O*-mesyl-α-D-glucopyranoside has been reported [19].



Scheme 2.



Scheme 3.

With the aim of preparing 4-thio-D-galactofuranosamine derivatives, we have tried the hydrolysis of the methyl galactoside **7** under various conditions. Acetolysis, as described for some 4-thiopyranosides [1,11], gave a complex mixture of products that could not be processed; however, the treatment with the acidic resin ion exchange Amberlite IR-120(H^+) in water under nitrogen yielded the O-unprotected compound **10** (Scheme 3). Conventional acetylation of **10** afforded the mixture of the α-(**11**) and β-(**12**) tetra-*O*-acetyl derivatives that could be resolved by chromatography. The structure of compounds **10–12** was based on analytical and spectroscopic data. Both the ^{1}H- and ^{13}C-NMR spectra of **10** showed that this compound exists in solution in methanol as a mixture of thiofuranose anomers, without the presence of pyranoid structures, in agreement with reported data for other 4-thiohexose derivatives [11,20]. Digital integration of the ^{1}H-NMR signals of **10** showed an α/β ratio of 75:25. The assignments of these anomeric configurations and also of those for **11** and **12** were based on polarimetric measurements and on the comparison of $^3J_{H,H}$ and δ ^{13}C values with reported data for related 4-thio-D-galactofuranose derivatives. Thus, the resonance for C-1 in **10**α (75.5 ppm) appeared at higher field than that for **10**β (81.6 ppm) similarly to that described for the same resonances in α-(79.8 ppm) and β-(84.1 ppm)-4-thio-D-galactofuranoses [11]. Additionally, the NMR spectra of the acetyl derivatives **11** and **12** showed $J_{2,3}$, $J_{3,4}$, $J_{4,5}$ (4.5, 10.9 and 8.8 Hz for **11** and 4.2, 7.5 and 7.7 Hz for **12**) and δ C-1 values (74.9 for **11** and 80.4 for **12**) close to that described for related α-(4.3, 9.7, 7.7 Hz and 74.6 ppm) and β-(3.1, 5.4, 6.4 Hz and 80.3 ppm) per-*O*-acetyl-4-thio-D-galactofuranose derivatives [11]. The same similarities are observed by comparison of the above NMR data for **10–12** with those for 6-deoxy-4-thio-D-galactoses [12]. The α(**11**) and β(**12**) anomers have specific rotations (+143° and −123°, respectively) similar to those for the reported α-(+98°, +154°)- and β (−123°, −146°)-4-thio-D-galactofuranose and 6-deoxy-4-thiogalactofuranose derivatives, respectively [11,12].

When the treatment of **7** with Amberlite IR-120(H^+) was performed, using methanol as solvent, an inseparable mixture of the α (**15**) and β (**16**) methyl galactofuranosides in an 8:2 ratio was obtained. No galactopyranosides were detected. Acetylation of this mixture gave the tri-*O*-acetyl derivatives **13** and **14** which could be isolated by preparative TLC in 37% and 6% yield from **7**, respectively. Compounds **13** and **14** were also obtained from **6** by successive deacetylation, treatment with Amberlite IR-120(H^+) and acetylation in 51 and 7% yield from **6**, respectively. Deacetylation of **13** and **14** with ammonia in dry methanol afforded the α methyl (**15**) and β (**16**) 4-thiogalactofuranosides in high yields, respectively. The transformation of **7** into **10**, **15** and **16** probably takes place through sulfonium cations **17** and **18**, similarly to that proposed for 4-thio-D-galactopyranoses [11,12]. The NMR data (Tables 1 and 2) for **13–16** were similar to that discussed for **10–12**, except the chemical shifts for H-1 and C-1 were in agreement with the presence of the methoxy group at C-1.

For the α anomers **10**α, **11**, **13** and **15**, the $^3J_{1,2}$ (ca. 4.3 Hz), $^3J_{2,3}$ (ca. 10.7 Hz), $^3J_{3,4}$ (7.9–8.8 Hz) values are in agreement with a $^2T_3$ conformation (Fig. 1), located in the South (*S*) part of the pseudorotational circle [21,22], suggesting that this is the

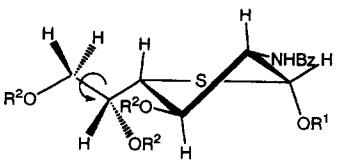


Fig. 1. $^2T_3$ Conformation for **10**α, **11**, **13**, and **15**.

major conformation of the thiofuranose ring for solutions in methanol or chloroform. This result is in agreement with reported data [11,12] for other thiofuranose derivatives. The coupling constants between the vicinal protons of the sugar backbone at C-4 ($J_{4,5}$, $J_{5,6}$, $J_{5,6'}$) are of intermediate value indicating a conformational chain-end flexibility similar to that described for polyhydroxy and polyacetoxy sugar derivatives [16,23]. In the case of the β anomers **10β**, **12**, **14** and **16**, all the $^3J_{H,H}$ (Table 1) were of intermediate value supporting a complex conformational equilibrium.

3. Experimental

General methods.—Melting points were determined with an Electrothermal apparatus and were uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. IR spectra (KBr discs) were recorded with a FT–IR Bomem MB-120 spectrophotometer. ^{1}H- (300 and 500 MHz) and ^{13}C-NMR spectra (75.5 and 125.8 MHz) were recorded with a Bruker AMX-300 and AMX-500 for solutions in $CDCl_3$ and MeOH-d_4, using Me_4Si as internal standard. The assignments of ^{1}H signals were confirmed by COSY experiments and heteronuclear 2D correlated spectra were used for ^{13}C signal assignments. Chemical shifts are expressed in δ (ppm) and coupling constants (J) in Hz. FAB–mass spectra were taken with a Kratos MS-80 RFA instrument. The samples were dissolved in thioglycerol and NaI was added as cationising agent. Ions were produced by a beam of Xe atoms with a maximum energy of 8 KeV, and the positive ions were separated and accelerated over a potential of 7 kV. All reactions were monitored by TLC on aluminum sheets coated with Silica Gel 60 F_{254} (E. Merck) with visualisation by UV light and by charring with 10% H_2SO_4 in MeOH. Column chromatography and preparative TLC were carried out using Silica Gel 60 HF_{254} (E. Merck). Microanalyses were performed at the 'Instituto Químico de Sarriá', Barcelona, Spain.

Methyl 2-benzamido-3,6-di-O-benzoyl-4-O-(4-bromobenzenesulfonyl)-2-deoxy-α-D-glucopyranoside (**2**).—To a solution of **1** (0.4 g; 0.79 mmol) in dry pyridine (4 mL) was added 4-bromobenzenesulfonyl chloride (0.8 g; 3.1 mmol). The mixture was kept at room temperature for 24 h. Then water (0.8 mL) was added, and the resulting mixture was stirred for 0.5 h. The solution was slowly poured into ice-water affording a solid, which was filtered and washed with water. The solid was crystallized from EtOH to give **2** (0.45 g, 79%); mp 149–150°C; $[\alpha]_D^{25}$ +68° (*c* 1.0, $CHCl_3$); R_f 0.81 (80:1 CH_2Cl_2–MeOH); ν_{max} 3347 (NH), 1723 (C=O benzoate), 1649 (C=O amide), 1530, 1520 (amide), 1368 and 1190 cm^{-1} (SO_2); FABMS: *m/z* 748 and 746 ([*M* + Na]$^+$, 100 and 88%), 726 and 724 ([*M* + H]$^+$, 26 and 24), 694 and 692 ([*M*–OMe]$^+$, 5 and 5); ^{1}H-NMR (500 MHz), Table 1 and δ 3.43 (3H, OMe); ^{13}C-NMR (125.8 MHz), Table 2 and δ 167.18 (CON), 166.52, 165.93 (COO), 55.57 (OMe). Anal. Calcd for $C_{34}H_{30}BrNO_{10}S$: C, 56.36; H, 4.17; N, 1.93; S, 4.43. Found: C, 55.93; H, 4.43; N, 2.19; S, 4.94.

Methyl 2-benzamido-3,6-di-O-benzoyl-2,4-dideoxy-4-thiocyanato-α-D-galactopyranoside (**3**).—To a soln of the 4-*O*-brosyl derivative **2** (0.4 g; 0.55 mmol) in dry DMF (3 mL) was added potassium thiocyanate (0.37 g; 3.8 mmol). The mixture was stirred at 110 °C under nitrogen atmosphere for 20 h, and then it was poured into ice-water (100 mL) affording a solid (0.30 g, 99%). Preparative TLC (160:1 CH_2Cl_2–MeOH) gave analytically pure compound **3** (88%) as an amorphous solid; $[\alpha]_D^{25}$ +10° (*c* 1.0, $CHCl_3$); R_f 0.76 (80:1 CH_2Cl_2–MeOH); ν_{max} 3337 (NH), 2158 (SCN), 1723 (C=O benzoate), 1653 (C=O amide), 1522 cm^{-1} (amide); FABMS: *m/z* 569 ([*M* + Na]$^+$, 100%), 547 ([*M* + H]$^+$, 22), 515 ([*M*–OMe]$^+$, 7); ^{1}H-NMR (500 MHz), Table 1 and δ 3.43 (3H, OMe); ^{13}C-NMR (125.8 MHz), Table 2 and δ 167.21 (CON), 166.57, 165.81 (COO), 111.11 (SCN), 55.69 (OMe). Anal. Calcd for $C_{29}H_{26}N_2O_7S$: C, 63.72; H, 4.79; N, 5.13; S, 5.87. Found: C, 63.58; H, 4.81; N, 4.72; S, 6.03.

Methyl 2-benzamido-3,6-di-O-benzoyl-2-deoxy-4-thio-α-D-galactopyranoside (**4**).—To a soln of **3** (0.6 g; 1.09 mmol) in glacial acetic acid (20 mL) was added powdered zinc (0.71 g; 10.9 mmol). The mixture was heated under reflux for 24 h and filtered. The filtrate was slowly poured into cold water, affording crude **4** (0.51 g, 90%) homogeneous by TLC. An analytical sample was crystallized from EtOH; mp 137–139°C; $[\alpha]_D^{25}$ +126° (*c* 1.0, $CHCl_3$); R_f 0.76 (80:1 CH_2Cl_2–MeOH); ν_{max} 3434, 3324 (NH), 2575 (SH), 1719 (C=O benzoate), 1669 (C=O amide), 1518 cm^{-1} (amide); FABMS: *m/z* 1065 ([2*M* + Na]$^+$, 5%), 566 ([*M* + 2 Na–H]$^+$, 8), 544 ([*M* + Na]$^+$, 100), 522 ([*M* + H]$^+$, 14), 490 ([*M*–OMe]$^+$, 23); ^{1}H-NMR (500 MHz), Table 1 and δ 3.43 (3H, OMe), 1.82 (d, 1H, *J* 8.7 Hz, SH); ^{13}C-NMR (125.8 MHz), Table 2 and δ 167.23 (CON), 166.44, 166.01 (COO), 55.23 (OMe). Anal. Calcd for $C_{28}H_{27}NO_7S$: C, 64.48; H, 5.22; N, 2.69; S, 6.15. Found: C, 64.45; H, 5.40; N, 2.78; S, 6.68.

Methyl 2-benzamido-3,6-di-O-benzoyl-2-deoxy-4-O-trifluoromethanesulfonyl-α-D-glucopyranoside (**5**).—To a stirred soln of trifluoromethanesulfonic anhydride (2 mL, 12.2 mmol) in CH_2Cl_2 (20 mL) at −18°C was added dropwise pyridine (2 mL, 24.7 mmol) diluted with CH_2Cl_2 (1 mL), and then a soln of **1** (3.1 g, 6.1 mmol) in CH_2Cl_2 (30 mL). After 30 min, the mixture was diluted with CH_2Cl_2, washed with 2 M HCl, saturated aq $NaHCO_3$ and with water, dried ($MgSO_4$), and evaporated to give **5** (3.4 g, 87%) that could be used for the next step. A sample (0.3 g) was purified by preparative TLC (1:3 EtOAc–hexane), yielding pure **5** (0.25 g) as an amorphous solid; $[\alpha]_D^{29}$ +120° (*c* 1.0, CH_2Cl_2); R_f 0.73 (80:1 CH_2Cl_2–MeOH); ν_{max} 3445 (NH), 1726 (C=O benzoate), 1668, 1663 (C=O amide) 1539, 1533 cm^{-1} (amide); FABMS: *m/z* 660 ($[M + Na]^+$, 38), 638 ($[M + H]^+$, 64), 606 ($[M-OMe]^+$, 2), 488 ($[M-TfO]^+$, 42) 366 ($[M-TfO-BzOH]^+$, 8), 244 ($[M-TfO-2\ BzOH]^+$, 10), 134 ($[F_3CSO_2H]^+$, 100); HR-FABMS: *m/z* 722.0313 ($[M + Rb]^+$, 6%; calcd 722.0346); ^{1}H-NMR (300 MHz) Table 1 and δ 3.48 (3H, OMe); ^{13}C-NMR (75.5 MHz), Table 2 and δ 167.20 (CON), 166.78, 165.83 (COO), 118.03 ($^1J_{C,F}$ 319 Hz, CF_3), 55.86 (OMe). Anal. Calcd for $C_{29}H_{26}F_3NO_{10}S$: C, 54.63; H, 4.11; N, 2.20; S, 5.03. Found: C, 54.70; H, 4.36; N, 2.21; S, 5.18.

Methyl 4-S-acetyl-2-benzamido-3,6-di-O-benzoyl-2-deoxy-4-thio-α-D-galactopyranoside (**6**).—(a) Starting from methyl 2-benzamido-3,6-di-*O*-benzoyl-2-deoxy-4-*O*-trifluoromethanesulfonyl-α-D-glucopyranoside (**5**). To a soln of crude **5** (3.1 g, 4.86 mmol) in butanone (40 mL) was added potassium thioacetate (1 g, 9.1 mmol) and the mixture was boiled under reflux for 2 h. The insoluble material was separated by filtration and washed with acetone. The combined filtrate and washings were concentrated to dryness. A soln of the residue in CH_2Cl_2 was washed with water, dried ($MgSO_4$), and evaporated. The residue, recrystallized from MeOH after treatment with activated charcoal, gave **6** (2.1 g, 77%); mp 182–184 °C; $[\alpha]_D^{22}$ +48° (*c* 1.0, CH_2Cl_2); R_f 0.45 (80:1 CH_2Cl_2–MeOH); ν_{max} 3355, 3300 (NH), 1725 (C=O, benzoate), 1700 (C=O, thioacetate), 1655, 1651 (C=O amide), 1530 cm^{-1} (amide); FABMS: *m/z* 586 ($[M + Na]^+$, 39%), 387 ($[M-Bz-SAc]^+$, 44), 281 ($[M-2Bz-CH_2CO]^+$, 100); ^{1}H-NMR (300 MHz), Table 1 and δ 3.43 (3 H, OMe), 2.35 (3 H, SAc); ^{13}C-NMR (75.5 MHz), Table 2 and δ 193.23 (COS), 167.15 (CON), 166.29, 165.93 (COO), 55.33 (OMe), 30.67 (SAc). Anal. Calcd for $C_{30}H_{29}NO_8S$: C, 63.93; H, 5.19; N, 2.48. Found: C, 63.83; H, 4.98; N, 2.68.

(b) Starting from methyl 2-benzamido-3,6-di-*O*-benzoyl-2,4-dideoxy-4-thiocyanato-α-D-galactopyranoside (**3**). A suspension of **3** (93 mg; 0.17 mmol) and powdered zinc (93 mg) in glacial acetic acid (1 mL) and acetic anhydride (1 mL) was kept at 110 °C under nitrogen for 18 h. The mixture was poured into ice-water and extracted with CH_2Cl_2. The organic extract was washed with saturated aq $NaHCO_3$ and water, dried ($MgSO_4$) and evaporated. The residue was purified by preparative TLC (160:1 CH_2Cl_2–MeOH). This gave 51 mg (53%) of **6**.

Methyl 2-benzamido-2-deoxy-4-thio-α-D-galactopyranoside (**7**).—(a) Starting from methyl 4-*S*-acetyl-2-benzamido-3,6-di-*O*-benzoyl-2-deoxy-4-thio-α-D-galactopyranoside (**6**). A soln of **6** (1.92 g; 3.4 mmol) in 0.1 M NaOMe in MeOH (10 mL) was stirred for 1 h at room temperature. The soln was diluted with MeOH, made neutral with Amberlite IR-120 (H^+) and filtered. The filtrate was evaporated and the residue was scratched with Et_2O, affording a solid which was filtered and crystallized from EtOH to give **7** (0.96 g; 90%); mp 203–205 °C (dec.); R_f 0.41 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{22}$ +135° (*c* 1.0, pyridine); R_f 0.41 (9:1 CH_2Cl_2–MeOH); ν_{max} 3369, 3313 (OH, NH), 2560 (SH), 1639, 1630 (C=O amide), 1535 cm^{-1} (amide); FABMS: *m/z* 647 ($[2M-2H + Na]^+$, 100%), 625 ($[2M-H]^+$, 24), 593 ($[2M-OMe]^+$, 9), 367 ($[M + Na + S]^+$, 7); 366 ($[M + Na]^+$, 38), 314 ($[M + H]^+$, 18); ^{1}H-NMR (500 MHz), Table 1 and δ 3.25 (3H, OMe), 1.95 (d, 1H, *J* 5.5 Hz, SH); ^{13}C-NMR (125.8 MHz), Table 2 and δ 166.65 (CON), 54.51 (OMe). Anal. Calcd for $C_{14}H_{19}NO_5S$: C, 53.66; H, 6.11; N, 4.47. Found: C, 53.74; H, 6.00; N, 4.57.

(b) Starting from methyl 2-benzamido-3,6-di-*O*-benzoyl-2,4-dideoxy-4-thiocyanato-α-D-galactopyranoside (**3**). A soln of **3** (0.7 g, 1.28 mmol) in 0.2 M NaOMe in MeOH (30 mL) was stirred for 8 h at room temperature. The soln was made neutral with Amberlite IR-120(H^+), filtered and evaporated. The residue was scratched with Et_2O affording an amorphous solid which was purified by preparative TLC (20:1 EtOAc–MeOH). This gave 103 mg (25%) of **7**.

(c) Starting from methyl 2-benzamido-3,6-di-*O*-benzoyl-2-deoxy-4-thio-α-D-galactopyranoside (**4**). A suspension of **4** (55 mg, 0.11 mmol) in a 0.1 M NaOMe in MeOH (5 mL) was stirred for 3 h at room temperature. The reaction mixture was diluted with MeOH, made neutral with Amberlite IR-120(H^+)

and filtered. The filtrate was evaporated and the residue was scratched with ether to give 31 mg (94%) of **7**.

Methyl 2-benzamido-3-O-benzoyl-2,4,6-trideoxy-4,6-epidithio-α-D-galactopyranoside (**9c**).—To a soln of methyl 2-benzamido-3,6-di-*O*-benzoyl-2-deoxy-4-*O*-methanesulfonyl-α-D-glucopyranoside **8** (200 mg; 0.34 mmol) in dimethylsulfoxide (6 mL) was added potassium thioacetate (98 mg; 0.86 mmol), and the mixture was kept at 140 °C for 5 h. The mixture was diluted with water (60 mL) and extracted with CH_2Cl_2 (2 × 30 mL); the extract was washed with water, dried ($MgSO_4$), and concentrated to give 136 mg of a mixture whose ^{1}H-NMR spectrum showed signals for methyl 3-*O*-acetyl (and 3-*O*-benzoyl)-2-benzamido-2,4,6-trideoxy-4,6-*epi*dithio-α-D-galactopyranoside (**9b** and **9a**) as the main compounds in 1:1 ratio. Conventional deacetylation of the mixture with 0.1 M NaOMe in MeOH (5 mL) followed by preparative TLC (20:1 CH_2Cl_2–MeOH) gave **9c** (46 mg, 41%) which crystallized from EtOH; mp 262–264 °C (dec.); R_f 0.66 (20:1 CH_2Cl_2–MeOH); ν_{max} 3297 (NH, OH), 1636 (C=O amide), 1537 cm^{-1} (amide); FABMS: *m/z* 350 ([*M* + Na]$^+$, 100); ^{1}H-NMR (300 MHz), Table 1 and δ 3.51 (3H, OMe); ^{13}C-NMR (75.5 MHz), Table 2 and δ 169.85 (CON), 55.61 (OMe). Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 51.35; H, 5.23; N, 4.28; S, 19,59. Found: C, 51.08; H, 5,29; N, 4.37; S, 20,04.

2-Benzamido-2-deoxy-4-thio-D-galactofuranose (**10**).—To a suspension of **7** (0.1 g; 0.32 mmol) in water (6 mL) was added Amberlite IR-120(H$^+$) (0.187 g). The mixture was stirred at 90 °C under nitrogen for 6 h and then it was filtered. The filtrate was neutralized with Amberlite IR-45 (OH$^-$), evaporated to dryness and the residue was purified by preparative TLC (9:1 CH_2Cl_2–MeOH). This gave 38 mg (40% yield) of **10** as an amorphous solid; $[\alpha]_D^{25}$ +79° (*c* 1.0, pyridine); R_f 0.33 (9:1 CH_2Cl_2–MeOH); ν_{max} 3325, 3304 (OH, NH), 1638 (C=O amide), 1539 cm^{-1} (amide); FABMS: *m/z* 621 ([2*M* + Na]$^+$, 3%), 344 ([*M* + 2 Na–H]$^+$, 3), 322 ([*M* + Na]$^+$, 100), 304 ([*M* + Na–H_2O]$^+$, 3). ^{1}H-NMR (500 MHz), Table 1; ^{13}C-NMR (125.8 MHz), Table 2 and δ 170.74 and 170.23 (CON). Anal. Calcd for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.72; N, 4.68; S, 10.71. Found: C, 52.04; H, 5.64; N, 4.69; S, 10.75.

1,3,5,6-Tetra-O-acetyl-2-benzamido-2-deoxy-4-thio-α- and β-D-galactofuranose (**11** and **12**).—Conventional acetylation of **10** (0.63 g; 2.12 mmol) in 1:1 pyridine–Ac_2O (6.5 mL) gave a residue which was purified by preparative TLC (20:1 acetone–CH_2Cl_2). The fraction having R_f 0.60 afforded 0.41 g (47%) of compound **11** as an amorphous solid; $[\alpha]_D^{25}$ +143° (*c* 1.0, $CHCl_3$); ν_{max} 3349 (NH); 1746 (C=O acetate); 1665 (C=O amide), 1528 cm^{-1} (amide); FABMS: *m/z* 512 ([*M* + 2 Na–H]$^+$, 5%); 490 ([*M* + Na]$^+$, 100), 430 ([*M*–AcOH + Na]$^+$, 12), 370 ([*M*–2 AcOH + Na]$^+$, 3), 310 ([*M*–3 AcOH + Na]$^+$, 4), 246 ([*M*–3 AcOH–CH_2CO + H]$^+$, 13); ^{1}H-NMR (300 MHz), Table 1 and δ 2.13, 2.10, 2.09, 2.07 (4s, 3H each, 4 OAc); ^{13}C-NMR (75.5 MHz), Table 2 and δ 170.77, 170.27, 170.23 and 170.14 (COO), 167.10 (CON), 20.86, 20.62 (OAc), 20.57 (2 OAc). Anal. Calcd for $C_{21}H_{25}NO_9S$: C, 53.95; H, 5.39; N, 3.00; S, 6.85. Found: C, 53.80; H, 5.39; N, 2.91; S, 6.97.

The fraction having R_f 0.44 afforded 46 mg (7%) of compound **12** which crystallized from EtOH; mp 196–197 °C; $[\alpha]_D^{25}$ −123° (*c* 1.0, $CHCl_3$); ν_{max} 3320 (NH), 1740 (C=O acetate), 1643 (C=O amide), 1535 cm^{-1} (amide); FABMS: *m/z* 512 ([*M* + 2Na–H]$^+$, 3%); 490 ([*M* + Na]$^+$, 100), 430 ([*M*–AcOH + Na]$^+$, 13), 370 ([*M*–2AcOH + Na]$^+$, 4), 310 ([*M*–3 AcOH + Na]$^+$, 4); ^{1}H-NMR (300 MHz), Table 1 and δ 2.12, 2.10, 2.09, and 2.08 (4s, 3H each, 4 OAc); ^{13}C-NMR (125.8 MHz), Table 2 and δ 171.50, 170.23, 169.79, 169.27 (COO), 167.00 (CON), 20.98, 20.71, 20.57, 20.53 (OAc). Anal. Calcd for $C_{21}H_{25}NO_9S$: C, 53.95; H, 5.39; N, 3.00; S, 6.85. Found: C, 53.93; H, 5.55; N, 3.07; S, 6.93.

Methyl 3,5,6-tri-O-acetyl-2-benzamido-2-deoxy-4-thio-α- and β-D-galactofuranosides (**13** and **14**).—To a soln of **7** (0.174 g; 0.56 mmol) in dry MeOH (5 mL) was added Amberlite IR-120(H$^+$) (0.45 g). The mixture was refluxed with stirring under N_2 for 7 h. The residue obtained after filtration and concentration of the resulting soln was purified by preparative TLC (9:1 CH_2Cl_2–MeOH) to give 0.091 g (52% yield) of a mixture of **15** and **16**, both of which showed the same chromatographic mobility on TLC with different solvents. Conventional acetylation of this mixture with 1:1 pyridine–Ac_2O (1 mL) gave, after evaporation, a residue which showed two spots on TLC (R_f 0.44 and 0.35 on 80:1 CH_2Cl_2–MeOH). Preparative TLC gave **13** (R_f 0.44) 91 mg (37% yield from **7**) as an amorphous solid; $[\alpha]_D^{25}$ +84° (*c* 1.0, $CHCl_3$); ν_{max} 3462, 3322 (NH), 1742 (C=O acetate), 1645 (C=O amide), 1530 cm^{-1} (amide); FABMS: *m/z* 462 ([*M* + Na]$^+$, 100%), 440 ([*M* + H]$^+$, 10), 408 ([*M*–OMe]$^+$, 8), 246 ([*M*–2AcOH–CH_2CO–OMe]$^+$, 24); ^{1}H-NMR (500 MHz), Table 1 and δ 3.35 (3H, OMe), 2.12, 2.08, and 2.05 (3s, 3H each, 3 OAc); ^{13}C-NMR (125.8 MHz), Table 2 and δ 170.99, 170.28, 169.87 (COO), 167.11 (CON), 55.95 (OMe),

20.73, 20.65, and 20.57 (OAc). Anal. Calcd for $C_{20}H_{25}NO_8S$: C, 54.66; H, 5.73; N, 3.19; S, 7.29. Found: C, 54.64; H, 5.75; N, 3.38; S, 7.56.

The fraction having R_f 0.35 afforded **14** (14 mg, 6% yield from **7**) which crystallized from EtOH; mp 186–187 °C; $[\alpha]_D^{25}$ −72° (*c* 0.8, $CHCl_3$); ν_{max} 3325 (NH), 1742, 1250, 1221 (C=O acetate), 1645 (C=O amide), 1528 cm^{-1} (amide); FABMS: *m/z* 484 ($[M + 2Na–H]^+$, 8%), 462 ($[M + Na]^+$, 100), 440 ($[M + H]^+$, 10), 402 ($[M + Na–AcOH]^+$, 4), 251 ($[M–3AcOH–OMe + Na]^+$, 15); ^{1}H-NMR (500 MHz), Table 1 and δ 3.41 (3H, OMe), 2.09, 2.08, and 2.07 (3s, 3H each, 3 OAc); ^{13}C-NMR (125.8 MHz), Table 2 and δ 170.86, 170.31, 170.19 (COO), 166.95 (CON), 56.64 (OMe), 20.66 and 20.60 (OAc). Anal. Calcd for $C_{20}H_{25}NO_8S$: C, 54.66; H, 5.73; N, 3.19; S, 7.29. Found: C, 54.81; H, 5.85; N, 3.37; S, 7.17.

Compounds **13** and **14** were also obtained from **6** (2 g) which was deacetylated to give crude **7** (1.11 g). A mixture of **7** and Amberlite IR-120(H^+) (2 g) in dry MeOH (25 mL) was stirred at reflux temperature under N_2 for 7 h. Filtration and concentration gave a residue (1.33 g) which was acetylated. Column chromatography (CH_2Cl_2) gave **13** (0.79 g, 51% yield from **6**) and **14** (0.11 g, 7% yield from **6**).

Methyl 2 - benzamido - 2 - deoxy - 4 - thio - α - D - galactofuranoside (**15**).—A soln of **13** (0.20 g, 0.46 mmol) in MeOH (5 mL) saturated with ammonia was kept at room temperature for 8 h. The soln was evaporated to dryness and purified by preparative TLC (9:1, CH_2Cl_2–MeOH) to give **15** (95 mg, 67% yield); mp 160–162 °C (from MeOH); $[\alpha]_D^{25}$ +187°(*c* 1, pyridine); R_f 0.69 (9:1 CH_2Cl_2–MeOH), ν_{max} 3391, 3327 (OH, NH), 1642 (C=O amide), 1535 cm^{-1} (amide); FABMS: *m/z* 358 ($[M + 2Na–H]^+$, 15%), 336 ($[M + Na]^+$, 100), 304 ($[M + Na–MeO]^+$, 2); ^{1}H-NMR (300 MHz), Table 1 and δ 3.32 (3H, OMe); ^{13}C-NMR (75.5 MHz), Table 2 and δ 170.71 (CON), 56.47 (OMe). Anal. Calcd for $C_{14}H_{19}NO_5S$: C, 53.66; H, 6.11; N, 4.47; S, 10.23. Found: C, 53.99; H, 6.35; N, 4.63; S, 10.27.

Methyl 2 - benzamido - 2 - deoxy - 4 - thio - β - D - galactofuranoside (**16**).—Compound **14** (0.10 g; 0.23 mmol) was deacetylated as described for **13** to give **16** (63 mg, 84%); mp 196–198 °C (from EtOH); $[\alpha]_D^{25}$ −91° (*c* 0.7, pyridine); R_f 0.69 (80:1 CH_2Cl_2–MeOH); ν_{max} 3368, 3268 (OH, NH); 1640 (C=O amide), 1537 cm^{-1} (amide); FABMS: *m/z* 358 ($[M + 2Na–H]^+$, 14%), 336 ($[M + Na]^+$, 100), 281 ($[M–MeOH]^+$, 4); ^{1}H-NMR (300 MHz), Table 1 and δ 3.34 (3H, OMe); ^{13}C-NMR (75.5 MHz), Table 2 and δ 169.79 (CON), 56.82 (OMe). Anal. Calcd for $C_{14}H_{19}NO_5S$: C, 53.66; H, 6.11; N, 4.47; S, 10.23. Found: C, 53.40; H, 6.25; N, 4.75; S, 10.38.

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