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Synthesis of 4-substituted phenyl 3,6-anhydro-1,3-dithio-D-glucofuranosides and -pyranosides as well as 2,6-anhydro-1,2-dithio-α-D-altrofuranosides possessing antithrombotic activity☆

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Abstract

1,2,5-Tri-*O*-acetyl-3,6-anhydro-3-thio-D-glucofuranose was synthesised starting from D-glucose and was used as a donor for the glycosidation of 4-cyano- and 4-nitrobenzenethiol. In the latter reaction, besides an anomeric mixture of the 4-nitrophenyl 2,5-di-*O*-acetyl-3,6-anhydro-1,3-dithio-D-glucofuranosides, the corresponding 2,6-anhydro-1,2-dithio-D-altrofuranosides were also obtained, formed via a rearrangement of the sugar moiety. A similar rearrangement could be observed during the hydrolysis of the glycosidic bond of methyl 3,6-anhydro-2,4-di-*O*-(4-nitrobenzoyl)-3-thio-α-D-glucopyranoside with aqueous trifluoroacetic acid, affording after acetylation besides 1-*O*-acetyl-3,6-anhydro-2,4-di-*O*-(4-nitrobenzoyl)-3-thio-α-D-glucopyranose (**32α**), 1,1,5-tri-*O*-acetyl-3,6-anhydro-2,4-di-*O*-(4-nitrobenzoyl)-3-thio-D-glucose, methyl 3,6-anhydro-2,4-di-*O*-(4-nitrobenzoyl)-3-thio-β-D-glucopyranoside and 1,5-di-*O*-acetyl-2,6-anhydro-3-*O*-(4-nitrobenzoyl)-2-thio-α-D-altrofuranose (**40**). Glycosidation of 4-cyanobenzethiol with **32α** in the presence of trimethylsilyl triflate as promoter afforded 4-cyanophenyl 3,6-anhydro-2,4-di-*O*-(4-nitrobenzoyl)-1,3-dithio-β-D-glucopyranoside as a minor component only, besides 4-cyanophenyl 3,6-anhydro-2-*S*-(4-cyanophenyl)-4-*O*-(4-nitrobenzoyl)-1,2,3-trithio-β-D-glucopyranoside. When boron trifluoride etherate was used as promoter in the reaction of **32α** with 4-cyano- and 4-nitrobenzenethiol, the corresponding β-thioglycosides were obtained, while **40** gave under identical conditions the α anomers exclusively. All thioglycosides obtained after deacylation were submitted to biological evaluation. Among these glycosides, the 4-cyanophenyl 3,6-thioanhydro-1,3-dithio-D-glucofuranoside possessed the strongest oral antithrombotic effect.

Keywords: 3,6-Anhydro-3-thio-D-glucofuranosides; 3,6-Anhydro-3-thio-D-glucopyranosides; Rearrangement reactions; Glycosidation reactions; Thioglycosides; Oral antithrombotic activity

1. Introduction

During our search for thioglycosides with potential oral antithrombotic activity, we found that some of the conclusions in the literature, based on previous structure activity

☆ Orally active antithrombotic thioglycosides, Part XII. For Part XI, see Ref. [1].

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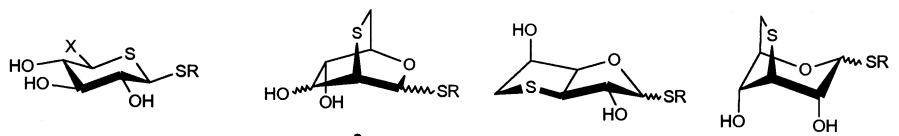
relationship studies [2] should be reconsidered. In particular, the statement that the β-D-xylopyranose configuration of the carbohydrate moiety, as well as the presence of the ring sulfur atom (**1**) is vital for biological activity. According to our findings, other 5-thio-pentopyranosides [3] and even 5-thio-glucopyranosides **2** [4], as well as glycosides with over-bridged bicyclic [2,2,2] structures like **3** possess significant antithrombotic activity [5]. In the latter, the ring oxygen is not replaced by sulfur, but an additional sulfur atom is introduced into the molecule via a 2,6-thioanhydro bridge. For studying the scope and limitations of this alteration, the synthesis of thioglycosides derived from 3,6-thioanhydro-D-glucose, which might form furanosides **4** as well as pyranosides **5**, was decided (Scheme 1).

2. Results and discussion

Synthesis of the furanosides.—For the synthesis of the corresponding thioglycosides the bicyclic triacetate **12** was needed as donor, which was obtained from D-glucose by converting it according to the literature [6,7] in six steps into the 3-*O*-mesyl-allofuranose derivative **6** (Scheme 2). The primary OH group of **6** was selectively tosylated, but attempts to exchange the tosyloxy group of the obtained tosylate **7** by thioacetate resulted in a mixture, due to the presence of the free 5-OH group, which might interfere with the substitution reaction. In order to avoid any unwanted side-reaction, the OH group of **7** was protected by acetylation. The resulting mixed ester **8** could be smoothly converted with potassium thioacetate in *N*,*N*-dimethylformamide into the 6-*S*-acetate **9**, which on treatment with methanolic sodium methoxide afforded the crystalline 3,6-thioanhydro derivative **10** in high yield (82%). Hydrolysis of the isopropylidene group of **10** was carried out in a mixture of acetic acid and 0.1 M hydrochloric acid at 100 °C. It afforded, after subsequent acetylation, **12** in satisfactory yield (72%), containing the α and β anomers in a ratio of 1:2. Neither the yield, nor the anomeric ratio was changed significantly when, instead of **10** its acetylated derivative **11** was submitted to the same reaction conditions. The pure **12α** isomer could be separated from the anomeric mixture by crystallisation, but for the glycosidation reactions the mixture was used as donor. The anomeric configuration of **12α** was deduced from the optical rotation ($[\alpha]_D$ +213°), which was in good agreement with the value ($[\alpha]_D$ +203°) reported [8] for the corresponding oxygen analogue. A further proof of the anomeric structures was obtained from the NMR data of both isomers, which were very similar to those data [8] for the oxygen analogues, except for the shift of H-3 and H-6 which, due to the attached sulfur atom, appeared with an expected upfield shift (H-3 = 4.75 → 3.75; H-6 = ~3.9 → ~3.0).

For the glycosidation reaction the furanose triacetate **12** was used as donor, 4-cyanobenzenethiol as acceptor and trimethylsilyl triflate as promoter. The mixture of the formed anomeric thioglycosides was separated by column chromatography affording **13α** (8%) and **13β** (72%). When 4-nitrobenzenethiol was used as aglycon and boron trifluoride etherate as promoter, a complex mixture was formed that contained according to NMR spectroscopy, besides the expected two anomers **14α** and **14β**, two further isomers, the anomers of 3,5-di-*O*-acetyl-2,6-anhydro-2-thio-D-altrofuranoside (**23α**) and (**23β**). Despite the fact that this mixture of isomers could only be partly separated by column chromatography, yielding a 2:1 mixture of **14α** + **23α** (9%), a 2:3 mixture of **23α** + **23β** (4%) and pure **14β** (68%), the structure of every component was



Scheme 1.

Table 1
Selected ^{1}H NMR data for solutions in $CDCl_3$

Compound	Chemical shift δ							
	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	Others
8	5.68	4.71	4.65	4.12	5.12	4.05	4.18	1.28; 1.48 (6 H, CMe_2); 3.07(3 H, Ms); 1.94 (3 H, Ac); 2.38 (3 H, Ts-Me)
9	5.80	4.70–4.85	4.70–4.85	4.22	5.21	3.03	3.37	1.37; 1.58 (6 H, CMe_2); 3.16 (3 H, Ms); 2.09 (3 H, OAc); 2.34 (3 H, SAc)
10	6.00	4.66	3.76	4.83	4.25	2.81	2.91	1.32; 1.52 (6 H, CMe_2)
11	6.06	4.66	3.78	4.97	5.13	2.90–3.10	2.90–3.10	1.31; 1.50 (6 H, CMe_2); 2.12(3 H, Ac)
12α	6.58	5.25	3.75	5.02	5.08	2.92–3.08	2.92–3.08	2.08-2.15,3 (9 H, Ac)
12β	6.25	5.23	3.52	5.03–5.14	5.03–5.14	2.95–3.15	2.95–3.15	2.08-2.15,3 (9 H, Ac)
12β [b]	6.50	5.22	3.22	4.80–5.00	4.80–5.00	3.13	2.68	1.51; 1.55; 1.63 (9 H, Ac)
13α	5.97	5.46	3.78	5.10	5.12	2.90–3.12	2.90–3.12	2.08; 2.15 (6 H, Ac)
13β	5.67	5.34	3.78	5.06	5.10	3.28	3.06	2.08; 2.11 (6 H, Ac)
14α	6.01	5.46	3.79	5.05–5.18	5.05–5.18	2.95–3.10	2.95–3.10	2.10; 2.15 (6 H, Ac)
14β	5.70	5.35	3.77	5.08	5.11	3.27	3.07	2.11; 2.12 (6 H, Ac)
16 [a]	5.90	4.32	3.62	4.72	4.08	2.65–2.85	2.65–2.85	6.18 (2-OH); 5.32 (5-OH)
17 [a]	5.56	4.24	3.58	4.74	4.08	2.90	2.67	6.02 (2-OH); 5.32 (5-OH)
18 [a]	5.48	4.22	3.55	4.71	4.08	2.94	2.76	6.00 (2-OH); 5.32 (5-OH); 3.79 (3 H, OMe); 8.95 (1 H, NH)
19 [a]	5.66	4.30	3.62	4.78	4.12	2.88	2.75	6.06 (2-OH); 5.33 (5-OH)
20 [a]	5.25	4.16	3.49	4.63	4.05	2.96	2.75	5.88 (2-OH); 5.25 (5-OH); 10.00 (1 H, NH); 2.04 (3 H, Ac)
21 [a]	5.50	4.23	3.55	4.72	4.08	2.94	2.77	6.00 (2-OH); 5.31 (5-OH); 9.47; 9.83 (2 H, NH_2)
22 [a]	5.64	4.26	3.60	4.76	4.10	2.90	2.78	2.09 (3 H, SMe)
23α	5.87	3.56	5.14	4.70	5.04	2.80–2.90	2.80–2.90	2.02; 2.15 (6 H, Ac)
23β	6.02	3.44	5.25	4.52	5.08	3.28	2.86	2.05; 2.08 (6 H, Ac)
25	5.27	5.08	3.85	4.65–4.78	4.65–4.78	2.97	3.05	3.56 (3 H, OMe) 2.10; 2.18 (6 H, Ac)
26α	5.45	5.31	4.24	5.03	4.97	3.14	3.21	3.61 (3 H, OMe)
26β	5.30	5.18	4.14	4.93	4.83	3.31	3.11	3.59 (3 H, OMe)
32α	6.73	5.36	4.32	5.09	4.97	3.28	3.22	2.08 (3 H, Ac)
35	5.80	5.58	4.30	5.20	4.96	3.80	3.15	
36 [a]	5.62	4.05	3.38	4.10	4.44	3.18	2.96	6.00–6.08 (2 H, OH-2,4)
37	5.84	5.58	4.32	5.20	4.97	3.78	3.15	
38 [a]	5.69	4.08	3.40	4.13	4.46	3.17	2.98	6.03–6.13 (2 H, OH-2,4)
39	6.90	5.66	4.18	6.02	5.42	2.95–3.10	2.95–3.10	1.94; 1.94; 2.00 (9 H, Ac)
40	6.51	3.53	5.42	4.86	5.06	2.92	2.85	2.01; 2.09 (6 H, Ac)
42	5.88	4.12	4.08	5.35	4.92	3.81	3.18	
43	5.94	3.72	5.51	4.87	5.15	2.80–3.00	2.80–3.00	2.18 (3 H, Ac)
44 [a]	5.83	3.35	4.06	4.30	3.74	2.64	2.60	5.78; 5.35 (2 H, OH-3,5)
45	5.98	3.70	5.52	4.87	5.15	2.85–3.00	2.85–3.00	2.13 (3 H, Ac)
46 [a]	5.89	3.36	4.07	4.32	3.77	2.68	2.62	5.80; 5.36 (2 H, OH-3,5)

Table 1 (*Continued*)

	Coupling constants (Hz)							
	$^3J_{1,2}$	$^3J_{2,3}$	$^3J_{3,4}$	$^3J_{4,5}$	$^3J_{5,6a}$	$^3J_{5,6b}$	$^2J_{6a,6b}$	Others
8	3.4	4.6	8.3	6.6	5.9	3.7	11.2	
9	3.6	nd	8.0	5.4	8.5	3.9	14.4	
10	3.2	0	4.4	3.2	10.3	6.6	10.3	
11	3.4	0	3.9	2.9	(10.0)	(7.1)	~10.0	
12α	4.4	3.4	5.6	3.9	(8.8)	(7.1)	nd	
12β	~0	~0	5.0	nd	nd	nd	nd	
12β [b]	~0	~0	5.6	nd	10.0	6.4	10.0	
13α	4.1	1.2	4.9	nd	(10.2)	(6.8)	10.2	
13β	~0	~0	4.6	nd	9.8	6.6	9.8	
14α	4.2	1.7	4.9	nd	nd	nd	nd	
14β	~0	~0	4.6	nd	10.2	6.5	9.8	
16 [a]	3.3	~1	4.6	~4	(9.7)	(6.6)	~10	$J_{2,OH}$ 5.4; $J_{5,OH}$ 6.6
17 [a]	~0	~0	4.6	3.5	10.0	6.3	10.0	$J_{2,OH}$ 4.2; $J_{5,OH}$ 5.9
18 [a]	~0	~0	4.6	3.5	10.0	6.4	10.0	
19 [a]	~0	~0	4.6	3.4	10.0	6.3	9.8	$J_{2,OH}$ 4.2; $J_{5,OH}$ 5.9
20 [a]	1.5	~0	4.9	3.4	10.1	6.3	9.5	$J_{2,OH}$ 4.2; $J_{5,OH}$ 6
21 [a]	1.2	~0	4.6	3.4	10.0	6.1	9.5	$J_{2,OH}$ 3.9; $J_{5,OH}$ 5.8
22 [a]	~0	~0	4.6	3.7	(9.8)	(6.6)	~9.8	
23α	~0	1.0	~0	~0	(8.3)	(6.1)	nd	
23β	3.9	0.7	~0	~0	10.3	5.8	12.5	$J_{1,3}$ 1.0
25	2.7	3.6	3.7	nd	~0	4.4	12.5	
26α	2.4	3.6	3.7	3.0	~0	4.4	12.5	
26β	~3.0	3.5	~3.5	~3.5	~0	4.9	11.7	
32α	2.9	3.4	4.2	2.1	~0	4.4	12.6	$J_{2,4}$ 0.8; $J_{3,5}$ 1.0
35	~0	2.7	4.5	3.2	~0	4.4	12.2	$J_{2,4}$ 0.8
36 [a]	1.4	2.5	4.2	2.9	~0	3.9	11.7	
37	~0	2.7	4.1	3.2	~0	4.4	12.2	
38 [a]	1.2	~3.0	~4.5	~3.0	~0	3.9	11.7	
39	2.7	9.5	4.4	3.4	(8.4)	(8.4)	nd	
40	~0	~0	~0	~0	9.8	6.1	12.6	
42	~0	1.5	4.6	2.2	~0	4.4	12.0	$J_{2,4}$ 0.8
43	~0	~0	~0	~0	(7.8)	(7.8)	nd	
44 [a]	~0	~0	~0	~0	(9.3)	(6.1)	12.7	$J_{3,OH}$ 2.2; $J_{5,OH}$ 5.2
45	~0	~0	~0	~0	(7.7)	(7.7)	nd	$J_{2,4}$ 0.8
46 [a]	~0	~0	~0	~0	(9.3)	(5.9)	12.7	$J_{3,OH}$ 2,4; $J_{5,OH}$ 4.8

[a] In Me_2SO-d_6.

[b] In benzene-d_6; nd, not determined; values in parentheses, not first-order spin systems.

Table 2
Selected ^{13}C NMR data for solutions in $CDCl_3$

Compound	Chemical shift δ						
	C-1	C-2	C-3	C-4	C-5	C-6	Others
8	104.0	69.7 [a]	74.5 [a]	77.3 [a]	77.3 [a]	67.4	113.9; 26.5; 26.6 (CMe_2); 38.9 (Ms); 169.9; 20.6 (Ac); 21.5 (Ts-Me)
9	104.0	70.5 [a]	77.0 [a]	77.2 [a]	77.3 [a]	29.6	113.8; 26.5; 26.6 ($iCMe_2$); 39.0 (Ms); 170.0; 20.7 (OAc); 194.4; 30.4 (SAc)
10	106.4	77.3 [a]	49.6	84.6 [a]	88.0 [a]	34.1	113.1; 26.8; 27.3 (CMe_2)
11	106.5	76.2 [a]	49.3	82.1 [a]	86.5 [a]	30.1	112.3; 26.3; 26.8 (CMe_2); 169.8; 20.4 (Ac)
12α [d]	95.7	80.4	48.3	81.5	76.0	31.0	169.0; 169.4; 170.2; 20.4; 20.7; 20.8 (Ac)
12β	101.1	83.1	48.0	83.1	76.4	30.8	169.1; 169.2; 170.1; 20.6; 20.7; 20.9 (Ac)
12β [b,c]	102.0	84.6	49.2	85.6	77.8	32.0	169.5; 169.7; 170.5; 20.8; 20.9; 21.1 (Ac)
13α	89.5	81.2 [a]	49.6	82.2 [a]	76.6	31.0	169.4; 170.2; 20.5; 20.8 (Ac)
13β	91.9	84.6 [a]	49.1	85.0 [a]	76.1	31.6	169.3; 170.1; 20.6; 20.7 (Ac)
14α	89.3	81.3 [a]	49.7	82.3 [a]	76.7	31.1	169.4; 170.2; 20.5; 20.9 (Ac)
23α	92.5	48.7	78.5	84.3	72.3	25.3	169.7; 169.8; 20.8; 20.9 (Ac)
23β	89.8	47.4	79.5	84.2	72.0	27.4	169.7; 169.8; 20.8; 20.9 (Ac)
25	95.5	69.5 [a]	40.5	73.2 [a]	74.2 [a]	29.2	57.8, q (OMe) 169.8; 170.7; 20.8; 21.0 (Ac)
26α	95.6	71.3 [a]	40.5	74.2 [a]	74.5 [a]	29.2	57.8, q (OMe)
26β	99.8	75.3 [a]	39.2	72.7 [a]	73.9 [a]	31.1	56.8, q (OMe)
32α [d]	86.9	70.8	40.2	74.2	75.3	28.7	168.3; 20.6 (Ac)
35	82.8	76.5 [a]	39.4	73.7	74.6 [a]	30.6	
36 [b]	85.4	76.2	43.3	73.7	76.2	31.8	
37	82.5	76.4 [a]	39.4	73.7	74.6 [a]	30.6	
38 [b]	85.2	76.3 [a]	43.2	73.7	76.0 [a]	31.8	
39	86.9	75.0 [a]	44.4	73.7	72.3 [a]	29.4	168.0; 168.2; 169.9; 20.4; 20.5; 20.5 (Ac)
40 [d]	100.6	46.2	79.0	84.3	72.0	25.4	169.1; 169.7;20.8; 20.9 (Ac);
42 [d]	85.8	52.6	42.7	73.1	74.1	31.3	
43	92.8	48.7	79.4	84.3	72.3	25.3	
44 [b]	91.4	50.4	77.1	90.0	70.5	27.7	
45	92.7	48.7	79.6	84.4	72.4	25.4	
46 [b]	91.1	50.4	77.1	89.9	70.5	27.7	

[a] Arbitrary assignment.
[b] In Me_2SO-d_6.
[c] In benzene-d_6
[d] A heterocorrelation spectrum was recorded.

unambiguously established by NMR spectroscopy. From ^1H NMR double resonance experiments it was evident that in **23α** and **23β** the thioanhydro bridge was shifted from C-3 to C-2 and an acetoxy group was attached to C-3 (H-2 = 5.46 → 3.56 ppm, H-3 = 3.79 → 5.14 ppm, for the corresponding ^{13}C NMR data see Table 2). Further NMR data (Tables 1–4), which proved the change in configuration, will be discussed in detail later, together with those of the 3-*O*-(4-nitrobenzoyl) analogue **45**.

The formation of **23** from **14** can be explained via a transannular participation reaction of the sulfur atom of the 3,6-thioanhydro bridge, which attacks C-2 while simultaneously the carbonyl group of the 2-*O*-acetyl group attacks C-3 (**15**). This will result in the formation of the 2,6-thioanhydro derivatives with migration of the involved acetoxy group from C-2 to C-3. As a consequence, the chirality of both C-2 and C-3 will be inverted, consequently the configuration of the furanosides changes from D-gluco to D-altro (Scheme 2).

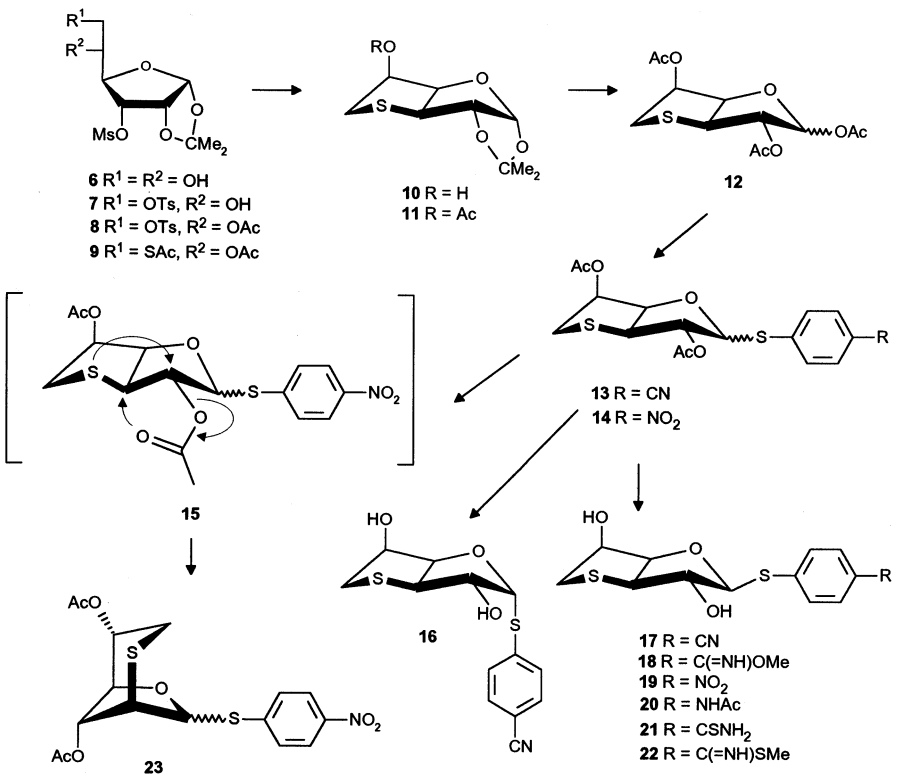
Zemplén deacetylation of **13α** afforded **16**, whereas **13β** gave under the same conditions besides **17** (58%) the corresponding 4-(imino)(methoxy)phenyl glycoside (**18**) (15%). The 4′-cyano group of **17** could be converted by standard methods [9] into the 4′-aminothiocarbonyl derivative **21**, which on methylation afforded **22**. These transformations, by which the antithrombotic activity of **1** could be in-

creased [9], had an opposite effect in the present case (see Table 5).

Deacetylation of the 4-nitrophenyl analogue **14β** gave **19**, the nitro group of which was reduced with sodium borohydride to give after acetylation and selective *O*-deacetylation the corresponding 4′-acetamidophenyl thioglycoside **20**.

Table 3
NMR–NOE difference data

Compound	Saturated signal	Intensity enhancement (%)							
		H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	Others
25	H-1		8.2				5.0		3.56 ppm 3.4%
32α	H-1		10.7				6.0		
35	H-1		4.2						7.60 ppm 4.5%
37	H-1		4.5						7.68 ppm 4.8%
38	H-1		5.0						7.64 ppm 7.0%
39	H-3	2.2	2.4		9.9	4.0			
40	H-1		4.3				4.5		
	H-2	3.3		4.0					
	H-3		3.5		2.5	6.4			
	H-4			2.4		2.0			
42	H-1		6.0						7.58 ppm 9.0%
43	H-1		4.1				4.1		7.60 ppm 7.0%
	H-2	4.2		5.6					
	H-3		5.5		3.2	**7.7**			
	H-4			3.3		3.9			



Scheme 2.

Table 4
Long-range heteronuclear correlations determined by selective INEPT measurements [a]

Compound	Pulsed ^{1}H signal	Signals that appeared in the selective INEPT spectrum						
		C-1	C-2	C-3	C-4	C-5	C-6	Others
32α	H-1		+					168.3
	H-2			+	+			163.7
	H-4		+	+				164.2
	H-5	+		+	+			
35	H-1		+	+		+		143.9
39	H-1							168.0; 168.2
	H-2			+				163.4
	H-4						+	163.5
	H-5				+			169.9
40	H-1			+	+			169.1
	H-2	+		+	+		+	
	H-3	+			+			163.4
	H-4	+	+	+			+	
	H-5					+		169.7
42	H-1		+	+		+		143.7
	H-2	+		+	+			142.6
	H-3	+			+	+		
	H-4		+	+				164.1
	H-5	+		+				
43	H-1		+	+	+			142.6
	H-3	+			+			163.3

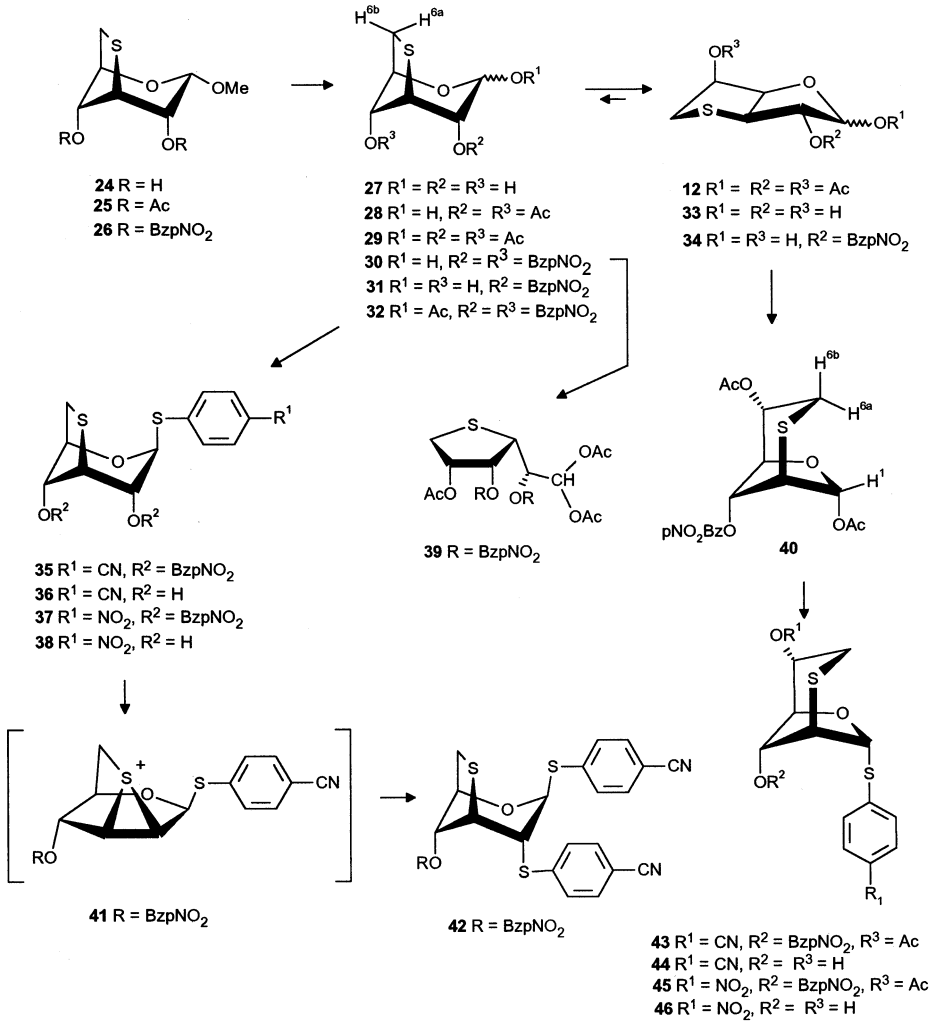
[a] The pulse sequence was optimized for the 6 Hz heteronuclear coupling constant.

Table 5
Oral antithrombotic activity of 4-substituted phenyl 3,6-anhydro-1,6-dithio-D-glucofuranosides and pyranosides, as well as 2,6-anhydro-1,6-dithio-α-D-altrofuranosides in rats using Pescador's model [15]

Compound	**Ref** [a]	**17**	**19**	**20**	**21**	**22**	**36**	**38**	**44**	**46**
C-4′–R	CN	CN	NO_2	NHAc	$CSNH_2$	CNHSMe	CN	NO_2	CN	NO_2
Inhibition [b] (%)	50	51	26	27	13	38	35	17	39	24

[a] 4-Cyanophenyl 2,6-anhydro-1,2-dithio-β-D-mannopyranoside [5] was chosen as reference compound.
[b] Inhibition % at an oral dose of 2 mg/kg.

Synthesis of the pyranosides.—For their synthesis, the triacetate **29** was needed as donor. The corresponding methyl pyranoside **24** (Scheme 3), as well as its hydrolysis with aqueous trifluoroacetic acid has already been described in the literature [10]. Nevertheless, the free sugar (**27**) was not characterised but reduced immediately into the corresponding thioanhydro-hexitol. When we converted this free sugar into its peracetate, instead of **29**, its furanoside **12** was obtained. That means that similarly to the oxygen analogues [11], the thioanhydro pyranose **27** ⇆ furanose **33** equilibrium is completely shifted towards the latter. In order to avoid this isomerisation, the free hydroxyl groups of **24** were blocked by acetylation, but hydrolysis of the glycosidic bond of the resulting diacetate **25** was also accompanied by isomerisation, affording, after acetylation, exclusively **12**. That means that the acetyl group at O-4 could not withstand the influence of the aqueous trifluoroacetic acid. As the stability of ester groups towards acids can be increased by applying electron-withdrawing substituents [12], the methyl pyranoside was converted into the corresponding 2,4-di-*O*-(4-nitrobenzoate) **26**. According to thin-layer chromatography (TLC), a longer reaction time (24 h) was needed for the complete hydrolysis of the glycosidic bond of **26** compared with the acetate **25** (4 h), and a mixture of several compo-



Scheme 3.

nents was obtained from which after acetylation three compounds, the rearranged 2,6-thioanhydro-altrofuranose derivative **40**, the monocyclic 3,6-thioanhydro-D-glucose derivative **39**, as well as the 1-acetate **32α** of the needed pyranose donor molecule were isolated by column chromatography in a ratio of 2:1:4. The formation of the triacetate **39** means that the hemiacetal ring of the intermediate **30** is not stable and is at least partially opened leading to the aldehyde-hydrate, which is then acetylated. The formation of **40** can be explained in the following way. During the hydrolysis of the glycosidic bond of **26**, the 4-*O*-(4-nitrobenzoyl) group of the intermediate **30** is partially split off affording **31**, which rearranges to the furanose derivative **34**. This latter undergoes a further rearrangement via an attack of the 2-*O*-(4-nitrobenzoyl) group on C-3 with a simultaneous shift of the thioanhydro bridge from C-3 to C-2, as suggested for the formation of **23**, yielding after acetylation **40**. The location of the *O*-(4-nitrobenzoyl) group at C-3 of **40** was proven by NMR spectroscopy using HETCOR, as well as selective INEPT and NOE measurements (Tables 1–4). The latter also proved the α-position of the 1-*O*-acetyl group, as a strong NOE intensity enhancement was detected on H-6_{ax} on irradiating H-1. The reaction time of the hydrolysis of **26** could be shortened to 8 h without influencing the ratio or the yield of **32α** (38%), **39** (11%) and **40** (23%), but in addition some of the β anomer **26β** (12%) of the starting methyl glycoside could be separated. That means that the hydrolysis of the glycosidic bond of **26** is accompanied by an anomerisation process, and the corresponding

β anomer is less prone to hydrolysis. The chirality of C-1 in **26β** as well as in **32α** could be established unambiguously by NMR spectroscopy, as in the former a long-range coupling between H-1 and H-3 ($^4J_{1,3}$ 1 Hz) proved the equatorial arrangement of these protons, while in **32α** a strong NOE effect (6.0%) was detected at H-6a on irradiating H-1.

When the pyranose acetate **32α** was used as donor for the glycosidation of 4-cyanobenzenethiol in the presence of trimethylsilyl triflate as promoter, the corresponding β-thioglycoside **35** was formed in a very low yield (15.5%) and a further product **42** (35.7%), containing a second 4-cyanophenylthio moiety attached to C-2 could be separated by column chromatography. The structure of **42** was evident comparing its NMR data with that of **35**, as in the ^{13}C spectra the signal of C-2 was shifted from 76.5 to 52.6 ppm, due to the change of the C–O bond into a C–S one. As in the ^1H spectra of both **35** and **42**, a long-range coupling between H-2 and H-4 could be detected ($^4J_{2,4}$ 0.8 Hz), these protons are diequatorially arranged, consequently both compounds possess the D-*gluco* configuration. The retention of the chirality at C-2 in **42** can be explained via a cyclic sulfonium ion intermediate **41**, which can be formed from **35** via elimination of the activated 2-*O*-(4-nitrobenzoyl) group with inversion of configuration. The so formed strained sulfonium ion **41** can be attacked from the α-side only, leading to **42** with retention of the original configuration at C-2. An attack of the thiolate moiety at C-3 of **41** is less favoured because of the cis relation with the bulky substituent at C-4 (Scheme 3). As the yield of **35** could not be increased by altering the reaction conditions, boron trifluoride etherate was chosen as promoter, which is a weaker Lewis acid than trimethylsilyl triflate and should therefore not activate the 2-*O*-(4-nitrobenzoyl) group. According to the literature [13], this promoter afforded the corresponding *O*-glucoside in low yield only when 4-cyano phenol was the acceptor because of a Ritter reaction of the cyano group. In our case, however, the reaction of acetate **32α** with 4-cyanobenzenethiol yielded the thioglycoside **35** with a yield of 47%, and no products resulting from a Ritter reaction [14] could be detected. Deacylation of **35** according to Zemplén afforded **36**. When 4-nitrobenzenethiol was glycosylated with **32α** using boron trifluoride etherate as promoter, the corresponding β-thioglycoside **37** was obtained in 57% yield and afforded after deacylation **38**. It should be mentioned that, according to NMR spectroscopy, the bulky aglycon is forced in a quasi equatorial position, due to the presence of the 3,6-thioanhydro bridge. As a consequence, the dihedral angle between H-1 and H-2 approaches 90%, resulting in the observed small coupling constant ($J_{1,2}$ 1.2 Hz).

Condensation of the altrofuranose 1-acetate **40** with 4-cyano- and 4-nitrobenzenethiol in the presence of boron trifluoride etherate afforded the corresponding α anomers **43** and **45** in high yield (85 and 87%), which gave **44** and **46**, respectively, on deacetylation. The exclusive formation of the α anomers is not surprising, as the presence of the space-demanding 2,6-thioanhydro bridge prevents the approach of the bulky aglycon from the β-side. The structure of these 2,6-thioanhydro derivatives was established by NMR spectroscopy comparing the data of **43**, **45** and the diacetate anomers **23α** and **23β** with those of the corresponding 3,6-thioanhydro derivatives **35** and **37**. The shift of the thioether bridge from C-3 to C-2 is evident from both the ^1H and the ^{13}C spectra (Tables 1 and 2). The altro configuration of the skeleton was proven by the long-range ($^4J_{2,4}$ 0.8 Hz) coupling existing between H-2 and H-4 and the NOE difference measurements, as in **43** the intensity of H-5 was enhanced by 7.7% on irradiating H-3 (Table 3).

Biological results.—The oral antithrombotic activity of **17**, **19**, **20**, **21**, **22**, **36**, **38**, **44** and **46** was determined on rats using Pescador's model [15] and 4-cyanophenyl 2,6-anhydro-1,2-dithio-β-D-mannopyranoside (**3**-type compound) [5] as reference. All compounds were administered orally 3 h before ligation. From the data listed in Table 5, it can be seen that while **17** was as active as the reference compound, all other derivatives possessed a less pronounced biological activity. It is worthwhile mentioning that the 4-cyano-

phenyl thioglycosides (**17**, **36** and **44**) were about twice as active as the corresponding 4-nitrophenyl derivatives (**19**, **38** and **46**, respectively).

3. Experimental

General methods.—Organic solns were dried over $MgSO_4$ and concd under diminished pressure at or below 40 °C. TLC: E. Merck precoated Silica Gel 60 F_{254} plates, with EtOAc (A), EtOAc–hexane mixtures (B, 1:1; C, 1:2; D, 1:3, E, 1:4, F, 2:1), EtOAc–EtOH mixture (G, 19:1), and toluene–MeOH mixture (H, 4:1); detection by spraying the plates with a 0.02 M soln of I_2 and a 0.30 M soln of KI in 10% aq H_2SO_4 soln, followed by heating at ca. 200 °C. For column chromatography, Kieselgel 60 was used. Melting points are uncorrected. Optical rotations were determined on 1.0% solns in $CHCl_3$ at 20 °C unless stated otherwise. NMR spectra were recorded with a Bruker AC 250 at 250 MHz (^1H) and 62.9 MHz (^{13}C) or with a Varian XL-400 spectrometer MHz (^1H) and 100 MHz (^{13}C) or for solns in $CDCl_3$ (internal Me_4Si) unless stated otherwise. Multiplicities of the ^{13}C NMR spectra were obtained from DEPT experiments. The assignment of the protons were based on homonuclear decoupling. Connectivities between identified protons and protonated carbons were observed by means of HETCOR experiments. The ratio of α:β anomeric mixtures was determined by ^1H NMR.

1,2-O-Isopropylidene-3-O-methanesulfonyl-α-D-allofuranose (**6**).—To a soln of 1,2:5,6-di-*O*-isopropylidene-3-*O*-mesyl-D-allofuranose [6] (24 g) in MeOH (240 mL), 1 M HCl (24 mL) was added at 50 °C. The mixture was kept at 50 °C for 30 min and was neutralized after cooling with solid $NaHCO_3$. The residue obtained on concentration was dissolved in acetone, filtered, and Silica Gel 60 (100 g) was added to the filtrate. The slurry was concd to dryness, and the residue was washed with EtOAc to yield, after concentration, **6** (18 g, 85.7%) as a syrup. $[\alpha]_D$ +81°; Lit. [7]: $[\alpha]_D$ +84° (*c* 0.28, $CHCl_3$).

5-O-Acetyl-1,2-O-isopropylidene-3-O-methanesulfonyl-6-O-p-toluenesulfonyl-α-D-allofuranose (**8**).—To a stirred soln of **6** (14.8 g, 50 mmol) in pyridine (150 mL), TsCl (11.4 g, 60 mmol), and after 1 h, Ac_2O (15 mL) were added at 0 °C. The mixture was kept at 20 °C for 8 h and was then processed the usual way. The residue, obtained on concentration of the CH_2Cl_2 soln (22 g, 89%) was pure enough for subsequent reactions. Pure **8** could be obtained by column chromatography (solvent B); $[\alpha]_D$ +60°; R_f 0.5 (solvent B); Anal. Calcd for $C_{19}H_{26}O_{11}S_2$: C, 46.15; H, 5.30; S, 12.97. Found: C, 46.02; H, 5.44; S, 12.83.

5-O-Acetyl-6-S-acetyl-1,2-O-isopropylidene-3-O-methanesulfonyl-6-thio-α-D-allofuranose (**9**).—A stirred soln of crude **8** (22 g) and KSAc (5.3 g) in DMF (100 mL) was heated at 100 °C for 1 h. The residue, obtained on concentration was dissolved in CH_2Cl_2, washed with water, dried, filtered over charcoal and concd. The residue was dissolved in ether (50 mL) and hexane (200 mL) was added gradually when crystallisation took place. The precipitate was filtered and washed with hexane to give **9** (16 g, 90%); mp 132–134 °C; $[\alpha]_D$ +121°; R_f 0.6 (solvent B); Anal. Calcd for $C_{14}H_{22}O_9S_2$: C, 42.20; H, 5.57; S, 16.09. Found: C, 42.22; H, 5.54; S, 15.98.

3,6-Anhydro-1,2-O-isopropylidene-3-thio-α-D-glucofuranose (**10**).—To a stirred soln of **9** (8 g, 20 mmol) in CH_2Cl_2 (80 mL) and MeOH (80 mL), 4.5 M methanolic NaOMe (5 mL 22.5 mmol) was added at 20 °C. The mixture was concd after 30 min, the residue dissolved in CH_2Cl_2, washed with water and concd. The solid residue was filtered with ether–hexane to give **10** (3.6 g, 82%); mp 116–118 °C; $[\alpha]_D$ +71°; R_f 0.4 (solvent C); Anal. Calcd for $C_9H_{14}O_4S$: C, 49.53; H, 6.47; S, 14.69. Found: C, 49.48; H, 6.44; S, 14.55.

5-O-Acetyl-3,6-anhydro-1,2-O-isopropylidene-3-thio-α-D-glucofuranose (**11**).—Acetylation of **10** (4.4 g) with Ac_2O (5 mL) in pyridine (10 mL) afforded after usual processing and column chromatography (solvent E) **11** (4.8 g, 93%) as a syrup; $[\alpha]_D$ +107°; R_f 0.8 (solvent C); Anal. Calcd for $C_{11}H_{16}O_5S$: C, 50.76; H, 6.20; S, 12.32. Found: C, 50.52; H, 6.34; S, 12.14.

1,2,5-Tri-O-acetyl-3,6-anhydro-3-thio-D-glucofuranose (**12**).—(i) A soln of **10** (4.4 g) or **11** (5 g) in AcOH (16 mL) and 0.1 M HCl (16 mL) was kept at 100 °C for 10 min. The soln was cooled, then $NaHCO_3$ (0.6 g) was added gradually to neutralise the HCl and was then concd. The residue was dissolved in Ac_2O (15 mL), heated at 100 °C for 10 min to give after usual processing and column chromatography (solvent C) of the residue **12** (4.4 g, 72%) as a semi-solid residue, which according to NMR spectroscopy contained **12α** and **12β** in a ratio of ~1:2; R_f 0.3 (solvent C). Anal. Calcd for $C_{12}H_{16}O_7S$: C, 47.36; H, 5.30; S, 10.54. Found: C, 47.22; H, 5.44; S, 10.50.

(ii) A soln of **24** (0.5 g) or **25** (0.7 g) in CF_3COOH (7.5 mL) and water (2.5 mL) was kept at 20 °C for 5 h. The residue, obtained after concentration was dissolved in pyridine (5 mL) and Ac_2O (3 mL) was added. The mixture was kept at 20 °C for 24 h to give after usual processing and column chromatography (solvent C) **12** (0.55 g, 71%), which according to NMR spectroscopy was a 3:2 mixture of **12α** and **12β.**

On recrystallisation from ether (80 mL) pure **12α** (1.7 g, 27.8%) can be obtained; mp 109–111 °C; $[\alpha]_D$ +213°.

4-Cyanophenyl 2,5-di-O-acetyl-3,6-anhydro-1,3-dithio-D-glucofuranoside (**13**).—Under argon, to a stirred soln of **12** (0.5 g, 1.6 mmol) and 4-cyanobenzenethiol (0.43 g, 3.2 mmol) in dry 1,2-dichloroethane (20 mL), Me_3SiOTf (0.34 mL, 1.8 mmol) was added at −10 °C. After stirring at rt for 30 min, the reaction was quenched with Et_3N, concd and the residue submitted to column chromatography (solvent C). Concentration of the first fraction gave **13α** (50 mg, 8%) as a syrup; $[\alpha]_D$ +232° (*c* 0.6, $CHCl_3$); R_f 0.5 (solvent C); Anal. Calcd for $C_{17}H_{17}NO_5S_2$: C, 53.81; H, 4.52; N, 3.69; S, 16.90. Found: C, 53.75; H, 4.63; N, 3.61; S, 16.80.

Concentration of the second fraction gave **13β** (0.45 g, 72%) as a syrup; $[\alpha]_D$ +9° (*c* 0.5, $CHCl_3$); R_f 0.4 (solvent C); Calcd for $C_{17}H_{17}NO_5S_2$: C, 53.81; H, 4.52; N, 3.69; S, 16.90. Found: C, 53.89; H, 4.61; N, 3.57; S, 16.93.

4-Nitrophenyl 2,5-di-O-acetyl-3,6-anhydro-1,3-dithio-D-glucofuranoside (**14**) *and 4-nitrophenyl 3,5-di-O-acetyl-2,6-anhydro-1,2-dithio-D-altrofuranoside* (**23**).—To a stirred soln of **12** (1.8 g, 5.9 mmol) and 4-nitrobenzenethiol (1.2 g, 7.7 mmol) in dry 1,2-dichloroethane (60 mL), $BF_3{\cdot}EtO_2$ (0.73 mL, 5.9 mmol) was added. The mixture was kept at rt for 24 h and then poured into an ice-cold 6% aq $NaHCO_3$ soln (100 mL). The separated organic layer was washed with water, 6% aq $NaHCO_3$ and concd. The residue was submitted to column chromatography (solvent C). Concentration of the first fraction gave, according to NMR, a 2:1 mixture of **14α** + **23α** (210 mg, 9%); R_f 0.5 (solvent C).

Concentration of the second fraction gave a 2:3 mixture of **23α** + **23β** (100 mg, 4%); R_f 0.45 (solvent C).

Concentration of the third fraction gave **14β** (1.6 g, 68%); $[\alpha]_D$ −43 (*c* 0.34, $CHCl_3$); R_f 0.4 (solvent C); Anal. Calcd for $C_{16}H_{17}NO_7S_2$: C, 48.11; H, 4.29; N, 3.51; S, 16.05. Found: C, 48.22; H, 4.33; N, 3.59; S, 16.11.

4-Cyanophenyl 3,6-anhydro-1,3-dithio-α-D-glucofuranoside (**16**).—Deacetylation of **13α** (240 mg, 0.6 mmol) with 1 M NaOMe (0.1 mL) in MeOH (10 mL) yielded, after neutralization with solid CO_2 and column chromatography (solvent H), **16** (150 mg, 80%): mp 165–169 °C (ether); $[\alpha]_D$ +315° (*c* 0.5, MeOH); R_f 0.4 (solvent H); Anal. Calcd for $C_{13}H_{13}NO_3S_2$: C, 52.86; H, 4.44; N, 4.74; S, 21.71. Found: C, 52.91; H, 4.33; N, 4.82; S, 21.79.

4-Cyanophenyl 3,6-anhydro-1,3-dithio-β-D-glucofuranoside (**17**) *and 4-[(imino)(methoxy)-methyl]phenyl 3,6-anhydro-1,3-dithio-β-D-glucofuranoside* (**18**).—Deacetylation of **13β** (300 mg, 0.8 mmol) with 1 M NaOMe (0.1 mL) in MeOH (15 mL) yielded, after neutralization with solid CO_2 and column chromatography (solvent H), **17** (135 mg, 58%): mp 192–194 °C (ether); $[\alpha]_D$ −138° (*c* 0.5, MeOH); R_f 0.4 (solvent H); Anal. Calcd for $C_{13}H_{13}NO_3S_2$: C, 52.86; H, 4.44; N, 4.74; S, 21.71. Found: C, 52.81; H, 4.38; N, 4.72; S, 21.65.

Concentration of the second fraction gave **18** (40 mg, 15%): mp 148–153 °C (ether); $[\alpha]_D$ −104° (*c* 0.35, MeOH); R_f 0.3 (solvent H); Calcd for $C_{14}H_{17}NO_4S_2$: C, 51.36; H, 5.23; N, 4.28; S, 19.58. Found: C, 51.41; H, 5.28; N, 4.33; S, 19.65.

4-Nitrophenyl 3,6-anhydro-1,3-dithio-β-D-glucofuranoside (**19**).—Deacetylation of **14β** (1.6 g, 4 mmol) with 1 M NaOMe (0.2 mL) in MeOH (30 mL) yielded, after neutralization with solid CO_2 and column chromatography (solvent H), **19** (0.95 g, 75%): mp 188–190 °C (MeOH); $[\alpha]_D$ −193° (*c* 0.5, MeOH); R_f 0.3 (solvent H); Anal. Calcd for $C_{12}H_{13}NO_5S_2$: C, 45.70; H, 4.16; N, 4.44; S, 20.33. Found: C, 45.79; H, 4.28; N, 4.42; S, 20.40.

4-Acetamidophenyl 3,6-anhydro-1,3-dithio-β-D-glucofuranoside (**20**).—To a stirred soln of **19** (0.44 g, 1.4 mmol) in EtOH (60 mL), $NaBH_4$ (330 mg) and $NiCl_2 \cdot 6\ H_2O$ (30 mg) were added. After 30 min at rt, the mixture was neutralized with 4% aq HCl, filtered and washed with EtOH. The filtrate was concd, the residue was dissolved in pyridine (10 mL) and Ac_2O (10 mL) was added. The mixture was kept at rt overnight and then processed in the usual way. The residue was dissolved in MeOH (30 mL) and methanolic 3 M NaOMe (0.1 mL) was added. After 1 h at rt the mixture was neutralized with solid CO_2 and concd. The residue was submitted to column chromatography (solvent G) to yield **20** (300 mg, 66%): mp 178–183 °C (ether); $[\alpha]_D$ −96° (*c* 0.4, MeOH); R_f 0.5 (solvent G); Anal. Calcd for $C_{14}H_{17}NO_4S_2$: C, 51.36; H, 5.23; N, 4.28; S, 19.58. Found: C, 51.40; H, 5.29; N, 4.22; S, 19.55.

4-(Aminothiocarbonyl)phenyl 3,6-anhydro-1,3-dithio-β-D-glucofuranoside (**21**).—A stirred soln of **17** (0.75 g, 2.5 mmol) in dry pyridine (20 mL) and Et_3N (20 mL) was saturated with a slow stream of dry H_2S for 1 h. The mixture was kept at rt overnight and was then concd. The residue was recrystallized from MeOH to yield **21** (0.79 g, 94%): mp 179–183 °C (MeOH); $[\alpha]_D$ −149° (*c* 0.4, Me_2SO); R_f 0.4 (solvent A); ^1H NMR: Anal. Calcd for $C_{13}H_{15}NO_3S_3$: C, 47.40; H, 4.59; N, 4.25; S, 29.19. Found: C, 47.48; H, 4.48; N, 4.22; S, 29.25.

4-[(Imino)(methylthio)methyl]phenyl 3,6-anhydro-1,3-dithio-β-D-glucofuranoside hydroiodide (**22**).—To a stirred soln of **21** (0.52 g, 1.6 mmol) in dry acetone (50 mL), MeI (0.7 mL) was added and the mixture was refluxed for 2 h. After cooling to rt, the precipitated crystals were filtered off and washed with ether to give **22** (0.55 g, 74%): mp 110–114 °C (ether); $[\alpha]_D$ −85° (*c* 0.5, Me_2SO); R_f 0.3 (solvent A); Anal. Calcd for $C_{14}H_{18}INO_3S_3$: C, 35.67; H, 3.85; I, 26.92; N, 2.97; S, 20.40. Found: C, 35.72; H, 3.91; I, 26.81; N, 2.90; S, 20.47.

Methyl 3,6-anhydro-3-thio-α-D-glucopyranoside (**24**).—To a soln of **25** (2.8 g) in CH_2Cl_2 (20 mL) and MeOH (10 mL), 3 M methanolic NaOMe (0.1 mL) was added. After 20 h at 20 °C the mixture was neutralized with solid CO_2 to give after concentration and column chromatography (solvent B), **24** (1.4 g, 77%); mp 81–83 °C, lit. mp 83–84 °C [10]; R_f 0.3 (solvent B).

Methyl 2,4-di-O-acetyl-3,6-anhydro-3-thio-α-D-glucopyranoside (**25**).—Under argon, 3 M methanolic NaOMe (34 mL) was added to a stirred soln of crude methyl-6-*S*-acetyl-2,4-di-*O*-benzoyl-3-*O*-methanesulfonyl-6-thio-α-D-glucopyranoside [10] (38.7 g) in MeOH (580 mL) at 20 °C. The mixture was neutralised with solid CO_2 after 24 h and the residue obtained after concentration was re-evaporated with toluene (2 × 50 mL). The residue was dissolved in pyridine (150 mL), and Ac_2O (85 mL) was added at 20 °C. After 20 h, the mixture was processed in the usual way to give, after concentration and column chromatography (solvent B), **25** (13.7 g, 69%) as a solid residue; mp 106–109 °C (ether–hexane); $[\alpha]_D$ +64°; R_f 0.4 (solvent B); Anal. Calcd for $C_{11}H_{16}O_6S$: C, 47.82; H, 5.84; S, 11.60. Found: C, 47.94; H, 5.99; S, 11.52.

Methyl 3,6-anhydro-2,4-di-O-(4-nitrobenzoyl)-3-thio-α-D-glucopyranoside (**26**).—To a soln of **24** (1.92 g, 10 mmol) in pyridine (30 mL), 4-nitrobenzoyl chloride (5.6 g, 30 mmol) was added and the slurry was stirred at 20 °C for 24 h. Thereafter water (1.5 mL) was added and after 30 min the mixture was poured into water, extracted with CH_2Cl_2 and processed in the usual way. The residue obtained on concentration was filtered with Et_2O to give **26** (4.6 g, 94%); mp 199–202 °C (acetone–hexane); $[\alpha]_D$ +25°; R_f 0.6 (solvent B); Anal. Calcd for $C_{21}H_{18}N_2O_{10}S$: C, 51.43; H, 3.70; N, 5.71; S, 6.54. Found: C, 51.40; H, 3.76; N, 5.67; S, 6.52.

Hydrolysis of **26** *with aq* CF_3COOH.—A soln of **26** (980 mg, 1 mmol) in CF_3COOH (10 mL) and water (2 mL) was kept at 25 °C for 8

h. Thereafter toluene (2 × 5 mL) was evaporated from the residue obtained on concentration. The residue was dissolved in pyridine (10 mL) and Ac_2O (6 mL) was added at 20 °C. The mixture was processed after 3 h in the usual way and the residue submitted to column chromatography (solvent C). The fractions having R_f 0.6 gave on concentration 1,5-di-*O*-acetyl-2,6-anhydro-3-*O*-(4-nitrobenzoyl)-2-thio-α-D-altrofuranose (**40**) (190 mg, 23%); mp 182–184 °C (Et_2O); $[\alpha]_D$ +63°; Anal. Calcd for $C_{17}H_{17}NO_9S$: C, 49.63; H, 4.17; N, 3.40; S, 7.79. Found: C, 49.53; H, 4.15; N, 4.11; S, 7.66.

The fractions having R_f 0.5 gave on concentration methyl 3,6-anhydro-2,4-di-*O*-(4-nitrobenzoyl)-3-thio-β-D-glucopyranoside (**26β**) (120 mg, 12%); mp 153–157 °C (Et_2O); $[\alpha]_D$ −40 (*c* 0.5, $CHCl_3$); Anal. Calcd for $C_{21}H_{18}N_2O_{10}S$: C, 51.43; H, 3.70; N, 5.71; S, 6.54. Found: C, 51.38; H, 3.73; N, 5.65; S, 6.48.

The fractions having R_f 0.5 gave on concentration 3,6-anhydro-1,1,5-tri-*O*-acetyl-2,4-di-*O*-(4-nitrobenzoyl)-3-thio-D-glucose (**39**) (102 mg, 11%); mp 64–66 °C (Et_2O); $[\alpha]_D$ +116° (*c* 0.5, $CHCl_3$); Anal. Calcd for $C_{26}H_{24}N_2O_{14}S$: C, 50.32; H, 3.90; N, 4.51; S, 5.17. Found: C, 50.38; H, 3.73; N, 4.65; S, 5.02.

The fractions having R_f 0.3 gave on concentration 1-*O*-acetyl-3,6-anhydro-2,4-di-*O*-(4-nitrobenzoyl)-6-thio-α-D-glucopyranose (**32α**) (400 mg, 38.6%); mp 188–192 °C (Et_2O); $[\alpha]_D$ −23°; Anal. Calcd for $C_{22}H_{18}N_2O_{11}S$: C, 50.97; H, 3.50; N, 5.40; S, 6.18. Found: C, 51.09; H, 3.68; N, 5.23; S, 6.09.

4-Cyanophenyl 3,6-anhydro-2,4-di-O-*(4-nitrobenzoyl)-1,6-dithio-β-*D-*glucopyranoside* (**35**) *and 4-cyanophenyl 3,6-anhydro-2*-S-*(4-cyanophenyl)-4*-O-*(4-nitrobenzoyl)-1,2,6-trithio-β*-D-*glucopyranoside* (**42**).—(i) Under argon, to a stirred soln of **32α** (260 mg, 0.5 mmol) and 4-cyanobenzenethiol (140 mg, 1 mmol) in dry 1,2-dichloroethane (10 mL), Me_2SiOTf (0.12 mL, 0.6 mmol) was added at −10 °C. After stirring at −10 °C for 30 min, the reaction was quenched with Et_3N, concd and the residue submitted to column chromatography (solvent C). Concentration of the first fraction gave **42** (100 mg, 35.7%) as a syrup; $[\alpha]_D$ +277° (*c* 0.6, $CHCl_3$); R_f 0.55 (solvent C); Anal. Calcd for $C_{27}H_{19}N_3O_5S_3$: C, 57.74; H, 3.41; N, 7.48; S, 17.12. Found: C, 57.65; H, 3.53; N, 7.43; S, 16.89.

Concentration of the second fraction gave **35** (40 mg, 13.5%); mp 106–111 °C (Et_2O); $[\alpha]_D$ +18° (*c* 0.5, $CHCl_3$); R_f 0.5 (solvent C); Anal. Calcd for $C_{27}H_{19}N_3O_9S_2$: C, 54.63; H, 3.23; N, 7.08; S, 10.80. Found: C, 54.58; H, 3.36; N, 6.95; S, 10.65.

The ratio, as well as the yield of **36β** and **41** remained essentially unchanged when the amount of 4-cyanobenezenethiol was diminished to 0.6 mmol. At −20 °C the reaction was very sluggish, but gave no better results.

(ii) Under argon, to a stirred soln of **32α** (260 mg, 0.5 mmol) and 4-cyanobenzenethiol (100 g, 0.75 mmol) in dry 1,2-dichloroethane (10 mL), $BF_3{\cdot}Et_2O$ (0.1 mL, 0.8 mmol) was added at 20 °C. After stirring at rt for 1.5 h, the mixture was poured into water, and extracted with CH_2Cl_2. The combined organic extracts were washed with 5% aq $NaHCO_3$, dried, concd and the residue purified by column chromatography (solvent D) to give **35** (140 mg, 47.2%) identical with that described above.

4-Cyanophenyl 3,6-anhydro-1,3-dithio-β-D-*glucopyranoside* (**36**).—To a stirred slurry of **35** (1 g) in CH_2Cl_2 (10 mL) and MeOH (15 mL), 3 M methanolic NaOMe was added at 20 °C. After 1 h, the clear soln was neutralized with solid CO_2 and the residue obtained on concentration was purified by column chromatography (solvent C) to give **36** (330 mg, 66%) as a solid foam; mp 51–55 °C; $[\alpha]_D$ −147° (*c* 1, MeOH); R_f 0.45 (solvent B); Anal. Calcd for $C_{13}H_{13}NO_3S_2$: C, 52.86; H, 4.44; N, 4.74; S, 21.71. Found: C, 52.99; H, 4.62; N, 4.56; S, 21.38.

4-Nitrophenyl 3,6-anhydro-2,4-di-O-*(4-nitrobenzoyl)-1,3-dithio-β*-D-*glucopyranoside* (**37**).—Under argon, to a stirred soln of **32α** (520 mg, 1 mmol) and 4-nitrobenzenethiol (purity 80%) (250 mg, 1.25 mmol) in dry 1,2-dichloroethane (20 mL), $BF_3{\cdot}Et_2O$ (0.15 mL, 1.2 mmol) was added at 20 °C. After stirring at rt for 30 min, the mixture was poured into water, and extracted with CH_2Cl_2. The combined organic extracts were washed with 5% aq $NaHCO_3$, dried, concd and the

residue purified by column chromatography (solvent D) to give **37** (350 mg, 57.1%); mp 88–92 °C (Et_2O); $[\alpha]_D$ +32° (*c* 0.5, $CHCl_3$); R_f 0.5 (solvent C); Anal. Calcd for $C_{26}H_{19}N_3O_{11}S_2$: C, 50.89; H, 3.12; N, 6.85; S, 10.43. Found: C, 50.90; H, 3.16; N, 6.75; S, 10.35.

*4-Nitrophenyl 3,6-anhydro-1,3-dithio-β-*D*-glucopyranoside* (**38**).—A soln of **37** (0.6 g) was treated, as described for **36**, to give after column chromatography (solvent C), **38** (190 mg, 61%) as a solid foam; mp 63–66 °C; $[\alpha]_D$ −133° (*c* 1, MeOH); R_f 0.5 (solvent C); Anal. Calcd for $C_{12}H_{13}NO_5S_2$: C, 45.70; H, 4.16; N, 4.44; S, 20.33. Found: C, 45.76; H, 4.22; N, 4.36; S, 20.18.

*4-Cyanophenyl 5-*O*-acetyl-2,6-anhydro-3-*O*-(4-nitrobenzoyl)-2-thio-α-*D*-altrofuranoside* (**43**).—Under argon, to a stirred soln of **40** (0.97 g, 2 mmol) and 4-cyanobenzenethiol (280 mg, 2.07 mmol) in dry 1,2-dichloroethane (25 mL), $BF_3{\cdot}Et_2O$ (0.25 mL, 2 mmol) was added at 20 °C. After stirring at rt for 1 h, the mixture was poured into water, and extracted with CH_2Cl_2. The combined organic extracts were washed with 5% aq $NaHCO_3$, dried, concd and the residue purified by column chromatography (solvent C) to give **43** (1 g, 85%) as a syrup; $[\alpha]_D$ +162°; R_f 0.5 (solvent C); Anal. Calcd for $C_{22}H_{18}N_2O_7S_2$: C, 54.31; H, 3.73; N, 5.76; S, 13.18. Found: C, 54.22; H, 3.78; N, 5.68; S, 13.02.

*4-Cyanophenyl 2,6-anhydro-2-thio-α-*D*-altrofuranoside* (**44**).—A soln of **43** (970 mg, 2 mmol) was deacylated, as described for **36**, to give after column chromatography (solvent F), **44** (260 mg, 44%); mp 156–160 °C (Et_2O); $[\alpha]_D$ +311° (*c* 1, MeOH); R_f 0.4 (solvent F); Anal. Calcd for $C_{13}H_{13}NO_3S_2$: C, 52.86; H, 4.44; N, 4.74; S, 21.71. Found: C, 52.88; H, 4.50; N, 4.66; S, 21.62.

*4-Nitrophenyl 5-*O*-acetyl-2,6-anhydro-3-*O*-(4-nitrobenzoyl)-2-thio-α-*D*-altrofuranoside* (**45**).—Under argon, to a stirred soln of **40** (410 mg, 1 mmol) and 4-nitrobenzenethiol (purity 80%) (300 mg, 1.54 mmol) in dry 1,2-dichloroethane (20 mL), $BF_3{\cdot}Et_2O$ (0.2 mL, 1.5 mmol) was added at 20 °C and the mixture was processed as described for **37** to give **45** (440 mg, 87%); mp 83–86 °C (hexane); $[\alpha]_D$ +231°; R_f 0.4 (solvent C); Anal. Calcd for $C_{21}H_{18}N_2O_9S_2$: C, 49.80; H, 3.85; N, 5.53; S, 12.66. Found: C, 49.77; H, 3.82; N, 5.48; S, 12.51.

*4-Nitrophenyl 2,6-anhydro-2-thio-α-*D*-altrofuranoside* (**46**).—A soln of **45** (970 mg, 2 mmol) was deacylated, as described for **36**, to give after column chromatography (solvent F), **46** (210 mg, 64%); mp 204–208 °C (Et_2O); $[\alpha]_D$ +404° (*c* 0.5, MeOH); R_f 0.4 (solvent F); Anal. Calcd for $C_{12}H_{13}NO_5S_2$: C, 45.70; H, 4.16; N, 4.44; S, 20.33. Found: C, 45.62; H, 4.52; N, 4.37; S, 20.21.

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