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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-1,2dithio-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. © 2000 Elsevier Science Ltd. All rights reserved.

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

 $^{\rm *}$ Orally active antithrombotic thiogly cosides, Part XII. For Part XI, see Ref. [1].

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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

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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 overbridged 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 ($[\alpha]_D + 203^\circ$) 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 = $4.75 \rightarrow 3.75$; H- $6 = \sim 3.9 \rightarrow \sim 3.0$).

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 14 α and 14 β , 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 $14\alpha + 23\alpha$ (9%), a 2:3 mixture of $23\alpha + 23\beta$ (4%) and pure 14 β (68%), the structure of every component was



Table 1 Selected ¹H NMR data for solutions in CDCl₃

Compound Chemical shift δ

	H-1	H-2	H-3	H-4	H-5	Н-6а	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	(3 H, 13 HC) 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)
23a	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)
26a	5.45	5.31	4.24	5.03	4.97	3.14	3.21	3.61 (3 H, OMe)
26 β	5.30	5.18	4.14	4.93	4.83	3.31	3.11	3.59 (3 H, OMe)
32a	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)
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	Coupl	ing consta	nts (Hz)					
	$\overline{{}^{3}J_{1,2}}$	${}^{3}J_{2,3}$	${}^{3}J_{3,4}$	${}^{3}J_{4,5}$	${}^{3}J_{5,6a}$	${}^{3}J_{5,6b}$	${}^{2}J_{6a,6b}$	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	$J_{2,\text{OH}}$ 5.4; $J_{5,\text{OH}}$ 6.6
17 ^a	~ 0	~ 0	4.6	3.5	10.0	6.3	10.0	$J_{2 \text{ OH}} 4.2; J_{5 \text{ OH}} 5.9$
18 ^a	~ 0	~ 0	4.6	3.5	10.0	6.4	10.0	2,011 0,011
19 ^a	~ 0	~ 0	4.6	3.4	10.0	6.3	9.8	$J_{2,\text{OH}}$ 4.2; $J_{5,\text{OH}}$ 5.9
20 ^a	1.5	~ 0	4.9	3.4	10.1	6.3	9.5	$J_{2 \text{ OH}} 4.2; J_{5 \text{ OH}} 6$
21 ^a	1.2	~ 0	4.6	3.4	10.0	6.1	9.5	$J_{2 \text{ OH}} 3.9; J_{5 \text{ OH}} 5.8$
22 ^a	~ 0	~ 0	4.6	3.7	(9.8)	(6.6)	~9.8	2,011 0,011
23a	~ 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	•••
26a	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	
32a	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 Me₂SO- 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 8 9 10 11 12α ^d 12β 12β ^{b,c} 13α 13β 14α 23α 25 26α 26β 32α ^d 35 36 ^b	Chemi	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 (CM e_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)					
26a	95.6	71.3 ^a	40.5	74.2 ^a	$74.5^{\rm a}$	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 Me₂SO-*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 = $5.46 \rightarrow 3.56$ ppm, H-3 = $3.79 \rightarrow 5.14$ ppm, for the corresponding ¹³C 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 increased [9], had an opposite effect in the present case (see Table 5).

Deacetylation of the 4-nitrophenyl analogue 14 β gave 19, the nitro group of which was

Table 3		
NMR-NOE	difference	data

reduced with sodium borohydride to give after
acetylation and selective O-deacetylation the
corresponding 4'-acetamidophenyl thioglyco-
side 20 .

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				



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Scheme 2.

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		
32a	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		
10	H-1			+	+			169.1		
	H-2	+		+	+		+			
	H-3	+			+			163.4		
	H-4	+	+	+			+			
	H-5					+		169.7		
2	H-1		+	+		+		143.7		
	H-2	+	·	+	+			142.6		
	H-3	+			+	+				
	H-4	·	+	+	·			164.1		
	H-5	+		+						
13	- H-1		+	+	+			142.6		
	H-3	+	'	'	+			163.3		

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

^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 $27 \Leftrightarrow$ 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-



nents was obtained from which after acetylation three compounds, the rearranged 2,6thioanhydro-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 **26** β (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 **26**β 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 (${}^{4}J_{1,3}$ 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-cvanophenylthio 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 (${}^{4}J_{2.4}^{-}$ 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 **32** α 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 spacedemanding 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 ${}^{1}H$ and the ¹³C spectra (Tables 1 and 2). The altro configuration of the skeleton was proven by the long-range (${}^{4}J_{2,4}$ 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 2,6anhydro-1,2-dithio- β -D-mannopyranoside (3type 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-cyanophenyl 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 MgSO4 and concd under diminished pressure at or below 40 °C. TLC: E. Merck precoated Silica Gel 60 F₂₅₄ 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 I₂ 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 CHCl₃ at 20 °C unless stated otherwise. NMR spectra were recorded with a Bruker AC 250 at 250 MHz (1H) and 62.9 MHz (¹³C) or with a Varian XL-400 spectrometer MHz (¹H) and 100 MHz (¹³C) or for solns in CDCl₃ (internal Me₄Si) unless stated otherwise. Multiplicities of the ¹³C 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 $\alpha:\beta$ 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 NaHCO₃. 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. $[\alpha]_D + 81^\circ$; Lit. [7]: $[\alpha]_D$ $+ 84^\circ$ (c 0.28, CHCl₃). 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, Ac₂O (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 CH₂Cl₂ soln (22 g, 89%) was pure enough for subsequent reactions. Pure **8** could be obtained by column chromatography (solvent B); [α]_D + 60°; R_f 0.5 (solvent B); Anal. Calcd for C₁₉H₂₆O₁₁S₂: 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 CH₂Cl₂, 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 C₁₄H₂₂O₉S₂: 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 CH₂Cl₂ (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 CH₂Cl₂, 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 C₉H₁₄O₄S: 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 Ac₂O (5 mL) in pyridine (10 mL) afforded after usual processing and column chromatography (solvent E) 11 (4.8 g, 93%) as a syrup; $[\alpha]_D + 107^\circ$; R_f 0.8 (solvent C); Anal. Calcd for C₁₁H₁₆O₅S: 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-Dglucofuranose (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 NaHCO₃ (0.6 g) was added gradually to neutralise the HCl and was then concd. The residue was dissolved in Ac₂O (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 12 α and 12 β in a ratio of ~ 1:2; R_f 0.3 (solvent C). Anal. Calcd for C₁₂H₁₆O₇S: 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 CF₃COOH (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 Ac₂O (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; $[\alpha]_{\rm D}$ + 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), Me₃SiOTf (0.34 mL, 1.8 mmol) was added at -10 °C. After stirring at rt for 30 min, the reaction was quenched with Et₃N, concd and the residue submitted to column chromatography (solvent C). Concentration of the first fraction gave 13 α (50 mg, 8%) as a syrup; [α]_D + 232° (c 0.6, CHCl₃); R_f 0.5 (solvent C); Anal. Calcd for C₁₇H₁₇NO₅S₂: 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 **13** β (0.45 g, 72%) as a syrup; $[\alpha]_D + 9^\circ$ (*c* 0.5, CHCl₃); R_f 0.4 (solvent C); Calcd for C₁₇H₁₇NO₅S₂: 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), BF₃·EtO₂ (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 NaHCO₃ soln (100 mL). The separated organic layer was washed with water, 6% aq NaHCO₃ 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 $14\alpha + 23\alpha$ (210 mg, 9%); R_f 0.5 (solvent C).

Concentration of the second fraction gave a 2:3 mixture of $23\alpha + 23\beta$ (100 mg, 4%); R_f 0.45 (solvent C).

Concentration of the third fraction gave **14** β (1.6 g, 68%); $[\alpha]_D - 43$ (*c* 0.34, CHCl₃); R_f 0.4 (solvent C); Anal. Calcd for C₁₆H₁₇NO₇S₂: 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 -Dglucofuranoside (16).—Deacetylation of 13 α (240 mg, 0.6 mmol) with 1 M NaOMe (0.1 mL) in MeOH (10 mL) yielded, after neutralization with solid CO₂ 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 C₁₃H₁₃NO₃S₂: 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 -Dglucofuranoside (17) and 4-[(imino)(methoxy)methyl]phenyl 3,6-anhydro-1,3-dithio- β -D-glucofuranoside (18).—Deacetylation of 13 β (300 mg, 0.8 mmol) with 1 M NaOMe (0.1 mL) in MeOH (15 mL) yielded, after neutralization with solid CO₂ and column chromatography (solvent H), 17 (135 mg, 58%): mp 192– 194 °C (ether); [α]_D – 138° (*c* 0.5, MeOH); *R*_f 0.4 (solvent H); Anal. Calcd for C₁₃H₁₃NO₃S₂: 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 C₁₄H₁₇NO₄S₂: 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 -Dglucofuranoside (19).—Deacetylation of 14 β (1.6 g, 4 mmol) with 1 M NaOMe (0.2 mL) in MeOH (30 mL) yielded, after neutralization with solid CO₂ and column chromatography (solvent H), 19 (0.95 g, 75%): mp 188–190 °C (MeOH); [α]_D – 193° (*c* 0.5, MeOH); *R_f* 0.3 (solvent H); Anal. Calcd for C₁₂H₁₃NO₅S₂: 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), NaBH₄ (330 mg) and NiCl₂·6 H₂O (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 Ac₂O (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); $[\alpha]_{D} - 96^{\circ}$ (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 Et₃N (20 mL) was saturated with a slow stream of dry H₂S 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); [α]_D – 149° (*c* 0.4, Me₂SO); R_f 0.4 (solvent A); ¹H NMR: Anal. Calcd for C₁₃H₁₅NO₃S₃: 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); $[\alpha]_D - 85^\circ$ (*c* 0.5, Me₂SO); R_f 0.3 (solvent A); Anal. Calcd for C₁₄H₁₈INO₃S₃: 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 CH₂Cl₂ (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 CO₂ 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-thioα-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-Dglucopyranoside [10] (38.7 g) in MeOH (580 mL) at 20 °C. The mixture was neutralised with solid CO₂ after 24 h and the residue obtained after concentration was re-evaporated with toluene $(2 \times 50 \text{ mL})$. The residue was dissolved in pyridine (150 mL), and Ac₂O (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); $[\alpha]_{\rm D}$ + 64°; $R_{\rm f}$ 0.4 (solvent B); Anal. Calcd for C₁₁H₁₆O₆S: 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 CH₂Cl₂ and processed in the usual way. The residue obtained on concentration was filtered with Et₂O to give **26** (4.6 g, 94%); mp 199–202 °C (acetone–hexane); [α]_D + 25°; R_f 0.6 (solvent B); Anal. Calcd for C₂₁H₁₈N₂O₁₀S: 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 $(2 \times 5 \text{ mL})$ was evaporated from the residue obtained on concentration. The residue was dissolved in pyridine (10 mL) and Ac₂O (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 (Et₂O); $[\alpha]_D$ + 63°; Anal. Calcd for C₁₇H₁₇NO₉S: 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-ni-trobenzoyl)-3-thio- β -D-glucopyranoside (**26** β) (120 mg, 12%); mp 153–157 °C (Et₂O); [α]_D – 40 (*c* 0.5, CHCl₃); Anal. Calcd for C₂₁H₁₈N₂O₁₀S: 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 (Et₂O); $[\alpha]_D + 116^\circ$ (*c* 0.5, CHCl₃); Anal. Calcd for C₂₆H₂₄N₂O₁₄S: 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-ni-trobenzoyl)-6-thio- α -D-glucopyranose (**32** α) (400 mg, 38.6%); mp 188–192 °C (Et₂O); [α]_D – 23°; Anal. Calcd for C₂₂H₁₈N₂O₁₁S: 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) - 1,2,6trithio- β -D-glucopyranoside (42).—(i) Under argon, to a stirred soln of 32 α (260 mg, 0.5 mmol) and 4-cyanobenzenethiol (140 mg, 1 mmol) in dry 1,2-dichloroethane (10 mL), Me₂SiOTf (0.12 mL, 0.6 mmol) was added at - 10 °C. After stirring at - 10 °C for 30 min, the reaction was quenched with Et₃N, 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, CHCl₃); 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 (Et₂O); $[\alpha]_D$ + 18° (*c* 0.5, CHCl₃); R_f 0.5 (solvent C); Anal. Calcd for C₂₇H₁₉N₃O₉S₂: 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), BF₃·Et₂O (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 CH₂Cl₂. The combined organic extracts were washed with 5% aq NaHCO₃, 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 -Dglucopyranoside (**36**).—To a stirred slurry of **35** (1 g) in CH₂Cl₂ (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 CO₂ 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 C₁₃H₁₃NO₃S₂: 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 32 α (520 mg, 1 mmol) and 4-nitrobenzenethiol (purity 80%) (250 mg, 1.25 mmol) in dry 1,2-dichloroethane (20 mL), BF₃·Et₂O (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 CH₂Cl₂. The combined organic extracts were washed with 5% aq NaHCO₃, dried, concd and the residue purified by column chromatography (solvent D) to give **37** (350 mg, 57.1%); mp 88–92 °C (Et₂O); $[\alpha]_D$ + 32° (*c* 0.5, CHCl₃); *R_f* 0.5 (solvent C); Anal. Calcd for C₂₆H₁₉N₃O₁₁S₂: 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 -Dglucopyranoside (**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 C₁₂H₁₃NO₅S₂: 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), BF₃·Et₂O (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 CH₂Cl₂. The combined organic extracts were washed with 5% aq NaHCO₃, 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 C₂₂H₁₈N₂O₇S₂: 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 (Et₂O); $[\alpha]_D$ + 311° (*c* 1, MeOH); R_f 0.4 (solvent F); Anal. Calcd for C₁₃H₁₃NO₃S₂: 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), BF₃·Et₂O (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); [α]_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 (Et₂O); $[\alpha]_{\rm D}$ + 404° (*c* 0.5, MeOH); *R_f* 0.4 (solvent F); Anal. Calcd for C₁₂H₁₃NO₅S₂: 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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