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Synthesis of sulfur-linked analogues of nigerose, laminarabiose, laminaratriose, gentiobiose, gentiotriose, and laminaran trisaccharide Y [1]

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Abstract

Sulfur-linked analogues of 3-*O*-α-D-glucopyranosyl-D-glucose (nigerose), 3-*O*-β-D-glucopyranosyl-D-glucose (laminarabiose), 6-*O*-β-D-glucopyranosyl-D-glucose (gentiobiose), *O*-β-D-glucopyranosyl-(1 → 3)-*O*-β-D-glucopyranosyl-(1 → 3)-D-glucose (laminaratriose), *O*-β-D-glucopyranosyl-(1 → 6)-*O*-β-D-glucopyranosyl-(1 → 6)-D-glucose (gentiotriose) and 3,6-di-*O*-β-D-glucopyranosyl-D-glucose (laminaran trisaccharide Y), namely, respectively, 3-thionigerose (**6**), 3-thiolaminarabiose (**11**), 6-thiogentiobiose (**21**), $3^{I},3^{II}$-dithiolaminaratriose (**16**), $6^{I},6^{II}$-dithiogentiotriose (**29**) and $3^{I},6^{I}$-dithiolaminaran trisaccharide Y (**37**) have been conveniently prepared by S_N2 reactions of the corresponding anomer of D-glucopyranose 1-thiolate with suitably activated monosaccharide derivatives in *N,N*-dimethylformamide (for **6** and **21**) or in tetrahydrofuran in the presence of a crown ether (for **11**). A sequence involving the reaction of non-anomeric thiolates with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide was alternatively used for the preparation of **11** and **21** but proved less satisfactory. The preparation of thiotrisaccharides **16**, **29**, and **37** involved a mixed approach.

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Keywords: Sulfur-linked oligosaccharides; 3-Thionigerose; 3-Thiolaminarabiose; 6-Thiogentiobiose; $3^{I},3^{II}$-Dithiolaminaratriose; $6^{I},6^{II}$-Dithiogentiotriose; $3^{I},6^{I}$-Dithiolaminaran trisaccharide Y

1. Introduction

The α-(1 → 3)-, β-(1 → 3)- and β-(1 → 6)-glucosidic linkage is common in polysaccharides of fungi [2]. In view of the reported stability of the thioglycosidic linkage in enzymic processes involving the corresponding *O*-glycosides as substrates, *S*-linked thiodisaccharides and thiotrisaccharides having such types of linkage might be of interest as metabolic inhibitors. A further aim of this paper is to optimize the synthetic methodologies used for the preparation of *S*-linked oligosaccharides [1,3] in view of the interest in more-complex structures that could incorporate the thioglycosidic linkage [4].

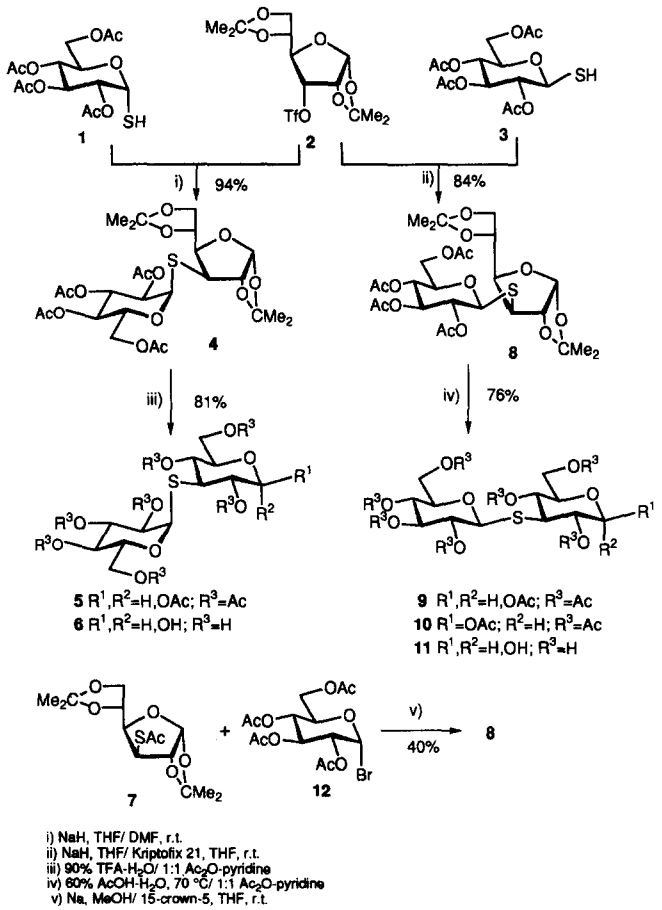
2. Results and discussion

α- and β-(1 → 3)-Thioglucosidic linkages.—The preparation of the protected 3-thionigerose derivative (**4**) was readily achieved in 94% yield by nucleophilic displacement of the triflate group in 1,2:5,6-di-*O*-isopropylidene-3-*O*-trifluoromethylsulfonyl-α-D-allofuranose (**2**) [5] with the sodium salt of 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranose (**1**) [1,6] in *N,N*-dimethylformamide. Hydrolysis of the *O*-isopropylidene groups in **4** with 90% aq trifluoroacetic acid and subsequent acetylation of the partially acylated product gave 3-thionigerose octaacetate **5** (81%) as an 1:1 α:β anomeric mixture, from which thionigerose **6** was obtained by Zemplén *O*-deacylation. A synthesis of **4** and **6** has been recently reported [7]. The β-(1 → 3)-thiodisaccharide **8** was analogously obtained in excellent yield (84%) by reaction of the triflate **2** with the sodium salt of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (**3**) [8] in tetrahydrofuran in the presence of Kriptofix 21 at room temperature. An alternative strategy involving reaction of the sodium salt of 1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-glucofuranose, prepared by sodium methoxide treatment of the corresponding *S*-acetate (**7**) [9] with tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**12**) [10], proved less satisfactory for the preparation of the protected 3-thiolaminarabiose derivative **8** (40% yield). Using the same deprotection sequence as applied to **4**, **8** yielded the octaacetate **9** (76%, α:β ratio 1:1), which was deacylated to 3-thiolaminarabiose **11** (Scheme 1). The β anomer of **9** (**10**) was prepared in pure form by acetylation of deacetonated **8** with sodium acetate–acetic anhydride. The high-field chemical shifts for H-3 and C-3 in the ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) of the thiodisaccharides **4–6**, **8–11** support the presence of the (1 → 3)-thioglycosidic linkage. The respective α (for **4**, **5**) and β (for **8–10**) anomeric configurations were inferred from the corresponding $J_{1',2'}$ values (3.5–5.7 and 10.1–10.2 Hz, respectively).

The α,β anomeric mixture of 3-thiolaminarabiose octaacetate (**9**) was used as starting material in the preparation of the $3^{I},3^{II}$-dithiolaminaratriose **16** (Scheme 2). Treatment of **9** with 33% hydrogen bromide in acetic acid afforded the α-glycosyl bromide **13** in 95% yield. Nucleophilic displacement with the sodium salt of **7** gave the

trisaccharide **14** in 30% yield. Deacetonation followed by sodium acetate–acetic anhydride peracetylation led to acetylated laminaratriose **15** (50% yield, α:β ratio 3:7) which was deacylated to **16** (Scheme 2). The ^{1}H and ^{13}C NMR spectra of **14–16** (Tables 3 and 4) show the expected high-field shifts for the H-3^{II} and C-3^{II} signals, as compared with H-3′ and C-3′ in the parent thiodisaccharides **8**, **9–11**. The vicinal coupling constant values also agreed with the proposed structures.

β-(1 → 6)-Thioglucosidic linkage.—In a first approach, the synthesis of 6-thiogentiobiose **21** was undertaken by reaction of a 6-thioglucose derivative with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**12**) [10]. When the sodium salt of 1,2,3,4-tetra-*O*-acetyl-6-thio-β-D-glucopyranose (**18**) [11] was allowed to react with **12** in *N,N*-dimethylformamide, only 1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose [12] was obtained. The latter compound could result from the opening of a thio-*ortho*ester formed by reaction of the thiolate with the intermediate acetoxonium ion. However, reaction of **18** with **12** in the presence of potassium carbonate gave thiogentiobiose octaacetate (**20**) in 40% yield



Scheme 1.

Table 1
^{1}H NMR data ($CDCl_3$) for thiodisaccharides **4**, **5**, **8–10**, **13**, **19**, **20**, **26**, **27** and **30–33** [a]

	Chemical shifts (δ)													
	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	H-1′	H-2′	H-3′	H-′4′	H-5′	H-6′a	H-6′
4	5.75d	4.65d	3.49d	4.10dd	4.28ddd	4.09dd	3.93dd	5.88d	5.06dd	5.32dd	4.99dd	4.42ddd	4.10dd	4.25dd
5α	6.27d	4.94dd	3.37dd	5.13dd	3.94ddd	← 4.07dd →		5.81d	4.95m	5.32t	5.10t	4.39dt	4.10m	4.30m
5β	5.60d	4.98dd	3.14t	5.12dd	3.71ddd	4.03dd	4.18dd	5.80d	4.95m	5.29t	5.01t	4.31dt	4.10m	4.30m
8	5.80d	4.81d	3.52d	4.21dd	4.28ddd	3.95dd	4.08dd	4.70d	5.00dd	5.19t	5.06dd	3.66ddd	4.19dd	4.13dd
9α	6.25d	5.06dd	3.19t	4.98dd	4.03ddd	4.11dd	4.27dd	4.75d	4.88dd	5.18t	5.03t	3.74ddd	4.11dd	4.27dd
10	5.60d	5.13dd	3.00t	4.91dd	3.79ddd	4.01dd	4.18dd	4.66d	4.89dd	5.15t	5.03t	3.67ddd	4.01dd	4.18dd
13	6.62d	4.84dd	3.36t	5.03t	4.25m	4.09dd	4.25m	4.78d	4.93dd	5.23t	5.06t	3.75ddd	4.14dd	4.25m
19	5.90d	4.49d	5.31d	4.45dd	5.17td	← 3.05d →		4.76d	4.96t	5.18t	5.07t	3.70ddd	4.11dd	4.24dd
20	5.66d	5.06dd	5.20t	4.94t	3.80ddd	2.75dd	2.80dd	4.60d	4.91dd	5.15t	5.00t	3.61ddd	4.11dd	4.20dd
26	6.56d	4.75dd	5.49t	5.04t	4.25ddd	2.86dd	2.83dd	4.55d	4.93dd	5.19t	5.03dd	3.67ddd	4.10dd	4.23dd
27	5.43d	5.05dd	5.04t	4.85t	3.81ddd	2.54dd	2.86dd	4.76d	4.85t	5.22t	4.97t	3.50ddd	4.05dd	4.17dd
30	5.76d	4.75d	3.51d	4.21d	3.88ddd	3.77dd	3.61dd	4.60d	5.00t	5.18t	5.03t	3.69ddd	4.17dd	4.11dd
31	5.76d	4.86d	3.44d	4.60dd	4.97ddd	4.40dd	4.14dd	4.66d	4.88dd	5.17t	5.01t	3.62ddd	4.18dd	4.11dd
32	5.87d	4.92d	3.41d	4.48dd	5.20m	3.05dd	3.65m	4.74d	4.93t	5.22t	5.03t	3.65m	4.21dd	4.11dd
33	5.83d	4.87d	3.45d	4.56dd	4.40ddd	3.50dd	3.66dd	4.69d	4.90dd	5.18t	5.01ddd	3.63ddd	4.18dd	4.11dd

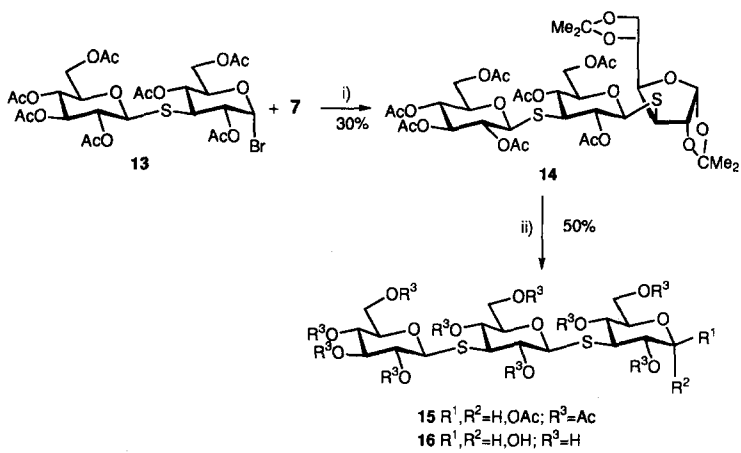
	Coupling constants (Hz)													
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{5',6'a}$	$J_{5',6'b}$	$J_{6'a,6'b}$
4	3.5	0	3.5	8.8	6.2	5.1	8.7	5.7	10.3	9.3	10.3	2.3	6.0	12.3
5α	3.5	11.0	11.5	10.0	2.2	4.1	–	3.5	–	9.3	9.3	2.5	4.6	12.3
5β	8.0	10.9	10.9	9.6	2.3	4.6	12.3	3.5	–	9.3	9.3	2.5	4.6	12.3
8	3.5	0	3.9	8.6	4.4	5.9	8.8	10.1	9.3	9.3	10.0	2.4	4.8	12.4
9α	3.5	11.0	11.4	10.0	2.2	4.1	12.3	10.2	9.3	9.3	9.3	2.5	4.6	12.3
10	8.0	10.8	10.9	9.6	2.3	4.6	12.3	10.1	9.3	9.3	9.3	2.5	4.6	12.3
13	3.5	11.2	11.2	11.2	2.2	–	12.3	10.2	9.3	9.3	9.3	2.5	4.6	12.3
19	3.5	0	3.0	9.5	4.0	4.0	–	9.8	9.8	9.8	9.8	2.5	4.8	12.5
20	8.3	9.5	9.5	9.5	3.6	7.1	14.5	10.1	9.6	9.6	9.6	2.2	5.0	12.5
26	4.0	9.7	9.7	9.9	2.2	4.9	14.0	10.1	9.5	9.5	10.1	2.2	4.8	12.4
27	10.6	9.3	9.2	9.8	2.1	8.6	14.4	10.2	9.8	9.3	9.5	2.2	4.8	12.5
30	3.5	0	3.8	9.2	3.5	6.0	11.5	10.0	9.8	9.7	9.9	2.4	4.6	12.5
31	3.4	0	4.1	9.5	2.3	3.2	11.5	10.2	9.3	9.3	9.3	2.2	4.9	12.4
32	3.5	0	4.0	9.5	4.5	–	14.0	10.0	10.0	10.0	10.0	5.0	2.0	12.5
33	3.4	0	4.0	9.2	2.9	3.3	11.3	10.2	9.5	9.4	9.9	2.3	5.2	12.5

[a] At 400 MHz except for **13**, **19** and **32** at 300 MHz.

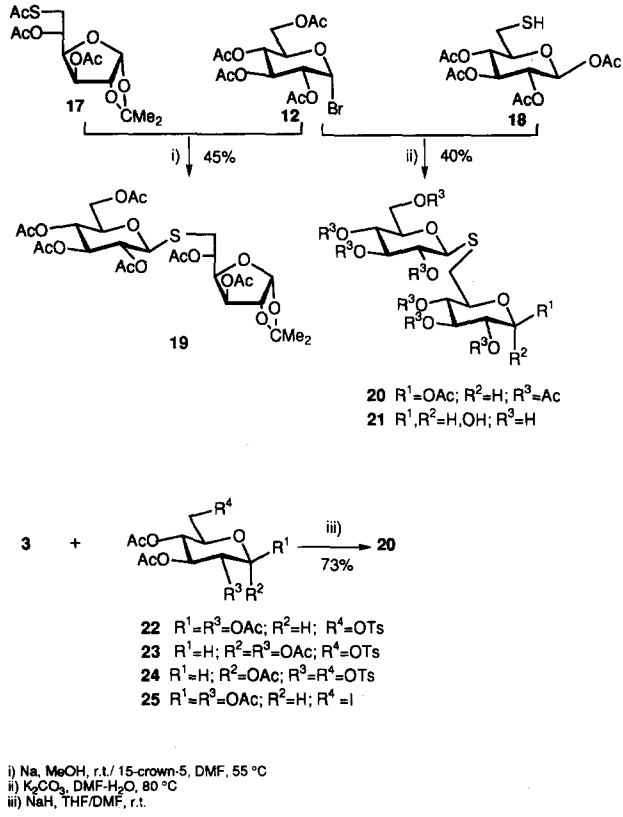
Table 2
^{13}C NMR data for thiodisaccharides **4–6**, **8–11**, **19–21**, **26**, **27**, and **30–33** [a]

	Carbon											
	C-1	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
4 [b]	104.7	86.4	50.4	80.4	74.5	67.8	82.7	70.1	70.1	68.7	68.3	62.1
5α [c]	88.6	70.7	42.9	67.5	70.9	61.4	81.7	69.9	69.9	68.5	67.8	61.5
5β [c]	93.1	70.3	46.1	68.0	75.3	60.9	81.4	70.5	69.8	68.8	67.8	61.5
6α [c]	91.6	72.5	50.6	69.0	80.0	62.5	85.1	74.2	79.0	70.8	81.5	62.3
6β [c]	97.3	74.7	53.9	74.1	81.6	62.9	85.1	74.2	79.0	70.8	81.5	62.3
8 [b]	104.9	86.2	50.1	80.1	73.8	67.4	82.7	70.1	73.9	68.3	76.3	62.1
9α [b]	88.9	70.8	46.6	66.3	71.0	62.1	83.0	70.3	73.8	68.3	75.8	62.1
10 [b]	93.2	71.8	50.2	65.8	75.5	61.9	83.9	70.2	73.8	68.2	75.7	61.9
11α [c]	92.9	72.5	53.0	69.0	80.0	62.5	86.0	74.2	79.0	70.8	81.5	62.3
11β [c]	99.0	74.7	56.5	74.1	81.6	62.9	86.3	74.2	79.0	70.8	81.5	62.3
19 [b]	105.0	83.5	74.7	77.7	70.6	31.6	83.1	68.5	73.9	68.1	75.8	62.1
20 [b]	91.8	70.5	72.8	71.4	75.7	30.4	93.1	70.2	74.0	68.6	76.1	62.2
21α [c]	92.2	71.6	74.3	71.4	79.9	31.6	86.0	72.5	75.9	69.6	77.3	61.0
21β [c]	96.1	72.7	75.7	72.5	79.9	31.4	86.0	72.5	75.9	69.6	77.3	61.0
26 [b]	86.2	70.8	70.2	70.6	74.3	30.1	83.4	70.1	73.9	68.4	76.1	62.2
27 [b]	85.9	68.5	74.1	71.5	80.6	30.1	82.2	70.5	73.9	68.5	76.0	62.1
30 [b]	104.9	86.6	51.0	78.9	70.0	64.3	83.2	70.5	73.6	68.1	76.3	61.8
31 [b]	105.0	86.2	49.6	76.1	69.4	68.3	82.1	70.3	73.8	68.1	75.8	62.0
32 [b]	104.8	86.3	49.9	79.3	68.1	30.7	82.2	70.0	73.8	68.1	76.3	62.1
33 [b]	104.9	86.4	49.1	79.3	68.7	8.3	82.3	70.1	73.7	68.0	76.3	62.1

[a] At 50.3 MHz except for **19** and **32** at 75.5 MHz.
[b] In $CDCl_3$.
[c] In D_2O.



Scheme 2.

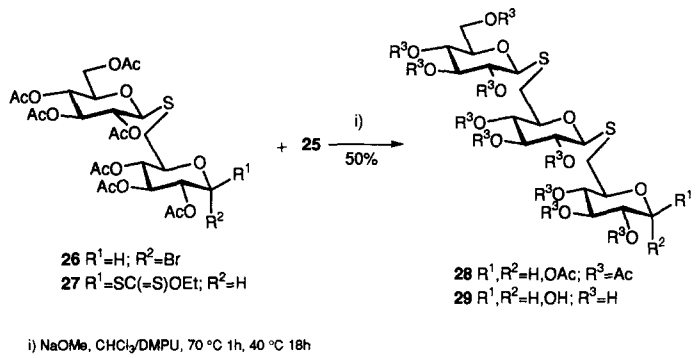


Scheme 3.

(Scheme 3). A similar result was obtained from the reaction of 3,5-di-*O*-acetyl-6-*S*-acetyl-1,2-*O*-isopropylidene-6-thio-α-D-glucofuranose (**17**) with **12**. Compound **19** was then isolated in 45% yield.

In view of these rather modest yields, a reverse strategy involving 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (**3**) [8] as nucleophile was devised. Coupling of **3** with 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranose (**25**) [13], obtained in 98% yield from the corresponding 6-*O*-*p*-tolylsulfonyl derivative **22**, resulted in the peracetylated thiogentiobiose derivative **20** in 73% yield.

The synthesis of 1,2,3,4-tetra-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (**22**) deserves a further comment. Previous results in the literature on the selective *p*-toluenesulfonylation of D-glucose [13,14] pointed out that the primary hydroxyl group reacted preferentially with *p*-toluenesulfonyl chloride in pyridine yielding **22** after subsequent in situ acetylation. A reinvestigation of this reaction [15] led us to observe that a notable proportion of the anomeric α-tetraacetate **23** and the 2,6-di-*O*-tosyl derivative **24** was also present in the reaction mixture when a stoichiometric amount of reactants was used. Both could be isolated by further fractional crystallization.



Scheme 4.

The position of the thioglycosidic linkage in **19** and **20** was clearly deduced from the high field chemical shifts of H-6a,b and C-6 in the ^{1}H and ^{13}C NMR spectra (Tables 1 and 2), respectively. Conventional deprotection of **19** and **20** led to the fully unprotected 6-thiogentiobiose **21**. The ^{13}C NMR spectra (Table 2) show signals for the corresponding α and β anomers at the reducing end (Scheme 3).

Table 3
^{1}H NMR data ($CDCl_3$) for thiotrisaccharides **14**, **15**, **28**, **35**, and **36**

	Unit	Chemical shifts (δ)						
		H-1	H-2	H-3	H-4	H-5	H-6a	H-6b
14 [a]	I	5.84d	4.85d	3.55d		← 4.41–3.98m →		
	II	4.61d	5.08t	3.00t	4.90m	3.68m	← 4.41–3.98m →	
	III	4.66d	4.90t	5.19t	5.07t	3.68m	← 4.41–3.98m →	
15α [a]	I	6.29d	5.06m	3.15t	5.06m	← 4.31–4.02m →		
	II	4.73d	4.93t	3.02t	4.86t	3.67m	← 4.31–4.02m →	
	III	4.64d	4.89t	5.17t	4.90m	3.67m	← 4.31–4.02m →	
15β [a]	I	5.61d	5.21dd	3.06t	5.06m	3.79ddd	← 4.31–4.02m →	
	II	4.65d	4.93t	3.02t	4.86t	3.67m	← 4.31–4.02m →	
	III	4.63d	4.89t	5.17t	4.90m	3.67m	← 4.31–4.02m →	
28α [b]	I	6.25d	5.06dd	5.20t	4.94t	3.80ddd	← 2.78m →	
	II	4.50d	[c]	[c]	[c]	[c]	← 2.78m →	
	III	4.63d	4.90dd	5.15t	5.00t	3.60ddd	4.11dd	4.21dd
28β [b]	I	5.70d	5.06dd	5.20t	4.94t	3.80ddd	← 2.78m →	
	II	4.61d	[c]	[c]	[c]	[c]	← 2.78m →	
	III	4.70d	4.90dd	5.15t	5.00t	3.60ddd	4.12dd	4.22dd
35 [b]	I	5.86d	4.93d	3.45d	4.62dd	5.10dt	← 3.13d →	
	II	4.70d	4.93dd	5.20t	5.04dd	3.66ddd	4.12dd	4.14dd
	III	4.79d	4.97dd	5.18t	5.07dd	3.71ddd	4.21dd	4.25dd
36α [b]	I	6.15d	4.96dd	3.13t	4.81dd	3.97ddd	2.73d	2.73d
	II	4.71d	4.83dd	5.15t	4.97dd	4.65ddd	4.07dd	4.19dd
	III	4.56d	4.88dd	5.11t	5.01dd	3.59ddd	4.07dd	4.19dd
36β [b]	I	5.55d	5.04dd	2.97t	4.70dd	3.74ddd	2.73d	2.73d
	II	4.60d	4.85dd	5.14t	4.98dd	3.70ddd	4.07dd	4.19dd
	III	4.55d	4.89dd	5.11t	5.01dd	3.59ddd	4.07dd	4.19dd

Table 3 (continued)

	Unit	Coupling constants (Hz)						
		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
14	I	3.5	0	3.4	–	–	–	–
	II	10.0	10.0	10.0	–	–	–	–
	III	10.5	9.0	9.0	9.0	–	–	–
15α	I	3.5	10.5	10.5	–	–	–	–
	II	10.0	10.0	10.0	10.0	–	–	–
	III	10.0	10.0	10.0	–	–	–	–
15β	I	8.0	10.5	10.5	–	–	–	–
	II	10.0	10.0	10.0	10.0	–	–	–
	III	10.0	10.0	10.0	–	–	–	–
28α [b]	I	3.7	9.5	9.5	9.5	–	–	–
	II	10.3	[c]	[c]	[c]	–	–	–
	III	10.1	9.6	9.6	9.6	2.2	4.8	12.4
28β [b]	I	8.3	9.5	9.5	9.5			
	II	10.1	[c]	[c]	[c]	–	–	–
	III	10.2	9.6	9.6	9.6	2.2	4.8	12.4
35 [b]	I	3.6	0	4.1	9.5	3.6	3.6	–
	II	10.1	9.2	9.2	10.3	2.5	4.8	12.5
	III	10.1	9.2	9.3	9.8	2.3	4.8	12.4
36α [b]	I	3.5	11.5	11.3	9.3	5.1	5.1	–
	II	10.1	9.2	9.3	11.8	2.2	4.7	12.4
	III	10.1	9.2	9.4	10.1	2.4	4.7	12.4
36β [b]	I	8.1	10.9	10.8	9.3	5.3	5.3	–
	II	10.2	9.1	9.2	11.8	2.2	4.7	12.4
	III	10.1	9.2	9.4	10.1	2.4	4.7	12.4

[a] At 300 MHz.
[b] At 400 MHz.
[c] Not assigned.

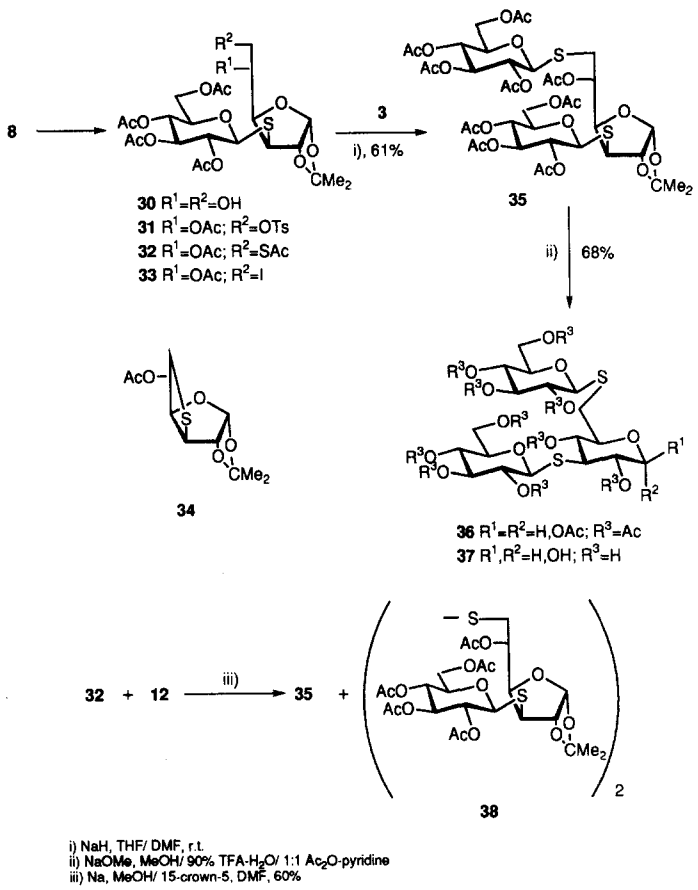
The synthesis of dithiogentiotriose **29** was accomplished by using the reverse coupling strategy referred to above (Scheme 4). Thus, thiogentiobiose octaacetate **20** was converted into the thiogentiobiosyl ethylxanthate **27** via the corresponding α-glycosyl bromide **26** (79% overall yield). Compound **27** was treated with sodium methoxide, and the resulting 1-thiolate was allowed to react with 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranose **25** in 1,3-dimethyl-2-oxo-hexahydropyrimidine (DMPU) to give, after acetylation, the peracetate **28** (50%, α:β ratio 1:1). Catalytic deacetylation afforded $6^{I},6^{II}$-dithiogentiotriose **29**. Comparison of the ^{1}H and ^{13}C NMR data for **28** and **29** (Tables 3 and 4) with those for **20** and **21** (Tables 1 and 2) supports the structural assignments.

β-(1 → 3),β-(1 → 6)-Dithioglucosidic linkages.—Both aforementioned general synthetic schemes have been considered for the preparation of the branched dithiotrisaccharide **37** containing both β-(1 → 3) and β-(1 → 6) linkages (Scheme 5). An early attempt, which involved the reaction of the sodium salt of 5-*O*-acetyl-6-*S*-acetyl-1,2-*O*-isopropylidene-3-*S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-3,6-dithio-α-D-glucofuranose (**32**) with tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**12**), led to a mixture of the

Table 4
^{13}C NMR data for compounds **14–16**, **28**, **29**, and **35–37** [a]

	Unit	Carbon					
		C-1	C-2	C-3	C-4	C-5	C-6
14 [b]	I	104.9	86.2	50.2	80.3	73.8	67.4
	II	84.7	70.2	52.3	66.6	78.6	62.1
	III	84.4	71.9	73.8	68.3	75.8	62.7
15α [b]	I	88.7	70.1	46.3	65.6	70.8	62.6
	II	52.1	70.1	52.1	66.7	77.8	62.1
	III	84.0	71.8	73.6	68.1	75.6	61.9
15β [b]	I	93.3	71.3	49.8	65.9	75.3	62.6
	II	84.7	70.1	52.1	66.7	77.8	62.1
	III	84.0	71.8	73.6	68.1	75.6	61.9
16α [c]	I	91.5	67.3	51.1	66.7	73.4	60.8
	II	84.5	72.3	55.9	69.4	81.6	61.1
	III	85.9	72.6	77.2	72.6	79.8	61.7
16β [c]	I	97.1	70.7	54.4	67.1	78.4	60.8
	II	84.5	72.3	55.9	69.4	81.6	61.1
	III	85.9	72.6	77.2	72.6	79.8	61.7
28α [b]	I	88.9	69.1	72.0	71.2	76.0	30.3
	II	82.8	69.9	73.6	71.6	78.1	30.1
	III	83.4	70.1	73.7	68.2	76.0	62.1
28β [b]	I	91.6	69.5	72.4	71.3	75.5	30.1
	II	83.3	70.0	73.6	71.6	78.0	30.2
	III	83.3	70.2	73.7	68.2	76.0	62.1
29α [c]	I	92.2	71.6	74.3	71.4	79.6	31.7
	II	86.0	72.7	77.0	72.6	79.9	32.5
	III	86.2	72.5	75.7	69.6	77.3	61.0
29β [c]	I	95.9	72.7	75.6	72.5	79.9	31.9
	II	86.8	72.7	77.0	72.6	79.9	32.5
	III	86.1	72.5	75.7	69.6	77.3	61.0
35 [b]	I	105.0	86.5	49.5	76.9	70.4	30.7
	II	82.3	70.1	73.8	68.6	76.4	62.0
	III	82.6	70.9	74.1	68.2	75.8	62.1
36α [b]	I	88.7	70.8	46.6	69.0	73.6	30.4
	II	83.1	70.3	73.9	68.4	75.8	61.7
	III	82.7	70.3	73.9	68.2	76.0	61.7
36β [b]	I	93.2	71.6	49.9	69.4	78.0	30.2
	II	84.2	70.3	73.9	68.3	75.8	61.7
	III	83.1	70.3	73.9	68.3	76.0	61.7
37α [c]	I	91.6	73.4	51.1	70.7	78.3	31.7
	II	84.4	72.5	77.2	69.4	79.9	60.8
	III	86.0	72.7	77.2	69.5	79.7	61.0
37β [c]	I	97.1	72.2	54.2	69.9	79.9	31.9
	II	84.4	72.5	77.2	69.4	79.9	60.8
	III	86.0	72.7	77.2	69.5	79.7	61.0

[a] At 50.3 MHz except for **14** and **15** at 75.5 MHz.
[b] In $CDCl_3$.
[c] In D_2O.



Scheme 5.

expected trisaccharide **35** and the disulfide **38** (FABMS), which could not be separated. In contrast, preparation of the branched trisaccharide was readily achieved in 61% yield by nucleophilic substitution of the iodo derivative **33** with the sodium salt of 1-thio-β-D-glucopyranose in *N,N*-dimethylformamide at room temperature. The iodo derivative **33** was prepared by selective cleavage of the 5,6-*O*-isopropylidene group in **8** followed by treatment with *p*-toluenesulfonyl chloride, subsequent acetylation to **31** (87% yield) and displacement of the tosyloxy group by iodine. When the latter reaction was conducted in *N,N*-dimethylformamide at 100 °C using sodium iodide, concomitant formation of a 3,6-epithio derivative (**34**) was observed (^{1}H NMR). After 5 h, a 2:2:1 mixture of unreacted tosylate **31**, iodide **33**, and 5-*O*-acetyl-3,6-dideoxy-3,6-epithio-1,2-*O*-isopropylidene-α-D-glucofuranose (**34**) was obtained. Intramolecular nucleophilic displacement of sulfonate groups by a sulfur atom has previously been observed [16]. Nevertheless, this undesired competitive reaction could be avoided by performing the iodination in toluene in the presence of a phase-transfer catalyst. Compound **33** was then

obtained in 83% yield. Deacetonation and acetylation of **35** provided a 1:1 anomeric mixture of **35** in 68% yield (Scheme 5). The FAB mass spectrum of **35** showed the expected pseudomolecular ion $[M + Na]^+$ at m/z 1021. Deacetylation with sodium methoxide of **36** afforded $3^1,6^1$-dithiolaminaran trisaccharide Y **37** which was purified by LC and further characterized by ^{13}C NMR spectroscopy (Table 4).

3. Experimental

General methods.—Melting points were determined in capillary tubes, with a Büchi 535 apparatus, and are uncorrected. Optical rotations were measured with a Jobin-Yvon (Paris) "Digital Micropolarimeter". The ^1H (200, 300, and 400 MHz) and ^{13}C NMR spectra (50.3 and 75.5 MHz) were recorded with Bruker AC 200, MLS 300, and AM 400 spectrometers, respectively, with reference signals at 7.34 ppm (^1H) and the central line of the $CDCl_3$-triplet (δ 76.9 for ^{13}C) for solutions in $CDCl_3$, or signals at 29.2 ppm (^{13}C) and 2.17 ppm (^1H) when acetone-d_6 was used as internal reference for solutions in D_2O. Assignments of ^1H and ^{13}C signals were assisted by 2D ^1H-COSY, 2D ^1H–^{13}C CORR and NOE experiments. Positive FABMS spectra (Xe, accelerating potential 8 kV) were recorded with a ZAB-SEQ (VG) spectrometer. Sodium iodide was usually added as a cationizing agent. Reactions were monitored by TLC on Silica Gel 60 F_{254} (E. Merck) and detection was accomplished by charring with H_2SO_4. Separations were performed by flash chromatography on Silica Gel 60 (230–400 mesh, E. Merck) with Büchi 680 equipment fitted with a Knauer refractometric detector 188.00. LC (4 × 103 kPa) of unprotected thiooligosaccharides was carried out with a Perkin–Elmer chromatograph, fitted with an LC 250 isocratic pump, an LC 30 refractometric detector, and a 1020S integrator, on a Lichrosorb NH_2 (7 mm) column (250 × 10 cm, eluent MeCN–water). Elemental analyses were performed by the Service Central d'Analyse (CNRS, Vernaison).

1,2:5,6-Di-O-isopropylidene-3-S-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-3-thio-α-D-glucofuranose (**4**).—Sodium hydride (54 mg, 2.25 mmol) was added to a solution of 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranose (**1**) [1,6] (0.76 g, 2.1 mmol) in dry THF (25 mL) at room temperature. The suspension was stirred under N_2 until hydrogen evolution had ceased. The resulting solution was then concentrated under reduced presure, and the residue dissolved in DMF (5 mL). To this solution, 1,2:5,6-di-*O*-isopropylidene-3-*O*-trifluoromethylsulfonyl-α-D-allofuranose (**2**) [5] (0.80 g, 2.1 mmol) in DMF (5 mL) was added dropwise and the mixture was stirred for 3.5 h at room temperature, then concentrated. A solution of the residue in CH_2Cl_2 (25 mL) was washed with water (2 × 5 mL), dried ($MgSO_4$), and concentrated to yield **4** (1.2 g, 94%) as a white solid, $[\alpha]_D$ +129° (*c* 0.7, $CHCl_3$); ref. [7] reports a yield of 71% and no optical rotation data; NMR: ^1H (400 MHz, $CDCl_3$): Table 1; ^{13}C (50.3 MHz, $CDCl_3$): Table 2. Anal. Calcd for $C_{26}H_{38}O_{14}S$: C, 51.40; H, 6.26; S, 5.27. Found: C, 51.52; H, 6.25; S, 5.63.

1,2,4,6-Tetra-O-acetyl-3-S-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-3-thio-α,β-D-glucopyranose (**5**).—A solution of **4** (0.7 g, 1.15 mmol) in 90% TFA–water (10 mL) was kept at 30 °C under reduced pressure in a rotary evaporator until evolution of

acetone had ceased. Further concentration yielded a syrupy residue which was dried (P_2O_5) and acetylated (1:1 Ac_2O–pyridine, 10 mL) for 3 h at room temperature yielding **5** (0.65 g, 81%), which crystallized from EtOH; $\alpha:\beta$ ratio 1:1 (from NMR integration of H-1 signals), mp 213 °C, $[\alpha]_D$ +154° (*c* 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): Table 1; ^{13}C NMR (50.3 MHz, $CDCl_3$): Table 2. Anal. Calcd for $C_{28}H_{38}O_{18}S$: C, 48.41; H, 5.48; S, 4.61. Found: C, 48.23; H, 5.46; S, 4.93.

3-S-(α-D-Glucopyranosyl)-3-thio-D-glucopyranose (3-thionigerose, **6***).*—Zemplén *O*-deacetylation of **5** (225 mg, 0.32 mmol) with methanolic NaOMe (1.0 m, 72 mL), followed by purification by preparative LC (7:3 MeCN–water) and freeze-drying from an aq solution, afforded **6** (65 mg, 57%), $[\alpha]_D$ +50° (*c* 0.4, water); no data for optical rotation in ref. [7]; ^{13}C NMR (50.3 MHz, D_2O): Table 2; FABMS: *m/z* 381 (100, $[M + Na]^+$), 359 (42, $[M + H]^+$), 341 (45, $[M - OH]^+$). Anal. Calcd for $C_{12}H_{22}O_{10}S$: C, 40.22; H, 6.15; S, 8.94. Found: C, 39.76; H, 6.18; S, 8.48.

3-S-Acetyl-1,2:5,6-di-O-isopropylidene-3-thio-α-D-glucofuranose (**7**).—To 1,2:5,6-di-*O*-isopropylidene-3-*O*-trifluoromethylsulfonyl-α-D-allofuranose (**2**) [5] (7.2 g, 18.9 mmol) in toluene, methyltrioctylammonium chloride (2.4 g) and KSAc (3 g, 28.3 mmol) in water (200 mL) were added. The reaction mixture was stirred at 80 °C for 15 h, then it was cooled and the aq phase was extracted with CH_2Cl_2. The dried (Na_2SO_4) CH_2Cl_2 extract was evaporated to a syrup which showed a main component in TLC (1:4 hexane–EtOAc). Flash chromatography (same eluent) yielded **7** as a syrup (4.93 g, 82%); $[\alpha]_D$ −44.5° (*c* 1, $CHCl_3$); lit. [9] $[\alpha]_D$ −46°.

1,2:5,6-Di-O-isopropylidene-3-S-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-thio-α-D-glucofuranose (**8**).—(a) Sodium hydride (70 mg, 2.92 mmol) was added to a solution of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (**3**) [8] (1g, 2.75 mmol) in dry THF (50 mL) at 0 °C. The suspension was stirred under N_2 until hydrogen formation had ceased. To this solution, 1,7,10-trioxa-4,13-diazacyclopentadecane (Kriptofix 21, 105 mg, 0.18 equiv) and a solution of 1,2:5,6-di-*O*-isopropylidene-3-*O*-trifluoromethylsulfonyl-α-D-allofuranose (**2**) [5] (1.08 g; 2.80 mmol) in THF (20 mL) was added and the mixture was stirred for 2 h at room temperature under N_2, then concentrated under reduced pressure. A solution of the residue in CH_2Cl_2 (20 mL) was washed with water (15 mL), dried (Na_2SO_4), and concentrated. The crude product was crystallized from EtOH giving **8** (1.4 g, 84%), mp 155–156 °C, $[\alpha]_D$ −35° (*c* 1.08, $CHCl_3$); NMR: ^1H (400 MHz, $CDCl_3$): Table 1; ^{13}C (50.3 MHz, $CDCl_3$): Table 2. Anal. Calcd for $C_{26}H_{38}O_{14}S$: C, 51.48; H, 6.27; S, 5.28. Found: C, 50.73; H, 6.19; S, 5.31.

(b) 3-*S*-Acetyl-1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-glucofuranose (**7**) (2.0 g, 6.28 mmol) was dissolved in MeOH (20 mL) containing NaOMe (1.0 m, 5.78 mL). After standing under nitrogen overnight at room temperature, the solution was concentrated. To the residue were added 1,4,7,10,13-pentaoxacyclopentadecane (15-crown-5, 1.5 mL), tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**12**) [10] (5 g, 12 mmol) and THF (25 mL). After 5 h at room temperature, the mixture was filtered and evaporated to a residue which was purified by column chromatography using 1:2 EtOAc–hexane as eluent to yield 1.40 g (37%) of **8** identical in all respects with the compound prepared in (a).

1,2,4,6-Tetra-O-acetyl-3-S-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-thio-α,β-D-glucopyranose (**9**).—A solution of **8** (0.4 g, 0.66 mmol) in 60% aq AcOH (25 mL) was heated for 24 h at 70 °C, then concentrated under reduced pressure and the residue

dissolved in water and freeze-dried. Conventional acetylation of the resulting solid (1:1 Ac_2O–pyridine, 10 mL) yielded **9** (0.34 g, 74%); $\alpha:\beta$ ratio 1:1 (from ^1H NMR integration of H-1 signals), mp 196 °C, $[\alpha]_D$ +20.5° (*c* 1, $CHCl_3$); NMR: ^1H (400 MHz, $CDCl_3$): Table 1; ^{13}C (50.3 MHz, $CDCl_3$): Table 2; FABMS: *m/z* 717 (15, $[M + Na]^+$), 635 (5, $[M - AcO]^+$), 331 (25). Anal. Calcd for $C_{28}H_{38}O_{18}S$: C, 48.41; H, 5.48; S, 4.61. Found: C, 48.19; H, 5.59; S, 4.57.

1,2,4,6-Tetra-O-*acetyl-3*-S-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-3-thio-β*-D-*glucopyranose* (**10**).—To the dried deacetonated product resulting from treatment of **8** (1.5 g, 2.48 mmol) in aq AcOH (75 mL), Ac_2O (9.3 mL) and NaOAc (8 g) were added and the solution was heated at 100 °C for 1 h. It was then cooled, poured on crushed ice and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed to neutrality with satd $NaHCO_3$ and dried (Na_2SO_4). Concentration resulted in an oily material (0.89 g, 52%) which crystallized in EtOH; mp 204–207 °C; $[\alpha]_D$ −7.5° ($CHCl_3$); NMR: ^1H (400 MHz, $CDCl_3$): Table 1; ^{13}C (50.3 MHz, $CDCl_3$): Table 2. Anal. Calcd for $C_{28}H_{38}O_{18}S$: C, 48.41; H, 5.51; S, 4.61. Found: C, 48.04; H, 5.59; S, 4.7.

3-S-*(β*-D-*Glucopyranosyl)-3-thio*-D-*glucopyranose (3-thiolaminarabiose,* **11**).—To a solution of either of the peracetylated thiodisaccharides **9** or **10** (0.15 g, 0.22 mmol) in MeOH (15 mL) was added methanolic NaOMe (1.0 m, 0.1 mL). The mixture was stirred for 2 h at room temperature, then demineralized with Amberlite IRN-77 (H^+) cation-exchange resin and filtered. Evaporation of the solvent gave an amorphous powder wich was purified by preparative LC (7:3 MeCN–water) and freeze-dried from an aq solution affording **11** (77 mg, 100%), $[\alpha]_D$ −16° (5 min) → 0° (equil.) (*c* 0.12, water); ^{13}C NMR (50.3 MHz, D_2O): Table 2; FABMS: *m/z* 381 (12, $[M + Na]^+$), 359 (5, $[M + H]^+$). Anal. Calcd for $C_{12}H_{22}O_{10}S \cdot 1.5\ H_2O$: C, 37.40; H, 6.49; S, 8.31. Found: C, 37.90; H, 6.41; S, 8.40.

2,4,6-Tri-O-*acetyl-3*-S-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-3-thio-α*-D-*glucopyranosyl bromide* (**13**).—To a solution of the peracetylated thiodisaccharide **9** (1.7 g, 2.45 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C was added dropwise commercial 33% HBr in AcOH (1.8 mL, 12 equiv). After the mixture was stirred for 2 h at room temperature, TLC (1:1 EtOAc–hexane) showed complete conversion of **9** into a single product. Toluene was added (50 mL), and the solution was concentrated under reduced pressure to give a residue which crystallized in $CHCl_3$–hexane to give **13** (1.66 g, 95%), mp 180–182 °C, $[\alpha]_D$ +92.5° (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): Table 1, which was used without further characterization in the following step.

1,2:5,6-Di-O-*isopropylidene-3*-S-*[2,4,6-tri*-O-*acetyl-3*-S-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-3-thio-β*-D-*glucopyranosyl]-3-thio-α*-D-*glucofuranose* (**14**).—The thioacetate 7 (0.4 g, 1.25 mmol) was dissolved in MeOH (10 mL) and sodium (30 mg) was added. After standing overnight at room temperature, the solution was concentrated. To a solution of the residue in THF (15 mL) were added 15-crown-5 (0.3 mL) and **13** (0.9 g, 1.25 mmol). After the mixture was stirred for 6 h at room temperature, the solvent was evaporated and the residue purified by column chromatography (1:1 EtOAc–hexane) to give **14** (0.34 g, 30%), mp 101 °C, $[\alpha]_D$ −23° (*c* 1, $CHCl_3$); NMR: ^1H (300 MHz, $CDCl_3$): Table 3; ^{13}C (75.5 MHz, $CDCl_3$): Table 4. Anal. Calcd for $C_{38}H_{54}O_{21}S_2$: C, 50.10; H, 5.97; S, 7.04. Found: C, 50.11; H, 5.94; S, 7.05.

1,2,4,6-Tetra-O-*acetyl-3*-S-*[2,4,6-tri*-O-*acetyl-3*-S-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glu-*

*copyranosyl)-3-thio-β-*D*-glucopyranosyl]-3-thio-α,β-*D*-glucopyranose* (**15**).—A solution of **14** (0.3 g, 0.33 mmol) in aq AcOH (60%, 15 mL) was heated at 80 °C for 24 h, then concentrated and toluene evaporated from the residue. Acetylation with NaOAc (1.1 g) and Ac_2O (1.25 mL) for 1 h at 100 °C and conventional work-up gave **15** (0.17 g, 50%) which was purified by column chromatography (1:1 EtOAc–hexane); $\alpha:\beta$ ratio 3:7 (from ^1H integration), mp 98–101 °C, $[\alpha]_D$ +2° (*c* 1, $CHCl_3$); NMR: ^1H (300 MHz, $CDCl_3$): Table 3; ^{13}C (75.5 MHz, $CDCl_3$): Table 4. Anal. Calcd for $C_{40}H_{54}O_{25}S_2$: C, 48.09; H, 5.45; S, 6.42. Found: C, 48.02; H, 5.40; S, 6.32.

*3-S-[3-S-(β-*D*-glucopyranosyl)-3-thio-β-*D*-glucopyranosyl]-3-thio-*D*-glucopyranose (3′, 3″-dithiolaminaratriose,* **16**).—To the anomeric mixture of **15** (100 mg, 0.1 mmol) in MeOH (5 mL) was added methanolic NaOMe (m, 0.05 mL). After 2 h, the base was neutralized with Amberlite IR-120 (H^+) cation-exchange resin. After the mixture was filtered, concentration gave **16** (54 mg, 100%) which was freeze-dried from its aq solution, $[\alpha]_D$ −30.6° (*c* 1, water); ^{13}C NMR (50.3 MHz, D_2O): Table 4.

*3,5-Di-*O*-acetyl-6-S-acetyl-1,2-*O*-isopropylidene-6-thio-α-*d*-glucofuranose* (**17**).—Potassium thioacetate (1.2 g, 10.52 mmol) was added to a stirred solution of 3,5-di-*O*-acetyl-1,2-*O*-isopropylidene-6-*O*-methylsulfonyl-α-D-glucofuranose [17] (2.0 g, 5.23 mmol) in DMF (40 mL) and the mixture was heated for 1 h at 70 °C, then evaporated. The residue was extracted with EtOAc and subjected to column chromatography (1:1 EtOAc–hexane) to yield **17** (1.70 g, 90%); mp 83–85 °C; $[\alpha]_D$ +39.6° (*c* 1, $CHCl_3$); lit. [18] mp 89–90 °C; $[\alpha]_D$ +37°. NMR ^1H (60 MHz, $CDCl_3$): δ 5.90 (d, $J_{1,2}$ 3.5 Hz, H-1), 5.40–5.00 (m, H-3, H-5), 4.55–4.15 (m, H-2, H-4), 3.55 (dd, $J_{5,6b}$ 3.5 Hz, H-6a), 3.00 (dd, $J_{a,b}$ 14.5, $J_{5,6a}$ 6.5 Hz, H-6a), 2.30 (s, 3 H, S*Ac*), 2.05 and 1.95 (2s, 6 H, OAc), 1.50 and 1.30 (2s, 6 H, CMe_2). Anal. Calcd for $C_{15}H_{22}O_8S$: C, 49.72; H, 6.07; S, 8.84. Found: C, 49.29; H, 5.98; S, 9.01.

*3,5-Di-*O*-acetyl-1,2-*O*-isopropylidene-6-*S*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-6-thio-α-*D*-glucofuranose* (**19**).—To a solution of **17** (1 g, 2.76 mmol) in MeOH (15 mL), sodium (80 mg) was added and the mixture was stirred under N_2 for 1 h at room temperature. The solvent was evaporated, the residue was dissolved in DMF (20 mL), and 15-crown-5 (0.7 mL) and tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**12**) [10] (2.2 g, 5.35 mmol) were added. The mixture was kept for 4 h at 55 °C and then evaporated, and acetylated (1:15 Ac_2O–pyridine, 16 mL) for 4 h. Conventional work-up and purification by column chromatography (1:2 EtOAc–hexane) yielded **19** (0.82 g, 45%), mp 56–58 °C, $[\alpha]_D$ −52.4° (*c* 1, $CHCl_3$); NMR: ^1H (400 MHz, $CDCl_3$): Table 1; ^{13}C (50.3 MHz, $CDCl_3$): Table 2. Anal. Calcd for $C_{27}H_{38}O_{16}S$: C, 49.84; H, 5.84; S, 4.92. Found: C, 49.28; H, 5.97; S, 5.11.

*1,2,3,4-Tetra-*O*-acetyl-6-S-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-6-thio-β-*D*-glucopyranose* (**20**).—(a) To a mixture of 1,2,3,4-tetra-*O*-acetyl-6-thio-β-D-glucopyranose (**18**) [11] (50 mg, 0.14 mmol) in 2:1 DMF–water (1.5 mL) containing K_2CO_3 (20 mg, 0.14 mmol), a solution of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**12**) [10] (62 mg, 0.14 mmol) in DMF (1 mL) was added dropwise. The mixture was stirred for 2 h at 80 °C, then neutralized with aq AcOH. The two phases were separated and the organic layer was concentrated to a syrup which was purified by column chromatography (1:1 EtOAc–hexane) and crystallized from EtOH giving **20** (40 mg, 40%), mp 170–171 °C, $[\alpha]_D$ −7.6° (*c* 1.06, $CHCl_3$); NMR: ^1H (400 MHz, $CDCl_3$): Table 1; ^{13}C

(50.3 MHz, $CDCl_3$): Table 2. Anal. Calcd for $C_{28}H_{38}O_{18}S$: C, 48.41; H, 5.48; S, 4.61. Found: C, 48.70; H, 5.30; S, 4.70.

(b) Sodium hydride (34.4 mg, 1.43 equiv) was added to a solution of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (**3**) [8] (0.5 g, 1.40 mmol) in dry THF (5 mL) at 0 °C. The suspension was stirred under N_2 until hydrogen formation had ceased. The resulting solution was then concentrated under reduced pressure, and the residue was dissolved in DMF (5 mL). To this solution, the iodo derivative **25** (0.63 g, 1.39 mmol) was added dropwise and the mixture was stirred for 2 h at room temperature, then concentrated. A solution of the residue in CH_2Cl_2 (25 mL) was washed with water (2 × 5 mL), dried ($MgSO_4$), and concentrated. The crude product was crystallized from EtOH affording **20** (0.7 g, 73%) identical in all respects with the product prepared in (a).

6-S-(β-D-Glucopyranosyl)-6-thio-D-glucopyranose (6-thiogentiobiose, **21***).*—(a) To a solution of the peracetylated thiodisaccharide **20** (0.6 g, 0.86 mmol) in MeOH (40 mL) was added methanolic NaOMe (1.0 m, 0.42 mL). The mixture was stirred for 2 h at room temperature, then deionized with Amberlite IRN-77 (H^+) cation-exchange resin, and filtered. Evaporation of the solvent gave an amorphous powder which was dissolved in water and further purified by preparative LC (7:3 MeCN–water). Freeze-drying from an aq solution afforded **21** (230 mg, 74%), $[\alpha]_D$ 0° (*c* 0.35, water); lit. [19] $[\alpha]_D$ −104° (water). ^{13}C NMR (50.3 MHz, D_2O): Table 2; FABMS: *m/z* 381 (100, $[M + Na]^+$), 359 (40, $[M + H]^+$). Anal. Calcd for $C_{12}H_{22}O_{10}S$: C, 40.22; H, 6.14; S, 8.94. Found: C, 40.02; H, 6.21; S, 8.83.

(b) Conventional *O*-deacetylation of **19** (0.5 g, 0.77 mmol) in MeOH (10 mL) with NaOMe (m, 0.1 mL) for 2 h at room temperature, followed by concentration and treatment of the residue with 80% TFA–water (5 mL) for 1 h at room temperature, afforded **21** (0.11 g, 40%) identical in all respects with the product obtained in (a).

*1,2,3,4-Tetra-*O*-acetyl-6-*O*-p-tolylsulfonyl-β-D-glucopyranose* (**22**).—*p*-Toluenesulfonyl chloride (11.6 g, 61.05 mmol) was added to a solution of D-glucose (10 g, 55.5 mmol) in dry pyridine (150 mL). The mixture was kept for 3 days at room temperature, then acetylated with Ac_2O (40 mL) for 3 h. The solution was poured into cold water (2 L) and the resulting precipitate was filtered, dissolved in $CHCl_3$ (150 mL), washed with cold aq $NaHCO_3$, dried ($MgSO_4$), and concentrated. The crude product was purified by crystallization from EtOH yielding **22** (9.2 g, 33%), mp 204–206 °C, $[\alpha]_D$ +22.2° (*c* 0.5, $CHCl_3$); lit. [20] mp 204–205 °C, $[\alpha]_D$ +23.7° (*c* 0.7, $CHCl_3$); lit. [13] mp 194 °C, $[\alpha]_D$ +23° (*c* 0.7, $CHCl_3$); FABMS: *m/z* 525 (75, $[M + Na]^+$), 443 (70, $[M - AcO]^+$); NMR: ^1H (400 MHz, $CDCl_3$): δ 5.70 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 5.23 (t, 1 H, $J_{2,3} = J_{3,4} = 10.0$ Hz, H-3), 5.01 (dd, 1 H, H-2), 5.00 (t, 1 H, $J_{4,5}$ 10.0 Hz, H-4), 4.15 (2dd; each 1 H, $J_{6a,6b}$ 11.3, $J_{5,6a}$ 2.8, $J_{5,6b}$ 4.5 Hz, H-6a,b), and 3.85 (ddd, 1 H, H-5); ^{13}C (50.3 MHz, $CDCl_3$): δ 91.6 (C-1), 72.7 (C-3), 72.3 (C-5), 70.2 (C-2), 68.0 (C-4), and 66.9 (C-6).

Further crystallization of the mother liquor of **22** from EtOH–$CHCl_3$ afforded 1,2,3,4-tetra-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranose (**23**, 2.0 g, 7%), mp 124–125 °C, $[\alpha]_D$ +95° (*c* 0.5, $CHCl_3$); lit. [20] mp 128–129 °C, $[\alpha]_D$ +92° (*c* 2.0, $CHCl_3$); FABMS: *m/z* 525 (60, $[M + Na]^+$), 443 (40, $[M - AcO]^+$); NMR: ^1H (400 MHz, $CDCl_3$): δ 6.20 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.40 (t, 1 H, $J_{2,3} = J_{3,4} = 9.7$ Hz, H-3), 5.00 (t, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 4.90 (dd, 1 H, H-2), 4.10 (2 dd, each 1 H, $J_{5,6a}$

2.5, $J_{5,6b}$ 4.4 Hz, H-6a,b), and 4.10 (ddd, 1 H, H-5); ^{13}C (50.3 MHz, $CDCl_3$): δ 88.8 (C-1), 69.9 (C-3), 69.8 (C-5), 69.2 (C-2), 68.3 (C-4), and 67.3 (C-6).

Further crystallization of the mother liquor of **23** in EtOH–$CHCl_3$ afforded 1,3,4-tri-*O*-acetyl-2,6-di-*O*-*p*-tolylsulfonyl-α-D-glucopyranose (**24**, 4.8 g, 14%), mp 141–143 °C, $[\alpha]_D$ +81.9° (*c* 0.8, $CHCl_3$); lit. [21] mp 168 °C, $[\alpha]_D$ +97° ($CHCl_3$); lit. [14] mp 175–176 °C, $[\alpha]_D$ +103° (*c*, 1.3); FABMS: *m/z* 637 (20, $[M + Na]^+$), 555 (10, $[M - AcO]^+$); NMR: ^1H (400 MHz, $CDCl_3$): δ 6.13 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 5.34 (t, 1 H, $J_{2,3} = J_{3,4} = 9.7$ Hz, H-3), 4.96 (t, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 4.48 (dd, 1 H, H-2), 4.10 (2dd; each 1 H, $J_{6a,6b}$ 10.0, $J_{5,6a}$ 2.4, $J_{5,6b}$ 4.4 Hz, H-6a,b), and 4.10 (ddd, 1 H, H-5); ^{13}C (50.3 MHz, $CDCl_3$): δ 88.6 (C-1), 74.5 (C-2), 69.3 (C-3), 69.2 (C-5), 67.9 (C-4), and 66.9 (C-6).

2,3,4-Tri-O-*acetyl-6*-S-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-6-thio-α*-D-*glucopyranosyl bromide* (**26**).—To a solution of the octaacetylated thiogentiobiose **20** (1.47 g, 2.12 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C was added commercial 33% HBr in AcOH (3.0 mL, 12 equiv). After 2 h at room temperature, toluene was added (30 mL), and the solution was concentrated under reduced pressure to give a solid which was washed with ether and crystallized from ether–petroleum ether to give **26** (1.22 g, 81%), mp 134–135 °C, $[\alpha]_D$ +58.9° (*c* 0.98, $CHCl_3$); NMR: ^1H (400 MHz, $CDCl_3$): Table 1; ^{13}C (50.3 MHz, $CDCl_3$): Table 2. Anal. Calcd for $C_{26}H_{35}BrO_{16}S$: C, 43.64; H, 4.89; S, 4.47. Found: C, 43.77; H, 4.80; S, 4.76.

2,3,4-Tri-O-*acetyl-6*-S-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-6-thio-β*-D-*glucopyranosyl ethylxanthate* (**27**).—A solution of the bromide **26** (0.79 g, 1.1 mmol) and potassium ethylxanthate (0.19 g, 1.1 mmol) in EtOH (3 mL) was heated at 80 °C for 1 h, then water (20 mL) was added. The solid product was collected and crystallized from ether–petroleum ether yielding **27** (0.81 g, 97%), mp 92–93 °C, $[\alpha]_D$ −46.5° (*c* 0.21, $CHCl_3$); NMR: ^1H (400 MHz, $CDCl_3$): Table 1; ^{13}C (50.3 MHz, $CDCl_3$): Table 2; FABMS: *m/z* 795 (30, $[M + K]^+$), 779 (10, $[M + Na]^+$). Anal. Calcd for $C_{29}H_{40}O_{17}S_3$: C, 46.03; H, 5.29; S, 12.70. Found: C, 46.28; H, 5.03; S, 11.65.

1,2,3,4-Tetra-O-*acetyl-6*-S-*[2,3,4-tri*-O-*acetyl-6*-S-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-6-thio-β*-D-*glucopyranosyl]-6-thio-α,β*-D-*glucopyranose* (**28**).—The ethylxanthate **27** (0.23 g, 0.3 mmol) was dissolved in $CHCl_3$ (0.94 mL) at −15 °C and NaOMe (0.5 M, 0.9 mL) was added. After 30 min at this temperature, the solution was evaporated and to the residue was added 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranose **25**, obtained from **22** according to ref. [12] (153 mg, 0.33 mmol), in 1,3-dimethyl-2-oxo-hexahydropyrimidine (DMPU, 3 mL). After standing for 1 h at 70 °C and 18 h at 40 °C, the solvent was evaporated, the residue dissolved in water (10 mL), washed with CH_2Cl_2 (3 × 5 mL), concentrated and acetylated (1:1 Ac_2O–pyridine, 10 mL). Concentration and purification by column chromatography (3:2 EtOAc–hexane) yielded **28** as a solid (0.15 g, 50%), α:β ratio 1:1 (from ^1H NMR); NMR: ^1H (400 MHz, $CDCl_3$): Table 3; ^{13}C (50.3 MHz, $CDCl_3$): Table 4; FABMS: *m/z* 1021 (4, $[M + Na]^+$).

6-S-*[6*-S-*(β*-D-*glucopyranosyl)-6-thio-β*-D-*glucopyranosyl]-6-thio*-D-*glucopyranose (6^I,6^{II}-dithiogentiotriose,* **29**).—Zemplén *O*-deacetylation of **28** (100 mg, 0.1 mmol) with methanolic NaOMe (1.0 m, 0.05 mL), followed by purification by preparative LC (6:4 MeCN–water) and freeze-drying from an aq solution afforded **29** (50 mg, 93%),

^{13}C NMR (50.3 MHz, D_2O): Table 4; FABMS: m/z 559 (50, $[M + Na]^+$), 537 (20, $[M + H]^+$), 519 (30, $[M - OH]^+$).

1,2-O-Isopropylidene-3-S-(2,3,4,6-tetra-O-acetyl-β-d-glucopyranosyl)-3-thio-α-D-glucofuranose (**30**) .—A solution of **8** (0.25 g, 0.41 mmol) in 50% aq AcOH was heated at 60 °C for 90 min, then cooled to room temperature and neutralized with saturated aq $NaHCO_3$ (50 mL). The product was extracted with CH_2Cl_2 (3 × 50 mL), washed with water (2 × 50 mL), dried (Na_2SO_4), and concentrated to a syrup which was crystallized from EtOH affording **30** (0.21 g, 91%), mp 154–155 °C, $[\alpha]_D$ −32.5° (*c* 0.6, $CHCl_3$); NMR: ^1H (400 MHz, $CDCl_3$): Table 1; ^{13}C (50.3 MHz, $CDCl_3$): Table 2; FABMS: m/z 589 (20, $[M + Na]^+$), 509 (10, $[M - Me_2CO]^+$). Anal. Calcd for $C_{23}H_{34}O_{14}S$: C, 48.76; H, 6.00; S, 5.65. Found: C, 48.93; H, 6.02; S, 5.43.

5-O-Acetyl-1,2-O-isopropylidene-6-O-p-tolylsulfonyl-3-S-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-thio-α-D-glucofuranose (**31**).—To a solution of **30** (0.35 g, 0.62 mmol) in pyridine (5 mL) at −10 °C, *p*-tolylsulfonyl chloride (0.2 g, 2.5 equiv) in pyridine (3 mL) was added dropwise. The mixture was stirred at −10 °C for 2 h, then 18 h at room temperature, and acetylated by addition of Ac_2O (5 mL) for 2 h to yield **31** (0.45 g, 95%) which crystallized from EtOH, mp 131–132 °C, $[\alpha]_D$ −14.3° (*c* 0.42, $CHCl_3$); NMR: ^1H (400 MHz, $CDCl_3$): Table 1; ^{13}C (50.3 MHz, $CDCl_3$): Table 2. Anal. Calcd for $C_{32}H_{42}O_{17}S_2$: C, 50.39; H, 5.51; S, 8.40. Found: C, 50.42; H, 5.56; S, 8.61.

5-O-Acetyl-6-S-acetyl-1,2-O-isopropylidene-3-S-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3,6-dithio-α-D-glucofuranose (**32**).—Potassium thioacetate (0.7 g, 6.14 mmol) was added to a solution of **31** (1.5 g, 1.97 mmol) in DMF (20 mL) and the mixture was heated for 1 h at 80 °C, then concentrated. After extraction with EtOAc, the residue was purified by column chromatography (1:2 EtOAc–hexane) affording **32** (1.18 g, 90%) which was directly used for the subsequent step. NMR: ^1H (300 MHz, $CDCl_3$): Table 1; ^{13}C (75.5 MHz, $CDCl_3$): Table 2.

5-O-Acetyl-6-deoxy-6-iodo-1,2-O-isopropylidene-3-S-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-thio-α-D-glucofuranose (**33**).—Sodium iodide (5.94 g, 39 mmol) and methyltrioctylammonium chloride (1.55 g, 3.83 mmol) were added to a solution of **31** (4.87 g, 6.39 mmol) in dry toluene (70 mL). After stirring at 85 °C for 24 h, the solvent was evaporated and the resulting residue was treated with CH_2Cl_2 (3 × 25 mL), washed with water (15 mL), dried (Na_2SO_4), and concentrated to a syrup. Flash chromatography (3:5 EtOAc–hexane) and crystallization from EtOH gave **33** (3.80 g, 83%), mp 158–159 °C, $[\alpha]_D$ −38.2° (*c* 1.2, $CHCl_3$); NMR: ^1H (400 MHz, $CDCl_3$): Table 1; ^{13}C (50.3 MHz, $CDCl_3$): Table 2. Anal. Calcd for $C_{25}H_{35}IO_{14}S$: C, 41.78; H, 4.87; S, 4.46. Found: C, 41.82; H, 4.84; S, 3.86.

Reaction of sulfonate **31** *with sodium iodide in* N,N *-dimethylformamide; 5-O-acetyl-1,2-O-isopropylidene-3,6-epithio-α-D-glucofuranose* (**34**).—A solution of **31** (350 mg, 0.46 mmol) in DMF (5 mL) was treated with NaI (690 mg, 4.6 mmol). The mixture was stirred at 100 °C for 5 h, then concentrated, extracted with CH_2Cl_2, washed with water, and chromatographed (1:2 EtOAc–hexane) giving successively syrupy **34** (25 mg, 20%), iodide **33** (129 mg, 40%), and unreacted tosylate **31** (135 mg, 40%). The 3,6-epithio derivative **34** had: FABMS: m/z 283 (10, $[M + Na]^+$), 261 (50, $[M + H]^+$), 245 (40, $[M - Me]^+$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.98 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 5.05

(ddd, 1 H, $J_{4,5}$ 3.5, $J_{5,6b}$ 6.8, $J_{5,6a}$ 10.0 Hz, H-5), 4.89 (dd, 1 H, $J_{3,4}$ 4.0 Hz, H-4), 4.58 (d, 1 H, $J_{2,3}$ 0 Hz, H-2), 3.70 (d, 1 H, H-3), 2.95 (t, 1 H, $J_{6a,6b}$ 10.0 Hz, H-6a), 2.90 (dd, 1 H, H-6b); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 107.0 (C-1), 87.0 (C-5), 82.7 (C-2), 76.7 (C-4), 49.9 (C-3), 30.6 (C-6). Heap and Owen [16] report for the C-5 benzoylated analogue of **34** in ^{1}H NMR ($CDCl_3$): δ 6.02 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 5.30 (ddd, 1 H, $J_{4,5}$ 3.3, $J_{5,6a}$ 7.7, $J_{5,6b}$ 9.6 Hz, H-5), 5.01 (t, 1 H, $J_{3,4}$ 3.9 Hz, H-4), 4.60 (d, 1 H, $J_{2,3}$ 0 Hz, H-2), 3.75 (d, 1 H, H-3), 3.06 (m, 2 H, H-6a, H-6b).

5-O-Acetyl-1,2-O-isopropylidene-3,6-di-S-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3,6-dithio-α-D-glucofuranose (**35**).—(a) Sodium hydride (11 mg, 0.46 equiv) was added to a solution of **3** (0.14 g, 0.38 mmol) in THF (3 mL). The suspension was stirred under N_2 until hydrogen evolution ceased, then concentrated. To the amorphous solid dissolved in DMF (3 mL), a solution of **33** (0.24 g, 0.33 mmol) in DMF (3 mL) was added dropwise. After being stirred for 2 h at room temperature, work-up as described for **20** and crystallization from EtOH yielded **35** (0.22 g, 61%), mp 178–179 °C, $[\alpha]_D$ −68.0° (*c* 0.73, $CHCl_3$); NMR: ^{1}H (400 MHz, $CDCl_3$): Table 3; ^{13}C (50.3 MHz, $CDCl_3$): Table 4; FABMS: *m/z* 977 (90, $[M + Na]^+$), 895 (10, $[M - AcO]^+$), 777 (10, $[M - 3\ AcO]^+$), 331 (100). Anal. Calcd for $C_{39}H_{54}O_{23}S_2$: C, 49.06; H, 5.66; S, 6.71. Found: C, 49.20; H, 5.97; S, 6.99.

(b) The sodium salt of **32** (0.5 g, 0.75 mmol), prepared as described for **18** (procedure b), was added to a solution of 15-crown-5 (0.35 mL) and **12** (0.6 g, 1.46 mmol) in DMF (12 mL). After 4 h at 60 °C, the solvent was evaporated and the mixture was acetylated with Ac_2O–pyridine (1:1, 11 mL) for 3 h at room temperature. Conventional work-up gave a mixture which contained **35** and the disulfide **38** (FABMS: *m/z* 1247, $[M + H]^+$) which could not be completely separated.

1,2,4-Tri-O-acetyl-3,6-di-S-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3,6-dithio-α,β-D-glucopyranose (**36**).—Compound **35** (0.5 g, 0.52 mmol) in MeOH (40 mL) was stirred with 1.0 M NaOMe (0.24 mL) for 2 h at room temperature. The solution was made neutral by shaking with Amberlite IRN 77(H^+) cation-exchange resin, the suspension filtered, and the filtrate concentrated. The residue was treated with 90% TFA–water (8 mL) for 10 min at 30 °C under reduced pressure until evolution of acetone had ceased, then concentrated. Acetylation with Ac_2O–pyridine (1:1, 40 mL) for 2 h at room temperature, followed by conventional work-up and crystallization from EtOH, gave **36** (0.35 g, 67%); α:β ratio 1:1 (^{1}H integration), mp 216–218 °C, $[\alpha]_D$ −18.9° (*c* 0.53, $CHCl_3$); NMR: ^{1}H (400 MHz, $CDCl_3$): Table 3; ^{13}C (50.3 MHz, $CDCl_3$): Table 4; FABMS: *m/z* 1021 (20, $[M + Na]^+$), 939 (5, $[M - AcO]^+$), 331 (60). Anal. Calcd for $C_{40}H_{54}O_{25}S_2$: C, 48.10; H, 5.41; S, 6.41. Found: C, 48.08; H, 5.29; S, 6.12.

3,6-Di-S-(β-D-glucopyranosyl)-3,6-dithio-D-glucopyranose (3^1,6^1-dithiolaminaran trisaccharide Y, **37**).—The anomeric mixture of **36** (50 mg, 0.05 mmol) was deacetylated in MeOH (5 mL) with NaOMe (1.0 M, 0.03 mL) for 2 h at room temperature, then neutralized with Amberlite IRN-77 (H +) cation-exchange resin, filtered and concentrated. An aq solution of the residue was freeze-dried and purified by preparative LC (6:4 MeCN–water) affording **37** (24 mg, 90%); $[\alpha]_D$ −19.4° (*c* 0.51, water); FABMS: *m/z* 559 (100, $[M + Na]^+$), 537 (90, $[M + H]^+$); ^{13}C NMR (50.3 MHz, D_2O): Table 4. Anal. Calcd for $C_{18}H_{32}O_{14}S_2 \cdot H_2O$: C, 38.99; H, 6.14; S, 11.55. Found: C, 38.57; H, 6.24; S, 11.13.

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