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Carbohydrate Research 270 (1995) 51–62

CARBOHYDRATE RESEARCH

Synthesis of a thio analogue of *n*-propyl kojibioside, a potential glucosidase inhibitor *

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Received 18 July 1994; accepted 15 November 1994

Abstract

The disaccharide α-D-Glc*p*-(1-*S*-2)-β-D-Glc*p*-(1-*O*Pr) **1**, a thio analogue of α-D-Glc*p*-(1 → 2)-α-D-Glc*p*-(1-OPr)(*n*-propyl kojibioside) in which the inter-glycosidic oxygen atom is replaced by sulfur, has been synthesized for evaluation as a potential glucosidase inhibitor. Glycosylation of the 2-thiol glucopyranosyl acceptor **4** with the trichloroacetimidate of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose **5** gave the α-linked disaccharide **6** stereoselectively. Deprotection was performed by hydrogenolysis in the presence of Pd/C to give **1** as the β-*n*-propyl glycoside. Glycosylation of the thiol **4** with the trichloroacetimidate of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose **8** gave a 1:2.3 mixture of the α and β disaccharides (**9** and **10**); evidence is presented for the occurrence of the orthoester **11**, as an intermediate in the formation of the β-disaccharide.

Keywords: Thio analogue; *n*-Propyl kojibioside; Glucosidase inhibitor

1. Introduction

The synthesis of novel glycosidase inhibitors is of fundamental interest because, although different glycosidases may be grouped according to substrate and product specificity, mechanistic questions regarding the importance of key chemical characteristics of the transition state (e.g., shape or charge) remain unanswered [1,2]. There is also the expectation that inhibitors with therapeutic value will be discovered. For example, inhibition of the glycosidase enzymes involved in the trimming pathway of glycoprotein processing might offer a therapeutic strategy for interfering with HIV viral infectivity since infection of T-lymphocytes by HIV is initiated by the interaction of the viral envelope glycoprotein gp120 and the T-cell surface antigen cd4 [3]. The correct

* Presented at The 75th Canadian Chemical Conference, Edmonton, Canada, June 1992, Abstr. No. 528.

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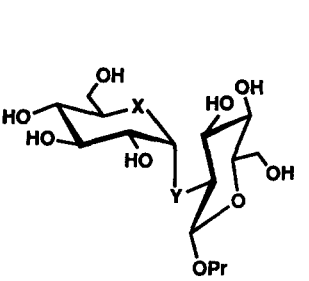
SSDI 0008-6215(95)00014-3



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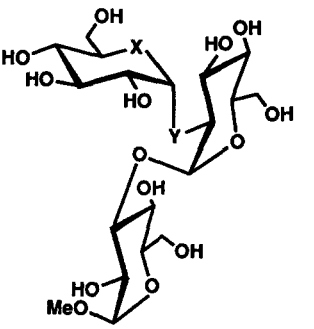

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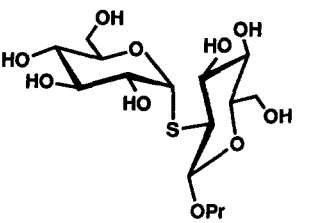

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N-linked oligosaccharide structures on gp120 are known to be involved in the cd4–gp120 interaction, and glycoproteins containing aberrant oligosaccharides have been implicated in breaking the virus replication cycle [3].

We have initiated a program of research to synthesize heteroanalogues of oligosaccharides containing sulfur and/or selenium in the ring and/or interglycosidic linkages for evaluation as glycosidase inhibitors. We have targeted the inhibition of α-glucosidase I of the trimming pathway and propose the synthesis of analogues of kojibiose (α-D-Glc*p*-(1 → 2)-α-D-Glc*p*) **A** and the related trisaccharide, α-D-Glc*p*-(1 → 2)-α-D-Glc*p*-(1 → 3)-α-D-Glc*p* **B**. Thus far, we have reported the synthesis of an analogue of methyl kojibioside containing sulfur in the ring of the non-reducing sugar [4] and, in a related study, the synthesis of heteroanalogues of methyl maltoside [5]. We now report the synthesis of a kojibiose analogue **1** containing sulfur in the interglycosidic linkage with particular focus on the control of S-glycoside stereochemistry.

Thio-linked oligosaccharides have recently gained attention due to their potential as competitive glucosidase inhibitors [6–14]. Several methods have been published for the synthesis of such compounds; these include an S_N2-type reaction involving the action of a thiolate anion on a glycosyl halide [6], the displacement of a leaving group by a 1-thio-glycopyranose [7], and the condensation of a 4-thioglucopyranoside with a 1,6-anhydro glucopyranoside [8]. The first two methods have been used to synthesize thiogentiobiose [6] (the first thioglycosidic analogue of a reducing disaccharide), thiolac-

tose [9] and thiocellobiose [10], and the second method has been used extensively by Defaye, Driguez and co-workers since 1982 for the synthesis of thiomaltose [11], various α-amylase inhibitors [12,13] and 4-thiocellooligosaccharides [14]. A method has recently been developed for the in situ S-deacetylation and activation of 1-thiols, thereby improving the yields in the ensuing displacement reactions [12].

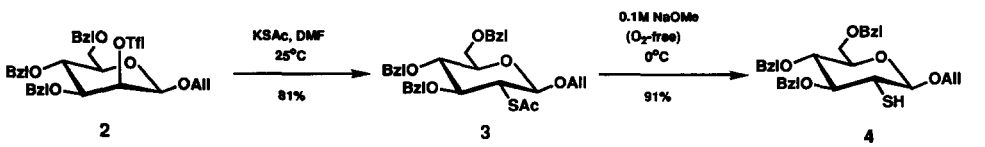
The efficiency of the displacement method relies heavily upon the propensity of a particular ring-carbon-sulfonate to displacement/inversion. Thus, all of the aforementioned examples utilize the displacement of either 4- or 6-sulfonate derivatives of D-galactopyranosides or D-glucopyranosides, respectively. The corresponding S_N2 displacement reactions of 2-sulfonates of α-D-mannopyranosides (and glucopyranosides) do not proceed readily [15,16]. This finding has been attributed in part to stereoelectronic effects in the transition state [15].

Earlier attempts at the displacement of the 2-sulfonate of the less stereoelectronically hindered β-D-mannopyranoside also proceeded poorly with carbohydrate nucleophiles [17], although very recently Defaye et al. [18] have published the efficient synthesis of 2-thiosophorose and 2-thiokojibiose via the S_N2 displacement reaction of 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-β-D-mannopyranose with the β and α anomers, respectively, of 2,3,4,6-tetra-*O*-acetyl-1-thio-D-glucopyranose.

Publication of the latter results has prompted us to report our findings on the synthesis of *n*-propyl 2-thiokojibioside which was based on more traditional glycosylation methodology [19]. This synthesis would therefore require a novel 2-thiol derivative of a D-glucopyranoside as a glycosyl acceptor and an appropriately protected D-glucopyranosyl donor.

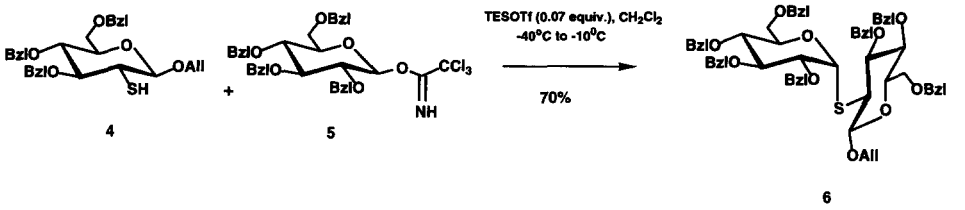
2. Results and discussion

The allyl glycoside **2** was synthesized from the corresponding 2-alcohol [20] by the method of Pavilak et al. [21] using triflic anhydride in pyridine in 82% yield. The inversion of the 2-triflate in **2** with sulfur nucleophiles to give 2-thioglucopyranose analogues was best achieved with potassium thioacetate in DMF at room temperature to give the thioacetate **3** (81%) (Scheme 1). Selective deprotection of the S-acetate **3** was achieved quantitatively with deoxygenated 0.1 N NaOMe in methanol. In the presence of oxygen, the corresponding disulfide was formed in appreciable quantities. The thiol **4** is a convenient thio-glycosyl acceptor for the synthesis of oligosaccharides in which an inter-glycosidic sulfur atom is required, since it can be stored indefinitely over P_2O_5 under vacuum at room temperature.



2 3 4

Scheme 1.



Scheme 2.

Glycosylation of the thiol **4** with either the α or β trichloroacetimidate of 2,3,4,6-tri-*O*-benzyl-D-glucopyranose [22] using triethylsilyltriflate (TESOTf) as a catalyst gave rise to the desired α-linked thiodisaccharide **6** stereoselectively as well as the α-amide **7**, resulting from the rearrangement of the trichloroacetimidates, as reported by Hoffmann and Schmidt [23]. For example, the thiol **4** reacted with the β-trichloroacetimidate **5** in CH_2Cl_2 with 0.07 equivalents of TESOTf as catalyst to give the α-disaccharide **6** in 70% yield and the α-amide **7** (20%) (Scheme 1).

The stereochemical integrity of the benzylated disaccharide **6** was confirmed by observation of $^3J_{H'_1,H'_2}$ and $^1J_{C'_1,H'_1}$ (5.6 Hz and 170 Hz, respectively) for the α-thioglycosidic linkage (see Tables 1 and 2). Deprotection of **6** was achieved by hydrogenolysis in the presence of one equivalent of 10% palladium on activated carbon to give the β-*n*-propyl glycoside **1** in 50% yield.

The acetylated α-trichloroacetimidate **8**, prepared from the corresponding hemiacetals using potassium carbonate and trichloroacetonitrile [22], was examined next as a glycosyl donor in reactions with the thiol acceptor **4**. When 0.14 equivalents of the catalyst TESOTf were used, both the α and β disaccharides **9** and **10** were formed in a ratio of 1:2.3 in 59% yield (Scheme 3). However, when low concentrations of TESOTf were used (0.07 equiv), the orthoester **11** was isolated (78%), even at room temperature (Scheme 3). In contrast, an isolated sample of the pure orthoester rearranged in a separate experiment using 0.14 equivalents of catalyst to give a 1:8 mixture of the α and β disaccharides. Schmidt et al. [24] have used the same trichloroacetimidates in glycosylation reactions with simple alkyl thiols using BF_3 etherate as catalyst and have observed the exclusive formation of the β-glycoside.

The stereochemical integrity of **9** and **10** was confirmed by observation of $^3J_{H'_1,H'_2}$ (6.0 Hz for the α- and 10.0 Hz for the β-disaccharide) (see Table 1), and by observation

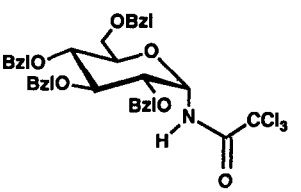


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Table 1
^{1}H NMR data [a,b] for ring protons in compounds **3**–**11**

Cmpd no.	Ring protons											
	1′	2′	3′	4′	5′	6′	1	2	3	4	5	6
3	4.56	3.60	3.72 [c]	3.67	3.5	7.31-3.77						
	(9.0)	(10.0)		(8.5)	(4.5,2.4)	(10.5)						
4	4.27	3.05	3.43	3.62	3.44	3.66,3.68						
	(8.5)	(10.0,3.0 [d])	(8.8)	(9.5)	(2.5,4.0)	(11.0)						
6	6.03	3.88 [c]	3.88 [c]	3.67 [c]	4.23	3.40 [e]	4.51	3.01	3.37	3.60	3.46	3.73 [e]
	(4.5)				(2.5,2.5)		(9.0)	(11.0)	(8.5)	(9.5)	(2.5,4.0)	
1	5.74	3.80 [c]	3.63 [c]	3.40 [c]	3.41 [c]	3.69,3.88 [c]	4.61	2.60	3.41 [c]	3.40 [c]	4.08	3.76 [c],3.79 [c]
	(5.4)					(12.3)	(9.0)	(10.5)			(4.8,2.5)	
9	5.98	5.06	5.37	4.98	4.33 [c]	3.89 [e]	4.41	2.89	3.33	3.62	3.42	3.73 [c]
	(6.0)	(10.0)	(9.8)	(10.0)			(9.0)	(11.5)	(9.0)	(10.0)	(3.0)	
10	4.96	5.00	5.11	5.09	3.62	4.08,4.2	4.47	3.06	3.45	3.62	3.62 [c]	3.72 [c]
	(10.0)				(2.2,4.5)	(12.5)	(8.7)	(10.7)	(8.5)	(9.5)		
		Obscured complex multiplet										
11	5.67	4.42 [f]	5.09	4.80 [f]	3.88	4.14	4.26	2.91	3.31	3.63	3.40	4.74-3.67 [c]
	(5.2)	(2.6,1.0)	(1.9)	(9.5,1.0)	(4.5)	(4.5)	(9.0)	(11.2)	(8.5)	(9.5)	(4.0,2.0)	

[a] In $CDCl_3$. The numbers in parentheses denote coupling constants in Hz.
[b] Other signals: see Experimental Section.
[c] Obscured in 1D spectrum.
[d] $^1J_{H'_2,SH}$.
[e] Not first order.
[f] Long-range coupling.

Table 2

Cmpd no.	Ring carbons											
	1′	2′	3′	4′	5′	6′	1	2	3	4	5	6
3	100.0	50.4	81.8	79.4	75.0	69.0						
4	102.9	46.3	84.9	79.2	75.3	68.9						
6	82.9 (170)	79.3 [c]	82.5 [c]	77.4	70.7	68.4	104.6 (164)	48.1	82.3	79.7	74.9	69.0
1	86.8 (171)	73.7	76.2	73.5	75.6	63.6	106.9 (162)	52.3	78.3	72.3	75.0	63.3
9	81.1 (176)	70.7	70.8	68.3	67.6	61.5	103.9 (164	48.3	82.0	79.9	75.0	68.8
10	83.6 (162)	71.7	74.1	68.3	75.9	62.3	102.3 (156)	52.2	83.3	79.4	75.0	68.8
11	97.4 (183)	72.9	69.6	68.4	77.0	63.4	102.6	51.6	83.6	79.7	74.8	69.9

[a] In $CDCl_3$. The numbers in parentheses denote $^1J_{CH}$ in Hz.
[b] Other signals: see Experimental section.
[c] Assignments may be reversed.

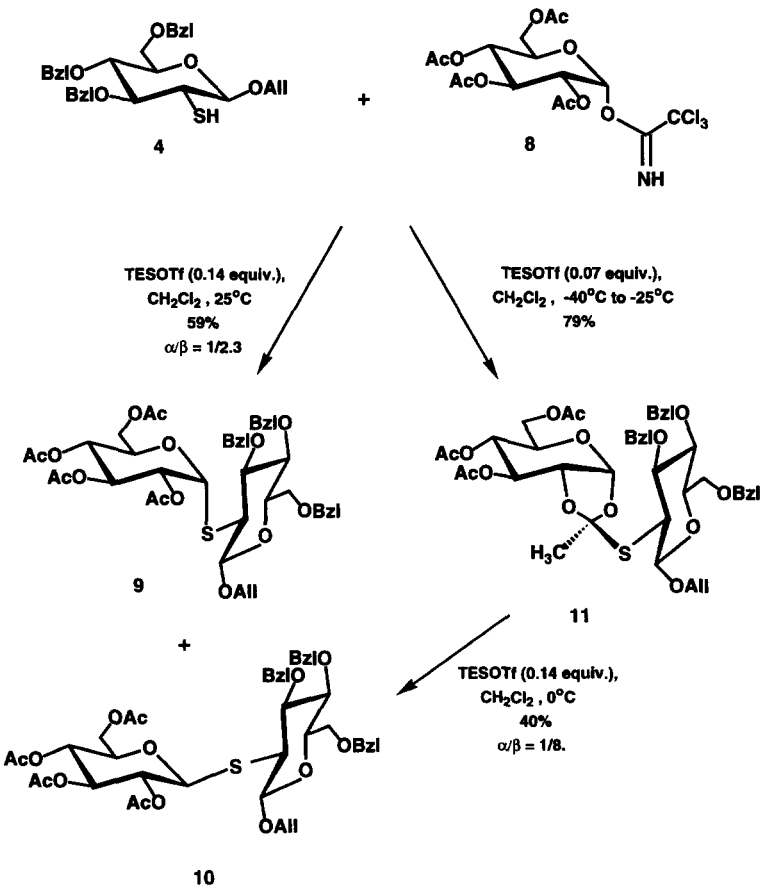
of $^1J_{C_1',H_1'}$ (176 Hz for α and 162 Hz for β) (see Table 2). For the orthoester, a NOESY experiment was performed in order to determine its *exo* or *endo* configuration. The NOESY correlations of interest were those between the orthoester-methyl and ring-protons of the two glucopyranose rings. The assignment of the orthoester-methyl protons and the acetate-methyl protons in the ^{1}H NMR (400 MHz) spectrum (2.08, 2.07, 1.96 and 1.95 ppm) was made on the basis of a ^{13}C–^{1}H chemical-shift correlated experiment. Thus, the ^{13}C orthoester-methyl resonance at 28.9 ppm (distinguishable from the acetate methyl carbon resonances at 20.7 ppm) correlated with the methyl proton resonance at 1.95 ppm in the ^{1}H NMR spectrum. NOESY correlations were then observed between the orthoester-methyl protons and H-5′ and H-2 ring protons, suggesting the presence of the *exo* configuration. The expected contact with H-3′ was not observed due to a changed conformation of the *A* -ring of the orthoester. $^3J_{H-H}$ derived from the ^{1}H NMR spectra indicate that the ring exists in a boat conformation. For example, $^3J_{2',3'} = 2.6$ Hz and $^3J_{H_3',H_4'} = 1.9$ Hz, and long-range coupling (1.0 Hz) is observed between H-2′ and H-4′. The $^1J_{CH}$ coupling constant for C-1′ of the A-ring is 182 Hz and agrees with typical values in the literature.[25]

In conclusion, a viable method for the synthesis of a thio-linked kojibiose analogue, with control of S-glycoside stereochemistry, has been established.

3. Experimental section

Analytical thin-layer chromatography (tlc) was performed using precoated aluminum plates with Merck silica gel 60-F254 as the adsorbent. The developed plates were air dried, exposed to UV light and/or sprayed with a solution of 1% ceric sulfate and 1.5% molybdic acid in 10% aqueous H_2SO_4 and heated to 150°C. Purification of compounds by medium pressure column chromatography was performed using Silica Gel 60 (Merck, 230–400 mesh).

Optical rotations were measured with a Rudolph Research Autopol II automatic polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX-400 NMR spectrometer operating at 400.13 and 100.6 MHz for proton and carbon, respectively.

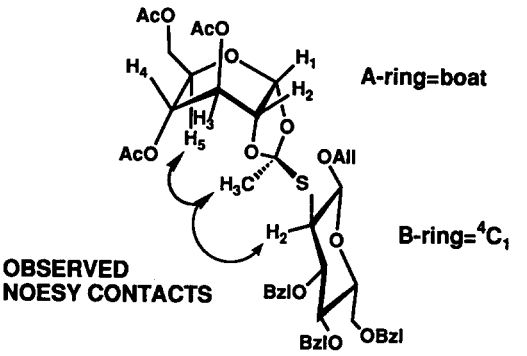


Scheme 3.

All spectra were recorded in $CDCl_3$ except for **9** (D_2O) and chemical shifts are given in ppm downfield from TMS. Chemical shifts and coupling constants were obtained from a first-order analysis of the spectra. The NMR data for the ring protons and carbons are given in Tables 1 and 2.

All compounds were fully characterized by the use of routine ^1H, ^{13}C, $^{13}C\{^1H\}$ and $^1H-^{13}C$-inverse detected NMR spectra as well as ^1H-homonuclear chemical-shift correlated (COSY) spectra [26] (see Tables 1 and 2). COSY spectra were acquired with initial data sets of 512×1024 data points which were zero-filled once in the F_1 direction to give a final data set of 1024×1024 real data points. For the inverse detection experiments, a four-pulse sequence was used for the $^1H\{^{13}C\}-^{13}C$ correlation [27–29]. The data sets of 512×2048 data points were zero-filled once in both the F_1- and F_2-directions, to give a final data set of 1024×2048 real data points.

*Allyl 3,4,6-tri-*O*-benzyl-2-*O*-trifluoromethanesulfonyl-β-*D*-mannopyranoside* **2**.—The title compound was synthesized from the corresponding 2-hydroxy derivative [20] by the method of Pavilak et al. [21]. Purification by column chromatography using hexane–ethyl



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acetate (4:1, R_f 0.35) as eluent gave **2** as a yellow syrup (82%) which was used directly in the following reaction. $[\alpha]_D^{22}$ −37.0° (c 1.0 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.39–7.12 (m, 15 H, 3 $OCH_2C_6H_5$), 5.88 (m, 1 H, OCH_2CHCH_2), 5.31 (m, 1 H, J_{trans} = 17.5 Hz, $CH_2CHCH_ZH_E$), 5.22 (m, 1 H, J_{cis} = 10.5 Hz, $OCH_2CHCH_ZH_E$), 5.17 (d, 1 H, $J_{1,2}$ = 2.8 Hz, H-2), 4.87 (d, 1 H, $J_{A,B}$ = 11.5 Hz, $OCH_AH_BC_6H_5$), 4.83 (d, 1 H, $J_{A,B}$ = 10.5 Hz, $OCH_AH_BC_6H_5$), 4.63–4.51(m, 5 H, 4 $OCH_2C_6H_5$, H-2), 4.42 (m, 1 H, $OCHaHbCHCH_2$), 4.10 (m, 1 H, $OCHaHbCHCH_2$), 3.78–3.70 (m, 3 H, H-4, H-6a, H-6b), 3.68 (dd, 1 H, $J_{2,3}$ = 2.8 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 3.45 (m, 1 H, $J_{4,5}$ = 9.6 Hz, $J_{5,6a}$ = 5.0 Hz, $J_{5,6b}$ = 2.2 Hz, H-5).

*Allyl 3,4,6-tri-*O*-benzyl-2-*S*-acetyl-β-D-glucopyranoside* **3**.—The triflate **2** (3.1 g, 4.98 mmol) and potassium thioacetate (0.816 g, 7.14 mmol) were dissolved in freshly distilled DMF (25 mL). The mixture was stirred under nitrogen at room temperature for 5 min at which time tlc (hexane–ethyl acetate 4:1) indicated the reaction to be complete. The DMF was removed in vacuo and the orange syrup was dissolved in CH_2Cl_2 (100 mL) and washed successively with H_2O (3 × 20 mL) and aqueous sodium chloride solution. The organic layer was dried (Na_2SO_4) and concentrated to give an orange syrup that was chromatographed using hexane–ethyl acetate (4:1, R_f 0.35) as eluent to yield **3** as a light yellow syrup (2.12 g, 81%). $[\alpha]_D^{22}$ − 22.0° (c 1.0 in CH_2Cl_2); Other signals: ^{1}H NMR ($CDCl_3$) δ 7.35–7.15 (m, 15 H, 3 $OCH_2C_6H_5$), 5.88 (m, 1 H, OCH_2CHCH_2), 5.28 (m, 1 H, J_{trans} = 17.0 Hz, $CH_2CHCH_ZH_E$), 5.16 (m, 1 H, J_{cis} = 10.5 Hz, $OCH_2CHCH_ZH_E$), 4.82–4.74 (m, 3 H, 3 $OCH_2C_6H_5$), 4.63 (d, 1 H, $J_{A,B}$ = 12 Hz, $OCH_AH_BC_6H_5$), 4.57 (d, 1 H, $J_{A,B}$ = 11 Hz, $OCH_AH_BC_6H_5$), 4.56 (d, 1 H, $J_{A,B}$ = 12 Hz, $OCH_AH_BC_6H_5$), 4.34 (m, 1 H, $OCHaHbCHCH_2$), 4.09 (m, 1 H, $OCHaHbCHCH_2$), 2.30 (s, 3 H, $SC(O)CH_3$); ^{13}C NMR ($CDCl_3$) δ 193.6 ($SC(O)CH_3$), 138.2, 138.1 (3 $OCH_2C_5C_{1(ipso)}H_5$), 134.0 (OCH_2CHCH_2), 128.3–127.5 (3 $OCH_2C_5C_{1(ipso)}H_5$), 117.0 (OCH_2CHCH_2), 75.3, 74.7, 73.5 ($OCH_2C_6H_5$), 69.8

(OCH_2CHCH_2), 30.6 ($SC(O)CH_3$). Anal. Calcd for $C_{32}H_{36}O_6S$: C, 70.05; H, 6.61. Found: C, 70.04; H, 6.55%.

Allyl 3,4,6-tri-O-benzyl-2-thio-β-D-gluco-pyranoside **4**.—A freshly prepared, oxygen-free (freeze–thaw) 0.1 N NaOMe solution (1.4 mL, 0.14 mmol) was cooled to 0°C and transferred dropwise, by means of a cannula, to a cooled (0°C) solution of the thioacetate **3** (0.075 g, 0.137 mmol) in freshly distilled oxygen-free methanol (2 mL). The reaction mixture was stirred at 0°C and checked by tlc (hexane–ethyl acetate 3:1) which indicated the reaction to be complete after approximately 5 min. The reaction was quenched with cold 1 N HCl solution (2 mL), extracted into CH_2Cl_2 (3 × 10 mL) and washed with water (2 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated to a light green/yellow syrup which was dried over P_2O_5 under vacuum to give a waxy solid (0.065 g, 97%) that was used without further purification. The thiol could be purified if necessary by column chromatography (silica gel) using hexane–ethyl acetate (6:1, R_f 0.45) as eluent. $[\alpha]_D^{22}$ 6.0° (c 1.08 in CH_2Cl_2); Other signals: ^{1}H NMR ($CDCl_3$) δ 7.38–7.16 (m, 15 H, 3 $OCH_2C_6H_5$), 5.88 (m, 1 H, OCH_2CHCH_2), 5.27 (m, 1 H, J_{trans} = 17.0 Hz, $CH_2CHCH_ZH_E$), 5.21 (m, 1 H, J_{cis} = 10.5 Hz, $OCH_2CHCH_ZH_E$), 4.83 (d, 1 H, $J_{A,B}$ = 11 Hz, $OCH_AH_BC_6H_5$), 4.81 (d, 1 H, $J_{A,B}$ = 11 Hz, $OCH_AH_BC_6H_5$), 4.80 (d, 1 H, $J_{A,B}$ = 11 Hz, $OCH_AH_BC_6H_5$), 4.48 (d, 1 H, $J_{A,B}$ = 11 Hz, $OCH_AH_BC_6H_5$), 4.61 (d, 1 H, $J_{A,B}$ = 12 Hz, $OCH_AH_BC_6H_5$), 4.47 (d, 1 H, $J_{A,B}$ = 12 Hz, $OCH_AH_BC_6H_5$), 4.29 (m, 1 H, $OCHaHbCHCH_2$), 4.16 (m, 1 H, $OCHaHbCHCH_2$), 2.05 (d, 1 H, J = 3.0 Hz, SH); ^{13}C NMR ($CDCl_3$) δ 130.3–126.1 (3 $OCH2C_6H_5$), 117.7 (OCH_2CHCH_2), 75.6, 74.9, 73.4 ($OCH_2C_6H_5$), 70.2 (OCH_2CHCH_2). Anal. Calcd for $C_{30}H_{34}O_5S$: C, 71.12; H, 6.76. Found: C, 71.31; H, 6.88%.

Allyl 3,4,6-tri-O-benzyl-2-thio-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-β-D-glucopyranoside **6**.—The thiol **4** (0.159 g, 0.313 mmol) and 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl trichloroacetimidate **5** (0.214 g, 0.313 mmol) were dissolved in dry CH_2Cl_2 (1.5 mL) containing 4 Å molecular sieves in a Schlenk tube under an N_2 atmosphere and cooled to −40°C. Triethylsilyl trifluoromethanesulfonate (4.95 μL, 0.07 eq.) was added to the stirred solution at −40°C. The reaction mixture was warmed to −10°C over 1.5 h at which time tlc (hexane–ethyl acetate 3:1) indicated the absence of the trichloroacetimidate. The reaction mixture was quenched at −10°C with triethylamine (30 μL). The evaporated residue was purified by column chromatography using hexane–ethyl acetate (5:1) as eluent (R_f 0.25) to yield **6** (225 mg; 70%) and the amide **7** (43 mg; 20%). Compound **6**: $[\alpha]_D^{23}$ 61.8° (c 1.12 in CH_2Cl_2); Other signals: ^{1}H NMR ($CDCl_3$) δ 7.38–7.04 (m, 35 H, 7 $OCH_2C_6H_5$), 5.95 (m, 1 H, OCH_2CHCH_2), 5.30 (m, 1 H, J_{trans} = 17.0 Hz, $CH_2CHCH_ZH_E$), 5.15 (m, 1 H, J_{cis} = 10.5 Hz, $OCH_2CHCH_ZH_E$), 4.95–4.27 (m, 14 H, 7 $OCH_2C_6H_5$), 4.46 (m, 1 H, $OCHaHbCHCH_2$), 4.12 (m, 1 H, $OCHaHbCHCH_2$); Other signals: ^{13}C NMR ($CDCl_3$) δ 137.9–138.9 (7 $OCH_2C_5C_{1(ipso)}H_5$), 134.1 (OCH_2CHCH_2), 127.3–128.4 (7 $OCH_2C_5C_{1(ipso)}H_5$), 117.4 (OCH_2CHCH_2), 71.4, 73.3, 73.5, 74.8, 74.9, 75.5, 76.6 ($OCH_2C_6H_5$), 70.3 (OCH_2CHCH_2). Anal. Calcd for $C_{64}H_{68}O_{10}S$: C, 74.68; H, 6.66. Found: C, 74.71; H, 6.80%.

n-Propyl 2-O-(α-D-glucopyranosyl)-2-thio-β-D-glucopyranoside **1**.—A solution of **6** (56 mg, 0.054 mmol) in 80% aq. acetic acid (1 mL) and 80% aq. tetrahydrofuran (1 mL)

containing 10% palladium on activated carbon (Degussa type, 50% H_2O; 110 mg) was treated with H_2 at a pressure of 50 psi. After 3 days, tlc (ethyl acetate–methanol–water 7:3:1) indicated that the reaction was complete. The solution was filtered through Celite and codistilled with 100% ethanol to remove acetic acid. Purification by flash chromatography using dichloromethane–methanol (2: 1) as eluent (R_f 0.3) gave **1** as a glass (10.8 mg ; 50%). $[\alpha]_D^{19}$ 164.8° (c 0.54 in MeOH); Other signals: ^{1}H NMR (D_2O) δ 3.61, 3.88 ($OCH_2CH_2CH_3$), 1.61 ($OCH_2CH_2CH_3$), 0.91 ($OCH_2CH_2CH_3$); Other signals: ^{13}C NMR (D_2O) δ 75.3 ($OCH_2CH_2CH_3$), 25.0 ($OCH_2CH_2CH_3$), 12.6 ($OCH_2CH_2CH_3$). Anal. Calcd for $C_{15}H_{28}O_{10}S$: C, 44.99; H, 7.05. Found: C, 44.65; H, 7.11%.

Allyl 2-O-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-3,4,6-tri-O-benzyl-2-thio-β-D-glucopyranoside ***9*** *and allyl 2-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3,4,6-tri-O-benzyl-2-thio-β-D-glucopyranoside* ***10***.—The thiol **4** (0.075 g, 0.148 mmol) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate [22] **8** (0.115 g, 0.223 mmol) were dissolved in dry CH_2Cl_2 (2 μL) containing 4 Å molecular sieves in a Schlenk tube under an N_2 atmosphere. Triethylsilyl trifluoromethanesulfonate (7.0 μL, 0.031 mmol; 0.14 eq.) was added to the stirred solution at room temperature. Tlc (hexane–ethyl acetate 2:1) indicated the reaction to be complete after 30 min. The reaction mixture was quenched with triethylamine (30 μL) and concentrated to a syrup that was chromatographed using hexane–ethyl acetate (5:3) as eluent. Chromatography yielded starting thiol **4** (and disulfide) (0.012 g) and **9** and **10** (0.074 g, 59% or 75% based on recovered thiol); α/β ratio 1/2.3 as estimated by ^{1}H NMR. The isomers were separable by further chromatography. α-isomer: $[\alpha]_D^{22}$ 103.6° (c 0.55 in CH_2Cl_2); β-isomer: $[\alpha]_D^{22}$ − 18.8° (c 1.04 in CH_2Cl_2). Other signals: α-^{1}H NMR ($CDCl_3$) δ 7.49–7.14 (m, 15 H, 3 $OCH_2C_6H_5$), 5.87 (m, 1 H, OCH_2CHCH_2), 5.27 (m, 1 H, J_{trans} = 17.5 Hz, $CH_2CHCH_ZH_E$), 5.17 (m, 1 H, J_{cis} = 10.5 Hz, $OCH_2CHCH_ZH_E$), 4.92 (d, 1 H, $J_{A,B}$ = 11 Hz, $OCH_AH_BC_6H_5$), 4.79 (d, 1 H, $J_{A,B}$ = 11 Hz, $OCH_AH_BC_6H_5$), 4.83 (d, 1 H, $J_{A,B}$ = 11 Hz, $OCH_AH_BC_6H_5$), 4.59 (d, 1 H, $J_{A,B}$ = 11 Hz, $OCH_AH_BC_6H_5$), 4.63 (d, 1 H, $J_{A,B}$ = 12.5 Hz, $OCH_AH_BC_6H_5$), 4.55 (d, 1 H, $J_{A,B}$ = 12.5 Hz, $OCH_AH_BC_6H_5$), 4.33 (m, 1 H, $OCHaHbCHCH_2$), 4.08 (m, 1 H, $OCHaHbCHCH_2$), 2.04, 2.01, 2.00, 1.96 (s, 3 H, $OC(O)CH_3$); ^{13}C NMR ($CDCl_3$) δ 170.0, 169.4, 169.3 (4 $OC(O)CH_3$), 138.2, 138.0 (3 $OCH_2C_5C_{1(ipso)}H_5$), 134.0 (OCH_2CHCH_2), 128.5–127.6 (3 $OCH_2C_5C_{1(ipso)}H_5$), 117.5 (OCH_2CHCH_2), 76.4, 75.0, 73.6 ($OCH_2C_6H_5$), 70.4 (OCH_2CHCH_2), 20.7, 20.6 (4 $OC(O)CH_3$). β - ^{1}H NMR ($CDCl_3$) δ 7.35–7.12 (m, 15 H, 3 $OCH_2C_6H_5$), 5.97 (m, 1 H, OCH_2CHCH_2), 5.34 (m, 1 H, J_{trans} = 17.0 Hz, $CH_2CHCH_ZH_E$), 5.22 (m, 1 H, J_{cis} = 10.5 Hz, $OCH_2CHCH_ZH_E$), 4.82 (d, 1 H, $J_{A,B}$ = 11 Hz, $OCH_AH_BC_6H_5$), 4.57 (d, 1 H, $J_{A,B}$ = 11 Hz, $OCH_AH_BC_6H_5$), 4.81–4.76 (m, 2 H, $OCH_2C_6H_5$), 4.62 (d, 1 H, $J_{A,B}$ = 12 Hz, $OCH_AH_BC_6H_5$), 4.54 (d, 1 H, $J_{A,B}$ = 12 Hz, $OCH_AH_BC_6H_5$), 4.42 (m, 1 H, $OCHaHbCHCH_2$), 4.15(m, 1 H, $OCHaHbCHCH_2$), 2.04, 2.01, 1.99, 1.82 (s, 3 H, $OC(O)CH_3$); ^{13}C NMR ($CDCl_3$) δ 170.6, 170.1, 169.3 (4 $OC(O)CH_3$), 138.1, 138.0 (3 $OCH_2C_5C_{1(ipso)}H_5$), 134.1 (OCH_2CHCH_2), 128.4–127.6 (3 $OCH_2C_5C_{1(ipso)}H_5$), 117.5 (OCH_2CHCH_2), 76.3, 74.9, 73.5 ($OCH_2C_6H_5$), 70.0 (OCH_2CHCH_2), 20.6, 20.5 (4 $OC(O)CH_3$). α-Anal. Calcd for $C_{44}H_{52}O_{14}S$: C, 63.14; H, 6.26. Found: C, 63.15; H, 6.26%; β-Anal. Calcd for $C_{44}H_{52}O_{14}S$: C, 63.14; H, 6.26. Found: C, 63.36; H, 6.43%.

3,4,6-Tri-O-acetyl-1,2-(1-O-allyl-3,4,6-tri-O-benzyl-2-S-β-D-glucopyranos-2-yl)-orthoacetate 11.—The thiol **4** (0.103 g, 0.203 mmol) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **9** (0.158 g, 0.305 mmol) were dissolved in dry CH_2Cl_2 (3 mL) containing 4 Å molecular sieves in a Schlenk tube and cooled to −40°C. Triethylsilyl trifluoromethanesulfonate (4.8 μL, 0.021 mmol; 0.07 eq.) was added to the stirred solution at −40°C. Tlc (hexane–ethyl acetate 2:1, developed twice) after 2 h indicated the reaction to be complete. The reaction was quenched at −25°C with triethylamine (60 mL) and concentrated to a syrup which was chromatographed using hexane–ethyl acetate 1.9:1 (+1% triethylamine) as eluent to yield **11** as a clear syrup (0.135 g, 79%). $[\alpha]_D^{21}$ − 28.4° (c 1.04 in CH_2Cl_2); Other signals: ^{1}H NMR ($CDCl_3$) δ 7.36–7.13 (m, 15 H, 3 $OCH_2C_6H_5$), 5.96 (m, 1 H, OCH_2CHCH_2), 5.34 (m, 1 H, J_{trans} = 17.0 Hz, $CH_2CHCH_ZH_E$), 5.19 (m, 1 H, J_{cis} = 10.5 Hz, $OCH_2CHCH_ZH_E$), 4.92 (d, 1 H, $J_{A,B}$ = 11 Hz, $OCH_AH_BC_6H_5$), 4.88 (d, 1 H, $J_{A,B}$ = 11 Hz, $OCH_AH_BC_6H_5$), 4.78 (d, 1 H, $J_{A,B}$ = 10.5 Hz, $OCH_AH_BC_6H_5$), 4.56 (d, 1 H, $J_{A,B}$ = 10.5 Hz, $OCH_AH_BC_6H_5$), 4.63 (d, 1 H, $J_{A,B}$ = 12 Hz, $OCH_AH_BC_6H_5$), 4.56 (d, 1 H, $J_{A,B}$ = 12 Hz, $OCH_AH_BC_6H_5$), 4.49 (m, 1 H, $OCHaHbCHCH_2$), 4.12 (m, 1 H, $OCHaHbCHCH_2$), 2.08, 2.07, 1.96, (s, 3 H, 3 $OC(O)CH_3$), 1.95 (s, 3 H, CH_3-orthoester); ^{13}C NMR ($CDCl_3$) δ 170.6, 169.5, 168.8 (4 $OC(O)CH_3$), 138.5, 138.2, 138.0 (3 $OCH_2C_5C_{1(ipso)}H_5$), 134.0 (OCH_2CHCH_2), 128.3–127.4 (3 $OCH_2C_5C_{1(ipso)}H_5$), 117.8 (OCH_2CHCH_2), 116.2 (*C*-orthoester), 76.4, 75.0, 73.5 ($OCH_2C_6H_5$), 70.6 (OCH_2CHCH_2), 28.9 (OCH_3-orthoester), 20.7 (3 $OC(O)CH_3$). Anal. Calcd for $C_{44}H_{52}O_{14}S$: C, 63.14; H, 6.26. Found: C, 62.89; H, 6.36%.

Rearrangement of the orthoester 11.—A sample of the pure orthoester (16 mg, 0.019 mmol) was dissolved in dry CH_2Cl_2 (0.5 mL) containing freshly activated 4 Å molecular sieves in a Schlenk tube under an N_2 atmosphere and cooled to 0°C. Triethylsilyltriflate (3 μL of a 20% solution in CH_2Cl_2, 0.003 mmol) was added to the stirred solution at 0°C. The reaction mixture was warmed to room temperature over 30 min at which time tlc (hexane–ethyl acetate 2:1) indicated the reaction to be complete. The reaction was cooled to −78°C and quenched with triethylamine (30 μL). The evaporated residue was purified by column chromatography using hexane–ethyl acetate (1.75:1, R_f 0.35) to yield 6.5 mg (40%) of a 1:8 mixture of **9**:**10** as determined by ^{1}H NMR spectroscopy.

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