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Synthesis of a dithio analogue of *n*-propyl kojibioside as a potential glucosidase I inhibitor

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Abstract

Procedures for the preparation of 3,4,6-protected 2-thio-α-D-glucopyranoside derivatives by thiolate nucleophilic displacement of the 2-*O*-triflate of α-D-mannopyranoside derivatives were investigated. A synthesis of *n*-propyl 3,4,6-tri-*O*-benzyl-2-thio-β-D-glucopyranoside was developed. Glycosylation of this derivative with 2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl trichloroacetimidate gave an α/β mixture of protected *n*-propyl β-dithiokojibioside and β-dithiosophoroside. Deprotection of the mixture by standard methods and separation by chromatography gave *n*-propyl β-dithiokojibioside (**1**) which is a potential enzyme inhibitor of glucosidase I.

Keywords: 5-Thio-α-D-glucopyranosyl trichloroacetimidate; Thio sugars; *n*-Propyl kojibioside dithio analogue; Glucosidase inhibitor

1. Introduction

The major biosynthetic pathway to complex *N*-linked oligosaccharides in higher eukaryotes occurs by processing of oligosaccharides via the trimming pathway [1–3]. In the initial events, the trimming of the high mannose structure, $Glc_3Man_9(GlcNAc)_2$ by α-glucosidases I and II removes the three glucose residues, and a collection of processing mannosidases then removes the four α-1,2-mannose residues to yield $Man_5(GlcNAc)_2$. A wide variety of more complex bi-, tri- and tetra-antennary structures may then be obtained through the trimming action of mannosidase II enzymes and the addition of specific sugar residues by the corresponding glycosyl transferases. Certain complex structures have been linked to the propagation of tumors and the infectivity of HIV [4]. Interference with the trimming process by glucosidase or mannosidase inhibitors might constitute, therefore, an effective therapeutic strategy.

Thus far, we have reported the synthesis of heteroanalogues of disaccharides, Glc-α-(1→2)-Glc-OR, in which the ring and/or glycosidic oxygen atoms have been O/S [5], S/O [6], and S/N [7]. Previous studies [7–14] have shown that disaccharides with sulfur in the non-reducing sugar ring or with sulfur in the glycosidic linkage are weak to moderately-strong inhibitors of glycosidase enzymes. Thus, it is of interest to investigate

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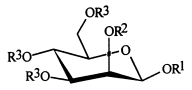
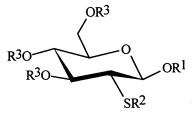
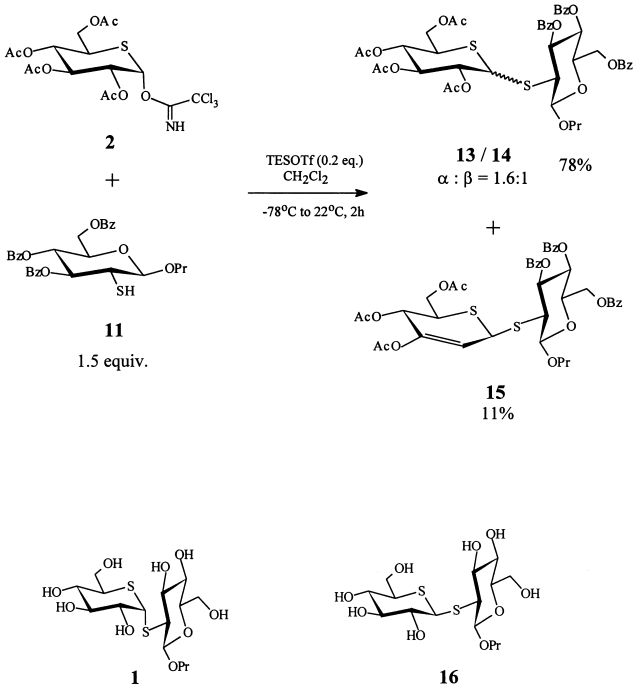
whether these effects are synergistic when sulfur is present in both locations. We now report the synthesis of this type of disaccharide, heteroanalogue **1**, as a potential inhibitor of Glucosidase I.



	R^1	R^2	R^3
4	$CH_2CH{=}CH_2$	H	Bn
5	$CH_2CH{=}CH_2$	Ac	Bn
6	$CH_2CH_2CH_3$	Ac	H
7	$CH_2CH_2CH_3$	Ac	Bz
8	$CH_2CH_2CH_3$	H	Bz
9	$CH_2CH_2CH_3$	Tf	Bz



	R^1	R^2	R^3
3	$CH_2CH{=}CH_2$	H	Bn
10	$CH_2CH_2CH_3$	Ac	Bz
11	$CH_2CH_2CH_3$	H	Bz
12	$CH_2CH_2CH_3$	CN	Bz



2. Results and discussion

Initial attempts at the synthesis of the dithiokojibioside **1** were made using the reaction of 2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl trichloroacetimidate (**2**) [6] with allyl 3,4,6-tri-*O*-benzyl-2-thio-β-D-glucopyranoside (**3**) [5]. In contrast to ordinary trichloracetimidate glycosyl donors, 5-thio trichloroacetimidate donors with ester protecting groups at the 2-position generally give good yields of α-glycosides [6,12]. However, in glycosylation reactions of **3** using triethylsilyl triflate as the catalyst, a complex inseparable mixture was produced, whose ^{1}H NMR spectrum suggested a mixture of at least three different products of undetermined structure. It was therefore decided that a thiol glycosyl acceptor with ester protecting groups instead of benzyl ethers might simplify the reaction by increasing the proportion of the α-disaccharide formed in the glycosylation reaction due to the expected lower reactivity of the ester-protected thiol. This approach was also expected to simplify the deprotection of the disaccharide, based on our previous experience [5].

The alcohol **4** [15] was acetylated using acetic anhydride in pyridine to give **5**. Simultaneous debenzylation and hydrogenation of the allyl to the propyl aglycon, with hydrogen and activated palladium on carbon gave the triol **6**. Benzoylation of **6** using benzoyl chloride in pyridine gave the propyl glycoside **7** in an 85% overall yield from **4**. Selective deprotection of the 2-acetate group was best achieved using anhydrous 1% HCl in MeOH to give the desired 2-alcohol **8** in 89% yield. The selective deprotection of acetate esters in the presence of benzoate esters is normally achieved using 3% HCl in MeOH [16]. However, at this concentration, substantial removal of the 6-benzoate was observed. Quantitative formation of the 2-triflate **9** was achieved by a reaction analogous to the known procedure [17] for the triflation of 1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranose using trifluoromethanesulfonic anhydride in CH_2Cl_2 containing pyridine.

The route to a suitable thiol precursor was examined next. The 2-thioacetyl glucopyranoside **10** was synthesized in 74% yield by stirring the crude triflate with potassium thioacetate in DMF for 1 h. Selective deprotection of the 2-thioacetate of **10** in the presence of the benzoate esters was complicated due to the fact that *S*-acetates are more stable towards acid hydrolysis than *O*-acetates. In order to hydrolyze the *S*-acetate, anhydrous,

oxygen-free, 2% HCl in MeOH–CH_2Cl_2 was required, with heating to 40 °C. However, under these conditions, the simultaneous hydrolysis of the 6-benzoate was observed if the hydrolysis of the *S*-acetate was allowed to reach completion. At room temperature, the reaction was slow [after 16 h the reaction was approximately 50% complete (by TLC)]. Quenching the reaction with ice after heating the reaction mixture at 40 °C for 3 h resulted in the isolation of the desired thiol **11** in 64% yield (74% based on unrecovered thioacetate **10**).

Degassed solvents were used in these reactions to avoid oxidation of the thiol to the disulfide, although this occurs less readily in acidic rather than basic solutions. Nevertheless, small amounts of the disulfide were detected by TLC, although the thiol **11** was far more stable towards oxidation than the benzyl ether-protected thiol **3**. Selective deprotection was also attempted using cysteamine in acetonitrile [18] and diethylamine in DMF [19], but these methods were unsuccessful. The corresponding thiocyanate **12** was also synthesized in order to circumvent the problem of selective deprotection of the thioacetate **10**. This was achieved in approximately the same yield (77%) as the thioacetate by heating a crude mixture of the triflate with potassium thiocyanate in DMF at 70 °C for 3 h. Attempted reduction of the thiocyanate using sodium borohydride in oxygen-free THF–EtOH gave rise to a mixture of products including the desired thiol, as judged by comparison of TLC standards. This approach was discontinued in favor of the thioacetate route.

The glycosylation of the thiol **11** with the trichloroacetimidate **2** was first attempted using a 1:1 mixture of **2** and **11** and 0.25 equiv of triethylsilyl triflate at −50 to +20 °C. Chromatographic purification of the crude product mixture was successful in separating a byproduct, the unsaturated disaccharide **15** (27%), but did not result in resolution of the α- and β-disaccharides **13** and **14** (1:1 mixture, 35%). These two products appeared as a single spot in TLC analysis using a variety of development solvents. Reduction of the amount of triethylsilyl triflate while retaining the same ratio of **2** and **11** gave less **15** (15%), although the isolated yield of the α- and β-disaccharides (~1:1) was 38%, or 78% based on recovered thiol. Based on observations of glycosylation reactions with similar systems, in which the use of an excess of the acceptor led to increased yields of the desired products [14], the above reactions were repeated using a 50% excess of the thiol **11**. A significant reduction in the quantity of molecular sieves (4 Å) was also made, since it was assumed that an excess of sieves was slowing the glycosylation reaction, resulting in incomplete reactions and elimination reactions with the disaccharide to give **15**. Indeed, when the glycosylation reaction was performed using 0.2 equiv. of triethylsilyl triflate and a 50% excess of the thiol, an α/β mixture (1.6:1) of the disaccharides was isolated in 72% yield. A reduction in the yield (11%) of **15** was also observed. No corresponding orthoesters [5] were observed or isolated due to the substantial concentration of triethylsilyl triflate used in the reaction and the temperature to which the reaction mixture was warmed (22 °C) before quenching with base.

The ^{1}H NMR spectrum of a mixture of the α- and β-disaccharides **13** and **14** was well resolved, permitting the proof of anomeric configuration by observation of $^3J_{H1',H2'}$ (4.5 Hz for the α- and 10.5 Hz for the β-thioglycosidic linkage). Pure samples of the β-anomer **14** were obtained by fractional crystallization of the anomeric mixture of disaccharides from Et_2O–CH_2Cl_2-hexanes, but successive crystallizations did not yield the pure α-anomer. The structural assignment of the byproduct disaccharide **15** was made on the basis of ^{1}H NMR and COSY spectra. The value of $^3J_{H1',H2'}$ (< 1 Hz) and long-range coupling between H-2′ and H-4′ led to the assignment of the structure of the unsaturated ring. The anomeric configuration was assigned as β by comparison of $^1J_{C1',H1'}$ (156 Hz) to that for **14** (156 Hz).

Deprotection of a 1.6:1 mixture of the α- and β-disaccharides **13** and **14** was achieved in 85% yield using 0.1 M NaOMe in MeOH. Propyl 2,5′-dithio-β-kojibioside **1** and propyl 2,5′-dithio-β-sophoroside **16** were partially separable by careful chromatography using 2:1 CH_2Cl_2–MeOH as eluent (R_f 0.38–0.55). The stereochemical integrity of the two dithiodisaccharides was confirmed by $^3J_{H1',H2'}$ and $^1J_{C1',H1'}$ values (4.5 and 159 Hz, respectively, for **1**, and 10.5 and 156 Hz, respectively, for **16**). It should be noted that the differences in the $^1J_{C,H}$ coupling constants for α/β pairs is not as pronounced with these *S,S*-acetals as compared to *O,O*-acetals [20] and, in certain cases, may be too small to provide reliable evidence for assignment of anomeric configuration.

In conclusion, the synthesis of a dithio analogue of *n*-propyl β-D-kojibioside, for evaluation as an inhibitor of glucosidase I, has been described.

3. Experimental

For general experimental methods see [5].

Allyl 2-O-acetyl-3,4,6-tri-O-benzyl-β-D-mannopyranoside (**5**).—Acetylation of allyl 3,4,6-tri-*O*-benzyl-*β*-D-mannopyranoside [14] by the standard acetic anhydride/pyridine method gave a quantitative yield of syrupy **5**, which was used without further purification in the preparation of **7**.

Propyl 2-O-acetyl-3,4,6-tri-O-benzoyl-β-D-mannopyranoside (**7**).—To a solution of **5** (0.567 g, 1.06 mmol) in 5:3 MeOH-80% aq HOAc (8 mL) was added dry 10% palladium on carbon (0.250 g) and the mixture was stirred under hydrogen at a pressure of 50 p.s.i. for 24 h. The mixture was filtered through Celite and concentrated, and the acetic acid removed by repeated codistillation with 100% EtOH. The resulting syrupy **6** was dissolved in pyridine (5 mL) and cooled to 0 °C. Benzoyl chloride (0.65 mL, 5.60 mmol) was added dropwise to the stirred mixture which was then heated to 60 °C. After 1 h, TLC (3:1 hexanes-EtOAc) indicated that the reaction was complete. Ice was added to the stirred solution to hydrolyze excess benzoyl chloride and the mixture was stirred for a further 20 min. Pyridine was removed by codistillation with toluene to yield a yellow syrup that was dissolved in CH_2Cl_2 and washed consecutively with H_2O, 10% aq HCl, aq $NaHCO_3$ and H_2O. The organic layer was dried (Na_2SO_4) and the solvent evaporated. The resulting syrup was chromatographed using 3:1 hexanes-EtOAc as eluent (R_f 0.35) to yield **7** (0.486 g, 85%). The pure syrup was crystallized from MeOH: mp 125–127 °C; $[\alpha]_D^{22}$ −58.5° (*c* 1.06, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, $OCH_2CH_2CH_3$), 1.62 (m, 2H $OCH_2CH_2CH_3$), 2.19 (3H, s, $COCH_3$), 3.53 (1H, m, $OCH_aH_bCH_2CH_3$), 3.88 (1H, m, $OCH_aH_bCH_2CH_3$), 4.08 (ddd, 1H, $J_{4,5}$ 9.8, $J_{5,6a}$ 3.5, $J_{5,6b}$ 6.0 Hz, H-5), 4.53 (dd, 1H, $J_{6a,6b}$ 12.0 Hz, H-6b), 4.65 (dd, 1H, H-6a), 4.85 (d, 1H, $J_{1,2}$ 1.0 Hz, H-1), 5.50 (dd, 1H, $J_{2,3}$ 3.2, $J_{3,4}$ 10.0 Hz, H-3), 5.73 (dd, 1H, H-2), 5.82 (t, 1H, H-4), 7.32–8.04 (m, 15H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.3 ($OCH_2CH_2CH_3$), 20.7 ($COCH_3$), 22.7 ($OCH_2CH_2CH_3$), 63.8 (C-6), 67.7 (C-4), 69.2 (C-2), 71.9 (C-3, $OCH_2CH_2CH_3$), 72.5 (C-5), 98.9 (C-1), 128.3-133.4 (Ph), 165.5, 166.1 (3*C*OPh), 169.9 (*C*OCH_3). Anal. Calcd for $C_{32}H_{32}O_{10}$: C, 66.66; H, 5.59. Found: C, 66.68; H, 5.55.

Propyl 3,4,6-tri-O-benzoyl-β-D-mannopyranoside (**8**).—Compound **7** (2.5 g, 4.34 mmol) was dissolved in an anhydrous solution of 1% HCl in MeOH (25 mL) containing dry CH_2Cl_2 (5 mL), and the mixture was stirred at 22 °C under nitrogen. TLC (3:1 hexanes–EtOAc) after 16 h indicated that the reaction was complete. The reaction mixture was diluted with CH_2Cl_2, made basic with solid $NaHCO_3$, and washed consecutively with H_2O and saturated aq NaCl. After drying with Na_2SO_4, the solvent was evaporated and the resulting syrup was crystallized from MeOH to give **8** (2.05 g, 89%): mp 164–165 °C; $[\alpha]_D^{22}$ −54.4° (*c* 1.03, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, 3H, $OCH_2CH_2CH_3$), 1.67 (m, 2H $OCH_2CH_2CH_3$), 2.45 (br s, 1H, OH), 3.57 (m, 1H, $OCH_aH_bCH_2CH_3$), 3.92 (m, 1H, $OCH_aH_bCH_2CH_3$), 4.03 (ddd, 1H, $J_{4,5}$ 9.5, $J_{5,6a}$ 3.5, $J_{5,6b}$ 5.5 Hz, H-5), 4.38 (dd, 1H, $J_{1,2}$ 1.0, $J_{2,3}$ 3.0 Hz, H-2), 4.51 (dd, 1H, $J_{6a,6b}$ 12.0 Hz, H-6b), 4.63 (dd, 1H, H-6a), 4.78 (d, 1H, H-1), 5.38 (dd, 1H, $J_{3,4}$ 9.5 Hz, H-3), 5.95 (t, 1H, H-4), 7.31–8.04 (m, 15H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.3 ($OCH_2CH_2CH_3$), 22.7 ($OCH_2CH_2CH_3$), 63.7 (C-6), 67.4 (C-4), 69.3 (C-2), 71.6, 72.4, 73.9 (C-3, C-5, $OCH_2CH_2CH_3$), 99.5 (C-1), 128.3–133.3 (Ph), 165.4, 166.0, 166.2 (3*C*OPh). Anal. Calcd for $C_{30}H_{30}O_9$: C, 67.41; H, 5.66. Found: C, 67.19; H, 5.61.

Propyl 3,4,6-tri-O-benzoyl-2-S-acetyl-2-thio-β-D-glucopyranoside (**10**).—To a stirred solution of **8** (1.635 g, 3.06 mmol) in dry CH_2Cl_2 (20 mL) containing pyridine (0.57 mL, 7.04 mmol) at −15 °C under nitrogen was added over a period of 1 h, via a dropping funnel, triflic anhydride (1.03 mL, 6.18 mmol) in CH_2Cl_2 (15 mL). The reaction was brought to room temperature and after 1 h TLC (3:1 hexanes: EtOAc) indicated that the reaction was complete. The reaction mixture was diluted with CH_2Cl_2 and extracted consecutively with ice cold H_2O, saturated aq $NaHCO_3$, H_2O, and saturated aq NaCl, and dried with Na_2SO_4 to yield, after removal of solvent, a light yellow foam **9**; the compound was pure by TLC and was used immediately in the following reaction.

To the triflate **9** (0.40 g, 0.60 mmol) in dry DMF (5 mL) was added potassium thioacetate (0.089 g, 0.78 mmol) and the mixture was stirred at room temperature for 1 h. TLC (3:1 hexanes–EtOAc) indicated that the reaction was complete. The DMF was removed in vacuo and the resulting orange syrup was diluted with CH_2Cl_2 and extracted consecutively with H_2O (x2) and saturated aq NaCl, and dried over Na_2SO_4. After removal of the solvent, the syrup was chromatographed using 4:1 hexanes–EtOAc as the eluent (R_f 0.35) to yield

10 (0.261 g, 74%), which was crystallized from the chromatography solvent: mp 142–143 °C; $[\alpha]_D^{22}$ −49° (*c* 0.54, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 0.40 (t, 3H, $OCH_2CH_2CH_3$), 1.61 (m, 2H $OCH_2CH_2CH_3$), 2.25 (3H, s, $SCOCH_3$), 3.50 (m, 1H, $OCH_aH_bCH_2CH_3$), 3.85 (m, 1H, OCH_aH_b CH_2CH_3), 3.88 (dd, 1H, $J_{1,2}$ 9.0, $J_{2,3}$ 11.2 Hz, H-2), 4.08 (ddd, 1H, $J_{4,5}$ 9.5, $J_{5,6a}$ 3.5, $J_{5,6b}$ 5.5 Hz, H-5), 4.48 (dd, 1H, $J_{6a,6b}$ 12.0 Hz, H-6b), 4.59 (dd, 1H, H-6a), 4.79 (d, 1H, H-1), 5.57 (t, 1H, $J_{3,4}$ 9.5 Hz, H-4), 5.76 (dd, 1H, H-3), 7.03–8.04 (m, 15H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.3 ($OCH_2CH_2CH_3$), 22.8 ($OCH_2CH_2CH_3$), 30.6 ($SCOCH_3$), 49.1 (C-2), 63.5 (C-6), 71.2, 71.9, 72.0, 72.1 (C-3, C-4, C-5, $OCH_2CH_2CH_3$), 101.2 (C-1), 128.3–133.3 (Ph), 163.5 (3*C*OPh), 193.2 (S*C*OCH_3). Anal. Calcd for $C_{32}H_{32}O_9S$: C, 64.85; H, 5.44. Found: C, 64.49; H, 5.39.

Propyl 3,4,6-tri-O-*benzoyl-2-thio*-β-D-*glucopyranoside* (**11**).—A solution of **10** (0.45 g, 0.76 mmol) in anhydrous 2% HCl in MeOH (4 mL, oxygen-free) containing CH_2Cl_2 (1.5 mL) was prepared at 0 °C and stirred under nitrogen at room temperature. After 16 h TLC (3:1 hexanes–EtOAc) indicated that the reaction was approximately 60% complete. The reaction was heated to 40 °C and after 3 h TLC indicated that a small amount of the starting thioacetate was unreacted. The reaction was quenched with ice and extracted with CH_2Cl_2 (x3). The organic layer was washed with cold aq NaCl and dried over $MgSO_4$, and the solvent evaporated to yield a light yellow syrup. Chromatography with 6:1 hexanes–EtOAc as eluent (R_f 0.36) yielded **11** (0.261 g, 64%) (74% based on recovered **10**) and **10** (0.063 g). **11**: $[\alpha]_D^{22}$ −34° (*c* 0.87, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 0.45 (t, 3H, $OCH_2CH_2CH_3$), 1.68 (m, 2H $OCH_2CH_2CH_3$), 1.92 (d, 1H, $J_{2,SH}$ 4.8 Hz, SH), 3.31 (ddd, 1H, $J_{1,2}$ 8.5, $J_{2,3}$ 9.8 Hz, H-2), 3.57 (m, 1H, $OCH_aH_bCH_2CH_3$), 3.90 (m, 1H, $OCH_aH_bCH_2CH_3$), 4.07 (ddd, 1H, $J_{4,5}$ 9.0 Hz, $J_{5,6a}$ 3.5 Hz, $J_{5,6b}$ 5.5 Hz, H-5), 4.47 (dd, 1H, $J_{6a,6b}$ 12.0 Hz, H-6b), 4.56 (d, 1H, H-1), 4.58 (dd, 1H, H-6a), 5.53 (m, 2H, H-3, H-4), 7.30–8.00 (m, 15H, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.5 ($OCH_2CH_2CH_3$), 22.8 ($OCH_2CH_2CH_3$), 45.1 (C-2), 63.5 (C-6), 71.0 (C-4), 72.2 (C-5, OCH_2 CH_2CH_3), 74.9 (C-3), 104.2 (C-1), 128.3-133.2 (Ph), 165.4, 165.9 (3*C*OPh). Anal. Calcd for $C_{30}H_{30}O_8S$: C, 65.44; H, 5.49. Found: C, 65.25; H, 5.48.

Propyl 3,4,6-tri-O-*benzoyl-2-deoxy-2-thiocyanato*-β-D-*glucopyranoside* (**12**).—To a solution of the triflate **9** (0.750 g, 1.125 mmol) in dry DMF (10 mL) was added potassium thiocyanate (0.164 g, 1.688 mmol) and the mixture was heated at 70 °C for 3 h, after which time TLC (3:1 hexanes-EtOAc) indicated that the reaction was complete. The DMF was removed in vacuo and the resulting syrup diluted with CH_2Cl_2, extracted consecutively with H_2O (x2) and saturated aq NaCl, and dried over Na_2SO_4. After removal of the solvent the syrup was chromatographed using 3:1 hexanes–EtOAc as the eluent (R_f 0.43) to yield **12** (0.496 g, 77%): ^1H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, 3H, $OCH_2CH_2CH_3$), 1.70 (m, 2H $OCH_2CH_2CH_3$), 3.31 (dd, 1H, $J_{1,2}$ 9.0, $J_{2,3}$ 11.5 Hz, H-2), 3.65, 3.95 (2H, 2m, $OCH_2CH_2CH_3$), 4.11 (m, 1H, H-5), 4.48 (dd, 1H, $J_{5,6b}$ 5.5, $J_{6a,6b}$ 12.0 Hz, H-6b), 4.60 (dd, 1H, $J_{5,6a}$ 3.5 Hz, H-6a), 4.81 (d, 1H, $J_{1,2}$ 9.0 Hz, H-1), 5.59 (t, 1H, $J_{3,4} = J_{4,5} = 9.5$ Hz, H-4), 5.77 (dd, 1H, H-3), 7.03–8.00 (m, 15H, aromatic).

Propyl 2-S-*(2′,3′,4′,6′-tetra*-O-*acetyl-5′-thio*-α-D-*glucopyranosyl)-3,4,6-tri*-O-*benzoyl-2-thio*-β-D-*glucopyranoside* (**13**) *and 2*-S-*(2′,3′,4′,6′-tetra*-O-*acetyl-5′-thio*-β-D-*glucopyranosyl)-3,4,6-tri*-O-*benzoyl-2-thio*-β-D-*glucopyranoside* (**14**).—The thiol **11** (0.200 g, 0.363 mmol) and *O*-(2,3,4,6-tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl)-trichloroacetimidate (**2**) (0.123 g, 0.242 mmol) [6] were dissolved in dry CH_2Cl_2 (2.5 mL) containing activated 4Å molecular sieves (0.135 g) in a Schlenk tube under nitrogen. Trimethylsilyl triflate (10.9 μL, 0.048 mmol) was added to the stirred solution at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and then warmed to 0 °C over 2 h at which time TLC (3:2 hexanes–EtOAc) indicated that the reaction was complete. The reaction was warmed to room temperature for 20 min and then quenched at −78 °C with triethylamine (20 μL). The reaction mixture was filtered and the solvent evaporated, and the resulting syrup purified by chromatography using 3:2 hexanes–EtOAc as eluent (R_f 0.33) to yield a mixture of **13** and **14** (one spot on TLC) (0.156 g, 72%) and **15** (0.023 g, 11%) and unreacted thiol (0.05 g). The ratio of **13:14** was determined by ^1H NMR spectroscopy to be 1.6:1. Fractional crystallization of the mixture of **13** and **14** yielded pure **14**; pure fractions of the α-anomer **13** were not obtained due to the preferential crystallization of **14**.

13: ^1H NMR (400 MHz, $CDCl_3$): δ 1.00 (t, 3H, $OCH_2CH_2CH_3$), 1.61 (m, 2H $OCH_2CH_2CH_3$), 1.82, 1.94, 2.03 (12H, 3s, $4COCH_3$), 3.09 (m, 1H, H-5′), 3.45 (dd, 1H, $J_{1,2}$ 8.8, $J_{2,3}$ 11.2 Hz, H-2), 3.51 (m, 1H, $OCH_aH_bCH_2CH_3$), 3.52 (dd, 1H, $J_{5',6'a}$ 2.4, $J_{6'a,6'b}$ 12.0 Hz, H-6′a), 3.81 (m, 1H, OCH_a

$H_bCH_2CH_3$; 3.81 (dd, 1H, $J_{5',6'b}$ 4.0 Hz, H-6′b), 4.03 (ddd, 1H, $J_{4,5}$ 9.5, $J_{5,6a}$ 5.5, $J_{5,6b}$ 3.5 Hz, H-5), 4.48 (dd, 1H, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.58 (dd, 1H, H-6b), 4.69 (d, 1H, H-1), 4.91 (d, 1H, $J_{1',2'}$ 4.5 Hz, H-1′), 5.12 (m, 2H H-3′, H-4′), 5.26 (dd, 1H, $J_{2',3'}$ 9.8 Hz, H-2′), 5.52 (dd, 1H, $J_{3,4}$ 9.5 Hz, H-3), 5.59 (t, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.4 ($OCH_2CH_2CH_3$), 20.5–20.6 ($4COCH_3$), 22.6 ($OCH_2CH_2CH_3$), 39.0 (C-5′), 49.9 (C-2), 50.9 (C-1′), 60.3 (C-6′), 63.3 (C-6), 70.9 (C-4), 71.1 (C-3), 71.2, 71.5 (C-3′, C-4′), 71.9 (C-5), 72.2 ($OCH_2CH_2CH_3$), 73.9 (C-2′), 104.9 (C-1), 128.3–133.4 (Ph), 165.3–166.1 ($3COPh$), 169.2–170.4 ($4COCH_3$). Anal. Calcd for $C_{44}H_{48}O_{16}S_2$: C, 58.92; H, 5.39. Found (α/β mixture): C, 58.99; H, 5.31.

14: mp 164–165 °C; $[\alpha]_D^{19}$ −14° (*c* 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (t, 3H, $OCH_2CH_2CH_3$), 1.68, 1.89, 1.98, 2.07 (12H, 4s, $4COCH_3$), 1.72 (m, 2H, $OCH_2CH_2CH_3$), 3.16 (ddd, 1H, $J_{4',5'}$ 10.5, $J_{5',6'a}$ 3.5, $J_{5',6'b}$ 5.5 Hz , H-5′), 3.35 (dd, 1H, $J_{1,2}$ 8.5, $J_{2,3}$ 10.8 Hz, H-2), 3.61, 3.91 (2H, 2m, $OCH_2CH_2CH_3$), 4.02 (ddd, 1H, $J_{4,5}$ 9.5 Hz, $J_{5,6a}$ 3.5 Hz, $J_{5,6b}$ 5.5 Hz, H-5), 4.10 (dd, 1H, $J_{6'a,6'b}$ 12.0 Hz, H-6′a), 4.19 (dd, 1H, H-6′b), 4.29 (d, 1H, $J_{1',2'}$ 10.8 Hz, H-1′), 4.48 (dd, 1H, $J_{6a,6b}$ 12.0 Hz, H-6b), 4.58 (dd, 1H, H-6a), 4.59 (d, 1H, H-1), 4.78 (t, 1H, $J_{2',3'} = J_{3',4'} = 9.5$ Hz, H-3′), 5.04 (dd, 1H, H-2′), 5.17 (dd, 1H, $J_{3',4'}$ 9.5 Hz, H-4′), 5.45 (dd, 1H, $J_{3,4}$ 9.5 Hz, H-3), 5.55 (t, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.6 ($OCH_2CH_2CH_3$), 20.1, 20.3, 20.4, 20.5 ($4COCH_3$), 22.9 ($OCH_2CH_2CH_3$), 44.9 (C-5′), 48.0 [$^1J_{C1,H1}$ 156 Hz (C-1′)], 52.0 (C-2), 61.4 (C-6′), 63.4 (C-6), 70.8 (C-4), 71.9 (C-4′), 72.0 (C-5), 72.5 ($OCH_2CH_2CH_3$), 72.9 (C-3), 74.6 (C-3′), 74.9 (C-2′), 104.1 [$^1J_{C1,H1}$ 164 Hz (C-1)], 128.3–133.4 (Ph), 165.4, 165.8, 166.1 ($3COPh$), 168.8, 169.2, 169.4, 170.3 ($4COCH_3$). Anal. Calcd for $C_{44}H_{48}O_{16}S_2$: C, 58.92; H, 5.39. Found: C, 58.83; H, 5.38.

15: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, 3H, $OCH_2CH_2CH_3$), 1.44 (m, 2H $OCH_2CH_2CH_3$), 1.96, 2.02, 2.13 (9H, 3s, $3COCH_3$), 3.13 (1H, dt, $J_{4',5'}$ 10.5, $J_{5',6'a} = J_{5',6'b}$ 3.0 Hz, H-5′), 3.35 (dd, 1H, $J_{1,2}$ 9.0, $J_{2,3}$ 11.5 Hz, H-2), 3.55 (m, 1H, $OCH_aH_bCH_2CH_3$), 3.58 (dd, 1H, $J_{6'a,6'b}$ 12.0 Hz, H-6′b), 3.87 (m, 1H, $OCH_aH_bCH_2CH_3$), 3.97 (dd, 1H, H-6′a), 4.02 (ddd, 1H, $J_{4,5}$ 9.8, $J_{5,6a}$ 3.5, $J_{5,6b}$ 5.5 Hz, H-5), 4.48 (dd, 1H, $J_{6a,6b}$ 12.0 Hz, H-6b), 4.59 (dd, 1H, H-6a), 4.73 (d, 1H, $J_{1,2}$ 9.0 Hz, H-1), 4.97 (broad s, 1H, H-1′), 5.44 (d, 1H, $J_{2',4'}$ 2.5 Hz, H-2′), 5.47 (dd, 1H, $J_{3,4}$ 9.0 Hz, H-3), 5.58 (1H, obscured m, H-4′), 5.59 (1H, obscured m, H-4), 7.03–8.00 (m, 15H, $3COPh$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.4 ($OCH_2CH_2CH_3$), 20.5, 20.7 ($3COCH_3$), 22.8 ($OCH_2CH_2CH_3$), 37.7 (C-5′), 48.1 [$^1J_{C1',H1'}$ 156 Hz (C-1′)], 52.2 (C-2), 61.1 (C-6′), 63.4 (C-6), 68.5 (C-4), 71.1 (C-4′,C-5), 72.0, 72.1 (C-3, $OCH_2CH_2CH_3$), 105.0 [$^1J_{C1,H1}$ 163 Hz (C-1)], 119.7 (C-2′), 128.3–133.4 (Ph), 146.7 (C-3′), 165.3, 165.6, 166.1 ($3COPh$), 168.0, 170.0, 170.3 ($4COCH_3$).

*Propyl 2-thio-2-*S*-(5′-thio-*α*-*D*-glucopyranosyl)-*β*-*D*-glucopyranoside* (**1**) *and propyl 2-thio-2-*S*-(5′-thio-*β*-*D*-glucopyranosyl)-*β*-*D*-glucopyranoside* (**16**).—A 1.6:1 mixture of **13:14** (0.098 g, 0.109 mmol) in 0.1 M NaOMe was stirred under nitrogen. After 12 h the reaction mixture was diluted with MeOH (~10 mL) and neutralized with Rexyn 101 (H^+) resin. After washing the resin with MeOH, the solvent was removed and the syrupy residue was purified by column chromatography using 2:1 CH_2Cl_2–MeOH as the eluent (R_f 0.38–0.55). Fractions were analyzed by TLC, with multiple development, using 1:1:1:0.4 EtOAc–CH_2Cl_2–MeOH–H_2O as the eluent. A total of 0.039 g (85%) of **1/16** was obtained of which 0.011 g was the pure, less-polar β-isomer **16** and 0.008 g was the pure, more-polar α-isomer **1**.

1: $[\alpha]_D^{19}$ +231° (*c* 0.52, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, 3H, $OCH_2CH_2CH_3$), 1.60 (m, 2H, $OCH_2CH_2CH_3$), 2.96 (t, 1H, $J_{1,2} = J_{2,3} = 9.0$ Hz, H-2), 3.32 (m, 1H, H-5′), 3.39 (m, 1H, H-4), 3.40 (m, 2H, H-3, H-5), 3.57 (m, 2H, H-3′, H-4′), 3.60 (m, 1H, $OCH_aH_bCH_2CH_3$), 3.68 (dd, 1H, $J_{5,6a}$ 4.8, $J_{6a,6b}$ 12.0 Hz, H-6a), 3.85 (m, 1H, $OCH_aH_bCH_2CH_3$), 3.88 (3H, m, H-6b, H-6′a, H-6′b), 4.04 (m, 1H, H-2′), 4.63 (d, 1H, $J_{1,2}$ 9.0 Hz, H-1), 4.68 (d, 1H, $J_{1',2'}$ 4.5 Hz, H-1′); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.7 ($OCH_2CH_2CH_3$), 25.0 ($OCH_2CH_2CH_3$), 46.5 (C-5′), 54.3 (C-2), 55.2 [$^1J_{C1',H1'}$ 159 Hz, (C-1′)], 62.8 (C-6′), 63.8 (C-6), 73.7 (C-4), 75.4 (C-5, $OCH_2CH_2CH_3$), 76.5, 77.2 (C-3′, C-4′), 77.5 (C-2′), 78.4 (C-3), 107.2 [$^1J_{C1,H1}$ 161 Hz, (C-1)]. Anal. Calcd for $C_{15}H_{28}O_9S_2$: C, 43.26; H, 6.78. Found: C, 43.63; H, 6.37.

16: $[\alpha]_D^{19}$ +26° (*c* 0.73, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, 3H, $OCH_2CH_2CH_3$), 1.63 (m, 2H $OCH_2CH_2CH_3$), 2.84 (dd, 1H, $J_{1,2}$ 9.0, $J_{2,3}$ 10.5 Hz, H-2), 2.98 (ddd, 1H, $J_{4',5'}$ 10.5, $J_{5',6'a}$ 3.0, $J_{5',6'b}$ 6.0 Hz, H-5′), 3.25 (t, 1H, $J_{2',3'} = J_{3',4'} = 9.0$ Hz, H-3′), 3.34 (dd, 1H, $J_{3,4}$ 8.5, $J_{4,5}$ 9.5 Hz, H-4), 3.40 (m, 1H, H-5), 3.45 (dd, 1H, $J_{1',2'}$ 10.5 Hz, H-2′), 3.46 (dd, 1H, H-3), 3.53 (dd, 1H, H-4′), 3.62 (m, 1H, $OCH_aH_bCH_2CH_3$), 3.67 (dd, 1H, $J_{5,6a}$ 4.5, $J_{6a,6b}$ 12.5 Hz, H-6a), 3.67 (dd, 1H,

$J_{6'a,6'b}$ 12.0 Hz, H-6′a), 3.83–3.89 (3H, m, H-6b, H-6′b, $OCH_aH_bCH_2CH_3$), 4.08 (d, H-1′), 4.52 (d, 1H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.6 ($OCH_2CH_2CH_3$), 25.0 ($OCH_2CH_2CH_3$), 51.6 (C-5′), 51.7 [$^1J_{C1',H1'}$ 156 Hz, (C-1′)], 55.4 (C-2), 63.0 (C-6′), 63.7 (C-6), 73.5 (C-4), 75.3 ($OCH_2CH_2CH_3$), 75.8 (C-4′), 77.3 (C-3), 78.4 (C-5), 79.6 (C-2′), 80.5 (C-3′), 105.2 [$^1J_{C1,H1}$ 161 Hz, (C-1)]. Anal. Calcd for $C_{15}H_{28}O_9S_2$: C, 43.26; H, 6.78. Found: C, 43.71; H, 6.41.

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