Carbohydrate Research, 50 (1976) 215–225

O-BENZYLATED THIOGLUCOSES, INTERMEDIATES FOR THE SYNTHESIS OF (1→6)- AND (1→4)-LINKED OLIGOSACCHARIDES: *S*-BENZYLATION, COUPLING, AND THIOGLYCOSIDE CLEAVAGE

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(Received December 2nd, 1975; accepted for publication in revised form, March 1st, 1976)

ABSTRACT

2,3,4-Tri-*O*-benzyl (**11**) and 2,3,6-tri-*O*-benzyl (**12**) -1-thio-D-glucopyranose were prepared as intermediates for the synthesis, by the thioglycoside scheme, of (1→6)- and (1→4)-linked oligosaccharides of D-glucose. The 6-hydroxyl isomer **11** was *S*-benzylated to the thioglucoside **13**, which is a model for a partially benzyl-protected sugar attached to a macromolecular support by a benzyl thioglycoside linkage. This linkage in **13** is readily cleaved by methyl iodide plus a nucleophile in acetone or benzene. The "alcoholysis" coupling of **13** with 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide gave largely the α-linked product (isomaltoside), together with a little β-linked isomer (gentiobioside).

INTRODUCTION

In a previous paper from this laboratory[1] thioglycosides carrying *O*-benzyl "persistent" blocking groups, and a free hydroxyl group, were suggested as starting materials for systematic, sequential oligosaccharide synthesis. The synthesis of isomaltose from 3-phenylpropyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside was described, and it was proposed that, in oligosaccharide synthesis in the solid phase, the first sugar be attached to the support by a thioglycoside linkage. About the same time, Koto *et al.*[2] reported using ethyl 2,3,4-tri-*O*-benzyl-1-thio-α-D-glucopyranoside as the starting sugar in a synthesis of isomalto-oligosaccharides.

In our early work, the *O*-benzyl protecting groups were removed with sodium–liquid ammonia, to which the phenylpropyl thioglycoside function is stable. The cleavage of the thioglycoside linkage was accomplished, in a final step, with aqueous mercuric chloride. Later[3], we studied the reaction of *O*-benzylated *benzyl* (and 2-phenylethyl) thioglucosides with sodium–liquid ammonia, and showed that *O*-deprotection and thioglycoside cleavage could be accomplished in a single step.

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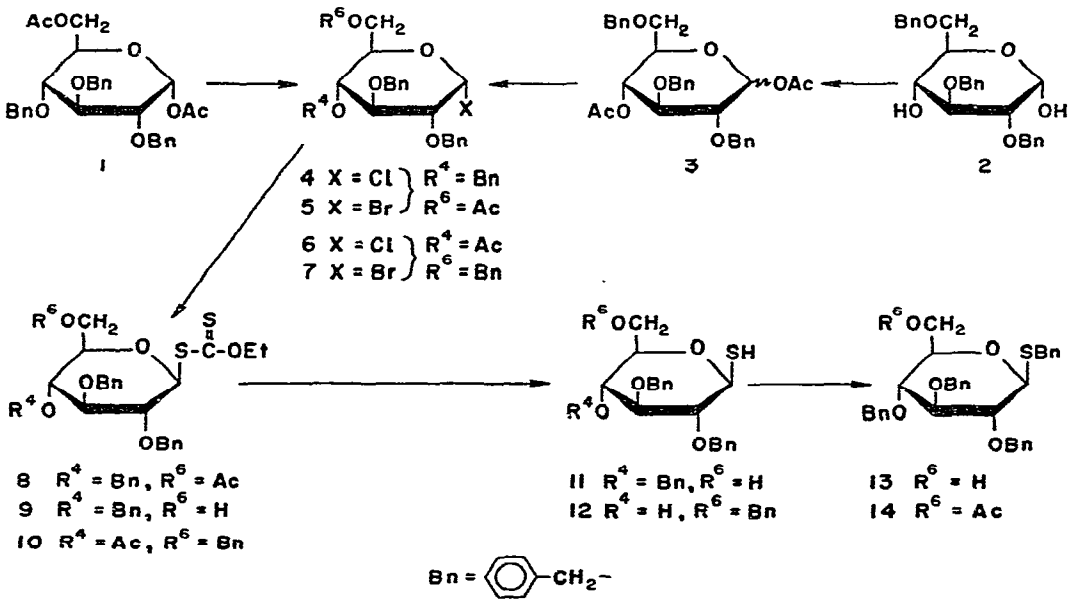
As we turned to actual work with macromolecular supports, described in an accompanying paper[4] and others to come, we found that the attachment of the first sugar to the support by a benzyl thioglycoside linkage was indeed feasible. Here we report the synthesis of two tri-*O*-benzyl-1-thio-D-glucopyranoses suitable for reaction with support-bound benzyl halide functions. Also reported is the conversion of one of the thioglucoses into the benzyl thioglucoside (**13**), and the use of this thioglucoside as a model compound in experiments on the coupling and cleavage procedures used with macromolecular supports.

RESULTS AND DISCUSSION

The preparation of isomers of tri-*O*-benzyl-1-thio-D-glucose having free hydroxyl groups at position 6 (**11**) and position 4 (**12**), respectively, was accomplished by conventional means, as shown in Scheme I. For the isomer having the 6-hydroxyl group free, the well known 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranose (**1**) served as starting material. This compound was obtained, by chromatography on silica gel, in a higher state of purity than previously reported. However, the product made from 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose by the directions of Zemplén, Csűrös, and Angyal[5] is suitable for conversion into the known glucosyl chloride (**4**) and bromide (**5**). Entry into the 4-*O*-acetyl and 4-hydroxyl series was via the known, crystalline 2,3,6-tri-*O*-benzylglucose (**2**), originally prepared[6] from phenyl hepta-*O*-benzyl-α-D-maltoside. We found it convenient to make **2** by the hydrolysis

SCHEME I



of tri-*O*-benzylamylose. Treatment of **2** with acetic anhydride–pyridine gave the syrupy diacetate **3**, which from its p.m.r. spectrum contained 8–10% of β anomer. This diacetate was readily converted into the chloride **6** and bromide **7**. The p.m.r. spectra of **6** and **7** showed the characteristic H-1 signals of α-halides, but the preparations were syrups, and may have contained a little β-anomer. Indeed, the chloride showed a slight upward mutarotation when dissolved in dichloromethane.

The chlorides **4** and **6** readily underwent displacement with potassium ethylxanthate to yield glucosyl ethylxanthates. Partial deacetylation was observed in some trials of this reaction, and in the 2,3,4-tri-*O*-benzyl series both the acetylated (**8**) and the deacetylated (**9**) xanthate were isolated. Deacetylation could be minimized by using a stoichiometric amount of recrystallized potassium ethylxanthate (the crude reagent evidently contains residual alkali), and this is to be recommended because having a single product simplifies the processing of the mixture. Both the acetylated and the deacetylated xanthates are suitable for the next step, namely, saponification to the 1-thio sugar. As the H-1 signals in the p.m.r. spectra of the ethylxanthates were those expected for the β-configuration, the crystalline compounds (**8**, **9**) of the 2,3,4-tri-*O*-benzyl series are designated as β-anomers. Compound **10**, obtained as a syrup, may have contained a little α-anomer.

The configurations of the 1-thio sugars **11** and **12** could not be assigned from their p.m.r. spectra because H-1 is not sufficiently deshielded to give a distinct, low-field signal. However, alkylation of **11** with benzyl bromide gave, in nearly quantitative yield, a benzyl 1-thioglucoside (**13**) showing $[\alpha]_D^{25}$ $-20°$ and $[\alpha]_{436}^{25}$ $-39°$. This value is in the same range as those for benzyl tetra-*O*-benzyl-1-thio-β-D-glucopyranoside[3] (**15**) and the β-anomers[7,8] of the *O*-glycosides **16** and **17**. On the other hand, the α-anomer[7] of **16** has a strong, positive, optical rotation ($[\alpha]_D$ $+56°$). Hence the thioglucoside **13** and its precursor **11** are designated as β-anomers. The thioglucose derivative **12**, isolated as a syrup, may have been a mixture of anomers.

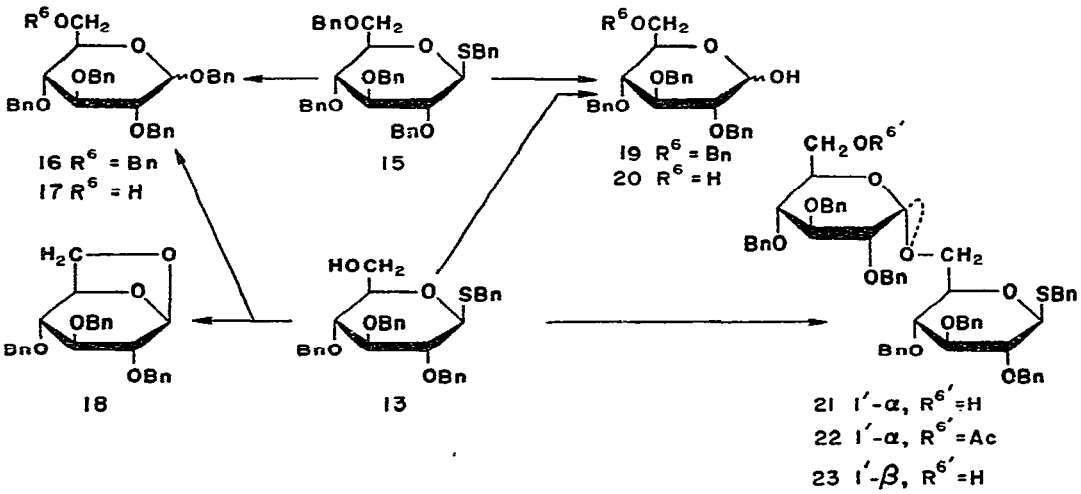
After attachment to a macromolecular support through its sulfur atom, 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranose (**11**) is a suitable starting material for the elaboration of oligosaccharides having a 6-linked glucose residue at the reducing end[4]. Similarly, the 2,3,6-isomer **12** is the potential parent of oligosaccharides having 4-linked glucose as the reducing unit.

Unsatisfactory results with the methods proposed earlier for the release of product oligosaccharides from polystyrene supports required us to find an alternative procedure[4]. Treatment with methyl iodide plus benzyl alcohol in refluxing benzene accomplished the desired cleavage. However, a substantial proportion of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (**18**) was found among the products, especially when the resin carried only monomer (2,3,4-tri-*O*-benzyl-D-glucopyranosyl) groups. The significance of this finding was clarified by studying the cleavage reactions of the model thioglucosides **15** and **13**. From the tetra-*O*-benzyl compound **15**, the only product was benzyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranoside (**16**). The tri-*O*-benzyl compound **13** gave primarily **17**, together with 16% of **18**. Presumably, a displacement reaction of an intermediate sulfonium salt is involved, and when a

properly placed, internal nucleophile (the 6-OH group) is available it competes with the external nucleophile (benzyl alcohol).

Under the conditions of Fétizon and Jurion[9] (refluxing acetone containing a little water) methyl iodide readily converted the thioglucosides **15** and **13** into sugars (**19**, **20**) having free anomeric hydroxyl groups. The reaction was complete in 2.5–3 days, indicating that acetone is the preferred solvent for systems (porous glass) where swelling of the polymer is not a consideration. Overall, the results demonstrated the considerable utility of methyl iodide plus a nucleophile for cleaving protected thioglycosides.

SCHEME II



Some trials were conducted, in benzene solution, of the alcoholysis coupling-reaction[10] between the model thioglucoside **13** and 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide (**5**). The primary purpose of these experiments was to determine whether elevated temperatures[10] could be used with this bromide–acceptor system as a means of increasing the reaction rate. After 5 days at 55°, with a bromide: acceptor ratio of 2:1, unconsumed reactants were present, together with coupling product, and only moderate amounts of side products. Further increasing the temperature to 85° caused the complete disappearance of the reactants (bromide:acceptor 4.4:1), but the yield of coupling product (50%) was not improved because of increased formation of side products. One of the side products, isolated after a deacetylation step, was benzyl 2,3,4-tri-*O*-benzyl-α,β-D-glucopyranoside (**17**). This product was unexpected; its formation suggests the dissociation of the glucosyl bromide to an oxycarbonium ion, which then attacks and detaches a labile benzyloxy group from **13**, or from a second molecule of the bromide. There are distant precedents for such a

loss of a benzyloxy group, but no close ones that we are aware of. The identity (position) of the labile benzyloxy group remains a matter for speculation.

The disaccharide products of the coupling reaction were isolated, after deacetylation. The spectra and analyses of these products are consistent with their formulation as benzyl hexa-*O*-benzyl-1-thio-β-D-isomaltoside (**21**) and benzyl hexa-*O*-benzyl-1-thio-β-D-gentiobioside (**23**). On the basis of its more-positive optical rotation, the major product (90% of the total) is assigned the α-D-linked, isomaltoside structure.

EXPERIMENTAL

General methods. — Chromatographic and instrumental procedures were as described in the first two papers of the series[1,3]. Melting points were determined in Pyrex capillaries heated in an oil bath. Solutions were evaporated *in vacuo*. Compounds were purified to homogeneity, as judged by t.l.c. on 20-cm plates. The solvent systems most commonly used were: A, 9:1 chloroform–ethyl acetate; B, 19:1 chloroform–ethyl acetate; C, 1:1 ether–hexane (Skellysolve B) (all ratios are *v*/*v*).

2,3,6-Tri-O-*benzyl*-D-*glucose derivatives*

2,3,6-Tri-O-*benzyl*-α-D-*glucopyranose* (**2**) *from tri*-O-*benzylamylose.* — To 10 g of tri-*O*-benzylamylose (Superlose®, benzylated as described by BeMiller and Wing[11]) in 240 ml of 1,4-dioxane was added 28 ml of concentrated hydrochloric acid, and the mixture was stirred at 100°. The reaction was stopped after 20 h, even though t.l.c. (3:2 chloroform–ethyl acetate) showed substantial amounts of incompletely hydrolyzed materials, because further heating caused the accumulation of decomposition products. The cooled mixture was diluted with 200 ml of water and extracted with 2 200-ml portions of chloroform. The combined chloroform layers were washed twice with 5% potassium hydroxide (200-ml portions) and then 3 times with water (200-ml portions) and dried (sodium sulfate). Evaporation of the solvent gave 10 g of residue, which was purified by chromatography on silica gel (1350 g, column 7-cm diameter, 3:2 chloroform–ethyl acetate, 1.30 ml/min, 9-ml fractions). Crystallization, from benzene–Skellysolve B, of the residue from fractions 221–341 gave 7.28 g of the title compound. The incompletely hydrolyzed material (fractions 81–200, 2.50 g) on retreatment as just described gave an additional 1.70 g of product. The overall yield was 8.98 g (86%); m.p. 107.5–108° (lit.[6] 108°), $[\alpha]_D^{25}$ +11.2°, $[\alpha]_{436}^{25}$ +18.2° (*c* 0.53, chloroform) (lit.[6] $[\alpha]_D^{20}$ +6.0°). The compound gave a satisfactory elemental analysis and the expected p.m.r. spectrum in $CDCl_3$ (after D_2O exchange τ 4.76, d, 1, $J_{1,2}$ 3.0 Hz, H-1).

1,4-Di-O-*acetyl-2,3,6-tri*-O-*benzyl*-D-*glucopyranose* (**3**). — Acetic anhydride (2 ml) was added to 2.00 g (4.44 mmol) of compound **2** in 8 ml of pyridine. After storage for 20 h at room temperature, the solution was poured into 50 ml of water, and the mixture extracted twice with chloroform. The combined chloroform layers were washed with 5% hydrochloric acid (5 times), 5% sodium hydroxide (3 times),

and water (3 times), dried, and evaporated. The product, a colorless syrup, failed to crystallize; yield 2.14 g (90%); $[\alpha]_D^{25}$ +37°, $[\alpha]_{436}^{25}$ +72.3° (*c* 0.52, chloroform); p.m.r. ($CDCl_3$): τ 2.66 (ps, 15, Ph-*H*), 3.62 (d, ~1, $J_{1,2}$ 3.0 Hz, H-1), 4.62–5.57 (m, 6, PhCH_2), 5.76–6.60 (m, 6, H-2,3,4,5, and 2H-6), 7.83 (s, 2.75, 1α-COCH_3), 7.97 (s, 0.25, 1β-COCH_3), and 8.17 (s, 3, 4-COCH_3). Found: C, 69.39; H, 6.20. $C_{31}H_{34}O_8$ (534.58) requires C, 69.65; H, 6.41.

4-O-Acetyl-2,3,6-tri-O-benzyl-D-glucopyranosyl chloride (*mainly* α) (**6**). — The 1,4-diacetate **3** (1.00 g, 1.87 mmol) was dissolved in 5 ml of abs. ether saturated at 0° with hydrogen chloride gas (dried by passage over calcium chloride). T.l.c. in system C showed the complete disappearance of the starting material after 5 days. The solvent was evaporated off and the remaining hydrogen chloride removed by repeated evaporation of portions of abs. benzene from the residue. The product was a yellow syrup that failed to crystallize; yield 0.95 g (99%); $[\alpha]_D^{25}$ +89° at 30 min (constant, after slight initial increase), $[\alpha]_{436}^{25}$ +178.5° (constant) (*c* 0.50, dichloromethane); p.m.r.* ($CDCl_3$): τ 3.60 (d, 1, $J_{1,2}$ 3.5 Hz, H-1), at high field only τ 8.20 (s, 3, COCH_3). Found: C, 68.48; H, 6.00; Cl, 6.79. $C_{29}H_{31}ClO_6$ (511.00) requires C, 68.16; H, 6.12; Cl, 6.94.

4-O-Acetyl-2,3,6-tri-O-benzyl-D-glucopyranosyl bromide (*mainly* α) (**7**). — One g (1.87 mmol) of the 1,4-diacetate **3** was dissolved in 10 ml of dry dichloromethane saturated with hydrogen bromide gas (dried by passage over calcium chloride). After 0.5 h at room temperature, t.l.c. in system A showed the complete disappearance of the starting material. The solution was concentrated, and residual hydrogen bromide removed by evaporation of successive portions of dry benzene from the residue. The product was a yellow syrup that failed to crystallize; yield 1.05 g (quantitative); $[\alpha]_D^{25}$ +106° (constant for 12 h) (*c* 0.50, dichloromethane); p.m.r. ($CDCl_3$): τ 3.60 (d, 1, $J_{1,2}$ 3.5 Hz, H-1), at high field only τ 8.20 (s, 3, COCH_3). Found: C, 62.47; H, 5.53; Br, 14.17. $C_{29}H_{31}BrO_6$ (555.45) requires C, 62.70; H, 5.63; Br, 14.39.

4-O-Acetyl-2,3,6-tri-O-benzyl-D-glucopyranosyl ethylxanthate (*primarily* β) (**10**). — To 1.00 g (1.96 mmol) of the glucosyl chloride **6** in 25 ml of dry benzene was added 0.35 g (2.18 mmol) of potassium ethylxanthate[3,12] in 25 ml of abs. ethanol. The solution was stirred at room temperature for 5 h, diluted with chloroform, and washed twice with water. The organic layer was dried (sodium sulfate) and evaporated to a yellow syrup, which was chromatographed on silica gel (180 g, 2.5 cm diameter, 9:1 benzene–acetone, 0.5 ml/min, 5-ml fractions). Fractions 67–78 gave 0.56 g (48%) of a colorless syrup. [The low yield may have been due to partial deacetylation during the displacement reaction (see Discussion)]; $[\alpha]_D^{25}$ +9.2°, $[\alpha]_{436}^{25}$ +60° (*c* 0.95, chloroform); p.m.r. ($CDCl_3$): τ 4.58 (d. 1, $J_{1,2}$ 9.5 Hz, H-1), 8.20 (s, 3, COCH_3), and 8.68 (t, 3, *J* 6.2 Hz, CH_2CH_3). Found: C, 64.21; H, 6.18; S, 10.82. $C_{32}H_{36}O_7S_2$ (596.74) requires C, 64.40; H, 6.08; S, 10.75.

2,3,6-Tri-O-benzyl-1-thio-D-glucopyranose (**12**). — The ethylxanthate **10** (0.50 g, 0.84 mmol) was stirred with 10 ml of abs. methanol, and metallic sodium was added

*For this and subsequent derivatives of **3** we note only significant differences from the spectrum of **3**.

in small increments until a clear solution resulted. At this point, t.l.c. in system B indicated complete disappearance of the starting material. On neutralization of the solution with dilute acetic acid, the product precipitated as a syrup. The mixture was extracted with chloroform, and the chloroform layer washed 3 times with water, dried, and evaporated to a colorless syrup, yield 0.32 g (82%); $[\alpha]_D^{25}$ −16.7°, $[\alpha]_{436}^{25}$ −27.3° (*c* 0.82, chloroform); p.m.r. ($CDCl_3$): no signals between τ 2.6 and 4.6; τ 7.40 (bs, 1, exch., O*H*) and 7.71 (d, 1, *J* 8.0 Hz, exch., S*H*)[13]; no signals at higher field. Found: C, 69.18; H, 6.15; S, 7.01. $C_{27}H_{30}O_5S$ (466.58) requires C, 69.50; H, 6.48; S, 6.87.

*2,3,4-Tri-*O*-benzyl-*D*-glucose derivatives*

*1,6-Di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-*D*-glucopyranose* (**1**) *of improved purity.* — The crystalline compound made according to Zemplén, Csűrös, and Angyal[5] was found by t.l.c. in system A to contain a minor, slower moving impurity. Chromatography on a silica gel column (23:2 chloroform–ethyl acetate) gave fractions containing pure **1**. The residue from these fractions was crystallized from methanol; m.p. 73° (lit.[5] 66°, lit.[14] 64–65.5°), $[\alpha]_D^{25}$ +68.3°, $[\alpha]_{436}^{25}$ +120° (*c* 1.25, chloroform) ($[\alpha]_D^{21}$ lit.[5] +62.5°, lit.[14] +68°); p.m.r. ($CDCl_3$): τ 2.63 (ps, 15, Ph-*H*), 3.65 (d, 1, $J_{1,2}$ 3.0 Hz, H-1), no signal for H-1 β at 4.37; τ 4.86–5.35 (m, 6, PhCH_2), 5.50–6.67 (m, 6, H-2,3,4,5, and 2 H-6), 7.88 (s, 3, 1-COCH_3), and 8.00 (s, 3, 6-COCH_3).

*6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-β-*D*-glucopyranosyl ethylxanthate* (**8**). — To 6.4 g (12.5 mmol) of crude 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl chloride[14] (**4**) in 100 ml of anhydrous benzene was added an equimolar portion (2.01 g) of potassium ethylxanthate[12] in 25 ml of warm, abs. ethanol. The mixture was stirred for 24 h at room temperature, filtered, and the filtrate concentrated to a turbid syrup. This was diluted with chloroform and again filtered. Solid, crude product (7.5 g, quantitative) was obtained from the filtrate by evaporation *in vacuo*. Recrystallization from benzene–Skellysolve B or methanol gave the pure title compound; m.p. 105°, $[\alpha]_D^{25}$ +31.4°, $[\alpha]_{436}^{25}$ +112.6° (*c* 1.16, chloroform); p.m.r.* ($CDCl_3$): τ 4.63 (d, 1, $J_{1,2}$ 10 Hz, H-1), 7.99 (s, 3, the only COCH_3 signal), and 8.60 (t, 3, *J* 7.0 Hz, CH_2CH_3). Found: C, 64.52; H, 5.73; S, 10.71. $C_{32}H_{36}O_7S_2$ (596.74) requires C, 64.40; H, 6.08; S, 10.75.

*2,3,4-Tri-*O*-benzyl-β-*D*-glucopyranosyl ethylxanthate* (**9**). — Repetition of the foregoing procedure with two molar portions of potassium ethylxanthate gave a partially deacetylated product. This was readily separated into its components, **8** and **9**, by chromatography on a silica gel column (23:2 chloroform–ethyl acetate). On recrystallization from ethyl acetate–Skellysolve B, the title compound **9** had m.p. 95–96°, $[\alpha]_D^{25}$ +27.7°, $[\alpha]_{436}^{25}$ +114° (*c* 1.03, $CHCl_3$); p.m.r. ($CDCl_3$): τ 4.60 (d, 1, $J_{1,2}$ 9.0 Hz, H-1), 8.18 (bs, 1, O*H*), and 8.59 (t, 3, *J* 7.0 Hz, CH_2CH_3). Found: C, 64.78; H, 6.16; S, 11.60. $C_{30}H_{34}O_6S_2$ (554.70) requires C, 64.95; H, 6.18; S, 11.56.

*2,3,4-Tri-*O*-benzyl-1-thio-β-*D*-glucopyranose* (**11**). — Ethylxanthate **8**, or the mixture of **8** and **9**, was saponified as already described for the preparation of

*For this and subsequent derivatives of **1** we note only significant differences from the spectrum of **1**.

compound **12**. On neutralization of the mixture, crystals of the title compound appeared. To complete the crystallization, water was added, and the mixture was stored for 1 h at 4°. Recrystallization of the product from methanol or benzene–Skellysolve B gave an 85–90% yield of **11** as fine needles; m.p. 139–140°, $[\alpha]_D^{25}$ +14.2°, $[\alpha]_{436}^{25}$ +35.1° (*c* 0.96, chloroform); p.m.r. ($CDCl_3$): no signals between τ 2.65 and 4.85; 7.70 (d, 1, *J* 8.0 Hz, exchangeable, S*H*) and 8.10 (bs, 1, exchangeable, O*H*). Found: C, 69.35; H, 6.30; S, 6.54. $C_{27}H_{30}O_5S$ (466.58) requires C, 69.51; H, 6.48; S, 6.87.

*Benzyl 2,3,4-tri-*O*-benzyl-1-thio-β-*D*-glucopyranoside* (**13**). — To a solution of 0.175 g (0.38 mmol) of the thioglucose **11** in 4 ml of acetone was added 0.065 g (0.38 mmol) of benzyl bromide, and then 0.053 g (0.38 mmol) potassium carbonate in 1 ml of water. After stirring for 10 min at room temperature, t.l.c. in system B showed the reaction to be complete. After neutralization of the excess base with dilute acetic acid, the product was precipitated by pouring the solution onto 1 g of ice. The mixture was kept for 1 h at 4°, and then filtered to yield 0.201 g (96%) of the white, crystalline, title compound. The substance was recrystallized from methanol, 95% ethanol, or benzene–Skellysolve B. When pure it had m.p. 101°, $[\alpha]_D^{25}$ −17.2°, $[\alpha]_{436}^{25}$ −33.5° (*c* 5.5, chloroform). Found: C, 73.42; H, 6.61; S, 5.90. $C_{34}H_{36}O_5S$ (556.69) requires C, 73.35; H, 6.52; S, 5.76. Compound **13** was also obtained by treatment of the sodium salt of thio sugar **11** (generated with sodium methoxide) with an excess of benzyl chloride in benzene solution for 10 h. Filtration, and evaporation of the filtrate, gave the crude product.

*Benzyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-1-thio-β-*D*-glucopyranoside* (**14**). — A sample (0.136 g, 0.24 mmol) of the thioglucoside **13** was acetylated in the usual way (see the foregoing preparation of **3**). Evaporation of the chloroform extract gave a colorless glass. On storage for 3 days at 0° an ethanol–water solution of the glass deposited 0.116 g (79%) of the crystalline title compound as colorless needles, m.p. 83–83.5°, $[\alpha]_D^{25}$ −41.0°, $[\alpha]_{436}^{25}$ −85° (*c* 0.28, $CHCl_3$); p.m.r. (C_6D_6): τ 8.21 (s, 3, $COCH_3$). Found: C, 72.25; H, 6.57; S, 5.49. $C_{36}H_{38}O_6S$ (598.73) requires C, 72.21; H, 6.40; S, 5.36.

Model reactions for solid-phase synthesis

Cleavage of thioglucosides with methyl iodide–water in acetone. — Samples of 0.14 to 0.15 mmol of the thioglucosides were dissolved in 4 ml of acetone. Water (1 ml) and methyl iodide (1 ml) were added, and the mixture was magnetically stirred and boiled under reflux. Progress of the cleavage was monitored by t.l.c. in system A or B. After 2.5–3 days, the starting material had disappeared and a single product-spot was observed in each case. The mixture was partitioned between chloroform and water, and the combined chloroform layers were washed twice with water, dried, and evaporated under diminished pressure. Each residue was then crystallized and identified. Benzyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside[3] (**15**) gave a 94% yield of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose having m.p. 150–152°, $[\alpha]_D^{25}$ +20.8°, and the expected p.m.r. spectrum (lit.[15] m.p. 151–152°, $[\alpha]_D^{20}$ +21.7°).

Compound **13** gave a 95% yield of crystalline (from benzene–Skellysolve B) 2,3,4-tri-*O*-benzyl-D-glucopyranose (**20**) having m.p. (82–84°) and p.m.r. spectrum identical with those of an authentic sample prepared from **1**.

Cleavage of thioglucosides with methyl iodide–benzyl alcohol in benzene. — Benzyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside[3] (**15**, 53.6 mg, 0.083 mmol), methyl iodide (1.5 ml), and benzyl alcohol (92 mg, 0.85 mmol) were added to 12 ml of dry benzene, and the solution was boiled under reflux. T.l.c. in 2:3 ether–Skellysolve B on commercial (E. Merck, silica gel) 20-cm plates showed the complete disappearance of **15** after 6 days. There were two products, having slightly different R_f values, one corresponding to authentic benzyl tetra-*O*-benzyl-β-D-glucopyranoside (**16**β). The mixture was evaporated first under a water-pump vacuum, and then by use of an oil pump. Purification of the residue by thick-layer chromatography, and then column chromatography (silica gel, elution with 2:3 ether–Skellysolve B) gave 30 mg of substance. After recrystallization from methanol the product was still a mixture (t.l.c.). Its n.m.r. spectrum, m.p. (81–83°), and optical rotation ($[\alpha]_D^{25}$ +30.3° at *c* 1.22 in chloroform) were consistent with its formulation as benzyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranoside (**16**); α-anomer lit.[7] m.p. 93.5–94.5°, $[\alpha]_D$ +55.8°; β-anomer lit.[5,7] m.p. 83–84°, $[\alpha]_D$ −14.9°).

A similar experiment was performed with compound **13** (102.5 mg, 0.184 mmol), methyl iodide (0.5 ml), and benzyl alcohol (0.256 g, 2.37 mmol) in 8 ml of dry benzene. The reaction was complete in 4.5 days (t.l.c. in 23:2 chloroform–ethyl acetate). The initial residue was dissolved in chloroform (10 ml), and the solution was washed twice with 0.2M sodium thiosulfate, 3 times with water, dried, and evaporated first under water-pump vacuum, and then with an oil pump.

T.l.c. of the product showed spots previously identified[4] as benzyl 2,3,4-tri-*O*-benzyl-α,β-D-glucopyranoside (**17**) and 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (**18**). A sample was debenzylated by hydrogenolysis (95% ethanol, 5% Pd/C, 2.5 days). The residue was trimethylsilylated[4] and analyzed by g.l.c. (3% SE-30 on Chromosorb W, 3.2 mm × 1.56 m, 150°, or 135–170° programmed). The weight ratio of glucose:1,6-anhydroglucose thus found was 21:4.

Coupling of thioglucoside **13** *with 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucosyl bromide* **5**. — The desired amounts of **13** and the glucosyl bromide (**5**, made from **1** according to Fréchet and Schuerch[16]) were dissolved in dry benzene, and 2,6-lutidine (~2 mmol per mmol of **5**) was added. The proportions used (mmol, ml benzene) and the reaction temperatures, were as follows: expt. 1: **13**, 1.63; **5**, 1.63; 2 ml; 25°; expt. 2: **13**, 1.46; **5**, 3.00; 10 ml; 55°; expt. 3: **13**, 0.53; **5**, 2.36; 5 ml; 85°. After 5 days, each mixture was filtered to remove lutidinium bromide. Chloroform and water were added to the filtrate, and the layers were separated. The aqueous layer was extracted twice with chloroform, and then the combined organic layers were washed 4 times with water, dried, and evaporated. At this point, t.l.c. in system B revealed both unreacted glucosyl bromide and acceptor (**13**) in expts. 1 and 2, but neither in expt. 3.

Chromatography of each residue on a column of silica gel (solvent B) gave a product peak and then unreacted **13**, and hydrolysis products of the glucosyl bromide.

The material in the product-band from each experiment was deacetylated with sodium methoxide in methanol–tetrahydrofuran. The solution was neutralized with dilute acetic acid and partitioned between chloroform and water. The chloroform layer, after washing and drying, was evaporated. The components of the residue, namely **17**, the isomaltoside **21**, and the gentiobioside **23**, were separated by chromatography on columns of silica gel, with 3:2 heptane–ethyl acetate as eluant. Pure fractions of **17** and **21** were obtained from the first column, together with a mixture of **21** and **23**. This was resolved on a multibore column (15 g, 15-cm segments, diameters 1.5, 1.0, 0.8, and 0.6 cm, loading not over 150 mg). The yields (% based on **13**) of isomaltoside **21** were: expt. 1, 30; expt. 2, 49; expt. 3, 50. In expt. 2, the ratio **17**:**21**:**23** was 3:87:10. Benzyl 2,3,4-tri-*O*-benzyl-α,β-D-glucopyranoside (**17**) was identified as described in the accompanying paper[4].

Benzyl 2,3,4,2',3',4'-hexa-O-*benzyl-1-thio-β*-D-*isomaltoside* (**21**). — Evaporation of the appropriate chromatographic fractions, just described, yielded the title compound. On crystallization from methanol it had m.p. 115.5–116°, $[\alpha]_D^{25}$ +14.7°, $[\alpha]_{436}^{25}$ +24.3° (*c* 1.22, chloroform); p.m.r. ($CDCl_3$): τ 2.61 (ps, 35, Ph-*H*), 4.81–5.93 (m, 16, PhCH_2, H-1, H-1'), 5.93–6.95 (m, 12, sugar C*H* and CH_2), and 8.32 (bs, 1, exchangeable, O*H*). Found: C, 74.17; H, 6.48; S, 3.29; $C_{61}H_{64}O_{10}S$ (989.19) requires C, 74.06; H, 6.52; S, 3.24.

Benzyl 6'-O-*acetyl-2,3,4,2',3',4'-hexa*-O-*benzyl-1-thio-β*-D-*isomaltoside* (**22**). — Acetylation of a sample (0.1 g) of **21** in the usual way (see preparation of **3** already described) gave a plastic semi-solid that could not be crystallized; $[\alpha]_D^{25}$ +15.2°, $[\alpha]_{436}^{25}$ +25.4° (*c* 0.43, chloroform); p.m.r. ($CDCl_3$): τ 8.00 (s, 3, COCH_3). Found: C, 73.16; H, 6.36; S, 3.10. $C_{63}H_{66}O_{11}S$ (1031.22) requires C, 73.37; H, 6.45; S, 3.11.

Benzyl 2,3,4,2',3',4'-hexa-O-*benzyl-1-thio-β*-D-*gentiobioside* (**23**), separated as already described, was a colorless syrup, free of **21**; $[\alpha]_D^{25}$ −3.1° (*c* 0.27, chloroform); p.m.r. ($CDCl_3$) closely similar to that of **21**. Found: C, 73.89; H, 6.70; S, 3.08. $C_{61}H_{64}O_{10}S$ (989.19) requires C, 74.06; H, 6.52; S, 3.24.

ACKNOWLEDGMENTS

This work was supported by the College of Agricultural and Life Sciences, University of Wisconsin-Madison, and by grant No. AM-10588 from the National Institute of Arthritis, Metabolism, and Digestive Diseases, NIH. S.A.H. held a traineeship on training grant No. GM-00236 BCH from the National Institute of General Medical Sciences. We are indebted to Prof. Dexter French, and to Mr. Dick Lewis of Stein–Hall and Co., for generous supplies of Superlose, and to Ed Blake for the preparation of compound **1**.

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