1,6-Anhydro-β-D-glucopyranose Derivatives as Glycosyl Donors for Thioglycosidation Reactions

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1,6-Anhydro derivatives of D-glucopyranose, maltose, and maltotriose reacted at room temperature with trimethylsilylated benzenethiol (**2**) and cyclohexanethiol (**3**) in the presence of zinc iodide (ZnI_2) or trimethylsilyl triflate (TMSOTf), giving the corresponding thioglycosides with predominance of one anomer in high yield. 1,6-Anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (**1**) condensed with a more complex thiol derivative, methyl 2,3,6-tri-*O*-benzyl-4-thio-4-*S*-trimethylsilyl-α-D-glucopyranoside (**19**), to give the 4-thiomaltose derivative (**20**), whereas no condensation took place between the 1,6-anhydro disaccharide homologue (**21**) and thiol derivative (**19**). The difference in reactivity between 1,6-anhydro mono- and di-saccharides was utilized for a specific cross-coupling reaction.

1,6-Anhydro-β-D-aldohexopyranoses, readily available from the parent hexoses,[1] are currently used as versatile synthons in carbohydrate chemistry.[2] Not only the 1,6-anhydro derivatives of monosaccharides, *e.g.*, of β-D-glucose, but also those of di- and tri-saccharides such as maltose, cellobiose, and maltotriose have been obtained in moderate yield by improved methods.[3] These derivatives have shown their utility in synthesis,[4] owing to the difference in selectivity between various protecting reagents in reactions with the D-glucopyranose moieties of these oligosaccharides.[5,6]

Meanwhile, aryl, alkyl, and glycosyl derivatives of thioglycosides are receiving considerable attention, and have been used as potential enzyme substrates,[7] as enzyme inhibitors,[8] and as intermediates of *O*-glycoside synthesis.[9] A frequently used synthetic method for this group of compounds is the Lewis acid-catalysed reaction of glycosyl acetates with thiols[10] but, recently, an extension of this method, by conversion of methyl glycosides into the corresponding phenyl 1-thioglycosides using phenylthio(trimethyl)silane (PhSTMS) and ZnI_2, has been reported by Hanessian *et al.*[11] Also, Nicolaou *et al.*[12] prepared a series of useful phenyl 1-thioglycosides from methyl glycosides by employing trimethylsilyl triflate (TMSOTf) as the promoter. These findings in monosaccharide chemistry prompted us to apply thioglycosidation reactions to 1,6-anhydro disaccharide derivatives. We[13] have found that this PhSTMS–ZnI_2 system at low temperature selectively cleaves the 1,6-anhydro ring without affecting the internal glycosidic linkage, to give the corresponding phenyl 1-thioglycoside derivative of the disaccharide. Here we describe another extension of such a thioglycosidation reaction that uses 1,6-anhydro-β-D-glucopyranose moieties of mono-, di-, and tri-saccharide derivatives as the substrates.

Results and Discussion

First, benzenethiol and cyclohexanethiol were chosen as simple, six-membered glycosyl acceptors of aromatic and aliphatic nature, respectively. With TMSOTf as the promoter, 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (**1**) was treated at room temperature with trimethyl(phenylthio)silane (**2**) or cyclohexylthio(trimethyl)silane (**3**), and subsequently with methanolic potassium carbonate for de-*O*-silylation. In both cases the corresponding 1-thioglycoside, phenyl or cyclohexyl 2,3,4-tri-*O*-benzyl-1-thio-D-glucopyranoside [(**4a**)† and (**4b**), respectively] was obtained in high yield (α:β >20:1) (Table, entries 1 and 2). Condensation of 1,6-anhydro derivative (**1**) and thiol derivative (**3**) was also successful with ZnI_2 as the promoter, giving thioglycoside (**4b**) in good yield (α:β 3:1). The thioglycosidation using compound (**3**) also proceeded smoothly when monosaccharide glycosyl donor (**1**) was replaced by its trisaccharide homologue. Thus, per-*O*-benzylated 1,6-anhydro-β-maltotriose (**5**) similarly reacted with compound (**3**) in the presence of TMSOTf or ZnI_2, giving cyclohexyl 2,2′,2″,3,3′,3″,4″,6′,6″-nona-*O*-benzyl-1-thiomaltotrioside (**6**) in *ca.* 70% yield after de-*O*-silylation (entries 4 and 5). No fission of the internal glycosidic linkages in trisaccharide (**5**) occurred under the reaction conditions employed, but higher temperatures and/or prolonged reaction times led to undesired reactions. For example, compound (**6**) (the product in entry 5) seemed to undergo de-*O*-benzylation on the C-6′ and/or C-6″ positions (TLC and/or ^1H NMR) when the reaction (entry 5) was continued for another hour. A substrate not containing a primary benzyloxy group, such as 4-*O*-(6-*O*-acetyl-2,3-di-*O*-benzyl-4-*O*-mesyl-α-D-glucopyranosyl)-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucose (**7**), was stable under similar conditions for 24 h (entry 6). The azido and mesyloxy groups were also stable under these conditions (entry 6). In contrast to the 1,6-anhydro derivatives bearing non-participating groups (OBn and N_3) at C-2 [such as 1,6-anhydro derivatives (**1**), (**5**), and (**7**)], per-*O*-acetate (**9**) of 1,6-anhydro-β-maltose gave exclusively 1-thio-β-glycoside (**10**) on treatment with compound (**3**) under similar conditions, suggesting common stereocontrol for *O*-glycosidation reactions[14] in this type of thioglycosidation.

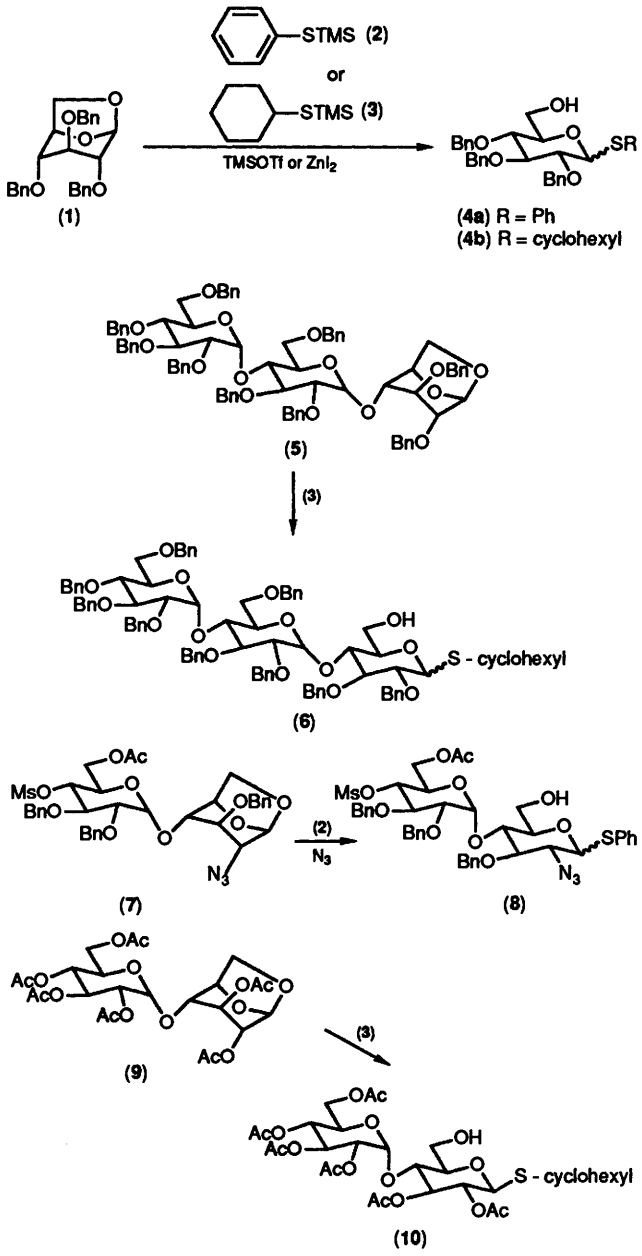
Next, we examined analogous reactions of more complex glycosyl acceptors, *e.g.* 4-thio-D-glucose derivatives. In this way, one could produce oligosaccharides with an internal thioglycosidic bond.[7,15] For this purpose, methyl 2,3,6-tri-*O*-benzyl-4-thio-α-D-glucopyranoside (**14**) was prepared from methyl 2,3,6-tri-*O*-benzyl-α-D-glucoside (**11**). Compound (**11**) was iodinated[16] at C-4, giving the iodide (**12**) with the *galacto* configuration. The iodine atom was smoothly replaced by thioacetate anion, with inversion of the configuration at C-4, when iodide (**12**) was treated with potassium thioacetate in N,N-dimethylformamide (DMF). Zemplen deacetylation of the

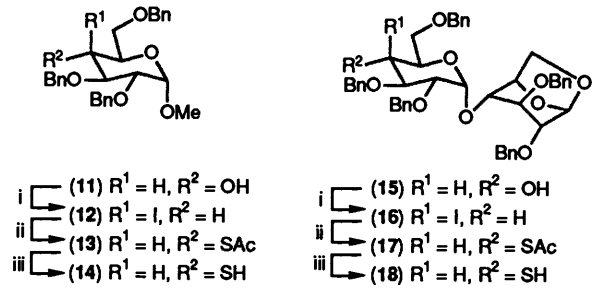
† During the preparation of this manuscript, Taylor and co-workers reported the reaction of compound (**1**) with compound (**3**) to give the 1-thioglycoside (**4a**) (see ref. 20).

Table. Preparation of phenyl and cyclohexyl thioglycosides.[a]

Entry	1,6-Anhydro derivative (A)	RSTMS (B)	Promoter (C)	Molar proportion (A:B:C)	Time (h)	Product	Yield[b] (%)	Ratio[c] (α:β)
1	(1)	(2)	TMSOTf	1:1.5:1	10	(4a)	91	20:1
2	(1)	(3)	TMSOTf	1:3:0.2	10	(4b)	80	20:1
3	(1)	(3)	ZnI_2	1:3:3	1	(4b)	91	3:1
4	(5)	(3)	TMSOTf	1:4:2	24	(6)	77	20:1
5	(5)	(3)	ZnI_2	1:3:3	1	(6)	60	5:1
6	(7)	(2)	ZnI_2	1:5:4	24	(8)	64	1.8:1
7	(9)	(3)	ZnI_2	1:3:3	2.5	(10)	97	0:100

[a] Reactions were performed at room temperature in CH_2Cl_2 or $(CH_2Cl)_2$. [b] Total yield after flash column chromatography. [c] These ratios were determined by ^1H NMR spectroscopy.



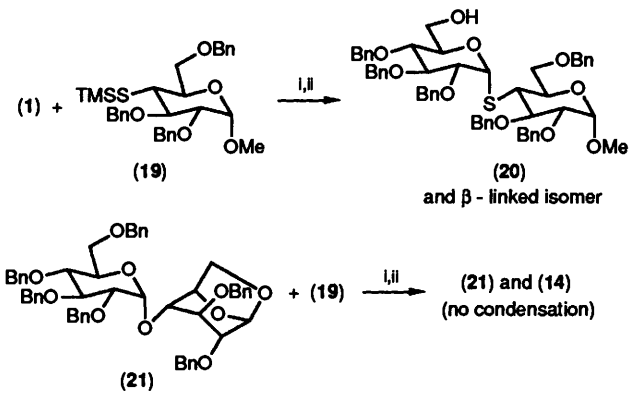


Scheme 1. *Reagents and solvents:* 1, Tri-iodoimidazole–imidazole–triphenylphosphine, toluene; ii, KSAc, DMF; iii, MeOH–MeONa, then Dowex 50w-x8 (H^+).

resulting methyl 4-*S*-acetyl-2,3,6-tri-*O*-benzyl-4-thio-α-D-glucopyranoside (**13**) gave thiol (**14**) in excellent yield (Scheme 1). Before the coupling with 1,6-anhydro derivatives, the thiol (**14**) was *S*-trimethylsilylated according to Glass's procedure.[17] The reaction was monitored by ^1H NMR spectroscopy. The proton signals assignable to the 4-H and SH of thiol (**14**) appeared at δ 3.03 and 1.64 as a multiplet and a doublet, respectively. When the silylation was complete, those signals disappeared, and a new triplet appeared at δ 2.73, which was assigned to 4-H of the trimethylsilylated compound (**19**). The not-quite-stable compound (**19**) was used for the next glycosidation reaction without purification. Thus, 1,6-anhydro monosaccharide (**1**) was treated with compound (**19**) in the presence of ZnI_2 to give, after column chromatography, the expected thiodisaccharide in 66% yield. The ^1H NMR spectrum of the thiodisaccharide revealed a doublet (*J* 5.4 Hz) at δ 5.96 assignable to 1′-H, strongly suggesting the product to be an α-linked thioglycoside.* However, a pair of triplets in the ratio 15:1 with the same *J*-value (11 Hz) appeared at δ 3.06 and 2.84. These signals were assignable to the 4-H atoms of α- and β-linked isomers, respectively, and suggested that the thiodisaccharide obtained might be a mixture of the α- and the β-isomer in the ratio 15:1, while the 1′-H signal of the β-isomer overlapped with other signals and was unidentifiable. Purification by chromatography gave methyl 2,3,6-tri-*O*-benzyl-4-thio-4-*S*-(2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**20**) as a syrup.

Next, the possibility of the use of 1,6-anhydro disaccharides as glycosyl donors was examined. Unexpectedly, condensation of 1,6-anhydro-2,2′,3,3′,4′,6′-hexa-*O*-benzyl-β-maltose (**21**) with thiol derivative (**19**) under conditions similar to those used before gave only starting material (**21**) and thiol (**14**) derived from the thiol derivative (**19**) by desilylation during work-up

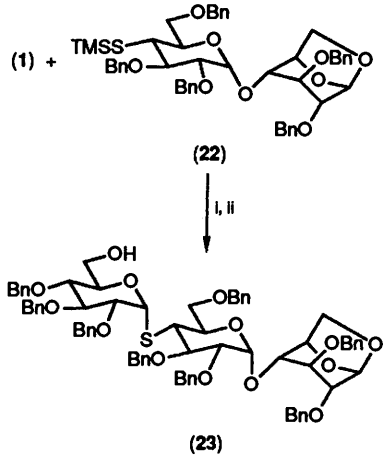
* The $J_{1,2}$-value of α-D-1-thio-glycoses and -glycosides is 5–6 Hz, differing from the 3–4 Hz value found for their *O*-analogues, and 1-H of α-1-thioglycosides was deshielded by *ca.* 0.3 ppm compared with that of their *O*-analogues (see M. Apparu, M. Blanc-Muesser, J. Defaye, and H. Driguez, *Can. J. Chem.*, 1981, **59**, 314; ref. 15).



Scheme 2. *Reagents and solvents:* i, ZnI_2, $(CH_2Cl)_2$; ii, K_2CO_3, MeOH.

(Scheme 2). As di- and tri-saccharide derivatives (**7**) and (**5**) reacted smoothly with simple thiols like compound (**2**) and (**3**), the failure of this reaction between 1,6-anhydro disaccharide (**21**) and thiol derivative (**19**) indicated the limited reactivity of 1,6-anhydro oligosaccharides as glycosyl donors.

The difference found between the reactivities of the 1,6-anhydro mono- and oligo-saccharides prompted us to explore selective thioglycosidation reactions. 1,6-Anhydro-2,3-di-*O*-benzyl-4-*O*-(2,3,6-tri-*O*-benzyl-4-thio-α-D-glucopyranosyl)-β-D-glucopyranose (**18**) was prepared from 1,6-anhydro-2,2′,3,3′,6′-penta-*O*-benzyl-β-maltose (**15**) in a similar manner to the preparation of thiol (**14**) from compound (**11**). Two intermediates, the iodide (**16**) and the 4′-thioacetate (**17**), were obtained in moderate yield, and the deacetylation of compound (**17**) smoothly yielded thiol (**18**). Though both a 1,6-anhydro ring and a thiol group were present in the molecule, thiol (**18**) was expected to function as a glycosyl acceptor only. As in the case of monosaccharide thiol (**14**), compound (**18**) was silylated, and the resulting compound (**22**) was used for the next condensation reaction without purification. When compound (**22**) was treated with 1,6-anhydro monosaccharide (**1**) in the presence of ZnI_2, the α-linked thiotrisaccharide (**23**) was obtained in 48% yield (Scheme 3). In this case, no β-isomer was



Scheme 3. *Reagents and solvents:* i, ZnI_2, $(CH_2Cl)_2$; ii, K_2CO_3, MeOH.

detectable by ^1H NMR spectroscopy. It is noteworthy that self-condensation of compound (**22**) was not observed under these conditions, confirming the large difference in the reactivity of 1,6-anhydro functions between 1,6-anhydro monosaccharide (**1**) and disaccharide (**22**).

Conclusions

The utility of 1,6-anhydro-β-D-glucopyranose derivatives as glycosyl donors in the preparation of alkyl, aryl, and glycosyl thioglycosides is described. The reactivities of the 1,6-anhydro rings of the studied mono- and di-saccharides are different, which enables specific cross-coupling between these species.

Experimental

M.p.s were determined with a Yamato micro melting point apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer Model 241 MC polarimeter, for solutions in $CHCl_3$. IR spectra were recorded with a Shimadzu IR-27 spectrophotometer, using KBr discs for solid samples and KRS (thallium bromide–iodide) for liquid samples, unless otherwise specified. ^1H NMR spectra were recorded with either JEOL JNM-GX 400 or JEOL JNM-GX 500 spectrometers, with tetramethylsilane as the internal standard for solutions in $CDCl_3$. Reactions were monitored by TLC on precoated plates of silica gel $60F_{254}$ (layer thickness 0.25 mm; E. Merck, Darmstadt, Germany), spots being visualized under UV light and/or by charring with a solution of MeOH–conc. H_2SO_4–*p*-anisaldehyde (85:10:5 v/v). Flash column chromatography was performed on silica gel 60 (230–400 mesh; E. Merck, Darmstadt, Germany). All extractions were evaporated under reduced pressure below 45 °C.

Phenyl 2,3,4-*Tri*-O-*benzyl*-1-*thio*-D-*glucopyranoside* (**4a**).—To a solution of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (**1**)[18] (0.216 g, 0.5 mmol) and compound (**2**) (0.142 ml, 0.73 mmol) in CH_2Cl_2 (2 ml) at 0 °C under argon was added TMSOTf (31 μl, 0.16 mmol). The mixture was stirred at room temperature for 10 h, poured into aq. $NaHCO_3$, and extracted with EtOAc. The organic layer was washed successively with brine and water, dried ($MgSO_4$), and evaporated. The residue was dissolved in dry tetrahydrofuran (THF)–MeOH (1:1; 10 ml) containing K_2CO_3 and the mixture was stirred for 10 min at room temperature. The mixture was diluted with EtOAc, washed successively with brine and water, dried (Na_2SO_4), and evaporated. The solid residue was subjected to flash column chromatography (toluene–EtOAc, 15:1), giving the 1-thioglycoside (**4a**) (0.248 g, 91%) (α:β >20:1) as a white solid. Recrystallization from EtOH afforded the α-anomer of compound (**4a**) as crystals, m.p. 100–101 °C (Found: C, 73.2; H, 6.3; S, 5.9. Calc. for $C_{33}H_{34}O_5S$: C, 73.0; H, 6.3; S, 5.9%); $[\alpha]_D^{23}$ +152° (*c* 0.4 in $CHCl_3$); {lit.,[19] 103–104 °C; $[\alpha]_D$ +169° (*c*, 1); lit.,[20] 93–94 °C}; ν_{max}^{KBr} 3 500 cm^{-1} (OH).

Cyclohexyl 2,3,4-*Tri*-O-*benzyl*-1-*thio*-D-*glucopyranoside* (**4b**).—(a) *With* ZnI_2. To a solution of compound (**1**) (0.216 g, 0.5 mmol) and compound (**3**)[17] (0.283 g, 1.5 mmol) in $(CH_2Cl)_2$ (5 ml) under argon was added ZnI_2 (0.478 g, 1.5 mmol). The resulting suspension was stirred at room temperature for 1 h, diluted with EtOAc, and filtered through a Celite pad. The filtrate was washed successively with aq. $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated. The residue was dissolved in dry THF–MeOH (1:1, 10 ml) containing K_2CO_3. The mixture was stirred for 10 min at room temperature, diluted with EtOAc, washed successively with brine and water, dried (Na_2SO_4), and evaporated. The residue was subjected to flash column chromatography (toluene–EtOAc, 15:1), giving an anomeric mixture (α:β 3:1) of thioglycoside (**4b**) (0.251 g, 91%) as a white solid, δ_H 5.38 (0.75 H, d, *J* 5.5 Hz, 1-H_α), 4.56 (0.25 H, d, *J* 9.7 Hz, 1-H_β), 2.95 (0.25 H, m, SCH of β-anomer), and 2.73 (0.75 H, m, SCH of α-anomer).

(b) *With* TMSOTf. A mixture of compound (**1**) (0.216 g, 0.5 mmol), compound (**3**) (0.283 g, 1.5 mmol), and TMSOTf (20 μl, 0.1 mmol) in $(CH_2Cl)_2$ (4 ml) was stirred at room temperature

under argon for 10 h. Work-up as described for thioglycoside (**4a**) gave thioglycoside (**4b**) (0.220 g, 80%) (α:β >20:1) as a white solid. Recrystallization from EtOH gave pure *α-anomer of the thioglycoside* (**4b**), m.p. 110–110.5 °C (Found: C, 72.15; H, 7.3; S, 5.7. $C_{33}H_{40}O_5S$ requires C, 72.2; H, 7.35; S, 5.8%); $[\alpha]_D^{21}$ +122° (*c* 0.7 in $CHCl_3$); ν_{max}^{KBr} 3 525 cm^{-1} (OH); δ_H 7.15–7.40 (15 H, m, 3 × Ph), 5.36 (1 H, d, *J* 5.6 Hz, 1-H), 4.62–4.97 (6 H, m, 3 × C*H*$_2$Ph), 4.11 (1 H, dd, *J* 3.2, 10.0 Hz, 5-H), 3.85 (1 H, t, *J* 9.1 Hz, 3-H), 3.72–3.75 (3 H, m, 2-H and 6-H$_2$), 3.52 (1 H, t, *J* 9.1 Hz, 4-H), 2.71 (1 H, m, SCH), and 1.27–1.99 (11 H, m, 5 × CH_2 in cyclohexyl and OH).

Cyclohexyl 2,2′,2″,3,3′,3″,4″,6′,6″-*Nona*-O-*benzyl*-1-*thio-maltotrioside* (**6**).—(a) *With* ZnI_2. A suspension of 1,6-anhydro-2,3,2′,3′,2″,3″,4″,6′,6″-nona-*O*-benzyl-β-maltotriose (**5**)* (0.194 g, 0.15 mmol), compound (**3**) (90 mg, 0.45 mmol), and ZnI_2 (0.22 g, 0.60 mmol) in $(CH_2Cl)_2$ (4 ml) was stirred at room temperature under argon for 1 h. Work-up as described for thioglycoside (**4b**) (with ZnI_2) gave an anomeric mixture (α:β 5:1) of thioglycoside (**6**) (0.13 g, 60%) as a syrup, δ_H 5.69 and 5.51 (1 H each, two doublets, *J* 3.9, 3.4 Hz, 1′- and 1″-H), 5.44 (5/6 H, d, *J* 5.4 Hz, 1-H$_a$), 2.76 (5/6 H, m, SC*H* of α-isomer), and 2.93 (1/6 H, m, SCH of β-isomer).

(b) *With* TMSOTf. A solution of compound (**5**) (0.155 g, 0.119 mmol), compound (**3**) (0.10 g, 0.53 mmol), and TMSOTf (50 μl, 0.26 mmol) in CH_2Cl_2 (5 ml) was stirred at room temperature under argon for 24 h. Work-up as described for thioglycoside (**4a**) afforded thioglycoside (**6**) (0.13 g, 77%) (α:β 20:1) as a syrup. Repeated column chromatography (toluene–EtOAc, 15:1) gave the *α-isomer of thioglycoside* (**6**) as a syrup (Found: C, 73.8; H, 6.9; S, 2.2. $C_{87}H_{96}O_{15}S$ requires C, 73.9; H, 6.8; S, 2.3%); $[\alpha]_D^{23}$ +93.2° (*c* 0.8 in $CHCl_3$); ν_{max}^{KBr} 3 450 cm^{-1} (OH); δ_H 7.01–7.28 (45 H, m, 9 × Ph), 5.70 and 5.51 (1 H each, 2 d, *J* 3.9 and 3.4 Hz, 1′- and 1″-H), 5.43 (1 H, d, *J* 5.4 Hz, 1-H), 5.04–3.28 (36 H, m), 2.76 (1 H, m, SCH), and 1.31–1.98 (11 H, m, 5 × CH_2 in cyclohexyl and OH).

Phenyl 4-O-(6-O-*Acetyl*-2,3-*di*-O-*benzyl*-4-O-*mesyl*-α-D-*glucopyranosyl*)-2-*azido*-3-O-*benzyl*-2-*deoxy*-1-*thio*-D-*gluco-pyranoside* (**8**).—A suspension of 4-*O*-(6-*O*-acetyl-2,3-di-*O*-benzyl-4-*O*-mesyl-α-D-glucopyranosyl)-1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-β-D-glucose (**7**)† (0.1 g, 0.135 mmol), compound (**2**) (127 μl, 0.675 mmol), and ZnI_2 (0.22 g, 0.68 mmol) in $(CH_2Cl)_2$ (2 ml) was stirred at room temperature under argon atmosphere for 24 h. Work-up as described for thioglycoside (**4b**) (with ZnI_2) followed by repeated column chromatography (toluene–EtOAc, 15:1) gave the *α-isomer of thioglycoside* (**8**) (45 mg, 41%) and the *β-isomer of thioglycoside* (**8**) (25 mg, 23%) as white foams.

α-Isomer of compound (**8**) (Found: C, 59.2; H, 5.6; N, 4.8; S, 7.5. $C_{42}H_{47}N_3O_{12}S_2$ requires C, 59.3; H, 5.6; N, 4.9; S, 7.5%); $[\alpha]_D^{20}$ +125° (*c* 1.56 in $CHCl_3$); ν_{max}^{film} 3 500 (OH), 2 100 (N_3), and 1 740 cm^{-1} (OAc); δ_H 7.15–7.52 (20 H, m, 4 × Ph), 5.62 (1 H, d, *J* 5.1 Hz, 1-H), 5.52 (1 H, d, *J* 3.7 Hz, 1′-H), 4.25–4.67 (8 H, m, 3 × C*H*$_2$Ph and 6′-H$_2$), 3.80–4.32 (9 H, m, 2-, 3-, 3′-, 4-, 4′-, 5-, and 5′-H and 6-H$_2$), 3.55 (1 H, dd, *J* 3.7, 9.7 Hz, 2′-H), 2.83 (3 H, s, OMs), 2.07 (3 H, s, OAc), and 1.87 (1 H, dd, *J* 5.1, 7.8 Hz, OH).

β-Isomer of compound (**8**) (Found: C, 59.3; H, 5.6; N, 4.8; S, 7.6%); $[\alpha]_D^{20}$ +38.4° (*c* 2.45 in $CHCl_3$); ν_{max}^{film} (KRS CCl_4 film) 3 500 (OH), 2 080 (N_3), and 1 730 cm^{-1} (OAc); δ_H 7.14–7.56 (20 H, m, 4 × Ph), 5.49 (1 H, d, *J* 3.7 Hz, 1′-H), 3.35–4.95 (19 H, m), 2.84 (3 H, s, OMs), 2.08 (3 H, s, OAc), and 1.97 (1 H, m, OH).

Cyclohexyl 2,2′,3,3′,4′,6′-*Hexa*-O-*acetyl*-1-*thio*-β-*maltoside* (**10**).—A suspension of 2,2′,3,3′,4′,6′-hexa-*O*-acetyl-1,6-anhydro-β-maltose (**9**)[3] (0.288 g, 0.5 mmol), compound (**3**) (0.283 g, 1.5 mmol), and ZnI_2 (0.478 g, 1.5 mmol) in $(CH_2Cl)_2$ (15 ml) was stirred at room temperature for 2.5 h. Work-up as described for thioglycoside (**4b**) (with ZnI_2) followed by flash column chromatography (toluene–EtOAc, 3:1) gave *thioglycoside* (**10**) (0.335 g, 97%) as a white solid. Recrystallization from EtOH afforded crystals, m.p. 85–87 °C (Found: C, 52.05; H, 6.3; S, 4.5. $C_{30}H_{44}O_{16}S$ requires C, 52.0; H, 6.4; S, 4.6%); $[\alpha]_D^{23}$ +47.8° (*c* 0.56 in $CHCl_3$); ν_{max}^{KBr} 3 450 (OH) and 1 735 cm^{-1} (OAc); δ_H 5.43 (1 H, d, *J* 3.9 Hz, 1′-H), 5.35 (1 H, t, *J* 10.2 Hz, 3′-H), 5.29 (1 H, t, *J* 9.2 Hz, 3-H), 5.02 (1 H, t, *J* 10.0 Hz, 4′-H), 4.81 (1 H, dd, *J* 3.9, 10.3 Hz, 2′-H), 4.79 (1 H, t, *J* 9.5 Hz, 2-H), 4.62 (1 H, d, *J* 10.0 Hz, 1-H), 4.27 (1 H, dd, *J* 4.0, 12.4 Hz, 6′-H$_a$), 4.11 (2 H, m, 4-H and 6′-H$_b$), 3.96–4.02 (1 H, m, 5′-H), 3.75–3.95 (2 H, m, 6-H$_2$), 3.47–3.49 (1 H, m, 5-H), 2.86–2.90 (1 H, m, SCH), 2.07, 2.02, 2.01, 2.00, 1.99 (2) (3 H each, each s, 6 × Ac), and 1.25–1.98 (11 H, m, 5 × CH_2 in cyclohexyl and OH).

Methyl 2,3,6-*Tri*-O-*benzyl*-4-*deoxy*-4-*iodo*-α-D-*galacto-pyranoside* (**12**).—A solution of methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**11**)[21] (8.20 g, 17.67 mmol), triphenylphosphine (18.52 g, 70.69 mmol), imidazole (4.81 g, 70.69 mmol), and iodine (13.46 g, 53.01 mmol) in dry toluene (300 ml) was refluxed for 1.5 h, cooled, and diluted with toluene. The solution was washed successively with aq. $NaHCO_3$, aq. sodium thiosulphate, brine, and water, dried ($MgSO_4$), and evaporated. The residue was triturated in diethyl ether and the resulting solid was filtered off through a Celite pad. The filtrate was evaporated, and the residue underwent flash column chromatography (toluene–EtOAc, 20:1), giving the *iodide* (**12**) (8.48 g, 83%) as a syrup (Found: C, 57.9; H, 5.35; I, 22.05. $C_{28}H_{31}IO_5 \cdot 0.3H_2O$ requires C, 58.0; H, 5.5; I, 21.9%); $[\alpha]_D^{23}$ +72.3° (*c* 2.0 in $CHCl_3$); δ_H 7.25–7.37 (15 H, m, 3 × Ph), 4.86–4.52 (6 H, m, 3 × C*H*$_2$Ph), 4.64 (1 H, m, 4-H), 4.59 (1 H, d, *J* 3.9 Hz, 1-H), 3.83 (1 H, dd, *J* 3.9, 9.5 Hz, 3-H), 3.62 (1 H, dd, *J* 5.9, 9.5 Hz, 6-H$_a$), 3.50 (1 H, dd, *J* 6.3, 9.8 Hz, 6-H$_b$), 3.37 (3 H, s, OMe), 3.29 (1 H, m, 5-H), and 3.20 (1 H, dd, *J* 4.2, 9.6 Hz, 2-H).

Methyl 4-S-*Acetyl*-2,3,6-*tri*-O-*benzyl*-4-*thio*-α-D-*glucopyrano-side* (**13**).—A mixture of the iodide (**12**) (5.26 g, 9.15 mmol) and potassium thioacetate (4.18 g, 36.6 mmol) in dry DMF (150 ml) was stirred at 80–90 °C for 1.5 h. After most of the DMF had been evaporated off, the resulting residue was diluted with EtOAc (250 ml) and washed with water, dried ($MgSO_4$), and evaporated. Flash column chromatography (toluene–EtOAc, 30:1) of the residue afforded *compound* (**13**) (3.31 g, 70%) as a pale yellow foam (Found: C, 68.85; H, 6.5; S, 6.1. $C_{30}H_{34}O_6S$ requires C, 68.9; H, 6.6; S, 6.1%); $[\alpha]_D^{23}$ +17.4° (*c* 0.8 in $CHCl_3$); ν_{max}^{film} 1 690 cm^{-1} (SAc); δ_H 7.20–7.35 (15 H, m, 3 × Ph), 4.50–4.95 (6 H, m, 3 × C*H*$_2$Ph), 4.66 (1 H, d, *J* 3.7 Hz, 1-H), 3.80–3.95 (2 H, m, 3- and 5-H), 3.66 (1 H, t, *J* 11.2 Hz, 4-H), 3.61 (3 H, m, 2-H and 6-H$_2$), 3.39 (3 H, s, OMe), and 2.23 (3 H, s, SAc).

Methyl 2,3,6-*Tri*-O-*benzyl*-4-*thio*-α-D-*glucopyranoside* (**14**).—A solution of compound (**13**) (0.70 g, 1.34 mmol) in THF–MeOH (1:1; 20 ml) containing a catalytic amount of sodium methoxide was stirred at room temperature for 1 h, neutralized with Dowex 50w-x8 (H^+) ion-exchange resin, and filtered. The filtrate was evaporated and the residue was subjected to flash column chromatography (toluene–EtOAc, 30:1), giving *thiol* (**14**) (0.612 g, 95%) as a pale yellow syrup (Found: C, 70.1; H, 6.7; S, 6.8. $C_{28}H_{32}O_5S$ requires C, 70.0; H, 6.7; S, 6.7%); $[\alpha]_D^{23}$ +7.51° (*c* 1.3 in $CHCl_3$); ν_{max}^{film} 2 545 cm^{-1} (SH); δ_H 7.20–7.45 (15

* Compound (**5**) was prepared by the benzylation of 1,6-anhydro-β-maltotriose (BnBr–NaH–DMF; 25 °C).

† Compound (**7**), giving satisfactory microanalyses and ^1H NMR data, was provided by Dr. S. Nishimura of Seikei University, to whom we are indebted.

H, m, 3 × Ph), 4.49–4.98 (6 H, m, 3 × CH_2Ph), 4.67 (1 H, d, *J* 3.4 Hz, 1-H), 3.66–3.80 (4 H, m, 3- and 5-H and 6-H_2), 3.53 (1 H, dd, *J* 3.4, 9.3 Hz, 2-H), 3.39 (3 H, s, OMe), 3.07 (1 H, m, 4-H), and 1.65 (1 H, d, *J* 6.6 Hz, SH).

Methyl 2,3,6-*Tri*-O-*benzyl*-4-*thio*-4-S-(2,3,4-*tri*-O-*benzyl*-α-D-*glucopyranosyl*)-α-D-*glucopyranoside* (**20**).—*Trimethylsilylation of thiol* (**14**). A mixture of thiol (**14**) (0.312 g, 0.650 mmol), hexamethyldisilazane (2 ml), and imidazole (5 mg) was heated at 130 °C under nitrogen; the reaction was monitored by measuring the ^{1}H NMR spectrum at intervals. The signals at δ 3.07 (m, HSC*H*) and 1.65 (d, *H*SCH) became smaller and a new signal at δ 2.76 (t, C*H*SSiMe$_3$) appeared. After the complete disappearance of the signals at δ 3.07 and 1.65 (50 h), the reaction mixture was cooled and the excess of hexamethyldisilazane was removed by evaporation under reduced pressure, giving a pale yellow syrup of methyl 2,3,6-tri-*O*-benzyl-4-thio-4-*S*-trimethylsilyl-α-D-glucopyranoside (**19**), δ_H 7.15–7.40 (15 H, m, 3 × Ph), 4.50–4.90 (6 H, m, 3 × CH_2Ph), 4.65 (1 H, d, *J* 3.5 Hz, 1-H), 3.66–3.80 (4 H, m, 3- and 5-H and 6-H_2), 3.50 (1 H, dd, *J* 3.4, 9.3 Hz, 2-H), 3.33 (3 H, s, OMe), 2.73 (1 H, t, *J* 11 Hz, 4-H), and 0.25 (9 H, s, SiMe$_3$). After being dried over P_2O_5 at reduced pressure, the product was used for the next reaction without further purification.

Condensation of compounds (**1**) *and* (**19**). Compound (**19**), derived from thiol (**14**) (0.312 g, 0.65 mmol), and compound (**1**) (0.14 g, 0.325 mmol) were dissolved in $(CH_2Cl)_2$ (4 ml). To the solution was added ZnI_2 (0.223 g, 0.70 mmol) and the resulting suspension was stirred at room temperature for 5 h. Work-up as described for thioglycoside (**4b**) (with ZnI_2) followed by flash column chromatography (toluene–EtOAc, 25:1) gave thiodisaccharide (**20**) (0.152 g, 66%) (α:β 15:1) as a syrup. Repeated chromatography (toluene–EtOAc, 30:1) gave the pure α-*anomer of the thiodisaccharide* (**20**) as a syrup (Found: C, 71.9; H, 6.6; S, 3.5. $C_{55}H_{60}O_{10}S$ requires C, 72.3; H, 6.6; S, 3.5%); $[\alpha]_D^{21}$ +100° (*c* 0.7 in $CHCl_3$); ν_{max}^{film} 3 450 cm^{-1} (OH); δ_H 7.15–7.35 (30 H, m, 6 × Ph), 5.96 (1 H, d, *J* 5.4 Hz, 1′-H), 4.69 (1 H, d, *J* 3.4 Hz, 1-H), 4.42–5.18 (12 H, m, 6 × CH_2Ph), 4.04 (1 H, t, *J* 10.0 Hz, 3-H), 3.84–3.90 (1 H, m, 5′-H and 6-H_a), 3.73–3.80 (3 H, m, 3′- and 5-H and 6-H_b), 3.56–3.70 (4 H, m, 2- and 2′-H and 6′-H_2), 3.45 (1 H, t, *J* 9.0 Hz, 4′-H), 3.39 (3 H, s, OMe), 3.06 (1 H, t, *J* 11.0 Hz, 4-H), and 1.85 (1 H, dd, *J* 4.5, 8.1 Hz, OH).

1,6-*Anhydro*-2,3-*di*-O-*benzyl*-4-O-(2,3,6-*tri*-O-*benzyl*-4-*deoxy*-4-*iodo*-α-D-*galactopyranosyl*)-β-D-*glucopyranose* (**16**).—The reaction of 1,6-anhydro-2,2′,3,3′,6′-penta-*O*-benzyl-β-maltose (**15**)* (2.70 g, 3.48 mmol) with triphenylphosphine (3.10 g, 11.81 mmol), iodine (2.25 g, 8.87 mmol), and imidazole (1.20 g, 17.72 mmol) was performed as described for the preparation of iodide (**12**), giving the *iodide* (**16**) (2.32 g, 75%) as a syrup (Found: C, 64.1; H, 5.6; I, 14.3. $C_{47}H_{49}IO_9$ requires C, 63.8; H, 5.6; I, 14.3%); $[\alpha]_D^{20}$ +45° (*c* 0.86 in $CHCl_3$); δ_H 7.15–7.40 (25 H, m, 5 × Ph), 5.44 (1 H, s, 1-H), 4.94 (1 H, d, *J* 3.9 Hz, 1′-H), 4.72 (1 H, d, *J* 4.9 Hz, 5-H), 4.65 (1 H, m, 4′-H), 4.38–4.78 (10 H, m, 5 × CH_2Ph), 3.83–3.86 (2 H, m, 2′-H and 6-H_a), 3.65–3.70 (3 H, m, 3-H and 6′-H_2), 3.56 (1 H, br s, 4-H), 3.45–3.50 (2 H, m, 5′-H and 6-H_b), 3.33 (1 H, br s, 2-H), and 3.29 (1 H, dd, *J* 4.1, 9.8 Hz, 3′-H).

4′-S-*Acetyl*-1,6-*anhydro*-2,2′,3,3′,6′-*penta*-O-*benzyl*-4′-*thio*-β-*maltose* (**17**).—The reaction of the iodide (**16**) (2.10 g, 2.37 mmol) with potassium thioacetate (1.17 g, 10.25 mmol) was performed as described for compound (**13**), giving syrupy *compound* (**17**) (1.62 g, 82%) as a pale yellow foam (Found: C, 70.5; H, 6.3; S, 3.6. $C_{49}H_{52}O_{10}S$ requires C, 70.7; H, 6.3; S, 3.85%); $[\alpha]_D^{20}$ +19.58° (*c* 0.88 in $CHCl_3$); δ_H 7.20–7.30 (25 H, m, 5 × Ph), 5.47 (1 H, s, 1-H), 5.01 (1 H, d, *J* 3.7 Hz, 1′-H), 4.76 (1 H, m, 5-H), 4.45–4.89 (10 H, m, 5 × CH_2Ph), 4.17 (1 H, m, 5′-H), 3.86–3.95 (2 H, m, 3′-H and 6-H_a), 3.59–3.70 (6 H, m, 2′-, 3-, 4-, and 4′-H and 6′-H_2), 3.54 (1 H, m, 6-H_b), 3.37 (1 H, br s, 2-H), and 2.25 (3 H, s, SAc).

1,6-*Anhydro*-2,2′,3,3′,6′-*penta*-O-*benzyl*-4′-*thio*-β-*maltose* (**18**).—Deacetylation of compound (**17**) (0.40 g, 0.48 mmol) was performed as described for the preparation of thiol (**14**), giving syrupy *thiol* (**18**) (0.32 g, 84%) (Found: C, 70.6; H, 6.2; S, 3.7. $C_{47}H_{50}O_9S{\cdot}0.5H_2O$ requires C, 70.6; H, 6.4; S, 4.0%); $[\alpha]_D^{20}$ +3.33° (*c* 0.36 in $CHCl_3$); δ_H 7.23–7.39 (25 H, m, 5 × Ph), 5.47 (1 H, s, 1-H), 5.01 (1 H, d, *J* 3.7 Hz, 1′-H), 4.72 (1 H, m, 5-H), 4.45–4.95 (10 H, m, 5 × CH_2Ph), 4.03 (1 H, m, 5′-H), 3.38–3.93 (9 H, m), 3.04 (1 H, m, 4′-H), and 1.63 (1 H, d, *J* 7.3 Hz, SH).

1,6-*Anhydro*-2,3-*di*-O-*benzyl*-4-O-[2,3,6-*tri*-O-*benzyl*-4-*thio*-4-S-(2,3,4-*tri*-O-*benzyl*-α-D-*glucopyranosyl*)-α-D-*glucopyranosyl*]-β-D-*glucopyranose* (**23**).—*Trimethylsilylation of thiol* (**18**). A mixture of thiol (**18**) (0.270 g, 0.34 mmol), imidazole (15 mg), and hexamethyldisilazane (5 ml) was refluxed for 40 h. Work-up as described for compound (**19**) gave 1,6-anhydro-2,2′,3,3′,6′-penta-*O*-benzyl-4′-thio-4′-*S*-trimethylsilyl-β-maltose (**22**) as a pale yellow syrup, which was used directly for the next reaction without further purification; δ_H 7.25–7.35 (25 H, m, 5 × Ph), 5.47 (1 H, s, 1-H), 5.02 (1 H, d, *J* 3.6 Hz, 1′-H), 4.74 (1 H, m, 5-H), 4.06 (1 H, m, 5′-H), 3.36–3.95 (9 H, m), 2.75 (1 H, t, *J* 10.0 Hz, 4′-H), and 0.24 (9 H, s, SiMe$_3$).

Thioglycosidation of 1,6-*anhydro monosaccharide* (**1**) *and disaccharide* (**22**). Compound (**22**), derived from thiol (**18**) (0.27 g, 0.34 mmol), and 1,6-anhydro monosaccharide (**1**) (90 mg, 0.21 mmol) were dissolved in $(CH_2Cl)_2$ (2 ml) under argon. After addition of ZnI_2 (0.18 g, 0.564 mmol), the suspension was stirred for 24 h at room temperature. Work-up as described for thioglycoside (**4b**) (with ZnI_2) followed by flash column chromatography (toluene–EtOAc, 20:1) gave *thiotrisaccharide* (**23**) (0.125 g, 48%) as a syrup (Found: C, 72.1; H, 6.4; S, 2.6. $C_{74}H_{78}O_{14}S{\cdot}0.5H_2O$ requires C, 72.1; H, 6.5; S, 2.6%); $[\alpha]_D^{20}$ +71.66° (*c* 0.2 in $CHCl_3$); δ_H 7.10–7.40 (40 H, m, 8 Ph), 5.96 (1 H, d, *J* 5.5 Hz, 1″-H), 5.47 (1 H, s, 1-H), 5.01 (1 H, d, *J* 3.5 Hz, 1′-H), 4.45–5.20 (17 H, m, 8 × CH_2Ph and 5-H), 4.12–4.20 (2 H, m, 3′- and 5′-H), 3.35–3.90 (10 H, m, 2-, 3-, 3″-, and 5″-H and 6-, 6′-, and 6″-H_2), 3.63 (1 H, dd, *J* 5.5, 9.5 Hz, 2″-H), 3.55 (1 H, dd, *J* 3.5, 3.9 Hz, 2′-H), 3.45 (1 H, t, *J* 9.2 Hz, 4″-H), 3.36 (1 H, br s, 4-H), 3.01 (1 H, t, *J* 10.6 Hz, 4′-H), and 1.82 (1 H, m, OH).

* Compound (**15**) was prepared from 1,6-anhydro-2,2′,3,3′-tetra-*O*-benzyl-4′,6′-*O*-benzylidene-β-maltose according to the method in ref. 21.

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