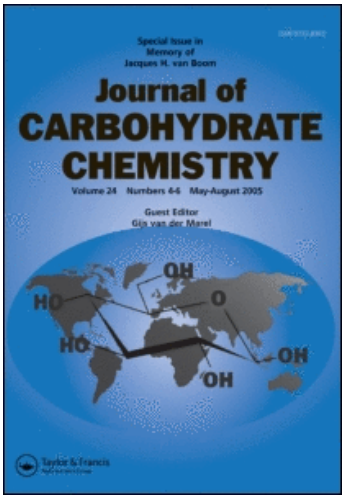

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A GENERAL METHOD BASED ON THE USE OF *N*-BROMOSUCCINIMIDE FOR REMOVAL OF THE THIOPHENYL GROUP AT THE ANOMERIC POSITION TO GENERATE A REDUCING SUGAR WITH THE ORIGINAL PROTECTING GROUPS STILL PRESENT

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ABSTRACT

Efficient conversion of a range of different phenyl thioglycosides into their hemiacetals has been achieved by treatment with *N*-bromosuccinimide in aqueous acetone. The method is mild and general since it does not interfere with the presence of other protecting groups like acetate, benzyl, benzylidene acetal, *tert*-butyldiphenylsilyl groups, and the *O*-glycosidic bond (e.g. di-, tetra-, and pentasaccharide thioglycosides).

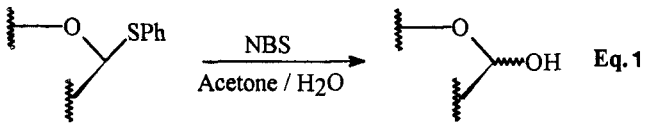
INTRODUCTION

Stepwise chemical synthesis of complex oligosaccharides requires sugar derivatives with both persistent (e.g. benzyl and allyl) and temporary (e.g. ester) blocking groups.[1-3] The desired distribution of persistent and temporary substituents is achieved through a number of appropriate blocking and deblocking reactions. The anomeric center is of particular importance since it plays a key role in obtaining suitable building blocks. A number of temporary protective groups are available for the anomeric center. [4] However, among these thioalkyl and thioaryl functions offer advantages due to their relative stability at the chemical conditions typically used for manipulation of other protective groups. On the other hand, their reactivity towards thiophiles[5] and their sensitivity to nucleophiles after conversion into glycosyl halides[6] offer convenient possibilities for subsequent manipulations at the anomeric center. Electrophilic[7] and radical[8] reactions have also been reported.

Thioglycosides are more resistant to acid hydrolysis[9] than their *O*-glycoside analogs. This is demonstrated by relative rate constants of 1:25:350:80 for acid hydrolysis of phenyl 1-thio-β-D-glucopyranoside, ethyl 1-thio-β-D-glucopyranoside and the two oxygen analogs, respectively.[10] The aryl thioglycoside is more stable than the alkyl thioglycoside whereas the reverse situation is observed for the *O*-glycosides. The reduced stability of ethyl thioglycosides compared to phenyl thioglycosides often constitutes a problem since during synthetic routes to complex oligosaccharides, the thioethyl function may compete with free hydroxy groups in the reaction with a glycosyl donor resulting in a low yield of the desired product e.g. as experienced in the chemical synthesis of the trisaccharide corresponding to the blood group P_1 determinant.[11] Methyl thioglycosides are less stable compared to ethyl thioglycosides and thus even more prone to undergo unwanted reactions with glycosyl donors. The main reason for the resistance of thioglycosides to acidic hydrolysis is the low basicity of the bivalent sulphur atom.[12] Thioglycosides are unaffected by mild alkali. In hot, strong alkali, however, thioglycosides are converted to the corresponding 1,6-anhydro-β-D-glucopyranoses in the same manner as *O*-glycosides. [13] Thus, neither acidic nor alkaline hydrolysis provides efficient deprotection. Deprotection of some alkyl thioglycosides is facilitated by the presence of mercuric chloride, probably due to the high affinity of mercury towards the sulphur function. This principle has successfully been used as an alternative to acid hydrolysis to convert thioglycosides into free sugars without cleavage of acid labile

groups. The mercuric chloride procedure is unfortunately not generally applicable, probably because mercuric chloride often effects desulphurisation of acyclic dithioacetals.[12,14] Deprotection may also be accomplished through the use of silver salts which however are expensive and the reactions are time consuming.[15] As glycosyl donors thioglycosides can be activated for glycosylation reactions by conversion into glycosyl halides to be employed using halophilic reagents such as silver or mercury salts or tetraethylammonium bromide.[16] Alternatively, thioglycosides can be directly employed in glycoside synthesis using thiophilic reagents as promoters such as phenylmercury triflate,[17] sulfuryl chloride,[18] benzeneselenyl triflate,[19] methylsulfenyl triflate,[20] iodonium di(collidine)perchlorate,[21] methyl triflate,[22] dimethyl(methylthio)sulfonium triflate,[23,24] dimethyl (methylthio)sulfonium tetrafluoroborate[23,25] and nitrosyl tetrafluoroborate.[26] However, these methods have to our knowledge not been reported to generate the free anomeric center from a phenyl thioglycoside, probably reflecting the high stability of the phenylthio function compared to the *S*-alkyl functions. Treatment of phenyl thioglycosides with *N*-bromosuccinimide under anhydrous conditions in the presence of either diaminosulphur trifluoride (DAST)[27] or a hydroxy compound[28] results in formation of glycosyl fluorides and *O*-glucosides respectively. The glycoside bond forming reaction involves the initial electrophilic activation of sulphur, generating a reactive sulphonium species.[28] Stereo chemical control of glycoside-bond formation is therefore more dependent on the type of solvent used than on the stereochemistry of the thioglycoside bond.

Based on these observations we have studied the action of *N*-bromosuccinimide on phenyl thioglycosides in aqueous medium to develop a method for the conversion of phenyl thioglycosides to the corresponding hemiacetals without interference with the other protecting proups present. In this paper we report that this is achieved under simple and mild conditions by reacting the phenyl thioglycosides with *N*-bromosuccinimide in aqueous acetone (eq. 1) which permits the generation of HOBr and serves to retain the reactants and products formed in solution:



Eq. 1

RESULTS AND DISCUSSION

A number of differently protected phenyl thioglycosides were chemically synthesized to demonstrate that *N*-bromosuccinimide in aqueous acetone can be used to remove the thiophenyl group at the anomeric position without interfering with the presence of other protecting groups. As many of the phenyl thioglycosides used in the present study are new compounds their synthesis and chemical characterization are reported.

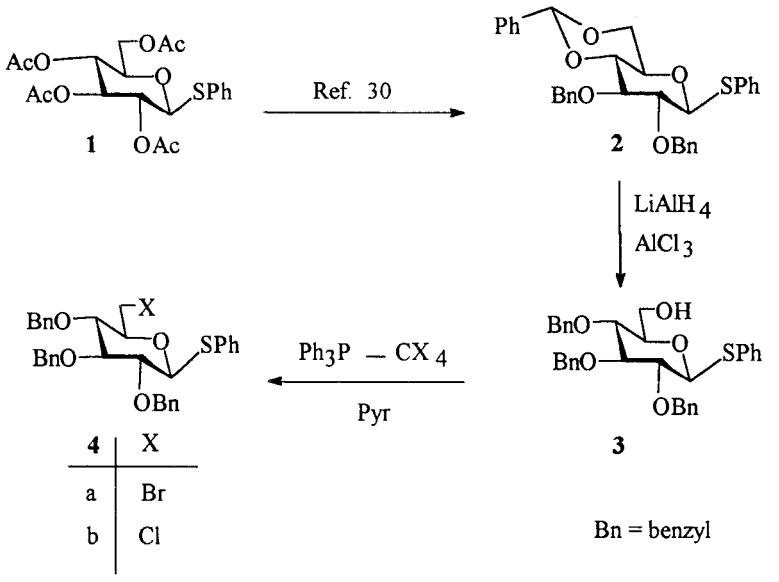
The route used to chemically synthesize differently protected phenyl thioglucopyranosides is outlined in scheme 1.

Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside[29,30] (**1**) was converted in four steps to phenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside[30] (**2**). Compound **2** is of special interest because it contains an acid-sensitive (benzylidene acetal) as well as a radical anion-sensitive (benzyl ether) protecting group. Regioselective reductive cleavage of the benzylidene acetal function of **2** was performed using the $LiAlH_4$-$AlCl_3$ reagent[31] in diethyl ether/dichloromethane (1:1 v/v) to give phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside(**3**) in quantitative yield. Treatment of **3** with triphenylphosphine-carbon tetrabromide/or carbon tetrachloride in anhydrous pyridine[32] afforded the corresponding halogeno derivatives, phenyl 2,3,4-tri-*O*-benzyl-6-bromo-6-deoxy-1-thio-β-D-glucopyranoside (**4a**) or phenyl 2,3,4-tri-*O*-benzyl-6-chloro-6-deoxy-1-thio-β-D-glucopyranoside (**4b**) in 92 and 98% yield, respectively.

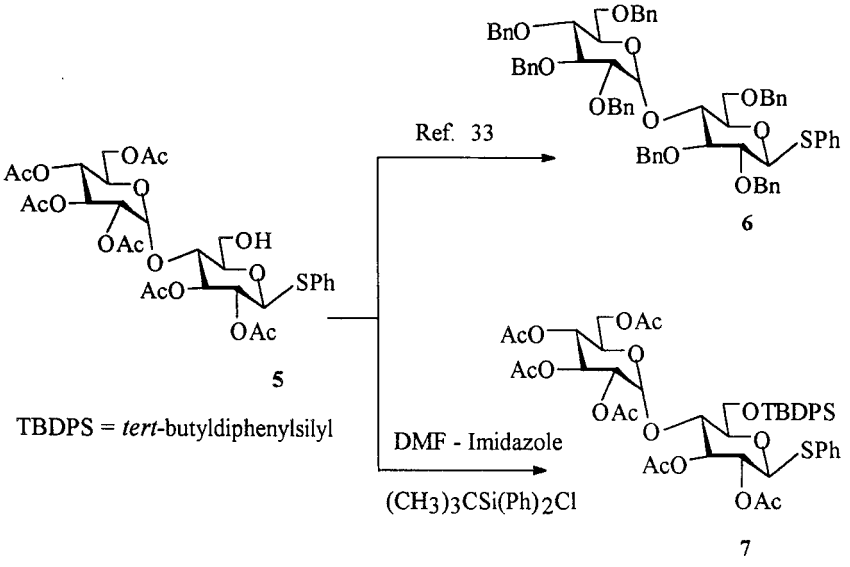
The route to the disaccharide phenyl thioglycosides used is outlined in scheme 2.

The use of phenyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (**6**) as a synthesis intermediate has recently been reported.[33] Compound **6** was obtained from phenyl 2,3-di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-1-thio-β-D-glucopyranoside[33,34] (**5**) by *O*-deacetylation and subsequent benzylation in a standard manner.[33] Reaction of **5** with *tert*-butyldiphenylsilyl chloride in DMF in the presence of imidazole[35] gave phenyl 2,3-di-*O*-acetyl-6-*O*-(*tert*-butyldiphenylsilyl)-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (**7**) in 85% yield after chromatographic purification.

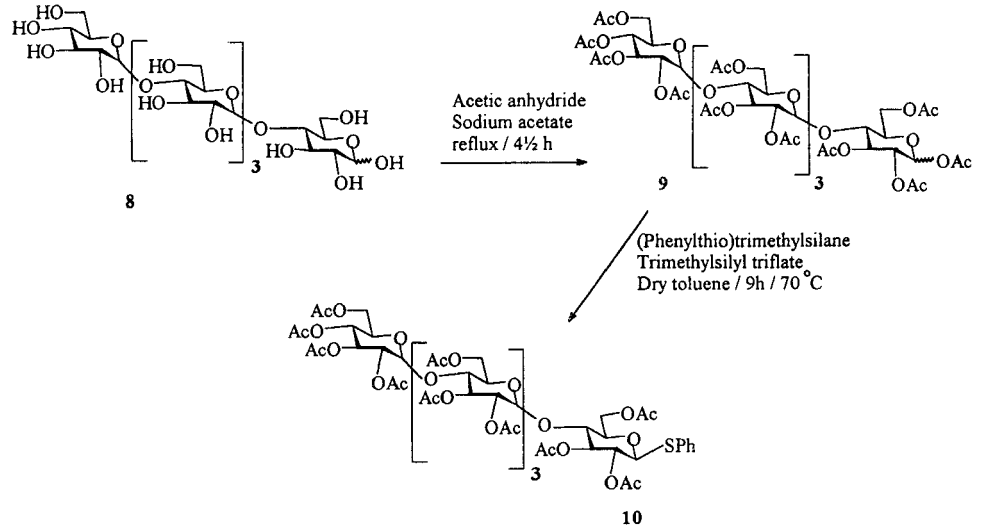
The commercially available linear pentasaccharide, maltopentaose (**8**) was acetylated with acetic anhydride in the presence of anhydrous sodium acetate to give the fully acetylated



Scheme 1



Scheme 2



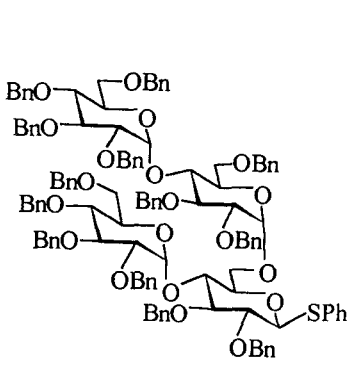
Scheme 3

derivative **9** (Scheme 3) in 88 % yield. Thiophenolysis of **9** in dry toluene using trimethylsilyl triflate resulted in the formation of the corresponding pentasaccharide thioglycoside **10**, which was obtained in 78% yield after column chromatography.

The chemical synthesis of the branched-tetrasaccharide thioglycoside **11** and of the branched-pentasaccharide thioglycoside **12** (figure 1) have recently been reported.[33]

The results of using *N*-bromosuccinimide in 90% aqueous acetone for removal of the phenylthio group from the anomeric position of different phenyl thioglycosides in the presence of a number of other frequently used blocking groups are summarized in Table 1.

The data presented demonstrate that the commonly used hydroxyl-protecting groups such as benzyl, acetyl and *tert*-butyldiphenylsilyl are unaffected by the reaction conditions. The benzylidene acetal functionality (Table 1, entry 2) is also not affected by these mild reaction conditions although its reaction with *N*-bromosuccinimide has been widely used for its conversion into sugar bromobenzoate.[36] We envision that the method may also be used for the removal of the phenylthio group from phenyl thioglycosides containing *p*-methoxy-benzyl,[37] allyl[37] protecting groups, azido[38] and protected amino[38] functions. Furthermore, in our hands the method was applied successfully in the presence of iodo and protected phosphate groups.[38]



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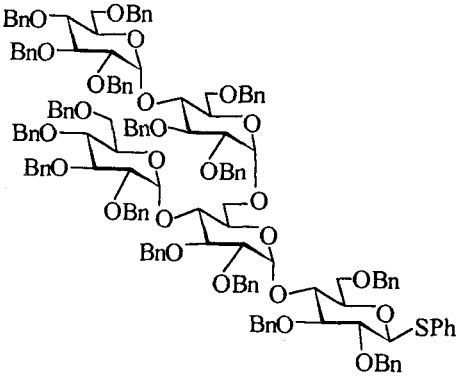

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Figure 1

Table 1. Removal of the phenylthio group of different phenyl thioglycosides with NBS

R-SPh	NBS equiv.	Reaction time	Eluant system	% Yield	Anomeric ^{13}C shift	
					substrate	product(α, β)*
1[30]	4	2h	C	74	85.6	**13**(89.8, 95.2)
2[30]	3.8	2h	B	82	88.3	**14**(92.1, 97.8)
4a	4	1h	G	73	87.3	**15**(91.2, 97.4)
4b	4	1h	G	86	87.4	**16**(91.3, 97.4)
6[33]	1.2	45 min	E	96	88.0	**17**[33](90.7, 97.3)
7	4	30 min	A	95	86.1	**18**(89.8, 94.6)
10	4	30 min	D	93	84.8	**19**(89.9, 94.7)
11[30]	2.8	10 min	F	94	88.0	**20**[30](90.4, 97.1)
12[30]	3	10 min	E	97	87.3	**21**[30](90.9, 97.2)

A : $CHCl_3$, B : $CHCl_3$ / MeOH (99:1 v/v), C : $CHCl_3$ / MeOH (98:2 v/v), D : $CHCl_3$ / MeOH (97:3 v/v), E : Et_2O / *n*-pentane (3:2 v/v), F : Et_2O / *n*-pentane (4:1 v/v), G: *n*-pentane / EtOAc (4:1 v/v).
R-SPh = phenyl thioglycoside
*: α/β ratios are 5:3, 2:9, 3:1, 2:1, 5:3, 5:1, 3:1, 5:6 and 3:2 for compounds **13-21** respectively.

The yields reported in the table are those obtained after chromatographic purification. The identity of the reaction products was verified by ^{1}H and ^{13}C NMR spectroscopy (See Experimental). The anomeric purity of the obtained products was determined principally from the ^{13}C NMR data due to masking of the anomeric ^{1}H signals by other protons in the ^{1}H NMR spectra. The removal of the phenylthio function is apparent from the ^{13}C NMR spectra as the disappearance of the diagnostic signal resonating at 85-88 ppm and reflecting the β-configuration of the anomeric carbon in all substrates. Its concomitant replacement with a hydroxy group at the anomeric position is apparent from the ^{13}C NMR spectra by the appearance of two signals resonating at 90-92 and 94-97 ppm which correspond to the α- and β-configuration, respectively, at the anomeric carbon of the obtained hemiacetals.

CONCLUSION

The gentle, versatile and efficient method here reported for the conversion of phenyl thioglycosides into their corresponding hemiacetals constitutes a useful step in sequential chemical synthesis of complex oligosaccharides since typically it would neither affect other protecting groups nor cause an undesired hydrolysis of *O*-glycosidic bonds. Using this approach it is possible to generate glycosyl donors with different chemical reactivity while retaining the existing construction. This is important, e.g., in the synthesis of complex oligosaccharides where the access of the glycosyl donor to the coupling site might be stereochemically hindered either due to folding of the oligosaccharide chain or because of the bulkiness of the protective groups. When this problem becomes apparent at an advanced stage in a synthetic scheme where valuable chemicals are involved, the possibility to change the reactivity of the glycosyl donor molecule may circumvent the necessity to design a completely new synthetic route. The high stability of phenylthio glycosides as compared to alkylthio glycosides (e.g. SMe or SEt) is of major advantage since it permits the use of a number of different reaction conditions during the synthetic manipulations of carbohydrate derivatives. An adverse effect of the stability of the phenylthio function has been the difficulties encountered during attempts to regenerate a free anomeric center. The *N*-bromosuccinimide method here reported circumvents this problem and greatly facilitates the use of the phenylthio function as an anomeric center blocking group.

EXPERIMENTAL

General methods. Melting points were determined with a Mettler FP81 MBC Cell connected to a Mettler FP80 Central Processor unit and are uncorrected. Optical rotations were measured with an Optical Activity AA-1000 Polarimeter at 21 ± 2 °C. NMR spectra were recorded on a Bruker AC250P instrument (250 MHz for ^1H and 62.5 MHz for ^{13}C), using TMS as internal standard (unless otherwise apecified). The δ_C ($CDCl_3$ = 77.0), and δ_H (internal TMS = 0) values were measured in $CDCl_3$ unless otherwise stated.

The composition of the reaction mixtures was monitored by TLC using aluminium sheets precoated with silica gel $60F_{254}$ (0.2 mm thickness, E. Merck, Darmstadt, Germany); detection was affected by observation under short wavelength UV light (254 nm), then dipping the chromatograms into 10 % sulfuric acid in methanol and charring them with a heat gun. Column chromatography was performed using silica gel 60 (0.040-0.063 mm, 230-400 mesh ASTM, E. Merck, Darmstadt, Germany). Elemental analyses were performed at the Chemistry Department, Leo Pharmaceuticals, Copenhagen, Denmark.

Phenyl 2,3,4-Tri-*O*-benzyl-1-thio-β-D-glucopyranoside (3). Compound **2** (0.5 g, 0.92 mmol) was dissolved in 1:1 diethyl ether-dichloromethane (20 mL) and $LiAlH_4$ (0.2 g) was added in two portions with stirring. The mixture was slowly heated to reflux temperature after which $AlCl_3$ (0.5 g) in diethyl ether (10 mL) was added to the hot solution over a 45 min period and reflux was continued for another 45 min. The mixture was cooled and excess $LiAlH_4$ was decomposed with ethyl acetate (5 mL). The $Al(OH)_3$ formed was precipitated by the addition of water (15 mL) and filtered off. The filtrate was diluted with diethyl ether (50 mL) and the organic phase was separated, washed with water (3 x 20 mL) and dried over anhydrous sodium sulfate. The solution was concentrated to dryness to give pure crystalline **3** (0.5 g, 99.6 % yield). An analytical sample was obtained as colorless fibers from 96 % ethanol: mp 122-123 °C; $[\alpha]_D$ + 9.3° (*c* 0.6, chloroform); ^1H NMR ($CDCl_3$) δ 1.94 (t, 1H, $J_{6,OH}$= 6.8 Hz, OH-6), 3.38 (dq, 1H, $J_{5,6b}$= $J_{5,OH-6}$= 2.7, $J_{5,6a}$= 4.8, $J_{4,5}$= 9.6 Hz, H-5), 3.48 (dd, 1H, $J_{2,3}$= 8.7, $J_{1,2}$= 9.8 Hz, H-2), 3.58 (t, 1H, $J_{3,4}$= $J_{4,5}$= 9.3 Hz, H-4), 3.69 (ddd, 1H, $J_{5,6a}$= 4.8, $J_{6,OH}$= 7.2, $J_{6a,6b}$= 11.7 Hz, H-6a), 3.73 (t, 1H, $J_{2,3}$= $J_{3,4}$= 8.9 Hz, H-3), 3.87 (ddd, 1H,

$J_{5,6b}$= 2.7, $J_{6,OH}$= 6.3, $J_{6a,6b}$= 12.0 Hz, H-6b), 4.65 (d, 1H, J = 11.0 Hz, $PhCH_2O$), 4.72 (d, 1H, $J_{1,2}$= 9.8 Hz, H-1), 4.76 (d, 1H, J = 10.6 Hz, $PhCH_2O$), 4.83-4.94 (m, 4H, $PhCH_2O$), 7.30-7.60 (m, 20H, H_{Ar}, SPh and $PhCH_2O$); ^{13}C NMR ($CDCl_3$) δ 62.1 (C-6), 75.1, 75.5, 75.8 (3 $PhCH_2O$), 77.6 (C-5), 79.3 (C-4), 81.1 (C-2), 86.5 (C-3), 87.5 (C-1), 127.6, 127.7, 127.8, 127.9, 127.9, 128.0, 128.2, 128.4, 128.4,128.5, 129.0, 131.8, 133.5, 137.8, 137.9, 138.3 (C_{Ar}, SPh & $PhCH_2O$).

Anal. Calcd for $C_{33}H_{34}O_5S$ (542.70): C, 73.04; H, 6.32; S, 5.91. Found: C, 73.14; H, 6.27; S, 5.83.

Phenyl 2,3,4-Tri-*O*-benzyl-6-bromo-6-deoxy-1-thio-ß-D-glucopyranoside (4a). Carbon tetrabromide (2.15 g, 6.48 mmol) was added at 0 °C to a stirred solution of **3** (1.63 g, 3.0 mmol) and triphenylphosphine (1.56 g, 6.0 mmol) in anhydrous pyridine (30 mL). Stirring was continued and the temperature was raised to room temperature over a period of 1½ h. The mixture was diluted with ethyl acetate (100 mL) and poured into ice-cold water (50 mL). The organic phase was washed with water (4 x 50 mL), brine (25 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by chromatography under medium pressure on a column of silica gel (60 g) with *n*-pentane/ethyl acetate (95:5 v/v) as eluant to give crystallline **4a** (1.68 g, 92 %). An analytical sample was obtained as colorless needles from *n*-pentane: mp 99-100 °C; $[\alpha]_D$ -4.6° (*c* 1.4, chloroform); ^1H NMR (250 MHz, $CDCl_3$) δ 3.49 (dd, 1H, $J_{2,3}$= 8.7, $J_{1,2}$= 9.6 Hz, H-2), 3.50-3.60 (m, 3H, H-4, H-5, H-6a), 3.70 (dd, 1H, $J_{5,6b}$= 1.7, $J_{6a,6b}$= 10.7 Hz, H-6b), 3.72 (t, 1H, $J_{2,3}$= $J_{3,4}$= 8.7 Hz, H-3), 4.67 (d, 1H, $J_{1,2}$= 9.8 Hz, H-1), 4.69 (d, 1H, J = 10.9 Hz, $PhCH_2O$), 4.71 (d, 1H, J = 10.9 Hz, $PhCH_2O$), 4.80-4.93 (m, 4H, $PhCH_2O$), 7.24-7.66 (m, 20H, H_{Ar}, SPh and $PhCH_2O$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 32.8 (C-6), 75.3, 75.4, 75.8 (3 $PhCH_2O$), 77.7 (C-5), 79.2 (C-4), 80.6 (C-2), 86.4 (C-3), 87.3(C-1), 127.7, 127.8, 127.8, 127.9, 128.0, 128.0, 128.1, 128.4, 128.5, 128.5, 128.9, 132.5, 133.0, 137.7, 137.9, 138.1 (C_{Ar}, SPh and $PhCH_2O$).

Anal. Calcd for $C_{33}H_{33}BrO_4S$ (605.59): C, 65.45; H, 5.49; Br, 13.19; S, 5.29. Found: C, 65.45; H, 5.55; Br, 13.31; S, 5.18.

Phenyl 2,3,4-Tri-*O*-benzyl-6-chloro-6-deoxy-1-thio-ß-D-glucopyranoside (4b). Carbon tetrachloride (10 mL) was added at 0 °C to a stirred solution of **3** (1.63 g, 3.0 mmol)

and triphenylphosphine (1.56 g, 6.0 mmol) in anhydrous pyridine (30 mL). The mixture was heated at 60 °C for 1 h with magnetic stirring after which methanol (10 mL) was added and the stirring continued for another 25 min at 60 °C. The solution was concentrated to dryness and the resulting solid was purified by column chromatography on silica gel (60 g) with *n*-pentane/ethyl acetate (95:5 v/v) as eluant to afford crystalline **4b** (1.65 g, 98 %). An analytical sample was obtained as colorless needles from *n*-pentane: mp 84-85 °C; $[\alpha]_D$ -4.4° (*c* 0.5, chloroform); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.49 (dd, 1H, $J_{2,3}$= 8.6, $J_{1,2}$= 9.7 Hz, H-2), 3.54 (m, 1H, H-5), 3.61 (t, 1H, $J_{3,4}$= $J_{4,5}$= 8.8 Hz, H-4), 3.70 (dd, 1H, $J_{5,6a}$= 4.6, $J_{6a,6b}$= 11.8 Hz, H-6a), 3.72 (t, 1H, $J_{2,3}$= $J_{3,4}$= 8.6 Hz, H-3), 3.83 (dd, 1H, $J_{5,6b}$= 2.1, $J_{6a,6b}$= 11.8 Hz, H-6b), 4.66 (d, 1H, $J_{1,2}$= 9.7 Hz, H-1), 4.69-4.94 (m, 6H, $PhCH_2O$), 7.24-7.63 (m, 20H, H_{Ar}, SPh and $PhCH_2O$); ^{13}C NMR (62.5 MHz,$CDCl_3$) δ 44.2 (C-6), 75.2, 75.4, 75.8 (3 $PhCH_2O$), 78.1, 78.1 (C-4 and C-5), 80.6 (C-2), 86.5 (C-3), 87.4 (C-1), 127.7,127.7,127.7, 127.9, 128.0, 128.0, 128.1,128.4, 128.5, 128.5, 128.9, 132.3, 133.2, 137.7,137.9, 138.1 (C_{Ar}, SPh and $PhCH_2O$).

Anal. Calcd for $C_{33}H_{33}ClO_4S$ (561.14): C, 70.63; H, 5.93; Cl, 6.32; S, 5.71. Found: C, 70.63; H, 6.05; Cl, 6.32; S, 5.63.

Phenyl 2,3-Di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-6-*O*-*tert*-butyldiphenylsilyl--1-thio-ß-D-glucopyranoside (7). *Tert*-Butylchlorodiphenylsilane (0.5 mL, 1.92 mmol) was added dropwise at 0 °C to a stirred solution of **5**[19,20] (0.96 g, 1.40 mmol) and imidazole (0.30 g, 4.41 mmol) in dry DMF (25 mL) and stirring continued at room temperature for 3 h. The mixture was poured into ice-water and the precipitate formed was filtered off. The air dried product was purified by column chromatography on silica gel with dichloromethane/ethyl acetate (95:5 v/v) as eluant to obtain crystalline **7** (1.1 g, 85 %). Recrystallization of **7** from ethanol/water gave white crystals: mp 85-86 °C; $[\alpha]_D$ + 36.2° (*c* 0.4, chloroform); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.09 (s, 9H, *t*-Bu), 1.91, 1.99, 1.99, 2.01, 2.04, 2.06 (6s, 18H, OAc), 3.57-3.65 (m, 1H, H-5), 3.63 (dd, 1H, $J_{5,6b}$= 1.6, $J_{6a,6b}$= 12.0 Hz, H-6b), 3.70-3.77 (m, 1H, H-5'), 3.82 (dd, 1H, $J_{5,6a}$= 4.1 Hz, H-6a), 3.95 (dd, 1H, $J_{5',6'a}$= 5.0, $J_{6'a,6'b}$= 11.4 Hz, H-6'a), 3.98 (t, 1H, $J_{3,4}$= $J_{4,5}$= 9.3 Hz, H-4), 4.05 (dd, 1H, $J_{5',6'b}$= 2.1, $J_{6'a,6'b}$= 11.4 Hz, H-6'b), 4.81 (dd, 1H, $J_{1',2'}$= 3.2, $J_{2',3'}$= 10.0 Hz, H-2'), 4.84 (d, 1H, $J_{1,2}$= 10.3 Hz, H-

1), 4.89 (dd, 1H, $J_{2,3}$= 8.7, $J_{1,2}$= 10.1 Hz, H-2), 4.95 (t, 1H, $J_{3',4'}$= $J_{4',5'}$= 9.9 Hz, H-4'), 5.28 (dd, 1H, $J_{3',4'}$= 9.5, $J_{2',3'}$= 10.4 Hz, H-3'), 5.31 (t, 1H, $J_{2,3}$= $J_{3,4}$= 8.8 Hz, H-3), 5.40 (d, 1H, $J_{1',2'}$= 3.9 Hz, H-1'), 7.16-7.75 (m, 15H, H_{Ar}, SPh and $Si(Ph)_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 19.2 ($C(CH_3)_3$), 20.5, 20.5, 20.5, 20.7, 20.7, 20.9 (6 OAc), 26.8 ($C(CH_3)_3$), 61.4, 63.3 (C-6 and C-6'), 67.8, 68.3 (C-4' and C-5'), 69.4 (C-3'), 70.1, 70.8 (C-2' and C-4), 72.7 (C-2), 76.3 (C-3), 79.3 (C-5), 86.1 (C-1), 95.5 (C-1'), 127.7, 127.7, 127.7, 127.8, 127.8, 129.0, 129.0, 129.8, 129.8, 131.6, 131.6, 132.7, 133.2, 133.3, 135.5, 135.8 (C_{Ar}, SPh and $Si(Ph)_2$), 169.3, 169.6, 169.8, 170.2, 170.3, 170.3 (6 OAc).

Anal. Calcd for $C_{46}H_{56}O_{16}SSi$ (925.09): C, 59.72; H, 6.10; S, 3.47. Found: C, 59.91; H, 6.22; S, 3.30.

_O_-(2,3,4,6-Tetra-_O_-acetyl-α-D-glucopyranosyl)-(1→4)-_O_-(2,3,6-tri-_O_-acetyl-α-D-glucopyranosyl)-(1→4)-_O_-(2,3,6-tri-_O_-acetyl-α-D-glucopyranosyl)-(1→4)-_O_-(2,3,6-tri-_O_-acetyl-α-D-glucopyranosyl)-(1→4)-_O_-2,3,6-tri-_O_-acetyl-α,ß-D-glucopyranose (9). A mixture of **8** (3.0 g, 3.62 mmol), acetic anhydride (75 mL), and sodium acetate (7.5 g) was refluxed at 140-150 °C for 4½ h. The mixture was cooled and poured onto crushed-ice and stirred at room temperature for 2 h. The aqueous phase was extracted with dichloromethane (3 x 100 mL) and the extract was washed with water (3 x 50 mL), saturated aq sodium hydrogen carbonate (3 x 50 mL), water (3 x 50 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by column chromatography on silica gel (120 g) with chloroform/methanol (98:2 v/v) as eluant to obtain crystalline **9** (4.94 g, 88 %). An analytical sample was obtained by recrystallization from 96 % ethanol: mp 127-128 °C; $[\alpha]_D$ 123.1 ° (*c* 0.5, chloroform); ^1H NMR (250 MHz, $CDCl_3$) δ 6.25 (d, 0.2H, $J_{1,2}$= 3.7 Hz, H-1α), 5.76 (d, 0.8H, $J_{1,2}$= 8.0 Hz, H-1β); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 88.7 (C-1α), 91.2 (C-1β).

Anal. Calcd for $C_{64}H_{86}O_{43}.H_2O$ (1561.39): C, 49.23 H, 5.68. Found: C, 49.23; H, 5.72.

Phenyl _O_-(2,3,4,6-Tetra-_O_-acetyl-α-D-glucopyranosyl)-(1→4)-_O_-(2,3,6-tri-_O_-acetyl-α-D-glucopyranosyl)-(1→4)-_O_-(2,3,6-tri-_O_-acetyl-α-D-glucopyranosyl)-(1→4)-_O_-(2,3,6-tri-_O_-acetyl-α-D-glucopyranosyl)-(1→4)-_O_-2,3,6-tri-_O_-acetyl-1-thio-β-D-glucopyranoside (10). Trimethylsilyl triflate (2.2 mL, 12.13 mmol) was added at room

temperature to a stirred solution of **9** (7.6 g, 4.92 mmol) and phenylthiotrimethylsilane (4.5 mL, 23.86 mmol) in dry toluene (100 mL). The stirred mixture was heated gradually to 65-70 °C under an argon atmosphere and kept for 9 h. The mixture was then cooled to room temperature and solid sodium hydrogen carbonate (5 g) was added. After stirring for 10 min the mixture was diluted with ethyl acetate (200 mL), water (100 mL) was added and the organic phase was separated and washed successively with 1M sodium hydroxide (3 x 25 mL), water (3 x 50 mL), and brine (25 mL) and dried over anhydrous sodium sulfate and concentrated. The residue was chromatographed on silica gel (230 g) with chloroform as eluant to obtain crystalline **10** (6.12 , 78 % yield): mp 121-122 °C (from 96 % ethanol); $[\alpha]_D$ + 157.7° (*c* 0.7, chloroform).

Anal. Calcd for $C_{68}H_{88}O_{41}S.2H_2O$ (1629.53): C, 50.12; H, 5.69. Found: C, 50.17; H, 5.72.

General procedure for removal of the phenylthio group. *N*-Bromosuccinimide (1.2-4.0 equiv) was added at room temperature to a stirred solution of the phenyl thioglycoside (1 equiv) in 9:1 acetone-water (15 mL/mmol). Stirring was continued for a period of 10 min-2 h (Table 1). The solvent was evaporated at room temperature until turbidity arose. The residue was dissolved in ethyl acetate (200 mL), washed with a saturated aqueous solution of sodium hydrogen carbonate (3 x 50 mL), water (3 x 50 mL), dried over anhydrous sodium sulfate and the solvent evaporated. The product was isolated by column chromatography on silica gel using the eluant system indicated in Table 1.

2,3,4,6-Tetra-*O*-acetyl-D-glucopyranose (13). Colorless syrup $[\alpha]_D$ + 74.7° (*c* 0.5, chloroform). The purity is about 90 % and no further purification was accomplished.

4,6-*O*-Benzylidene-2,3-di-*O*-benzyl-D-glucopyranose (14). White powder from diethyl ether / *n*-pentane: mp 153-154 °C, $[\alpha]_D$ - 31.6° (*c* 0.4, chloroform).

Anal. Calcd for $C_{27}H_{28}O_6$ (448.52): C, 72.30; H, 6.29. Found: C, 72.14; H, 6.35.

2,3,4-Tri-*O*-benzyl-6-bromo-6-deoxy-D-glucopyranose (15). White powder: mp 91-92 °C; $[\alpha]_D$ + 24.9° (*c* 0.5, chloroform).

Anal. Calcd for $C_{27}H_{29}BrO_5$ (513.43): C, 63.16; H, 5.69; Br, 15.56. Found: C, 63.33; H, 5.77; Br, 15.67.

2,3,4-Tri-*O*-benzyl-6-chloro-6-deoxy-D-glucopyranose (16). White powder: mp 98-99 °C; $[\alpha]_D$ + 19.8° (*c* 0.5, chloroform).

Anal. Calcd for $C_{27}H_{29}ClO_5$ (468.98): C, 69.15; H, 6.23; Cl, 7.56. Found: C, 68.96; H, 6.27; Cl, 7.59.

2,3-Di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-6-*O*-*tert*-butyldiphenylsilyl-D-glucopyranose (18). Recrystallization from ethanol/water gave white powder: mp 91-92 °C; $[\alpha]_D$ + 79.1° (*c* 0.3, chloroform).

Anal. Calcd for $C_{40}H_{52}O_{17}Si.½H_2O$ (841.94): C, 57.06; H, 6.35. Found: C, 57.05; H, 6.33.

***O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-*O*-2,3,6-tri-*O*-acetyl-D-glucopyranose (19).** White powder: mp 126-127 °C; $[\alpha]_D$ + 126.1° (*c* 0.2, chloroform).

Anal. Calcd for $C_{62}H_{84}O_{42}.1½H_2O$ (1528.36): C, 48.72; H, 5.73. Found: C, 48.74; H, 5.76.

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