Stereospecific Synthesis of 1,2-*trans*-1-Phenylthio-β-D-Disaccharides Under Phase Transfer Catalysis

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Peracetylated α-glycobiosyl bromides **1–5** derived from commercially available disaccharides, were transformed with complete anomeric stereocontrol into phenyl 1,2-*trans*-1-thio-β-D-glycobiosides **6–10** by nucleophilic displacement under phase transfer catalyzed glycosidation in 77–92% yields. The reaction proceed rapidly for most bromides in dichloromethane, but failed under similar conditions, to provide complete conversion of the melibiosyl bromide **4** into the *S*-phenyl thioglycoside **9**. Nevertheless, the reaction gave good results when performed in toluene or ethyl acetate.

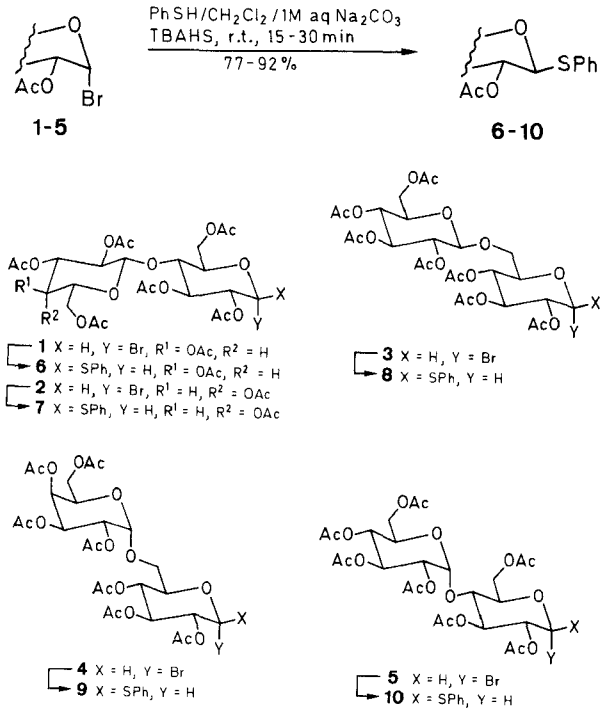
Thioglycosides constitute an important family of carbohydrate derivatives. They are known to be competitive inhibitors for a number of glycohydrolases.[1] As such, they have been extensively used as ligands on solid supports for the purification of glycosidases by affinity chromatography.[2] Recently, they have gained interest because they represent stable latent glycosyl donors[3] which resist most standard functional group manipulations so common to carbohydrate chemistry.

A wide variety of methods are known for the synthesis of thioglycosides including phase transfer catalysis (PTC).[4] They can be prepared from 1-halo,[5] 1-thio,[6] 1-acyl[7] and pseudothiourea[8] of per-*O*-acetylated aldoses. They have also been prepared from their corresponding *O*-alkyl glycosides.[9] The most widely utilized procedures for the synthesis of 1,2-*trans*-thioglycosides are those based on Lewis acid catalyzed reactions between per-*O*-acetyl derivatives and thiols,[7] or those using glycosyl halides with thiophenoxides.[5] However, both procedures suffer from some drawbacks. For instance, the Lewis acid catalyzed reactions may give mixtures of α,β-anomers[8] and dithioacetals, while the one phase phenoxide methods afford products extensively contaminated with de-*O*-acetylation.

The recent use of PTC for the synthesis of both *O*-[10–12] and *S*-aryl[4] monosaccharides prompted us to attempt for the first time, the reaction of thiophenol on per-*O*-acetylated glycobiosyl bromides under PTC conditions. Hence, the procedure would give access to phenyl 1,2-*trans*-1-thio-β-glycobiosides. Disaccharides are of interest since they constitute integral components of a number of polysaccharide repeating units which can be adequately synthesized using the widespread thioglycosyl donor technology.[3]

Most recent syntheses of aryl glycosides under PTC conditions[10] use either refluxing benzene or chloroform solutions and benzyltriethylammonium bromide (BTEAB) as catalyst. Our own recent investigations on *O*-aryl glycosides[11] have demonstrated that the more lipophilic tetrabutylammonium hydrogen sulfate (TBAHS) gave much faster reactions than BTEAB in both dichloromethane and benzene. Moreover, we have also confirmed the results of Bogusiak and Szeja,[4] who showed that similar reactions in benzene could be conducted at room temperature with the overall results that the reactions proceeded in high yields within 30 minutes. However, in our hands, dichloromethane was found to be more efficient than benzene. Therefore glycosidation of the bromides **1–3, 5** using 3 equivalents of thiophenol and TBAHS in dichloromethane at room temperature afforded the corresponding thiodisaccharides **6–8, 10** in more than 77% yields (Table 1). The more slowly reacting

bromide **4** gave incomplete conversion under these conditions. The reaction had stopped at ~ 50% conversion. Changing the solvents to toluene or ethyl acetate gave, however, the expected thioglycosides **9** in high yields (TBAHS, 30 min, 90%). In this last case, it was suspected that the nucleophilic thiophenoxide was adversely competing for the solvent (dichloromethane). A control experiment was therefore run in which the glycobiosyl bromides were omitted. Using dichloromethane as solvent and under essentially the same reaction conditions as in the general procedure, bis(phenylthio)methane and chloromethylphenyl sulfide were isolated and characterized (EI-MS, ^{1}H- and ^{13}C-NMR). Thus, it was concluded that when the bromides were not converted rapidly enough into the thiodisaccharides, competing nucleophilic displacement with the solvent occurred. The situation was obviously avoided in toluene or ethyl acetate without adverse effect on the reaction time. A slight increase in the molar ratio of the thiophenol gave no appreciable improvements.



The ^{1}H- and ^{13}C-NMR spectroscopic data of the thiodisaccharides **6–10** are in complete agreement with the 1,2-*trans* anomeric configurations ($J_{1,2}$ ~ 10 Hz; C-1, δ = 85.0–85.5) (Table 2). Besides hydrolysis and dehydrobromination side reactions, the only products isolated were the 1,2-*trans*-β-D-glycosides. No 1,2-*cis*-α-glycosides were observed from the crude reaction mixture (^{1}H-NMR). The reaction is therefore stereospecific and occurred with complete anomeric stereocontrol by nucleophilic displacement.

In conclusion, a new, mild and stereospecific entry into phenyl 1,2-*trans*-1-thio-β-glycobiosides (thiodisaccharides) has been achieved under PTC conditions. The procedure should be compatible with acid-labile protecting groups. Readily available reagents were used without the requirements of metals or Lewis acids.

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter for 0.5–1.0% solutions in $CHCl_3$ at r.t. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian XL-300 Spectrometer at 300 MHz in $CDCl_3$ with references at δ = 7.24 ($CHCl_3$) and 77.0, respectively. Assignments were based on COSY and HETCOR experiments. Combustion analyses were peformed by M-H-W Laboratories (Phoenix, AZ) or Guelph Chemical Laboratories Ltd (Ont.). All the per-*O*-acetylated glycobiosyl bromides were prepared by the standard HBr/HOAc (35% w/w) procedure[13] and purified by silica gel column chromatography before use. TLC was performed on silica gel 60-F254 plates using hexane, EtOAc (1:1) containing 0.5% isopropanol as eluent; detection was made under UV light and by charring with the $CeSO_4/(NH_4)_6Mo_7O_{24}/H_2SO_4$ reagent. Column chromatography was performed on silica gel 60 (230–400 mesh, Merck No. 9385).

PTC Glycosidation of the α-Glycobiosyl Bromides 1–5; General Procedure:

To a solution of the appropriate acetobromoglycobiose **1–5** (1 equiv) and Bu_4NHSO_4 (1 equiv) in CH_2Cl_2(for **1, 2, 3, 5**), or toluene (or EtOAc) (for **4**) (1 mL/100 mg of the bromide) is added 1 M aq Na_2CO_3 (1 mL/100 mg of the bromide) and thiophenol (3 equiv). The two phase reaction mixture is vigorously stirred at r.t. for 15–30 min, after which time TLC indicates complete transformation of the bromide. When the bromides and the thioglycosides have the same R_f, **(3/8,4/9)** conversions are confirmed by ^{1}H- and ^{13}C-NMR spectroscopy. CH_2Cl_2 (20 mL) is then added, the organic phase separated and successively washed with 1 M NaOH (20 mL), water (2 × 20 mL) and brine (15 mL). The combined organic extracts are dried (Na_2SO_4), filtered and evaporated under reduced pressure to afford the crude thiodisaccharides **6–10**. Products **6** and **7** are purified by crystallization from absolute EtOH and compound **8** is purified by silica gel radial column chromatography with 2% EtOH in CH_2Cl_2 as eluent followed by crystallization from absolute alcohol. Compounds **9** and **10** are purified by column chromatography on silica gel using a gradient of toluene/EtOAc (1:0, 5:1, 2:1) and CH_2Cl_2/EtOAc (1:0, 1:1), respectively, as eluents (Tables 1 and 2).

Financial support by NSERC is gratefully acknowledged. F.D.T. and G.C.-M. are thankful to NSERC (Canada) and to FCAR (Quebec), respectively, for scholarships.

Table 1. PTC Glycosylation of Thiophenol With Per-*O*-acetylglycobiosyl Bromides

Substrate	Product	Yield (%)	mp (°C)	Molecular Formula[a] or Lit. mp (°C)	$[\alpha]_D^{23}$ (c = 1, $CHCl_3$) found	reported[5]
Acetobromocellobiose **1**	**6**	85	224–225	295 (dec)	−29.0°	−28.5°
Acetobromolactose **2**	**7**	92	165.1–166.7	155–156	−18.2°	−19.6°
Acetobromogentiobiose **3**	**8**	77	167.4–169.0	$C_{32}H_{40}O_{17}S$ (728.7)	−12.8°	–
Acetobromomelibiose **4**	**9**	90	glass	$C_{32}H_{40}O_{17}S$ (728.7)	+75.0°	–
Acetobromomaltose **5**	**10**	89	82	93–95	+47.4°	+49.0°

[a] Satisfactory microanalysis obtained C ±0.26, H ±0.20, S ±0.23.

Table 2. ^{1}H- and ^{13}C-NMR Data of Compounds **6–10** Prepared

Compound	^{1}H-NMR ($CDCl_3$/TMS, 300 MHz) δ, J (Hz)	^{13}C-NMR ($CDCl_3$/TMS, 75.4 MHz) δ
6	1.96, 2 × 1.98, 2.00, 2.04, 2.06, 2.09 (7 s, 3 H each, 7 × $COCH_3$), 3.60–3.65 (m, 2 H, H-5,5'), 3.71 (dd, 1 H, $J_{3,4}$ = 9.0, $J_{4,5}$ = 10.0, H-4), 4.00 (dd, 1 H, $J_{5,6}$ = 2.2, $J_{6,6'}$ = 12.6, H-6), 4.07 (dd, 1 H, $J_{5,6}$ = 5.4, $J_{6,6'}$ = 11.9, H-6), 4.36 (dd, 1 H, $J_{5,6}$ = 4.3, $J_{6,6'}$ = 12.5, H-6'), 4.47 (d, 1 H, $J_{1,2}$ = 7.8, H-1'), 4.54 (dd, 1 H, $J_{5,6}$ = 1.9, $J_{6,6'}$ = 11.9, H-6), 4.64 (d, 1 H, $J_{1,2}$ = 10.0, H-1), 4.89 (dd, 1 H, $J_{1,2}$ = 10.0, $J_{2,3}$ = 9.2, H-2), 4.90 (dd, 1 H, $J_{1,2}$ = 8.0, $J_{2,3}$ = 9.2, H-2'), 5.04 (dd, 1 H, $J_{3,4}$ = 9.3, $J_{4,5}$ = 9.5, H-4'), 5.12 (dd, 1 H, $J_{2,3}$ = 9.1, $J_{3,4}$ = 9.4, H-3'), 5.18 (dd, 1 H, $J_{2,3}$ = 9.1, $J_{3,4}$ = 9.0, H-3), 7.26–7.31 (m, 3 $H_{o,p\text{-arom}}$), 7.43–7.46 (m, 2 $H_{m\text{-arom}}$)	20.3, 20.4, 20.5, 20.6 (7 × $COCH_3$), 61.3 (C-6'), 61.8 (C-6), 67.5 (C-4'), 70.0 (C-2), 71.4 (C-2'), 71.8 (C-5'), 72.8 (C-3'), 73.4 (C-3), 76.2 (C-4), 76.6 (C-5), 85.4 (C-1), 100.7 (C-1'), 128.3 (p-C_{arom}), 128.9 (o-C_{arom}), 131.7 (*ipso*-C_{arom}), 133.0 (m-C_{arom}), 169.1, 169.4, 169.6, 169.8, 170.3, 170.6 (C=O)
7	1.94, 2.00, 2.01, 2.02, 2.07, 2.08, 2.12 (7 s, 3 H each, 7 × $COCH_3$), 3.62 (ddd, 1 H, $J_{4,5}$ = 9.9, $J_{5,6}$ = 2.0, $J_{5,6'}$ = 5.6, H-5), 3.72 (dd, 1 H, $J_{3,4}$ = 9.1, $J_{4,5}$ = 9.9, H-4), 3.84 (ddd, 1 H, $J_{4,5}$ = 1.0, $J_{5,6'}$ = 6.7, $J_{5,6}$ = 7.2, H-5'), 4.04 (dd, 1 H, $J_{5,6}$ = 7.2, $J_{6,6'}$ = 10.2, H-6'), 4.08 (dd, 1 H, $J_{5,6}$ = 5.6, $J_{6,6}$ = 11.9, H-6), 4.10 (dd, 1 H, $J_{5,6}$ = 6.7, $J_{6,6'}$ = 10.2, H-6'), 4.44 (d, 1 H, $J_{1,2}$ = 7.9, H-1'), 4.56 (dd, 1 H, $J_{5,6}$ = 2.0, $J_{6,6'}$ = 11.9, H-6), 4.65 (d, 1 H, $J_{1,2}$ = 10.1, H-1), 4.88 (dd, 1 H, $J_{2,3}$ = 9.2, H-2), 4.92 (dd, 1 H, $J_{2,3}$ = 10.5, H-3'), 5.08 (dd, 1 H, $J_{1,2}$ = 7.9, $J_{2,3}$ = 10.5, H-2'), 5.19 (dd, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.2, H-3), 5.32 (dd, 1 H, $J_{3,4}$ = 3.4, $J_{4,5}$ = 1.0, H-4'), 7.27–7.31 (m, 3 $H_{o,p\text{-arom}}$), 7.44–7.47 (m, 2 $H_{m\text{-arom}}$)	20.5, 20.6, 20.7, 20.8 (7 × $COCH_3$), 60.8 (C-6'), 62.1 (C-6), 66.6 (C-4'), 69.0 (C-2'), 70.2 (C-2), 70.7 (C-5'), 70.9 (C-3'), 73.8 (C-5), 76.1 (C-3), 76.6 (C-4), 85.5 (C-1), 101.0 (C-1'), 128.7 (p-C_{arom}), 128.9 (o-C_{arom}), 131.7 (*ipso*-C_{arom}), 133.0 (m-C_{arom}), 169.0, 169.5, 169.7, 170.0, 170.1, 170.2, 170.3 (C=O)
8	1.94, 1.96, 1.99, 2.00, 2.01, 2.05, 2.07 (7 s, 3 H each, 7 × $COCH_3$), 3.57–3.65 (m, 1 H, H-5'), 3.61 (dd, 1 H, $J_{5,6}$ = 7.4, $J_{6,6'}$ = 11.1, H-6), 3.72 (ddd, 1 H, $J_{4,5}$ = 9.7, $J_{5,6}$ = 1.9, $J_{5,6'}$ = 7.4, H-5), 3.85 (dd, 1 H, $J_{5,6}$ = 1.9, $J_{6,6'}$ = 11.1, H-6), 4.10 (dd, 1 H, $J_{5,6}$ = 2.3, $J_{6,6'}$ = 12.3, H-6'), 4.23 (dd, 1 H, $J_{5,6}$ = 4.7, $J_{6,6'}$ = 12.3, H-6'), 4.68 (d, 1 H, $J_{1,2}$ = 10.1, H-1), 4.89 (dd, 1 H, J_{4} = 9.4, $J_{4,5}$ = 9.7, H-4), 4.92 (dd, 1 H, $J_{1,2}$ = 10.1, $J_{2,3}$ = 9.3, H-2), 4.97 (dd, 1 H, $J_{1,2}$ = 8.1, $J_{2,3}$ = 9.5, H-2'), 5.06 (dd, 1 H, $J_{3,4}$ = 9.3, $J_{4,5}$ = 9.7, H-4'), 5.16 (dd, 1 H, $J_{2,3}$ = 9.5, $J_{3,4}$ = 9.3, H-3'), 5.18 (dd, 1 H, $J_{2,3}$ = 9.3, $J_{3,4}$ = 9.4, H-3), 7.32–7.36 (m, 3 $H_{o,p\text{-arom}}$), 7.42–7.46 (m, 2 $H_{m\text{-arom}}$)	20.5, 20.7 (7 × $COCH_3$), 61.7 (C-6'), 68.2 (C-4'), 68.3 (C-6), 68.7 (C-4), 69.8 (C-2), 71.0 (C-2'), 71.8 (C-5'), 72.7 (C-3'), 73.8 (C-3), 77.3 (C-5), 85.7 (C-1), 100.6 (C-1'), 128.3 (p-C_{arom}), 131.9 (*ipso*-C_{arom}), 132.3 (m-C_{arom}), 169.2, 169.3, 169.4, 169.5, 170.0, 170.1, 170.5 (C=O)
9	1.98, 1.99, 2.00, 2.02, 2.06, 2.09, 2.12 (7 s, 3 H each, $COCH_3$), 3.54 (m, 1 H, H-6), 3.69–3.75 (m, 2 H, H-5,6), 4.00–4.02 (m, 2 H, H-6'), 4.20 (m, 1 H, H-5'), 4.75 (d, 1 H, $J_{1,2}$ = 10.1, H-1), 4.94 (dd, 1 H, $J_{1,2}$ = 10.1, $J_{2,3}$ = 9.2, H-2), 5.01 (dd, 1 H, $J_{3,4}$ = 9.5, $J_{4,5}$ = 9.9, H-4), 5.06–5.12 (m, 2 H, H-1', 2'), 5.22 (dd, 1 H, $J_{2,3}$ = 9.3, $J_{3,4}$ = 9.4, H-3), 5.27–5.34 (m, 2 H, H-3', 4'), 7.30–7.37 (m, 3 $H_{o,p\text{-arom}}$), 7.41–7.44 (m, 2 $H_{m\text{-arom}}$)	20.6, 20.8 (7 × $COCH_3$), 61.5 (C-6'), 66.3 (C-5'), 66.7 (C-6), 67.2 (C-3'), 68.0 (C-2', 4'), 68.5 (C-4), 69.9 (C-2), 73.9 (C-3), 76.6 (C-5), 85.4 (C-1), 96.2 (C-1'), 128.2 (p-C_{arom}), 129.1 (o-C_{arom}), 131.9 (*ipso*-C_{arom}), 132.0 (m-C_{arom}), 169.2, 169.3, 169.6, 170.1, 170.3, 170.4 (C=O)
10	1.94, 1.95, 1.97, 1.98, 2.01, 2.05, 2.08 (7 s, 3 H each, $COCH_3$), 3.67 (ddd, 1 H, $J_{4,5}$ = 9.6, H-5), 3.89 (ddd, 1 H, $J_{4,5}$ = 10.2, H-5'), 3.89 (dd, 1 H, $J_{3,4}$ = 9.1, $J_{4,5}$ = 9.6, H-4), 3.99 (dd, 1 H, $J_{5,6'}$ = 2.2, $J_{6,6'}$ = 12.4, H-6'), 4.17 (dd, 1 H, $J_{5,6}$ = 8.7, $J_{6,6'}$ = 12.4, H-6'), 4.23 (dd, 1 H, $J_{5,6}$ = 4.8, $J_{6,6'}$ = 12.0, H-6), 4.49 (dd, 1 H, $J_{5,6}$ = 2.5, $J_{6,6'}$ = 12.0, H-6), 4.79 (dd, 1 H, $J_{1,2}$ = 3.9, $J_{2,3}$ = 10.5, H-2'), 4.99 (dd, 1 H, $J_{3,4}$ = 9.6, $J_{4,5}$ = 10.2, H-4'), 5.18 (AB system, H-1,2), 5.24 (dd, 1 H, $J_{2,3}$ = 8.8, $J_{3,4}$ = 9.1, H-3), 5.29 (dd, 1 H, $J_{2,3}$ = 10.5, $J_{3,4}$ = 9.6 Hz, H-3'), 5.34 (d, 1 H, $J_{1,2}$ = 3.9 Hz, H-1'), 7.27–7.32 (m, 3 $H_{o,p\text{-arom}}$), 7.42–7.46 (m, 2 $H_{m\text{-arom}}$)	20.5, 20.6, 20.7, 20.8 (7 × $COCH_3$), 61.4 (C-6'), 62.7 (C-6), 67.9 (C-4'), 68.5 (C-5'), 69.2 (C-3'), 69.9 (C-2'), 70.6 (C-2), 72.4 (C-4), 76.0 (C-5), 76.4 (C-3), 85.0 (C-1), 95.5 (C-1'), 128.4 (p-C_{arom}), 128.8 (o-C_{arom}), 131.2 (*ipso*-C_{arom}), 133.3 (m-C_{arom}), 169.3, 169.4, 169.8, 170.1, 170.2, 170.4 (C=O)

Received: 13 March 1991

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