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Note

Phase transfer catalyzed synthesis of 4-nitrophenyl 1-thio-β-D-glycobiosides

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Thioglycosides have recently gained interest because of their intrinsic versatility. They have long been recognized as enzyme inhibitors and thus have been used as ligands for affinity chromatography[1]. They are now widely used as glycosyl donors in block-oligosaccharide syntheses[2], and more recently, long-chain alkyl 1-thio-D-glucopyranosides have demonstrated liquid-crystal behavior[3].

A wide variety of methods exists for the preparation of thioglycosides[4]. One of the very successful approaches for the synthesis of both *O*- (ref. 5) and *S*-aryl glycosyl compounds utilizes phase-transfer catalysis[6]. The efficiency of this method for the preparation of alkyl 1-thioglycosides is hampered, however, by considerable *O*-deacetylation and, therefore, provides low yields of thioglycosides[6]. Phase-transfer catalysis has not yet been used for the efficient and general synthesis of 4-nitrophenyl 1-thioglycosides and for the synthesis of 1,2-*trans*-1-phenylthio-β-D-disaccharides.

Our own recent interest for phase-transfer catalysis in carbohydrate chemistry[7–10], as well as the versatile transformations of the 4-nitrophenyl group into latent thioglycosyl donor groups[9] and the usefulness of the 4-(*N*-acrylamido)-phenyl group for the synthesis of protein and polymer conjugates[10], prompted us to study the practical transformation of four commonly encountered glycobioses into 4-nitrophenyl 1-thio-β-D-disaccharides.

Treatment of glycobiosyl bromides **1**, **3**, **5**, and **7**, in the presence of a catalytic two-phase system using either dichloromethane or ethyl acetate as solvent and M sodium carbonate and lipophilic tetrabutylammonium hydrogen sulfate, afforded the 4-nitrophenyl 1-thio-β-D-disaccharides **2**, **4**, **6**, and **8** in 70–91% yields (Table I). The reaction, performed at room temperature, occurred with complete stereo-

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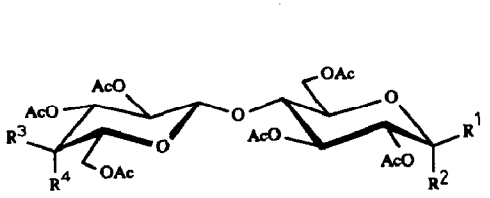
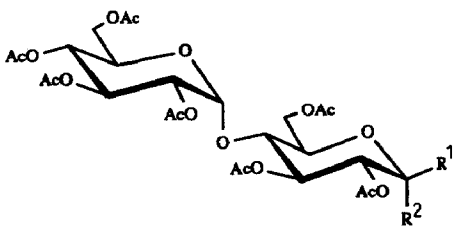
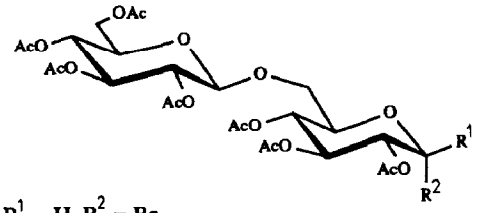


1 R^1 = H, R^2 = Br, R^3 = OAc, R^4 = H
2 R^1 = $SPhNO_2(4)$, R^2 = H, R^3 = OAc, R^4 = H
3 R^1 = H, R^2 = Br, R^3 = H, R^4 = OAc
4 R^1 = $SPhNO_2(4)$, R^2 = H, R^3 = H, R^4 = OAc



5 R^1 = H, R^2 = Br
6 R^1 = $SPhNO_2(4)$, R^2 = H



7 R^1 = H, R^2 = Br
8 R^1 = $SPhNO_2(4)$, R^2 = H

control by nucleophilic displacement with inversion of configuration. No 1-thio-α-D-glycoside could be detected in the crude reaction mixtures. All the chemical shifts of protons at the new anomeric centres were observed at δ 4.81 $\pm$ 0.07 with $^3J_{1,2}$ 10.1 $\pm$ 0.1 Hz, and the signals for the anomeric carbon atoms appeared between δ 83.8 and 84.4, indicative of 1,2-*trans*-β-D configurations.

Interestingly, the per-*O*-acetyl-α-lactosyl (**3**) and -maltosyl bromide (**5**) reacted smoothly in dichloromethane within 4–6 h at room temperature, whereas per-*O*-

TABLE I

Glycosylation of 4-nitrothiophenol with per-*O*-acetylglycobiosyl bromides

Per-*O*-acetylglycobiosyl bromide		Glycosides obtained			
			Yield (%)	Mp (Solvent of crystallization)	$[\alpha]_D^{23}$ (*c* 1, $CHCl_3$; degrees)
Cellobiosyl	(1)	**2**	89	233–234 (EtOAc–hexane)	−39
Lactosyl	(3)	**4**	91	122–124 (MeOH)	−26
Maltosyl	(5)	**6**	71	165–166 (EtOH)	+42
Gentiobiosyl	(7)	**8**	70	190–191 (EtOH)	−25

acetyl-α-cellobiosyl (1) and -gentiobiosyl bromide (7) failed to give complete conversion under the same conditions; when the same three equivalents of 4-nitrothiophenol were used, the reaction stopped at ~ 50% conversion with 1 and 7 in dichloromethane. The use of refluxing benzene or toluene, as proposed by others[5,6], did not improve the yield as the 4-nitrothiophenoxide ion is not soluble in these solvents. Replacing dichloromethane with ethyl acetate was however beneficial, and the corresponding thioglycosides 2 and 8 could be obtained in good yields within the same reaction time (4–5.5 h). Obviously, when the reaction takes place in a dichloromethane solution, there are possible competing reactions between a nucleophilic attack at both the anomeric center and on the solvent. Indeed, in one instance, bis(4-nitrothiophenyl)methane was isolated from the reaction mixture and characterized by ^{1}H- and ^{13}C-NMR spectroscopy, and mass spectrometry. Other side reactions, such as oxidation give 4-nitrophenyl disulfide, isolated and characterized by ^{1}H- and ^{13}C-NMR spectroscopy, and mass spectroscopy, and monosubstitution of the solvent could be accounted for. In conclusion, treatment of glycobiosyl bromides under liquid two-phase conditions with 4-nitrothiophenol afforded 1,2-*trans*-1-thio-β-D-glycobiosides in good yields with complete anomeric stereocontrol resulting in inversion of configuration.

EXPERIMENTAL

Methods. — Melting points were determined with a Gallenkamp apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. The ^{1}H- and ^{13}C-NMR spectra were recorded with a Varian XL-300 Spectrometer at 300 MHz for solutions in deuterochloroform with references at δ 7.24 ($CHCl_3$) and δ 77.0, respectively; analyses were done as first-order approximation, and all assignments were based on COSY and HETCOR experiments. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ) or Guelph Chemical Laboratories Ltd. (Guelph, ON). All per-*O*-acetylglycobiosyl bromides were prepared by the standard 35% (w/w) HBr–HOAc procedure[11] and purified by flash chromatography using a hexane–EtOAc gradient. TLC was performed on Silica Gel 60 F_{254} plates with 1:1 (v/v) hexane-EtOAc containing 0.5% 2-propanol as eluent; spots were detected by UV light and by charring with the 1% (w/v) $CeSO_4$–2.5% (w/v) $(NH_4)_6Mo_7O_{24}$–10% aq H_2SO_4 reagent. Column chromatography was performed on Silica Gel 60 (230–400 mesh, Merck No. 9385).

Glycosidation of α-glycobiosyl bromides **1**, **3**, **5**, *and* **7**. — To a solution of α-glycobiosyl bromide (515 mg, 0.74 mmol) and tetrabutylammonium hydrogen sulfate (250 mg, 1 equiv), CH_2Cl_2 for **3** and **5** or EtOAc for **1** and **7** (2.5 mL) were added M aq Na_2CO_3 (2.5 mL) and 4-nitrothiophenol (3 equiv). The two-phase reaction mixture was vigorously stirred at room temperature for 1.5–6 h until TLC indicated complete conversion. Dichloromethane or EtOAc was added (20 mL) and the organic phase was successively washed with M NaOH (20 mL), water

(2 × 20 mL), and satd NaCl (15 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford crude 4-nitrothiophenyl β-D-disaccharides **2**, **4**, **6**, or **8**. The products were purified by silica gel chromatography and crystallized as indicated (Table I).

4-Nitrophenyl 2,3,6,2',3',4',6'-hepta-O-acetyl-1-thio-β-cellobioside (**2**). — ^{1}H-NMR ($CDCl_3$): δ 8.13 (d, 2 H, *J* 9.0 Hz, H-3 of C_6H_4), 7.54 (d, 2 H, *J* 9.0 Hz, H-2 of C_6H_4), 5.22 (dd, 1 H, $J_{2,3}$ 9.1, $J_{3,4}$ 8.9 Hz, H-3), 5.13 (dd, 1 H, $J_{2',3'}$ 9.1, $J_{3',4'}$ 9.4 Hz, H-3'), 5.05 (dd, 1 H, $J_{4',5'}$ 9.6 Hz, H-4'), 4.95 (dd, 1 H, $J_{1,2}$ 10.0 Hz, H-2), 4.91 (dd, 1 H, $J_{1',2'}$ 7.9 Hz, H-2'), 4.80 (d, 1 H, $J_{1,2}$ 10.0 Hz, H-1), 4.56 (dd, 1 H, $J_{5,6a}$ 1.7, $J_{6a,6b}$ 12.1 Hz, H-6a), 4.49 (d, 1 H, $J_{1',2'}$ 7.9 Hz, H-1'), 4.36 (dd, 1 H, $J_{5',6a'}$ 4.2, $J_{6a',6b'}$ 12. 5 Hz, H-6a'), 4.10 (dd, 1 H, $J_{5,6b}$ 5.5, $J_{6a,6b}$ 11.9 Hz, H-6b), 4.01 (dd, 1 H, $J_{5',6b'}$ 2.3 Hz, H-6b'), 3.78–3.70 (m, 2 H, H-4,5), 3.64 (ddd, 1 H, H-5'), and 2.12–1.96 (7 s, 21 H, 7 OAc); ^{13}C-NMR ($CDCl_3$): δ 170.5–169.1 (7 C=O), 146.8 (C-4 of C_6H_4), 142.0 (C-*ipso*), 130.7 (2 C, C-3 of C_6H_4), 123.8 (2 C, C-2 of C_6H_4), 100.7 (C-1'), 83.9 (C-1), 76.8 (C-5), 76.0 (C-4), 73.1 (C-3), 72.6 (C-3'), 71.7 (C-5'), 71.3 (C-2'), 69.5 (C-2), 67.4 (C-4'), 61.7 (C-6), 61.2 (C-6'), and 20.5–20.2 (7 $OCOCH_3$).

Anal. Calcd for $C_{32}H_{39}NO_{19}S$: C, 49.68; H, 5.08; N, 1.81; S, 4.14. Found: C, 49.73; H, 5.14; N, 1.83; S, 4.09.

4-Nitrophenyl 2,3,6,2',3',4',6'-hepta-O-acetyl-1-thio-β-lactoside (**4**). — ^{1}H-NMR ($CDCl_3$): δ 8.13 (d, 2 H,*J* 9.0 Hz, H-3 of C_6H_4), 7.54 (d, 2 H, *J* 9.0 Hz, H-2 of C_6H_4), 5.33 (dd, 1 H, $J_{3',4'}$ 3.4, $J_{4'5'}$ 1.0 Hz, H-4'), 5.24 (dd, 1 H, $J_{2,3}$ 9.0, $J_{3,4}$ 8.9 Hz, H-3), 5.09 (dd, 1 H, $J_{1',2'}$ 7.8 Hz, H-2'), 4.95 (dd, 1 H, $J_{1,2}$ 10.1 Hz, H-2), 4.94 (dd, 1 H, $J_{2',3'}$ 10.4 Hz, H-3'), 4.81 (d, 1 H, $J_{1,2}$ 10.1 Hz, H-1), 4.53 (dd, 1 H, $J_{5,6a}$ 1.7, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.46 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1'), 4.12 (dd, 1 H, $J_{5',6a'}$ 6.3, $J_{6a',6b'}$ 11.0 Hz, H-6a'), 4.10 (dd, 1 H, $J_{5,6b}$ 4.4, $J_{6a,6b}$ 12.0 Hz, H-6b), 4.04 (dd, 1 H, $J_{5',6b'}$ 7.3 Hz, H-6b'), 3.85 (ddd, 1 H, $J_{4',5'}$ 1.0 Hz, H-5'), 3.74 (6-line AB pattern, 2 H, H-4,5), and 2.13–1.95 (7 s, 21 H, 7 OAc); ^{13}C-NMR ($CDCl_3$): δ 170.2–169.0 (7 C=O), 146.8 (C-4 of C_6H_4), 142.0 (C-*ipso*), 130.6 (2 C, C-3 of C_6H_4), 123.7 (2 C, C-2 of C_6H_4), 100.9 (C-1'), 83.8 (C-1), 76.7 (C-4), 75.7 (C-3), 73.3 (C-5), 70.6 (C-3'), 70.4 (C-5'), 69.6 (C-2), 68.8 (C-2'), 66.4 (C-4'), 61.8 (C-6), 60.7 (C-6'), and 20.4–20.1 (7 $OCOCH_3$); lit.[12] amorphous, $[\alpha]_D^{23}$ −65.8° ($CHCl_3$).

Anal. Calcd for $C_{32}H_{39}NO_{19}S$: C, 49.68; H, 5.08; N, 1.81; S, 4.14. Found: C, 49.47; H, 5.18; N, 1.72; S, 4.33.

4-Nitrophenyl 2,3,6,2',3',4',6'-hepta-O-acetyl-1-thio-β-maltoside (**6**). — ^{1}H-NMR ($CDCl_3$): δ 8.14 (d, 2 H, *J* 9.0 Hz, H-3 of C_6H_4), 7.55 (d, 2 H, *J* 9.0 Hz, H-2 of C_6H_4), 5.38 (d, 1 H, $J_{1',2'}$ 4.0 Hz, H-1'), 5.33 (dd, 1 H, $J_{2',3'}$ 10.5, $J_{3',4'}$, 9.7 Hz, H-3'), 5.31 (dd, 1 H, $J_{2,3}$ 8.8, $J_{3,4}$ 8.8 Hz, H-3), 5.03 (dd, 1 H, $J_{3',4'}$ 9.7, $J_{4',5'}$ 10.0 Hz, H-4'), 4.88 (5-line AB pattern, 2 H, H-1,2), 4.83 (dd, 1 H, $J_{2',3'}$ 10.5 Hz, H-2'), 4.52 (dd, 1 H, $J_{5,6a}$ 2.5, $J_{6a,6b}$ 12.3 Hz, H-6a), 4.22 (dd, 1 H, $J_{5,6b}$ 5.1 Hz, H-6b), 4.22 (dd, 1 H, $J_{5',6a'}$ 3.9, $J_{6a',6b'}$ 12.5 Hz, H-6a'), 4.04 (dd, 1 H, $J_{5',6b'}$ 2.5 Hz, H-6b'), 3.96 (dd, 1 H, $J_{4,5}$ 9.8 Hz, H-4), 3.93 (ddd, 1 H, $J_{4',5'}$ 10.0 Hz, H-5'), 3.84 (ddd, 1 H, $J_{4,5}$ 9.8 Hz, H-5), and 2.13–1.98 (7 s, 21 H, 7 OAc); ^{13}C-NMR ($CDCl_3$): δ 170.5–169.4

(7 C=O), 147.0 (C-4 of C_6H_4), 141.4 (C-*ipso*), 131.2 (2 C, C-3 of C_6H_4), 123.8 (2 C, C-2 of C_6H_4), 95.7 (C-1'), 83.9 (C-1), 76.3 (C-3), 76.0 (C-5), 72.4 (C-4), 70.4 (C-2), 69.9 (C-2'), 69.2 (C-3'), 68.6 (C-5'), 67.9 (C-4'), 62.8 (C-6), 61.5 (C-6'), and 20.8–20.9 (7 $COCH_3$).

Anal. Calcd for $C_{32}H_{39}NO_{19}S$: C, 49.68; H, 5.08; N, 1.81; S, 4.14. Found: C, 49.75; H, 5.13; N, 1.77; S, 4.21.

4-Nitrophenyl 2,3,4,2',3',4',6'-hepta-O-acetyl-1-thio-β-gentiobioside (**8**). — ^{1}H-NMR ($CDCl_3$): δ 8.21 (d, 2 H, *J* 8.9 Hz, H-3 of C_6H_4), 7.54 (d, 2 H, *J* 8.9 Hz, H-2 of C_6H_4), 5.23 (dd, 1 H, $J_{2,3}$ 9.2, $J_{3,4}$ 9.1 Hz, H-3), 5.17 (dd, 1 H, $J_{2',3'}$ 9.1, $J_{3',4'}$ 9.3 Hz, H-3'), 5.07 (dd, 1 H, $J_{4',5'}$ 9.8 Hz, H-4'), 5.00 (dd, 1 H, $J_{1,2}$ 10.1 Hz, H-2), 4.99 (dd, 1 H, $J_{1',2'}$ 7.9 Hz, H-2'), 4.92 (dd, 1 H, $J_{4,5}$ 9.9 Hz, H-4), 4.81 (d, 1 H, $J_{1,2}$ 10.1 Hz, H-1), 4.52 (d, 1 H, $J_{1',2'}$ 7.9 Hz, H-1'), 4.25 (dd, 1 H, $J_{5',6a'}$, 4.9, $J_{6a',6b'}$, 12.4 Hz, H-6a'), 4.11 (dd, 1 H, $J_{5',6b'}$ 2.3 Hz, H-6b'), 3.92 (dd, 1 H, $J_{5,6a}$ 2.1, $J_{6a,6b}$ 10.9 Hz, H-6a), 3.81 (ddd, 1 H, $J_{5,6b}$ 6.9 Hz, H-5), 3.65 (ddd, 1 H, H-5'), 3.59 (dd, 1 H, $J_{5,6b}$ 6.9 Hz, H-6b), and 2.07–1.91 (7 s, 21 H, 7 OAc); ^{13}C-NMR ($CDCl_3$): δ 170.5–169.1 (7 C=O), 146.9 (C-4 of C_6H_4), 141.9 (C-*ipso*), 130.4 (2 C, C-3 of C_6H_4), 124.2 (2 C, C-2 of C_6H_4), 100.7 (C-1'), 84.4 (C-1), 77.1 (C-5), 73.3 (C-3), 72.5 (C-3'), 72.0 (C-5'), 70.9 (C-2'), 69.4 (C-2), 68.4 (C-4), 68.2 (C-6), 68.0 (C-4'), 61.7 (C-6'), and 20.5–20.7 (7 $COCH_3$).

Anal. Calcd for $C_{32}H_{39}NO_{19}S$: C, 49.68; H, 5.08; N, 1.81; S, 4.14. Found: C, 49.37; H, 5.08; N, 1.67; S, 4.04.

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