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Note

Simultaneous regioselective protection of phenyl 1-thioglucosides at the C-3 and C-6 or at the C-2 and C-6 hydroxy groups

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Abstract

Simultaneous regioselective 3,6- or 2,6-selective protection of 1-thio-β- or α-D-glucopyranosides is described. The C-3 and C-6 hydroxy groups of the β-thioglucoside were selectively protected with triisopropylsilyl or *tert*-butyldiphenylsilyl trifluoromethanesulfonate. The C-2 and C-6 hydroxy groups of the α-thioglucoside were selectively protected with *tert*-butyldiphenylsilyl trifluoromethanesulfonate. © 2002 Elsevier Science Ltd. All rights reserved.

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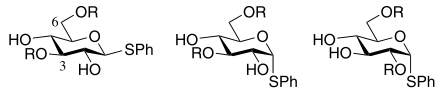
The chemical synthesis of sugar-containing compounds is often accompanied by protections and deprotections of the hydroxy groups that sometimes require many steps. Regioselective protections of sugar alcohols have resulted in simplification of the synthetic routes.[1–3] In this communication, we disclose the regioselective protection of phenyl 1-thio-β-D-glucopyranoside (**1**)[4] and phenyl 1-thio-α-D-glucopyranoside (**2**).[5] Reaction of **1** and triisopropylsilyl triflate (TIPSOTf hereafter) or *tert*-butyldiphenylsilyl triflate (TBDPSOTf)[6] afforded excellent 3,6-selectivity. On the other hand, treatment of **2** with TBDPSOTf afforded high 2,6-selectivity.

Treatment of the β-thioglucoside **1** with *tert*-butyldimethylsilyl triflate (TBDMSOTf), TIPSOTf, or TBDPSOTf selectively afforded 3,6-disilylated compounds **3**–**5**, respectively. The data are summarized in Table 1. Thus, treatment of **1** with TBDMSOTf gave 81% of **3** along with a mixture of corresponding 2,6-disilylated and 4,6-disilylated compounds (16% yield). The yields in the entries 2 and 3 were excellent giving 3,6-disilylated compounds **4** or **5** as the sole product, respectively. Another substrate, the α-isomer **2**, showed interesting selectivity. Thus, treatment of **2** with TBDMSOTf provided a 3,6-disilylated compound **6** (77% yield) along with a mixture of 2,6-disilylated **9** and 4,6-disilylated compounds (12%). Reaction of **2** with TIPSOTf afforded a 3,6-disilylated compound **7** as a major product (65% yield) along with a 2,6-disilylated compound **10** (9%). In contrast, the reaction with TBDPSOTf yielded a 2,6-disilylated compound **11** (88% yield) as the major product. The 3,6-disilylated **8** was isolated as a minor product (12% yield).



1: R = H
3: R = TBDMS
4: R = TIPS
5: R = TBDPS

2: R = H
6: R = TBDMS
7: R = TIPS
8: R = TBDPS

9: R = TBDMS
10: R = TIPS
11: R = TBDPS

All new compounds (**3**–**11**) were fully characterized by ^{1}H NMR spectroscopy. The spectra of **3**–**8** showed two peaks due to the hydrogen of the hydroxy groups that are coupled with the H-2 or H-4. Significant downfield-shift of H-2 and H-4 was also observed on the spectra of acetylated **4**, phenyl 2,4-di-*O*-acetyl-3,6-di-*O*-triisopropylsilyl-1-thio-β-D-glucopyranoside. The spectra of **9**–**11** also showed two peaks due to the hydrogens of the hydroxy groups related to the H-3 or H-4. The hydrogens on each pyranose ring were assigned based on decoupling experiments or H–H COSY spectra.

In conclusion, the four hydroxy groups of phenyl 1-thio-β- and α-D-glucopyranoside were clearly discriminated based on steric bulkiness of the silyl protecting

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Table 1
Introduction of silyl protecting groups to thioglucosides **1** and **2**

Entry	Substrate	Reaction conditions [a]	Product	Yield (%) [b]
1	**1**	A	**3**	81
2	**1**	B	**4**	95
3	**1**	C	**5**	94
4	**2**	D	**6**	77
5	**2**	B	**7**	65
6	**2**	E	**11**	88

[a] (A) TBDMSOTf (2.4 equiv), 2,6-lutidine (3.4 equiv), DMF, −20 to −5 °C; (B): see Experimental; (C) TBDPSOTf (2.9 equiv), 2,6-lutidine (3.8 equiv), DMF, 0 °C to rt; (D) TBDMSOTf (2.4 equiv), 2,6-lutidine (3.6 equiv), DMF, −20 to −10 °C; (E) see Experimental.
[b] Isolated yield.

groups. Alkylthio groups have played roles of a protecting groups during preparation of glycosyl donors, and have behaved as activating groups at the stage of glycosylation.[7] Because of the high regioselectivity presented here and the usefulness of the thioglucosides, the methods should be applicable to synthetic use.

1. Experimental

Typical procedure for 3,6-selective silylation of **1** *(Table 1, entry 2).*—TIPSOTf (4.79 g, 15.6 mmol) was added to a solution of **1** (2.03 g, 7.47 mmol) and 2,6-lutidine (2.58 g, 24.0 mmol) in DMF (75 mL) at 0 °C (ice bath). The mixture was stirred for 5 h. The reaction temperature rose gradually to 8 °C during the reaction. Addition of water and extraction with EtOAc gave a crude product. Column chromatography on silica gel (160 g) eluting with 1:0 to 30:1 (gradient) *n*-hexane–EtOAc gave **4** (4.17 g, 95% yield).

Typical procedure for 2,6-selective silylation of **2** *(Table 1, entry 6).*—TBDPSOTf (97 mg, 0.25 mmol) was added to a solution of **2** (31 mg, 0.11 mmol) and 2,6-lutidine (46 mg, 0.43 mmol) in DMF (3 mL) at −15 °C. The mixture was stirred for 8 h at −15 to 0 °C. Addition of water and extraction with EtOAc gave a crude product. Column chromatography on silica gel (7 g) eluting with 40:1 to 3:1 (gradient) *n*-hexane–EtOAc gave **11** (R_f 0.44 with 3:1 *n*-hexane–EtOAc, 75 mg, 88% yield) and **8** (R_f 0.58, 10 mg, 12% yield). Careful maintaining of the reaction temperature ensured the reproductibility of the selectivity.

Data for the new compounds.—Chemical shifts of the ^{1}H NMR data (400 MHz) are reported in δ units downfield from tetramethylsilane. The data are indicated by chemical shift with the number of the protons, coupling pattern, coupling constants (Hz), and assignment in parentheses in this order. The words "*J*" and "Hz" are not indicated. Splitting patterns are designated as s: singlet, d: doublet, t: triplet, q: quartet, br: broad and m: multiplet.

Phenyl 3,6-di-O-tert-*butyldimethylsilyl-1-thio-β*-D-*glucopyranoside* (**3**).—$[\alpha]_D^{21}$ −40.8° (*c* 2.43, $CHCl_3$); IR 3509, 2953, 2930, 2888, 2857, 1472, 1254, 1136, 1073, 781, 743, 691 cm^{-1}; ^{1}H NMR (C_6D_6): δ 0.04 (3 H, s), 0.05 (3 H, s), 0.23 (3 H, s), 0.26 (3 H, s), 0.92 (9 H, s), 1.00 (9 H, s), 2.07 (1 H, d, 2.4, OH), 2.38 (1 H, d, 2.4, OH), 3.12 (1 H, ddd, 8.8, 5.2, 4.0, H-5), 3.30 (1 H, ddd, 9.6, 8.4, 2.4, H-2), 3.45 (1 H, ddd, 8.8, 8.4, 2.4, H-4), 3.50 (1 H, dd, 8.4, 8.4, H-3), 3.78 (1 H, dd, 10.8, 5.2, H-6), 3.82 (1 H, dd, 10.8, 4.0, H-6), 4.33 (1 H, d, 9.6, H-1), 6.93–7.05 (3 H, m, Ar), 7.53–7.55 (2 H, m, Ar); HRFABMS: *m*/*z* Calcd for $C_{24}H_{44}O_5SSi_2Na$ [M + Na] 523.2346; found 523.2325.

Phenyl 3,6-di-O-*triisopropylsilyl-1-thio-β*-D-*glucopyranoside* (**4**).—$[\alpha]_D^{18}$ −37.5° (*c* 0.33, $CHCl_3$); IR 3509, 2944, 2866, 1464, 1142, 1069, 1017, 883, 683 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.07–1.09 (42 H, m), 2.41 (1 H, d, 2.0, OH), 2.83 (1 H, d, 2.0, OH), 3.33 (1 H, ddd, 9.6, 8.4, 2.0, H-2), 3.44 (1 H, dt, 9.6, 5.2, H-5), 3.51 (1 H, ddd, 9.6, 8.8, 2.0, H-4), 3.70 (1 H, dd, 8.8, 8.4, H-3), 3.98 (2 H, d, 5.2, H-6), 4.56 (1 H, d, 9.6, H-1), 7.28–7.29 (3 H, m, Ar), 7.53–7.56 (2 H, m, Ar); HRFABMS: *m*/*z* Calcd for $C_{30}H_{56}O_5SSi_2Na$ [M + Na] 607.3285; found 607.3294.

Phenyl 3,6-di-O-tert-*butyldiphenylsilyl-1-thio-β*-D-*glucopyranoside* (**5**).—$[\alpha]_D^{16}$ −20.7° (*c* 4.81, $CHCl_3$); IR 3567, 2932, 2859, 1472, 1427, 1113, 1071, 822, 741, 704, 611 cm^{-1}; ^{1}H NMR (C_6D_6): δ 1.15 (9 H, s), 1.17 (9 H, s), 1.77 (1 H, d, 3.7, OH), 1.96 (1 H, d, 2.7, OH), 2.91 (1 H, ddd, 9.5, 5.4, 2.4, H-5), 3.50 (1 H, ddd, 9.8, 8.3, 2.7, H-2), 3.59 (1 H, ddd, 9.5, 8.5, 3.7, H-4), 3.68 (1 H, dd, 8.5, 8.3, H-3), 3.80 (1 H, dd, 11.0, 5.4, H-6), 3.92 (1 H, dd, 11.0, 2.4, H-6), 4.11, (1 H, d, 9.8, H-1), 6.94–7.86 (25 H, m, Ar); HRFABMS: *m*/*z* Calcd for $C_{44}H_{52}O_5SSi_2Na$ [M + Na] 771.2972; found 771.2961.

Phenyl 3,6-di-O-tert-*butyldimethylsilyl-1-thio-α*-D-*glucopyranoside* (**6**).—$[\alpha]_D^{19}$ +176.0° (*c* 1.38, $CHCl_3$); IR 3507, 2953, 2930, 2857, 1472, 1254, 1138, 1065, 1024, 974, 837, 781 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.09 (6 H, s), 0.18 (3 H, s), 0.19 (3 H, s), 0.91 (9 H, s), 0.94 (9 H, s), 2.22 (1 H, d, 6.6, OH), 2.64 (1 H, d, 2.4, OH), 3.49 (1 H, ddd, 9.5, 8.5, 2.4, H-4), 3.62 (1 H, dd, 9.3, 8.5, H-3), 3.79 (1 H, ddd, 9.3, 6.6, 5.4, H-2), 3.85 (1 H, dd, 10.7, 4.6, H-6), 3.89 (1 H, dd, 10.7, 4.9, H-6), 4.14 (1 H, ddd, 9.5, 4.9, 4.6, H-5), 5.57 (1 H, d, 5.4, H-1), 7.26–7.33 (3 H, m, Ar), 7.51–7.54 (2 H, m, Ar); HRFABMS: *m*/*z* Calcd for $C_{24}H_{44}O_5SSi_2Na$ [M + Na] 523.2346; found 523.2319.

Phenyl 3,6-di-O-*triisopropylsilyl-1-thio-α*-D-*glucopyranoside* (**7**).—$[\alpha]_D^{16}$ +111.3° (*c* 1.84, $CHCl_3$); IR 3509, 2866, 1464, 1387, 1260, 1065, 883, 801 cm^{-1}; ^{1}H NMR

(C_6D_6): δ 1.00–1.04 (21 H, m), 1.18–1.25 (21 H, m), 2.05 (1 H, d, 6.3, OH), 2.84 (1 H, d, 2.4, OH), 3.64 (1 H, ddd, 9.4, 8.3, 2.4, H-4), 3.74 (1 H, ddd, 9.5, 6.3, 5.4, H-2), 3.93 (1 H, dd, 10.5, 4.9, H-6), 3.98 (1 H, dd, 10.5, 5.1, H-6), 4.04 (1 H, dd, 9.5, 8.3, H-3), 4.38 (1 H, ddd, 9.4, 5.1, 4.9, H-5), 5.48 (1 H, d, 5.4, H-1), 6.93–7.04 (3 H, m, Ar), 7.48–7.50 (2 H, m, Ar); HRFABMS: *m*/*z* Calcd for $C_{30}H_{56}O_5SSi_2Na$ [M + Na] 607.3285; found 607.3264.

Phenyl 3,6-di-O-tert-*butyldiphenylsilyl-1-thio-α*-D-*glucopyranoside* (**8**).—$[\alpha]_D^{17}$ + 66.5° (*c* 0.30, $CHCl_3$); IR 3567, 2930, 2857, 1427, 1262, 1113, 821, 739, 702, 613 cm^{-1}; ^1H NMR (C_6D_6): δ 1.14 (9 H, s), 1.23 (9 H, s), 1.69 (1 H, d, 7.7, OH), 1.93 (1 H, d, 3.7, OH), 3.73 (1 H, ddd, 9.8, 8.5, 3.7, H-4), 3.82 (1 H, ddd, 9.5, 7.7, 5.4, H-2), 3.94 (2 H, d, 3.8, H-6), 3.95 (1 H, dd, 9.5, 8.5, H-3), 4.21 (1 H, dt, 9.8, 3.8, H-5), 5.39 (1 H, d, 5.4, H-1), 6.91–7.88 (25 H, m, Ar); HRFABMS: *m*/*z* Calcd for $C_{44}H_{52}O_5SSi_2Na$ [M + Na] 771.2972; found 771.2955.

Phenyl 2,6-di-O-tert-*butyldimethylsilyl-1-thio-α*-D-*glucopyranoside* (**9**).—$[\alpha]_D^{18}$ + 166° (*c* 0.095, $CHCl_3$); IR 3405, 2930, 2857, 1472, 1254, 1136, 1067, 837, 779 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.08 (6 H, s), 0.12 (3 H, s), 0.13 (3 H, s), 0.90 (9 H, s), 0.95 (9 H, s), 2.44 (1 H, br s; OH), 2.95 (1 H, br s; OH), 3.60 (1 H, dd, 9.5, 8.8, H-4), 3.75 (1 H, dd, 9.3, 8.8, H-3), 3.81 (1 H, dd, 10.7, 4.9, H-6), 3.83 (1 H, dd, 9.3, 5.1, H-2), 3.86 (1 H, dd, 10.7, 4.9, H-6), 5.45 (1 H, d, 5.1; H-1), 7.22–7.31 (3 H, m, Ar), 7.46–7.50 (2 H, m, Ar); HRFABMS: *m*/*z* Calcd for $C_{24}H_{44}O_5SSi_2Na$ [M + Na] 523.2346; found 523.2366.

Phenyl 2,6-di-O-*triisopropylsilyl-1-thio-α*-D-*glucopyranoside* (**10**).—$[\alpha]_D^{18}$ + 87.9° (*c* 0.29, $CHCl_3$); IR 3420, 2944, 2866, 1464, 1138, 1065, 883, 687 cm^{-1}; ^1H NMR (C_6D_6): δ 1.00–1.18 (42 H, m), 2.26 (1 H, d, 2.4, OH), 2.57 (1 H, d, 2.4, OH), 3.68 (1 H, ddd, 9.6, 9.2, 2.4, H-3), 3.87 (1 H, ddd, 9.2, 9.2, 2.4, H-4), 3.94 (1 H, dd, 10.6, 4.6, H-6), 3.99 (1 H, dd, 10.6, 5.0, H-6), 4.10 (1 H, dd, 9.6, 5.2, H-2), 4.46 (1 H, ddd, 9.2, 5.0, 4.6, H-5), 5.72 (1 H, d, 5.2, H-1), 6.96 (1 H, m, Ar), 7.08 (2 H, m, Ar), 7.66 (2 H, m, Ar); HRFABMS: *m*/*z* Calcd for $C_{30}H_{56}O_5SSi_2Na$ [M + Na] 607.3285; found 607.3264.

Phenyl 2,6-di-O-tert-*butyldiphenylsilyl-1-thio-α*-D-*glucopyranoside* (**11**).—$[\alpha]_D^{19}$ + 122.9° (*c* 3.18, $CHCl_3$); IR 3420, 2932, 2859, 1474, 1427, 1113, 1065, 824, 739, 704, 613 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.99 (9 H, s), 1.14 (9 H, s), 2.46 (1 H, br s, OH), 2.84 (1 H, br s, OH), 3.53 (1 H, dd, 9.8, 8.5, H-4), 3.77 (1 H, dd, 11.0, 4.4, H-6), 3.81 (1 H, dd, 11.0, 4.6, H-6), 3.87 (1 H, dd, 9.3, 8.5, H-3), 3.92 (1 H, dd, 9.3, 5.4, H-2), 4.21 (1 H, ddd, 9.8, 4.6, 4.4, H-5), 5.02 (1 H, d, 5.4, H-1), 6.92–7.74 (25 H, m, Ar); HRFABMS: *m*/*z* Calcd for $C_{44}H_{52}O_5SSi_2Na$ [M + Na] 771.2972; found 771.2943.

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