A Convenient Synthesis of *S*-Glycosyl Donors of D-Glucose and *O*-Glycosylations Involving the New Reagent

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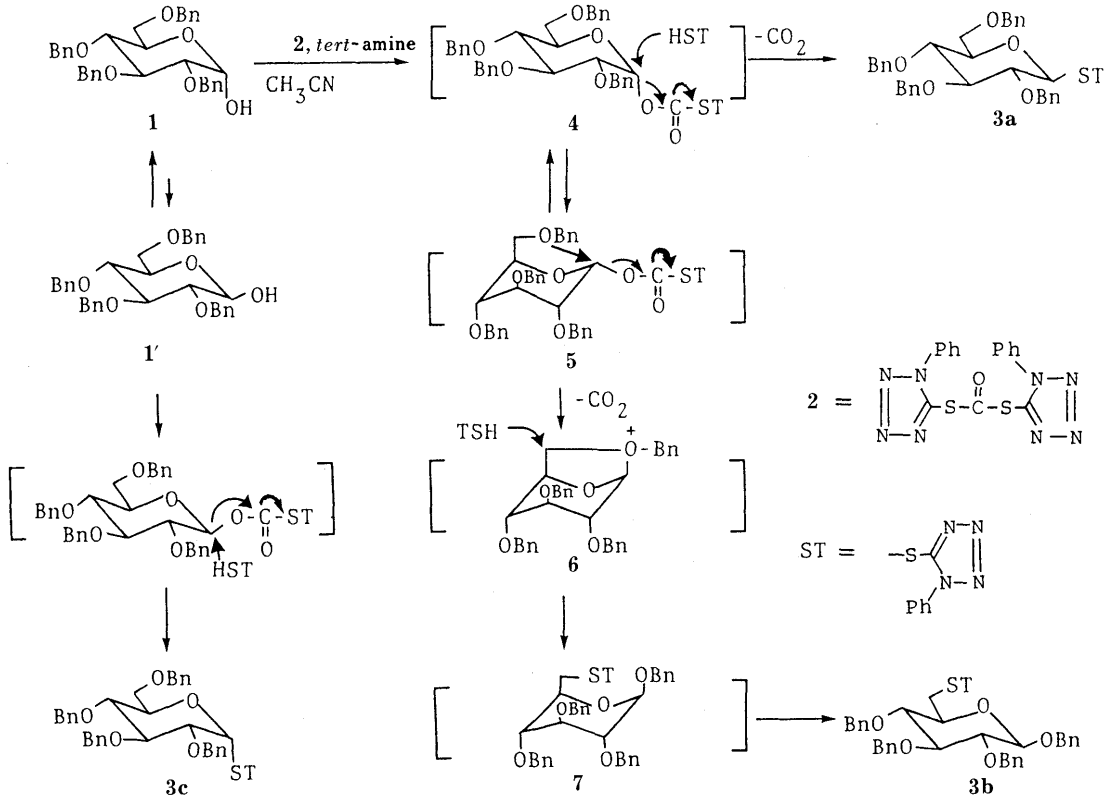
The synthesis of *S*-glycosyl donors from 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (1) using *S,S'*-bis(1-phenyl-1*H*-tetrazol-5-yl) dithiocarbonate (2) was carried out by a one-step reaction. One of the *S*-glycosyl donors, *S*-1-(1'-phenyl-1*H*-tetrazolyl) 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranose (3a), was utilized for glycosylation of glycosyl acceptors such as methanol or cholesterol using silver triflate as a promoter.

Keywords *S,S'*-bis(1-phenyl-1*H*-tetrazol-5-yl) dithiocarbonate; *O*-glycosylation; *S*-glycosyl donor; 1-phenyltetrazol-5-thio moiety; silver triflate; glycosyl acceptor

Various *S*-glycosides have been prepared as stable donors for glycosylation.[1] In most cases, *S*-glycosides have been obtained by the reactions of thiolate and unstable glycosyl halide. Recently, we reported on the use of the coupling reagent, *S,S'*-bis(1-phenyl-1*H*-tetrazol-5-yl) dithiocarbonate (**2**), to generate esters, macrolides, and peptides from carboxylic acids and nucleophiles.[2] The reagent (**2**) was also applied to single-step syntheses of allylic sulfides having a 1-phenyltetrazol-5-thio moiety as a synthon from allylic alcohols.[3] We reported the glycosylation of sialic acid by using the reagent (**2**) and found that the introduction of thiolate proceeded through an *SN*2 type mechanism, and glycosylation could be achieved when we used silver triflate (AgOTf) as a promoter and acetonitrile as the solvent.[4] By using this reagent (**2**), an *S*-glycosyl donor could be prepared in one step. It was stable, and could be stored at room temperature for some months.

In this report, we would like to describe the preparation of the *S*-glycosyl donors (**3**) from 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**1**)[5] with the reagent (**2**) and we demonstrate that **3a** can be applied for *O*-glycosylation.



	yield (%) triethylamine	DMAP
3a	47	63
3b	23	33
3c	<1	4

Chart 1

An acetonitrile solution of **1** and **2** was stirred at room temperature overnight in the presence of triethylamine or 4-(*N*,*N*-dimethylamino)pyridine (DMAP) to afford stable *S*-glycosides (**3a** and **3b**), as the main products, and a trace of an additional *S*-glycoside (**3c**). DMAP was superior to triethylamine as a catalyst. The structures of (**3a**, **3b**, and **3c**) were determined by proton nuclear magnetic resonance (^{1}H-NMR) and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectroscopy. $J_{1,2}$ values of **3a** and **3b** were 9.5 Hz, and 9.0 Hz, respectively. These comparably large coupling constants showed that both compounds, *S*-1-(1′-phenyl-1*H*-tetrazolyl) 2,3,4,6-tetra-*O*-benzyl-β-D-glycopyranose (**3a**) and *S*-6-(1′-phenyl-1*H*-tetrazolyl) 1,2,3,4-tetra-*O*-benzyl-β-D-glucopyranose (**3b**), probably adopt β-linked chair conformation. The structure of **3b** was confirmed by the LSPD (long-range selective proton decoupling) method in NMR spectroscopy. The doublet due to the imino carbon in the ^{13}C-NMR was collapsed to a singlet by decoupling the methylene protons at position 6. This means that the 1-phenyltetrazol-5-thio moiety is located at position 6 of glucose. The *S*-glycoside (**3c**), *S*-1-(1′-phenyl-1*H*-tetrazolyl) 2,3,4,6-tetra-*O*-benzyl-α-D-glycopyranose, adopts an α-linked chair conformation, having the 1-phenyltetrazol-5-thio moiety at the anomeric position of glucopyranose, because the $J_{1,2}$ value of **3c** was 5.2 Hz.

The reaction mechanism for the formation of **3a**, **3b**, and **3c** is considered to be as follows. The carbonyl group of the reagent (**2**) attacks the α-anomeric hydroxy group to give the intermediate (**4**), and the 1-phenyltetrazol-5-thio moiety is eliminated. It attacks the anomeric position by an *SN*2 mechanism to give the β-*S*-glycoside (**3a**) with liberation of carbon dioxide. The equilibrium between **1** and **1′** shifts to favor **1**, and so the amount of **3c** is very small. On the other hand, owing to repulsion between the benzyl moiety at position 2 and the moiety at the anomeric position in **4**, the ^{4}C$_1$ conformation of **4** changes into the ^{1}C$_4$ conformation of the intermediate (**5**). The lone pair of the *O*-benzyl moiety at position 6 attacks the anomeric carbon, and then the intermediate (**6**) is obtained with liberation of carbon dioxide by means of a push-pull mechanism. The eliminated 1-phenyltetrazol-5-thio moiety attacks the carbon at position 6, and the intermediate (**7**) is obtained. Furthermore, owing to repulsion between the 1-phenyltetrazol-5-thio moiety at position 6 and the benzyl moiety at the anomeric position in 7, the ^{1}C$_4$ conformation of **7** changes into the ^{4}C$_1$ conformation of **3b**.

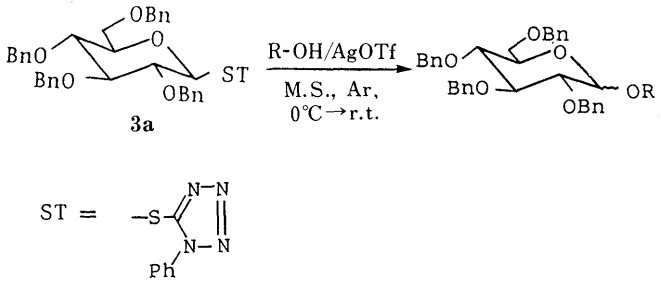


Chart 2

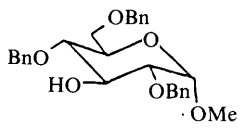
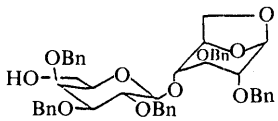
Glycosylation of alcohols with **3a** was carried out using silver triflate (AgOTf) as a promoter. In the case of primary and secondary alcohols such as methanol and cyclohexanol, the ratios of α- and β-anomer were 71:29 in 87% yield (methanol) and 33:67 in 95% yield (cyclohexanol) (runs 1 and 2). Similarly, cholesterol gave the glycoside in a good yield (run 3). Di- and trisaccharide were also prepared by the same method in fairly good yields (runs 4 and 5). The glycosylation using **3a** proceeded largely through an *SN*2-type mechanism because of the solvent effect.

In conclusion, **2** was found to be a versatile reagent for the syntheses of *S*-glycosyl donors, and one of the *S*-glycosyl donor obtained could effect *O*-glycosylations.

Experimental

Melting points were measured with Yamato melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-4 digital polarimeter. Thin-layer chromatography (TLC) was performed on Silica gel GE254 (Merck) plates, and the spots were detected by ultraviolet (UV) irradiation and with 5% sulfuric acid solution. Field desorption mass

TABLE I. *O*-Glycosylation with **3a**

Run	Acceptor	Acceptor (Molar equivalent)	Time (h)	Yield (%)	α : β [a]
1	MeOH	10	36	87	71 : 29 4.63 4.33 (d, $J_{1,2}$=3.5 Hz) (d, $J_{1,2}$=7.5 Hz)
2	Cyclohexanol	5	24	95	33 : 67 4.97 4.52 (d, $J_{1,2}$=3.5 Hz) (d, $J_{1,2}$=8.0 Hz)
3	Cholesterol	5	6	95	50 : 50 4.95 4.51 (d, $J_{1,2}$=3.5 Hz) (d, $J_{1,2}$=8.5 Hz)
4		5	6	48	66 : 34 5.59 5.07 (d, $J_{1,2}$=3.0 Hz) (d, $J_{1,2}$=8.5 Hz)
5		5	6	71	66 : 34 4.73 4.47 (d, $J_{1,2}$=3.5 Hz) (d, $J_{1,2}$=8.5 Hz)

a) These ratios of α to β-anomer were estimated from the integral values of ^{1}H-NMR chemical shifts for the α and β mixture.

spectra (FD-MS), fast atom bombardment mass spectra (FAB-MS) and infrared (IR) spectra were measured with JEOL JMS-DX 300, JMS-3100, and JASCO IR-A2 instruments, respectively. The NMR spectra were measured in chloroform-*d* ($CDCl_3$) and pyridine-d_5, with Varian XL-300 and XL-400 spectrometers.

***S*-1-(1′-Phenyl-1*H*-tetrazolyl) 2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranose (3a), *S*-6-(1′-Phenyl-1*H*-tetrazolyl) 1,2,3,4-Tetra-*O*-benzyl-β-D-glucopyranose (3b), and *S*-1-(1′-Phenyl-1*H*-tetrazolyl) 2,3,4,6-*O*-Benzyl-α-D-glucopyranose (3c)** A solution of DMAP (33 mg, 0.27 mmol) in acetonitrile (10 ml) was added to a solution of **2** (100 mg, 0.26 mmol) and **1** (135 mg, 0.25 mmol) in acetonitrile (10 ml) with stirring at room temperature. After 24 h, the mixture was concentrated and ethyl acetate was added to the residue. The organic layer was washed with 4% $NaHCO_3$, 0.5 N HCl, and saturated brine, dried with Na_2SO_4 and evaporated. The residue was subjected to TLC on silica gel (benzene). Yield was 93% (**3a** : **3b** : **3c** = 63 : 33 : 4). **3a**: mp 90—91 °C. MS *m/z*: 700 (M^+). $[\alpha]_D^{27}$ −44.7° (*c* = 0.93, chloroform). *Anal.* Calcd for $C_{41}H_{39}N_4O_5S$: C, 70.36; H, 5.61; N, 8.00. Found: C, 70.75; H, 5.76; N, 8.08. IR νcm^{-1}: 2925, 2870, 1590. ^{1}H-NMR (pyridine-d_5) δ: 3.70—3.80 (3H, m, 5-H, 6-H), 3.82 (1H, t, *J* = 9.5 Hz, 4-H), 3.91 (1H, t, *J* = 9.5 Hz, 3-H), 4.01 (1H, t, *J* = 9.5 Hz, 2-H), 4.34, 4.42, 4.63, 4.85 (4H, d, *J* = 11.2 Hz, PhCH × 4), 4.88—4.93 (4H, m, PhCH × 4), 5.70 (1H, d, *J* = 9.5 Hz, 1-H), 7.06—7.59 (25H, m, Ph × 5). **3b**: mp 113—114 °C, MS *m/z*: 700 (M^+). $[\alpha]_D^{27}$ +23.0° (*c* = 1.09, chloroform). *Anal.* Calcd for $C_{41}H_{39}N_4O_5S$: C, 70.36; H, 5.61, N, 8.00. Found: C, 70.26; H, 5.69; N, 8.02. IR νcm^{-1}: 2875, 2870, 1600. ^{1}H-NMR (pyridine-d_5) δ: 3.75—3.86 (2H, m, 6-H), 3.99—4.07 (2H, m, 4-H, 5-H), 4.15 (1H, t, *J* = 9.0 Hz, 3-H), 4.40, 4.49, 4.59, 4.74 (4H, d, *J* = 12.0 Hz, PhCH × 4), 4.55—4.62 (1H, br, 2-H), 4.87—5.01 (4H, m, PhCH × 4), 6.44 (1H, d, *J* = 9.0 Hz, 1-H), 7.02—7.85 (25H, m, Ph × 5). **3c**: mp 93—94 °C. MS *m/z*: 701 (M^{+1}). $[\alpha]_D^{28}$ +150.5° (*c* = 0.71, chloroform). *Anal.* Calcd for $C_{41}H_{39}N_4O_5S$: C, 70.36; H, 5.61; N, 8.00. Found C, 70.24; H, 5.72; N, 7.99. IR νcm^{-1}: 2920, 2870, 1600. ^{1}H-NMR ($CDCl_3$) δ: 3.51 (1H, dd, *J* = 1.8, 11.1 Hz, 6-H), 3.69 (1H, dd, *J* = 3.6, 11.1 Hz, 6-H), 3.70—3.75 (1H, br, 4-H), 3.75 (1H, t, *J* = 9.0 Hz, 3-H), 3.88—3.99 (1H, br, 5-H), 3.96 (1H, dd, *J* = 5.2, 9.0 Hz, 2-H), 4.47, 4.64, 4.70, 4.85 (8H, dd, $PhCH_2$ × 4), 6.57 (1H, d, *J* = 5.2 Hz, 1-H), 7.09—7.58 (25H, m, Ph × 5).

Methyl 2,3,4,6-Tetra-*O*-benzyl-α and β-D-glucopyranoside (Run 1) A typical glycosylation was carried out as follows. A solution of **3a** (70 mg, 0.1 mmol), molecular sieves 4A (400 mg) and methanol (32 mg, 1 mmol) in dichloromethane was cooled in an ice bath under argon and AgOTf (514 mg, 2 mmol) was added. The mixture was stirred in the ice bath for 4 h, then allowed to stand for 32 h at room temperature, and neutralized with triethylamine. Insoluble materials were removed by filtration, and the filtrate was evaporated. The residue was purified by TLC on a silica-gel plate (benzene : acetone = 10 : 1) and was identified by comparing its NMR and IR spectra with those of an authentic sample.[5] Yield was 87% (α : β = 71 : 29). Oil. MS *m/z*: 443 (M^+).

Cyclohexyl 2,3,4,6-Tetra-*O*-benzyl-α and β-D-glucopyranoside (Run 2) Yield was 95% (α : β = 33 : 67). Oil. MS *m/z*: 623 (M^{+1}). *Anal.* Calcd for $C_{40}H_{46}O_6$: C, 77.14; H, 7.45. Found: C, 76.91; H, 7.44. IR νcm^{-1}: 2930, 2860. ^{1}H-NMR ($CDCl_3$) δ: α-Isomer 1.10—1.97 (10H, m, cyclohexyl), 3.50—3.55 (1H, m, cyclohexyl 1-H), 3.57 (1H, dd, *J* = 3.5, 9.5 Hz, 2-H), 3.64 (1H, dd, *J* = 2.0, 11.0 Hz, 6-H), 3.64 (1H, t, *J* = 9.5 Hz, 4-H), 3.75 (1H, dd, *J* = 3.5, 11.0 Hz, 6-H), 3.89 (1H, ddd, *J* = 2.0, 3.5, 9.5 Hz, 5-H), 4.01 (1H, t, *J* = 9.5 Hz, 3-H), 4.55, 4.66, 4.71, 4.91 (8H, dd, $PhCH_2$ × 4), 4.97 (1H, d, *J* = 3.5 Hz, 1-H), 7.12—7.41 (20H, m, Ph × 4). β-Isomer 1.20—2.09 (10H, m, cyclohexyl), 3.46 (1H, dd, *J* = 8.0, 9.0 Hz, 2-H), 3.47 (1H, ddd, *J* = 1.8, 5.0, 9.5 Hz, 5-H), 3.56 (1H, t, *J* = 9.0 Hz, 3-H), 3.65 (1H, t, *J* = 9.0 Hz, 4-H), 3.67 (1H, dd, *J* = 5.0, 11.0 Hz, 6-H), 3.70—3.78 (1H, m, cyclohexyl 1-H), 3.76 (1H, dd, *J* = 1.8, 11.0 Hz, 6-H), 4.52 (1H, d, *J* = 8.0 Hz, 1-H), 4.60, 4.75, 4.81, 4.87 (8H, dd, $PhCH_2$ × 4), 7.16—7.40 (20H, m, Ph × 4).

Cholesteryl 2,3,4,6-Tetra-*O*-benzyl-α and β-D-glucopyranoside (Run 3) Yield was 95% (α : β = 50 : 50). mp 136—138 °C. MS *m/z*: 908 (M^+). *Anal.* Calcd for $C_{61}H_{80}O_6$: C, 80.57; H, 8.87. Found: C, 80.31; H, 9.00. IR νcm^{-1}: 2930, 2860. ^{1}H-NMR ($CDCl_3$) δ: α-Isomer 0.60—2.50 (44H, m, cholesterol), 3.41—3.53 (1H, m, cholesterol 3-H), 3.56 (1H, dd, *J* = 3.5, 9.0 Hz, 2-H), 3.64 (1H, dd, *J* = 1.5, 10.5 Hz, 6-H), 3.65 (1H, t, *J* = 9.0 Hz, 4-H), 3.75 (1H, dd, *J* = 3.8, 10.5 Hz, 6-H), 3.89 (1H, ddd, *J* = 1.5, 3.8, 9.0 Hz, 5-H), 4.01 (1H, t, *J* = 9.0 Hz, 3-H), 4.54, 4.66, 4.72, 4.92 (8H, dd, $PhCH_2$ × 4), 4.95 (1H, d, *J* = 3.5 Hz, 1-H), 5.29 (1H, d, *J* = 5.0 Hz, cholesterol 6-H), 7.15—7.39 (20 H, m, Ph × 4). β-Isomer 0.60 −2.50 (44H, m, cholesterol), 3.41—3.50 (1H, br, 5-H), 3.45 (1H, t, *J* = 8.5 Hz, 2-H), 3.55 (1H, t, *J* = 8.5 Hz, 3-H), 3.64 (1H, t, *J* = 8.5 Hz, 4-H), 3.65 (1H, dd, *J* = 5.0, 10.3 Hz, 6-H), 3.75 (1H, dd, *J* = 1.5, 10.3 Hz, 6-H), 4.51 (1H, d, *J* = 8.5 Hz, 1-H), 4.58, 4.74, 4.85, 4.81 (8H, dd, $PhCH_2$ × 4), 5.35 (1H, d, *J* = 5.0 Hz, cholesterol-6H).

1-Methyl-2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α and β-D-glucopyranosyl)-α-D-glucopyranose (Run 4) Yield was 48% (α : β = 66 : 34). Oil. FAB-MS 986 (M^+). *Anal* Calcd for $C_{62}H_{66}O_{11} \cdot 1/2H_2O$: C, 74.75; H, 6.77. Found: C, 74.67; H, 6.84. IR νcm^{-1}: 2925, 2860. ^{1}H-NMR ($CDCl_3$) δ: α-Isomer 3.32 (3H, s, OCH_3), 3.56 (1H, dd, *J* = 3.5, 9.5 Hz, 2-H), 3.57 (1H, dd, *J* = 3.0, 9.5 Hz, 2-H′), 4.06 (1H, t, *J* = 9.5 Hz, 3-H′), 4.30 (1H, dd, *J* = 7.0, 9.5 Hz, 3-H), 4.63 (1H, d, *J* = 3.5 Hz, 1-H), 5.59 (1H, d, *J* = 3.0 Hz, 1-H′), 6.95—7.45 (35H, m, Ph × 7). β-Isomer 3.32 (3H, s, OCH_3), 3.47 (1H, t, *J* = 8.5 Hz, 2′-H), 3.52 (1H, dd, *J* = 3.5, 9.5 Hz, 2-H), 3.70 (1H, t, *J* = 8.5 Hz, 3′-H), 4.39 (1H, t, *J* = 9.5 Hz, 3-H), 4.50 (1H, d, *J* = 3.5 Hz, 1-H), 5.07 (1H, d, *J* = 8.5 Hz, 1′-H), 7.10-7.48 (35H, m, Ph × 7).

***O*-(2,3,4,6-Tetra-*O*-benzyl-α and β-D-glucopyranosyl)-(1→6)-*O*-(2,3,4-tri-*O*-benzyl-α-D-galactopyranosyl)-(1→4)-1,6-anhydro-2,3-di-*O*-benzyl-α-D-glucopyranose (Run 5)** Yield was 71% (α : β = 66 : 34). Oil. FAB-MS 1296 (M^+). *Anal.* Calcd for $C_{81}H_{84}O_{15} \cdot 1/2H_2O$: C, 74.46; H, 6.55. Found: C, 74.49; H, 6.51. IR νcm^{-1}: 2900, 2850. ^{1}H-NMR ($CDCl_3$) δ: α-Isomer: 3.31 (1H, s, 2-H), 3.52 (1H, dd, *J* = 3.5, 9.5 Hz, 2″-H), 3.79 (1H, s, 3-H), 4.73 (1H, d, *J* = 3.5 Hz, 1″-H), 5.46 (1H, s, 1-H), 7.08—7.40 (45H, m, Ph × 9). β-Isomer 3.35 (1H, t, *J* = 8.5 Hz, 2″-H), 3.41 (1H, t, *J* = 7.0 Hz, 2′-H), 3.69 (1H, d, *J* = 7.0 Hz, 3′-H), 4.47 (1H, t, *J* = 8.5 Hz, 1″-H), 4.49 (1H, d, *J* = 7.0 Hz, 1′-H), 5.43 (1H, s, 1-H), 7.10—7.43 (45H, m, Ph × 9).

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