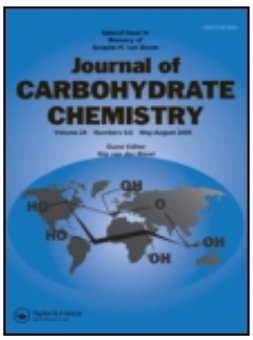

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STEREOSELECTIVE 1,2-*CIS*-1-THIOGLYCOSIDATION OF ALDOHEXOSES WITH *TERT*-BUTYL MERCAPTAN IN 90% TRIFLUOROACETIC ACID

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ABSTRACT

tert-Butyl 1,2-*cis*-1-thioglycopyranosides of various aldohexoses (D-glucose, D-galactose, D-mannose, and L-rhamnose), and disaccharides (cellobiose, lactose, and maltose) were preferentially prepared in good yields by reacting the corresponding free sugars with *tert*-butyl mercaptan in 90% trifluoroacetic acid at room temperature. No selectivity, however, was observed at all in the case of 2-deoxy-D-*arabino*-hexopyranose. A possible mechanism for the 1,2-*cis*-selectivity was discussed from a standpoint of thermodynamic and kinetic control.

INTRODUCTION

Thioglysosides have recently attracted considerable attention, especially as versatile glycosyl donors in oligosaccharide syntheses.[1] Of principal interest are aryl or alkyl 1,2-*trans*-1-thioglycosides because of their easy access.

As part of our comparative studies on α- and β-glycosyl sulfoxides and sulfones, we needed some *tert*-alkyl 1,2-*cis*-1-thioglycopyranosides. However, despite use of several procedures such as Lewis acid catalyzed anomerization[2] of alkyl 1-thio-β-D-

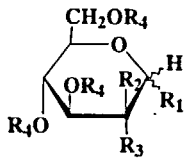
glycopyranosides to α-anomers. direct transformation[3] of aldose dialkyl dithioacetals into alkyl 1-thio-α-D-glycopyranosides in the presence of strong acid, and mercaptolysis[4] of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose, no 1,2-*cis*-selective and preparative methods for alkyl 1-thioglycopyranosides resulted directly from various free aldohexoses.

In a previous paper,[5] we proposed a novel synthetic method of diphenyl and/or trimethylene dithioacetals of various aldopentoses, aldohexoses and oligosaccharides by reacting free aldoses with benzenethiol and/or 1,3-propanedithiol in 90% trifluoroacetic acid. In addition to finding that this reaction is generally applicable to primary and secondary mercaptans, we newly found a different mode of reaction between common aldohexoses and disaccharides and *tert*-butyl mercaptan in 90% trifluoroacetic acid at room temperature. Interestingly, in place of the dithioacetals, *tert*-butyl 1,2-*cis*-1-thioglycopyranosides were predominantly obtained respectively in good yields. Therefore, we wish here to present a new and simple stereoselective methodology for the syntheses of *tert*-butyl 1,2-*cis*-1-thioglycopyranosides from common free aldohexoses such as D-glucose, D-galactose, D-mannose, and L-rhamnose as well as disaccharides such as cellobiose, lactose, and maltose.

RESULTS AND DISCUSSION

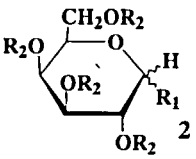
As we demonstrated in the previous paper,[5] 90% trifluoroacetic acid is a good and convenient solvent system for preparing various mono- and oligosaccharide dialkyl and diaryl dithioacetals, with interglycosidic linkages of oligosaccharides being reasonably stable at room temperature in this solvent for more than a week. At the same time, we observed that a prolonged treatment of cellobiose with ethanethiol or benzenethiol in this solvent at room temperature caused a gradual transformation of the initially formed cellobiose diethyl (diphenyl) dithioacetals into the corresponding ethyl (phenyl) 1-thio-α-cellobiosides, of which peracetates (**5c** and **5d**) were isolated in yields of 35-43%. This type of transformation converting alkyl or aryl dithioacetals into the corresponding 1-thioglycosides generally takes place more rapidly in concentrated hydrochloric acid (Fischer's dithioacetalation condition), but yields of the 1-thioglycosides are generally low despite α-selectivity.[3,6] Aparicio and coworkers,[7a] employing similar reaction conditions, prepared *tert*-butyl 1-thio-α-D-glucopyranoside (24.2%) and its β-anomer (27.3%) by reacting D-glucose and *tert*-butyl mercaptan in concentrated hydrochloric acid at ~15 °C for 12 hours. They also reported no appearance of the corresponding di-*tert*-butyl dithioacetals during the process.

We, therefore, undertook the reactions of *tert*-butyl mercaptan with various aldohexoses and disaccharides in 90% trifluoroacetic acid at room temperature over different periods of time, and beyond our expectation, we found a suitable condition to obtain stereoselectively and in good yields, *tert*-butyl 1,2-*cis*-1-thioglycopyranosides from these sugars. As a general rule, a higher concentration (>1.67 mmol/mL) and a shorter reaction time (<3 h) were more favorable for 1,2-*cis*-selectivity, especially in the case of D-mannose and L-rhamnose (Table1). No selectivity, however, was observed at all in the case of 2-deoxy-D-*arabino*-hexopyranose. Low solubility of disaccharides in 90% trifluoroacetic acid required much more time (three hours for the least soluble cellobiose, about one hour for lactose and maltose) for complete dissolution, and therefore, we adopted only reaction condition c shown in Table 1.



1

a) R_1=α-S-*t*-Bu, R_2=H, R_3= OAc, R_4=Ac
b) R_1=β-S-*t*-Bu, R_2=H, R_3= OAc, R_4=Ac
c) R_1=α-S-*t*-Bu, R_2= H, R_3= OBn, R_4=Bn
d) R_1=α-S-*t*-Bu, R_2= R_3=H, R_4=Ac
e) R_1= β-S-*t*-Bu, R_2= R_3=H, R_4=Ac



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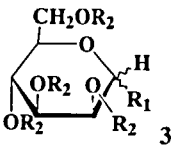

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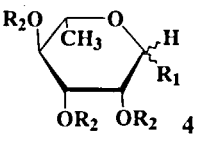


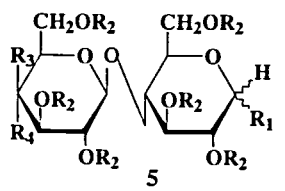
4

2,4

a) R_1=α-S-*t*-Bu, R_2= Ac
b) R_1=β-S-*t*-Bu, R_2= Ac

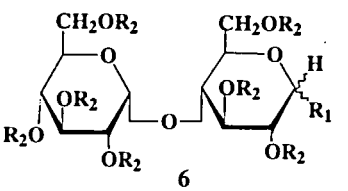
3

a) R_1=α-S-*t*-Bu, R_2= Ac
b) R_1=β-S-*t*-Bu, R_2= Ac
c) R_1=α-S-*t*-Bu, R_2=Bz
d) R_1=β-S-*t*-Bu, R_2= Bz



5

a) R_1=α/β-S-*t*-Bu, R_2= Ac, R_3= H, R_4=OAc
b) R_1=α/β-S-*t*-Bu, R_2=Ac, R_3= OAc, R_4=H
c) R_1=α-SEt, R_2= Ac, R_3= H, R_4=OAc
d) R_1=α-SPh, R_2= Ac, R_3= H, R_4=OAc



6

R_1=α/β-S-*t*-Bu, R_2= Ac

The product ratios of 1,2-*cis*- versus 1,2-*trans*-1-thioglycopyranosides thus obtained were determined respectively with ^{1}H NMR (the integral ratio of anomeric protons and/or H_5 protons of both anomers) of the peracetylated derivatives (**1a**, **1b**, **2a**, **2b**, **3a**, **3b**, **4a**, **4b**, **5a**, **5b**, and **6**) of *tert*-butyl 1-thio-α, β-D(L)- glycopyranosides, and the anomer ratios and yields of the peracetates (α+β) are listed respectively in Table 1.

Table 1. Anomer ratios and yields of *tert*-Butyl 1-thio-α/β-glycopyranoside peracetates

Compounds	$H_1(\alpha)$ (ppm)	$J_{1,2}$ (Hz)	$H_1(\beta)$ (ppm)	$J_{1,2}$ (Hz)	Ratio (α/β)	Yields (α+β)
D-Glc (**1a/1b**)	5.85	5.8	4.64	10.1	5.3/1[a]	77%
D-Gal (**2a/2b**)	5.94	5.8	4.63	9.9	3.7/1[a]	74%
D-Man (**3a/3b**)	5.45	1.4	4.84	1.2	1/7.9[b]	73%
L-Rham (**4a/4b**)	5.35	1.4	4.82	1.2	1/8.6[b]	71%
Cell (**5a**)	5.75	6.0	4.60	10.1	6.7/1[c]	65%
Lac (**5b**)	5.75	5.8	4.61	10.1	5.7/1[c]	68%
Mal(**6**)	5.74	5.8	4.68	10.1	4.9/1[c]	62%
2-deoxy-D-Glu (**1d/1e**)	5.63	5.7	4.76	11.8	1.2/1[a] 1/1[c]	65%

a) 1.67mmol/mL (2.3 h), b) 1.67mmol/mL (1h), c) 0.83mmol/mL (15h)

Full characterization of ^{1}H NMR parameters for the corresponding *tert*-butyl 1-thio-glycopyranoside peracetates of monosaccharides (**1a**, **1b**, **1c**, **1d**, **2a**, **2b**, **3a**, **3b**, **4a**, and **4b**) and perbenzoates (**3c** and **3d**) are also shown in Table 2.

Di-*tert*-butyl dithioacetals, which are presumed to be too difficult to be formed because of the bulkiness of *tert*-butyl group, were not detected at all throughout the reaction process. Though the observed anomeric ratios of 1,2-*cis*- to 1,2-*trans*-1-thio-glycopyranosides are in the range of about 4:1 to 9:1, except 2-deoxy-D-glucose as shown in Table 1, these ratios were quite dependent on the concentration of the free aldohexoses and the reaction time. We, therefore, tried to pursue the optical rotational changes of the above reactions of both cases of D-glucose and D-mannose, and the results are shown in Fig. 1. A remarkable difference between D-glucose and D-mannose was clearly observed at the different concentrations (0.2 to 1.0 mmol/mL) during the time-course from 0.5 to 8 hours. Extended measurements [over 9 hours in the case of D-mannose and over 3 hours in the case of D-glucose (0.6 mmol/mL)], however, were not practical because of strong coloration (deep brown or deep violet) of the reaction solutions. The reaction rates coming to the chemical equilibriums of both sugars are

Table 2. Full characterization of ^{1}H NMR parameters of *tert*-butyl 1-thio-α and β-glycopyranoside peracetates (1a, 1b, 2a, 2b, 3a, 3b, 4a, and 4b) and perbenzoates (3c and 3d)

Com-pounds	H_1	H_2	H_3	H_4	H_5	H_{6a}	H_{6b}	OAc (*t*-Bu)
(1a) αD*Glc*	5.85(d) $J_{1,2}$=5.8	4.95(dd) $J_{2,3}$=10.6	5.27(dd) $J_{3,4}$=9.2	5.03(dd) $J_{4,5}$=10.2	4.48(m) $J_{5,6a}$=4.6	4.30(dd) $J_{6a,6b}$=12.3	4.05(dd) $J_{5,6b}$=2.3	2.07,2.06 2.03,2.02 (1.35)
(1b) βD*Glc*	4.64(d) $J_{1,2}$=10	4.95(dd) $J_{2,3}$=9.3	5.26(dd) $J_{3,4}$=9.3	5.04(dd) $J_{4,5}$=9.7	3.72(m) $J_{5,6a}$=6.0	4.21(dd) $J_{6a,6b}$=12.3	4.05(dd) $J_{5,6b}$=2.4	2.05,2.04, 2.03,2.00 (1.37)
(2a) αD*Gal*	5.94(d) $J_{1,2}$=5.8	5.22(dd) $J_{2,3}$=11.1	5.12(dd) $J_{3,4}$=3.3	5.43(dd) $J_{4,5}$=1.4	4.658(m) $J_{5,6a}$=6.5	4.10(dd) $J_{6a,6b}$=6.5	4.10(dd) $J_{5,6b}$=6.5	2.14,2.07, 2.02,1.99 (1.35)
(2b) βD*Gal*	4.63(d) $J_{1,2}$=9.9	5.18(dd) $J_{2,3}$=9.9	5.09(dd) $J_{3,4}$=3.4	5.43(dd) $J_{4,5}$=1.0	3.94(m) $J_{5,6a}$=7.2	4.16(dd) $J_{6a,6b}$=11.4	4.105(dd) $J_{5,6b}$=5.8	2.15,2.05, 2.03,1.99 (1.37)
(3a) αD*Man*	5.45(d) $J_{1,2}$=1.5	5.30(dd) $J_{2,3}$=3.1	5.20(dd) $J_{3,4}$=10	5.31(t) $J_{4,5}$=9.9	4.45(m) $J_{5,6a}$=5.5	4.32(dd) $J_{6a,6b}$=12.3	4.08(dd) $J_{5,6b}$=2.2	2.18,2.08, 2.05,1.99 (1.37)
(3b) βD*Man*	4.84(d) $J_{1,2}$=1.2	5.50(dd) $J_{2,3}$=3.6	5.11(dd) $J_{3,4}$=10	5.22(t) $J_{4,5}$=10	3.72(m) $J_{5,6a}$=6.8	4.23(dd) $J_{6a,6b}$=12.1	4.13(dd) $J_{5,6b}$=2.7	2.18,2.05, 1.98 (1.37)
(3c) αD*Man*	5.73(d) $J_{1,2}$=1.5	5.76(dd) $J_{2,3}$=3.0	5.75(dd) $J_{3,4}$=10	6.15(t) $J_{4,5}$=10	4.86(m) $J_{5,6a}$=4.6	4.65(dd) $J_{6a,6b}$=12.2	4.50(dd) $J_{5,6b}$=2.4	(1.46)
(3d) βD*Man*	5.15(d) $J_{1,2}$=1.2	5.99(dd) $J_{2,3}$=3.4	5.70(dd) $J_{3,4}$=9.9	5.89(t) $J_{4,5}$=9.9	4.22(m) $J_{5,6a}$=6.5	4.67(dd) $J_{6a,6bb}$=12.1	4.53(dd) $J_{5,6b}$=2.7	(1.40)
(4a) αL*Rhm*	5.35(d) $J_{1,2}$=1.4	5.29(dd) $J_{2,3}$=3.1	5.18(dd) $J_{3,4}$=10	5.08(t) $J_{4,5}$=10	4.27(m) $J_{5,6}$=6.3	1.21(d)	1.21(d)	2.17,2.05, 1.99, (1.38)
(4b) βL*Rhm*	4.82(d) $J_{1,2}$=1.2	5.48(dd) $J_{2,3}$=2.9	5.06(dd) $J_{3,4}$=10	5.075(t) $J_{4,5}$=10	3.56(m) $J_{5,6}$=6.1	1.28(d)	1.28(d)	2.18,2.05, 1.98 (1.37)
(1d) 2-deoxy-αD*Glc*	5.64(dd) $J_{1,2a}$=5.7 $J_{1,2e}$=1.1	2.14(m) $J_{2a,3}$=11.5 $J_{2e,3}$=5.5	5.21(m) $J_{3,4}$=9.7	4.96(t) $J_{4,5}$=9.7	4.47(m) $J_{5,6a}$=4.7	4.34(dd) $J_{6a,6b}$=12.3	4.01(dd) $J_{5,6b}$=2.2	2.07,2.04, 2.00 (1.37)
(1e) 2-deoxy-βD*Glc*	4.76(dd) $J_{1,2a}$=11 $J_{1,2e}$=1.9	1.83(m) $J_{2a,3}$=11.5 $J_{2e,3}$=5.3	5.05(m) $J_{3,4}$=9.4	4.94(t) $J_{4,5}$=9.6	3.65(m) $J_{5,6a}$=6.5	4.21(dd) $J_{6a,6b}$=12.1	4.093(dd) $J_{5,6b}$=2.4	2.05,2.04, 2.03 (1.38)

faster at lower concentration of the aldoses and seem to be much slower at higher concentrations. In contrast to the behavior of D-glucose at both concentrations (a and b), different patterns among the three concentrations (c, d, and e) were observed in the case of D-mannose, suggesting that both a higher concentration and a shorter reaction time are much more favorable for 1,2- *cis*-selectivity of D-mannose. We could confirm the fast change of 1,2-*cis*-selectivity (α / β =1:7.9 after 1 hour, and α / β =1:3.5 after 2 hours) for D-mannose at a concentration of 1.67 mmol/mL. Similar results were also obtained in the case of L-rhamnose. However, prolonged reaction time (>15 h) and a lower concentration (<0.83 mmol/mL) reversed the 1,2-*cis*-selectivity rather toward α selectivity (α / β =2:1) of both thioglycosides of D-mannose and L-rhamnose, probably because of the anomerization accelerated by a catalytic action of relatively increased concentration of trifluoroacetic acid. Though the anomeric effect[8] is generally observed in non-polar solvents, Sugiyama et al.[9] reported that the ratio of α-anomer of D-glucose and 2-*O*-methyl-D-glucose in acidic solvents such as 2M hydrochloric acid and formic acid increased more than in neutral water, and they further proposed that an intramolecular hydrogen bond between the anomeric OH group and protonated 2-OH (OCH_3) group might play an important role for stabilization of the α anomer.

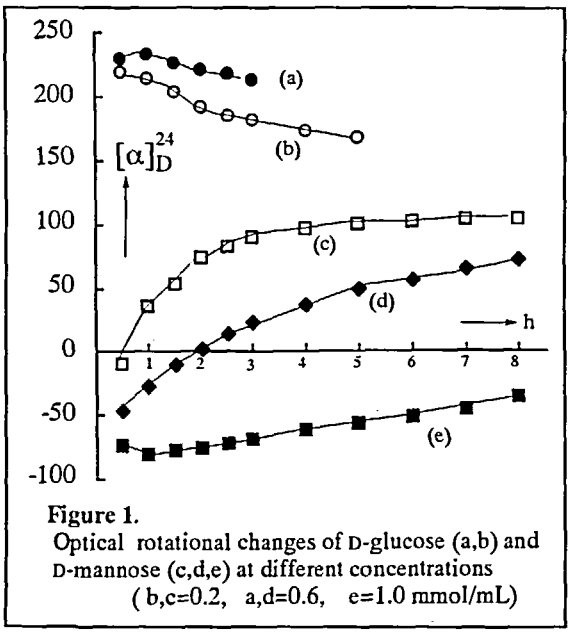
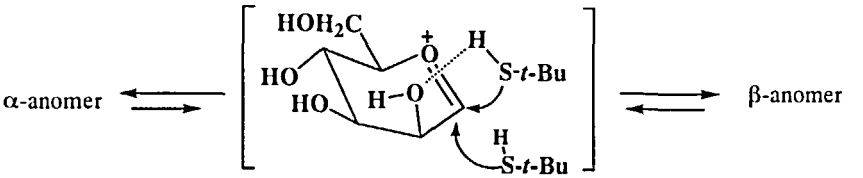


Figure 1.
Optical rotational changes of D-glucose (a,b) and D-mannose (c,d,e) at different concentrations
(b,c=0.2, a,d=0.6, e=1.0 mmol/mL)

In our case, the general tendency toward α selectivity, except for 2-deoxy-D-*arabino*-hexose, after prolonged reaction of free aldohexoses with *tert*-butyl mercaptan in 90% trifluoroacetic acid is understandable from the standpoint of anomeric effects. At the same time, such an intramolecular hydrogen bond between sulfur atom of the aglycon group and protonated 2-OH group may play a part in stabilization of 1,2-*cis*-1-thioglycopyranosides of D-glucose and D-galactose. The lack of selectivity in the case of 2-deoxy-D-*arabino*-hexose seems to support the above explanation. Though the lower 1,2-*cis*-selectivity of D-galctose is not simply explained, the axial 4-OH group must

control inevitably the equilibrium of anomerization. In the case of D-mannose and L-rhamnose, a kinetic control is responsible for the 1,2-*cis*-selectivity observed at an initial reaction stage, in which β-face nucleophilic attack of the thiol function is assumed to take place favorably via an intramolecular hydrogen bond between the axial 2-OH group of the oxocarbenium ion of D-mannose, and the SH group of *tert*-butyl mercaptan, as depicted below in Scheme1.



Scheme 1

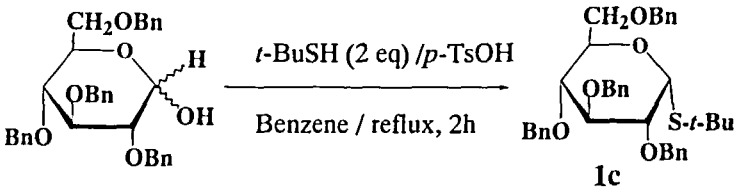
For the purpose of confirming the so-called anomeric effect in non-polar solvents, we further attempted the following reactions: (1) an anomerization between α-and β-anomer of thus obtained *tert*-butyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α/β-D-gluco, -galacto, -mannopyranosides (**1a,b**, **2a,b**, and **3a,b**) in the presence of Lewis acid, and (2) a direct thioglycosidation of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose with *tert*-butyl mercaptan in refluxing benzene in the presence of *p*-toluene sulfonic acid (*p*-TsOH).

The first anomerization experiment was effected in methylene chloride in the presence of excess amount of boron trifluoride-etherate at room temperature for 15 hours, and the results are shown in Table 3. The obvious change occurred not only in the case of D-manno derivatives (entry 3 : **3a** and **3b**), but also considerable anomerization took place in the case of both D-gluco and D-galacto derivatives (**1a,1b** and **2a,2b**).

Table 3. Anomerization of *tert*-Butyl 2,3,4,6-tetra-*O*- acetyl-1-thio -α,β- D-glycopyranosides with BF_3-OEt_2

Entry	Starting materials	anomer ratio (before:α/β)		anomer ratio (after:α/β)
1	D-Gluco (**1a,1b**)	5.3 : 1	→	1.5 : 1
2	D-Galacto (**2a,2b**)	3.7 : 1	→	1.3 : 1
3	D-Manno (**3a,3b**)	1 : 7.9	→	5.5 : 1

Secondly, we attempted reacting 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose directly with *tert*-butyl mercaptan in refluxing benzene in the presence of *p*-TsOH for 2 hours and isolated *tert*-butyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranoside (**1c**) in a yield of 59% in addition to unidentified degradation products. The compound **1c** was also conveniently prepared by the direct benzylation of *tert*-butyl 1-thio-α/β-D-glucopyranoside followed by crystallization after column chromatography (see experimental section).



1c

Both results described above are fully consistent with general anomerization reactions of *O*- or *S*-glycopyranosides in non-polar solvents having low dielectric constants. Quite interesting phenomena of anomerization, however, appeared in the reactions of free aldohexoses with *tert*-butyl mercaptan in polar 90% trifluoroacetic acid, and we found that making good choices for the concentration of free sugars and the reaction time were very critical, especially for 1,2-*cis*-selectivity of D-mannose. Further application of the present results are now in progress by using a much less noxious *tert*-alkyl mercaptan such as 1,1,3,3-tetramethylbutane-1-thiol or 1-mercaptoadamantane in place of *tert*-butyl mercaptan.

EXPERIMENTAL

General methods. ^{1}H NMR spectra were recorded with JEOL spectrometers (JNM-GSX 400 MHz) for solutions in $CDCl_3$ containing tetramethylsilane as the internal reference. Mass spectra were measured with a JEOL JMS-HX110 mass spectrometer. Melting points were determined on a Yazawa micro melting-point apparatus BY-2 and are uncorrected. Optical rotations were determined with a JASCO DIP-140 digital polarimeter. TLC was performed on precoated plates of silica gel 60 (Merck) with the solvent systems: A, 1-butanol-acetic acid-H_2O (8:1:2) for free thioglycosides; B, benzene-ethyl acetate (2:1) for the corresponding thioglycoside peracetates. Compounds were detected with iodine vapor or 5% methanolic sulfuric acid spray followed by

heating on a hot plate. Column chromatography was performed by the flash technique on silica gel (Wako-gel C-300).

General procedure for preparation of *tert*-butyl 1-thio-α/β-glycopyranosides and purification of the corresponding peracetates. A mixture of aldohexose (2.5 mmol) and *tert*-butyl mercaptan (5 mmol) in 90% trifluoroacetic acid (1.5 mL for monosaccharides and 3.0 mL for disaccharides) was stirred at room temperature in a powerful ventilator until a complete dissolution occurred (it took 5-10 minutes for D-mannnose, L-rhamnose, and 2-deoxy-D-glucose, 30-40 min for D-glucose and D-galactose, 30-60 min for maltose and lactose, and 3 h for cellobiose). The resulting pale yellow solution was then kept at room temperature for another 1.5 h for monosaccharides, and 12 h for disaccharides. The colour of the solution finally changed to red-orange after a few h and to deep violet or brown after 12 h. The solution was carefully poured into ice-water containing sodium carbonate (5 g), the neutralized solution was washed first with hexane (15 mL x 2) and the aqueous layer was then extracted with 1-butanol (15 mL x 3). The noxious hexane extracts were treated overnight with excess sodium hypochlorite solution before discard. The 1-butanol extracts were then washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*, with a trap containing sodium hypochlorite solution, to a crude syrupy residue. As complete removal of 1-butanol was rather difficult even *in vacuo*, the resulting dried residue was conventionally treated with pyridine (8 mL) and acetic anhydride (7 mL). After 2 h, methanol was added to the reaction solution, the solution concentrated *in vacuo* to a syrup, and then treated with ethyl acetate and aqueous sodium bicarbonate. The ethyl acetate extracts (15 mL x 3) were then washed with water, dried over magnesium sulfate, concentrted *in vacuo* to a syrupy or amorphous residue which was subjected to silica gel (Wako-gel C-300) column chromatography by successive elution with mixed solvents of toluene-ethyl acetate (10:1 to 2:1) or to preparative TLC (Merck-silica gel 60) using toluene-ethyl acetate (2:1). The corresponding *tert*-butyl 1-thioglycopyranoside peracetates (**1-6**) were obtained in reasonable yields (Table 1). Perbenzoates (**3c** and **3d**) were also conventionally prepared. The yields and physical data of these products are described below as follows.

***tert*-Butyl 2,3,4,6-Tetra-*O*-acetyl-1-thio-α- and -β-D-glucopyranoside (1a and 1b).** Column chromatography of a crude crystalline peracetate (0.92 g) afforded α-anomer (360 mg, 34%), α/β-mixture (330 mg, 31%), and β-anomer (105 mg, 12%) respectively : α-anomer (**1a**); mp 62-64 °C (from hexane) (lit.,[8b] mp 63-65 °C). $[\alpha]_D^{24}$+178° (*c* 0.49, acetone), (lit.,[8b] $[\alpha]_D^{20}$+185° (*c* 0.6, $CHCl_3$), β-anomer (**1b**): mp 142-143 °C (from hexane) (lit.,[8a] mp 144-146 °C), $[\alpha]_D^{24}$-5.4° (*c* 0.27, acetone); [lit.,[8a] $[\alpha]_D^{18}$-6° ($CHCl_3$)].

Anal. Calcd for $C_{18}H_{28}O_9S$: C, 51.42; H, 6.71. Found (**1a**): C, 51.34; H, 6.75. Found (**1b**): C, 51.48; H, 6.79.

***tert*-Butyl 2,3,4,6-Tetra-*O*-acetyl-1-thio-α-and-β-D-galactopyranoside(2a and 2b).** Column chromatography of a crude syrupy peracetate (0.95 g) afforded α-anomer (260 mg, 25%), α/β-mixture (390 mg, 37%), and β-anomer (128 mg, 12%): α-anomer (**2a**); mp 121-123 °C (from ethanol), $[\alpha]_D^{24}$+178° (*c* 0.51, acetone), β-anomer (**2b**); syrup, $[\alpha]_D^{24}$+33° (*c* 0.35, acetone).

Found (**2a**): C, 51. 55; H, 6.54. Found (**2b**): C, 51.49; H, 6.63.

***tert*-Butyl 2,3,4,6-Tetra-*O*-acetyl-1-thio-α-and-β-D-mannopyranoside (3a and 3b).** Column chromatography of a crude syrupy peracetate (0.94 g) afforded α-anomer (144 mg, 14%), α/β-mixture (340 mg, 32%), and β-anomer (280 mg, 27%) : α-anomer (**3a**) ; clear syrup, $[\alpha]_D^{24}$ +89° (*c* 0.51, acetone), β-anomer (**3b**); clear syrup, $[\alpha]_D^{24}$ -27° (*c* 0.47, acetone).

Found (**3a**): C, 51.33; H, 6.87. Found (**3b**): C, 51.29; H, 6.84.

***tert*-Butyl 2,3,4,6-Tetra-*O*-benzoyl-1-thio-α-and-β-D-mannopyranoside (3c and 3d).** A deacetylated and dried product (0.46 g, 1.8 mmol) prepared from the peracetate mixture (**3a** and **3b**) was treated at 0 °C with benzoyl chloride (1.4 g, 10 mmol) in dry pyridine (5 mL) and left at room temperature for 3 h. After usual workups, ethyl acetate extracts were concentrated *in vacuo* to a syrupy residue, which was then subjected to the column chromatography to give a crystalline α-anomer (114 mg, 9.4%) and β-anomer (680 mg, 56%): α-anomer (**3c**); mp 119-120 °C (from hexane), $[\alpha]_D^{24}$+21° (*c* 0.73, acetone), β-anomer (**2b**); powder , $[\alpha]_D^{24}$ -99° (*c* 0.21, acetone).

Anal. Calcd for $C_{38}H_{36}O_9S$: C, 68.25; H, 5.43. Found (**3c**): C, 68.37; H, 5.52, Found (**3d**): C, 68.18; H, 5.68.

***tert*-Butyl 2,3,4-Tri-*O*-acetyl-6-deoxy-1-thio-α-and-β-L-mannopyranoside (4a and 4b).** The column chromatography of the crude acetate (0.88 g) afforded α-anomer (144 mg,16%), α/β-mixture (230 mg, 25%), and β-anomer (270 mg, 30%): α-anomer (**4a**) ; syrup, $[\alpha]_D^{24}$ -53° (*c* 0.50, acetone), β-anomer (**4b**); syrup, $[\alpha]_D^{24}$+ 56° (*c* 0.9, acetone).

Anal. Calcd for $C_{16}H_{26}O_7S$: C, 53.02; H, 7.23. Found (**4a**): C, 52.90; H, 7.37. Found (**4b**): C, 52.82; H, 7.42.

***tert*-Butyl 3,4,6-Tri-*O*-acetyl-2-deoxy-1-thio-α-and-β-D-arabinopyranoside (1d and 1e).** Half of crude acetate (0.86 g) was subjected to preparative TLC (Wako-gel B-0) using toluene/ethyl acetate (2:1) to afford α-anomer (150 mg, 33%) and β-anomer (145 mg, 32%) respectively: α-anomer (**1d**); mp 69-70 °C, $[\alpha]_D^{19}$+172° (*c* 0.51, acetone), β-anomer (**1e**); mp 63-65 °C, $[\alpha]_D^{19}$ -48° (*c* 0.24, acetone).

Found (**1d**): C, 53.21; H, 7.28. Found (**1e**): C, 53.18; H, 7.15.

***tert*-Butyl 1-Thio-α/β-cellobioside heptaacetate (5a).** The crystalline crude acetate (0.65 g) was recrystallized from ethanol to afford an inseparable α/β mixture of the corresponding heptaacetate (**5a**) as needles (0.48 g, 65%): mp 210-212 °C, $[\alpha]_D^{27}$ +85° (*c* 1.0, acetone); FAB-MS *m/z*: 709 $[M+H]^+$, 619 $(M-SC_4H_3)$, 559. ^1H NMR (major α-anomer) δ1.33 (s, 9H, *t*-Bu), 1.98, 2.01, 2.03, 2.05, 2.09, and 2.10 (s, 21 H, Ac), 3.67 (t, 1 H, $J_{4,5}$ =9.5 Hz, H_4), 3.75-3.64 (m, 1 H, $H_{5'}$), 4.05 (dd, 1 H, $J_{5,6b}$ =4.8 Hz, H_{6b}), 4.18 (dd, 1 H, $J_{5',6b'}$ =4.8 Hz, $H_{6b'}$), 4.37 (dd, 1 H, $J_{5,6a}$=4.4 Hz, $J_{6a,6b}$ =12.5 Hz, H_{6a}), 4.39-4.34 (m, 1 H, H_5), 4.41 (dd, 1 H, $J_{5',6a'}$ =2.2 Hz, $J_{6a',6b'}$ =11.8 Hz, $H_{6a'}$), 4.87 (dd, 1 H, H_2), 4.51 (d, 1 H, $H_{1'}$), 4.92 (t, 1 H, $J_{1',2'}$ =7.7 Hz, $H_{2'}$), 5.08 (t, 1 H, $J_{4',5'}$ =9.5 Hz, $H_{4'}$), 5.14 (t, 1 H, $J_{2',3'}$ =9.3 Hz, $J_{3',4'}$ =9.3 Hz, $H_{3'}$), 5.24 (dd, 1 H, $J_{2,3}$ =10.4 Hz, $J_{3,4}$ =9.2 Hz, H_3), 5.75 (d, 1 H, $J_{1,2}$ =6.0 Hz, H_1), δ 4.60 (d, 1 H, $J_{1,2}$ =10.1 Hz, H_1 of minor β-anomer), and other protons of the minor isomer are not characterized.

Anal. Calcd for $C_{30}H_{44}O_{17}S$: C, 50.84; H, 6.25. Found: C, 50.75; H, 6.43.

***tert*-Butyl 1-Thio-α/β-lactoside heptaacetate (5b).** From fractions of toluene/ethyl acetate (5:1) of the crude acetate (0.78 g) was obtained an inseparable α/β mixture of the corresponding heptaacetate (**5b**) as a syrup (0.60 g, 68%): $[\alpha]_D^{27}$ +89° (*c* 1.10, acetone) ; FAB-MS *m/z*: 731$[M+Na]^+$, 709$[M+H]^+$, 619 $(M-SC_4H_3)$, 559. ^1H NMR δ1.35 (s, 9 H, *t*-Bu), 1.97, 2.05, 2.07, 2.10, and 2.16 (s, 21 H, Ac), 3.70 (t, 1 H, $J_{4,5}$ =9.7 Hz, H_4), 3.94 (t, 1 H, $J_{5',6a}$= 6.9 Hz, $J_{5',6b}$=6.9 Hz, $H_{5'}$), 4.20-4.06 (m, 4 H, H_6, H_{6b}, $H_{6a'}$ and $H_{6b'}$), 4.37 (m, 1 H, H_5), 4.47 (d, 1 H, $H_{1'}$), 4.87 (dd, 1 H, H_2), 4.95 (dd, 1 H, $H_{3'}$), 5.12 (dd, 1 H, $J_{1',2'}$ =8.0 Hz, $J_{2',3'}$ =10.5 Hz, $H_{2'}$), 5.26 (dd, 1 H, $J_{2,3}$ =10.4 Hz, $J_{3,4}$ =8.9 Hz, H_3), 5.35 (dd, 1 H, $J_{3',4'}$ =3.4 Hz, $H_{4'}$), 5.75 (d, 1 H, $J_{1,2}$ =5.8 Hz, H_1), δ 4.61 (d, 1 H, $J_{1,2}$ =10.1 Hz, H_1 of minor β-anomer), and the other protons of minor isomer are not characterized.

Anal. Calcd for $C_{30}H_{44}O_{17}S$: C, 50.84; H, 6.25. Found: C, 50.75; H, 6.43.

Ethyl 1-Thio-α-cellobioside heptaacetate (5c) and Phenyl 1-Thio-α-cellobioside heptaacetate (5d). Stirring a mixture of cellobiose (1 mmol) and RSH (2 mmol , R=Et or Ph) in 90% trifluoroacetic acid (3 mL) was continued at room temperature until a clear solution appeared. The resulting dark purple solution was kept at room tempeature for 5-7 days, monitoring the reaction products with TLC (1-butanol/ acetic acid /water=4:1:1). Less polar dithioacetals were gradually transformed into more polar thioglycosides. The solution was concentrated *in vacuo* , with a trap containing sodium hypochlorite solution in a ventilator to a syrup, which was then treated with acetic anhydride (3 mL) and pyridine (3 mL). After conventional work-ups, the desired acetates were separated from the less polar dithioacetals with flash chromatography (Wako-gel C-300). From fractions of toluene/ethyl acetate= 2:1 for **5c** and 5:1 for **5d** were isolated the compounds (**5c**: 43%) and (**5d**: 35%) respectively. Those physical data are as follows;

The product (**5 c**); mp 199-200 °C (from ethanol), $[\alpha]_D^{27}$+76.7° (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz) δ 1.279 (t, 3H, $CH_2\underline{CH_3}$), 2.011, 2.012, 2.020, 2.027, 2.048, 2.056, 2.090, 2.078 (21H, $CO\underline{CH_3}$), 2.54 (2H,m,$\underline{CH_2}CH_3$), 3.66 (o,1H, $H_{5'}$, $J_{4',5'}$ =9.7 Hz, $J_{5',6'a}$=4.2 Hz, $J_{5',6'b}$=2.4 Hz), 3.73 (dd, 1H, H_4, $J_{3,4}$= $J_{4,5}$=9.3 Hz), 4.05 (dd, 1H, $H_{6'b}$), 4.17 (dd, 1H, H_{6b} , $J_{5,6b}$=4.95 Hz, $J_{6a,6b}$=12.1 Hz,), 4.34 (m,1H, H_5 , $J_{5,6a}$= 2.0 Hz, $J_{5,6b}$ = 2.0 Hz,) , 4.36 (dd,1H, $H_{6'a}$, $J_{6'a,\ 6'b}$=12.4 Hz), 4.47 (dd, 1H, H_{6a}), 4.95 (t, 1H, H_2), 5.07 (t, 1H, $H_{4'}$, $J_{3',4'}$=$J_{4',5'}$=9.7 Hz), 5.15 (t, 1H, $H_{3'}$, $J_{2',3'}$=9.2 Hz), 5.34 (t, 1H, H_3, $J_{2,3}$=9.6 Hz), 5.59 (d, 1H, H_1 , $J_{1,2}$=5.7 Hz).

Anal. Calcd for $C_{30}H_{40}O_{17}S$: C, 51.13; H. 5.72. Found: C,51.18 ; H,5.83

The product (**5 d**); mp 225-226 °C (from 2-propanol), $[\alpha]_D^{27}$+120° (*c* 1.0, $CHCl_3$). ^1H NMR δ 1.987, 2.013, 2.047, 2.085, 2.094 (21H, $CO\underline{CH_3}$), 3.68 (o,1H, $H_{5'}$, $J_{4',5'}$= 9.1 Hz, H_{6b}, $J_{6'a,6b}$=12.4 Hz), 3.74 (t, 1H, H_4, $J_{3,4}$=9.6Hz, $J_{4,5}$=9.2Hz), 4.06 (dd,1H, H_{6b}, $J_{5',6b}$ =2.2 Hz), 4.17 (dd, 1H, H_{6b}, $J_{6a,6b}$=12.0 Hz, $J_{5,6b}$=5.4 Hz), 4.37 (dd, 1H, $H_{6'a}$, $J_{5',6'a}$ =4.4 Hz), 4.39 (dd, 1H, H_{6a}, $J_{5,6a}$ =1.93 Hz), 4.46 (m, 1H, H_5), 4.53 (d,1H, $H_{1'}$, $J_{1',2}$=8.0 Hz), 4.95 (t, 1H, $H_{2'}$, $J_{2',3}$= 9.2 Hz), 5.04 (dd, 1H, H_2, $J_{1,2}$ =5.78, $J_{2,3}$ =10.2 Hz), 5.15 (t, 1H, $H_{3'}$), 5.40 (t, 1H, H_3), 5.83 (d, 1H, $J_{1,2}$=5.78 Hz), 7.26-7.44 (m, 5H, Ph).

Anal. Calcd for $C_{34}H_{40}O_{17}S$: C, 52.67; H. 5.66. Found: C,52.63 ; H,5.82.

***tert*-Butyl 1-Thio-α/β-maltoside heptaacetate (6).** From fractions of toluene-ethyl acetate (5:1) of the crude acetate (0.72 g) was obtained an inseparable α/β mixture of the corresponding heptaacetate (**6a**) as an amorphous powder (0.55 g, 62%); $[\alpha]_D^{27}$+166° (*c* 0.68, acetone); FAB-MS *m/z*: 731 $[M+Na]^+$, 709 $[M+H]^+$, 619, 559. ^1H NMR (500MHz) δ1.36 (s, 9 H, *t*-Bu), 2.00, 2.02, 2.03, 2.04, 2.07, 2.10, and 2.13, (s, 21 H, Ac), 3.91 (t, 1 H, $J_{4,5}$ 9.7 Hz, H_4), 4.05 (dd, 1H, H_{6b}), 4.25 (dd, 1H, H_{6b}), 4.27 (dd, 1H, $J_{6a,6b}$=11.8 Hz, H_{6a}), 4.38 (dd, 1H, H_{6a}), 4.44 (o, 1 H, $J_{5,6a}$=2.3 Hz, $J_{5,6b}$ =2.5 Hz, H_5), 4.83 (dd, 1 H, H_2), 4.87 (dd, 1 H, $H_{2'}$), 5.07 (t, 1 H, $J_{4',5'}$=9.9 Hz, $H_{4'}$), 5.30 (dd, 1 H, $J_{2,3}$ =10.0 Hz, $J_{3,4}$= 8.3 Hz, H_3), 5.39 (t, 1 H, $J_{2',3'}$=10.0 Hz, $J_{3',4'}$ =10.0 Hz, $H_{3'}$), 5.74 (d, 1 H, $J_{1,2}$= 5.8 Hz, H_1), 5.39 (d, 1 H, $J_{1',2}$= 4.1 Hz, $H_{1'}$), δ 4.68 (d, 1 H, $J_{1,2}$= 10.1 Hz, H_1 of minor β-anomer), and the other protons of minor isomer are not characterized.

Anal. Calcd for $C_{30}H_{44}O_{17}S$: C, 50.84 ; H, 6.25. Found: C, 50.75; H, 6.43.

Anomerization of *tert*-butyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α/β-glycopyranosides (1-3) in the presence of boron trifluoride-etherate. Solutions of *tert*-butyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α/β-D-gluco-, D-galacto-, and -D-manno pyranoside (100 mg, 0.24 mmol) in methylene chloride (1mL) respectively were kept at room temperature in the presence of boron trifluoride-etherate (1 mL, 7.93 mmol) for 15 h, and then diluted with ethyl acetate (50 mL). Each combined solution

was washed with aqueous sodium bicarbonate, water, dried over magnesium sulfate, and concentrated *in vacuo* to dryness. These specimens were analyzed respectively using ^{1}H NMR.

Preparation of *tert*-butyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranoside (1c): (method A); reaction of 2,3,4,6-tetra-*O*-benzylglucopyranose with *tert*-butyl mercaptan in the presence of *p*-toluenesulfonic acid. To a solution of 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranose (540 mg, 1 mmol) and *tert*-butyl mercaptan (180 mg, 2 mmol) in benzene (10 mL) was added *p*-toluenesulfonic acid monohydrate (30 mg, 0.2 mmol). The solution was then heated to reflux for 2 h, washed with aqueous sodium bicarbonate, water, dried over magnesium sulfate, and concentrated *in vacuo* to dryness. The product was finally purified with column chromatography to afford a crystalline mass, which was recrystallized from ethanol to give long needles: mp 97-98 °C, $[\alpha]_D^{24}$+120° (*c* 1.06, acetone).

Anal. Calcd for $C_{30}H_{44}O_5S$: C, 51.42 ; H, 6.71. Found: C, 51.35; H, 6.83.

(method B); via perbenzylation of *tert*-butyl 1-thio-α/β-D-glucopyranoside (1a). *tert*-Butyl 1-thio-α/β-D-glucopyranoside (0.48 g, 2mmol) was conventionally benzylated with benzyl bromide (1.4 mL, 12 mmol) and sodium hydride (0.58 g, 12 mmol) in dry dimethylformamide (10 mL). After the usual work-ups, chloroform extracts were concentrated *in vacuo* to give a syrupy residue, which was purified using silica-gel column chromatography. From toluene/ethyl acetate (10/1-5/1) fractions were isolated a crystalline mass, which was recrystallized from ethanol to give pure *tert*-butyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-glucopyranoside (**1c**) in 65 % yield: mp 95-97°C, $[\alpha]_D^{24}$+114° (*c* 0.51, acetone).

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