β-Selective Glycosylation of 5-Thioglucopyranose Derivatives; Syntheses of β-(1 → 6) Linked 5′-Thioglucopyranosyl Disaccharides

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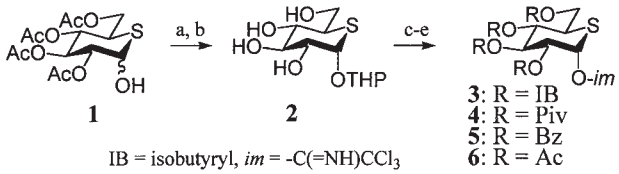
β-Stereoselctive and effective glycosylation with 5-thioglucopyranose was achieved by performing the reaction with pivaloyl- or benzoyl-protected glucopyranosyl trichloroacetimidates and BF_3OEt_2, a glycosyl activator, when C6-OH glucopyranosyl or galactopyranosyl derivatives were employed as acceptors.

In the last decade, carbohydrate analogues, carrying sulfur atoms in place of oxygens in their pyranose rings, have been developed as potent glycosidase inhibitors[1–3] and as probes to investigate enzymatic cleavage of glycosidic linkages in detail.[4] However, glycosylation reactions so far reported were α-stereoselective in most cases.[1,5,6] Only a β-selective glycosylation has been reported by utilizing galactosyl-transferase with UDP-5-thiogalactose.[7] We now for the first time disclose β-selective (up to 50 : 1 selectivity) chemical glycosylations with 6-OH pyranoses.

In the literature, 5-thioglucopyranosyl,[1,3,8] 5-thioarabinopyranosyl,[2] and 5-thiofucopyranosyl trichloroacetimidates[9] have been reported to serve as successful glycosyl donors, providing α-glycosides stereoselectively. Interestingly, all of those donors carried acetyl protective groups at the C2-equatorial hydroxyl position. According to the neighboring effects described in classic carbohydrate chemistry, this should result in β-selective glycosylation.[10] We supposed that β-selective glycosylation could be realized by choosing appropriate protective groups.

First, glycosyl trichloroacetimidates with a series of acyl protective groups **3** (R = isobutyryl, abbreviated as IB), **4** (R = Piv) and **5** (R = Bz) were synthesized from known 2,3,4,6-tetra-*O*-acetyl-5-thioglucopyranose (**1**).[1] After the anomeric hydroxyl group was protected in a form of THP, all acetyl groups were removed under basic methanolysis to yield tetraol **2** in 90% over two steps. Re-acylations with acid chlorides, such as isobutyryl, pivaloyl, or benzoyl chloride, were performed by slightly heating at 45 °C in pyridine with the addition of a catalytic amount of DMAP. After the THP ether in the products was cleaved in acidic methanol at 50 °C, the C1-hydroxyl functionality was converted into trichloroacetimidate to give donors **3–5** in good yields.[11] Comparison of the coupling constants of the anomeric protons in **3–5** (3.4 Hz in all cases) with that of known compound **6** (3.2Hz), prepared from **1**, suggested that the trichloroacetimidate groups were α-orientations.

In a previous report, reactions of acetate **6** with C6-OH acceptor **7** by TESOTf afforded α-glycosides predominantly (**Run 1**, in Table 1).[8] Our own experiment employing **6** with acceptor **8**, gave only α-isomer **13**α under similar conditions (**Run 2**). Reactions with TMSOTf or TfOH were not successful (**Run 3, 4**). In the case of TfOH, anomerization at the C1 position of the acceptor occurred during the reaction to give an inseparable mixture. However by employing BF_3OEt_2, in place of TESOTf, the reaction afforded β-glycoside **13**β predominantly (α : β = 1 : 1.5), albeit in low yield



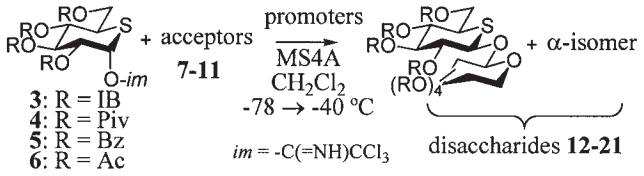
Scheme 1. a) DHP, *p*-TsOH, CH_2Cl_2, (90%), b) NaOMe, MeOH (100%), c) acyl chlorides, DMAP, pyridine, 45 °C (IB-Cl; 74%, PivCl; 82%, BzCl; 98%), d) *p*-TsOH, MeOH, 50 °C (R = IB; 89%, R = Piv; 73%, R = Bz; 85%) e) CCl_3CN, DBU, 0 °C (**3**; 77%, **4**; 82%, **5**; 72%).

(12%) (**Run 5**). Then, BF_3OEt_2 promoted reactions of the imidates with various ester groups (**3–5**) were investigated. When the reaction was performed with isobutyrate **3**, the disaccharide was only β-isomer **14**β, but the yield was not practical (12%) (**Run 6**). Reaction of pivaloate **4** with acceptors gluco-**8**, **9**, and galacto-**11** gave **15**β **16**β and **19**β, respectively in good yields (68, 81 and 67%, respectively). In particular, no **16**α was detected by TLC. Unfortunately, pivaloate esters of **16**β could not be removed cleanly as described below. It was found that benzoate **5** also had promise as an inducer of β-selectivity. Treatment of **8**, **9** and **11** with BF_3OEt_2 afforded **17**β, **18**β and **20**β in good yields and with moderate stereoselectivity (α : β = 1 : 5, 1 : 6 and 1 : 10, respectively) (**Run 10–12**).[12] The stereochemistry of those disaccharides was determined based on their ^{1}H-NMR spectra. Coupling constants of the signals due to the C1'H of **17**α (5.13 ppm), **18**α (5.10 ppm), and **20**α (5.04 ppm) were 3.0, 3.4, and 2.4 Hz, respectively, and showed that glycoside bonds newly formed have α-stereochemistry. On the other hand, β-stereochemistry at the C1'H in **17**β, **18**β, and **20**β was also established by their large coupling constants (**17**β : 7.8 Hz, **18**β : 8.8 Hz, and **20**β : 8.3 Hz). **Run 13–15** proved that TMSOTf, TfOH, or $ZnCl_2$ were less effective as glycosyl promoters (**Run 13–15**) than BF_3OEt_2. Notably, reaction with TfOH gave **17**α stereoselectively. Unfortunately, this method seemed applicable only to primary alcohols (**Run 16, 17**). A trace amount of **21**α was obtained, when donor **5** was treated with **10** and BF_3OEt_2 was employed.

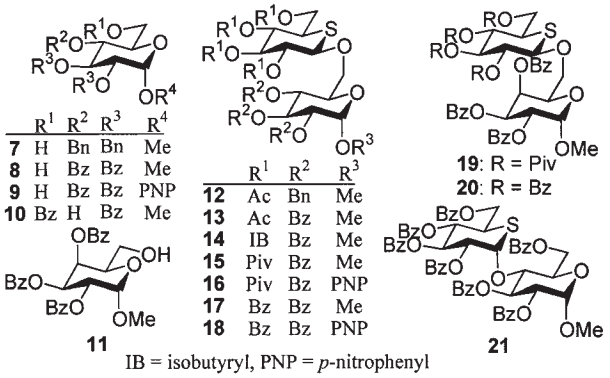
Finally, protective groups of disaccharides **15**, **16**, **18**, and **19** were cleaved (**Scheme** 2). Treatment of **15**β with sodium methoxide in methanol proceeded smoothly to provide methyl 5′-thio-α-gentiobioside (**22**) in quantitative yield.[13] In contrast, TLC of the reaction mixture indicated it was a complex mixture. None of **23** was observed, when similar conditions were applied to *p*-nitrophenyl glycoside **16**β, protected as the pivaloate ester. However, cleavage of benzoyl derivative **18**β gave *p*-nitrophenyl 5′-thio-α-gentiobioside **23** in 80% yield.[13] Similarly, methyl 6-*O*-(5′-thio-β-glucopyranosyl)-α-galactopyranoside (**24**)[13] was afforded from **20**β under almost the same conditions as above.

Enzymatic reaction employing β-glycosidase revealed that **18**β was not hydrolyzed at all under the conditions we employed (β-glycosidase from almond, purchased from Sigma; 2.3 mg/mL, **18**β;

Table 1. Glycosylation with donors **3–6** of acceptors **7–11**

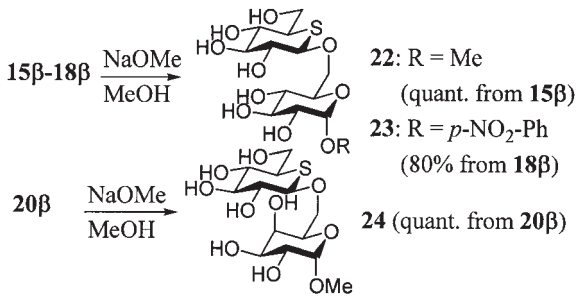


Run	Donors	Promoters	Acceptors	Disaccharides (Yield %)
1	**6**	TESOTf	**7**	**12α** (48%) **12β** (32%)
2	**6**	TESOTf	**8**	**13α** (5%)
3	**6**	TMSOTf	**8**	**13α** (14%)
4	**6**	TfOH	**8**	complex mixture*1
5	**6**	BF_3OEt_2	**8**	**13α** (8%) **13β** (12%)*2
6	**3**	BF_3OEt_2	**8**	**14β** (12%)
7	**4**	BF_3OEt_2	**8**	**15α** (1%) **15β** (68%)
8	**4**	BF_3OEt_2	**9**	**16β** (81%)*3
9	**4**	BF_3OEt_2	**11**	**19α** (4%) : **19β** (67%)
10	**5**	BF_3OEt_2	**8**	**17α** (13%) :**17β** (64%)
11	**5**	BF_3OEt_2	**9**	**18α** (12%) : **18β** (70%)
12	**5**	BF_3OEt_2	**11**	**20α** (7%) : **20β** (70%)
13	**5**	TMSOTf	**8**	**17α** (11%)*3
14	**5**	TfOH	**8**	**17α** (26%) : **17β** (7%)
15	**5**	$ZnCl_2$	**8**	No adduct
16	**4**	BF_3OEt_2	**10**	No adduct
17	**5**	BF_3OEt_2	**10**	**21α** (trace)



IB = isobutyryl, PNP = *p*-nitrophenyl

*1) See text. *2) Adducts were inseparable mixture, so that the yields were estimated by ^{1}H-NMR. *3) No isomer was detected by ^{1}H-NMR nor TLC.



Scheme 2.

4.1 μmol/mL, pH 5.0, 30 °C). However, under these conditions, 70% of the α-p-nitrophenyl gentibioside was consumed in 100 min to give α-p-nitrophenyl glucoside. Studies of the stability of α-5′-thioglucopyranosides have showed that α-5′-thioanalogues were much more stable than corresponding regular α-glucosides.[14] On the other hand, Whistler *et al.*, reported that methyl α- and β-5-thiopyranosides are hydrolyzed at least 10 times faster than the corresponding normal pyranosides.[15] Also, Bennet *et al.*, recently determined those stabilities in detail employing methyl 5-thiopyranosides or 5-thiopyranosyl fluorides.[16] Thus, exploring those differences between 5′-thioglycoside and 5′-oxoglycoside seems to be interesting. Development of β-selective glycosylation with secondary alcohols is under investigation in our group.

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12 Typical experiment is as follows (Table 1 Run 8). Boron trifluoride diethyl etherate (1.5 μl, 11.8 μmol) was added into a suspension of donor **4** (16.5 mg, 24.4 μmol), acceptor **9** (15.0 mg, 24.5 μmol), and molecular sieves 4A (50 mg) in CH_2Cl_2 (1.0 ml) at −78 °C into the mixture, which was allowed to warm to −40 °C over 1 hr. After triethylamine (10 μL) was added, the mixture was filtrated and concentrated. Silica gel column chromatography (hexane : AcOEt = 95 : 5) gave **16β** (22.2 mg, 19.6 mmol, 81%). ^{1}H-NMR ($CDCl_3$) δ 1.09, 1.11, 1.12, and 1.16 (each 9H, s), 3.08 (1H, ddd, 3.4, 5.4, 10.3 Hz), 3.70 (1H, dd, 7.3, 10.7 Hz), 3.89 (1H, dd, 2.4, 10.7 Hz), 4.04 (2H, m), 4.30 (1h, ddd, 2.4, 7.3, 10.3 Hz), 4.56 (1H, d, 8.8 Hz), 5.10 (1H, t, 8.8 Hz), 5.25 (1H, t, 8.8 Hz), 5.29 (1H, t, 8.8, 10.3 Hz) 5.39 (1H, dd, 3.4, 10.3 Hz), 5.50 (1H, t, 10.3 Hz), 5.92 (1H, d, 3.4 Hz), 6.30 (1H, t, 10.3 Hz), 7.22–7.57 (11H), 7.85 (2H, dd, 1.5, 8.3 Hz), 7.90–7.96 (4H), 8.27 (2H, brd 9.3 Hz).
13 ^{1}H-NMR for **22–24** are as follows; **22**: (D_2O) δ 2.81 (1H, ddd, 3.2, 6.0, 9.6 Hz), 3.18 (1H, t, 9.6 Hz), 3.29 (3H, s), 3.35 (1H, t, 9.6 Hz), 3.42 (1H, dd, 3.7, 9.6Hz), 3.45 (1H, dd, 9.6, 10.3Hz), 3.52 (2H, t, 9.6 Hz), 3.65 (1H, ddd, 2.0, 4.9, 9.6 Hz), 3.71 (1H, dd, 6.0, 12.0 Hz), 3.76 (1H, dd, 4.9, 11.3 Hz), 3.80 (1H, dd, 3.2, 12.0 Hz), 3.95 (1H, dd, 2.0, 11.3 Hz), 4.50 (1H, d, 9.3 Hz), 4.65 (1H, d, 3.7 Hz); **23**: (D_2O) 2.69 (1H, ddd, 3.9, 6.3, 9.3 Hz), 3.08 (1H, t, 9.3 Hz), 3.34 (1H, t, 9.3 Hz), 3.40 (1H, t, 9.8 Hz), 3.42 (1H, t, 9.3 Hz), 3.60 (1H, dd, 6.3, 12.0 Hz), 3.65 (1H, dd, 3.4, 9.8 Hz), 3.66 (1H, dd, 3.9, 12.0 Hz), 3.74 (2H, m), 3.81 (1H, t, 9.8 Hz), 3.83 (1H, d, 12.0 Hz), 4.38 (1H, d, 9.3 Hz), 5.69 (1H, d, 3.4 Hz), 7.14 (2H, d, 9.3 Hz), 8.12 (2H, d, 9.3 Hz); **24**: (CD_3OD) 2.78 (1H, ddd, 3.9, 6.3, 10.3 Hz), 3.18 (1H, t, 8.8 Hz), 3.41 (3H, s), 3.48 (1H, dd, 8.8, 10.3 Hz), 3.54 (1H, t, 8.8 Hz), 3.70(1H, dd, 3.4, 10.3 Hz), 3.72–3.83 (3H, m), 3.87 (1H, d, 2.9 Hz), 3.88–3.99 (3H, m), 4.50 (1H, d, 8.8 Hz), 4.69 (1H, d, 3.9 Hz).
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