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Solvent-Dependent, Kinetically Controlled Stereoselective Synthesis of 3- and 4-Thioglycosides

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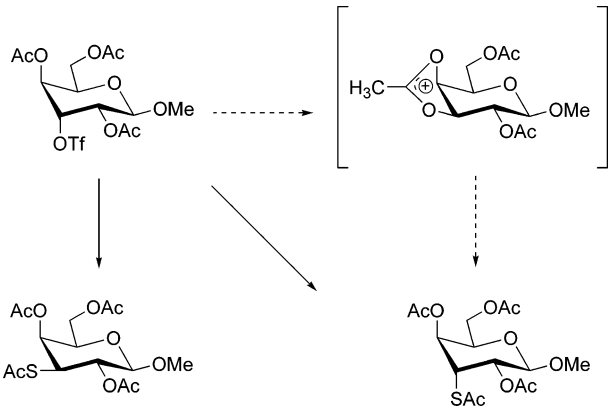

Facile approaches to prepare 3- and 4-thioglycosides of the galacto, gulo, and gluco type from the parent triflates are presented. The dependencies of the solvent and the protecting group pattern, as well as the configuration of the neighboring and leaving groups, have been studied for these reactions. The results clearly show that the efficient stereoselective synthesis of methyl 3-thio-galactoside depends highly on the solvent and the nucleophile concentration.

Thiosaccharides, where an exocyclic oxygen is replaced by a sulfur functionality, constitute an increasingly important group of compounds in glycochemistry, possessing unique characteristics compared to their oxygen-containing counterparts.[1] These compounds are often used as efficient glycoside donors and acceptors in oligosaccharide and neoglycoconjugate synthesis,[2−9] because the thiolate is a potent nucleophile and a weak base that reacts easily and selectively with soft electrophiles.[10] Furthermore, the resulting thioglycosides and S-linked conjugates possess increased resistance to degradation by glycosidases potentiating their use as efficient building blocks in drug design and therapeutics.[1] Special attention has been put on the synthesis of 1-thiosaccharides and their use in the synthesis of 1-thioglycosides, and to broaden the scope for thiosaccharides in organic synthesis, further studies involving nonanomeric analogues need to be pursued.[2,5,11,12]

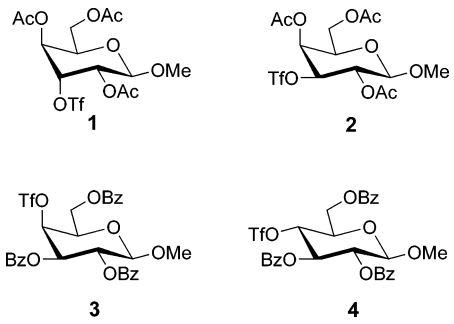

FIGURE 1. Structures of glycoside triflates studied.

The present study describes convenient routes to 3- and 4-thioglycosides of the galacto, gulo, and gluco type, using mainly ester protecting groups, from the reactions between the corresponding triflates and thioacetate. To distinguish the neighboring group participation from the ester moieties adjacent to the target position, four different carbohydrate reactants were chosen (Figure 1). These exert representative combinations of axial−equatorial relations between the participating ester and triflate groups. Thus, methyl β-D-guloside- (**1**), methyl β-D-galactoside- (**2**, **3**), and methyl β-D-glucoside- (**4**) derivatives were employed as reactants.[13]

Furthermore, the solvent dependence was studied where either tetrabutylammonium thioacetate (TBASAc) in toluene or CH_2Cl_2 or potassium thioacetate (KSAc) in DMF was used.

Scheme 1 represents the synthetic route from starting triflate **1** to generate 3-SAc-glycosides **5**[2] and **7**. The reaction was found to be highly dependent on both the solvent and the concentration of the thioacetate reagent. When TBASAc in toluene was employed to displace the OTf group, a straightforward S_N2 reaction was anticipated in yielding the 3-SAc-glycoside **5** of the galactose type. However, it was found that the corresponding thioacetate of the gulose type (**7**) was formed in strong competition with **5**. Up to 40% **7** could be afforded in the **5/7** mixture, strongly dependent on the nucleophile concentration. Table 1 summarizes this concentration dependence. The yield of **5** could be dramatically increased when the concentration of TBASAc was increased to close to the saturation limit (40 equiv), resulting in almost quantitative formation of **5**.

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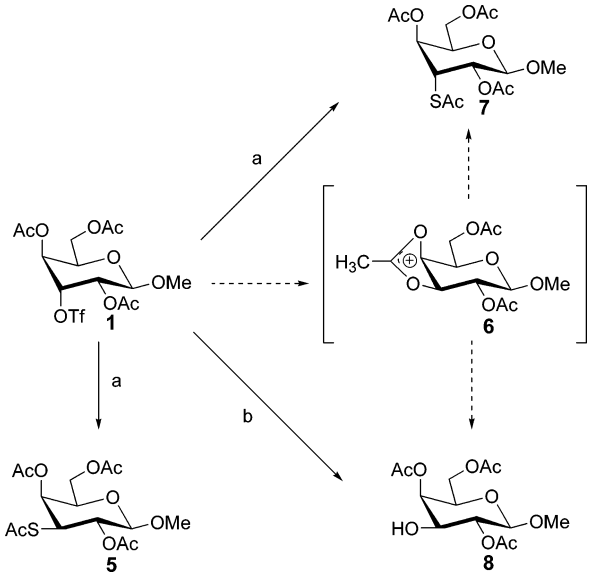
SCHEME 1[a]



[a] Reagents and conditions: (a) TBASAc, toluene, N_2, rt, 4 h; (b) DMF/KSAc or CH_2Cl_2/TBASAc, rt.

TABLE 1. Stereoselectivity in the Reaction of 1 and Different TBASAc Concentrations

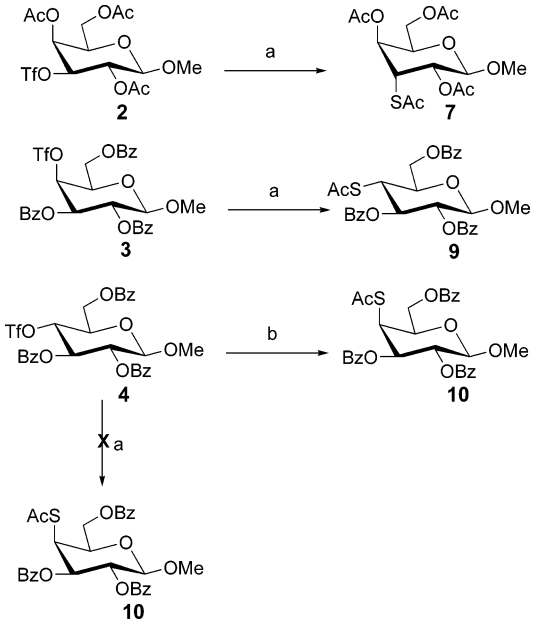
		relative yield (%)	
entry	TBASAc (equiv)	**5**	**7**
1	5	60	40
2	10	75	25
3	20	88	12
4	40	96	4

The main reason for this behavior is most likely ascribed to the competing formation of an acetoxonium intermediate (**6**) in the reaction pathway. When an ester functionality in the axial 4-position is present, establishing an anti-diaxial relationship between the ester and the triflate, **6** may form slowly with time to compete with the attacking thioacetate in nonpolar solvent. Preferred nucleophilic attack on the acetoxonium ion from the axial 3-position will then open the 5-ring and produce the gulose derivative. Attack at the equatorial 4-position proved less favored, and no 4-SAc-glucose analogues were identified in the reaction.

The increasing yield of galactose-derivative **5** with increasing nucleophile concentration supports the notion of competing inter- and intramolecular reaction pathways. In a nonpolar solvent (toluene), the formation of **6** is very slow, therefore favoring an intermolecular S_N2 reaction that is dependent on the nucleophile concentration. Therefore, the formation of **5** is under kinetic control in toluene. When the reaction was carried out at 50 °C with 40 equiv of TBASAc, a 66:34 ratio of **5** and **7** was obtained after workup, suggesting a thermodynamically controlled formation of **7** at these conditions.

For comparison, a polar solvent was also tested and **1** was reacted with KSAc (5 equiv) in DMF. In this case, mainly the hydrolysis product **8** was produced after workup and neither product **5** nor **7** was formed. The same behavior was found when TBASAc (40 equiv) was used in CH_2Cl_2. However, compound **8** was also quickly formed from **1** in the absence of thioacetate in CH_2Cl_2 or DMF at room temperature.

SCHEME 2[a]



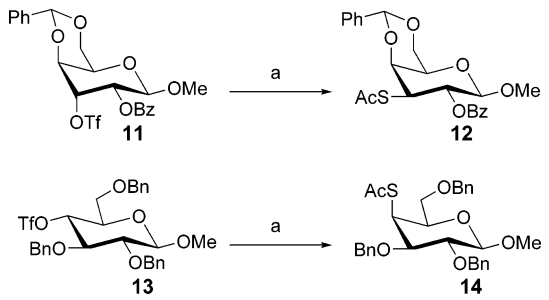
[a] Reagents and conditions: (a) KSAc, DMF, N_2, rt, 8 h; (b) TBASAc (<20 equiv), toluene, N_2, rt, 4 h.

This phenomenon of solvent-dependent kinetic control prompted the study of other possible configurational isomers, and compounds **2**−**4** were subjected to the same reactions as compound **1** (Scheme 2). When the 3-OTf-galactose derivative **2** was employed, no competing reactions and no concentration dependence were found and all reactions with SAc nucleophiles proceeded smoothly in DMF and toluene. Gulo-derivative **7** was thus formed in good yield without any complications. Likewise, reactions with 4-OTf-galactose derivative **3** in either solvent resulted in the glucose derivative **9** without any complicating side reactions. Both of these compounds present a 3,4-cis configuration, for which the acetoxonium intermediate is unlikely to form. Since no other species were identified in the products, formation of the 2,3-acetoxonium from **2** or the potential 4,6-acetoxonium ion from **3** can be largely ruled out.

On the other hand, compound **4** displayed behavior similar to that of **1**. In DMF the reaction led to a reaction mixture, whereas in toluene compound **10** was formed in good yield. In this case, however, no apparent concentration dependence was seen. Since the anti-diequatorial configurational relation between the triflate and the ester functionalities is less likely to produce an intermediate acetoxonium ring (cf. **2**), the main reason for this solvent dependence is likely the six-membered acetoxonium ring arising from 6-OBz group. The formation of this species is, however, kinetically less favored than the corresponding five-membered ring, and hence no concentration dependence could be seen.

This set of configurational isomers leads to the following conclusions concerning neighboring group participation in these reactions: (i) an anti-diaxial relationship between the ester and the triflate (**1**) likely leads to the formation of a reasonably stabilized acetoxonium intermediate in nonpolar solvent, (ii) axial-equatorial (**2**) or equatorial-axial (**3**) relationships are unlikely to generate

SCHEME 3[a]



[a] Reagents and conditions: (a) KSAc, DMF, N_2, rt.

any acetoxonium intermediates, (iii) an anti-diequatorial relationship (**2**, **4**) is likely inefficient in forming this intermediate, (iv) the 4,6-anti-diequatorial relationship in compound **4** may potentially form a moderately stable intermediate in DMF, whereas (v) a 4,6-axial-equatorial relation (**3**) is largely inefficient. As a comparison, an alternative route to 3-SAc-galactosides, using the 4,6-*O*-benzylidene **11** instead of ester protecting groups,[5,12] was followed (Scheme 3). In this case, compound **12** was formed devoid of any complications in good yield in DMF using KSAc as nucleophile. This supports the finding that an axial ester functionality in the 4-position is the major reason for competing reaction to occur and also supports the lack of participation from the ester in the equatorial 2-position. In addition, compound **14** could be efficiently obtained from compound **13** in DMF, supporting the participation from the 6-OBz ester functionality in compound **4**. In the latter case, however, benzyl protecting groups are less favorable in these syntheses, owing to complications in deprotection by hydrogenation.

In conclusion, 3- and 4-SAc glycosides of the galacto, gluco, and gulo series have been efficiently prepared using simple nucleophilic substitution of the parent triflates with thioacetate. The potential influence from adjacent ester protecting groups has been mapped, and the desired products could be formed in good yields in all cases. Strong solvent dependence was especially found for 3,4-anti-diaxial relationship between the ester and the leaving group, but the galacto species could nevertheless be formed under kinetic control.

Experimental Section

General Synthesis of Triflate Derivatives. To a solution of the suitably *O*-protected methyl β-D-glycoside,[13] carrying an unprotected OH at C-3 or C-4 (0.3 g, 0.94 mmol), in CH_2Cl_2 (5 mL) was added pyridine (0.65 mL) at −20 °C. Trifluoromethanesulfonic anhydride (0.53 g, 1.88 mol) in CH_2Cl_2 (2 mL) was added dropwise, and the mixture was stirred and allowed to warm from −20 to 10 °C over 2 h. The resulting mixture was subsequently diluted with CH_2Cl_2 and washed with 1 M HCl, aqueous $NaHCO_3$, water, and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo at low temperature. The residue was used directly in the next step without further purification.

General Synthesis of Thiolacetate Derivatives. TBASAc or KSAc (1−40 equiv) was added to a solution of the protected triflate residue (10 mg) in dry toluene, CH_2Cl_2, or DMF (1.0 mL), respectively. After stirring at room temperature for 4 h, the mixture was diluted with ethyl acetate and washed with brine. The organic phase was dried with $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash column chromatography (3:2 hexanes−ethyl acetate) afforded the thiolacetate derivative.

Methyl 3-Thio-tetra-*O*-acetate-β-D-galactopyranoside (5).[14] Yield 81%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.28 (d, 1 H, $J_{4,5}$ = 2.8 Hz, H-4), 5.03 (dd, 1 H, $J_{1,2}$ = 7.8 Hz, $J_{2,3}$ = 11.8 Hz, H-2), 4.44 (d, 1 H, $J_{1,2}$ = 7.8 Hz, H-1), 4.01−4.08 (m, 2 H, H-6), 3.99 (td, 1 H, $J_{5,6}$ = 6.7 Hz, H-5), 3.91 (dd, 1 H, $J_{2,3}$ = 11.8 Hz, $J_{3,4}$ = 3.0 Hz, H-3), 3.50 (s, 3 H, OMe), 2.30 (s, 1 H, SAc), 2.13 (s, 3 H, OAc), 2.05 (s, 3 H × 2, 2 × OAc); $[\alpha]^{22}_D$ +1.6 (*c* 0.1, $CHCl_3$).

Methyl 3-Thio-tetra-*O*-acetate-β-D-gulopyranoside (7). Yield 85%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.13 (dd, 1 H, $J_{1,2}$ = 7.3 Hz, $J_{2,3}$ = 4.5 Hz, H-2), 5.01 (dd, 1 H, $J_{4,3}$ = 4.5 Hz, $J_{4,5}$ = 2.0 Hz, H-4), 4.45 (d, 1 H, $J_{1,2}$ = 7.3 Hz, H-1), 4.27 (dd, $J_{2,3}$ = 4.5 Hz, $J_{3,4}$ = 4.5 Hz, H-3), 4.12−4.18 (m, 2 H, H-6), 4.01 (td, 1 H, $J_{5,4}$ = 2.0 Hz, $J_{5,6}$ = 6.3 Hz, H-5), 3.46 (s, 3 H, OMe), 2.35 (s, 3 H, SAc), 2.10 (s, 3 H, OAc), 2.01 (s, 3, OAc), 1.98 (s, 3 H, OAc); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192 (SAc) 170.8, 170.0, 169.8 (3 × OAc), 100.6 (C-1), 72.0 (C-5), 70.0 (C-4), 68.6 (C-2), 62.7 (C-6), 57.0 (OMe), 44.1 (C-3), 31.0 (SAc), 21.2 (3 × OAc); $[\alpha]^{22}_D$ −11.8 (*c* 0.45, $CHCl_3$). Anal. Calcd for $C_{15}H_{22}O_9S$: C, 47.61; H, 5.86; S, 8.47. Found: C, 47.38; H, 5.77; S, 8.48.

Methyl 2,4,6-Tri-*O*-acetyl-β-D-galactopyranoside (8).[15] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.32 (d, 1 H, $J_{3,4}$ = 3.5 Hz, H-4), 4.95 (dd, 1 H, $J_{1,2}$ = 8.0 Hz, $J_{2,3}$ = 10.1 Hz, H-2), 4.35 (d, 1 H, $J_{1,2}$ = 8.0 Hz, H-1), 4.15 (d, 2 H, $J_{5,6}$ = 6.7 Hz, H-6), 3.78−3.88 (m, 2 H, H-3, H-5), 3.51 (s, 3 H, OMe), 2.47 (d, 1 H, OH), 2.16 (s, 3 H, OAc), 2.12 (s, 3 H, OAc), 2.05 (s, 3 H, OAc); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.4, 171.0 (3 × OAc), 102.2 (C-1), 72.7 (C-2), 71.3 (2 × C, C-3, C-5), 70.2 (C-4), 62.4 (C-6), 57.2 (OMe), 21.3, 21.1 21.0 (3 × OAc); $[\alpha]^{22}_D$ −20 (*c* 0.2, $CHCl_3$).

Methyl 2,3,6-Tri-*O*-benzoyl-4-*S*-acetyl-β-D-glucopyranoside (9). Yield 82%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08−8.13 (m, 2 H, Ph), 7.86−7.96 (m, 4 H, Ph), 7.30−7.61 (m, 9 H, Ph), 5.72 (dd, 1 H, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ 10.8 Hz, H-3), 5.42 (dd, 1 H, $J_{2,3}$ = 9.5 Hz, $J_{1,2}$ = 8.0 Hz, H-2), 4.70 (dd, 1 H, $J_{5,6a}$ = 2.2 Hz, $J_{6a,6b}$ = 12.1 Hz, H-6a,), 4.66 (d, 1 H, $J_{1,2}$ = 8.0 Hz, H-1), 4.56 (dd, 1 H, $J_{5,6b}$ = 5.0 Hz, $J_{6a,6b}$ = 12.1 Hz, H-6b), 4.12 (ddd, 1 H, $J_{4,5}$ = 11.0 Hz, $J_{5,6a}$ = 2.1 Hz, $J_{5,6b}$ = 5.1 Hz, H-5), 4.04 (m, H-4), 3.50 (s, 3 H, OMe), 2.20 (s, 3 H, SAc); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.5 (SAc) 166.1, 165.6, 165.1 (3 C, Ph-C═O), 134.1, 133.0, 132.9, 129.7, 129.6, 129.2, 128.7, 128.3, 128.2, 128.5, 128.1 (18 C, Ph), 101.7 (C-1), 72.8 (C-5), 72.7 (C-2), 71.6 (C-3), 63.7 (C-6), 56.8 (OMe), 44.4 (C-4), 30.5 (SAc); $[\alpha]^{22}_D$ +45 (*c* 0.4, $CHCl_3$). Anal. Calcd for $C_{30}H_{28}O_9S$: C, 63.82; H, 5.00; S, 5.68. Found: C, 63.59; H, 5.01; S, 5.57.

Methyl 2,3,6-Tri-*O*-benzoyl-4-*S*-acetyl-β-D-galactopyranoside (10). Yield 81%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85−8.15 (m, 6H, Ph), 7.28−7.62 (m, 9 H, Ph), 5.64 (dd, 1 H, $J_{2,3}$ = 10.1 Hz, $J_{3,4}$ = 4.5 Hz, H-3), 5.46 (dd, 1 H, $J_{2,3}$ = 10.1 Hz, $J_{1,2}$ = 7.68 Hz, H-2), 4.61−4.72 (m, 3 H, H-6a, H-4, H-1), 4.43 (dd, 1 H, $J_{5,6b}$ = 6.0 Hz, $J_{6a,6b}$ = 11.2 Hz, H-6b), 4.37 (td, 1 H, $J_{5,6}$ = 6.3 Hz, $J_{4,5}$ = 1.4 Hz, H-5), 3.51 (s, 3 H, OMe), 2.27 (s, 3 H, SAc); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.9 (SAc) 166.1, 165.5, 165.2 (3 C, Ph-C═O), 133.4, 133.3, 133.2, 129.8, 129.7, 129.6, 129.5, 129.4, 129.1, 128.5, 128.4 (18 C, Ph), 102.7 (C-1), 71.8 (C-3), 71.5 (C-5), 70.7 (C-2), 63.6 (C-6), 57.0 (OMe), 46.5 (C-4), 30.6 (SAc); $[\alpha]^{22}_D$ −4.5 (*c* 0.8, $CHCl_3$). Anal. Calcd for $C_{30}H_{28}O_9S$: C, 63.82; H, 5.00; S, 5.68. Found: C, 63.63; H, 4.92; S, 5.56.

Methyl 2,3,6-Tri-*O*-benzyl-4-*S*-acetyl-β-D-galactopyranoside (14). Yield 83%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16−7.35 (m, 15 H, Ph), 4.83 (d, 1 H, *J* 11.0 Hz, Ph-CH2), 4.76 (d, 1 H, *J* 11.0 Hz, Ph-CH2), 4.57 (d, 1 H, *J* 11.0 Hz, Ph-CH2), 4.36−4.53 (m, 4 H, 3 × $PhCH_2$, H-4), 4.31 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 3.88 (dt, 1 H, $J_{5,6}$ 5.7 Hz, H-5), 3.82 (dd, 1 H, $J_{2,3}$ 9.5 Hz, $J_{3,4}$ 4.4 Hz, H-3), 3.52−3.66 (m, 2 H, H-6) 3.49 (s, 3 H, OMe), 3.16−3.25 (m, 1H, H-2), 2.32 (s, 3 H, SAc); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.0 (SAc) 139.0, 138.3, 138.3 (3 C, Ph), 128.0−129.0 (15 C, Ph) 105.5 (C-1), 81.0 (C-2), 79.8 (C-3), 75.8, 74.1 (2 × Ph-CH_2), 73.2 (C-5), 72.4 (Ph-CH_2), 70.5 (C-6), 57.7 (OMe), 46.8 (C-4), 31.3 (SAc); $[\alpha]^{22}_D$ −1.6 (*c* 0.1, $CHCl_3$). Anal. Calcd for $C_{30}H_{34}O_6S$: C, 68.94;

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H, 6.56; S, 6.14. Found: C, 68.94; H, 6.63; S, 6.25. HRMS for $C_{30}H_{34}O_6S$ 545.19738 (M + Na), found 545.19807.

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Supporting Information Available: General methods; NMR spectra of stereoselective reactions of **1** with TBASAc; and ^1H, ^{13}C, $^1H-^1H$ (COSY), and $^1H-^{13}C$ (HMQC) NMR spectra of compound **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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