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Glycosylation with Telluroglycosides. Stereoselective Construction of α- and β-Anomers

Shigeru Yamago*, Koji Kokubo, Hideo Murakami, Yosuke Mino, Osamu Hara and Jun-ichi Yoshida*

Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

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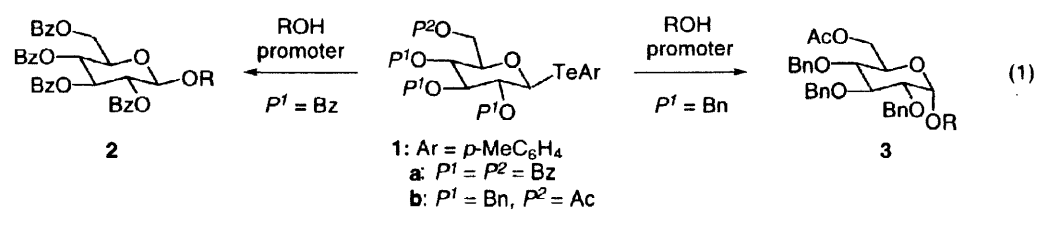
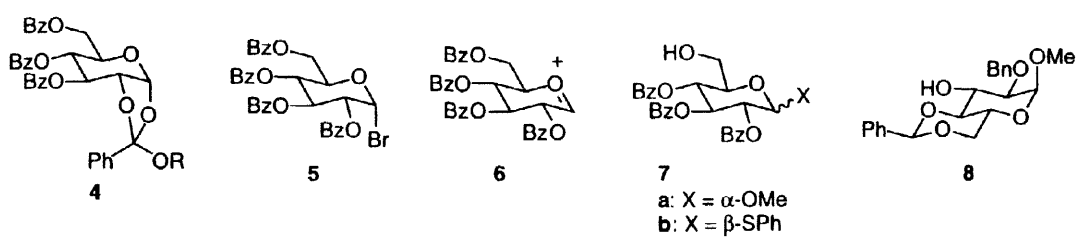
Abstract: Telluroglycosides are activated under neutral conditions and serve as excellent glycosyl donors in the glycosylation reaction. Both α- and β-anomers are selectively formed by the proper choice of the C-2 protecting group and solvent.

Development of the stereoselective glycosylation reaction has been a long standing topic in carbohydrate chemistry.[1] Since the reactivity as well as the selectivity are quite sensitive to the structures of the glycosyl donor and/or acceptor and reaction conditions, the development of a general method for the stereoselective preparation of both α- and β-anomers under a single set of conditions is highly expected.[2] It is also highly desirable that the reaction takes place under mild conditions which are compatible with a wide range of functional groups. We have already reported that the easily available telluroglycosides are activated under electrochemical oxidation and serve as glycosyl donors,[3] but that the stereoselectivity of the reaction is not always satisfactory, especially for the synthesis of the α-isomers.[4, 5] We report here that telluroglycosides are also activated under neutral conditions using chemical reagents, and that both the α– and β– anomers are selectively formed with a single set of reaction conditions under the proper choice of the C-2 protecting group (eq 1).





We first examined the appropriate chemical activator in the reaction of the benzoyl protected telluroglycoside **1a** and 3-phenylpropanol, and found that *N*-bromosuccinimide (NBS) was suitable. Thus,

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treatment of **1a** and 3-phenylpropanol (1.2 equiv.) with NBS (1.1 equiv.) in EtCN at -20 ℃ afforded the orthoester **4a** (R = $(CH_2)_3Ph$) in quantitative yield. The reaction in CH_2Cl_2 or toluene gave a mixture of **2a** (R = $(CH_2)_3Ph$) and **4a** (1:4 - 1:5 ratio) in good combined yield. Since **4a** isomerized to **2a** by treatment with acid,[3b, 6] successive treatment of **1a** and 3-phenylpropanol with NBS and Me_3SiOTf (1.0 equiv.) in EtCN afforded **2a** in 98% yield (Table 1, entry 1).[7] The reaction in CH_2Cl_2 or toluene also gave **2a** in excellent yield after *in situ* isomerization by a catalytic amount of Me_3SiOTf (10 mol%) or TfOH (10 mol%).[8] While the reaction took place faster in the polar solvent in the order of EtCN, CH_2Cl_2, and toluene, the complete β-selectivity was observed in all solvents. The observed β-selectivity was consistent with the well known intramolecular participation effects of the 2-acyl group.

In the glycosylation with sterically demanding alcohols, *N*-iodosuccinimide (NIS) was found to be superior to NBS (entry 4). In the NBS promoted reaction of **1a** with cyclohexanol in EtCN, the desired *O*-glycoside was formed in 49% yield and the α-glycosyl bromide **5** was obtained as a side product. Formation of **5** could be explained by considering the polarity of the Te-Br bond. The bromine atom of ArTeBr generated by the reaction of **1** with NBS bears a partial negative charge as judged by the electronegativity (Pauling electronegativity values: Te = 2.0, Br = 2.8),[9] and it reacted with the glycosyl cation **6** to form **5**. To minimize the Te-halogen polarization, NIS was employed for the glycosylation (electronegativity value: I = 2.2), and it proved to be successful. Thus, the same reaction using NIS followed by *in situ* isomerization with Me_3SiOTf afforded the desired *O*-glycoside in 85% yield. MeOTf (3 equiv.) also activated **1a**, and the *O*-glycoside **2a** was selectively formed.

The 2-benzyl protected telluroglycoside **1b** showed an interesting promoter and solvent dependent α-selectivity (entries 2, 3 and 5). In the reaction with 3-phenylpropanol, the use of NBS resulted in the highest α-selectivity (88% α), and the use of NIS or *t*-BuOCl slightly decreased the selectivity (entry 2). The primary alcohols usually showed lower selectivity than the sterically bulky alcohols, and the present method exhibited one of the highest α-selectivities for the glycosylation of primary alcohols so far reported.[5b] While silyl ethers are less nucleophilic than the corresponding alcohols, the virtually identical result was obtained in the glycosylation with the trimethylsilyl ether of 3-phenylpropanol (entry 3). In the reaction with secondary alcohols, the use of NIS in a nonpolar solvent gave high α-selectivity (entry 5). Thus, the NIS promoted reaction of **1b** with cyclohexanol in toluene or CH_2Cl_2 afforded the desired *O*-glycoside with 95% α-selectivity.[10] In EtCN, the α-selectivity decreased to 44%. The observed solvent dependent selectivity could be explained by considering the kinetic anomeric effects,[2] wherein the α-selectivity reflects a kinetic preference for axial attack in the glycosyl cation intermediate. However, involvement of the halide ion catalyzed reaction cannot be rigorously ruled out at the present time.[4]

Having the α- and β-selective glycosylation conditions in hand, we next examined the stereoselective synthesis of disaccharides (entries 6-11). The reaction of **1a** and **1b** with the 6-hydroxyl glycoside **7** selectively gave the corresponding β- and α-glycosides in good yield, respectively (entries 6-9). While thioglycosides are activated by NIS or NBS,[11, 12] the telluroglycosides were found to be selectively activated over thioglycosides

Table 1. Stereoselective Glycosylation with Telluroglycosides.[a]

entry	HOR	telluroglycoside (eq)	promoter[b]	solvent	%yield[c]	α:β[d]
1	$HO(CH_2)_3Ph$	**1a** (0.83)	NBS/Me_3SiOTf	EtCN	98	1:>99
				CH_2Cl_2	91	1:>99
				toluene	80	1:>99
2		**1b** (0.83)	NBS	CH_2Cl_2	78	88:12
			NIS		85	78:22
			t-BuOCl		62	74:26
3	$Me_3SiO(CH_2)_3Ph$	**1b** (0.83)	NBS	CH_2Cl_2	86	82:18
			NIS		68	75:25
			t-BuOCl		68	80:20
4	HOC_6H_{11}	**1a** (0.83)	NBS/Me_3SiOTf	EtCN	49	1:>99
			NIS/Me_3SiOTf		81	1:>99
			MeOTf[f]		77	1:>99
5		**1b** (0.83)	NIS	EtCN	64	44:56
				CH_2Cl_2	81	95:5
				toluene	80	95:5
			MeOTf[f]	CH_2Cl_2	74	74:26
			t-BuOCl		48	92:8
6	**7a**	**1a** (1.2)	NIS/Me_3SiOTf	EtCN	89	1:>99
7		**1b** (1.2)	NIS	CH_2Cl_2	87	>98:2
8	**7b**	**1a** (1.5)	NIS/Me_3SiOTf	CH_2Cl_2	66	1:>99
9		**1b** (1.5)	NIS	CH_2Cl_2	70	>94:6
10	**8**	**1a** (1.2)	NIS/Me_3SiOTf	CH_2Cl_2	50	1:>99
11		**1b** (1.5)	NIS	CH_2Cl_2	37	>95:5

[a] The reaction was carried out at -23 ℃ to room temperature for 5-12 h when **1a** was used, and at -72 ℃ to room temperature for 3-12 h for **1b**. [b] A slight excess of the promoter (1.1 eq to the acceptor) was used. [c] Yield was based on the donor for entries 1-5 and on the acceptor for the others. [d] Determined by ^1H-, ^{13}C NMR and/or HPLC. [f] Three equivalents of the promoter were used.

(entries 8 and 9). Thus, the reaction with **7b** selectively gave the corresponding disaccharides bearing the phenylthio functionality, and the unreacted **7b** was recovered in 26% and 30% for entries 8 and 9, respectively. The organothio group of the disaccharides would be activated under certain conditions for the next glycosylation reactions. The sterically hindered 3-hydroxyl glycoside **8** was found to have low reactivity, and the formation of 1-glycosyl iodide was observed.[13] However, both the β- and α-glycosides were exclusively formed depending on the choice of the C-2 protecting groups (entries 10 and 11).

In conclusion, we have found that the telluroglycosides are activated under neutral conditions and stereoselectively give both the α- and β-glycosides by the proper choice of the protecting groups and reaction conditions. The predictability of the stereochemistry makes it possible to rationally design the oligosaccharide

synthesis including structurally defined carbohydrate libraries.[14]

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