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A New, Iterative Strategy of Oligosaccharide Synthesis Based on Highly Reactive β-Bromoglycosides Derived from Selenoglycosides

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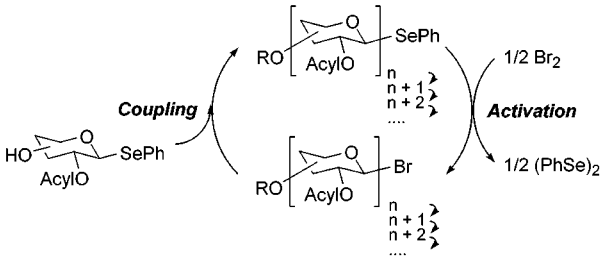
ABSTRACT



Stereoselective conversion of a selenoglycoside to a β-bromoglycoside in the absence of a glycosyl acceptor followed by the coupling with another selenoglycoside affords the corresponding glycosylated selenoglycoside, which could be directly used for the next glycosylation. The iteration of this sequence allows the synthesis of a variety of oligosaccharides including an elicitor active heptasaccharide.

Despite recent advances in synthetic carbohydrate chemistry, efficient and high throughput synthesis of oligosaccharides still remains a major challenge.[1,2] Since the reactivity control of anomeric substituents in glycosyl donors and acceptors is difficult, conventional synthetic methodologies require laborious protection-deprotection procedures that diminish overall synthetic efficiency. To overcome this problem, several glycosylation strategies, including the two-stage activation method,[3] armed-disarmed glycosylation,[4] one-pot synthesis,[5] the orthogonal method,[6] enzymatic glycosylation,[7] the programmable one-pot strategy,[8] and solid-phase synthesis,[9] have been recently developed.[10,11]

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While the use of a single anomeric substituent both for donors and acceptors is obviously desirable for ideal oligosaccharide synthesis, only a few examples have been reported so far, namely, the glycal assembly method.[12,13] We report here a new approach toward such strategy. 2-Acyl-protected selenoglycopyranoside **1** was found to be converted stereoselectively to the corresponding 1-β-bromoglycoside **2** upon treatment with Br_2.[14] While the reaction of halogly-cosides with glycosyl acceptors usually requires activators, e.g., heavy metal salts,[15] we found that β-bromoglycoside **2** reacts smoothly with various glycosyl acceptors in the absence of such activators.[16] When a selenoglycoside is used as an acceptor, the anomeric seleno group is retained in the product. Therefore, the repetition of the reaction sequence provides rapid construction of oligosaccharides. Thus, the present approach provides a new, powerful strategy for oligosaccharide synthesis.

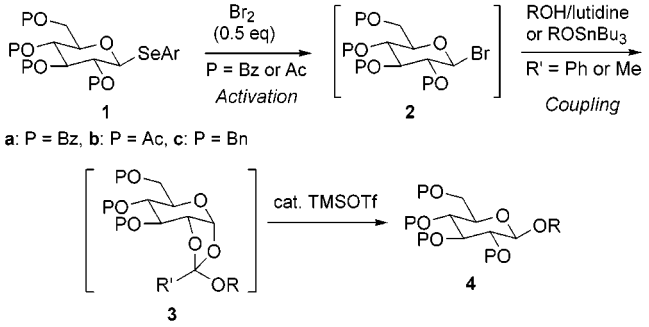
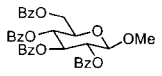
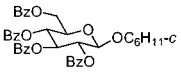
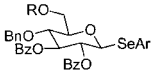
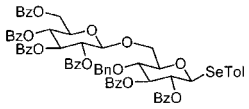
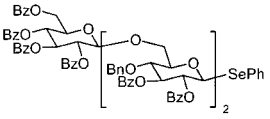
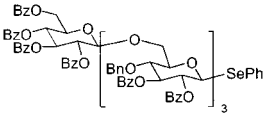
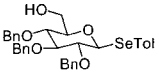
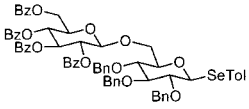
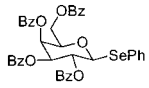
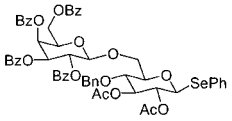


Figure 1. β-Bromoglycoside-mediated glycosylation.

The β-bromoglycoside **2a** was found to be formed quantitatively upon reaction of benzoyl-protected **1a** (Ar = Ph or Tol)[17] in CH_2Cl_2 with Br_2 (0.5 equiv) at −20 to 0 °C for 30 min, and the arylselenyl moiety was converted to the corresponding diselenide as judged by the ^{77}Se NMR of the reaction mixture. The diselenide was also isolated and identified after reaction with a glycosyl acceptor. The ^1H NMR experiments in CD_2Cl_2 revealed that the reaction was extremely stereoselective (95−98% β-selective). Treatment of **1a** with 1 equiv of ArSeBr also afforded β-**2a** in quantitative yield with high β-selectivity. Therefore, the reaction of **1a** with Br_2 seems to involve initial formation of **2a** and ArSeBr, which subsequently reacts with the remaining **1a** to give **2a** and the diselenide.[18] Because of the mild reaction conditions, isomerization of β-**2a** to the thermodynamically more stable α-isomer was very slow (less than 10% of β-**2a** isomerized after 1 day at room temperature).

Table 1. Glycosidation of Selenoglycosides

entry	donor	acceptor	product	%yield[a]
1	**1a**	MeOH or $MeOSnBu_3$		96
2	**1a**	*c*-$C_6H_{11}OH$		82
3	**1a**			
		9ii (R = H)	10	77
		9iii (R = $SnBu_3$)		71
4	**10**	**9iii**		81
			12	
5	**12**	**9iii**		56
6	**1a**			64
7		**6iii**		57

[a] Yield was based on the donor for entries 1, 2, 4, and 5, wherein a slight excess of the acceptor was used (1.1 equiv for entries 1 and 2, and 1.5 equiv for entries 3 and 4) and on the acceptor for the rest, wherein a slight excess of the donor was used (1.1 equiv for entry 6, and 1.5 equiv for entries 3 and 7).

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The acetyl-protected selenoglycoside **1b** also gave the corresponding β-bromoglycoside **2b**, whereas the benzyl-protected **1c** gave the α-isomer as the sole product (>97% α-selectivity). Thioglycoside **5**, however, gave the bromoglycoside in 65% yield with 76% β-selectivity after 3 days at room temperature.[19] The β-bromoglycosides **2a** and **2b** reacted with various glycosyl acceptors. Thus, treatment of **2a** with MeOH (1.0 equiv) and 2,6-lutidine (1.0 equiv) in CH_2Cl_2 afforded the ortho ester **3a** (P = Bz, R = Me, R′ = Ph) in quantitative yield. Tributylstannyl methyl ether[20] also reacted with **2a** to give the ortho ester in quantitative yield. It should be noted that β-fluoro- (**8d**), β-chloro- (**8e**), and α-bromoglycosides were far less reactive than **2** under identical conditions or even in the presence of Bu_4NI.[21] Treatment of the ortho ester with a catalytic amount of Me_3SiOTf gave quantitatively the corresponding *O*-glycoside (Table 1, entry 1).[22]

We next examined the use of the selenoglycoside as the glycosyl acceptor, since the coupling of **2** with glycosyl acceptors does not require any chemical activators that might destroy the anomeric seleno group. The coupling of **1a** with C-6 hydroxyl or C-6 tributylstannyloxyl selenoglycoside (**9ii** or **9iii**[23]) proceeded smoothly, and the desired disaccharide **10** was obtained in good yield after in situ isomerization of the initially formed ortho ester (entry 3). By repeating the same reaction sequence, we synthesized tri- and tetrasaccharides in good yields (entries 4 and 5). Because C-2 alkyl-protected glycosides are more reactive than C-2 acyl-protected glycosides, the former always acts as a donor and the latter acts as an acceptor in the armed and disarmed glycosylation strategy.[4] The present strategy, however, enables the use of a C-2 acyl-protected glycoside as a donor and a C-2 alkyl-protected glycoside as an acceptor (entry 6). It is also noteworthy that galactose derivatives could be used as glycosyl donors (entry 7).

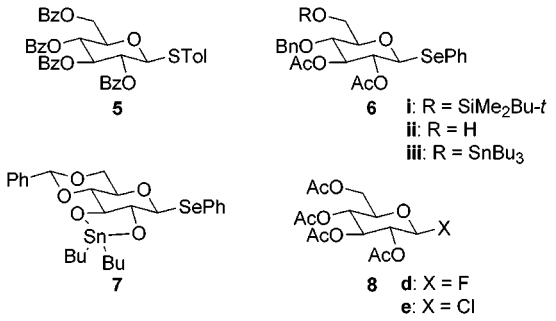
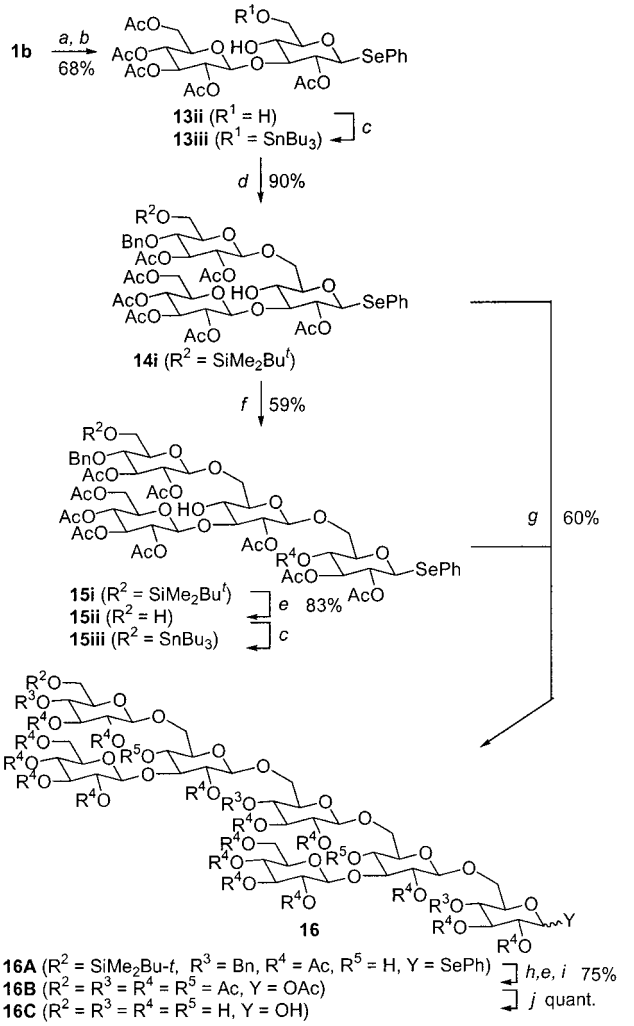


Figure 2. Substrates examined for the glycosylation.

The utility of the current strategy has been demonstrated in the synthesis of elicitor active heptasaccharide **16C**[24] (Scheme 1). Thus, activation of **1b** with Br_2, coupling with

Scheme 1. Synthesis of Elicitor Active Heptasaccharide[a]



[a] Reaction conditions: (a) **1b** (1.5 equiv)/Br_2 (0.75 equiv), CH_2Cl_2, 0 °C, 0.5 h, then **7** (1.0 equiv), rt, 5 h; Ac_2O (1.5 equiv), Et_3N (1.5 equiv), DMAP (0.1 equiv), rt, 0.5 h. (b) Me_3SiOTf (0.1 equiv), CH_2Cl_2, 0 °C, 0.5 h, then H_2O (10 equiv), rt, 0.5 h. (c) $C_3H_5SnBu_3$ (1.3 equiv), TfOH (0.3 equiv), CH_2Cl_2, rt, 2 h. (d) **6i** (1.2 equiv)/Br_2 (0.6 equiv), CH_2Cl_2, 0 °C, 0.5 h, then **13ii** rt, 10 min, and then Me_3SiOTf (0.1 equiv), 0 °C, 0.5 h. (e) 5% aqueous HF/MeCN/CH_2Cl_2, rt, 12 h. (f) **14i** (1.0 equiv)/Br_2 (0.5 equiv), CH_2Cl_2, 0 °C, 0.5 h, then **6iii** (1.2 equiv), rt, 10 min, and then Me_3SiOTf (0.1 equiv), 0 °C, 0.5 h. (g) **14i** (2.0 equiv)/Br_2 (1.0 equiv), CH_2Cl_2, 0 °C, 0.5 h, then **15iii** (1.0 equiv), rt, 1 h, then Me_3SiOTf (0.1 equiv), 0 °C, 0.5 h. (h) Br_2 (0.5 equiv), CH_2Cl_2, 0 °C, 0.5 h, then H_2O (20 equiv), rt, 0.5 h. (i) H_2 (50 atm), $Pd(OH)_2$/C, EtOH, 50 °C, 16 h then Ac_2O (14 equiv), DMAP (2 equiv), Et_3N (20 equiv), CH_2Cl_2, rt, 16 h. (j) MeONa (25 equiv), MeOH, rt, 0.5 h.

7, acetylation of the C2 hydroxyl group, isomerization of the ortho ester, and in situ hydrolysis of the benzylidene acetal afforded **13ii** in good combined yield. Stannyl ether

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13iii derived from **13ii** was coupled with the bromoglycoside prepared from **6i** to afford the trisaccharide **14i**, which was coupled with **6ii** to give the tetrasaccharide **15i**. Activation of **14i** by Br_2 and subsequent coupling with **15iii** derived from **15i** afforded the heptasaccharide **16A** in good yield. Treatment of **16A** with Br_2 followed by reaction with water, deprotection of the silyl and benzyl groups, and subsequent acetylation afforded per-acetylated glycoside **16B**, which easily hydrolyzed to **16C** upon treatment with MeONa. Since **16A** also possesses a selenoglycoside moiety, it can be used for further elongation of oligosaccharides.

In summary, we have developed a new iterative strategy for the synthesis of oligosaccharides using a single anomeric substituent both for glycosyl donors and acceptors. The success of the present strategy is ascribed to the activation of selenoglycosides to highly reactive β-bromoglycosides in the absence of glycosyl acceptors. Further development of this strategy is now under investigation.

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Supporting Information Available: Spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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