Orthogonal Glycosylation Strategy in Oligosaccharide Synthesis

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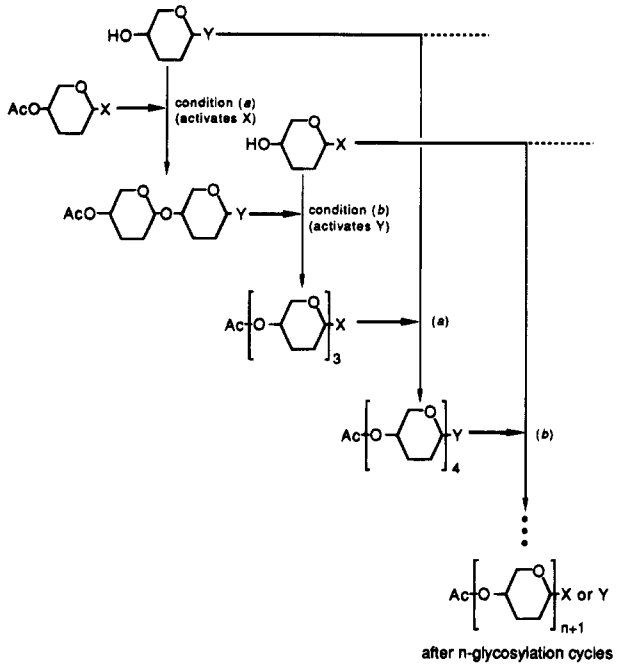
Recent research from a variety of fields has revealed numerous biological roles for glycoconjugates.[1] In order to investigate the functions of such molecules, extensive efforts have been directed toward the synthesis of natural and modified structures.[2] To this end, the efficiency of oligosaccharide synthesis has been improved dramatically due to the development of new glycosylation reactions using a wide range of leaving groups and mild activating conditions. A trend utilizing the concept of chemoselective glycosylation has emerged.[3] Such strategies take advantage of the differential chemical reactivities of glycosyl donors which can be controlled by protecting groups (ether- vs ester-type) and leaving groups.

The most straightforward method among these is the direct use of glycosylation products as donors for the next coupling reaction, thereby negating the need for additional steps in the further manipulation of the anomeric center after each glycosylation.[3a−c,e,g,i,j,l,n,o,q−t,v] However, the length of the resulting sugar chain has been limited by the number of available leaving groups and/or protecting groups.

To overcome the limitation of existing strategies, we investigated the possibility of using two sets of chemically distinct (orthogonal) glycosyl donors and activation conditions (Scheme 1). The criteria for this concept to be practical are that (1) X should be unaffected under condition b required to activate the other donor (i.e., Y), and *vice versa*, and (2) both X and Y should remain compatible with subsequent manipulations of temporary protecting groups. For this orthogonal strategy, we

Scheme 1



selected the phenylthio group for X and fluoride for Y as the leaving groups, and NIS−TfOH (or AgOTf)[4,5] (condition a) and Cp_2HfCl_2−$AgClO_4$[6] (condition b) as promoters, respectively.

For an initial attempt to demonstrate the feasibility of the strategy, *N*-phthaloyl (Phth) protected glucosamine (GlcN) derivatives were chosen as the monosaccharide units. This decision was based solely on the assumption that any stereochemical ambiguity could be eliminated by the strong 1,2-trans directing nature of the NPhth group.[2f,7] However, it is to be stressed that the basic principle should be applicable to a wide variety of oligosaccharide structures. In addition, the biological significance of β-1,4 linked oligomers of glucosamine (e.g., chitin) is well recognized.[8] Also, the hydroxyl group at the C-4 position of GlcN is known to be relatively unreactive.[2f] Therefore, the construction of this type of oligosaccharide is a challenging task.[9] The required GlcN derivatives **3**−**6** were synthesized according to the procedure described for closely related compounds.[10]

In order to assess the orthogonality of the above-mentioned combination of reactions, we examined glycosylations using **1**[11,12] and **2**[13,14] as donors. Thus, thioglycoside **1** was reacted

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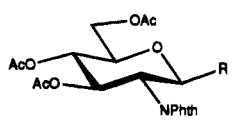
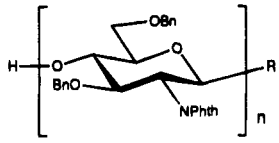
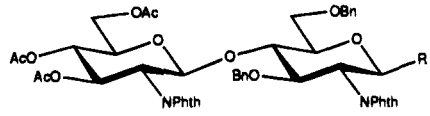
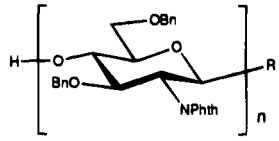
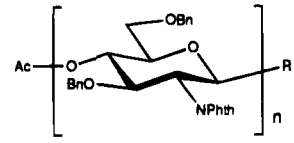
Table 1. Results of Glycosylations Utilizing Phenylthio and Fluoro Groups as Leaving Groups[c]

donor	acceptor	acceptor / donor[a]	condition	product (yield[b])
				
1 R = SPh 2 R = F	6 R = F n = 1 3 R = SPh n = 1	1 1	(*a*) (*b*)	7 R = F (90) 8 R = SPh (80)
				
4 R = SPh n = 1 5 R = F n = 1 9 R = F n = 2 11 R = SPh n = 3 11 R = SPh n = 3	6 R = F n = 1 3 R = SPh n = 1 3 R = SPh n = 1 6 R = F n = 1 13 R = F n = 4	1.5 1 2 3 1	(*a*) (*b*) (*b*) (*a*) (*a*)	9 R = F n = 2 (85) 10 R = SPh n = 2 (81) 11 R = SPh n = 3 (72) 12 R = F n = 4 (65) 14 R = F n = 7 (67)

[a] Mole ratio. [b] Yields were calculated on the basis of donors after column chromatography. [c] Condition a: NIS (1.3 equiv) and AgOTf (0.1 equiv) in CH_2Cl_2 at −50 °C → room temperature. Condition b: Cp_2HfCl_2 (1.3 equiv) and $AgClO_4$ (2.6 equiv) in CH_2Cl_2 at −78 °C → room temperature.

with acceptor **6** under condition a to afford disaccharide **7** in 90% yield. Fluoride **2** was also successfully activated under condition b and reacted with **3**, without affecting the thioglycosidic linkage, to give disaccharide **8** in 78% yield. No α-isomer nor self-condensed product was detected in either sequence. These results indicate that less reactive acyl-protected donors were activated preferentially compared to the potentially more reactive ether-protected acceptors. The chosen set of reactions is therefore shown to be orthogonal. Under the same conditions, selectively protected disaccharides **9** and **10** were synthesized in 85% and 81% yields, respectively (Table 1).

The applicability of the present strategy to the synthesis of longer chain oligosaccharides was next examined by constructing heptasaccharide **14** from disaccharide **9**. First, thioglycoside **9** and acceptor **3** were coupled to produce **11** (condition b, 72%). Subsequent reaction of **11** with **6** (condition a, 65%) gave tetrasaccharide **12**. Having accomplished the stepwise synthesis of a tetrasaccharide, we next examined the block condensation approach. Tetrasaccharide acceptor **13**, prepared by Zemplen deacetylation of **12**, was coupled with its precursor **11** to give compound **14** (condition a, 67%), which is again ready for further use as an oligosaccharide donor.

In summary, an orthogonal glycosylation strategy was developed by the combined use of phenylthioglycosides and glycosyl fluorides as both donors and acceptors. Extra steps, such as temporary protection of the anomeric position and subsequent conversion into donor, are thus eliminated.

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Supplementary Material Available: Listings of experimental procedures including analyses and ^1H and ^{13}C NMR data (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see current masthead page for ordering information.

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