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PHENYLSELENOGLYCOSIDES AS NOVEL, VERSATILE GLYCOSYL DONORS. SELECTIVE ACTIVATION OVER THIOGLYCOSIDES[1]

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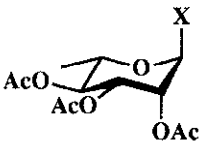
SUMMARY: Selective activation of phenylselenoglycosides over ethylthioglycosides with silver trifluoromethanesulfonate and anhydrous potassium carbonate gives an efficient synthesis of disaccharides from selenoglycoside donors and thioglycoside acceptors. Activation is quenched by addition of 1,1,3,3,-tetramethylurea or collidine.

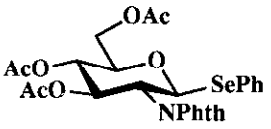
The importance of cell surface carbohydrates in biological processes ranging from antibody-antigen interaction to cell-cell recognition and development[2] has led to a great deal of activity at the carbohydrate frontier.[3] An integral component of this activity has involved the development of new chemical[4] methods of oligosaccharide synthesis requiring fewer manipulations and/or resulting in higher yields, increased stereoselectivity, and selective activation. Particularly noteworthy recent contributions include the use of "armed" and "disarmed" n-pentenyl glycosides,[5], glycals[6] and thioglycosides[7] for the selective activation of one of the partners in a glycosylation reaction. The latter approaches rely on the differential reactivity conferred upon each of the partners by the nature of the protecting groups. An alternative strategy, permitting greater flexibility in the choice of protecting groups, derives from the availability of glycosyl-X and glycosyl-Y units in which one of these units can be selectively activated in the presence of the other. We describe herein the successful implementation of the latter strategy, in particular, the selective activation of phenylselenoglycosides[8] over ethylthioglycosides in glycosylation reactions. We describe also conditions in which selenoglycosides remain inert but glycosyl halides are activated.

The phenylselenoglycosides 1 and 2 were readily prepared from the corresponding peracetylated sugar in the case of 1 and from 1,3,4,6-tetra-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose[9] in the case of 2 by treatment with phenylselenol (obtained by the hypophosphorus acid reduction of diphenyldiselenide[10]) and $BF_3.OEt_2$. The compounds 1 and 2 are crystalline, odorless and air-stable. Reactions with the glycosyl acceptors 3,[11] 4,[12] 5,[13] 6,[14] and 7[14] were examined.[15]

The strategy for the selective activation of selenoglycoside donors arose from three critical observations: 1) the donors could be activated by silver triflate, 2) the activation could be completely suppressed by the addition of conventional proton acceptors such as 1,1,3,3-tetramethylurea or collidine and 3) an inorganic base such as anhydrous potassium carbonate did not quench the reaction. Thus, reaction of the rhamnosyl donor 1 with the acceptors 3, 4, and 5 under silver triflate promotion, in the presence of anhydrous K_2CO_3 and molecular sieves, afforded the disaccharides 8, 9, and 10, respectively, and similar glycosylation of the acceptor 4 with the donor 2 afforded the disaccharide 11 (Table 1).[20] The question of selectivity was next addressed. A mixture of the selenoglycoside 1 and the thioglycoside 12 was treated with



1 X= SePh
12 X= SEt



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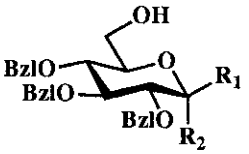
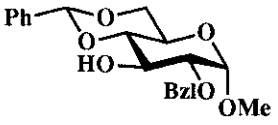


3 R_1=H; R_2=OMe
6 R_1=H; R_2=SEt
7 R_1=SEt; R_2=H



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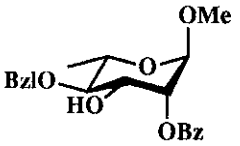

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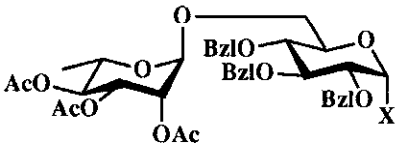
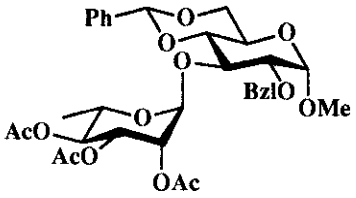


8 X=OMe
13 X=SEt



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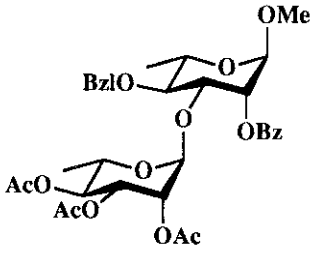

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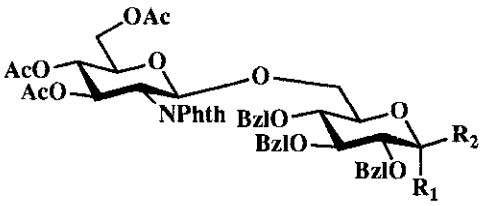

11 R_1=OMe; R_2=H
14 R_1=H; R_2=SEt

the acceptor 4 under the conditions described above. The disaccharide 9 was formed in 85% yield and the unreacted thioglycoside 12 was recovered in 91% yield. That the thioglycoside 12 is not activated under these conditions was also indicated by its inertness in a separate reaction with 4 (Table 1). Further compelling evidence for the selective activation of selenoglycosides over thioglycosides was obtained in the reaction of the more reactive thioglycoside acceptor 6 with the selenoglycoside donor 1. The disaccharide 13 was formed in 85% yield; in a separate experiment with only 6 present, no significant cross coupling was observed. Reaction of the thioglycoside acceptor 7 with the selenoglycoside donor 2 afforded the disaccharide 14 in 84% yield (Table 1). All of the reactions described above were stereospecific.

Table 1. RESULTS OF GLYCOSYLATION REACTIONS.

Entry	Donor	Acceptor	Molar Ratio[a]	Time (h)	Product[b]	Yield (%)
1	1	3	1:1.5:3.5	1	8	85
2	1	4	1:1.2:3.5	1	9	70
3	1	5	1:1.2:2	5	10	62
4	2	3	1:1.2:6	4	11	84
5	1+12	3	1:1:2:4	1	8	86
6	12	3	1:1:2	24	no reaction	
7	1	6	1:1:3	1.5	13	80
8	6	6	1:1:4.5	24	no reaction	
9	2	7	1:1:6	1	14	84

[a] donor:acceptor:AgTfl; [b] products were characterized by microanalysis and high resolution ^{1}H and ^{13}C NMR spectroscopy.

Finally, since glycosyl halides are activated by silver triflate in the presence of 1,1,3,3-tetramethylurea[21] or collidine[9] and the phenylselenoglycosides are not, it is probable that these two donors will also enjoy an ideal complementarity.

In summary, a simple method has been developed for the use of phenylselenoglycosides as glycosyl donors in glycosylation reactions. The selective activation of phenylselenoglycosides in the presence of thioglycosides together with the quenching of this reaction under conditions in which glycosyl halides remain activated offers a significant and powerful addition to the repertoire of the synthetic oligosaccharide chemist. The extension of this method to phenylselenoglycoside donors bearing different functionality in their protecting groups, their use in the synthesis of higher-order oligosaccharides, and the details of the mechanism of the selective activation are under active investigation.

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(14) Prepared in analogous fashion to the corresponding methyl glycoside.[11]

(15) Initial experiments indicated[1] that the selenoglycosides could be activated by promoters such as methyl triflate,[16] phenylselenenyl triflate,[17a] or $CuBr_2$-Bu_4NBr-AgTFl[17b], as described for the activation of thioglycosides. In addition, electrochemical oxidation, or oxidation with tris(4-bromophenyl)amminium hexachloroantimonate, as recently described for the case of the thioglycosides,[18,19] also resulted in activation.[1]

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(20) To a mixture of silver triflate (2-6 eq.), anhydrous K_2CO_3 (10-12 eq.) and 4A molecular sieves in CH_2Cl_2 was transferred a mixture of the phenylselenoglycoside (1 eq.) and the glycosyl acceptor (1-1.5eq.) in CH_2Cl_2 under nitrogen. The reaction mixture was stirred at room temperature for 1-5 h and the reaction was monitored by tlc. The solids were removed by filtration through celite and the filtrate was washed with $NaHCO_3$(aq), H_2O, and dried over K_2CO_3. Following evaporation of the solvent, the residue was chromatographed on silica gel.

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