Tetrahedron Letters,Vol.29,No.9,pp 1061-1064,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

BENZENESELENENYL TRIFLATE AS A PROMOTER OF THIOGLYCOSIDES : A NEW METHOD FOR O-GLYCOSYLATION USING THIOGLYCOSIDES[1)]

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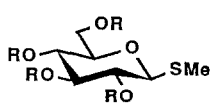
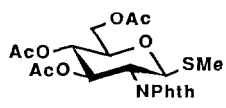
ABSTRACT: An efficient O-glycosylation was developed by use of thioglycosides and benzeneselenenyl triflate.

For the synthesis of complex oligosaccharides, O-glycosylation based on the activation of 1-thioglycosides is endowed with obvious advantage over other methods because of their stability under a variety of conditions commonly encountered in carbohydrates manipulations. Accordingly, various methods have been developed to activate 1-thioglycosides[2)]. We report here a new avenue to this subject by use of highly electrophilic benzeneselenenyl triflate (PhSeOTf), which was recently introduced as a selenolactonization agent[3)]. As described below, PhSeOTf effected the activation of various thioglycosides under notably mild conditions.



1 : R=Bn
2 : R=Ac
3 : R=Bz



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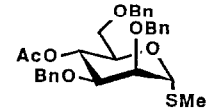

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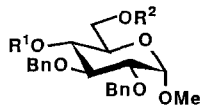
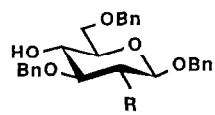
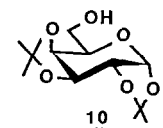


6 : R^1=Bn, R^2=H
7 : R^1=H, R^2=$SiPh_2tBu$



8 : R=OBn
9 : R=NPhth



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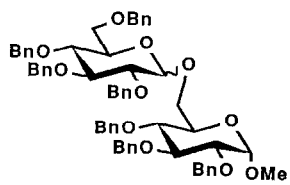

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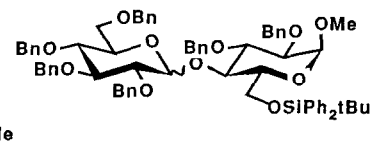

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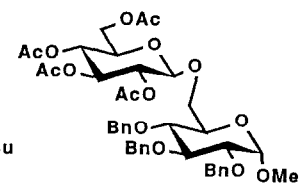

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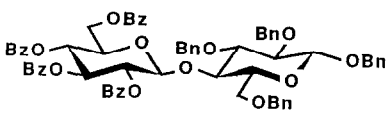

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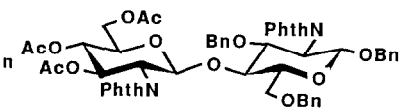

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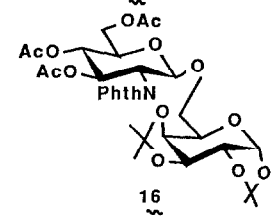

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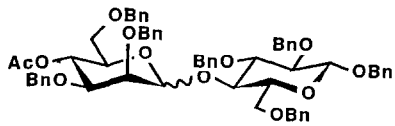

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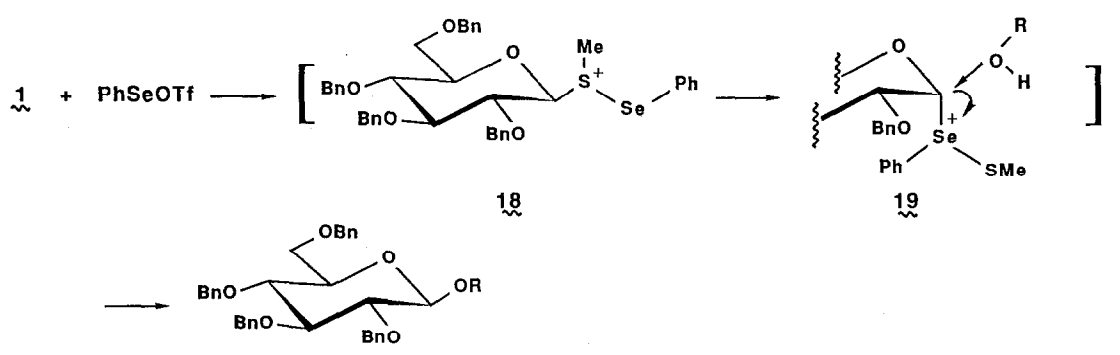
1-Thioglycosides **1**[2m], **2**[4], **3**[2j], **4**[5] and **5**[2m] were chosen as glycosyl donors and alcohols **6**[6], **7**[7], **8**[9], **9**[10] and **10**[11] were examined as glycosyl acceptors. All reactions proceeded smoothly at low temperature in the presence of 1.5 equiv of PhSeOTf and molecular sieves 4A and disaccharides **11**[12], **12**[2m], **13**[13], **14**[2j], **15**[14], **16**[15] and **17**[16] were obtained in good to excellent yield (Table 1). Interestingly, tetra-O-benzyl derivative **1** showed a considerable level of β-selectivity (entry 1,2). β-Selective glycosylation in the absence of neighbouring group participation has been performed by using insoluble silver catalysts[17] or solvents with cation interacting ability such as acetonitrile[2g)2K)2m)18]. Although the origin of the β-selectivity shown here is not clear at present, we would like to make a tentative explanation based on the reverse anomeric effect[19] as follows. Thus, a sulfonium salt **18** derived from the 1-thioglycoside **1** and PhSeOTf rearranges to the selenonium salt, which in turn reacts mainly in its more reactive α-configuration **19** to give β-glycosides predominantly (Scheme 1). As expected, 1-thioglycosides which carry 1,2-trans directing substituents gave β-glycosides exclusively (entry 3-6). Relatively low yield observed in tetra-O-acetyl derivative **2** (entry 3) was improved by use of tetra-O-benzoyl counterpart **3** (entry 4). Similar tendencies were reported by other authors both for glycosyl bromide[20] and 1-thioglycoside[2g]. The reaction of α-thiomannoside **5** with **8** afforded disaccharide **17** predominantly as an α-isomer (entry 7).

Table 1 Results of glycosylation reactions.

entry[a]	thioglycoside	acceptor	molar ratio[b]	solvent	temp(°C)/time	product	yield[c]	β : α
1	**1**	**6**	1.2 : 1	toluene	-40 / 30min	**11**	91%	88 : 12[f]
2	**1**	**7**	1 : 1.1	toluene	-40 / 1h	**12**	74%	75 : 25[f]
3	**2**	**6**	1.2 : 1	$(ClCH_2)_2$	0 / 10min	**13**	52%	e)
4	**3**	**8**	1.2 : 1	$(ClCH_2)_2$	0 / 10min	**14**	96%	e)
5	**4**	**9**	1.2 : 1	toluene	-40~0 / 1h	**15**	91%	e)
6	**4**	**10**	1.2 : 1	toluene	-40 / 30min	**16**	61%[d]	e)
7	**5**	**8**	1.2 : 1	toluene	-40 / 30min	**17**	99%	16 : 84[g]

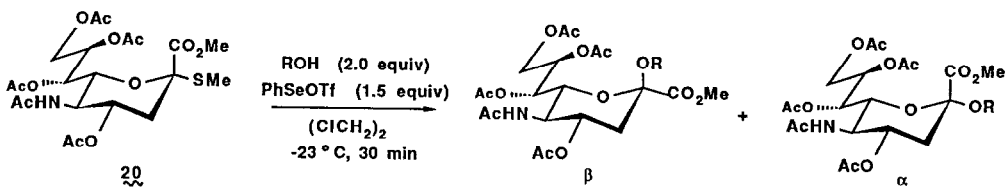
a) All reactions were carried out under atmosphere of dry nitrogen in the presence of PhSeOTf (1.5 equiv) and molecular sieves 4A. b) Corresponds to thioglycoside : acceptor. c) The yield of entry 2 was based on **1**. All other yields were based on acceptors. d) 74% based on consumed **4**. e) Only β-products were detected. f) Determined by ^{1}H-NMR (400 MHz). g) Determined by individual isomer separation.

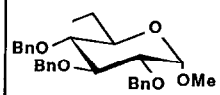
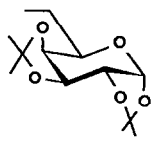


Scheme 1

A typical glycosylation procedure was as follows (entry 4). To a stirring mixture of benzeneselenenyl chloride (PhSeCl; 26 mg, 140 μmol) and molecular sieves 4A (0.3 g) in 1,2-dichloroethane (1 ml) was added silver triflate (AgOTf; 35 mg, 140 μmol) at 0°C. After stirring for 10 min, a solution of compounds **3** (69.5 mg, 111 μmol) and **8** (50.0 mg, 92.5 μmol) in 1,2-dichloroethane (4 ml) was added dropwise and the mixture was stirred for 10 min at 0°C. Aq. $NaHCO_3$ (5 ml) was added and the mixture was diluted with ethyl acetate (30 ml) and filtered through Celite. The filtrate was washed with water (30 ml) and the aqueous layer was extracted with ethyl acetate (30 ml). The combined organic layers were washed with brine (30 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by silica gel chromatography in 15:1 toluene-ethyl acetate to give **14** (99.6 mg, 96%), $[\alpha]_D$ -11.0° (c 0.8)[21], δ_H ($CDCl_3$, 500 MHz) 4.959 (d, 7.9 Hz, H-1b), 4.397 (d, 7.9 Hz, H-1a) which could be crystallized from n-hexane-ether, m.p. 104-105°C.

Finally, 2-thioglycoside **20**[22] derived from N-acetylneuraminic acid was briefly examined as a glycosyl donor to react with primary alcohols **6** and **10**. Although the major products turned out to be β-glycosides, corresponding disaccharides **21**[24] and **22**[25] were obtained in good yield (Scheme 2).



ROH	R	product	yield	β : α
6		21	63%	84 : 16
10		22	70%	59 : 41

Scheme 2

As described above, PhSeOTf was found to serve as a powerful promoter of thioglycosides. High efficiency as well as operational simplicity should allow the present method to find practical use in oligosaccharide synthesis.

Acknowledgment. We are indebted to Mr. Y. Shitori of MECT Co. for a generous supply of N-acetylneuraminic acid. We thank Dr. J. Uzawa and Mrs. T. Chijimatsu for recording and measuring the NMR spectra and Dr. H. Yamazaki and his staff for the elemental analyses. We also thank Ms. A. Takahashi and Ms. K. Moriwaki for their technical assistance.

Reference and Notes

1) Part of a series on "Novel approaches to glycoside synthesis". For the previous papers, see Ref. 2m).

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14) $[\alpha]_D$ -16.1° (c 1.0), $\delta_H(CDCl_3$, 400 MHz) 5.788 (dd, 10.5, 9.0 Hz, H-3b), 5.529 (d, 8.5 Hz, H-1b), 5.120 (dd, 10.0, 9.0 Hz, H-4b), 4.953 (d, 8.3 Hz, H-1a), 4.213 (dd, 12.2, 4.2 Hz, H-6b), 3.935 (dd, 12.2, 2.3 Hz, H-6b'), 3.606 (dd, 11.2, 1.2 Hz, H-6a), 3.500 (dd, 11.2, 3.4 Hz, H-6a'), 3.453 (ddd, 10.0, 4.2, 2.3 Hz, H-5b), 3.342 (ddd, 9.7, 3.4, 1.2 Hz, H-5a).

15) $[\alpha]_D$ -23.8° (c 1.0), m.p. 208-210°C, $\delta_H(CDCl_3$, 90 MHz) 5.84 (dd, 10.6, 9.0 Hz, H-3b), 5.44 (d, 8.6 Hz, H-1b), 5.15 (dd, 10.1, 9.0 Hz, H-4b).

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21) All values of $[\alpha]_D$ were measured for $CHCl_3$ solutions at 20±3°C. Compounds having $[\alpha]_D$ recorded gave satisfactory elemental analysis.

22) Prepared by methylation of corresponding sodium thiolate according to the procedure reported by Hasegawa et al[23], $[\alpha]_D$ +23.7° (c 1.0), $\delta_H(CDCl_3$, 500 MHz) 4.890 (ddd, 11.7, 10.6, 4.8 Hz, H-4), 3.813 (s, OMe), 2.731 (dd, 12.8, 4.8 Hz, H-3eq), 1.993 (dd, 12.8, 11.7 Hz, H-3ax), 2.171, 2.142, 2.115, 2.041, 2.034 and 1.881 (6 s, 5 Ac and SMe).

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(Received in Japan 9 December 1987)