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A Facile Method for β-Selenoglycoside Synthesis Using β-*p*-Methylbenzoyl Selenoglycoside as the Selenating Unit

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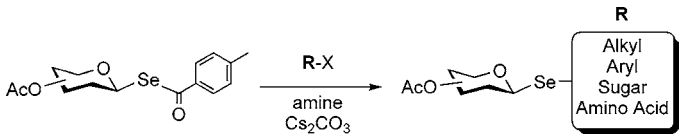
ABSTRACT



The reaction between α-glycosyl bromides and potassium *p*-methylselenobenzoate yields *β*-*p*-methylbenzoyl selenoglycosides. The acyl selenoglycosides were activated by the action of a secondary amine and Cs_2CO_3 to produce an anomeric selenolate anion, which reacted in situ with various electrophiles to yield novel selenoglycosides while retaining the anomeric stereochemistry.

The substitution of interglycosidic or intraring oxygen in carbohydrates with other elements such as carbon, nitrogen, and other chalcogens is an attractive carbohydrate mimicking technique.[1] Over the last two decades, thioglycosides in particular have become an important class of "pseudoglycosides" due to their notable potential as enzyme inhibitors,[2] enzyme-resistant scaffolds,[3] synthetic vaccines,[4] and so on. On the other hand, seleno- and telluroglycosides have been primarily exploited as glycosyl donors for *O*-glycoside formation.[5] To date, limited information is available on selenodisaccharide synthesis,[6] and there only exists a single report on the potential inhibitory behavior of selenodisaccharide by Pinto's group.

On the basis of our knowledge, to date, (1→*n*)-linked selenodisaccharides have been synthesized by Czernecky's group[6a] and Pinto's group.[6b] Czernecky's method exploited in situ selenolate anion formation by the reduction of symmetrical diglycosyl diselenide affected with sodium cyanoborohydride in ethanol−HMPA. This selenolate reacted with tosylated glycosyl units to yield Glc(1→6)Glc selenodisaccharides. On the other hand, Pinto's group first glyco-

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(6) (a) Czernecki, S.; Randriamandimby D. *J. Carbohydr. Chem.* **1996**, *15*, 183−190. (b) Mehta, S.; Andrews, J. S.; Johnson, B. D.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 9783−9790. (c) Wrede, F. *Z. Physiol. Chem.* **1921**, *115*, 284−304. (d) Schneider, W.; Wrede, F. *Ber.* **1917**, *50*, 793−804.

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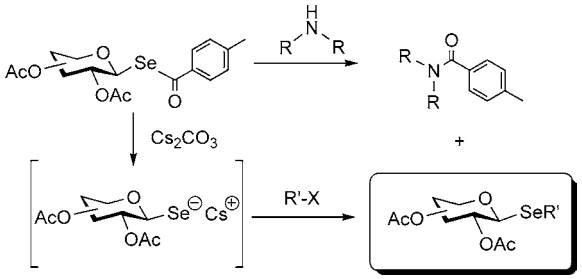
sylated a selenol mounted on an unanomeric ring carbon of glycoside with glycosyl trichloroacetimidate in the presence of a catalytic amount of TMSOTf, producing Glc(1→4)Glc selenodisaccharide. In the former method, concomitant deacetylation resulted in disaccharide yield decay (~70%), and in the latter method, the oxidation of selenolglycosyl acceptor in air to form diselenide was a drawback. The novel method that we have described in this paper can facilitate the synthesis of β-selenoglycosides by the in situ formation of anomeric selenolate anion.

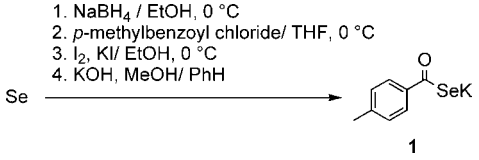
Scheme 1. New Selenoglycosylation Described in This Paper



As depicted in Scheme 1, the prominent feature of our new method is the β-glycosyl *p*-methylselenobenzoate unit that behaves as a key selenolate anion precursor. This acyl selenoglycoside that is activated by the action of a secondary amine and Cs_2CO_3 readily produces β-selenolate anion in situ; the β-selenolate anion immediately reacts with various electrophiles to yield β-selenoglycosides exclusively. Originally, this reaction was based on the selective de-*O*-acetylation at the anomeric position by hydrazine[7] or piperidine.[8] It was well-known that the seleno−carbonyl bond could be selectively activated to produce selenolate in the presence of *O*-acetyl groups because the pK_a value of selenol (10−11) is lower than that of alcohol (~16).

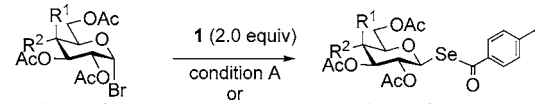
We first prepared β-glycosyl *p*-methylselenobenzoates. Potassium *p*-methylselenobenzoate **1**,[9] reported previously, was used as a selenating reagent. It has a long shelf life in a freezer and can easily be produced from *p*-methylbenzoyl chloride through the reaction sequences depicted in Scheme 2. As shown in Table 1, α-glucosyl, galactosyl, and lactosyl

Scheme 2. Preparation of Potassium *p*-Methylselenobenzoate



bromides **2** (1.0 equiv) reacted with **1** (2.0 equiv) in DMF and/or under biphasic condition in the presence of tetra-*n*-

Table 1. Synthesis of β-Acylselenoglycosides



2a R^1= H, R^2= OAc **3a** R^1= H, R^2= OAc
2b R^1= OAc, R^2= H **3b** R^1= OAc, R^2= H
2c R^1= H, R^2= Gal **3c** R^1= OAc, R^2= Gal

entry	sugar-Br	conditions[a]	time (h)	product	yield (%)
1	**2a**	A	3	**3a**	80
2	**2a**	B	2	**3a**	87
3	**2b**	A	3	**3b**	75
4	**2b**	B	1.5	**3b**	84
5	**2c**	B	3	**3c**	88

[a] Key: (A) DMF, rt; (B) ^{n}Bu$_4$NSO$_4$H (2.0 equiv), 1 M Na_2CO_3 aq/EtOAc, rt. Gal = 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyloxy.

butylammonium hydrogen sulfate as a phase-transfer catalyst. Although both conditions produced relatively high yields (75−88%) of β-acyl selenoglycosides **3** as single isomers (^{1}H NMR: $J_{1,2}$ = 10.2−10.8 Hz; ^{77}Se NMR: 622.8−630.7 ppm), biphasic conditions were employed for large-scale preparations in view of the efficacy of the workup. It should be noted that the crystalline acyl selenoglycosides were stable throughout the 6 months they were stored in a freezer.

The successfully prepared acyl β-selenoglycosides **3a** and **3b** were linked with various electrophiles **4**−**11** in the presence of an amine and Cs_2CO_3 (Figure 1, Table 2). During

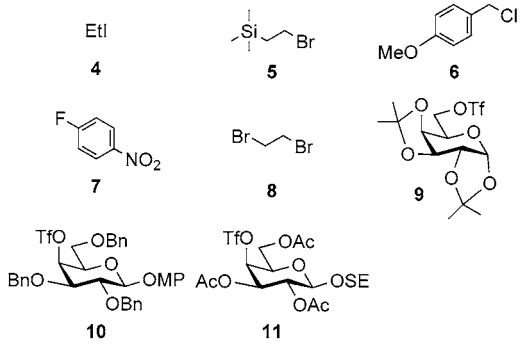
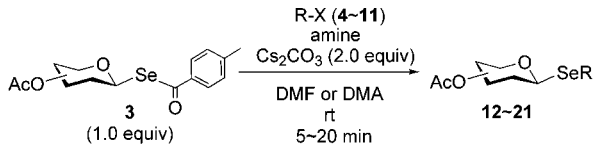


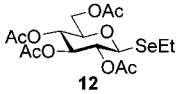
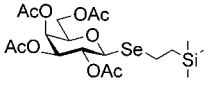
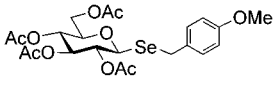
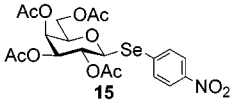
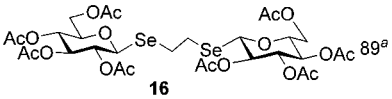
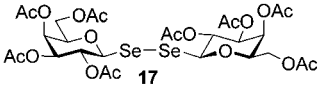
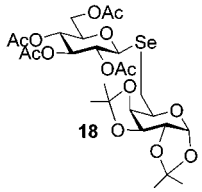
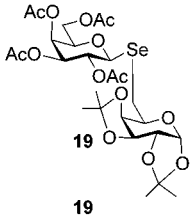
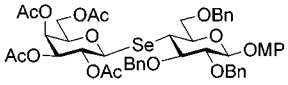
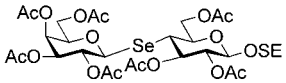
Figure 1. Coupling partners used in this study. MP = p-methoxyphenyl, Tf = trifluoromethanesulfonyl, SE = 2-(trimethylsilyl)ethyl.

the screening of a secondary amine to act as an activator, the smallest volatile amine—dimethylamine—was employed. In the case of reactions with **4**−**8**, the concomitant adduct *N*,*N*-dimethyl-*p*-methylbenzamide was not easily separated from the objective selenoglycosides by silica gel chromatography. Therefore, piperazine was used in entries 1−6 because its corresponding amide could be removed by acidic

(7) Roush, W. R.; Lin, X.-F. *J. Am. Chem. Soc.* **1995**, *117*, 2236−2250.
(8) Bovin, N. V.; Zurabyan, S. E.; Khorlin, A. Y. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1981**, 2806−2808.
(9) Ishihara, H.; Hirabayashi, Y. *Chem. Lett*. **1976**, 203−204. Ishihara, H.; Matsunami, N.; Yamada, Y. *Synthesis*, **1987**, 371−373.

Table 2. Reactions of **3** with Various Electrophiles



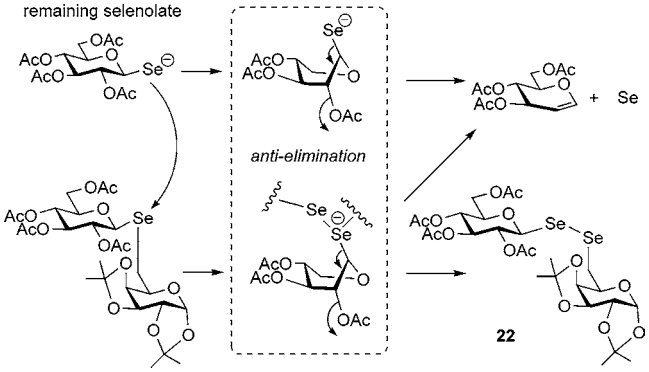
entry	R-X (equiv)	amine (equiv)	product	yield (%)
1	**4** (2.0)	PPZ (1.2)	 **12**	97
2	**5** (2.0)	PPZ (1.2)	 **13**	87
3	**6** (2.0)	PPZ (1.2)	 **14**	85
4	**7** (2.0)	PPZ (1.2)	 **15**	98
5	**8** (2.0)	PPZ (1.2)	 **16**	89[a]
6	-	PPZ (1.2)	 **17**	quant
7	**9** (4.0)	Me_2NH[b] (4.0)	 **18**	quant
8	**9** (4.0)	Me_2NH[b] (4.0)	 **19**	97
9	**9** (4.0)	PPZ (1.2)	**19**	quant
10	**10** (2.0)	Me_2NH[b] (4.0)	 **20**	92
11	**11** (2.0)	Me_2NH[b] (4.0)	 **21**	quant

[a] Yield was calculated on the basis of **8**. [b] 2.0 M solution in THF was used. DMA = *N*,*N*-dimethylacetamide. PPZ = piperazine.

aqueous workup. Consequently, alkylation with **4**, **5**, and **6** yielded the corresponding alkyl selenoglycosides **12**, **13**, and **14**, respectively, in high yields (entries 1−3). Aryl substitution with 1-fluoro-4-nitrobenzene **7** was also successful in almost quantitatively producing aryl selenoglycoside **15** (entry 4). The reaction with 1,2-dibromoethane **8** yielded symmetric diselenoethyl-tethered disaccharide **16** (entry 5). Further, in the absence of a coupling partner, **3b** could be quantitatively transformed into digalactosyl diselenide **17**[10] (entry 6). The corresponding α-isomers were not produced in any of the cases in entries 1−6.

During selenodisaccharide formation, we employed *O*-triflyl sugars **9**−**11**[11] as a glycosyl unit (entries 7−12). The acyl selenoglucoside **3a** was quantitatively incorporated with 6-*O*-triflyl-Gal derivative **9** to produce Glcβ(1→6)Gal selenodisaccharide **18** (entry 7). In this reaction, the use of excess **9** (4.0 equiv) was critical to suppress the formation of heterodiselenide **22**[12] as an inseparable byproduct, which resulted in the formation of the corresponding glucal and selenium as concomitant byproducts (Scheme 3). We rationalized the formation of these byproducts as illustrated in Scheme 3.

Scheme 3. Proposed Mechanism of Side Reaction during Selenoglycosylation



Thus, without excess electrophile **9**, the remaining β-selenolate anion decomposes to yield the corresponding triacetyl glucal and selenium via anti-elimination or it reacts with the resultant selenoglycoside to yield heterodiselenide **22**, triacetyl glucal, and selenium again via anti-elimination. In any case, in accordance with the proposed mechanism, galactosyl derivative **3b** was free from heterodiselenide formation, probably because the axially oriented C-4 acetoxy group prevented the conformational change to boat form by its steric repulsion with anomeric selenolate. In entries 8−10, dimethylamine and piperazine smoothly activated **3b** to

(10) Daniel, J. R.; Zingaro, R. A. *Phosphorus Sulfur* **1978**, *4*, 179−185.

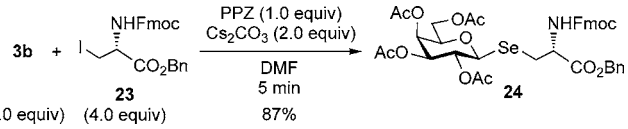
(11) For experimental details of preparation, see the Supporting Information.

(12) The structure of compound **22** was supported by MS (MALDI) and ^{1}H NMR spectrum of crude **22**; *m*/*z* (MALDI) found $[M + Na]^+$ 757.03, $C_{26}H_{33}O_{14}Se_2$ calcd for $[M + Na]^+$ 757.05; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.52 (d, J = 5.2 Hz, 1 H), 5.21 (m, 3 H), 5.10 (t, J = 9.2 Hz, 1 H), 4.94 (d, J = 9.7 Hz, 1 H), 4.64 (dd, J = 2.3, 8.0 Hz, 1 H), 4.31 (m, 2 H), 4.21 (dd, J = 5.1, 12.6 Hz, 1 H), 4.14 (dd, J = 2.3, 12.6 Hz, 1H), 4.03 (t, 1 H), 3.74 (m, 1 H), 3.23 (m, 2 H), 2.09−2.01 (4 s, 12 H), 1.59−1.32 (4 s, 12 H). For experimental details, see the Supporting Information.

produce a high yield of Galβ(1→6)Gal selenodisaccharide **19**. Further, the selenoglycosylation of less reactive 4-*O*-triflyl galactosides **10** and **11** successfully achieved selenolactose (Glcβ(1→4)Gal) frames **20** and **21** in high yields. All outcomes in entries 7−12 also retained the β-anomeric stereochemistry as confirmed by ^{1}H NMR ($J_{1,2}$ = 9.2−10.3 Hz) spectroscopy. Additionally, the resonances of the anomeric selenium in ^{77}Se NMR of compounds **18**−**21** were observed to lie in the range of 280.8−324.9 ppm, indicating the presence of acetalic selenium.

We have been the first to succeed in establishing the selenoglycosylserine structure (Scheme 4). Thus, Fmoc-

Scheme 4. Synthesis of Selenoglycosyl Serine Derivative



protected β-iodoalanine **23**,[11] which was prepared from an Fmoc-Ser derivative, swiftly reacted with selenoacyl galactoside **3b** to produce β-selenoglycosylated serine **24** with an 87% yield. Despite the anionic conditions, epimerization of the α-carbon and cleavage of the Fmoc group did not occur during the course of the reaction.

In conclusion, *p*-methylbenzoyl β-selenoglycosides **3** could be activated under mild conditions to form β-selenolates in situ, which coupled with various electrophilic partners to produce β-selenoglycosides **12**−**21** and **24** in high yields, each as a single isomer. In particular, the successful delivery of selenodisaccharide **21** and selenoglycosylamine **24** demonstrated that this method meets the criteria for practical selenooligosaccharide and selenoglycosyl peptide synthesis. These syntheses permit only acyl functionality during hydroxyl and amine protection because of the lability of selenoglycoside toward acidic, hydrogenolytic, and oxidative conditions. The easy preparation and long shelf life of **3** further reinforced the feasibility of this method. The synthesis of α-selenoglycoside will be reported in due course.

Acknowledgment. We thank Mr. Hidenori Tanaka for initial examinations on β-acylselenoglycoside synthesis. We also thank Ms. Yumiko Murase and Ms. Kyoko Sawa for technical assistance on instrumental analysis. This work was supported by MEXT of Japan (Grant-in-Aid for Scientific Research to H.A., No. 16780083) and Mitsubishi Chemical Corporation Fund (H.A.).

Supporting Information Available: Experimental details, spectral characterization, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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