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Stereoselective synthesis of various α-selenoglycosides using in situ production of α-selenolate anion

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Abstract—A large variety of α-selenoglycosides, including alkyl and aryl selenoglycosides, selenoglycosyl amino acid and selenodisaccharide have been synthesized in a stereoselective manner. The key precursor of α-anomeric selenolate anion was designed as *p*-methylbenzoyl selenoglycoside, which was synthesized by the reaction of β-glycosyl chloride with potassium *p*-methylselenobenzoate. Upon the action of piperazine or methylhydrazine in the presence of Cs_2CO_3, the acyl selenoglycoside produced an anomeric selenolate anion, which reacted in situ with various electrophilic counterparts to yield α-selenoglycoside.

Recently, the broad spectrum of use of aryl selenoglycosides as glycosyl donors has been demonstrated.[1] Aryl selenoglycoside donors can be activated in a chemoselective manner, and thioglycoside acts as its orthogonal coupling partner; hence, using aryl selenoglycosides in the synthesis of certain products appears to be an attractive option. Moreover, Yamago's group has extended the applicability of the selenoglycoside donor to iterative glycosylation, which successfully delivered an eliciter active heptasaccharide.[2] On the other hand, Pinto's group revealed that selenodisaccharides are glycosidase resistant, suggesting the potential of selenoglycoside as an alternative type of pseudoglycoside for carbohydrate-based drug development.[3] Further, taking into the account the successful use of selenium-incorporated nucleotides and peptides for multiwavelength anomalous dispersion (MAD) phasing for X-ray crystallography,[4] we have been particularly focusing on the unexplored potential of selenoglycosides as probes in the structural investigation of carbohydrate–protein complexes; the results of such an investigation will provide important information about the molecular basis underlying cell–cell, cell–virus, and cell–pathogen recognition mediated by carbohydrates.

By taking a step further forward realizing the complete potential of the contribution of selenoglycoside to glycoscience, we set an initial aim to establish a synthetic method capable of designing a large variety of selenoglycosides. Previously, we had reported a stereoselective method for *gluco*-type β-selenoglycoside synthesis that features the coupling reaction of its electrophilic counterpart and β-selenolate anion produced in situ from β-*p*-methylbenzoyl selenoglycoside in a chemoselective manner.[5] By this method, a wide spectrum of selenoglycosides linked to aryl, alkyl, amino acids, and monosaccharides were successfully synthesized. In this study, we demonstrate that the principle of our selenoglycosidation can be successfully applied to the synthesis of α-selenoglycoside.[6]

To obtain α-*p*-methylbenzoyl selenoglycoside, we first examined the synthesis of the key intermediate β-glycosyl chloride. Among our various attempts at β-chlorination, Ibatullin's method provided high yields of tetraacetylglucosyl and galactosyl chlorides; thus, the pentaacetate of glucose and galactose were reacted with PCl_5 in the presence of $BF_3{\cdot}OEt_2$ to yield **1a** and **1b**, respectively.[7]

Next, α-*p*-methylbenzoyl selenoglycoside was synthesized (Table 1). In a previous study on α-selenoglycoside synthesis,[5] β-*p*-methylbenzoyl selenoglycosides were successfully produced by the S_N2 reaction of β-bromide and potassium *p*-methylselenobenzoate under monophasic and biphasic

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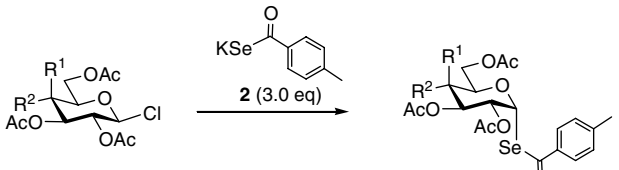
Table 1. Examination of the synthesis of α-*p*-methylbenzoyl selenoglycosides



1a R^1 = H, R^2 = OAc
1b R^1 = OAc, R^2 = H

3a R^1 = H, R^2 = OAc
3b R^1 = OAc, R^2 = H

Entry	β-Cl	Conditions[a]	Solvent	Time (h)	Product	Yield (%)
1	**1a**	A	DMF	2	**3a**	46
2	**1a**	A	Pyr	3	**3a**	34
3	**1a**	A	Diox	5.5	**3a**	11
4	**1a**	B	DMF	7	**3a**	0
5	**1a**	C	CH_2Cl_2	4	**3a**	0
6	**1b**	A	DMF	3	**3b**	65

Diox = 1,4-dioxane.
[a] (A) 18-crown-6 (3.0 equiv), rt; (B) $^nBu_4NCl$ (1.0 equiv), rt; (C) $^nBu_4NSO_4H$ (2.0 equiv), 1 M Na_2CO_3 aq, rt.

conditions. In contrast, the biphasic reaction of β-chloride and potassium *p*-methylselenobenzoate in the presence of TBAHS did not yield the desired product. The monophasic reaction yielded a complex mixture that contained α- and β-isomers and unidentified products.[8] From this mixture, a single α-isomer **3a** was obtained in a 46% yield by silica gel column chromatography and recrystallization (entry 1). Although we have examined the in situ anomerization method and the ethereal solvent-assisted α-selenoglycosidation, the α-products were not satisfactory (entries 2–5). Considering these results, the corresponding α-galactosyl selenoglycoside **3b** was prepared under similar conditions for entry 1 in a moderate yield (entry 6).[†] The α-anomeric configuration of selenoglycosides **3a** and **3b** was supported by the doublet signal of the C1 proton at 6.40 and 6.46 ppm with a coupling constant of 5.2 Hz ($J_{1,2}$) in ^{1}H NMR spectra, respectively.

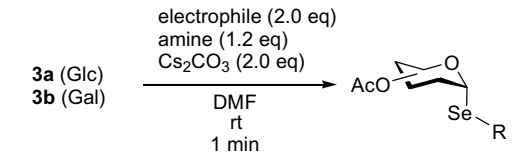
The available α-acyl selenoglycosides were reacted with electrophilic coupling partners[‡] (Table 2). As anticipated, the α-acyl selenoglycoside smoothly reacted with piperazine in the presence of Cs_2CO_3 to produce an anomeric selenolate anion that in turn reacted in situ with a coupling partner to yield the corresponding α-selenoglycoside. In contrast, α-acyl selenolate could not be produced in the absence of piperazine to recover quantitative amount of α-acyl selenoglycoside and coupling partner. In a previous paper, we have reported that piperazine has been used as the main activator with Cs_2CO_3; methylhydrazine was used as the stronger activator for comparison. In all events, the coupling reactions terminated within 1 min regardless of the type of amine. Consequently, in entries 1–5, *p*-methylbenzoyl group was successfully replaced with alkyl and aryl groups, thus giving high yields of compounds **4**–**8**. As expected, tosylated serine derivative **9**[9] functioned as a suitable electrophilic coupling partner to give α-linked selenocysteinyl galactoside **10**[10] in an 85% yield without racemization. For selenodisaccharide synthesis, 6-iodo-D-fucose derivative **11**, 4-*O*-triflyl galactoside **13**, and 4-*O*-triflyl glucoside **15** were employed as coupling partners. As a result, selenodisaccharide sequences Glc*p*α(1→6)Gal*p* (**12**), Glc*p*α(1→4)Glc*p* (**14**), and Gal*p*α(1→4)Gal*p* (**16**) were produced in high yields. Compounds **14** and **16** are the first examples of synthesized α-selenoglycoside that links to the carbon in the sugar ring. During all the reactions, the stereochemistry of selenoglycoside linkage was completely retained, thereby exclusively producing α-anomeric products. The configuration of the newly formed selenoglycosides was confirmed by ^{1}H NMR spectra ($J_{1,2}$ = 4.6–5.7 Hz). Additionally, ^{77}Se NMR spectra demonstrated that the resonance of α-amoneric selenium ranged from 152.3 to 327.1 ppm.

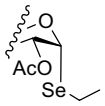
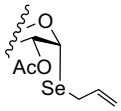
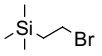
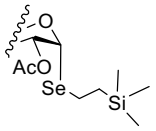
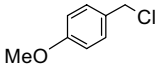
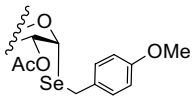
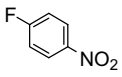
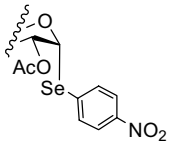
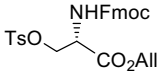
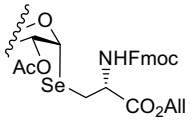
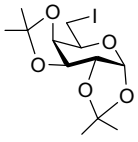
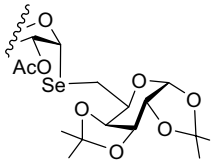
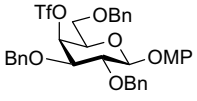
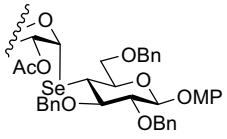
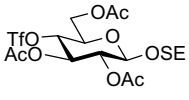
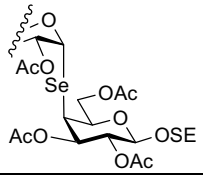
In the previous paper on β-selenoglycoside synthesis, we have reported a special case of the formation of asymmetric diselenodisaccharide and triacetyl glucal during the reaction of β-*p*-methylbenzoyl selenoglucoside with an electrophilic sugar partner.[5] We have rationalized that this was attributable to the antielimination of selenium and acetoxy anion from the corresponding boat conformer. To confirm the reaction mechanism, β- and α-*p*-methylbenzoyl selenoglycosides (**12** and **3a**) were re-

[†] *Experimental procedure of* **3b** *synthesis:* Potassium *p*-methylselenobenzoate **2** (1.29 g, 4.08 mmol) was added to a solution of compound **1b** (500 mg, 1.36 mmol) and 18-crown-6 (1.08 g, 4.08 mmol) in degassed DMF (5.0 mL) under an argon atmosphere. The mixture was stirred for 3 h at ambient temperature (TLC monitoring; EtOAc–toluene = 1:3). The reaction mixture was extracted twice with EtOAc, and the organic layer was washed with water and brine, dried over Na_2SO_4, and co-evaporated with toluene in vacuo. The residue was purified by column chromatography on silica gel (EtOAc–toluene = 1:9) and recrystallized from diethyl ether and *n*-hexane to afford **3b** as a pink needle (464 mg, 65%).

[‡] *Typical procedure of α-selenoglycosidation (the case of entry 8):* Cs_2CO_3 (76.2 mg, 234 μmol) and piperazine (12.1 mg, 140 μmol) were added to a solution of compound **3a** (62.1 mg, 117 μmol) in degassed DMF (0.5 mL) under an argon atmosphere, and successively a solution of compound **13** (352 μmol) in degassed DMF (1.0 mL) was added via cannula. The mixture was stirred for 1 min at ambient temperature (TLC monitoring; EtOAc–toluene = 1:3). The reaction mixture was extracted twice with EtOAc, and the organic layer was washed with 2 M HCl, water, satd Na_2CO_3 aq and brine, dried over Na_2SO_4, and co-evaporated with toluene in vacuo. The residue was purified by column chromatography on silica gel (EtOAc–toluene = 1:15) to afford **14** (99.9 mg, 90%).

Table 2. α-Selenoglycoside formation

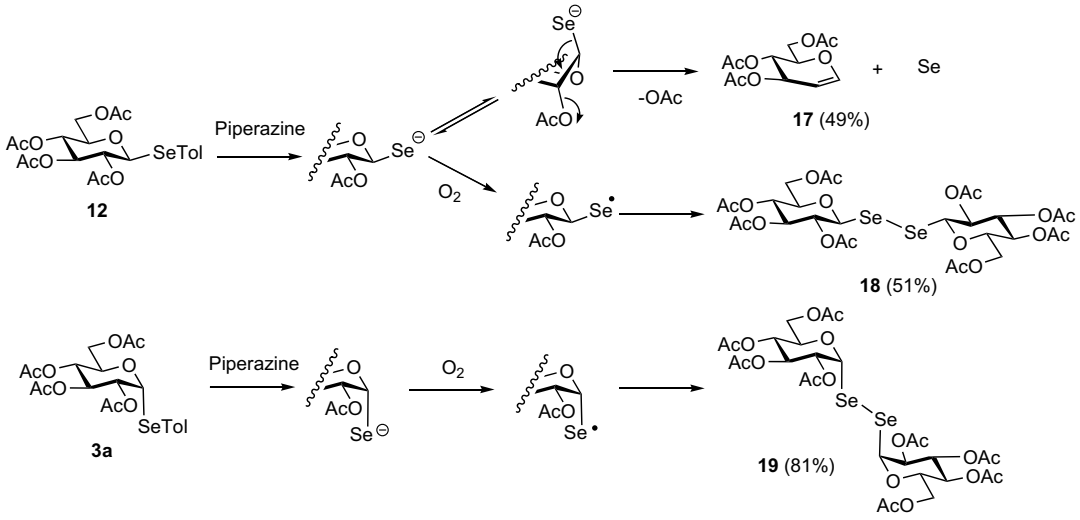


Entry	Sugar	Electrophile Base		Product		Yield (%)
1	**3a**	EtI $MeNHNH_2$			**4**	97
2	**3a**	 Piperazine			**5**	99
3	**3b**	 $MeNHNH_2$			**6**	95
4	**3a**	 $MeNHNH_2$			**7**	88
5	**3b**	 Piperazine			**8**	97
6	**3b**	 Piperazine	**9**		**10**	85
7	**3a**	 $MeNHNH_2$	**11**		**12**	90
8	**3a**	 Piperazine	**13**		**14**	90
9	**3b**	 Piperazine	**15**		**16**	89

MP = *p*-methoxyphenyl, SE = 2-(trimethylsilyl)ethyl.

acted with piperazine in the presence of Cs_2CO_3 under aerobic atmosphere, respectively (Scheme 1). The main product of the α-acyl selenoglycoside reaction was the corresponding symmetric diselenide **19**[11] without glucal formation, while the main product of the β-acyl selenoglycoside was glucal **17** (49%) and symmetric diselenide **18**[6b] (51%). In addition, the corresponding asymmetric diselenodisaccharides were not formed during the α-selenoglucosidation conducted at entries 7 and 8 shown in Table 2. This result strongly supports our proposed self-decomposition mechanism of β-glucosyl selenolate anion.

In conclusion, we have demonstrated that α-selenolate anion could be produced in situ from the corresponding *p*-methylbenzoyl selenoglycoside, which reacted rapidly



Scheme 1. Experiment on degradation of α- and β-glucosyl selenolate anion in the absence of an electrophile. Tol = *p*-methylbenzoyl.

with various electrophiles to produce a large variety of α-selenoglycosides.

Acknowledgment

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8. In the mixture the α- and β-isomers were contained in the ratio of 10/3 that was confirmed by ^{1}H NMR spectrum, while in the case of galactoside the ratio was 10/0.7.
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10. *Spectroscopic data of* **10**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77–7.31 (m, 8H, Ar), 6.05 (d, 1H, $J_{1,2} = 5.7$ Hz, H-1), 5.97–5.87 (m, 2H, C*H*=CH_2, NH), 5.45 (m, 1H, H-4^{Gal}), 5.37–5.27 (m, 2H, OCH_2CH=CH_2), 5.20 (dd, 1H, $J_{2,3} = 10.9$ Hz, H-2^{Gal}), 5.12 (dd, 1H, $J_{3,4} = 2.9$ Hz, H-3^{Gal}), 4.80 (m, 1H, $SeCH_2CH$), 4.70–4.64 (m, 2H, CH=CH_2), 4.87–4.39 (m, 3H, H-5^{Gal}, CH_2 of Fmoc), 4.25 (t, 1H, CH of Fmoc), 4.17–4.06 (m, 2H, H-6a^{Gal} and H-6b^{Gal}), 3.22–3.00 (2dd, 2H, $SeCH_2$), 2.16–2.00 (4s, 12H, 4Ac); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 170.0, 169.9, 169.8, 158.0, 155.7, 143.8, 143.6, 141.3, 131.3, 127.7, 127.7, 127.7, 127.0, 125.0, 120.0, 120.0, 119.3, 80.5, 68.8, 68.5, 68.1, 67.0, 66.4, 61.7, 54.1, 47.1, 26.3, 20.8, 20.6, 20.6, 20.5; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 161.4; *m*/*z* (MALDI): found $[M+Na]^+$ 784.15, $C_{35}H_{39}NO_{17}Se$ calcd for $[M+Na]^+$ 784.15.
11. *Spectroscopic data of* **19**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.01 (d, 2H, $J_{1,2} = 5.7$ Hz, H-1, H-1′), 5.32 (dd, 2H, $J_{2,3} = 10.3$, $J_{3,4} = 9.7$ Hz, H-3, H-3′), 5.11 (t, 2H, $J_{4,5} = 9.7$ Hz, H-4, H-4′), 4.98 (dd, 1H, H-2, H-2′), 4.32 (dd, 2H, $J_{gem} = 12.6$, $J_{5,6a} = 4.0$ Hz, H-6a, H-6′a), 4.19 (m, 2H, H-5, H-5′), 4.10 (dd, 2H, $J_{5,6b} = 2.3$ Hz, H-6b, H-6′b), 2.09–2.02 (4s, 24H, 8Ac); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 169.9, 169.5, 169.4, 83.4, 71.3, 70.7, 70.5, 67.8, 61.2, 20.6, 20.6, 20.6, 20.5; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 322.7; *m*/*z* (MALDI): found $[M+Na]^+$ 844.90, $C_{28}H_{38}O_{18}Se_2$ calcd for $[M+Na]^+$ 845.03.