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A facile method for synthesizing selenoglycosides based on selenium-transfer to glycosyl imidate

Tatsuya Suzuki [a,b], Naoko Komura [a,b], Akihiro Imamura [a], Hiromune Ando [a,b,*], Hideharu Ishida [a], Makoto Kiso [a,b,*]

[a] Department of Applied Bioorganic Chemistry, Gifu University, 1-1 Yanagido, Gifu-shi, Gifu 501-1193, Japan
[b] Institute for Integrated Cell-Material Sciences (WPI-iCeMS), Kyoto University, Yoshida Ushinomiya-cho, Sakyo-ku, Kyoto 606-8501, Japan

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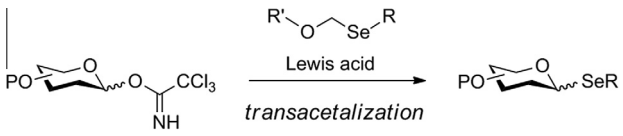
ABSTRACT

A facile reaction for constructing selenoglycosides has been developed based on the transacetalization reaction between a selenoacetal and a glycosyl imidate. Glycosyl imidates were activated with TMSOTf to produce oxocarbenium ion, which reacted with benzyloxymethyl alkyl (aryl) selenide, providing alky (or aryl) selenoglycosides in high yields. Furthermore, this reaction was utilized in the synthesis of 2-(trimethylsilyl)ethylselenoglycoside, which, upon treatment with TBAF in the presence of an electrophile, was transformed into other selenoglycosides.

Organoselenium compounds have broad applications in organic synthesis, where the dual characteristics of selenium as both a nucleophile and an electrophile are deliberately utilized. Recently, organoselenium compounds have also emerged as crucial therapeutic compounds that exhibit antiviral and anticancer activities.[1] Among organoselenium compounds, seleno-carbohydrates have been widely utilized as glycosyl donors in oligosaccharide synthesis, where an arylselenyl group introduced at the anomeric position functions as a leaving group during glycosylation.[2] In crystallography, by taking advantage of the anomalous dispersion of selenium in response to X-ray irradiation, the methylselenoglycoside of *N*-acetylglucosamine was successfully utilized as a carbohydrate ligand mimetic in X-ray structural determination of carbohydrate-binding protein with multi-wavelength anomalous dispersion (MAD) phasing.[3] On the basis of a similar principle, dodecyl-β-selenomaltoside has been successfully utilized as a selenium agent for MAD phasing in X-ray structural analysis of a membrane protein and as a detergent for stabilizing the protein in water.[4]

The introduction of selenium at the anomeric position of a monosaccharide can be achieved by treating a glycosyl halide with selenium under sodium borohydride reduction conditions,[5] or with alkyl (aryl) selenolate, which is generated in situ from the corresponding dialkyl (aryl) diselenide upon reaction with a hydride reducing agent,[6] Zn–$ZnCl_2$,[7] or InI.[8] Alternatively, reaction of glycosyl halide with acyl selenolates can provide acyl selenoglycosides.[9] Recent studies have shown that *p*-methylbenzoylselenoglycosides could be converted into a variety of selenoglycosides chemoselectively.[10] Arylselenoglycosides are obtained from glycosyl acetate by treatment with arylselenol generated in situ in the presence of $BF_3{\cdot}OEt_2$[2a] or by treatment with $Me_2Sn(SePh)_2$ and $Bu_2Sn(OTf)_2$.[11] Furthermore, the conversion of glycals into phenylselenoglycosides has been successfully demonstrated. However, the application of these methods in the modification of oligosaccharides as seleno-glycosyl donors or as seleno-carbohydrate mimetics remains difficult, mainly due to poor compatibility with the chemistry used in oligosaccharide synthesis. Therefore, a method for preparing selenoglycosides that is highly compatible with oligosaccharide synthesis is necessary to extend the potential of



Scheme 1. Outline of selenoglycoside formation through transacetalization between selenoacetal and glycosyl imidate.

* Corresponding authors. Tel./fax: +81 58 293 3452 (H.A.).
E-mail address: hando@gifu-u.ac.jp (H. Ando).

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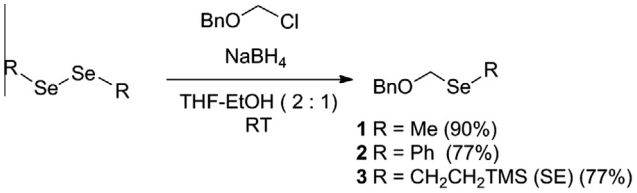


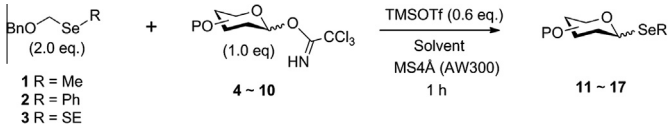
Scheme 2. Synthesis of bezyloxymethyl alky (aryl) selenides **1**–**3**.

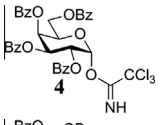
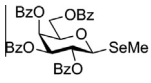
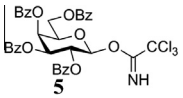
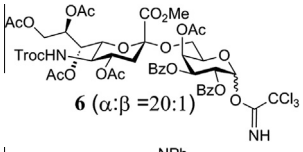
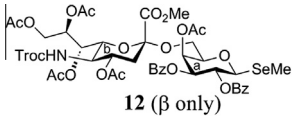
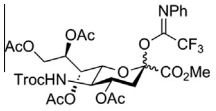
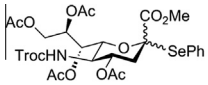
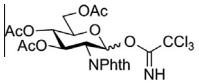
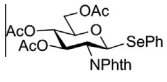
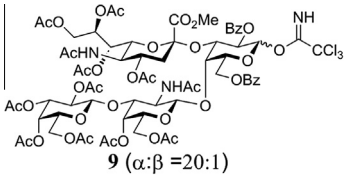
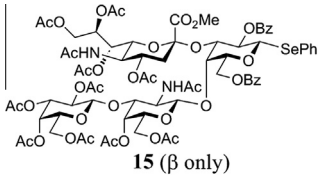
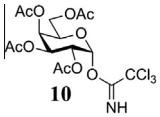
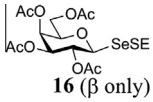
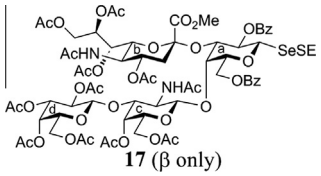
selenoglycosides, not only as synthetic intermediates but also as carbohydrate mimetics. In this Letter, we report a new synthetic method for selenoglycosides that also allows for the modification of oligosaccharides.

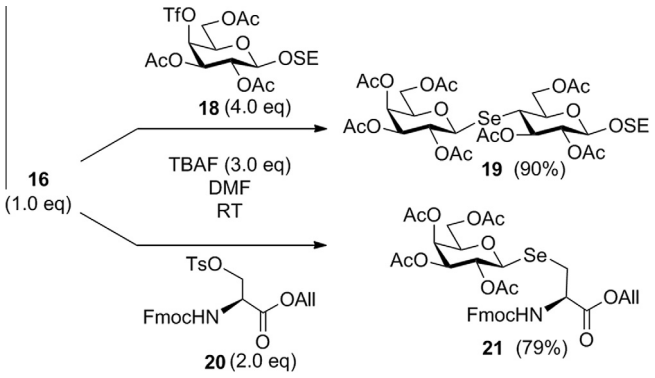
Inspired by the transacetalization reaction between a glycosyl imidate and a thioglycoside in the presence of a catalytic amount of Lewis acid—a reaction that was often observed as an undesired side reaction during glycosylation[12]—we envisioned a selenoglycoside formation method that utilizes a simple mix selenoacetal and a glycosyl imidate (Scheme 1).

We expected that selenium-transfer to an oxocarbenium ion would occur more efficiently than sulfur transfer, due to higher nucleophilicity of selenium. Benzyloxymethyl alkyl selenide (BOMSeR) was designed as a selenoacetal, in which the benzyl group functions as an electron-donating group and as a UV-sensitive group, to facilitate the monitoring of reactions by thin layer chromatography. The synthesis of BOMSeMe **1** and BOMSePh **2** was carried out by following a straightforward procedure for the

Table 1
Results for reactions of selenoacetal **1**–**3** with various glycosyl imidates **4** to **10**



Entry	Reagent	Glycosyl imidate	Solvent	Temp (°C)	Product	Yield (%)
1	**1**	 **4**	CH_2Cl_2	−40	 **11** (β only)	99
2	**1**	 **5**	CH_2Cl_2	−40	**11** (β only)	80
3	**1**	 **6** (α:β =20:1)	CH_2Cl_2-EtCN (1:1)	−40	 **12** (β only)	87
4	**2**	 **7** (α:β =1:2.2)	EtCN	−80	 **13** (α:β =2:1)	90
5	**2**	 **8** (α:β =1:7.9)	CH_2Cl_2	−20	 **14** (β only)	93
6	**2**	 **9** (α:β =20:1)	CH_2Cl_2-EtCN (1:1)	0	 **15** (β only)	92
7	**3**	 **10**	CH_2Cl_2	−40	 **16** (β only)	98
8	**3**	**9** (α:β = 20:1)	CH_2Cl_2-EtCN (1:1)	0	 **17** (β only)	85



Scheme 3. Conversion of 2-(trimethylsilyl)ethylselenoglycoside into other selenoglycosides.

alkylation of selenium: commercially available diselenides were reacted with BOMCl in the presence of $NaBH_4$ in THF-EtOH at room temperature, affording **1** and **2**, respectively (Scheme 2).[†] Similarly, di-2-(trimethylsilyl)ethyl diselenide[13] was successfully converted into the corresponding selenoacetal, thus giving **3** (BOMSeSE) in 77% yield.[14]

Next, we reacted the selenoacetals with glycosyl imidates. The optimized reaction conditions and the results obtained are summarized in Table 1.[‡] In entry 1, α-tetrabenzylgalactosyl imidate **4** and BOMSeMe **1** were reacted at −40 °C by the catalytic action of TMSOTf in the presence of acid-washed molecular sieves (AW-300) in CH_2Cl_2. This reaction produced β-methylselenoglycoside **11**. To obtain the best yield of **11** (99%), 2.0 equiv of **1** and 0.6 equiv of TMSOTf were used. When using 1.0 equiv of **1**, the yield decreased to 74% and benzyl β-glycoside was obtained in 9% yield as a byproduct. In entry 2, the β-isomer of **4** (**5**) also provided exclusively β-selenoglycoside **11** in high yield. In contrast, the reaction of disaccharyl imidate **6** with **1** in CH_2Cl_2 produced an anomeric mixture of selenoglycosides **12** (90%, $\alpha:\beta$ = 87:3), which were inseparable by chromatographic methods. Therefore, in entry 3, nitrile solvent was used as the co-solvent to direct β-selectivity,[15] thereby giving **12** as a single isomer in 87% yield. Similar to BOMSeMe, BOMSePh **2** produced selenoglycosides in high yields. Thus, sialyl imidate **7** and glucosaminyl imidate **8** were converted into phenyl selenoglycosides **13** and **14** in high yields, respectively (entries 4 and 5). Furthermore, the conversion of tetrasaccharyl imidate **9** into phenylselenoglycoside **15** was accomplished in excellent yields (entry 6). In entries 7 and 8, BOMSeSE **3** was shown to possess similar reactivity to that of **1** and **2**, providing high yields of the corresponding mono- and oligo-saccharyl selenoglycosides **16** and **17**.[16]

By the reported reaction of the 2-(trimethylsilyl)ethylselenyl group with TBAF to generate selenolate anion,[13,17] selenoglycoside **16** could be converted into glycosyl selenolate, which reacted in situ with electrophiles **18** and **20** to yield seleno-disaccharide **19** and glycosyl selenocystein **21**,[18] respectively in high yields while retaining the anomeric stereochemistry (Scheme 3).

In conclusion, transacetalization using BOMSeR (**1**–**3**) and glycosyl imidates has been shown to be an efficient, facile method for synthesizing various selenoglycosides. Since selenium-transfer proceeds under conditions similar to the conditions for imidate glycosidation, this method will be a reliable option for the synthesis of oligosaccharyl selenoglycosides. In addition, we demonstrated that 2-(trimethylsilyl)ethyl selenoglycoside served as a synthetic equivalent of glycosyl selenolate, which will be useful for synthesizing a selenoglycoside between the residues of oligosaccharides.

Acknowledgement

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14. *Spectroscopic data of compound* ***3****;* $[\alpha]_D$ −2.7° (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.28 (m, 5 H, Ph), 5.06 (s, 2 H, $SeCH_2O$), 4.61 (s, 2 H, $PhCH_2$), 2.76 (s, 2 H, CH_2CH_2TMS), 1.04 (s, 2 H, CH_2TMS), 0.27 (s, 9 H, TMS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 144.3, 136.9, 129.4, 127.2, 21.7, 21.4, 18.9, −1.9; ^{77}Se-NMR (95 MHz, $CDCl_3$) δ 258.1; *m/z* (ESI): found $[M+Na]^+$ 325.0501, $C_{13}H_{22}OSe$ calcd for $[M+Na]^+$ 325.0497.
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[†] *Typical procedure for the synthesis of BOMSeR (the case of BOMSePh* ***2****):* Sodium borohydride (132 mg, 3.50 mmol) and ethanol (3.2 mL) were added to a solution of diphenyldiselenide (500 mg, 1.61 mmol) in THF (6.4 mL) at 0 °C under argon atmosphere, and the reaction mixture was stirred for 10 min. Then, BOMCl (500 μL, 3.63 mmol) was added, and stirring was continued for 1.5 h at ambient temperature. Completion of reaction was confirmed by TLC analysis ($CHCl_3$/*n*-hexane = 1/1). After quenched by addition of satd aq NH_4Cl (10 mL), the mixture was extracted with CH_2Cl_2 three times. The combined organic solution was dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/*n*-hexane = 1/10) to give **2** (621 mg, 77%) as a colorless syrup.

[‡] *Typical procedure for selenoglycoside formation with BOMSeR (the case of entry 3 of Table 1):* A mixture of selenoacetal **2** (75 mg, 269 μmol), glycosyl imidate **4** (100 mg, 135 μmol), and AW-300 (135 mg) in CH_2Cl_2 was stirred for 30 min under argon atmosphere, and cooled to −40 °C, to which TMSOTf (16.4 μL, 81 μmol) was then added. The reaction mixture was stirred for 1 h at −40 °C as the progress of the reaction was monitored by TLC analysis (EtOAc/*n*-hexane = 1/4). After satd aq Na_2CO_3 (1.0 mL) was added to quench the reaction, the mixture was diluted with $CHCl_3$, filtered through a pad of Celite and washed with $CHCl_3$. The combined filtrate and washings were washed with satd aq $NaHCO_3$, and the organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane = 1/8) to give **11** (98 mg, 99%) as a colorless syrup.

16. *Spectroscopic data of selected compounds; compound* ***12****;* $[\alpha]_D$ 24.7° (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.99–7.33 (m, 10 H, Ph), 5.79 (d, 1 H, $J_{3,4}$ = 3.0 Hz, H-4^a), 5.74 (t, 1 H, $J_{1,2}$ = $J_{2,3}$ = 10.0 Hz, H-2^a), 5.53 (dd, 1 H, H-3^a), 5.43 (m, 1 H, H-8^b), 5.36 (dd, 1 H, $J_{6,7}$ = 1.6 Hz, $J_{7,8}$ = 9.3 Hz, H-7^b), 5.02–4.95 (m, 2 H, H-1^a, H-4^b), 4.92–4.89 (m, 2 H, NH, Cl_3CCH_2), 4.50 (d, 1 H, J_{gem} = 12.0 Hz, Cl_3CCH_2), 4.39 (dd, 1 H, $J_{8,9a}$ = 2.4 Hz, J_{gem} = 12.4 Hz, H-9a^b), 4.22 (dd, 1 H, $J_{5,6}$ = 10.8 Hz, H-6^b), 4.17–4.10 (m, 2 H, H-5^a, H-9b^b), 3.85–3.80 (m, 4 H, H-6a^a, COOMe), 3.62 (m, 1 H, H-5^b), 3.49 (dd, 1 H, $J_{5,6b}$ = 8.0 Hz, J_{gem} = 10.7 Hz, H-6b^a), 2.59 (dd, 1 H, $J_{3ax,4}$ = 4.7 Hz, J_{gem} = 12.9 Hz, H-3ax^b), 2.22–2.00 (m, 18 H, Ac, $SeCH_3$), 1.88 (t, 1 H, $J_{3eq,4}$ = 12.9 Hz, H-3eq^b); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 170.5, 170.3, 169.8, 169.7, 167.8, 165.5, 165.3, 154.0, 133.2, 133.2, 129.8, 129.6, 129.3, 129.2, 128.3, 99.1, 95.4, 77.2, 76.4, 74.5, 72.5, 72.1, 68.6, 68.0, 67.9, 67.7, 67.3, 63.1, 62.6, 60.4, 53.0, 51.5, 38.0, 31.5, 22.6, 21.0, 20.8, 20.6, 14.2, 14.1, 2.6; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 209.4; HRMS: *m*/*z* (ESI): found $[M+Na]^+$ 1136.0998, $C_{44}H_{50}Cl_3NO_{21}Se$ calcd for $[M+Na]^+$ 1136.0998; *Spectroscopic data of compound* ***15****;* $[\alpha]_D$ −4.9° (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.14–7.22 (m, 15 H, Ph), 5.55 (m, 1 H, H-8^b), 5.36–5.34 (m, 2 H, H-4^c, H-4^d), 5.28–5.24 (m, 2 H, H-2^a, NH^c), 5.18–5.15 (m, 3 H, H-7^b, H-1^c, H-2^d), 5.07–5.04 (m, 2 H, H-1^a, NH^b), 4.99–4.95 (m, 2 H, H-3^c, H-3^d), 4.75 (m, 1 H, H-4^b), 4.61–4.56 (m, 2 H, H-6a^a, H-1^d), 4.48 (dd, 1 H, $J_{3,4}$ = 2.5 Hz, $J_{2,3}$ = 9.5 Hz, H-3^a), 4.38 (dd, 1 H, $J_{5,6a}$ = 6.0 Hz, J_{gem} = 11.4 Hz, H-6b^a), 4.22 (dd, 1 H, $J_{8,9a}$ = 2.4 Hz, J_{gem} = 12.5 Hz, H-9a^b), 4.14–4.10 (m, 2 H, H-6a^c, H-6b^c), 4.00 (dd, 1 H, $J_{5,6a}$ = 5.4 Hz, J_{gem} = 11.6 Hz, H-6a^d), 3.85–3.80 (m, 5 H, H-5^a, H-5^b, H-9b^b, H-5^c, H-6b^d), 3.76 (s, 3 H, COOMe), 3.74–3.69 (m, 3 H, H-4^a, H-6^b, H-5^d), 2.95 (m, 1 H, H-2^c), 2.73 (dd, 1 H, $J_{3ax,4}$ = 4.4 Hz, J_{gem} = 13.1 Hz, H-3ax^b), 2.18–1.78 (m, 37 H, H-3eq^b, Ac); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 171.1, 170.8, 170.6, 170.3, 170.3, 170.1, 169.9, 169.9, 169.1, 168.3, 165.8, 164.8, 136.4, 133.1, 130.2, 130.1, 130.0, 129.6, 128.4, 128.4, 128.2, 128.2, 127.4, 101.3, 98.3, 97.4, 81.0, 77.6, 77.2, 76.4, 74.1, 74.0, 72.7, 71.8, 70.8, 70.8, 70.4, 69.5, 69.5, 69.0, 69.0, 68.8, 67.4, 66.8, 66.4, 63.7, 62.7, 62.3, 60.9, 60.4, 55.2, 53.8, 52.6, 49.1, 36.9, 31.7, 29.6, 29.2, 24.0, 23.0, 21.3, 21.0, 20.9, 20.8, 20.7, 20.7, 20.6, 20.5, 20.3, 20.1, 14.2; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 426.0; *m*/*z* (ESI): found $[M+Na]^+$ 1641.4069, $C_{72}H_{86}N_2O_{35}Se$ calcd for $[M+Na]^+$ 1641.4069; *Spectroscopic data of compound* ***17****;* $[\alpha]_D$ 5.2° (*c* 1.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.12-7.42 (m, 10 H, Ph), 6.02 (d, 1 H, $J_{2,NH}$ = 7.0 Hz, NH^c), 5.57 (m, 1 H, H-8^b), 5.49 (t, 1 H, $J_{1,2}$ = $J_{2,3}$ = 10.0 Hz, H-2^a), 5.36–5.34 (m, 2 H, H-4^c, H-4^d), 5.22 (dd, 1 H, $J_{6,7}$ = 2.5 Hz, $J_{7,8}$ = 10.0 Hz, H-7^b), 5.15 (d, 1 H, $J_{1,2}$ = 8.5 Hz, H-1^c), 5.12 (dd, 1 H, $J_{1,2}$ = 8.0 Hz, $J_{2,3}$ = 10.0 Hz, H-2^d), 5.07–5.04 (m, 2 H, H-1^a, NH^b), 4.98–4.94 (m, 2 H, H-3^c, H-3^d), 4.87 (m, 1 H, H-4^b), 4.66–4.60 (m, 2 H, H-6a^a, H-1^d), 4.46 (dd, 1 H, $J_{3,4}$ = 2.5 Hz, H-3^a), 4.35 (dd, 1 H, $J_{5,6b}$ = 6.5 Hz, J_{gem} = 12.5 Hz, H-6b^a), 4.26 (dd, 1 H, $J_{8,9a}$ = 2.0 Hz, J_{gem} = 12.5 Hz, H-9a^b), 4.16–4.09 (m, 2 H, H-6a^c, H-6b^c), 4.02–3.98 (m, 2 H, H-9b^b, H-5^d), 3.92–3.75 (m, 10 H, H-4^a, H-5^a, H-5^b, H-6^b, H-5^c, H-6a^d, H-6b^d, COOMe), 3.38 (m, 1 H, H-2^c), 2.83–2.73 (m, 3 H, H-3ax^b, $TMSCH_2CH_2$), 2.23–1.80 (m, 37 H, H-3eq^b, Ac), 0.95–0.90 (m, 2 H, $TMSCH_2$), −0.06 (s, 9 H, TMS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 170.9, 170.6, 170.4, 170.4, 170.3, 170.2, 170.0, 170.0, 169.2, 168.3, 165.9, 165.3, 133.2, 133.1, 130.2, 129.9, 129.8, 129.5, 128.4, 128.4, 101.1, 98.9, 97.7, 78.3, 74.1, 73.8, 73.8, 71.8, 70.8, 70.7, 70.4, 70.1, 69.0, 68.8, 67.3, 66.7, 66.4, 64.1, 62.6, 62.2, 60.8, 55.1, 53.7, 52.7, 49.1, 36.8, 31.7, 29.6, 29.2, 23.9, 23.1, 21.3, 20.8, 20.8, 20.7, 20.6, 20.5, 20.4, 20.2, 19.6, 18.1, -1.9; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 343.6; *m*/*z* (ESI): found $[M+Na]^+$ 1665.4460, $C_{71}H_{94}N_2O_{35}SeSi$ calcd for $[M+Na]^+$ 1665.4464.

17. Garud, D. R.; Ando, H.; Kawai, Y.; Ishihara, H.; Koketsu, M. *Org. Lett.* **2007**, *9*, 4455–4458.

18. *Spectroscopic data of compound* ***21****;* $[\alpha]_D$ −32.2° (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.77–7.30 (m, 8 H, Ar), 5.98 (d, 1 H, *J* = 8.0 Hz, NH), 5.90 (m, 1 H, CH of Allyl), 5.40 (m, 1 H, H-4), 5.36–5.25 (m, 3 H, CH=CH_2 of Allyl, H-2), 5.01 (dd, 1 H, $J_{3,4}$ = 3.4 Hz, $J_{2,3}$ = 10.3 Hz, H-3), 4.74 (d, 1 H, $J_{1,2}$ = 9.7 Hz, H-1), 4.67–4.66 (m, 3 H, CH–CH_2 of Allyl, CH of Cys), 4.55 and 4.35 (2 dd, 2 H, CH_2 of Fmoc), 4.26 (dd, 1 H, CH of Fmoc), 4.11–4.03 (m, 2 H, H-6a, H-6b), 3.80 (m, 1 H, H-5), 3.32 and 3.10 (2 dd, 2 H, CH_2 of Cys), 2.10–1.94 (4 s, 12 H, 4 Ac); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 170.1, 170.0, 169.7, 169.7, 155.9, 143.8, 143.6, 141.2, 131.4, 131.4, 127.7, 127.1, 125.1, 124.9, 120.0, 120.0, 118.9, 77.8, 75.8, 71.4, 67.6, 67.1, 66.9, 66.3, 61.5, 54.3, 47.0, 24.9, 20.8, 20.5, 20.5, 20.4; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 280.0; *m*/*z* (ESI): found $[M+Na]^+$ 784.1479, $C_{35}H_{39}NO_{13}Se$ calcd for $[M+Na]^+$ 784.1479.