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Photocatalyzed Oxidative Decarboxylation Forming Aminovinylcysteine Containing Peptides †

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† This paper is dedicated to late Professor Jiro Tsuji.

Abstract: The formation of (2*S*,3*S*)-*S*-[(*Z*)-aminovinyl]-3-methyl-D-cysteine (AviMeCys) substructures was developed based on the photocatalyzed-oxidative decarboxylation of lanthionine-bearing peptides. The decarboxylative selenoetherification of the *N*-hydroxyphthalimide ester, generated in situ, proceeded under mild conditions at −40 °C in the presence of 1 mol% of eosin Y-Na_2 as a photocatalyst and the Hantzsch ester. The following β-elimination of the corresponding *N*,*Se*-acetal was operated in a one-pot operation, led to AviMeCys substructures found in natural products in moderate to good yields. The sulfide-bridged motif, and also the carbamate-type protecting groups, such as Cbz, Teoc, Boc and Fmoc groups, were tolerant under the reaction conditions.

Keywords: (2*S*,3*S*)-*S*-[(*Z*)-aminovinyl]-3-methyl-D-cysteine (AviMeCys); photocatalytic reaction; oxidative decarboxylation; ribosomally synthesized and post-translationally modified peptides (RiPPs); β-thioenamide; *N*-hydroxyphthalimide (NHPI) ester; Eosin Y

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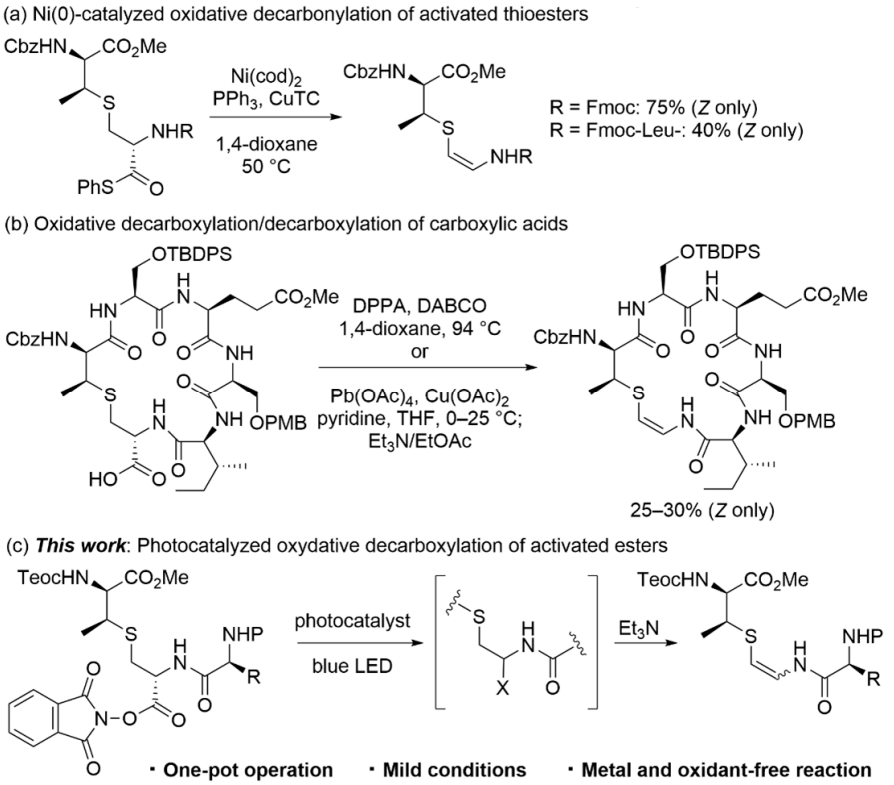
1. Introduction

Ribosomally synthesized and post-translationally modified peptides (RiPPs) are one of the largest classes of natural products that exhibit various biological properties [1–3]. Among the diverse substructures found in RiPPs, cross-linked sulfides between two amino acid residues have been identified as an important chemical functionality for constrained conformation in the peptide backbone, providing high target specificity and biological stability [4–7]. The major components of RiPPs with thioether bonds are (2*S*,6*R*)-lanthionine (Lan) and (2*S*,3*S*,6*R*)-3-methyllanthionine (β-MeLan). Thioether-bridged units in Lan/β-MeLan are biosynthetically constructed through a conjugated addition of thiols of cysteine residues to dehydroalanine (Dha)/dehydrobutyrine (Dhb) [8,9]. Intriguingly, (*Z*)-thioenolates, which are generated by the oxidative decarboxylation of cysteine residues positioned at the C-terminal, also attack Dhb/Dha residues to produce *S*-[(*Z*)-aminovinyl]-D-cysteine (AviCys) and (2*S*,3*S*)-*S*-[(*Z*)-aminovinyl]-3-methyl-D-cysteine (AviMeCys), respectively. Owing to β-thioenamide units including sp^2 α-carbons in the peptide backbone, AviCys/AviMeCys are attractive substructures for improving the structural rigidity and drug-like properties of cyclopeptides [10–12].

Biosynthesis-inspired approaches to obtain lanthionines have been accomplished through the stereoselective conjugated addition of thiols of cysteine derivatives to Dha/Dhb derivatives [13–15], whereas the synthesis of AviCys/AviMeCys motifs in a similar manner is a difficult task due to the chemical instability of thioenolates [16]. Thus, alternative methodologies for constructing AviCys/AviMeCys have been developed to date. There have been several reports on the synthesis of AviCys substructures by condensation using primary amides and α-thioaldehyde/acetals [17,18] and the β-addition of thiyl radicals to terminal ynamides [19]. However, the methodologies for constructing AviMeCys substructures in complex natural products are limited. One of the efficient approaches is a decarboxylative

olefination of carboxylic acid derivatives, as in the palladium-catalyzed reaction of allyl β-ketoesters reported by Tsuji [20]. Recently, oxidative decarboxylation/decarbonylation using lanthionine units has been reported for the AviMeCys formation. VanNieuwenhze et al. reported *Z*-selective AviMeCys formation via nickel(0)-promoted decarbonylation of activated thioesters in short peptide fragments during the synthesis of D-ring in mersacidin (Scheme 1a) [21]. Furthermore, they realized the direct conversion from carboxylic acids through two procedures: (i) Curtius rearrangement using diphenylphosphoryl azide (DPPA), followed by the collapse of the resulting isocyanate, and (ii) oxidative decarboxylation using lead tetraacetate, followed by the elimination of the resulting acetate (Scheme 1b) [22]. Nevertheless, there is no report on the total synthesis of any AviMeCys-containing natural peptides, due to harsh conditions and an excess amount of toxic oxidants during oxidative decarboxylation/decarbonylation steps in the late-stages of the synthesis. Considering the tolerance to functional groups in RiPPs, we focused on photocatalytic reactions mediated by visible light, which have been widely used in the modification of amino acids and peptides [23–25]. We envisioned that a radical species, generated from a *N*-hydroxyphthalimide (NHPI) ester of the corresponding lanthionine by oxidative decarboxylation [26], can be readily trapped in the presence of oxidation-sensitive sulfides under mild conditions. The following β-elimination with a weak base would yield the desired β-thioenamide motifs, suppressing the retro-thio-Michael reaction (Scheme 1c). Herein, we report the β-thioenamide formation through the photocatalyzed oxidative decarboxylation of lanthionine derivatives. A series of reactions were conducted in a one-pot operation under mild conditions, providing AviMeCys units with functional group compatibility.

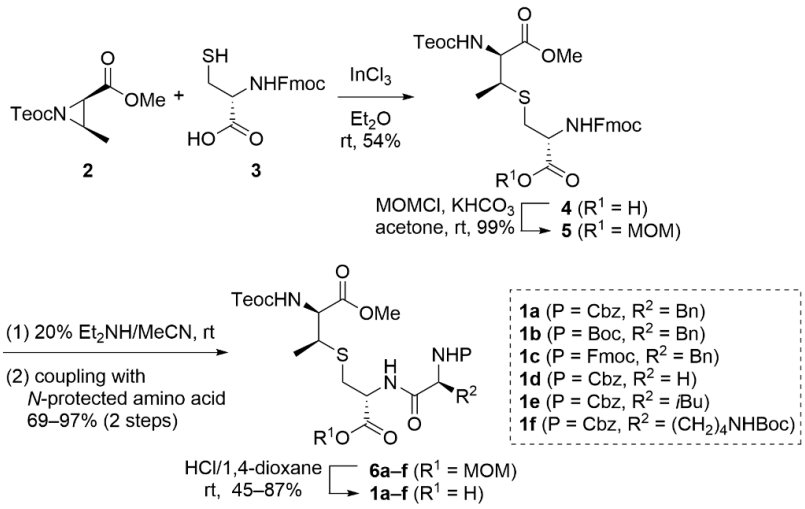


Scheme 1. AviMeCys formation via decarboxylation/decarbonylation of lanthionine derivatives.

2. Results and Discussion

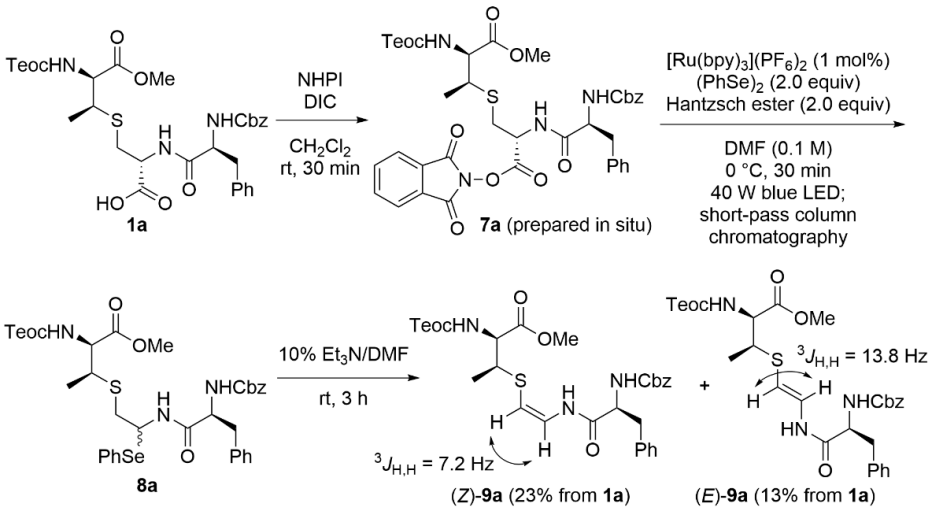
Our study began with the preparation of the lanthionine-containing peptides **1**, as shown in Scheme 2. According to the procedure reported by VanNieuwenhze [27], the regioselective ring-opening of the *N*-{2-(trimethylsilyl)ethoxycarbonyl} (Teoc)-protected aziridine **2**, which was prepared from D-threonine, with Fmoc-Cys-OH (**3**) was performed in the presence of indium(III) chloride, providing the lanthionine derivative **4** in a 54% yield.

The subsequent protection of the carboxylic acid group with a methoxymethyl (MOM) group provided the MOM ester **5** in a 99% yield. The removal of the Fmoc group in **5** with 20% diethylamine/acetonitrile, followed by the coupling of the resulting amine with *N*-protected amino acids afforded the peptides **6a–f** over two steps. Finally, the MOM group in **5** was removed under acidic conditions, yielding the carboxylic acids **1a–f**.



Scheme 2. Preparation of the lanthionine-bearing peptides **1**.

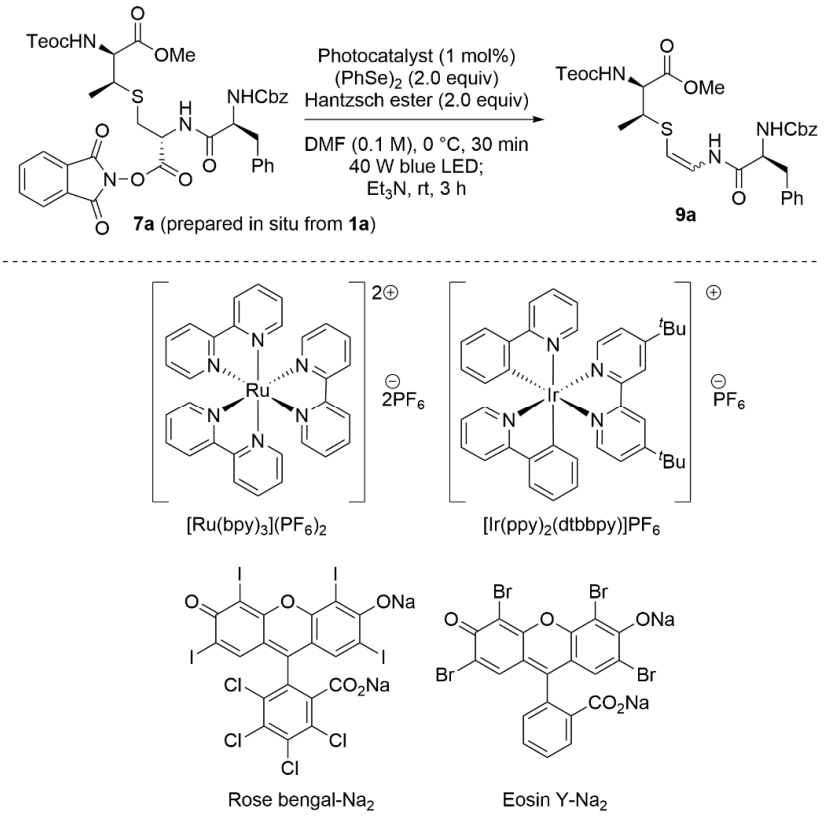
Next, we surveyed the formation of the AviMeCys unit using **1a** as the model lanthionine-bearing peptide as shown in Scheme 3. Given the immediate capture of the resulting radical species during the oxidative decarboxylation [28–30], diphenyl diselenide was selected as a radical trapping agent [31,32]. In addition, we envisioned that the resulting *N*,*Se*-acetal would be converted into the corresponding β-thioenamide without losing the β-methylcysteine unit due to high leaving activity of phenylselenolates [33–35]. According to the reported procedures [32,36,37], the NHPI ester **7a**, prepared from **1a** in situ, was treated with 1 mol% of $[Ru(bpy)_3](PF_6)_2$ as the photocatalyst in the presence of the Hantzsch ester and diphenyl diselenide under 40 W blue light-emitting diode (LED) irradiation. The following β-elimination of the obtained selenoether **8a** by treatment with triethylamine furnished the β-thioenamieds (*Z*)-**9a** and (*E*)-**9a** in 23% and 13% yields, respectively. The geometry of olefins in (*Z*)-**9a** and (*E*)-**9a** was determined by ^{1}H nuclear magnetic resonance (NMR) spectroscopy through the coupling constants ($^3J_{H,H}$ = 7.2 Hz for (*Z*)-**9a**, and 13.8 Hz for (*E*)-**9a**) of isolated compounds [19].



Scheme 3. Photocatalytic selenoetherification/β-elimination of the lanthionine-bearing peptide **1a**.

As a moderate yield was observed, we conducted the screening of photocatalysts, as shown in Table 1. When selenoetherification, followed by β-elimination was conducted in a one-pot operation, the combined yields of (*Z*)-**9a** and (*E*)-**9a** were slightly up to 49% (entry 1). After the optimization of metal and organic photosensitizers, eosin Y-Na_2 [38] promoted the transformation to increase the yields by up to 59% (entries 2–4). Intriguingly, selenoetherification of **7a** proceeded without eosin Y-Na_2, albeit with slightly lower yields, suggesting that the formation of the electron donor-acceptor (EDA) complex between the NHPI and Hantzsch esters should promote the reaction (entry 5) [39,40]. No product was obtained in the absence of the blue light (entry 6).

Table 1. Preliminary screening of photocatalysts for selenoetherification/β-elimination [a].



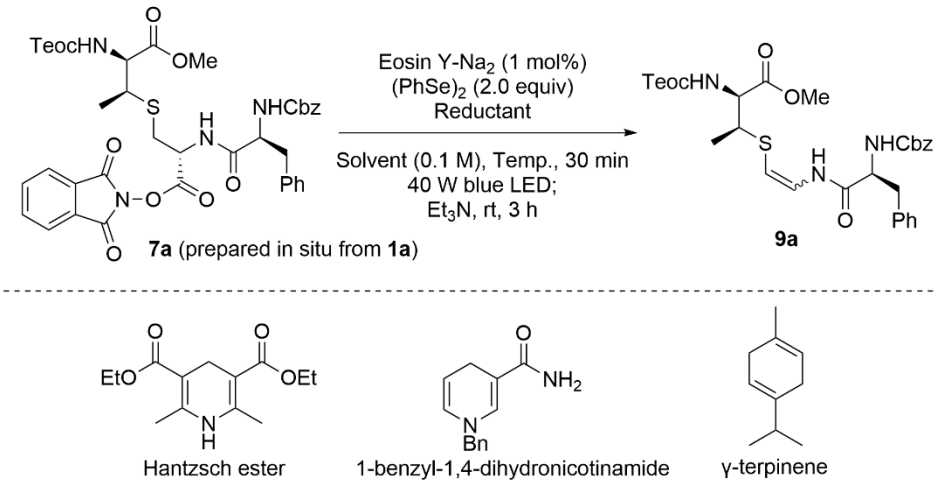
Entry	Photocatalyst	Yield [b]
1	$[Ru(bpy)_3](PF_6)_2$	49% (*Z*: 28%, *E*: 21%)
2	$[Ir(dtbbpy)(ppy)_2]PF_6$	48% (*Z*: 28%, *E*: 20%)
3	Rose bengal-Na_2	52% (*Z*: 30%, *E*: 22%)
4	Eosin Y-Na_2	59% (*Z*: 34%, *E*: 25%)
5	none	53% (*Z*: 31%, *E*: 22%)
6 [c]	Eosin Y-Na_2	-

[a] All reactions were conducted on a 0.1 mmol scale. [b] Isolated yield based on **1a**. [c] No reaction was performed in the absence of the blue light.

To further improve the yield, we optimized the reaction conditions using eosin Y-Na_2, and the results are summarized in Table 2. Using other solvents, such as CH_2Cl_2, MeCN, *N*,*N*-dimethylaniline (DMA) and dimethyl sulfoxide (DMSO), instead of *N*,*N*-dimethylformamide (DMF) was fruitless (entry 1 vs, entries 2–5). As reductants, 1-benzyl-1,4-dihydronicotinamide and γ-terpinene decreased the yield (entry 1 vs, entries 6 and 7). Notably, *N*,*N*-diisopropylethylamine (DIEA), widely used for photocatalytic reactions, involved the decomposition of the NHPI ester **7a** because of its strong basicity (entry 8). The yield increased to 68% when the amount of the Hantzsch ester was reduced to 1.0 equiv (entry 9). Excess amounts of the Hantzsch ester may interfere with the capture

of the resulting radical species by diphenyl diselenide [41,42]. Further reduction of the Hantzsch ester decreased the yield (entries 10 and 11). With a decrease in the reaction temperature at −40 °C, the yield was up to 74% (entry 12). In contrast, selenoetherification did not complete at −78 °C (entry 13). Thus, we determined that the optimized condition is observed in entry 12. Our developed methodology was performed on a 1.0 mmol scale, giving **9a** in a moderate yield (51%, entry 14).

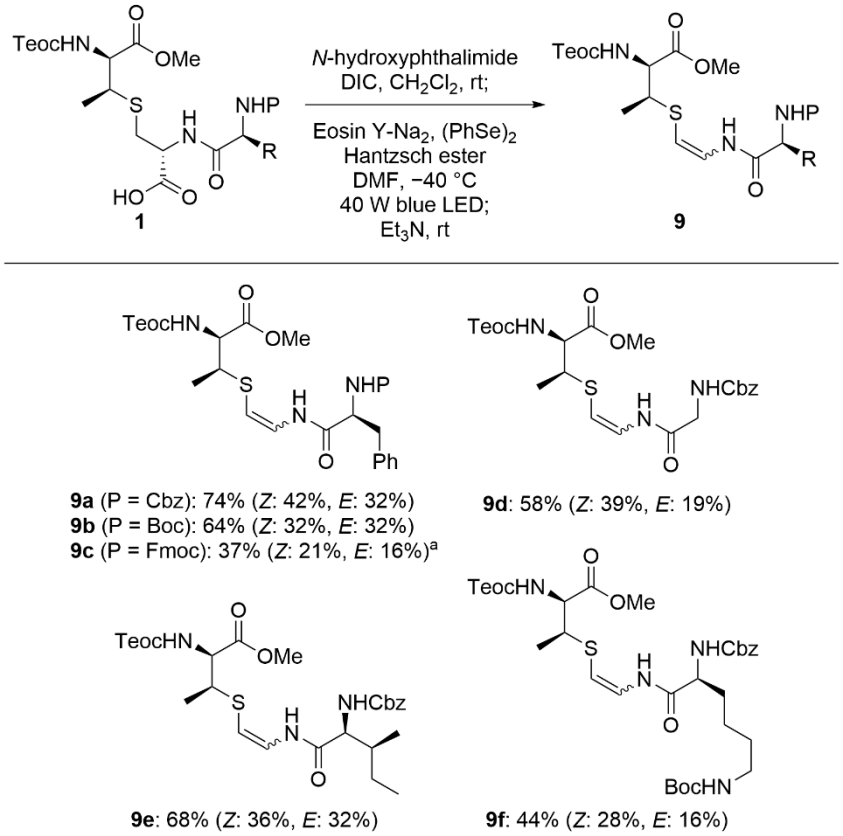
Table 2. Optimization of reaction conditions [a].



Entry	Reductant (Equiv)	Solvent	Temp. (°C)	Yield [b]
1	Hantzsch ester (2.0)	DMF	0	59% (*Z*: 34%, *E*: 25%)
2	Hantzsch ester (2.0)	CH_2Cl_2	0	33% (*Z*: 20%, *E*: 13%)
3	Hantzsch ester (2.0)	MeCN	0	52% (*Z*: 33%, *E*: 19%)
4	Hantzsch ester (2.0)	DMA	0	53% (*Z*: 30%, *E*: 23%)
5	Hantzsch ester (2.0)	DMSO	0	45% (*Z*: 26%, *E*: 19%)
6	1-benzyl-1,4-dihydronicotinamide (2.0)	DMF	0	38% (*Z*: 22%, *E*: 16%)
7	γ-terpinene (2.0)	DMF	0	6% (*Z*: 3%, *E*: 3%)
8	DIEA (2.0)	DMF	0	16% (*Z*: 9%, *E*: 7%)
9	Hantzsch ester (1.0)	DMF	0	68% (*Z*: 36%, *E*: 32%)
10	Hantzsch ester (0.5)	DMF	0	51% (*Z*: 28%, *E*: 23%)
11 [c]	none	DMF	0	22% (*Z*: 13%, *E*: 9%)
12	Hantzsch ester (1.0)	DMF	−40	74% (*Z*: 42%, *E*: 32%)
13	Hantzsch ester (1.0)	DMF	−78	34% (*Z*: 19%, *E*: 15%)
14 [d]	Hantzsch ester (1.0)	DMF	−40	51% (*Z*/*E* = 57:43) [e]

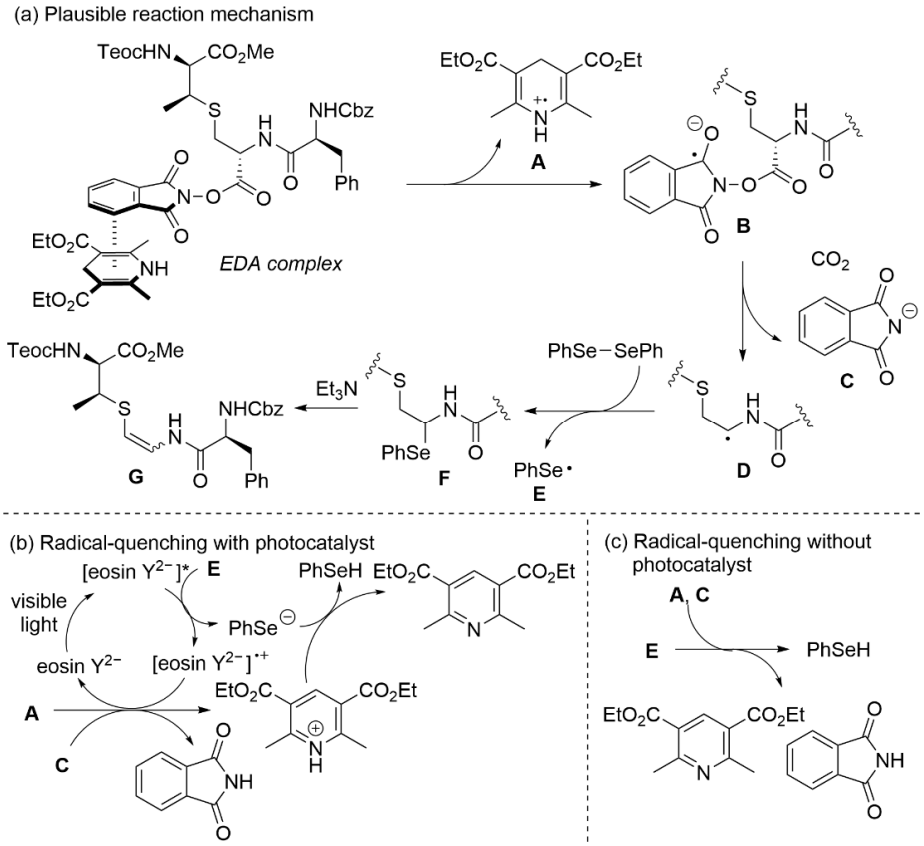
[a] All reactions were conducted on a 0.1 mmol scale. [b] Isolated yield based on **1a**. [c] Selenoetherification was conducted for 2 h. [d] 1.0 mmol scale. [e] The product was obtained as a *Z*/*E* mixture. The ratio was determined by ^{1}H NMR.

The substrate scope for our developed AviMeCys formation is shown in Scheme 4. Carbamate-type protecting groups, such as Cbz, Teoc, Boc and Fmoc groups, were tolerant under the reaction conditions, providing the corresponding β-thioenamides **9a–c** in moderate to good yields (37–74%). AviMeCys substructures in natural products, such as **9d** for cacaodin [43], **9e** for mersacidin [44], and **9f** for lexapeptide [45], were obtained from lanthionines **1d–1f** in 58–68% yields.



Scheme 4. Scope of lanthionine-bearing peptides in the AviMeCys formation. [a] 3.0 equiv of Et_3N was used.

A plausible reaction mechanism of the photocatalytic synthesis of AviMeCys is depicted in Scheme 5 according to the above results and previous reports on decarboxylative selenoetherification [31,46]. Given that the reaction proceeded without photocatalysts, we assumed the formation of an EDA complex between the NHPI and Hantzsch esters [39,40]. Photoirradiation induces intramolecular single-electron transfer, generating a phthalimide radical anion **B** with a dihydropyridine radical cation **A**. The resulting **B** undergoes decarboxylation to form a radical species **D** and a phthalimide anion **C**. The radical **D** is then captured by diphenyl diselenide to form a *N*,*Se*-acetal **F** with a seleno radical **E**. The β-elimination with the *N*,*Se*-acetal **F** in the presence of Et_3N affords the corresponding AviMeCys (**G**) (Scheme 5a). A (*Z*)-isomer will be obtained with slight priority because of the electrostatic attraction between a sulfur atom and the amide moiety [17]. The resulting **A**, **C**, and **E** are converted into phthalimide, pyridine derivative and phenylselenol, respectively, through two possible pathways. Although the radical-quenching of **A** and **E** automatically occurs (Scheme 5c), photocatalysts may mediate this step to improve the yields (Scheme 5b).



Scheme 5. Plausible reaction mechanism.

3. Materials and Methods

3.1. General Techniques

All commercially available reagents were purchased from commercial suppliers and used as received. Dry THF and CH_2Cl_2 (Kanto Chemical Co., Inc., Tokyo, Japan) were obtained by passing commercially available pre-dried, oxygen-free formulations. DMF (for peptide synthesis) was purchased from Watanabe Chemical Industries, Ltd. (Hiroshima, Japan). Photocatalyzed oxidative decarboxylation was performed with a Kessil A160WE Tuna Blue (Dicon Fiberoptic Inc., Richmond, CA, USA), as shown in Figure S1.

All reactions were monitored by TLC carried out on Merck silica gel plates (0.2 mm, 60F-254) with UV light, and visualized by *p*-anisaldehyde/H_2SO_4/EtOH solution, phosphomolybdic acid–EtOH solution or ninhydrin/AcOH/BuOH solution. Column chromatography was carried out with silica gel 60 N (Kanto Chemical Co. 100–210 μm). Preparative TLC was performed on 0.75 mm Wakogel® B-5F PLC plates (FUJIFILM Wako Pure Chemical Co., Ltd., Osaka, Japan). ^{1}H NMR spectra (400 and 600 MHz) and ^{13}C{^{1}H} NMR spectra (100 and 150 MHz) were recorded on JEOL JNM-AL400 and JEOL JNM-ECA600 spectrometers (JEOL Ltd., Tokyo, Japan) in the indicated solvent. Chemical shifts (δ) are reported in unit parts per million (ppm) relative to the signal for internal TMS (0.00 ppm for ^{1}H) for solutions in $CDCl_3$. NMR spectral data are reported as follows: $CHCl_3$ (7.26 ppm for ^{1}H) or $CDCl_3$ (77.0 ppm for ^{13}C), and DMSO (2.49 ppm for ^{1}H) or DMSO-d_6 (39.5 ppm for ^{13}C), when internal standard is not indicated. Multiplicities are reported by using standard abbreviations, and coupling constants are given in hertz.

High-resolution mass spectra (HRMS) were recorded on Thermo Scientific Exactive Plus Orbitrap Mass Spectrometer (Thermo Fisher Scientific K.K., Tokyo, Japan) for ESI or JEOL JMS-AX500 (JEOL Ltd., Tokyo, Japan) for FAB. IR spectra were recorded on a JASCO FTIR-4100 spectrophotometer (JASCO Co., Tokyo, Japan). Only the strongest and/or structurally important absorption are reported as the IR data afforded in wavenumbers (cm^{-1}). Optical rotations were measured on a JASCO P-1010 polarimeter (JASCO Co.,

Tokyo, Japan). Melting points were measured with Round Science Inc. RFS-10 (J-SCIENCE LAB Co., Ltd., Kyoto, Japan), and are not corrected.

3.2. Synthesis of the Lanthionine **5**

3.2.1. 2-Methyl 1-(2-(Trimethylsilyl)ethyl) (2R,3R)-3-methylaziridine-1,2-dicarboxylate (**2**)

To a solution of D-threonine (5.00 g, 42.0 mmol, 1.0 equiv) in MeOH (150 mL) was added $SOCl_2$ (15.3 mL, 210 mmol, 5.0 equiv) dropwise at 0 °C, and the mixture was stirred at the same temperature for 30 min. After being stirred at reflux in an oil bath for 12 h, the reaction mixture was cooled to room temperature, and concentrated in vacuo. The resulting crude methyl ester was used for the next reaction without further purification.

To a solution of the crude amine in dry CH_2Cl_2 (150 mL) were added Et_3N (14.6 mL, 105 mmol, 2.5 equiv) and TrtCl (11.7 g, 42.0 mmol, 1.0 equiv) at 0 °C under an argon atmosphere. After being stirred at room temperature for 43 h, the reaction mixture was washed with 10% aqueous citric acid, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the resulting crude *N*-Trt amine was used for the next reaction without further purification.

To a solution of the crude alcohol in dry THF (120 mL) were added Et_3N (14.6 mL, 105 mmol, 2.5 equiv) and MsCl (3.6 mL, 46.2 mmol, 1.1 equiv) at 0 °C under an argon atmosphere, and the mixture was stirred at the same temperature for 30 min. After being stirred at reflux in an oil bath for 72 h, the reaction mixture was concentrated in vacuo to remove THF. The resulting residue was diluted with EtOAc, and the organic layer was washed with 10% aqueous citric acid and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the resulting crude aziridine was used for next reaction without further purification.

To a solution of the crude *N*-Trt aziridine in dry CH_2Cl_2 (150 mL) were added dry MeOH (2.6 mL, 63.0 mmol, 1.5 equiv) and TFA (6.5 mL, 84.0 mmol, 2.0 equiv) at 0 °C under an argon atmosphere. After being stirred at the same temperature for 1 h, the reaction mixture was basified by Et_3N (20.5 mL, 147 mmol, 3.5 equiv). TeocOSu (10.9 g, 42.0 mmol, 1.0 equiv) was then added to the above mixture at 0 °C. After being stirred at room temperature for 19 h, the reaction mixture was washed with 10% aqueous citric acid and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was suspended in CH_2Cl_2/MeOH. The suspension was filtered through a pad of Celite®, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 4:1) to afford the *N*-Teoc aziridine **2** (5.98 g, 23.0 mmol, 55% in 4 steps) as a colorless oil. $[\alpha]^{22}_{D}$ +64 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18–4.22 (m, 2H), 3.79 (s, 3H), 3.15 (d, 1H, *J* = 6.8 Hz), 2.77–2.82 (m, 1H), 1.35 (d, 3H, *J* = 6.4 Hz), 1.00–1.04 (m, 2H), 0.00 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.7, 161.8, 65.3, 52.2, 39.7, 38.7, 17.4, 12.9, −1.5; IR (neat) 2955, 1756, 1729, 1442, 1425, 1285, 1252, 1201, 1181, 1081, 1038, 860, 838 cm^{-1}; HRMS [ESI] *m*/*z* calcd for $C_{11}H_{21}NO_4SiNa$ $[M+Na]^+$ 282.1132, found 282.1131.

3.2.2. Fmoc-Cys-OH (**3**)

To a solution of L-cystine (5.00 g, 20.8 mmol, 1.0 equiv) in 1,4-dioxane (90 mL) were added a solution of Na_2CO_3 (6.62 g, 62.4 mmol, 3.0 equiv) in water (60 mL) and a solution of FmocOSu (14.0 g, 41.6 mmol, 2.0 equiv) in 1,4-dioxane (90 mL) at 0 °C. After being stirred at the room temperature for 15 h, the reaction mixture was concentrated in vacuo to remove 1,4-dioxane. The aqueous layer was acidified with 6 M aqueous HCl until pH1, and extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was suspended in Et_2O. The white precipitate was filtered, and dried under vacuum to afford the *N*-Fmoc amine (12.7 g, 18.5 mmol, 89%) as a white solid. The spectral data of synthetic compound were in good agreement with those of reported [47]. Mp 153–154 °C [lit. 149–151 °C]; $[\alpha]^{20}_{D}$ −89 (*c* 1.2, MeOH) [lit. $[\alpha]^{24}_{D}$ −87.1 (*c* 1.0, MeOH)]; ^{1}H NMR (400 MHz, DMSO-d_6, rotamer mixture) δ 13.0 (s, 1H), 7.87 (d, 2H, *J* = 7.5 Hz), 7.78 (d, 1H,

J = 7.5 Hz), 7.69 (d, 2H, *J* = 7.5 Hz), 7.37–7.41 (m, 2H), 7.30 (t, 2H, *J* = 7.5 Hz), 4.26–4.31 (m, 3H), 4.21 (dd, 1H, *J* = 12.6, 5.6 Hz), 3.16 (dd, 1H, *J* = 13.5, 3.9 Hz), 2.94 (dd, 1H, *J* = 13.5, 10.3 Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6, rotamer mixture) δ 172.2, 156.0, 143.8, 143.7, 140.7, 127.6, 127.1, 125.3, 125.2, 120.1, 65.8, 53.0, 46.6, 39.1; IR (neat) 1696, 1515, 1448, 1331, 1228, 1049, 758, 739 cm^{-1}; HRMS [FAB] *m*/*z* calcd for $C_{36}H_{33}N_2O_8S_2$ $[M+H]^+$ 685.1673, found 685.1690.

To a solution of the disulfide (14.0 g, 20.4 mmol, 1.0 equiv) in dry THF (70 mL) were added 1 M aqueous HCl (70 mL) and activated zinc dust (4.00 g, 61.2 mmol, 3.0 equiv) at 0 °C. After being stirred at the room temperature for 30 min, the reaction mixture was filtered through of a pad of Celite®. The filtrate was concentrated in vacuo, and the resulting residue was diluted with 1 M aqueous HCl. The aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was suspended in CH_2Cl_2/hexane. The precipitate was filtered and dried under vacuum to afford the thiol **3** (10.7 g, 31.3 mmol, 77%) as a white solid. The spectral data of synthetic compound were in good agreement with those of reported [48]. Mp 119–123 °C; $[\alpha]^{20}_D$ −5.7 (*c* 0.93, MeOH); ^1H NMR (400 MHz, DMSO-d_6) δ 12.9 (s, 1H), 7.88 (d, 2H, *J* = 7.5 Hz), 7.69–7.73 (m, 3H), 7.41 (t, 2H, *J* = 7.5 Hz), 7.32 (t, 2H, *J* = 7.5 Hz), 4.29–4.31 (m, 2H), 4.23 (t, 1H, *J* = 7.0 Hz), 4.14 (dt, 1H, *J* = 8.3, 4.3 Hz), 2.89–2.92 (m, 1H), 2.71–2.78 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 171.8, 156.0, 143.8, 140.7, 127.6, 127.1, 125.2, 120.1, 65.7, 56.5, 46.6, 25.4; IR (neat) 3314, 1694, 1536, 1476, 1447, 1418, 1230, 1103, 1047, 756, 736, 620 cm^{-1}; HRMS [FAB] *m*/*z* calcd for $C_{18}H_{18}NO_4S$ $[M+H]^+$ 344.0951, found 344.0942.

3.2.3. The Lanthionine **4**

To a solution of the aziridine **2** (4.62 g, 17.8 mmol, 2.0 equiv) in dry Et_2O (90 mL) were added Fmoc-Cys-OH (**3**) (3.06 g, 8.91 mmol, 1.0 equiv) and $InCl_3$ (788 mg, 3.56 mmol, 0.4 equiv) at room temperature under an argon atmosphere. After being stirred at the same temperature for 18 h, the reaction mixture was quenched with water. The organic layer was separated, and aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with CH_2Cl_2/MeCN = 1:1) to afford the lanthionine **4** (2.89 g, 4.79 mmol, 54%) as a white amorphous solid. $[\alpha]^{24}_D$ +2.3 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, 2H, *J* = 7.5 Hz), 7.71–7.73 (m, 3H), 7.41 (t, 2H, *J* = 7.5 Hz), 7.31–7.33 (m, 3H), 4.21–4.34 (m, 4H), 4.09–4.15 (m, 1H), 4.04–4.06 (m, 2H), 3.65 (s, 3H), 3.21–3.24 (m, 1H), 2.95 (dd, 1H, *J* = 13.6, 4.7 Hz), 2.74 (dd, 1H, *J* = 13.5, 9.4 Hz), 1.21 (d, 3H, *J* = 7.0 Hz), 0.91–0.93 (m, 2H), 0.00 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 172.0, 170.8, 156.2, 155.9, 143.7, 140.7, 127.6, 127.0, 125.2, 120.0, 65.7, 62.2, 58.4, 54.0, 51.9, 46.6, 41.6, 32.1, 18.8, 17.3, −1.6; IR (neat) 3327, 3019, 2953, 1720, 1513, 1478, 1449, 1338, 1249, 1213, 1080, 1049, 859, 837, 758, 740 cm^{-1}; HRMS [ESI] *m*/*z* calcd for $C_{29}H_{38}N_2O_8NaSSi$ $[M+Na]^+$ 625.2010, found 625.2007.

3.2.4. The MOM Ester **5**

To a solution of the carboxylic acid **4** (2.89 g, 4.79 mmol, 1.0 equiv) in dry acetone (90 mL) were added $KHCO_3$ (1.20 g, 12.0 mmol, 2.5 equiv) and MOMCl (437 µL, 5.75 mmol, 1.2 equiv) at room temperature under an argon atmosphere. After being stirred at the same temperature for 15 h, the reaction mixture was concentrated in vacuo to remove acetone. The resulting residue was diluted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 1:1) to afford the MOM ester **5** (3.06 g, 4.73 mmol, 99%) as a white amorphous solid. $[\alpha]^{23}_D$ −16 (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, 2H, *J* = 7.5 Hz), 7.57–7.59 (m, 2H), 7.38 (t, 2H, *J* = 7.5 Hz), 7.29 (d, 2H, *J* = 7.5 Hz), 5.66 (d, 1H, *J* = 6.8 Hz), 5.41 (d, 1H, *J* = 8.5 Hz), 5.31 (d, 1H, *J* = 5.6 Hz), 5.27 (d, 1H, *J* = 5.6 Hz), 4.58–4.61 (m, 1H), 4.51 (d, 1H, *J* = 7.5 Hz), 4.36–4.44 (m, 2H), 4.22 (t, 1H, *J* = 6.9 Hz), 4.11–4.16 (m,

2H), 3.72 (s, 3H), 3.44–3.47 (m, 4H), 3.03 (dd, 1H, *J* = 13.4, 3.7 Hz), 2.91 (dd, 1H, *J* = 13.4, 5.4 Hz), 1.31 (d, 3H, *J* = 7.0 Hz), 0.95–0.97 (m, 2H), −0.01 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 171.1, 170.0, 156.7, 155.7, 143.7, 141.3, 127.7, 127.0, 125.0, 120.0, 91.8, 67.2, 63.7, 58.1, 58.0, 53.8, 52.5, 47.1, 43.7, 33.5, 19.4, 17.6, −1.6; IR (neat) 3335, 2953, 1722, 1511, 1450, 1339, 1249, 1210, 1157, 1081, 1047, 994, 928, 859, 837, 759, 741 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{31}H_{42}N_2O_9NaSSi$ $[M+Na]^+$ 669.2272, found 669.2280.

*3.3. Synthesis of the Tripeptide **1** by Solution-Phase Peptide Synthesis*

3.3.1. The Tripeptide **1a**

To a solution of the *N*-Fmoc-amine **5** (3.06 g, 4.73 mmol, 1.0 equiv) in dry MeCN (40 mL) was added Et_2NH (10 mL) at room temperature under an argon atmosphere. After being stirred at the same temperature for 40 min, the reaction mixture was concentrated in vacuo. The resulting residue was azeotroped three times with MeCN to remove Et_2NH, and the resulting crude amine was used for the next reaction without further purification.

To a solution of the crude amine in dry CH_2Cl_2 (50 mL) were added DIEA (1.7 mL, 9.46 mmol, 2.0 equiv), Cbz-Phe-OH (1.70 g, 5.68 mmol, 1.2 equiv), HOBt (773 mg, 5.68 mmol, 1.2 equiv) and EDCI·HCl (1.09 g, 5.68 mmol, 1.2 equiv) at 0 °C under an argon atmosphere. After being stirred at room temperature for 13 h, the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with 10% aqueous citric acid and saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 1:1) to afford the tripeptide **6a** (2.88 g, 4.08 mmol, 86% in 2 steps) as a white amorphous solid. $[\alpha]^{23}_D$ −25 (*c* 0.90, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.20–7.27 (m, 10H), 6.73 (d, 1H, *J* = 6.5 Hz), 5.45 (d, 1H, *J* = 9.2 Hz), 5.38 (d, 1H, *J* = 5.8 Hz), 5.29 (d, 1H, *J* = 5.8 Hz), 5.26 (d, 1H, *J* = 5.8 Hz), 5.08 (s, 2H), 4.72–4.74 (m, 1H), 4.48–4.50 (m, 2H), 4.15–4.17 (m, 2H), 3.75 (s, 3H), 3.48 (s, 3H), 3.37–3.41 (m, 1H), 3.00–3.18 (m, 3H), 2.84 (dd, 1H, *J* =13.9, 5.9 Hz), 1.27 (d, 3H, *J* = 7.0 Hz), 0.96–1.01 (m, 2H), 0.02 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 171.1, 171.0, 169.5, 156.6, 155.9, 136.2, 136.1, 129.3, 128.6, 128.4, 128.1, 127.9, 127.0, 91.7, 67.0, 63.7, 58.1, 57.9, 56.0, 52.5, 52.2, 43.3, 38.1, 32.8, 19.2, 17.6, −1.6; IR (neat) 3314, 3030, 2953, 1721, 1519, 1454, 1338, 1249, 1215, 1155, 1083, 1048, 931, 860, 837, 750, 699 cm^{-1}; HRMS [ESI] *m*/*z* calcd for $C_{33}H_{47}N_3O_{10}NaSSi$ $[M+Na]^+$ 728.2644, found 728.2650.

To a solution of the MOM ester **6a** (2.88 g, 4.08 mmol, 1.0 equiv) in 1,4-dioxane (30 mL) was added 4 M HCl/1,4-dioxane (10 mL) at 0 °C under argon atmosphere. After being stirred at room temperature for 1 h, the reaction mixture was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (eluted with CH_2Cl_2/MeOH = 50:1) to afford the carboxylic acid **1a** (2.35 g, 3.55 mmol, 87%) as a white amorphous solid. $[\alpha]^{23}_D$ −13 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 12.9 (brs, 1H), 8.38 (d, 1H, *J* = 7.7 Hz), 7.46 (d, 1H, *J* = 8.7 Hz), 7.19–7.31 (m, 11 H), 4.93 (s, 2H), 4,25–4.43 (m, 3H), 4.03–4.05 (m, 2H), 3.64 (s, 3H), 3.25–3.31 (m, 1H), 2.96–3.03 (m, 2H), 2.70–2.80 (m, 2H), 1.21 (d, 3H, *J* = 6.8 Hz), 0.90–0.92 (m, 2H), 0.00 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 171.7, 171.6, 170.8, 156.2, 155.7, 138.0, 136.9, 129.2, 128.2, 128.0, 127.6, 127.3, 126.2, 65.1, 62.2, 58.5, 55.9, 52.2, 51.9, 41.8, 37.4, 32.1, 18.7, 17.3, −1.5; IR (neat) 3315, 3064,3030, 2953, 1721, 1518, 1454, 1439, 1340, 1287, 1250, 1215, 1180, 1081, 1050, 860, 837, 753, 698 cm^{-1}; HRMS [ESI] *m*/*z* calcd for $C_{31}H_{43}N_3O_9NaSSi$ $[M+Na]^+$ 684.2381, found 684.2391.

3.3.2. The Tripeptide **1b**

Compound **6b** was prepared from the *N*-Fmoc-amine **5** (248 mg, 383 μmol) according to the procedure above described for **6a**, and obtained in 69% yield (178 mg, 265 μmol) as a white amorphous solid after purification by column chromatography on silica gel (eluted with hexane/EtOAc = 1:1). $[\alpha]^{22}_D$ −17 (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.18–7.28 (m, 5H), 6.75 (d, 1H, *J* = 7.2 Hz), 5.40 (d, 1H, *J* = 8.5 Hz), 5.26 (d, 1H, *J* = 5.8 Hz), 5.22 (d, 1H, *J* = 5.8 Hz), 5.01–5.03 (m, 1H), 4.69–4.71 (m, 1H), 4.39–4.46 (m, 2H), 4.13–4.15 (m, 2H), 3.74 (s, 3H), 3.44 (s, 3H), 3.35–3.37 (m, 1H), 3.11 (dd, 1H, *J* = 14.2, 5.8 Hz), 2.99–3.02 (m, 2H), 2.82 (dd, 1H, *J* = 13.8, 6.3 Hz), 1.36 (s, 9H), 1.26 (d, 3H, *J* = 7.2 Hz), 0.95–0.97 (m,

2H), 0.00 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 171.4, 171.1, 169.6, 156.7, 155.3, 136.5, 129.3, 128.7, 127.0, 91.7, 80.3, 63.7, 58.1, 58.0, 55.8, 52.5, 52.3, 43.5, 38.1, 33.1, 28.2, 19.3, 17.7, −1.5; IR (neat) 3317, 2953, 1719, 1510, 1454, 1366, 1339, 1249, 1210, 1168, 1086, 1048, 933, 860, 837, 776, 699 cm^{-1}; HRMS[ESI] m/z calcd for $C_{30}H_{49}N_3O_{10}NaSSi$ $[M+Na]^+$ 650.2800, found 650.2819.

To a solution of the MOM ester **6b** (158 mg, 235 μmol, 1.0 equiv) in 1,4-dioxane (4.20 mL) was added 4 M HCl/1,4-dioxane (0.6 mL) at 0 °C under argon atmosphere. After being stirred at room temperature for 2.5 h, the reaction mixture was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (eluted with CH_2Cl_2/MeOH = 10:1) to afford the carboxylic acid **1b** (109 mg, 173 μmol, 74%) as a white amorphous solid. $[\alpha]^{21}_D$ −12 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, 1H, *J* = 7.2 Hz), 7.20–7.36 (m, 5H), 7.14–7.20 (m, 1H), 6.84 (d, 1H, *J* = 8.5 Hz), 4.36–4.45 (m, 1H), 4.16–4.35 (m, 2H), 3.99–4.09 (m, 2H), 3.64 (s, 3H), 3.19–3.28 (m, 1H), 2.90–3.06 (m, 2H), 2.66–2.83 (m, 2H), 1.27 (s, 9H), 1.21 (d, 3H, *J* = 6.5 Hz), 0.89–0.94 (m, 2H), 0.00 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 171.7, 170.8, 156.2, 155.1, 138.0, 129.2, 127.9, 126.1, 78.0, 66.2, 58.4, 55.6, 52.0, 51.9, 41.8, 37.4, 32.2, 28.1, 18.7, 17.3, –1.5; IR (neat) 3320, 2954, 1721, 1512, 1453, 1367, 1339, 1249, 1170, 1080, 1049, 859, 837, 699 cm^{-1}; HRMS[ESI] m/z calcd for $C_{28}H_{45}N_3O_9NaSSi$ $[M+Na]^+$ 650.2538, found 650.2546.

3.3.3. The Tripeptide **1c**

Compound **6c** was prepared from the *N*-Fmoc-amine **5** (367 mg, 568 μmol) according to the procedure above described for **6a**, and obtained in 86% yield (388 mg, 488 μmol) as a white amorphous solid after purification by column chromatography on silica gel (eluted with hexane/EtOAc = 1:1). $[\alpha]^{20}_D$ −28 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, 2H, *J* = 7.5 Hz), 7.50 (t, 2H, *J* = 7.5 Hz), 7.37 (t, 2H, *J* = 7.5 Hz), 7.21–7.29 (m, 7H), 6.70–6.82 (m, 1H), 5.44 (d, 2H, *J* = 8.5 Hz), 5.23–5.26 (m, 2H), 4.71–4.72 (m, 1H), 4.46–4.48 (m, 2H), 4.39–4.42 Hz (m, 1H), 4.27–4.30 (m, 1H), 4.13–4.17 (m, 3H), 3.71 (s, 3H), 3.43 (s, 3H), 3.34–3.40 (m, 1H), 2.98–3.10 Hz (m, 3H), 2.81–2.85 (m, 1H), 1.24 (d, 3H, *J* = 7.1 Hz), 0.95–0.97 (m, 2H), −0.01 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 171.1, 171.0, 169.5, 156.6, 155.9, 143.71, 143.66, 141.2, 136.2, 129.3, 128.7, 127.7, 127.0, 125.0, 119.9, 91.7, 77.2, 67.1, 63.7, 58.0, 52.5, 52.2, 47.0, 43.3, 38.2, 32.8, 29.2, 19.2, 17.6, −1.6; IR (neat) 3310, 3064, 3025, 2953, 1719, 1670, 1517, 1450, 1412, 1381, 1338, 1287, 1249, 1217, 1154, 1084, 1047, 932, 860, 837, 757, 742, 700 cm^{-1}; HRMS[ESI] m/z calcd for $C_{40}H_{51}N_3O_{10}NaSSi$ $[M+Na]^+$ 816.2957, found 816.2960.

Compound **1c** was prepared from the MOM ester **6c** (340 mg, 428 μmol) according to the procedure above described for **1a**, and obtained in 85% yield (272 mg, 362 μmol) as a white amorphous solid after purification by column chromatography on silica gel (eluted with CH_2Cl_2/MeOH = 50:1). $[\alpha]^{24}_D$ −14 (*c* 0.96, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 8.37 (d, 1H, *J* = 7.5 Hz), 7.87 (d, 2H, *J* = 7.5 Hz), 7.60–7.64 (m, 3H), 7.16–7.42 (m, 10H), 4.25–4.40 (m, 3H), 4.09–4.16 (m, 3H), 4.03–4.05 (m, 2H), 3.64 (s, 3H), 3.25–3.26 (m, 1H), 2.95–3.03 (m, 2H), 2.78–2.80 (m, 2H), 1.19 (d, 3H, *J* = 7.0 Hz), 0.90–0.92 (m, 2H), 0.00 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 171.8, 171.5, 170.8, 156.2, 155.6, 143.7, 143.6, 140.6, 138.0, 129.2, 127.9, 127.5, 127.0, 126.1, 125.23, 125.17, 120.0, 65.6, 62.2, 58.4, 56.0, 52.3, 51.8, 46.5, 41.7, 37.4, 32.2, 18.7, 17.3, −1.6; IR (neat) 3313, 3064, 3028, 2953, 1721, 1516, 1450, 1338, 1249, 1216, 1180, 1081, 1048, 859, 837, 757, 742, 699 cm^{-1}; HRMS [ESI] m/z calcd for $C_{38}H_{47}N_3O_9NaSSi$ $[M+Na]^+$ 772.2694, found 772.2715.

3.3.4. The Tripeptide **1d**

Compound **6d** was prepared from the *N*-Fmoc-amine **5** (480 mg, 742 μmol) according to the procedure above described for **6a**, and obtained in 75% yield (344 mg, 558 μmol) as a white amorphous solid after purification by column chromatography on silica gel (eluted with hexane/EtOAc = 1:1 to hexane/acetone = 3:1). $[\alpha]^{23}_D$ −16 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.32 (m, 5H), 7.01 (s, 1H), 5.67 (s, 1H), 5.48 (d, 1H, *J* = 9.2 Hz), 5.28 (d, 1H, *J* = 5.8 Hz), 5.23 (d, 1H, *J* = 5.8 Hz), 5.10 (s, 2H), 4.77 (dt, 1H, *J* = 6.3, 5.6 Hz), 4.48 (dd, 1H, *J* = 8.8, 3.0 Hz), 4.12–4.15 (m, 2H), 3.92 (d, 2H, *J* = 5.6 Hz), 3.72 (s, 3H), 3.36–3.44 (m,

4H), 3.03 (dd, 1H, *J* = 13.6, 4.0 Hz), 2.86 (dd, 1H, *J* = 13.9, 6.2 Hz), 1.27 (d, 3H, *J* = 7.2 Hz), 0.95–0.97 (m, 2H), −0.01 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.1, 169.8, 169.2, 156.6, 156.5, 136.1, 128.5, 128.1, 128.0, 91.7, 77.2, 67.1, 63.7, 57.9, 52.5, 52.1, 44.4, 43.3, 32.7, 19.1, 17.6, −1.6; IR (neat) 3325, 2953, 1723, 1515, 1453, 1381, 1339, 1249, 1156, 1088, 1048, 927, 860, 837, 754, 698 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{26}H_{41}N_3O_{10}NaSSi$ $[M+Na]^+$ 638.2174, found 638.2180.

Compound **1d** was prepared from the MOM ester **6d** (215 mg, 349 µmol) according to the procedure above described for **1a**, and obtained in 45% yield (89.6 mg, 157 µmol) as a white amorphous solid after purification by column chromatography on silica gel (eluted with CH_2Cl_2/MeOH = 50:1 to 10:1). $[\alpha]^{24}_D$ +2.7 (*c* 0.95, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 12.9 (brs, 1H), 8.18 (d, 1H, *J* = 8.0 H), 7.30–7.44 (m, 7H), 5.02 (s, 2H), 4.37–4.40 (m, 1H), 4.23 (dd, 1H, *J* = 8.0, 6.0 Hz), 4.03–4.05 (m, 2H), 3.66 (d, 2H, *J* = 6.3 Hz), 3.63 (s, 3H), 3.18–3.20 (m, 1H), 2.91 (dd, 1H, *J* = 13.5, 5.1 Hz), 2.72 (dd, 1H, *J* = 13.5, 8.1 Hz), 1.18 (d, 3H, *J* = 6.8 Hz), 0.90–0.93 (m, 2H), 0.00 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 171.7, 170.7, 169.0, 156.4, 156.2, 137.0, 128.2, 127.7, 127.6, 65.4, 62.2, 58.4, 51.9, 51.8, 43.2, 41.8, 32.3, 18.6, 17.3, −1.6; IR (neat) 3327, 2953, 1722, 1523, 1453, 1438, 1340, 1249, 1081, 1050, 860, 837, 697 cm^{-1}; HRMS [ESI] *m*/*z* calcd for $C_{24}H_{37}N_3O_9NaSSi$ $[M+Na]^+$ 594.1912, found 594.1924.

3.3.5. The Tripeptide **1e**

To a solution of *N*-Fmoc-amine **5** (359 mg, 554 µmol, 1.0 equiv) in dry MeCN (4.4 mL) was added Et_2NH (1.1 mL) at room temperature under an argon atmosphere. After being stirred at the same temperature for 1.5 h, the reaction mixture was concentrated in vacuo. The resulting residue was azeotroped three times with MeCN, and the resulting crude amine was used for the next reaction without further purification.

To a solution of the crude amine in dry CH_2Cl_2 (5.5 mL) were added DIEA (193 µL, 1.11 mmol, 2.0 equiv), Cbz-Ile-OH (177 mg, 665 µmol, 1.2 equiv) and HATU (253 mg, 665 µmol, 1.2 equiv) at 0 °C under an argon atmosphere. After being stirred at room temperature for 7 h, the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with 10% aqueous citric acid and saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (eluted with hexane/EtOAc = 1:1) to afford the tripeptide **6e** (373 mg, 539 mmol, 97% in 2 steps) as a yellowish amorphous solid. $[\alpha]^{23}_D$ −19 (*c* 0.98, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.34 (m, 5H), 6.82 (d, 1H, *J* = 6.5 Hz), 5.51 (d, 1H, *J* = 9.2 Hz), 5.43 (d, 1H, *J* = 8.7 Hz), 5.32 (d, 1H, *J* = 5.8 Hz), 5.27 (d, 1H, *J* = 5.8 Hz), 5.11 (s, 2H), 4.78–4.80 (m, 1H), 4.52 (dd, 1H, *J* = 9.3, 3.0 Hz), 4.14–4.17 (m, 3H), 3.75 (s, 3H), 3.48 (s, 3H), 3.37–3.48 (m, 1H), 3.04 (dd, 1H, *J* = 13.8, 4.3 Hz), 2.89 (dd, 1H, *J* = 13.8, 6.0 Hz), 1.89–1.91 (m, 1H), 1.60–1.70 (m, 1H) 1.30 (d, 3H, *J* = 7.0 Hz), 1.07–1.26 (m, 1H), 0.90–1.01 (m, 8H), 0.03 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.4, 171.2, 169.7, 156.7, 156.2, 136.2, 128.5, 128.1, 128.0, 91.7, 67.1, 63.7, 59.6, 58.1, 58.0, 52.5, 52.0, 43.5, 37.4, 32.9, 24.6, 19.3, 17.6, 15.4, 11.3, −1.6; IR (neat) 3311, 2959, 1723, 1666, 1524, 1454, 1382, 1339, 1284, 1248, 1156, 1087, 1045, 932, 860, 837, 697 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{30}H_{49}N_3O_{10}NaSSi$ $[M+Na]^+$ 694.2800, found 694.2814.

Compound **1e** was prepared from the MOM ester **6e** (373 mg, 539 µmol) according to the procedure above described for **1a**, and obtained in 67% yield (228 mg, 362 µmol) as a white amorphous solid after purification by column chromatography on silica gel (eluted with CH_2Cl_2/MeCN = 3:1 to CH_2Cl_2/MeOH = 20:1). $[\alpha]^{21}_D$ −6.5 (*c* 0.99, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 12.8 (brs, 1H), 8.21 (d, 1H, *J* = 7.7 Hz), 7.24–7.33 (m, 7H), 5.02 (s, 2H), 4.35–4.38 (m, 1H), 4.25 (dd, 1H, *J* = 7.4, 5.7 Hz), 4.03–4.05 (m, 2H), 3.91–3.99 (m, 1H), 3.62–3.64 (m, 3H), 3.21 (s, 1H), 2.92 (dd, 1H, *J* = 13.0, 5.1 Hz), 2.72 (dd, 1H, *J* = 13.0, 8.2 Hz), 1.63–1.82 (m, 1H), 1.31–1.49 (m, 1H), 1.03–1.23 (m, 4H), 0.72–0.96 (m, 8H), 0.00 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 171.7, 171.2, 170.8, 156.2, 155. 9, 137.0, 128.2, 127.6, 127.5, 65.3, 62.2, 59.0, 58.4, 51.90, 51.85, 41.6, 36.6, 32.1, 24.2, 18.6, 17.3, 15.2, 10.8, −1.5; IR (neat) 3316, 2959, 1721, 1666, 1517, 1454, 1340, 1286, 1249, 1216, 1179, 1082, 1045, 859, 837 cm^{-1}; HRMS [ESI] *m/z* calcd for $C_{28}H_{45}N_3O_9NaSSi$ $[M+Na]^+$ 650.2538, found 650.2551.

3.3.6. The Tripeptide **1f**

Compound **6f** was prepared from the *N*-Fmoc-amine **5** (268 mg, 414 μmol) according to the procedure above described for **6a**, and obtained in 74% yield (242 mg, 307 μmol) as a white amorphous solid after purification by column chromatography on silica gel (eluted with hexane/EtOAc = 1:1). $[\alpha]^{22}_{D}$ −21 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.25–7.32 (m, 5H), 6.92–6.94 (m, 1H), 5.47–5.49 (m, 2H), 5.30 (d, 1H, *J* = 5.8 Hz), 5.23 (d, 1H, *J* = 5.8 Hz), 5.08 (s, 2H), 4.74 (dt, 1H, *J* = 6.8, 5.4 Hz), 4.65 (brs, 1H), 4.48 (dd, 1H, *J* = 8.7, 2.4 Hz), 4.21–4.22 (m, 1H), 4.13–4.15 (m, 2H), 3.73 (s, 3H), 3.37–3.43 (m, 4H), 3.02–3.04 (m, 3H), 2.86 (dd, 1H, *J* = 13.2, 5.9 Hz), 1.25–1.85 (m, 18H), 0.95–0.97 (m, 2H), −0.01 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*171.8, 171.2, 169.7, 156.7, 156.2, 156.1, 136.2, 128.4, 128.1, 128.0, 91.7, 79.0, 67.0, 63.7, 58.1, 57.9, 54.7, 52.5, 52.1, 43.3, 39.8, 32.7, 31.9, 29.6, 28.4, 22.3, 19.2, 17.6, −1.6; IR (neat) 3319. 2952, 1714, 1511, 1454, 1365, 1339, 1249, 1169, 1086, 1046, 860, 837 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{35}H_{58}N_4O_{12}NaSSi$ $[M+Na]^+$ 809.3433, found 809.3434.

Compound **1f** was prepared from the MOM ester **6f** (215 mg, 279 μmol) according to the procedure above described for **1b**, and obtained in 87% yield (180 mg, 242 μmol) as a white amorphous solid after purification by column chromatography on silica gel (eluted with CH_2Cl_2/MeCN = 1:1 to CH_2Cl_2/MeOH = 10:1). $[\alpha]^{24}_{D}$ −13 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 7.91 (d, 1H, *J* = 7.2 Hz), 7.28–7.32 (m, 5H), 7.11–7.12 (m, 1H), 6.90–6.91 (m, 1H), 6.47–6.48 (m, 1H), 5.02 (s, 2H), 4.32–4.37 (m, 1H), 4.23 (dd, 1H, *J* = 8.1, 5.9 Hz), 3.99–4.06 (m, 3H), 3.63 (s, 3H), 3.19–3.25 (m, 1H), 2.93–3.02 (m, 3H), 2,74 (dd, 1H, *J* = 13.4, 7.6 Hz), 1.61–1.64 (m, 1H), 1.51–1.53 (m, 1H), 1.13–1.37 (m, 16H), 0.90–0.93 (m, 2H), 0.00 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) *δ* 171.8, 171.7, 170.7, 156.1, 155.8, 155.4, 136.9, 128.2, 127.6, 127.5, 66.2, 65.3, 62.1, 58.4, 54.5, 52.0, 51.7, 41.6, 32.2, 31.6, 29.1, 28.1, 27.8, 22.6, 18.6, 17.2, −1.6; IR (neat) 3325, 2953, 1713, 1515, 1453, 1411, 1391, 1366, 1340, 1249, 1214, 1172, 1081, 1047, 860, 837, 754, 697 cm^{-1}; HRMS [ESI] *m*/*z* calcd for $C_{33}H_{54}N_4O_{11}NaSSi$ $[M+Na]^+$ 765.3171, found 765.3179.

*3.4. The Photocatalytic AviMeCys Formation Using **1***

3.4.1. The β-Thioenamides (*Z*)-**9a** and (*E*)-**9a**

To a solution of the carboxylic acid **6a** (66.6 mg, 100 μmol, 1.0 equiv) and *N*-hydroxyphthalimide (18.1 mg, 110 μmol, 1.1 equiv) in dry CH_2Cl_2 (1.0 mL) was added DIC (17.3 μL, 110 μmol, 1.1 equiv) at room temperature under an argon atmosphere, and the mixture was stirred at the same temperature for 30 min. After complete consumption of **6a** (monitored by TLC analysis), the reaction mixture was cooled to −40 °C. A solution of eosin Y-Na_2 (0.7 mg, 1.00 μmol, 1 mol%), Hantzsch ester (25.5 mg, 100 μmol, 1.0 equiv) and diphenyl diselenide (62.8 mg, 200 μmol, 2.0 equiv) in dry DMF (1.5 mL, used immediately after freeze-pump-thaw cycling) was then added to the above mixture at −40 °C. After being stirred at the same temperature for 30 min under irradiated Blue LEDs, Et_3N (250 μL, 1.79 mmol, 18 equiv) was added to the solution at −40 °C. After being stirred at room temperature for 3 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and stirred for 12 h. The aqueous layer was extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by preparative TLC (eluted with hexane/EtOAc = 7:2) to afford the β-thioenamide *(Z)*-**9a** (26.2 mg, 42.5 μmol, 42%) as a white amorphous solid and the β-thioenamide *(E)*-**9a** (19.6 mg, 31.8 μmol, 32%) as a white amorphous solid. (*Z*)-**9a**: $[\alpha]^{24}_{D}$ −41 (*c* 1.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.42 (d, 1H, *J* = 10.6 Hz), 7.19–7.34 (m, 10H), 7.15 (dd, 1H, *J* = 10.6, 7.2 Hz), 5.49–5.50 (m, 1H), 5.40–5.41 (m, 1H), 5.32 (d, 1H, *J* = 7.2 Hz), 5.07–5.09 (m, 2H), 4.56–4.58 (m, 1H), 4.51 (dd, 1H, *J* = 9.2, 3.9 Hz), 4.14–4.15 (m, 2H), 3.65 (s, 3H), 3.31–3.32 (m, 1H), 3.19 (dd, 1H, *J* = 13.9, 6.2 Hz), 3.09–3.11 (m, 1H), 1.32 (d, 3H, *J* = 7.2 Hz), 0.95–0.97 (m, 2H), 0.00 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) *δ* 171.3, 168.9, 156.8, 156.2, 136.2, 136.1, 129.7, 129.3, 128.9, 128.6, 128.3, 128.2, 127.2, 99.7, 67.3, 63.9, 58.9, 56.4, 52.6, 45.8, 38.1, 18.3, 17.8, −1.4; IR (neat) 3310, 3064, 3031, 2952, 1697, 1628, 1498, 1455, 1380, 1337, 1248, 1178, 1080, 1046, 860, 837, 742, 698 cm^{-1}; HRMS[ESI] *m/z* calcd for $C_{30}H_{41}N_3O_7NaSSi$ $[M+Na]^+$ 638.2327, found 638.2330. (*E*)-**9a**: $[\alpha]^{23}_{D}$ −3.5

(*c* 0.89, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (m, 1H), 7.14–7.32 (m, 10H), 6.99 (dd, 1H, *J* = 13.7, 6.6 Hz), 5.59 (d, 1H, *J* = 13.7 Hz), 5.42–5.44 (m, 2H), 5.05 (s, 2H), 4.48 (dd, 1H, *J* = 5.5, 2.7 Hz), 4.40–4.42 (m, 1H), 4.13–4.17 (m, 2H), 3.64 (s, 3H), 3.34–3.38 (m, 1H), 3.06 (d, 2H, *J* = 6.8 Hz), 1.29 (d, 3H, *J* = 7.5 Hz), 1.00–1.01 (m, 2H), 0.03 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 171.2, 168.3, 156.8, 156.3, 136.0, 135.9, 129.4, 129.3, 129.0, 128.7, 128.5, 128.2, 127.4, 104.1, 67.5, 63.9, 57.9, 56.4, 52.5, 45.3, 38.2, 18.6, 17.8, −1.4; IR (neat) 3303, 2953, 1725, 1688, 1669, 1629, 1505, 1454, 1341, 1288, 1261, 1246, 1209, 1176, 1079, 1046, 938, 862, 835, 750, 697 cm^{-1}; HRMS[ESI] *m*/*z* calcd for $C_{30}H_{41}N_3O_7NaSSi$ $[M+Na]^+$ 638.2327, found 638.2334.

3.4.2. The β-Thioenamides (*Z*)-**9b** and (*E*)-**9b**

Compounds *(Z)*-**9b** and *(E)*-**9b** were prepared from the carboxylic acid **6b** (63.7 mg, 101 μmol) according to the procedure above described for **9a**, and purified by preparative TLC (eluted with hexane/EtOAc = 7:2, hexane/IPA = 20:1) to be obtained in 32% yield (18.6 mg, 32.0 μmol) as a white amorphous solid and 32% yield (18.9 mg, 32.5 μmol) as a white amorphous solid, respectively. (*Z*)-**9b**: $[\alpha]^{24}_D$ −49 (*c* 1.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (d, 1H, *J* = 10.9 Hz), 7.28–7.30 (m, 2H), 7.22–7.24 (m, 3H), 7.12–7.15 (m, 1H), 5.45–5.47 (m, 1H), 5.28–5.29 (m, 1H), 5.14–5.16 (m, 1H), 4.52 (d, 2H, *J* = 10.3 Hz), 4.14–4.17 (m, 2H), 3.70 (s, 3H), 3.34–3.36 (m, 1H), 3.18 (dd, 1H, *J* = 14.0, 5.8 Hz), 3.04–3.06 (m, 1H), 1.39 (s, 9H), 1.32 (d, 3H, *J* = 6.8 Hz), 0.98–0.99 (m, 2H), 0.01 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 171.3, 169.3, 156.8, 155.6, 136.5, 129.5, 129.3, 128.8, 127.1, 99.6, 80.6, 63.9, 58.7, 55.8, 52.6, 45.8, 37.9, 28.3, 18.4, 17.8, −1.4; IR (neat) 3324, 2953, 1690, 1627, 1499, 1366, 1338, 1285, 1249, 1171, 1080, 1047, 860, 837, 754, 699 cm^{-1}; HRMS [ESI] *m*/*z* calcd for $C_{27}H_{43}N_3NaO_7SSi$ $[M+Na]^+$ 604.2483, found 604.2490. (*E*)-**9b**: $[\alpha]^{24}_D$ −6.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04–8.05 (m, 1H), 7.28 (t, 2H, *J* = 7.5 Hz), 7.22 (t, 1H, *J* = 7.5 Hz), 7.15 (d, 2H, *J* = 7.5 Hz), 7.00 (dd, 1H, *J* = 13.7, 10.9 Hz), 5.59 (d, 1H, *J* = 13.7 Hz), 5.42 (d, 1H, *J* = 6.0 Hz), 5.06 (d, 1H, *J* = 8.2 Hz), 4.47 (dd, 1H, *J* = 9.2, 3.1 Hz), 4.33 (s, 1H), 4.15–4.16 (m, 2H), 3.65 (s, 3H), 3.37–3.38 (m, 1H), 3.05–3.06 (m, 1H), 2.99–3.00 (m, 1H), 1.37 (s, 9H), 1.28 (d, 3H, *J* = 6.8 Hz), 0.98–1.00 (m, 2H), 0.04 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 171.2, 168.7, 156.8, 155.8, 136.3, 129.6, 129.3, 128.8, 127.2, 103.6, 80.8, 63.5, 57.9, 56.0, 52.5, 45.3, 38.0, 28.3, 18.5, 17.8, −1.4; IR (neat) 3310, 2954, 1723, 1681, 1628, 1513, 1454, 1391, 1367, 1339, 1289, 1248, 1211, 1169, 1079, 1047, 941, 860, 837, 754, 698 cm^{-1}; HRMS [ESI] *m*/*z* calcd for $C_{27}H_{43}N_3NaO_7SSi$ $[M+Na]^+$ 604.2483, found 604.2487.

3.4.3. The β-Thioenamides (*Z*)-**9c** and (*E*)-**9c**

To a solution of the carboxylic acid **6c** (75.2 mg, 100 μmol, 1.0 equiv) and *N*-hydroxyphthalimide (18.0 mg, 110 μmol, 1.1 equiv) in dry CH_2Cl_2 (1.0 mL) was added DIC (17.3 μL, 110 μmol, 1.1 equiv) at room temperature under an argon atmosphere, and the mixture was stirred at the same temperature for 5 h. After complete consumption of **5c** (monitored by TLC analysis), the reaction mixture was cooled to −40 °C. A solution of Eosin Y (696 μg, 1.00 μmol, 1 mol%), Hantzsch ester (25.4 mg, 100 μmol, 1.0 equiv) and diphenyl diselenide (62.6 mg, 200 μmol, 2.0 equiv) in dry DMF (1.5 mL, used immediately after Freeze-Pump-Thaw cycling) was then added to the above mixture at −40 °C. After being stirred at the same temperature for 30 min under irradiated Blue LEDs, Et_3N (41.9 μL, 300 μmol, 3.0 equiv) was added to the solution at −40 °C. After being stirred at room temperature for 3 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, diluted with Et_2O, and stirred for 12 h. The organic layer was separated, and the aqueous layer was extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by preparative TLC (eluted with hexane/EtOAc = 7:2, hexane/IPA = 10:1) to afford the β-thioenamide *(Z)*-**9c** (14.6 mg, 20.7 μmol, 21%) as a white amorphous solid and the β-thioenamide *(E)*-**9c** (11.1 mg, 15.8 μmol, 16%) as a white amorphous solid. (*Z*)-**9c**: $[\alpha]^{24}_D$ −25 (*c* 0.83, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.41–8.42 (m, 1H), 7.75 (d, 2H, *J* = 7.5 Hz), 7.49–7.52 (m, 2H), 7.39 (t, 2H, *J* = 7.5 Hz), 7.25–7.28 (m, 7H), 7.17 (dd, 1H, *J* = 10.8, 7.6 Hz) 5.53–5.55 (m, 1H), 5.38–5.40 (m, 1H), 5.33 (d, 1H, *J* = 4.6 Hz), 4.59–4.61 (m, 1H), 4.50–4.52

(m, 1H), 4.42 (dd, 1H, *J* = 10.8, 7.5 Hz), 4.34–4.35 (m, 1H), 4.12–4.18 (m, 3H), 3.68 (s, 3H), 3.31–3.33 (m, 1H), 3.12–3.19 (m, 2H), 1.32 (d, 3H, *J* = 6.8 Hz), 0.93–0.95 (m, 2H), 0.01 (s, 9H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 171.4, 168.9, 156.8, 156.2, 143.83, 143.80, 141.4, 136.2, 129.8, 129.4, 129.0, 127.9, 127.4, 127.2, 125.2, 120.1, 99.8, 67.4, 64.0, 59.0, 56.4, 52.7, 47.2, 45.9, 38.3, 18.3, 17.8, −1.4; IR (neat) 3308, 3064, 3028, 2952, 1696, 1628, 1499, 1451, 1336, 1248, 1178, 1080, 1045, 859, 837, 757, 740, 699 cm^{-1}; HRMS [ESI] *m*/*z* calcd for $C_{37}H_{45}N_3O_7NaSSi$ $[M+Na]^+$ 726.2640, found 726.2649. (*E*)-**9c**: $[\alpha]^{24}_D$ −16 (*c* 0.59, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, 2H, *J* = 7.5 Hz), 7.50 (t, 2H, *J* = 7.5 Hz), 7.40 (t, 2H, *J* = 7.5 Hz), 7.25–7.29 (m, 8H), 6.95–6.99 (m, 1H), 5.58 (d, 1H, *J* = 13.7 Hz), 5.39 (d, 1H, *J* = 9.6 Hz), 5.26–5.28 (m, 1H), 4.45–4.47 (m, 2H), 4.34–4.36 (m, 2H), 4.15–4.17 (m, 3H), 3.63 (s, 3H), 3.36–3.37 (m, 1H), 3.06–3.07 (m, 2H), 1.28 (d, 3H, *J* = 6.8 Hz), 0.99–1.00 (m, 2H), 0.04 (s, 9H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 171.1, 168.0, 156.7, 156.3, 143.6, 141.4, 136.0, 129.3, 129.0, 127.9, 127.4, 127.2, 125.0, 120.1, 104.2, 67.3, 63.8, 57.9, 56.3, 52.5, 47.1, 45.2, 38.0, 18.5, 17.8, −1.4; IR (neat) 3316, 3064, 3027, 2950, 1691, 1626, 1509, 1450, 1338, 1289, 1247, 1216, 1079, 1045, 937, 859, 837, 757, 739, 700 cm^{-1}; HRMS [ESI] *m*/*z* calcd for $C_{37}H_{45}N_3O_7NaSSi$ $[M+Na]^+$ 726.2640, found 726.2643.

3.4.4. The β-Thioenamides (*Z*)-**9d** and (*E*)-**9d**

Compounds *(Z)*-**9d** and *(E)*-**9d** were prepared from the carboxylic acid **6d** (57.1 mg, 99.9 μmol) according to the procedure above described for **9a**, and purified by preparative TLC (eluted with hexane/EtOAc = 7:2, toluene/acetone = 8:1, hexane/IPA = 10:1) to be obtained in 39% yield (20.2 mg, 38.4 μmol) as a white amorphous solid and 19% yield (9.9 mg, 19 μmol) as a white amorphous solid, respectively. (*Z*)-**9d**: $[\alpha]^{23}_D$ +3.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57–8.59 (m, 1H), 7.25–7.34 (m, 5H), 7.14 (dd, 1H, *J* = 10.9, 7.5 Hz), 5.75–5.77 (m, 1H), 5.59–5.61 (m, 1H), 5.32 (d, 1H, *J* = 7.5 Hz), 5.18 (d, 1H, *J* = 12.3 Hz), 5.14 (d, 1H, *J* = 12.3 Hz), 4.54 (dd, 1H, *J* = 8.9, 2.7 Hz), 4.12–4.14 (m, 2H), 3.98 (d, 2H, *J* = 5.5 Hz), 3.64 (s, 3H), 3.35–3.37 (m, 1H), 1.34 (d, 3H, *J* = 6.8 Hz), 0.93–0.95 (m, 2H), −0.01 (s, 9H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 171.3, 167.1, 156.9, 156.8, 136.1, 129.3, 128.6, 128.4, 128.2, 100.1, 67.5, 63.9, 58.7, 52.5, 46.4, 44.9, 18.5, 17.8, −1.4; IR (neat) 3320, 2952, 1700, 1629, 1517, 1338, 1248, 1176, 1081, 1046, 860, 837, 738, 697 cm^{-1}; HRMS [ESI] *m*/*z* calcd for $C_{23}H_{35}N_3O_7NaSSi$ $[M+Na]^+$ 548.1857, found 548.1864. (*E*)-**9d**: $[\alpha]^{23}_D$ +5.0 (*c* 0.50, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31–8.32 (m, 1H), 7.31–7.36 (m, 5H), 7.05 (dd, 1H, *J* = 13.7, 10.9 Hz), 5.72 (d, 1H, *J* = 13.7 Hz), 5.55–5.56 (m, 1H), 5.45 (d, 1H, *J* = 8.9 Hz), 5.12 (s, 2H), 4.48 (dd, 1H, *J* = 8.9, 3.4 Hz), 4.15–4.16 (m, 2H), 3.87 (d, 2H, *J* = 5.5 Hz), 3.70 (s, 3H), 3.37–3.39 (m, 1H), 1.29 (d, 3H, *J* = 6.8 Hz), 0.98–1.00 (m, 2H), 0.03, (s, 9H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 171.3, 166.4, 156.9, 156.7, 135.9, 129.5, 128.7, 128.5, 128.2, 103.7, 67.6, 63.8, 57.9, 52.6, 45.3, 44.8, 18.4, 17.8, −1.4; IR (neat) 3311, 2953, 1696, 1627, 1512, 1454, 1338, 1248, 1174, 1080, 1047, 860, 837, 697 cm^{-1}; HRMS [ESI] *m*/*z* calcd for $C_{23}H_{35}N_3O_7NaSSi$ $[M+Na]^+$ 548.1857, found 548.1866.

3.4.5. The β-Thioenamides (*Z*)-**9e** and (*E*)-**9e**

Compounds *(Z)*-**9e** and *(E)*-**9e** were prepared from the carboxylic acid **6e** (62.2 mg, 99.1 μmol) according to the procedure above described for **9a**, and purified by preparative TLC (eluted with hexane/EtOAc = 7:2) to be obtained in 36% yield (20.5 mg, 35.2 μmol) as a white amorphous solid and 32% yield (18.3 mg, 31.5 μmol) as a white amorphous solid, respectively. (*Z*)-**9e**: $[\alpha]^{24}_D$ −45 (*c* 1.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, 1H, *J* = 10.6 Hz), 7.30–7.33 (m, 5H), 7.19 (dd, 1H, *J* = 10.6, 7.5 Hz), 5.66 (d, 1H, *J* = 8.2 Hz), 5.41 (d, 1H, *J* = 10.0 Hz), 5.34 (d, 1H, *J* = 7.5 Hz), 5.15 (d, 1H, *J* = 12.3 Hz), 5.10 (d, 1H, *J* = 12.3 Hz), 4.55 (dd, 1H, *J* = 10.0, 5.0 Hz), 4.26–4.27 (m, 1H), 4.11–4.15 (m, 2H), 3.61 (s, 3H), 3.33–3.34 (m, 1H), 2.03–2.04 (m, 1H), 1.48–1.49 (m, 1H), 1.37 (d, 3H, *J* = 6.8 Hz), 1.18–1.24 (m, 1H), 0.97 (d, 3H, *J* = 7.6 Hz), 0.94–0.97 (m, 2H), 0.91 (t, 3H, *J* = 7.6 Hz), 0.01 (s, 9H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 171.5, 169.3, 156.8, 156.5, 136.2, 130.0, 128.6, 128.34, 128.26, 99.1, 67.4, 63.9, 60.1, 59.2, 52.6, 45.6, 37.3, 24.6, 18.2, 17.8, 15.7, 11.6, −1.4; IR (neat) 3314, 3065, 3033, 2959, 1720, 1695, 1628, 1512, 1381, 1337, 1283, 1248, 1178, 1127, 1080, 1043, 938, 860, 837,

773, 738, 696 cm^{-1}; HRMS [ESI] *m*/*z* calcd for $C_{27}H_{43}N_3NaO_7SSi$ $[M+Na]^+$ 604.2483, found 604.2487. (*E*)-**9e**: $[\alpha]^{24}_D$ +8.8 (*c* 0.78, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 8.35–8.37 (m, 1H), 7.30–7.35 (m, 5H), 7.04 (dd, 1H, *J* = 13.7, 10.3 Hz), 5.71 (d, 1H, *J* = 13.7 Hz), 5.46–5.47 (m, 2H), 5.10 (d, 1H, *J* = 12.0 Hz), 5.05 (d, 1H, *J* = 12.0 Hz), 4.48 (dd, 1H, *J* = 8.9, 3.4 Hz), 4.14–4.16 (m, 2H), 4.01 (t, 1H, *J* = 7.9 Hz), 3.65 (s, 3H), 3.40–3.41 (m, 1H), 1.85–1.93 (m, 1H), 1.48–1.50 (m, 1H), 1.29 (d, 3H, *J* = 6.8 Hz), 1.08–1.11 (m, 1H), 0.98–1.00 (m, 2H), 0.91 (d, 3H, *J* = 6.8 Hz), 0.87 (t, 3H, *J* = 7.5 Hz), 0.02 (s, 9H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 171.3, 168.8, 156.8, 156.7, 136.0, 129.5, 128.7, 128.4, 128.1, 103.9, 67.4, 63.8, 59.9, 57.9, 52.5, 45.4, 37.1, 24.8, 18.6, 17.8, 15.6, 11.3, −1.4; IR (neat) 3297, 2960, 2929, 1747, 1714, 1692, 1664, 1630, 1515, 1455, 1380, 1335, 1283, 1242, 1211, 1176, 1081, 1041, 862, 836, 697 cm^{-1}; HRMS [ESI] *m*/*z* calcd for $C_{27}H_{43}N_3NaO_7SSi$ $[M+Na]^+$ 604.2483, found 604.2485.

3.4.6. The β-Thioenamides (*Z*)-**9f** and (*E*)-**9f**

Compounds *(Z)*-**9f** and *(E)*-**9f** were prepared from the carboxylic acid **6f** (74.9 mg, 101 μmol) according to the procedure above described for **9a**, and purified by preparative TLC (eluted with hexane/EtOAc = 3.5:1 to 2:1, hexane/IPA = 20:1, toluene/acetone = 20:1, hexane/*t*BuOH = 9:1) to be obtained in 28% yield (19.9 mg, 28.6 μmol) as a white amorphous solid and 16% yield (11.5 mg, 16.5 μmol) as a white amorphous solid, respectively. *(Z)*-**9f**: $[\alpha]^{23}_D$ −7.6 (*c* 1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 8.58 (d, 1H, *J* = 10.3 Hz), 7.30–7.34 (m, 5H), 7.14 (dd, 1H, *J* = 10.3, 6.8 Hz), 5.63–5.65 (m, 2H), 5.31 (d, 1H, *J* = 6.8 Hz), 5.15 (d, 1H, *J* = 12.3 Hz), 5.10 (d, 1H, *J* = 12.3 Hz), 4.62–4.61 (m, 1H), 4.55 (dd, 1H, *J* = 9.6, 3.4 Hz), 4.24–4.25 (m, 1H), 4.12–4.14 (m, 2H), 3.63 (s, 3H), 3.38–3.40 (m, 1H), 3.16–3.18 (m, 1H), 3.07–3.08 (m, 1H), 1.96–1.97 (m, 1H), 1.82–1.83 (m, 1H), 1.69–1.70 (m, 1H), 1.41–1.48 (m, 12H), 1.35 (d, 3H, *J* = 7.5 Hz), 0.95–0.96 (m, 2H), 0.03 (s, 9H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 171.4, 169.7, 156.9, 156.6, 156.4, 136.2, 129.6, 128.6, 128.3, 99.9, 79.3, 67.4, 63.8, 58.8, 55.3, 52.5, 46.1, 39.7, 31.4, 29.7, 28.5, 22.5, 18.5, 17.8, −1.4; IR (neat) 3325, 2952, 1698, 1628, 1522, 1365, 1337, 1249, 1172, 1080, 1045, 860, 837, 754, 697 cm^{-1}; HRMS [ESI] *m*/*z* calcd for $C_{32}H_{52}N_4O_9NaSSi$ $[M+Na]^+$ 719.3116, found 719.3137. *(E)*-**9f**: $[\alpha]^{23}_D$ +0.1 (*c* 0.58, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 8.57–8.58 (m, 1H), 7.30–7.35 (m, 5H), 7.04 (dd, 1H, *J* = 13.3, 10.6 Hz), 5.71 (d, 1H, *J* = 13.3 Hz), 5.60–5.62 (m, 1H), 5.44 (d, 1H, *J* = 10.6 Hz), 5.08 (s, 2H), 4.68–4.70 (m, 1H), 4.47 (dd, 1H, *J* = 8.9, 3.4 Hz), 4.14–4.16 (m, 3H), 3.66 (s, 3H), 3.38–3.40 (m, 1H), 3.06–3.08 (m, 2H), 1.96–1.98 (m, 1H), 1.83–1.85 (m, 1H), 1.63–1.65 (m, 1H), 1.28–1.48 (m, 3H), 1.40 (s, 9H), 1.29 (d, 3H, *J* = 6.8 Hz), 0.98–1.00 (m, 2H), 0.02 (s, 9H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 171.3, 169.3, 156.8, 156.7, 156.5, 136.0, 129.9, 128.6, 128.4, 128.2, 103.5, 79.5, 67.4, 63.8, 57.9, 54.8, 52.5, 45.4, 39.4, 31.3, 29.5, 28.5, 22.3, 18.6, 17.8, −1.4; IR (neat) 3313, 2952, 1694, 1628, 1513, 1454, 1365, 1337, 1248, 1172, 1081, 1045, 860, 837, 754 cm^{-1}; HRMS [ESI] *m*/*z* calcd for $C_{32}H_{52}N_4O_9NaSSi$ $[M+Na]^+$ 719.3116, found 719.3125.

4. Conclusions

In summary, we have demonstrated the formation of AviMeCys using lanthionine-bearing peptides **1**. The decarboxylative selenoetherification of the NHPI esters **7** smoothly proceeded at a low temperature (−40 °C) in the presence of 1 mol% of eosin Y-Na_2 as a photocatalyst, and subsequent β-elimination in a one-pot operation resulted in the corresponding β-thioenamides **9** in moderate to good yields without losing the sulfide-bridged motif. The carbamate-type protecting groups, such as Cbz, Teoc, Boc and Fmoc groups, were tolerant under the reaction conditions, suggesting that the reaction should be useful in synthesizing structurally complicated RiPPs. The synthesis of neothioviridamide [49,50] and its related natural products [51–54] is underway.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/catal12121615/s1, Figure S1: Experimental setup for photocatalyzed oxidative decarboxylation; Figure S2. Emission spectrum for Kessil A160WE Tuna Blue; ^1H and $^{13}C\{^1H\}$ NMR spectra of synthetic compounds.

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