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Design and synthesis of caged ceramide: UV-responsive ceramide releasing system based on UV-induced amide bond cleavage followed by *O*–*N* acyl transfer

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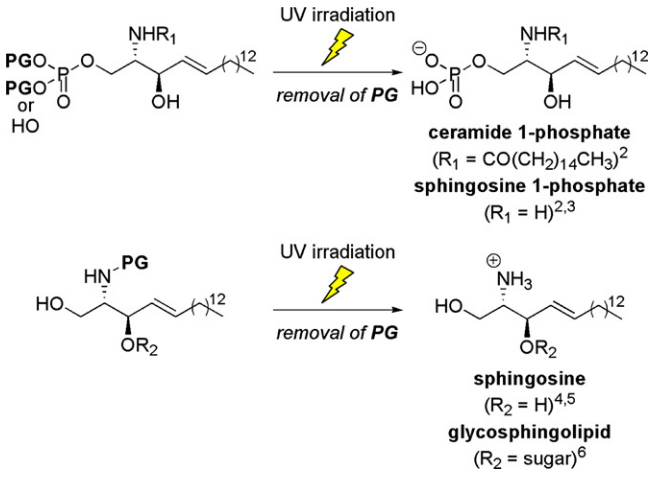
ABSTRACT

Sphingolipids, recognized as membrane constructs and as key signaling molecules, have been studied to examine intracellular function. Some caged sphingolipids that release parent sphingolipids after exposure to UV-irradiation have been previously developed, but caged ceramide has yet to be reported. In this study, we report the design and synthesis of a caged ceramide. Photo-irradiation experiment clarified that the caged ceramide can be successfully converted to the parent ceramide by UV-irradiation. Introduction of an alkyne-handle moiety for further modification of the caged ceramide is also reported.

1. Introduction

In the field of cell biology, sphingolipids have been recognized not only as membrane constructs but also as key signaling molecules in recent years.[1] In an effort to study on the mechanism of sphingolipid mediated biological phenomena, caged sphingolipids, which release sphingolipids after exposure to UV-irradiation are needed to enable spatiotemporal control of the function of sphingolipids. Recently, some caged sphingolipids, such as ceramide 1-phosphate,[2] sphingosine 1-phosphate,[2,3] sphingosine,[4,5] dehydrosphingosine,[5] phychosine,[5] and glycosphingolipids[6] were reported (Scheme 1). In these molecules, a highly polar phosphate or amine moiety was temporarily masked by a less polar photo-responsive protective group to suppress their biological activity. UV-irradiation induces release of the phosphate or the amine moiety followed by drastic polarity change to recover their bioactivity. Moreover, ceramide is a member of the sphingolipids and is also involved in critical cellular events such as apoptosis.[7,1] To our knowledge, however, a caged ceramide has not been reported so far presumably due to its lack of highly polar functional group available for caging. Therefore, we decided to design a caged ceramide in which the ceramide activity is recovered not via polarity change but via structural change. In this paper, we report development and photo-reactivity of a caged ceramide that generates a parent ceramide by acyl transfer-mediated structural change after exposure to UV-irradiation.



Scheme 1. Representative caged sphingolipids previously reported (PG: protective group removable by UV-irradiation).

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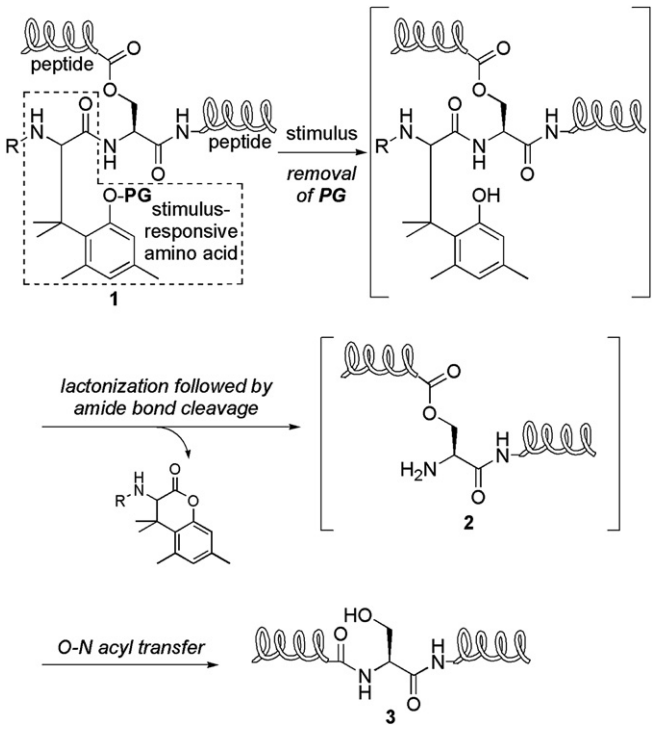
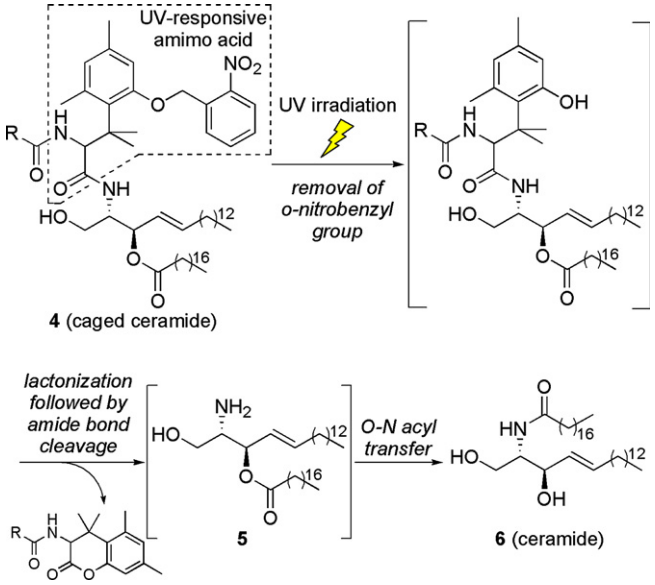
Previously, we reported the development of stimulus-responsive amino acids and their application to control peptidyl function in living cells (Scheme 2).[8] In this system, an amide bond in peptide **1** at a C-terminal position of the stimulus-responsive amino acid is cleaved by stimulus-induced removal of PG (protective group removable by a stimulus) followed by lactonization of trimethyl lock



Scheme 2. Stimulus-responsive controlling system of peptidyl function (PG: protective group removable by a stimulus).

moiety[9] to generate isopeptide **2**. In a manner similar to a click peptide or a switch peptide,[10] isopeptide **2** can easily isomerize via *O*–*N* acyl transfer to yield a linear bioactive peptide under physiological conditions. Ceramide **6** also possesses an *N*-acyl 1,2-aminoalcohol unit similar to peptide **3** (Scheme 3). Therefore, we designed caged ceramide **4** composed of *N*-UV-responsive amino acyl moiety and *O*-stearyl moiety at 1,2-position. Upon UV-induced removal of *o*-nitrobenzyl group and subsequent lactonization followed by amide bond cleavage, generated *O*-stearyl intermediate **5** should easily isomerize to afford ceramide **6** via *O*–*N* acyl transfer. Because intracellular distribution of ceramide is a key factor in its biological activity,[11] we planned to introduce a handle at R position for facile attachment of a functional moiety such as an intracellular localization signal peptide for controlling the distribution of the caged ceramide in living cells.



Scheme 3. Design of caged ceramide (R=functional moiety).

2. Results and discussion

2.1. Synthesis of caged ceramide

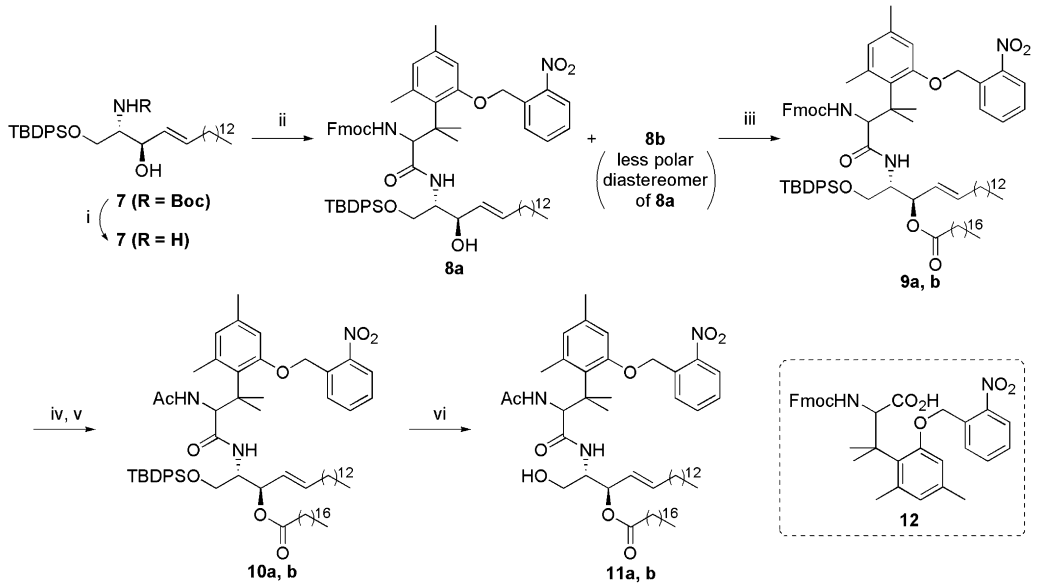
Model caged ceramide **11** was synthesized as shown in Scheme 4. For simplification, an acetyl group was introduced at N-terminal position of UV-responsive amino acid. Starting from known sphingosine derivative **7** (R=Boc),[12] the Boc group was removed under acidic conditions, and the generated amino group of **7** (R=H) was acylated with racemic Fmoc protected UV-responsive amino acid **12**[8e] using *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU). The obtained product was diastereomerically purified, and each diastereomer **8a** or **8b** was subjected to the following reactions, respectively. The hydroxyl group of **8** was acylated with stearic acid to afford **9**. The Fmoc group of **9** was replaced with acetyl group by treatment with piperidine followed by acylation with acetic acid. Finally, the TBDPS group was removed using HF/pyridine to generate model caged ceramide **11**.

2.2. UV-irradiation experiment

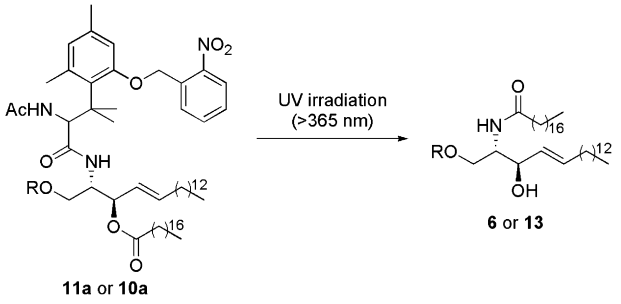
First, UV-irradiation experiment of caged ceramide **11a** was examined. Caged ceramide **11a** in *i*-PrOH[13] with 0.5% (v/v) triethylamine was irradiated by UV (>365 nm) for 1 h, and the reaction mixture was stirred overnight (Scheme 5). Although generation of ceramide **6** was confirmed by ESI-MS and TLC analysis of the crude reaction mixture, isolation of that was quite difficult because a complex mixture was obtained after evaporation. We thought that the complication after evaporation was caused by a side reaction of highly reactive *o*-nitrosobenzaldehyde or its derivative under concentrated conditions. Therefore, HPLC analysis of the crude material without evaporation was attempted. However, detection of an authentic sample of ceramide **6** by UV-absorption was difficult because of its low extinction coefficient. For sensitive HPLC analysis of the reaction, analogous **10a** possessing TBDPS group that absorbs UV efficiently was used rather than original **11a**, and ceramide analogue **13** was easily detected by UV-absorption. Therefore, we used caged ceramide analogue **10a** for HPLC monitoring of the UV-irradiation experiment as shown below. Caged ceramide analogue **10a** in *i*-PrOH/H_2O=1:1 with 0.5% (v/v) triethylamine was irradiated by UV (>365 nm) for 3 min,[14] and the reaction mixture was incubated at 37 °C. Reaction progress was monitored by HPLC, and ceramide analogue **13** was identified by ESI-MS and comparison of retention time with that of an authentic sample.[15] After UV-irradiation and subsequent 5 h incubation, caged ceramide analogue **10a** was completely converted to ceramide analogue **13** as shown in Fig. 1. This result suggests that caged ceramide **11** should also be converted to ceramide **6** in high purity.

2.3. Introduction of alkyne handle on caged ceramide

Intracellular distribution of ceramide is one of the key factors in its biological activity.[11] Therefore, introduction of a handle to enable facile attachment of a functional moiety, such as an intracellular localization signal peptide, is of value for spatiotemporal control of ceramide function. In this context, we planned to



Scheme 4. Reagents and conditions: (i) TFA, CH_2Cl_2, 76%; (ii) **12**, HBTU, *N*,*N*-diisopropylethylamine, DMF, 39% for **8a**, 41% for **8b**. Chemical yields of **8a** derivatives are presented in following text; (iii) stearic acid, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl), Et_3N, DMAP, CH_2Cl_2, 99%; (iv) piperidine, DMF; (v) AcOH, EDC·HCl, 1-hydroxybenzotriazole hydrate (HOBt·H_2O), Et_3N, DMF, 78% (two steps); (vi) HF, pyridine, 73%.



Scheme 5. Reagents and conditions: **11a** to **6** (R=H): UV-irradiation (>365 nm, 1 h) in *i*-PrOH with 0.5% (v/v) Et_3N followed by stirring at room temperature. **10a** to **13** (R=TBDPS): UV-irradiation (>365 nm, 3 min) in H_2O/*i*-PrOH (1:1 (v/v)) with 0.5% (v/v) Et_3N followed by incubation at 37 °C.

introduce an alkyne handle on the caged ceramide for click chemistry with a functional moiety (Scheme 6).[16] Caged ceramide **14** possessing an alkyne handle was synthesized starting from Fmoc derivative **9**. Briefly, the Fmoc group of **9** was removed by piperidine treatment, and the generated amine was acylated with 4-pentynoic acid. The obtained material was subjected to TBAF and acetic acid in THF to remove TBDPS group, and alkyne derivative **14** was synthesized successfully.

Next, we examined ligation of caged ceramide **14b** with a functional moiety (Scheme 7). For simplification of the reaction system, benzyl azide was used as a model of the functional moiety. To caged ceramide **14b** in H_2O/dichloromethane (1:1 (v/v)) were added benzyl azide, $CuSO_4$, sodium ascorbate, and tris(1-benzyl-1*H*-[1,2,3]triazol-4-ylmethyl)amine (TBTA) **16**;[17] ligated product **15b** was obtained in 91% isolated yield. This result suggests that the alkyne handle on the caged ceramide is potentially applicable for introduction of a functional moiety.

3. Conclusion

In conclusion, a caged ceramide was developed. UV-irradiation experiment clarified that the caged ceramide with TBDPS group can be completely converted to the corresponding ceramide derivative by 3 min of UV-irradiation followed by 5 h of incubation at 37 °C. Introduction of an alkyne-handle moiety on the caged ceramide was also examined, and the caged ceramide was successfully coupled with an azide derivative by click chemistry. Introduction of a functional moiety and biological application of the caged ceramide in living cells are underway.

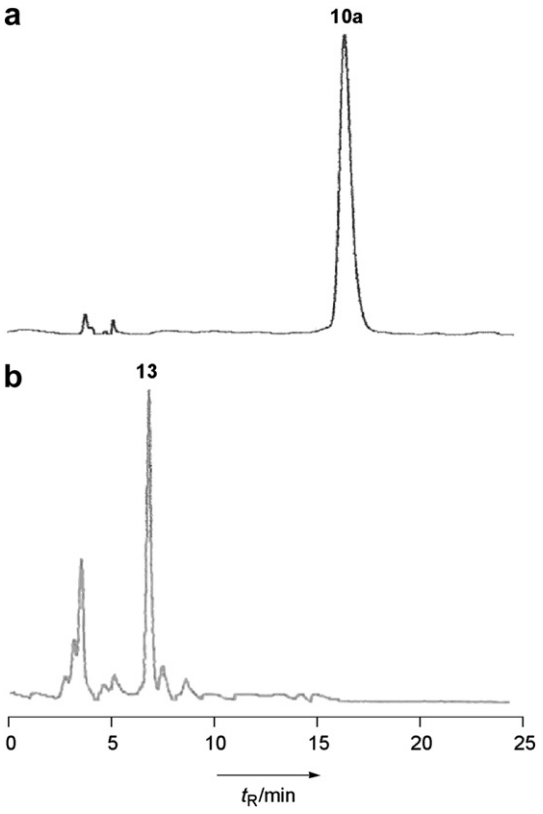
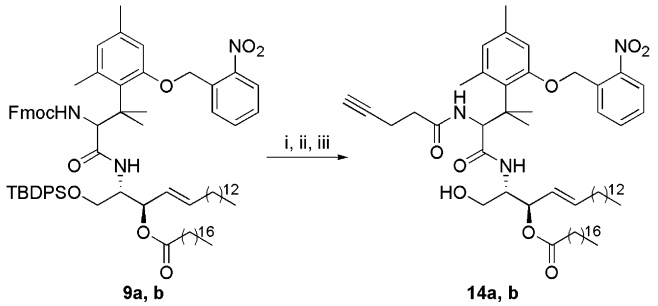
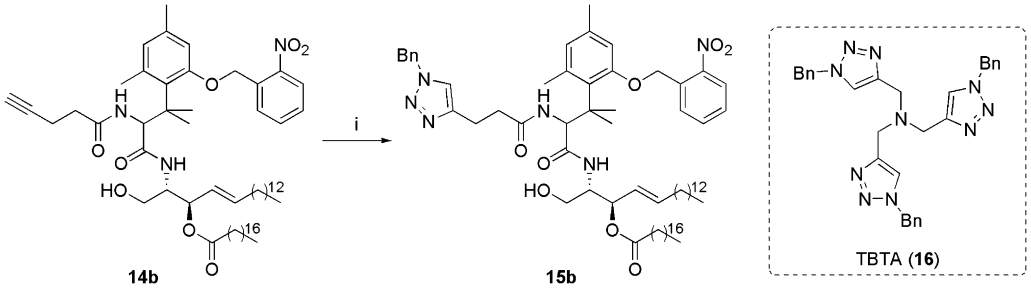


Fig. 1. HPLC profiles of UV-induced uncaging of caged ceramide analogue **10a**. Reaction conditions are shown in Scheme 5. (a) Before UV-irradiation. (b) After UV-irradiation (>365 nm, 3 min) followed by incubation at 37 °C for 5 h. Compounds eluted at 3–4 min are photo-cleaved derivatives of UV-responsive amino acid. HPLC conditions: TOSOH TSK-GEL (4.6×250 mm) with hexane/*i*-PrOH=99:1 (v/v) at a flow rate of 1.0 mL/min, detection at 220 nm.



Scheme 6. Reagents and conditions: (i) piperidine, DMF; (ii) 4-pentynoic acid, EDC·HCl, HOBt·H_2O, Et_3N, DMF; (iii) TBAF, AcOH, THF, 76% for **14a** (three steps).



Scheme 7. Reagents and conditions: (i) benzyl azide, 0.1 equiv $CuSO_4$, 0.3 equiv sodium ascorbate, 0.1 equiv TBTA (**16**), H_2O/CH_2Cl_2=1:1 (v/v), 91%.

4. Experimental section

4.1. General methods

All reactions were carried out under a positive pressure of argon. For column chromatography, silica gel (KANTO KAGAKU N-60) was employed. Exact mass spectra were recorded on a Waters MICROMASS® LCT PREMIER™ or a Bruker Esquire200 T. NMR spectra were measured using a JEOL GSX400 or a JEOL GSX300 spectrometer. For HPLC analysis, a TSK-GEL Silica-60 analytical column (TOSOH, 4.6×250 mm, flow rate at 1.0 mL/min) was employed, and eluting products were detected by UV at 220 nm (flow rate: 1.0 mL/min; solvent system: hexane and *i*-PrOH). Photolysis was performed using Moritex MUV-202U with the filtered output (>365 nm) of a 3000 mW/cm^2 Hg–Xe lamp. Optical rotations were measured using a JASCO P-2200 polarimeter (concentration in g/100 mL).

4.2. Synthesis of caged ceramide

*4.2.1. (2S,3R,4E)-2-Amino-1-(tert-butyldiphenylsilanyloxy)octadec-4-en-3-ol (**7** (R=H)).* Trifluoroacetic acid (2.0 mL) was added to a solution of *N*-Boc derivative **7** (R=Boc)[12] (1.50 g, 2.35 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C. The resulting mixture was stirred at room temperature for 5 h and was quenched by the addition of saturated aqueous solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with brine, dried over Na_2SO_4, **and** concentrated in vacuo. The obtained crude material was purified by column chromatography (hexane/AcOEt=2:1 (v/v)) and 0.960 g of amine **7** (R=H) (76%) was obtained as a colorless oil; $[\alpha]_D^{18}$ +8.80 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ=0.88 (3H, t, *J*=6.8 Hz), 1.06 (9H, s), 1.25 (22H, m), 2.01 (2H, dt, *J*=6.6 and 6.8 Hz), 2.93 (1H, q, *J*=5.6 Hz), 3.67 (1H, dd, *J*=5.4 and 10.0 Hz), 3.70 (1H, dd, *J*=5.9 and 10.0 Hz), 4.09 (1H, dd, *J*=5.6 and 6.8 Hz), 5.40 (1H, dd, *J*=6.8 and 15.4 Hz), 5.73 (1H, dt, *J*=6.6 and 15.4 Hz), 7.26–7.47 (6H, m), 7.64–7.69 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=14.0, 19.1, 22.6, 26.7, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 31.8, 32.2, 56.4, 65.9, 74.0, 127.6, 129.1, 129.6, 133.1, 133.6, 135.4; HRMS (ESI-TOF) calcd for $C_{34}H_{56}NO_2Si$ ([M+H]$^+$): 538.4080, found: 538.4078.

*4.2.2. {1-[(1S,2R,3E)-1-(tert-Butyldiphenylsilanyloxymethyl)-2-hydroxyheptadec-3-enylcarbamoyl]-2-[2,4-dimethyl-6-(2-nitrobenzyloxy)phenyl]-2-methylpropyl}carbamic acid 9H-fluoren-9-ylmethyl ester (**8a**, **b**).* *N*,*N*-Diisopropylethylamine (107 μL, 0.610 mmol) and HBTU (201 mg, 0.530 mmol) were added to a solution of carboxylic acid **12**[8e] (332 mg, 0.560 mmol) in DMF (1.0 mL) at room temperature. After 30 min of stirring at room temperature, TBDPS sphingosine **7** (R=H) (300 mg, 0.56 mmol) was added to the solution. The resulting mixture was stirred at room temperature for 3 h and was quenched by the addition of 5% (w/v) aqueous solution of $KHSO_4$. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The obtained crude product was purified by column chromatography (hexane/AcOEt=10:1 (v/v)) and 243 mg of **8a** (39%) and 253 mg of **8b** (41%, less polar diastereomer of **8a**) were obtained as a colorless amorphousness. Compound **8a** (polar diastereomer): $[\alpha]_D^{19}$ +0.88 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ=0.88 (3H, t, *J*=6.8 Hz), 1.00 (9H, s), 1.18–1.31 (22H, m), 1.50 (3H, s), 1.55 (3H, s), 1.91 (2H, dt, *J*=6.6 and 7.1 Hz), 2.00 (3H, s), 2.28 (3H, s), 2.97 (1H, br s), 3.14 (1H, dd, *J*=7.3 and 9.5 Hz), 3.42 (1H, dd, *J*=3.2 and 9.5 Hz), 3.97 (1H, m), 4.15 (2H, m), 4.20 (1H, m), 4.34 (1H, m), 5.29 (1H, dd, *J*=6.6 and 15.4 Hz), 5.32 (1H, d, *J*=8.3 Hz), 5.38 (1H, d, *J*=14.6 Hz), 5.48 (1H, d, *J*=8.3 Hz), 5.60 (1H, d, *J*=14.6 Hz), 5.64 (1H, dt, *J*=7.1 and 15.4 Hz), 5.70 (1H, d, *J*=8.3 Hz), 6.30 (1H, s), 6.47 (1H, s), 7.29 (2H, d, *J*=7.8 Hz), 7.34–7.51 (10H, m), 7.53–7.66 (6H, m), 7.75 (2H, d, *J*=7.8 Hz), 7.94 (1H, d, *J*=7.8 Hz), 8.16 (1H, d, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=14.1, 19.0, 20.6, 22.7, 25.6, 26.7, 28.0, 29.1, 29.3, 29.5, 29.6, 29.7, 31.9, 32.3, 45.1, 47.1, 54.4, 59.5, 62.8, 67.0, 68.8, 73.4, 113.2, 119.9, 125.1, 125.2, 127.0, 127.6, 127.8, 128.5, 128.8, 129.4, 129.6, 129.9, 132.5, 132.6, 133.4, 134.2, 134.4, 135.5, 137.2, 138.5, 141.2, 143.9, 146.9, 156.2, 157.8, 171.0; HRMS (ESI-TOF) calcd for $C_{69}H_{88}N_3O_8Si$ ([M+H]$^+$): 1114.6341, found: 1114.6370. Compound **8b** (less polar diastereomer): $[\alpha]_D^{18}$ −1.11 (*c* 1.09, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ=0.88 (3H, t, *J*=6.8 Hz), 0.93 (9H, s), 1.26 (22H, m), 1.58 (3H, s), 1.67 (3H, s), 1.96 (2H, q, *J*=6.8 Hz), 2.21 (3H, s), 2.53 (3H, s), 2.60 (1H, d, *J*=8.5 Hz), 3.59 (1H, m), 3.63 (1H, m), 3.72 (1H, dd, *J*=3.9 and 10.3 Hz), 3.78 (1H, m), 4.24 (2H, m), 4.46 (1H, m), 5.20 (1H, dd, *J*=5.6 and 15.4 Hz), 5.48 (1H, d, *J*=9.0 Hz), 5.55 (1H, d, *J*=15.1 Hz), 5.60 (1H, dt, *J*=6.8 and 15.4 Hz), 5.69 (1H, d, *J*=15.1 Hz), 5.75 (1H, d, *J*=9.0 Hz), 5.94 (1H, d, *J*=7.6 Hz), 6.64 (1H, s), 6.66 (1H, s), 7.26–7.44 (10H, m), 7.48–7.65 (8H, m), 7.77 (2H, d, *J*=7.8 Hz), 8.10 (1H, d, *J*=7.8 Hz), 8.15 (1H, d, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=14.1, 18.9, 20.7, 22.7, 25.8, 26.4, 28.3, 29.1, 29.3, 29.5, 29.6, 29.7, 31.9, 32.3, 45.5, 47.2, 53.9, 59.4, 63.4, 67.1, 68.9, 73.3, 113.5, 119.9, 125.2, 127.0, 127.7, 127.8, 128.3, 128.8, 129.4, 129.7, 129.9, 132.2, 132.4, 133.1, 133.6, 134.6, 135.4, 137.4, 138.7, 141.2,

143.9, 146.7, 156.2, 158.2, 170.9; HRMS (ESI-TOF) calcd for $C_{69}H_{87}N_3NaO_8Si$ ($[M+Na]^+$): 1136.6160, found: 1136.6167.

*4.2.3. Octadecanoic acid (1R,2E)-1-{(1S)-2-(tert-butyldiphenylsilanyloxy)-1-[3-[2,4-dimethyl-6-(2-nitrobenzyloxy)phenyl]-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-methylbutyrylamino]ethyl} hexadec-2-enyl ester (**9a**, **b**). Typical procedure*. Triethylamine (56.0 μL, 0.400 mmol), EDC·HCl (56.8 mg, 0.300 mmol), and DMAP (0.8 mg, 7 μmol) were added to a solution of stearic acid (77.0 mg, 0.270 mmol) in CH_2Cl_2 (0.50 mL) at room temperature. After 30 min of stirring at room temperature, alcohol **8a** (150 mg, 0.130 mmol) was added to the reaction mixture. The resulting solution was stirred at the same temperature for 3 h and was quenched by the addition of saturated aqueous solution of $NaHCO_3$. The obtained mixture was extracted with CH_2Cl_2, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The obtained residue was purified by column chromatography (hexane/AcOEt=10:1 (v/v)) and 185 mg of ester **9a** (99%) was obtained as a colorless amorphousness. Compound **9a**: $[\alpha]_D^{19}$ +2.22 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ=0.88 (6H, t, *J*=6.8 Hz), 1.01 (9H, s), 1.18–1.31 (52H, m), 1.50 (3H, s), 1.58 (3H, s), 1.88 (2H, dt, *J*=6.6 and 7.1 Hz), 1.99 (3H, s), 2.17 (2H, dt, *J*=2.7 and 7.6 Hz), 2.20 (3H, s), 2.88 (1H, m), 3.25 (1H, m), 4.17 (2H, m), 4.24 (1H, m), 4.37 (1H, m), 5.19 (1H, dd, *J*=7.1 and 15.4 Hz), 5.36 (1H, d, *J*=8.5 Hz), 5.41 (1H, d, *J*=15.4 Hz), 5.34–5.49 (2H, m), 5.62 (1H, d, *J*=15.4 Hz), 5.67 (1H, dt, *J*=7.1 and 15.4 Hz), 5.71 (1H, d, *J*=8.5 Hz), 6.23 (1H, s), 6.45 (1H, s), 7.29 (2H, q, *J*=7.8 Hz), 7.35–7.53 (10H, m), 7.55–7.67 (6H, m), 7.75 (2H, d, *J*=7.8 Hz), 8.00 (1H, d, *J*=7.8 Hz), 8.16 (1H, d, *J*=7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.1, 19.1, 20.6, 22.7, 24.8, 25.5, 26.7, 27.9, 28.9, 29.1, 29.2, 29.3, 29.5, 29.6, 29.7, 31.9, 32.4, 34.3, 45.2, 47.1, 52.4, 59.3, 61.5, 67.0, 68.8, 73.4, 113.2, 119.9, 123.5, 125.0, 125.1, 127.0, 127.6, 127.7, 127.8, 128.3, 128.7, 129.3, 129.4, 129.7, 129.8, 132.7, 133.1, 133.6, 134.4, 135.5, 135.6, 136.6, 137.0, 138.5, 141.2, 143.9, 146.7, 156.3, 157.8, 170.3, 172.8; HRMS (ESI-TOF) calcd for $C_{87}H_{121}N_3NaO_9Si$ ($[M+Na]^+$): 1402.8770, found: 1402.8751. Compound **9b**: $[\alpha]_D^{19}$ −6.63 (*c* 1.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ=0.88 (6H, t, *J*=6.6 Hz), 0.97 (9H, s), 1.26 (52H, m), 1.56 (3H, s), 1.65 (3H, s), 1.90 (2H, dt, *J*=6.8 and 7.1 Hz), 2.16 (3H, s), 2.16 (2H, t, *J*=7.3 Hz), 2.53 (3H, s), 3.47 (1H, dd, *J*=6.6 and 10.3 Hz), 3.59 (1H, dd, *J*=4.4 and 10.3 Hz), 4.14 (2H, m), 4.26 (1H, m), 4.33 (1H, m), 5.10 (2H, m), 5.40 (1H, d, *J*=9.0 Hz), 5.45–5.73 (4H, m), 5.76 (1H, d, *J*=9.0 Hz), 6.51 (1H, s), 6.58 (1H, s), 7.27 (2H, t, *J*=7.8 Hz), 7.31–7.43 (9H, m), 7.48–7.63 (7H, m), 7.74 (2H, d, *J*=7.8 Hz), 7.97 (1H, d, *J*=7.8 Hz), 8.12 (1H, d, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=14.0, 19.1, 20.7, 22.6, 24.8, 25.8, 26.8, 27.2, 27.9, 29.0, 29.2, 29.3, 29.5, 29.6, 29.7, 31.9, 32.3, 34.3, 45.1, 47.3, 53.3, 59.9, 62.3, 67.0, 68.9, 74.0, 113.5, 119.8, 119.9, 124.6, 124.9, 125.1, 125.2, 127.0, 127.6, 127.7, 128.3, 128.8, 129.6, 129.7, 133.1, 133.8, 134.2, 135.5, 136.4, 137.0, 138.5, 141.2, 141.3, 144.0, 147.1, 156.1, 158.3, 170.5, 172.5; HRMS (ESI-TOF) calcd for $C_{87}H_{122}N_3O_9Si$ ($[M+H]^+$): 1380.8950, found: 1380.8928.

*4.2.4. Octadecanoic acid (1R,2E)-1-[(1S)-1-{2-acetylamino-3-[2,4-dimethyl-6-(2-nitrobenzyloxy)phenyl]-3-methylbutyrylamino}-2-(tert-butyldiphenylsilanyloxy)ethyl]hexadec-2-enyl ester (**10a**, **b**). Typical procedure*. Fmoc derivative **9a** (150 mg, 110 μmol) was treated with 20% (v/v) piperidine/DMF (1.0 mL) at room temperature. After 30 min of stirring, the reaction mixture was evaporated to remove piperidine and DMF. To the residue dissolved in DMF (0.50 mL) was added a preactivated acetylation reagent (a 30-min stirred solution of acetic acid (31.0 μL, 540 μmol), HOBt·H_2O (92.0 mg, 600 μmol), and EDC·HCl (100 mg, 540 μmol) in DMF (0.50 mL)). The resulting mixture was stirred at room temperature for 3 h and was quenched by the addition of saturated aqueous solution of $NaHCO_3$. The mixture was extracted with ether, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The obtained residue was purified by column chromatography (hexane/AcOEt=5:1 (v/v)) and 100 mg of compound **10a** (78%) was obtained as a colorless oil. Compound **10a**: $[\alpha]_D^{20}$ +4.33 (*c* 0.84, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ=0.88 (6H, t, *J*=6.8 Hz), 1.01 (9H, s), 1.25 (52H, m), 1.45 (3H, s), 1.47 (3H, s), 1.87 (2H, dt, *J*=6.3 and 6.8 Hz), 1.98 (3H, s), 1.99 (3H, s), 2.16 (3H, s), 2.19 (2H, dt, *J*=2.7 and 7.6 Hz), 2.79 (1H, dd, *J*=9.0 and 10.0 Hz), 3.18 (1H, dd, *J*=4.6 and 10.0 Hz), 4.19 (1H, dddd, *J*=3.4, 4.6, 9.0 and 9.3 Hz), 5.14 (1H, dd, *J*=7.3 and 15.4 Hz), 5.31 (1H, d, *J*=9.3 Hz), 5.37 (1H, d, *J*=15.1 Hz), 5.44 (1H, dd, *J*=3.4 and 7.3 Hz), 5.59 (1H, d, *J*=9.0 Hz), 5.62 (1H, d, *J*=15.1 Hz), 5.64 (1H, dt, *J*=6.8 and 15.4 Hz), 6.19 (1H, s), 6.31 (1H, d, *J*=9.0 Hz), 6.45 (1H, s), 7.36–7.46 (6H, m),7.49 (1H, t, *J*=7.8 Hz), 7.58–7.65 (4H, m), 7.72 (1H, t, *J*=7.8 Hz), 8.07 (1H, d, *J*=7.8 Hz), 8.14 (1H, d, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=14.1, 19.1, 20.6, 22.7, 23.5, 24.8, 25.4, 26.4, 26.7, 28.1, 28.9, 29.1, 29.3, 29.5, 29.6, 29.7, 31.9, 32.4, 34.3, 45.3, 52.5, 57.2, 61.4, 68.9, 73.3, 113.2, 123.2, 125.0, 127.7, 127.8, 128.4, 128.7, 129.5, 129.8, 132.8, 133.5, 134.5, 135.5, 135.6, 136.5, 137.0, 138.5, 146.7, 157.9, 169.7, 170.5, 172.8; HRMS (ESI-TOF) calcd for $C_{74}H_{113}N_3NaO_8Si$ ($[M+Na]^+$): 1222.8195, found: 1222.8179. Compound **10b**: $[\alpha]_D^{19}$ −6.72 (*c* 0.81, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ=0.88 (6H, t, *J*=6.8 Hz), 0.97 (9H, s), 1.25 (52H, m), 1.53 (3H, s), 1.62 (3H, s), 1.89 (2H, dt, *J*=6.8 and 7.6 Hz), 1.92 (3H, s), 2.15 (2H, dt, *J*=7.3 and 8.3 Hz), 2.18 (3H, s), 2.51 (3H, s), 3.44 (1H, dd, *J*=6.6 and 10.3 Hz), 3.55 (1H, dd, *J*=4.6 and 10.3 Hz), 4.23 (1H, m), 5.02–5.12 (2H, m), 5.48 (1H, d, *J*=15.4 Hz), 5.57 (1H, dt, *J*=6.6 and 13.9 Hz), 5.65 (1H, d, *J*=9.3 Hz), 5.65 (1H, d, *J*=9.0 Hz), 5.66 (1H, d, *J*=15.4 Hz), 6.36 (1H, d, *J*=9.0 Hz), 6.53 (1H, s), 6.57 (1H, s), 7.32–7.44 (7H, m), 7.54–7.60 (4H, m), 7.63 (1H, t, *J*=7.8 Hz), 8.05 (1H, d, *J*=7.8 Hz), 8.13 (1H, d, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=14.1, 19.0, 20.8, 22.7, 23.3, 24.8, 25.8, 26.7, 27.2, 27.9, 29.0, 29.1, 29.2, 29.3, 29.5, 29.6, 29.7, 31.9, 32.3, 34.3, 45.1, 53.1, 57.6, 62.2, 69.0, 74.1, 113.4, 124.3, 124.9, 127.7, 128.3, 128.6, 129.5, 129.6, 129.7, 132.8, 133.9, 134.4, 135.5, 136.6, 137.0, 138.3, 146.8, 158.3, 169.4, 170.6, 172.6; HRMS (ESI-TOF) calcd for $C_{74}H_{113}KN_3O_8Si$ ($[M+K]^+$): 1238.7934, found: 1238.7924.

*4.2.5. Octadecanoic acid (1R,2E)-1-((1S)-1-{2-acetylamino-3-[2,4-dimethyl-6-(2-nitrobenzyloxy)phenyl]-3-methylbutyrylamino}-2-hydroxyethyl)hexadec-2-enyl ester (**11a**, **b**). Typical procedure*. To a solution of silylether **10a** (80.0 mg, 66.0 μmol) in THF (0.50 mL) were added TBAF in THF (1 M, 130 μL, 130 μmol) and AcOH (7.6 μL, 130 μmol) at 0 °C, and the mixture was stirred overnight. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ and the obtained mixture was extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a crude product, which was purified by column chromatography (hexane/AcOEt=4:1 (v/v)) and 47.0 mg of alcohol **11a** (73%) was obtained as a colorless oil. Compound **11a**: $[\alpha]_D^{20}$ +11.1 (*c* 1.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ=0.88 (6H, t, *J*=6.8 Hz), 1.25 (52H, m), 1.50 (3H, s), 1.61 (3H, s), 1.84 (1H, m), 1.92 (2H, dt, *J*=6.8 and 7.1 Hz), 2.00 (3H, s), 2.23 (2H, t, *J*=7.6 Hz), 2.24 (3H, s), 2.51 (3H, s), 3.02 (1H, m), 3.25 (1H, m), 3.84 (1H, m), 5.07 (1H, dd, *J*=6.1 and 7.6 Hz), 5.24 (1H, dd, *J*=7.6 and 15.4 Hz), 5.47 (1H, d, *J*=14.4 Hz), 5.60 (1H, d, *J*=9.0 Hz), 5.65 (1H, dt, *J*=6.8 and 15.4 Hz), 5.74 (1H, d, *J*=14.4 Hz), 5.78 (1H, d, *J*=8.5 Hz), 6.25 (1H, d, *J*=9.0 Hz), 6.64 (1H, s), 6.69 (1H, s), 7.54 (1H, t, *J*=7.8 Hz), 7.80 (1H, t, *J*=7.8 Hz), 8.11 (1H, d, *J*=7.8 Hz), 8.22 (1H, d, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=14.1, 20.7, 22.7, 23.5, 24.8, 25.7, 26.3, 28.3, 28.8, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 32.2, 34.3, 45.4, 53.5, 57.2, 61.3, 68.9, 73.8, 113.2, 124.3, 125.2, 128.6, 128.7, 129.6, 129.9, 133.2, 134.6, 136.8, 137.5, 138.7, 147.0, 158.2, 169.7, 171.2, 173.4; HRMS (ESI-TOF) calcd for $C_{58}H_{96}N_3O_8$ ($[M+H]^+$): 962.7197, found: 962.7186. Compound **11b**: $[\alpha]_D^{20}$ −4.43 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ=0.88 (6H, t, *J*=6.8 Hz), 1.25 (52H, m), 1.53 (3H, s), 1.58 (3H, s), 1.96 (2H, dt, *J*=5.4 and 6.8 Hz), 1.96 (3H, s), 2.21 (2H, t, *J*=7.8 Hz), 2.23 (3H, s), 2.49 (3H, s), 3.03 (1H, br s), 3.48 (1H, dd, *J*=3.9 and 11.7 Hz), 3.59 (1H, m), 3.80 (1H, m), 4.71 (1H, dd, *J*=4.2 and 6.8 Hz), 5.16

(1H, dd, J=7.1 and 15.4 Hz), 5.46 (1H, d, J=14.4 Hz), 5.58 (1H, d, J=8.8 Hz), 5.59 (1H, dt, J=7.1 and 15.4 Hz), 5.74 (1H, d, J=14.4 Hz), 6.03 (1H, d, J=7.1 Hz), 6.30 (1H, d, J=8.8 Hz), 6.60 (1H, s), 6.66 (1H, s), 7.54 (1H, t, J=7.8 Hz), 7.79 (1H, t, J=7.8 Hz), 8.06 (1H, d, J=7.8 Hz), 8.20 (1H, d, J=7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=14.1, 20.8, 22.7, 23.4, 24.8, 25.8, 26.8, 28.2, 28.9, 29.1, 29.2, 29.3, 29.5, 29.6, 29.7, 31.9, 32.2, 34.3, 45.1, 55.6, 57.6, 61.9, 68.8, 74.5, 113.1, 124.5, 125.2, 128.6, 128.7, 129.3, 130.0, 133.4, 134.5, 136.4, 137.2, 138.4, 147.2, 158.1, 169.8, 172.0, 173.4; HRMS (ESI-TOF) calcd for $C_{58}H_{96}N_3O_8$ ($[M+H]^+$): 962.7197, found: 962.7183.

4.3. UV-irradiation experiment

*4.3.1. UV-irradiation experiment of **11a**.* To caged ceramide **11a** (10.5 mg, 10.9 μmol) was added *i*-PrOH (400 μL) containing 0.5% (v/v) Et_3N, and the obtained mixture was irradiated by UV light (λ>365 nm) for 1 h. After stirring overnight at room temperature, the reaction mixture was analyzed by ESI-MS and TLC to confirm the generation of ceramide **6**. MS (ESI-Ion Trap) calcd for $[\mathbf{6}+H]^+$: 566.6, found 566.5. TLC (Merck, TLC Silica gel 60 F_{254}) $CHCl_3$/MeOH=9:1 (v/v), R_f=0.4. The R_f value was identical to that of authentic sample of ceramide.

*4.3.2. UV-irradiation experiment of **10a**.* Caged ceramide **10a** (30 μg, 0.025 μmol) in *i*-PrOH (120 μL) was added to H_2O (120 μL) containing 0.5% (v/v) Et_3N and the obtained mixture was irradiated by UV light (λ>365 nm) for 3 min. The resulting mixture was incubated at 37 °C, and reaction progress was monitored by HPLC. HPLC conditions: hexane/*i*-PrOH=99:1 (v/v). Retention times, **10a**: 17.2 min; **13**: 9.6 min. MS (ESI-Ion Trap) calcd for $C_{52}H_{90}NO_3Si$ ($[M+H]^+$) 804.7, found 804.6. The retention time and MS spectrum were identical to that of an authentic sample, which was prepared as follows. Triethylamine (26 μL, 0.19 mmol), EDC·HCl (21 mg, 0.11 mmol), and HOBt·H_2O (1.8 mg, 0.12 μmol) were added to a solution of stearic acid (77 mg, 0.27 mmol) in CH_2Cl_2 (0.50 mL) at room temperature. After 30 min of stirring at room temperature, **7** (R=H) (50 mg, 93 μmol) was added to the reaction mixture. The resulting solution was stirred at the same temperature for 3 h. The reaction mixture was quenched by the addition of saturated aqueous solution of $NaHCO_3$. It was extracted with CH_2Cl_2, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The obtained residue was purified by column chromatography (hexane/AcOEt=5:1 (v/v)) and 50 mg of **13** (67%) was obtained as a colorless oil; $[\alpha]_D^{19}$ +7.11 (*c* 1.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ=0.88 (6H, t, J=6.8 Hz), 1.07 (9H, s), 1.26 (52H, m), 2.03 (2H, dt, J=6.8 and 7.3 Hz), 2.15 (2H, t, J=7.8 Hz), 3.56 (1H, d, J=6.6 Hz), 3.76 (1H, dd, J=2.4 and 10.0 Hz), 3.95 (1H, dd, J=3.2 and 10.0 Hz), 3.98 (1H, m), 4.20 (1H, m), 5.47 (1H, dd, J=5.9 and 15.4 Hz), 5.77 (1H, dt, J=6.8 and 15.4 Hz), 6.11 (1H, d, J=7.8 Hz), 7.35–7.48 (6H, m), 7.59–7.65 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=14.1, 19.1, 22.7, 25.8, 26.9, 29.2, 29.3, 29.4, 29.5, 29.7, 31.9, 32.3, 36.8, 54.0, 64.0, 74.2, 127.9, 129.0, 130.1, 132.4, 133.4, 135.5, 173.3; HRMS (ESI-TOF) calcd for $C_{52}H_{89}NaNO_3Si$ ($[M+Na]^+$): 826.6509, found: 826.6484.

4.4. Introduction of handle on caged ceramide

*4.4.1. Octadecanoic acid (1R,2E)-1-((1S)-1-{3-[2,4-dimethyl-6-(2-nitrobenzyloxy)phenyl]-3-methyl-2-pent-4-ynoylaminobutyrylamino}-2-hydroxyethyl)hexadec-2-enyl ester (**14a**, **b**). Typical procedure*. Fmoc derivative **9a** (100 mg, 72.0 μmol) was treated with 20% (v/v) piperidine/DMF (1.0 mL) at room temperature. After 30 min of stirring, the reaction mixture was evaporated to remove piperidine and DMF. To the residue in DMF (0.50 mL) was added preactivated pentynylation reagent (a 30-min stirred solution of 4-pentynoic acid (21.0 mg, 210 μmol), HOBt·H_2O (36.0 mg, 240 μmol), and EDC·HCl (42.0 mg, 220 μmol) in DMF (0.50 mL)). The resulting mixture was stirred at room temperature for 3 h and was quenched by the addition of saturated aqueous solution of $NaHCO_3$. The mixture was extracted with ether, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The obtained residue was purified by column chromatography (hexane/AcOEt=5:1 (v/v)) and 74.0 mg of the alkyne derivative was obtained as a colorless oil. To a solution of the alkyne derivative (74.0 mg, 60.0 μmol) in THF were added TBAF in THF (1 M, 120 μL, 120 μmol) and AcOH at 0 °C, and the mixture was stirred overnight. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ and the mixture was extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a crude product, which was purified by column chromatography (hexane/AcOEt=3:1 (v/v)) and 55.0 mg of **14a** (76%) was obtained as a colorless oil. Compound **14a**: $[\alpha]_D^{20}$ +0.26 (*c* 0.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ=0.88 (6H, t, J=6.8 Hz), 1.25 (52H, m), 1.53 (3H, s), 1.63 (3H, s), 1.93 (2H, dt, J=6.8 and 7.1 Hz), 2.00 (1H, t, J=2.4 Hz), 2.22 (2H, t, J=7.6 Hz), 2.23 (3H, s), 2.41–2.48 (2H, m), 2.48–2.55 (2H, m), 2.52 (3H, s), 3.06 (1H, br d, J=11.7 Hz), 3.26 (1H, dd, J=3.7 and 11.7 Hz), 3.85 (1H, m), 5.08 (1H, dd, J=1.0 and 7.3 Hz), 5.24 (1H, dd, J=7.3 and 15.4 Hz), 5.52 (1H, d, J=14.9 Hz), 5.63 (1H, d, J=8.8 Hz), 5.65 (1H, dt, J=6.6 and 15.4 Hz), 5.73 (1H, d, J=14.9 Hz), 5.75 (1H, d, J=7.3 Hz), 6.43 (1H, d, J=8.8 Hz), 6.75 (1H, s), 6.78 (1H, s), 7.53 (1H, t, J=7.8 Hz), 7.78 (1H, t, J=7.8 Hz), 8.08 (1H, d, J=7.8 Hz), 8.21 (1H, d, J=7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=14.1, 15.0, 20.7, 22.7, 24.8, 25.7, 26.3, 28.4, 28.8, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 32.2, 33.0, 34.3, 35.6, 45.3, 53.6, 57.4, 61.3, 69.0, 69.5, 69.7, 73.8, 82.9, 113.4, 116.1, 124.3, 125.2, 128.6, 129.6, 129.7, 133.4, 134.6, 135.0, 136.8, 137.5, 138.7, 146.9, 158.2, 170.6, 171.0, 173.3; HRMS (ESI-TOF) calcd for $C_{61}H_{98}N_3O_8$ ($[M+H]^+$): 1000.7354, found: 1000.7365. Compound **14b**: $[\alpha]_D^{20}$ −1.22 (*c* 0.96, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ=0.88 (6H, t, J=6.8 Hz), 1.25 (52H, m), 1.56 (3H, s), 1.60 (3H, s), 1.97 (2H, dt, J=6.8 and 7.3 Hz), 1.99 (1H, t, J=2.4 Hz), 2.21 (2H, t, J=7.8 Hz), 2.23 (3H, s), 2.37–2.42 (2H, m), 2.44–2.49 (2H, m), 2.50 (3H, s), 3.01 (1H, br s), 3.48 (1H, dd, J=5.9 and 11.7 Hz), 3.58 (1H, br dd, J=2.4 and 11.7 Hz), 3.81 (1H, m), 4.71 (1H, dd, J=4.2 and 6.8 Hz), 5.16 (1H, dd, J=7.3 and 15.4 Hz), 5.49 (1H, d, J=14.6 Hz), 5.60 (1H, dt, J=7.1 and 15.4 Hz), 5.62 (1H, d, J=8.8 Hz), 5.74 (1H, d, J=14.6 Hz), 6.04 (1H, d, J=7.3 Hz), 6.50 (1H, d, J=8.8 Hz), 6.60 (1H, s), 6.64 (1H, s), 7.53 (1H, t, J=7.8 Hz), 7.77 (1H, t, J=7.8 Hz), 8.05 (1H, d, J=7.8 Hz), 8.20 (1H, d, J=7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=14.1, 14.9, 20.8, 22.6, 24.7, 25.8, 26.8, 28.2, 28.9, 29.1, 29.2, 29.3, 29.4, 29.6, 29.7, 31.9, 32.2, 34.2, 35.5, 45.1, 55.5, 57.6, 61.9, 68.8, 69.4, 74.4, 82.9, 113.2, 124.5, 125.2, 128.6, 129.3, 129.9, 133.5, 134.5, 136.4, 137.2, 138.4, 147.1, 158.1, 170.7, 171.8, 173.4; HRMS (ESI-TOF) calcd for $C_{61}H_{98}N_3O_8$ ($[M+H]^+$): 1000.7354, found: 1000.7358.

4.5. Click chemistry of caged ceramide

To a solution of alkynyl derivative **14b** (8.9 mg, 8.9 μmol) in CH_2Cl_2 (550 μL) were added benzyl azide in CH_2Cl_2 (0.18 mM, 150 μL, 27 μmol), $CuSO_4$ in H_2O (4.0 μM, 220 μL, 0.89 μmol), sodium ascorbate in H_2O (5.0 μM, 530 μL, 2.7 μmol), and TBTA **16**[16] in CH_2Cl_2 (19 μM, 47 μL, 0.89 μmol) at room temperature, and the mixture was stirred for 3 h. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ and the mixture was extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The obtained crude product was purified by column chromatography (hexane/AcOEt=1:1 (v/v)) and 9.0 mg of ligated product **15b** (91%) was obtained as a colorless oil; $[\alpha]_D^{19}$ +1.05 (*c* 0.70, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.88 (6H, t, J=6.8 Hz), 1.25 (52H, m), 1.44 (3H, s), 1.67 (3H, s), 1.95 (2H, dt, J=6.8 and 7.1 Hz), 2.21 (2H, t, J=7.6 Hz), 2.22 (3H, s), 2.47 (3H, s), 2.54 (2H, m), 2.95 (2H, t, J=7.1 Hz), 3.13 (1H, br s), 3.48 (1H, dd, J=5.4 and 11.0 Hz), 3.58 (1H, dd, J=4.9 and 11.0 Hz), 3.85 (1H, m), 4.76 (1H, dd, J=4.4 and 7.1 Hz), 5.14 (1H, dd, J=7.1 and 15.4 Hz), 5.46 (1H, d, J=14.4 Hz), 5.47 (2H, s), 5.52 (1H, d, J=8.8 Hz), 5.57 (1H, dt, J=6.8

and 15.4 Hz), 5.70 (1H, d, J=14.4 Hz), 6.05 (1H, d, J=7.6 Hz), 6.48 (1H, d, J=8.8 Hz), 6.59 (1H, s), 6.61 (1H, s), 7.22 (1H, s), 7.26 (2H, m), 7.35 (3H, m), 7.50 (1H, t, J=7.6 Hz), 7.73 (1H, d, J=7.6 Hz), 7.98 (1H, d, J=7.6 Hz), 8.16 (1H, d, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.2, 20.9, 21.6, 22.8, 24.9, 25.9, 26.9, 28.2, 29.0, 29.2, 29.3, 29.4, 29.7, 29.8, 32.0, 32.3, 34.3, 35.8, 44.8, 54.0, 55.4, 57.9, 61.9, 68.9, 74.4, 113.2, 121.2, 124.5, 125.2, 128.0, 128.5, 128.6, 128.9, 129.3, 129.8, 133.5, 134.4, 134.7, 136.3, 137.1, 138.4, 146.8, 147.0, 157.9, 171.6, 171.7, 173.2; HRMS (ESI-TOF) calcd for $C_{68}H_{104}N_6NaO_8$ ($[M+Na]^+$), 1155.7813; found 1155.7806.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.04.048.

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13. Because of low solubility of caged ceramide **11a** in aqueous buffer, isopropanol in which **11a** is soluble was used as a solvent.
14. Whereas removal of *o*-nitrobenzyl group of **11a** required 1 h UV-irradiation, that of **10a** was completed within 3 min because the reaction scale of **10a** was smaller than that of **11a**.
15. Synthesis of an authentic sample of ceramide analogue **13**, see Experimental section of UV-irradiation experiment of **10a**.
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