An Efficient and Convenient Approach to the Total Synthesis of Sphingofungin

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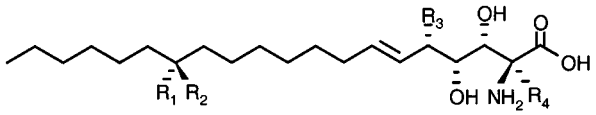
As a new member of the sphingofungin family, sphingofungin F exhibits interesting physiological activities with a structural unit of an α-substituted alanine. Described herein is an efficient and convenient stereoselective synthesis of sphingofungin F from L-(+)-tartaric acid, which utilizes Sharpless asymmetric epoxidation of allylic alcohol and Lewis acid-catalyzed intramolecular epoxide-opening reaction with an *N*-nucleophile, to introduce the other two desired stereogenic centers. Side chain functionality was incorporated into the chiral segment using a Wittig reaction.

Introduction

In recent years, more and more sphingosine-like compounds including sphingofungins A−F have been isolated from various natural resources. Due to their interesting physiological properties, the syntheses of these compounds have attracted considerable attention of synthetic chemists. Sphingofungin E and F (Figure 1), two new members of the sphingofungin family, were first isolated from the fermentation broth *of Poecilomyces variotii* by a Merck group in 1992.[1] Similar to sphingofungin A, B, C, and D,[2] these two compounds exhibit inhibitory effects toward *Serinepalmitoyl transferase*, an enzyme playing an important role in the biosynthesis of sphingolipids. Bearing a structural unit of a α-substituted serine or alanine, they have structural resemblance to myriocin.[3] Up to now, two groups[4,5] have reported preparations of sphingofungin F, basing their syntheses on either aldol or palladium-catalyzed alkylation reactions as key steps. As part of our continuing efforts to study the syntheses of sphingosine-like compounds, we describe herein an alternative approach to sphingofungin F, which utilizes Lewis acid-catalyzed intramolecular epoxide-opening reaction with an *N*-nucleophile as a key step.

Results and Discussion

As shown in Scheme 1, the known alcohol **3** could be readily prepared in four steps from L-(+)-tartaric acid according to literature procedures.[6] Swern oxidation[7] of **3** afforded an aldehyde, which was subjected to Wittig reaction with ylide **4** by refluxing the reaction mixture in benzene, to afford α,β-unsaturated ester **5**. The *E*/*Z* ratio of **5** was only 11:1. To improve stereoselectivity, we attempted to optimize the reaction condition. Consequently, a ratio of 17:1 *(E/Z)* was obtained when the reaction was performed at 0 °C in CH_2Cl_2. While optimizing the reaction conditions, occasionally, we used crude aldehyde stored in a refrigerator (−30 °C) overnight. To our surprise, an enhancement to 23:1(*E*/*Z*) was observed. Regarding this unexpected good stereogenic outcome, we surmised that it could potentially be attributed to self-polymerization of aldehyde at low temperature. Accordingly, depolymerization would be needed to release the aldehyde prior to reacting with ylide **4.** This could result in a slowed reaction rate, leading to remarkable elevation in stereoselectivity. Reduction of ester **5** with DIBAL-H afforded alcohol **6** in 91% yield. The next step required stereoselective epoxidation of compound **6**. Initially, using *m*-CPBA as oxidant, epoxide **7** was expected to predominate according to the transition state supposed by S. Takano et al.[8] However, the stereogenic outcome (**7**:**8** = 1:10) was opposite to this prediction. We envisioned that the different stereogenic outcome in their case might be due to steric factors arisen from a methyl group in their



sphingofungin B	R_1=OH, R_2=H, R_3=OH, R_4=H
sphingofungin E (**1**)	R_1, R_2=O, R_3=OH, R_4=CH_2OH
sphingofungin F (**2**)	R_1, R_2=O, R_3=OH, R_4=CH_3
myriocin	R_1, R_2=O, R_3=H, R_4=CH_2OH

Figure 1. Structure of sphingofungins.

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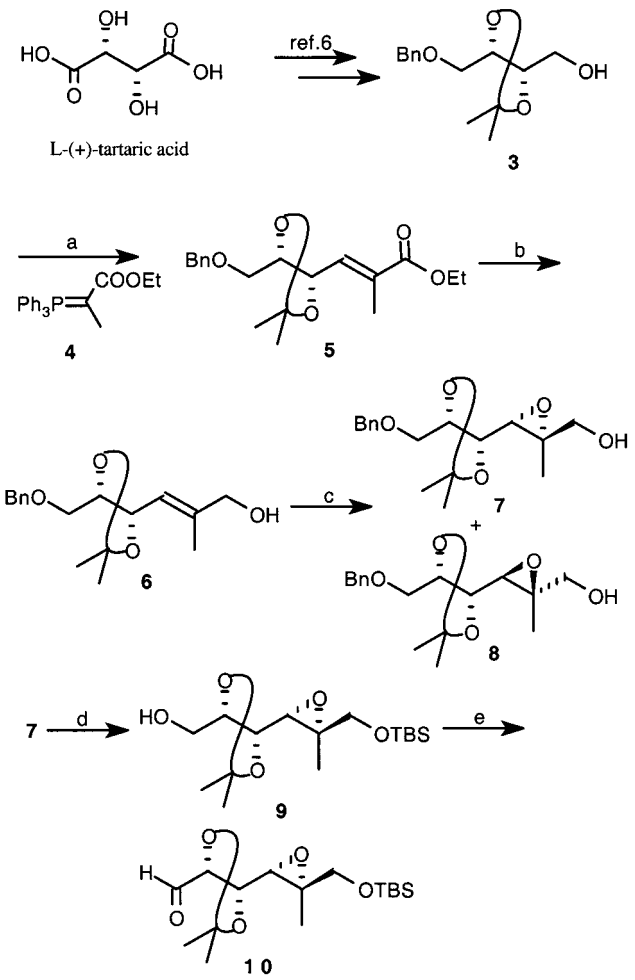
Scheme 1[a]



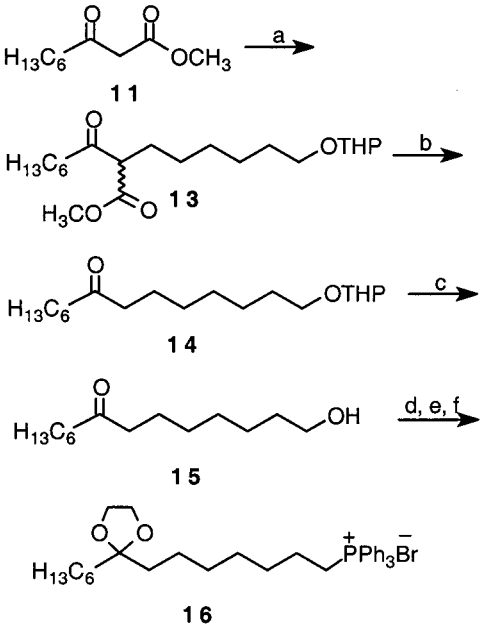
[a] (a) i. $(COCl)_2$, DMSO, −78 °C, NEt_3, CH_2Cl_2; ii. **4**, CH_2Cl_2, 0 °C, 85% (two steps); (b) DIBAL-H, CH_2Cl_2, −78 °C, 90%; (c) TBHP, L-(+)-DIPT, $Ti(OPr^i)_4$, 4 Å MS, CH_2Cl_2, −20 °C, 73%; (d) i. TBSCl, NEt_3, DMAP (cat.), CH_2Cl_2, 80%; ii. $Pd(OH)_2/C$ (20%), H_2, EtOAc/CH_3OH (4:1), 97%; (e) $(COCl)_2$, DMSO, −78 °C, NEt_3, CH_2Cl_2, 87%.

substrate, rather than a hydrogen bonding entity. We therefore turned our attention to the Sharpless assymetric epoxidation (AE) reaction.[9] When this reaction was conducted at −20 °C, epoxide **7** was obtained as the main product in a ratio of 3:1 (**7**:**8**). Protection of the hydroxy group of **7** as its TBS ether, followed by catalytic hydrogenation over 20% $Pd(OH)_2/C$, afforded alcohol **9**, which was subjected to Swern oxidation to give crude aldehyde **10**.

Our synthesis of phosphonium salt **16** was achieved from β-keto ester (**11**)[10] (Scheme 2). Treatment of **11** with iodide **12** and K_2CO_3 under reflux afforded the alkylation product **13** in 77% yield. Ketone **14** was obtained by refluxing **13** with 3% aqueous KOH. Treatment of **14** with PTS afforded alcohol **15**, which could be easily converted to phosphonium salt **16** in three known steps.[11]

With the two required segments in hand, Wittig reaction was conducted at −78 °C, to provide *Z*-**17**

Scheme 2[a]



[a] (a) $I(CH_2)_6OTHP$ (12), K_2CO_3, DMF, acetone, reflux, 77%; (b) 3% KOH (aq), CH_3OH, reflux, 100%; (c) PTS, CH_3OH, 99%; (d) PPh_3, CBr_4, CH_2Cl_2, 100%; (e) ethylene glycol, PTS, benzene, reflux, 98%; (f) PPh_3, Na_2CO_3, acetonitrile, reflux, 100%.

smoothly in 85% yield. Treatment of **17** with TBAF in THF, yielded alcohol **18.** To introduce the amino group regioselectively at C2, Hatakeyama's method[12] was employed. Thus, treatment of **18** with trichloroacetonitrile and DBU was followed by intramolecular epoxide-opening reaction catalyzed by $BF_3{\cdot}OEt_2$, to afford oxazoline **19** in 70% yield over two steps, in addition to a 20% yield of the hydrolysis product. According to Hatakeyama's report, $AlEt_2Cl$ is superior to $BF_3{\cdot}OEt_2$ in inhibiting oxazoline hydrolysis. However, in our case, a complex result was obtained. Subsequently, we found that oxazoline hydrolysis took place predominantly at workup stage. Therefore, the workup was modified by diluting the mixture with ethyl acetate prior to the addition of saturated $NaHCO_3$, resulting in the yield of **19** being improved to 80%. Treatment of **19** with triphosgene and pyridine,[13] followed by removal of the trichloroacetyl group with K_2CO_3, gave alcohol **20** in 83% yield over two steps. Oxidation of **20** with PDC in DMF, followed by methylation of the resulting carboxylic acid with CH_2N_2, yielded ester **21**. The stereochemistry of **21** was confirmed to be consistent with that of sphingofungin F by NOE experiments on γ-lactone **22**, which was obtained by refluxing **21** with PTS in EtOH (Scheme 3).

Finally, compound **21** was smoothly converted to sphingofungin F (**2**) in three sequential steps. Photoisomerization of *Z*-**21** with phenyl disulfide resulted in a mixture of *E*- and *Z*-**21** (*E*/*Z* = 5:1), which could be separated by flash chromatography on silica gel. Refluxing *E*-**21** with PTS afforded γ-lactone **23**, which was saponified with 1 N NaOH in EtOH−H_2O to give **2** after purification by chromatograph on Dowex-50 H^+ resin (elution with l N NH_3) (Scheme 4).

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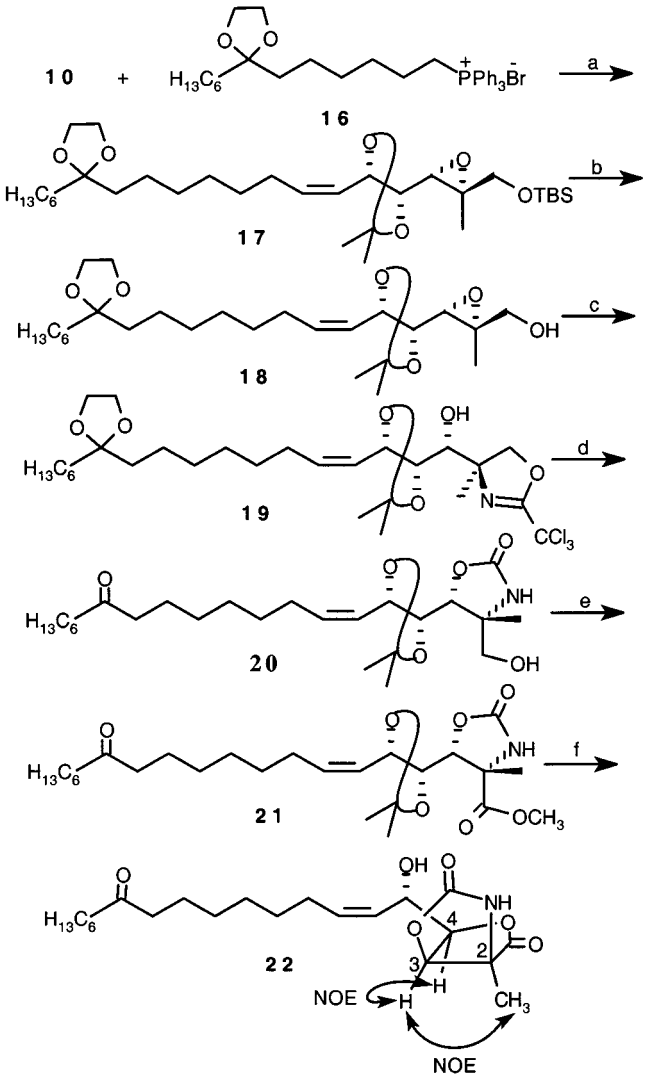
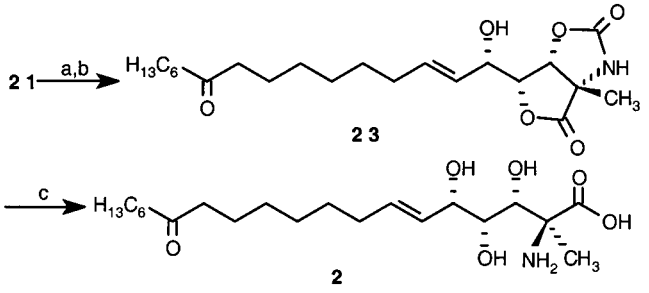
Scheme 3[a]



[a] (a) **16**, *n*-BuLi, then −78 °C, **10**, THF, 85%; (b) *n*-Bu_4NF, THF, 95%; (c) i. Cl_3CCN, DBU, CH_2Cl_2, 0 °C; ii. $BF_3{\cdot}OEt_2$, CH_2Cl_2, −23 °C, 80% (two steps); (d) i. $CO(OCCl_3)_2$, pyr, CH_2Cl_2, −35 °C to room temperature, 4 h; ii. K_2CO_3, CH_3OH, 82% (two steps); (e) i. PDC, DMF; ii. CH_2N_2, Et_2O, 78% (two steps); (f) PTS, 70% EtOH (aq), reflux, 80%.

Scheme 4[a]



[a] (a) PhSSPh, *hν*, cyclohexane, 1,4-dioxane, 95%; (b) PTS, 70% EtOH (aq), reflux, 81%; (c) 2 N NaOH, EtOH, reflux, 51%.

The sample **2** obtained by this route provided ^1H NMR, ^{13}C NMR, and IR spectra and MS identical with the natural product. However, the specific rotation and mp were different from those reported in the literature {our sample: $[\alpha]_D^{20} = -11$ (*c* 0.59, CH_3OH), mp: 123−125 °C; lit.[4]: $[\alpha]_D^{20} = +0.80$ (*c* 0.33, CH_3OH, 89% e.e.), mp 142−144 °C}. Since the stereochemistry of our intermediate **21** was confirmed by NOE experiments on its derivative **22**, we concluded that the discrepancy could only arise from the different purification procedure in the last step. As reported in the literature,[14] amino acid could come out as its ammonium salt after chromatography on Dowex-50 H^+ resin. Therefore, we surmised that the above sample might be a mixture of sphingofungin F and its ammonium salt. To verify this conjecture, **2** was treated with a weak acid resin (IRC-76) in CH_3OH to release the free amino acid and purified by silica gel flash chromatography to afford a white solid, which was observed with specific rotation of $[\alpha]_D^{20} = +0.91$ (*c* 0.22, CH_3OH) and mp of 145−147 °C. In this manner, all spectral data of our final product were consistent with literature values.

In conclusion, we have demonstrated an alternative and convenient approach to the synthesis of sphingofungin F from L-(+)-tartaric acid, which was achieved in 3.7% yield over 22 steps. In this route, Lewis acid-catalyzed intramolecular epoxide-opening reaction with an *N*-nucleophile has been successfully utilized to construct the α-substituted alanine structural unit. With the same protocol, our synthesis of sphingofungin E is in progress.

Experimental Section

General. All melting points are uncorrected. IR spectra were recorded with FT-IR apparatus. ^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz in $CDC1_3$ and CD_3-OD, respectively. Chemical shifts are reported in ppm relative to TMS as internal standard. Mass spectra were recorded by EI methods. Flash column chromatography was carried out with silica gel (200−300 mesh). Solvent THF was distilled over sodium, with dichloromethane and DMF being distilled over CaH_2.

***(2E*,4S,5S)-2-Methyl-4,5-*O*-isopropylidene-6-benzyloxy-4,5-diol-2-ene-1-hexanoic Acid Ethyl Ester (5).** To a solution of oxalyl chloride (0.69 mL, 7.94 mmol) in CH_2Cl_2 (8 mL) was added DMSO (1.13 mL, 15.88 mmol) at −78 °C under N_2. The mixture was stirred for 10 min, and then a solution of **3** (1.00 g, 3.97 mmol) in CH_2Cl_2 (1 mL) was added. The mixture was stirred for 1 h, triethylamine (5.5 mL, 39.7 mmol) was added, and the stirring was allowed to continue for 20 min. The mixture was allowed to warm to 0 °C and then quenched with saturated NaH_2PO_4 (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined extract was washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was filtered through silica gel column to give 0.90 g of crude aldehyde. To a solution of the above aldehyde (stored at −30 °C overnight) in CH_2Cl_2 (15 mL) was added ylide **4** (1.95 g, 5.4 mmol) at 0 °C. After being stirred for 30 min, the mixture was evaporated to give a residue, which was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1:10) to afford **5** (1.12 g, 85%) as a colorless oil with a *E*/*Z* ratio of 23:1 (determined by GC-MS). $[\alpha]_D^{19} = -32.7$ (*c* 2.20, $CHCl_3$); IR (film) *ν*: 2987, 2935, 1715, 1660, 1455, 1370, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 1.29 (3H, t, *J* = 7.1 Hz), 1.46 (6H, s), 1.86 (3H, d, *J* = 1.5 Hz), 3.56 (1H, dd, *J* = 4.8, 10.7 Hz), 3.63 (1H, dd, *J* = 3.6, 10.7 Hz), 3.97 (1H, ddd, *J* = 3.6, 4.8, 8.2 Hz), 4.20 (1H, q, *J* = 7.1 Hz), 4.21 (1H, q, *J* = 7.1 Hz), 4.56, 4.62 (2H, AB, J_{AB} = 12.1 Hz), 4.72 (1H, t, *J* = 8.5 Hz), 6.65 (1H, dt, *J* = 1.5, 8.7 Hz), 7.20−7.40 (5H, m) ppm; MS (*m*/*z*, %): 319 ($M^+ - CH_3$, 1.32), 126 (36.37), 98 (30.19), 91 (100); HRMS calcd for C18H2305 ($M^+ - CH_3$): 319.1545, Found: 319.1537.

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***(2E,4S,5S)*-l-Hydroxy-2-methyl-4,5-*O*-isopropylidene-6-benzyloxy-2-ene-4,5-hexanediol (6).** To a solution of **5** (1.2 g, 3.6 mmol) in dry CH_2Cl_2 (15 mL) was added 9.0 mL of DIBAL-H (1 M in hexane, 9.0 mmol) at −78 °C under argon. After being stirred for 2.5 h, the mixture was quenched with saturated NH_4Cl (10 mL). The mixture was allowed to warm to room temperature and stirred for 30 min. After filtration through Celite, the filtrate was extracted with CH_2Cl_2 (3 × 15 mL). The combined extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to give a residue, which was purified by flash chromatography (eluent: ethyl acetate/petroleum ether = 2:1) to afford **6** (0.94 g, 90%) as a colorless oil. $[\alpha]_D^{18} = -14.0$ (*c* 1.29, $CHCl_3$); IR (film) *ν*: 3439, 2987, 1454, 1370, 1243 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 1.45 (6H, s), 1.67 (3H, s), 1.74 (1H, s.b), 3.55 (1H, dd, *J* = 5.2, 10.7 Hz), 3.60 (1H, dd, *J* = 3.4, 10.7 Hz), 3.90 (1H, ddd, *J* = 3.4, 5.2, 8.7 Hz), 4.00 (2H, s), 4.56, 4.61 (2H, AB, J_{AB} = 12.1 Hz), 4.63 8 (1H, t, *J* = 8.7 Hz), 5.47 (1H, d, *J* = 8.7 Hz), 7.25−7.41 (5H, m) ppm; MS (*m*/*z*, %): 277 (0.85), 217 (15.77), 91 (100), 43 (36.39). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.62; H, 8.47.

(2*S*,3*S*,4*R*,5*S*)-l-Hydroxy-2,3-epoxy-2-methyl-4,5-O-isopropylidene-6-benzyloxy-4,5-hexanediol (7). To a suspension of 4 Å MS (1.5 g) in dry CH_2Cl_2 (40 mL) were added L-(+)-DIPT (0.13 mL, 0.61 mmol), $Ti(OPr^i)_4$ (0.15 mL, 0.51 mmol), and TBHP (1.1 mL, 6.78 M in CH_2Cl_2, 7.46 mmol) at −20 °C under argon. The mixture was stirred for 30 min, and then a solution of **6** (1.50 g, 5.14 mmol) in CH_2Cl_2 (5 mL) was added. After being stirred at −20 °C for 24 h, the reaction was quenched with acetone (50 mL) containing 2% (v/v) water at room temperature. The mixture was stirred for 3 h, filtered through Celite, dried over anhydrous Na_2SO_4, filtered, and evaporated to give a residue, which was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1: 2) to afford compound **7** (1.15 g, 73%) as a colorless oil and compound **8** (0.38 g, 24%). Compound **7**: $[\alpha]_D^{17} = -20.5$ (*c* 1.09, $CHCl_3$); IR (film) *ν*: 3460, 2988, 2935, 1455, 1372 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 1.24 (3H, s), 1.43 (3H, s), 1.46 (3H, s), 1.70−1.80 (1H, m), 3.14 (1H, d, *J* = 8.0 Hz), 3.50 (1H, dd, *J* = 8.5, 12.3 Hz), 3.58 (1H, dd, *J* = 3.3, 12.3 Hz), 3.62 (2H, d, *J* = 4.7 Hz), 3.89 (1H, t, *J* = 8.0 Hz), 4.08 (1H, dt, *J* = 4.7, 8.0 Hz), 4.55, 4.59 (2H, AB, J_{AB} = 11.9 Hz), 7.30−7.35 (5H, m) ppm; MS (*m*/*z*, %): 293 ($M^+ - CH3$, 1.68), 221 (3.08), 149 (9.03), 91 (100), 43 (13.82); HRMS calcd for C17H2405 (M^+): 308.1624, Found: 308.1646.

(2*S*,3*S*,4*R*,5*S*)-1-*tert*-Butyldimethylsilyloxy-2,3-epoxy-2-methyl-4,5-*O*-isopropyidene-6-hydroxy-4,5-hexanediol (9). To a solution of **7** (610 mg, 1.98 mmol) in CH_2Cl_2 (10 mL) were added DMAP (10 mg, 0.078 mmol), TBDMSCl (600 mg, 3.98 mmol), and triethylamine (0.68 mL, 4.88 mmol). After being stirred at room temperature for 24 h, the reaction mixture was diluted with ethyl acetate (50 mL), washed with 1 N HCl, water, and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to give a residue, which was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1:10) to afford a TBS-protected product (671 mg, 80%) as a colorless oil. The above product was hydrogenated over 20% $Pd(OH)_2$/C (67 mg) in ethyl acetate/methanol (4:1, 50 mL) at room temperature for 4 h. The mixture was filtered and evaporated to give a residue, which was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1:2) to afford compound **9** (410 mg, 97%) as a colorless oil. $[\alpha]_D^{20} = -14.9$ (*c* 1.75, $CHCl_3$); IR (film) *ν*: 3485, 2956, 2932, 1464, 1373, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 8: 0.04 (3H, s), 0.05 (3H, s), 0.89 (9H, s), 1.35 (3H, s), 1.43 (3H, s), 1.47 (3H, s), 2.00 (1H, b), 2.95 (1H, d, *J* = 7.8 Hz), 3.51, 3.63 (2H, AB, J_{AB} = 11.2 Hz), 3.55−3.65 (1H, m), 3.85−3.90 (1H, m), 3.89 (1H, dd, *J* = 7.8, 8.3 Hz), 3.98 (1H, dt, *J* = 3.3, 8.3 Hz) ppm; MS (*m*/*z*, %): 317 ($M^+ - CH_3$, 4.47), 145 (70.96), 131 (94.31), 75 (100), 59 (78.14), 43 (58.96); HRMS calcd for $C_{15}H_{29}O_5Si$ ($M^+ - CH_3$): 317.1784, Found: 317.1771.

2-(6′-Tetrahydropyranyloxyhexyl)-3-keto-l-nonanoic Acid Methyl Ester (13). To a solution of **11** (7.4 g, 39.8 mmol) in acetone (210 mL) and DMF (9.45 mL) were added **12** (13.6 g, 43.6 mmol) and K_2CO_3 (11.0 g, 79.6 mmol), the mixture was refluxed for 12 h. After being cooled to room temperature, the solvent was evaporated, and water (50 mL) was added. The mixture was extracted with EtOAc (3 × 70 mL). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to give a residue, which was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1:12) to afford compound **13** (11.4 g, 77%) as a colorless oil. IR (film) *ν*: 2936, 2860, 1748, 1717, 1439, 1353, 1201 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 8: 0.88 (3H, t, *J* = 7.0 Hz), 1.20−1.90 (24H, m), 2.50 (2H, m), 3.37 (1H, dt, *J* = 6.6, 9.7 Hz), 3.41 (1H, t, *J* = 7.6 Hz), 3.46−3.52 (1H, m), 3.72 (3H, s), 3.68−3.76 (1H, m), 3.83−3.95 (1H, m), 4.554.58 (1H, m) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 13.96, 19.67, 22.43, 23.40, 25.49, 25.95, 27.41, 28.19, 28.67, 29.16, 29.60, 30.76, 31.52, 41.84, 52.18, 58.95, 62.29, 67.46, 98.83, 170.37, 205.33 ppm; MS (*m*/*z*, %): 370 (1.54), 287 (100), 85 (61.44). Anal. Calcd for $C_{21}H_{38}O_5$: C, 68.07; H, 10.34. Found: C, 67.81; H, 10.61.

1-Tetrahydropyranyloxy-8-tetradecanone (14). To a solution of **13** (10.76 g, 29.0 mmol) in methanol (75 mL) was added 3% aqueous KOH (90 mL), the mixture was refluxed for 4 h. After being cooled to room temperature, methanol was evaporated and water (50 mL) was added. The mixture was extracted with EtOAc (3 × 70 mL). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to give a residue, which was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1:10) to afford compound **14** (9.07 g, 100%) as a colorless oil. IR (film) *ν*: 2933, 2857, 1714, 1465, 1368 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 0.88 (3H, t, *J* = 6.6 Hz), 1.20−1.90 (24H, m), 2.38 (2H, t, J = 7.5 Hz), 3.38 (1H, dt, *J* = 6.6, 9.5 Hz), 3.48−3.54 (1H, m), 3.73 (1H, dt, *J* = 6.7, 9.5 Hz), 3.83−3.90 (1H, m), 4.46−4.58 (1H, m) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 14.08, 19.78, 22.56, 23.90, 23.94, 25.59, 26.17, 29.02, 29.29, 29.33, 29.78, 30.87, 31.68, 42.85, 42.91, 62.43, 67.68, 98.95, 211.68 ppm; MS (*m*/*z*, %): 313 (3.33), 229 (88.17), 85 (100), 43 (15.21). Anal.-Calcd for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61. Found: C, 72.58; H, 11.90.

1-Hydroxy-8-tetradecanone (15). To a solution of **14** (9.07 g, 29.0 mmol) in methanol (100 mL) was added PTS·H_2O (20 mg), the mixture was stirred at room temperature for 4 h. The solvent was evaporated to give a residue, which was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1:2) to afford compound **15** (6.60 g, 99%) as a white solid. mp: 51−52 °C (lit.:[11a] 52−53 °C); ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 0.87 (3H, t, *J* = 7.0 Hz), 1.26−1.60 (18H, m), 2.37 (2H, t, *J* = 7.3 Hz), 3.62 (2H, t, *J* = 6.6 Hz) ppm.

(2*S*,3*S*,4*R*,5*S*,6*Z*)-1-*tert*-Butyldimethylsilyloxy-2,3-epoxy-2-methyl-4,5-*O*-isopropylidene-13-(2′-hexyl-1′,3′-dioxolan-2′-yl)-6-ene-4,5-tridecanediol (17). To a solution of oxalyl chloride (1.1 mL, 12.65 mmol) in CH_2Cl_2 (50 mL) was added DMSO (1.8 mL, 25.30 mmol) at −78 °C under argon. The mixture was stirred at −78 °C for 10 min, and then a solution of **9** (2.1 g, 6.32 mmol) in CH_2Cl_2 (15 mL) was added. The mixture was stirred at −78 °C for 1 h, triethylamine (8.8 mL, 63.2 mmol) was added, and the stirring was allowed to continue for 20 min. The reaction was quenched with saturated NaH_2PO_4 (25 mL), and the mixture was allowed to warm to room temperature and then extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to give crude aldehyde (1.82 g), which was used directly in the next step without purification. To a solution of **16** (4.0 g, 6.7 mmol) in dry THF (40 mL) was added 2.2 mL of *n*-BuLi (4.4 mmol, 2.0 M in hexane) at room temperature under argon. The mixture was stirred for 10 min, and then a solution of the above crude aldehyde (1.0 g, −3.0 mmol) in THF (10 mL) was added to the mixture at −78 °C. After being stirred for 1 h at −78 °C, the mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl (30 mL), and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to give a residue, which was purified by flash

chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1:20) to afford compound **17** (1.46 g, 85%) as a colorless oil. $[\alpha]_D^{20} = +15.1$ (*c* 1.39, $CHCl_3$); IR (film) *ν*: 2932, 1464, 1372, 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 0.05 (3H, s), 0.06 (3H, s), 0.88 (3H, t, *J* = 7.0 Hz), 0.89 (9H, s), 1.25 (3H, s), 1.25−1.43 (16H, m), 1.43 (3H, s), 1.47 (3H, s), 1.56−1.63 (4H, m), 1.95−2.25 (2H, m), 2.97 (1H, d, *J* = 7.8 Hz), 3.53, 3.60 (2H, AB, J_{AB} = 11.4 Hz), 3.62 (1H, t-like, *J* = 8.3 Hz), 3.92 (4H, s), 4.65 (1H, t-like, *J* = 8.8 Hz), 5.37 (1H, dd, *J* = 9.2, 10.8 Hz), 5.67−5.75 (1H, m) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: −5.39, −5.35, 14.10, 15.37, 18.39, 22.62, 23.79, 23.85, 25.91, 27.05, 27.10, 27.74, 29.24, 29.59, 29.64, 29.81, 31.86, 37.15, 37.19, 59.87, 60.53, 64.90, 67.18, 73.99, 80.13, 109.83, 111.85, 125.68, 136.49 ppm; MS (*m*/*z*, %): 553 ($M^+ - CH_3$), 409 (1.58), 215 (34.09), 157 (100), 127 (18.21). Anal. Calcd for $C_{32}H_{60}O_6Si$: C, 67.56; H, 10.63. Found: C, 67.48; H, 10.87.

(2*S*,3*S*,4*R*,5*S*,6*Z*)-l-Hydroxy-2,3-epoxy-2-methyl-4,5-*O*-isopropylidene-13-(2′-hexyl-1′,3′-dioxolan-2′-yl)-6-ene-4,5-tridecanediol (18). To a solution of **17** (2.70 g, 4.75 mmol) in THF (60 mL) was added 7.20 mL of *n*-Bu_4NF (7.20 mmol, 1 M in THF). After being stirred at room temperature for 10 min, the mixture was diluted with ethyl acetate, washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to give a residue, which was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1:4) to afford compound **18** (2.05 g, 95%) as a colorless oil. $[\alpha]_D^{20} = +15.4$ (*c* 1.02, $CHCl_3$); IR (film) *ν*: 3473, 2931, 1458, 1373 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 0.88 (3H, t, *J* = 7.0 Hz), 1.27 (3H, s), 1.20−1.50 (16H, m), 1.45 (3H, s), 1.48 (3H, s), 1.50−1.70 (4H, m), 1.75−1.95 (1H, b), 2.00−2.20 (2H, m), 3.17 (1H, d, *J* = 7.9 Hz), 3.55, 3.66 (2H, AB, J_{AB} = 12.4 Hz), 3.64 (1H, t-like, *J* = 8.4 Hz), 3.93 (4H, s), 4.67 (1H, t-like, *J* = 9.0 Hz), 5.38 (1H, dd, *J* = 9.3, 10.8 Hz), 5.70−5.78 (1H, m) ppm; MS (*m*/*z*, %): 397 (1.24), 311 (18.11), 157 (100), 43 (28.95). Anal. Calcd for $C_{26}H_{46}O_6$: C, 68.69; H, 10.20. Found: C, 68.23; H, 10.62.

***(1R,2R,3S,4Z,4″)*-1-(4′-Methyl-2′-trichloromethyl-2′-oxazolin-4′-yl)-1-hydroxy- 2,3-*O*-isopropylidene-11-(2″-hexyl-1′,3″-dioxolan-2 -yl)-4-ene-2,3-undecanediol (19).** To a solution of **18** (500 mg, 1.10 mmol) in CH_2Cl_2 (10 mL) were added trichloroacetonitrile (0.15 mL, 1.49 mmol) and DBU (0.030 mL, 0.20 mmol) at 0 °C under N_2. After being stirred at 0 °C for 30 min, the mixture was diluted with ethyl acetate, washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was filtered through a short silica gel column to afford crude epoxytrichloroacetimidate (633 mg), which was used immediately in the next step. To a stirred solution of the above epoxytrichloroacetimidate in CH_2Cl_2 (15 mL) was added $BF_3{\cdot}OEt_2$ (0.067 mL, 0.53 mmol) at −23 °C under argon. After being stirred at −23 °C for 30 min, the mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$, water, and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to give a residue, which was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1:5) to afford compound **19** (524 mg, 80%) as a colorless oil. $[\alpha]_D^{20} = 2.0$ (*c* 1.04, $CHCl_3$); IR (film) *ν*: 3466, 2933, 1660, 1457, 1373, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 0.88 (3H, t, J = 7.0 Hz), 1.20−1.42 (16H, m), 1.37 (3H, s), 1.43 (3H, s), 1.44 (3H, s), 1.56−1.62 (4H, m), 2.04−2.25 (2H, m), 2.41 (lH, d, *J* = 6.9 Hz), 3.57 (1H, d-like, *J* = 6.2 Hz), 3.81 (1H, dd, *J* = 8.5, 1.1 Hz), 3.92 (4H, s), 4.21, 4.88 (2H, AB, J_{AB} = 9.0 Hz), 4.88 (1H, t-like, *J* = 9.2 Hz), 5.35 (1H, ddt, J 1.4, 9.2, 10.8 Hz), 5.73 (1H, dt, *J* = 7.2, 10.8 Hz) ppm; MS (*m*/*z*, %): 598 (M^+), 540 (4.10), 454 (6.95), 157 (100), 43 (21.02).

***(1R,2S,3Z,4′R,5′R)*-1-(4′-Methyl-4′-hydroxymethyl-2′-oxazolidinon-5′-yl)-1,2-*O*-isopropylidene-11-keto-3-ene-1,2-heptadecanediol (20).** To a solution of **19** (655 mg, 1.10 mmol) in CH_2Cl_2 (8 mL) was added pyridine (0.113 mL, 1.40 mmol). The mixture was cooled to −35 °C, and then a solution of triphosgene (138 mg, 0.47 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The mixture was allowed to warm to room temperature slowly (∼4 h), and then water (0.060 mL, 3.30 mmol) was added. After being stirred for 30 min, the mixture was diluted with ethyl acetate, dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was stirred with K_2CO_3 (120 mg, 0.87 mmol) in methanol (20 mL) at room temperature for 20 min. The mixture was filtered through Celite, and the filtrate was evaporated to give a residue, which was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1:1) to afford compound **20** (406 mg, 82%) as a colorless oil. $[\alpha]_D^{20} = -22.4$ (*c* 1.02, $CHCl_3$); IR (film) *ν*: 3314, 2932, 1757, 1714, 1459, 1374, 1246 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 6: 0.86 (3H, t, *J* = 6.8 Hz), 1.20−1.45 (15H, m), 1.47 (6H, s), 1.51−1.56 (4H, m), 2.04−2.25 (2H, m), 2.37 (4H, t, *J* = 7.2 Hz), 3.46, 3.73 (2H, AB, J_{AB} = 12.6 Hz), 3.73 (1H, d, *J* = 9.0 Hz), 3.99 (1H, s), 4.79 (1H, b), 4.93 (1H, t, *J* = 9.0 Hz), 5.34 (1H, dd, *J* = 9.0, 10.8 Hz), 5.73 (1H, dt, *J* = 7.7, 10.8 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 14.03, 22.44, 22.49, 23.72, 23.86, 26.14, 27.41, 27.77, 28.87, 28.93, 29.03, 29.32, 31.61, 42.68, 42.85, 61.49, 65.91, 73.46, 76.70, 80.72, 110.53, 124.24, 138.63, 158.77, 211.69 ppm; MS (*m*/*z*, %): 454 (3.31), 452 (3.43), 438 (18.30), 395 (32.98), 113(56.05), 100 (100), 43 (88.43); HRMS calcd for $C_{24}H_{40}NO_6$ ($M^+ - CH_3$): 438.2856, Found: 438.2855.

***(1R,2S,3Z,4′S,5′R)*-1-(4′-Methyl-4′-methoxycarbonyl-2′-oxazolidinon-5′-yl)-1,2-*O*-isopropylidene-11-keto-3-ene-1,2-heptadecanediol (21).** To a solution of **20** (100 mg, 0.22 mmol) in DMF (1.2 mL) was added PDC (615 mg, 1.63 mmol) slowly. After being stirred at room temperature for 30 h, the reaction was quenched with water (3 mL). The mixture was extracted with ether (3 × 10 mL). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was dissolved in ether (2 mL), and a solution of CH_2N_2 in ether (3.5 mL, − 1.0 mmol) was added at 0 °C. After being stirred for 5 min, the reaction was quenched with acetic acid. The mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$, water, and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to give a residue, which was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1:2) to afford compound **21** (83 mg, 78%) as a colorless oil. $[\alpha]_D^{20} = -53.4$ (*c* 1.16, $CHCl_3$); IR (film) *ν*: 3321, 2931, 1778, 1713, 1459, 1372, 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 0.88 (3H, t, *J* = 7.0 Hz), 1.20−1.40 (12H, m), 1.36 (3H, s), 1.39 (3H, s), 1.52−1.60 (4H, m), 1.62 (3H, s), 2.00−2.25 (2H, m), 2.38 (2H, t, *J* = 7.4 Hz), 2.39 (2H, t, *J* = 7.4 Hz), 3.77 (3H, s), 3.89 (1H, dd, *J* = 0.7, 8.3 Hz), 4.16 (1H, d, *J* = 0.7 Hz), 4.88 (1H, dd, *J* = 8.3, 9.1 Hz), 5.37 (1H, dd, *J* = 9.1, 10.8 Hz), 5.76 (1H, dt, *J* = 7.7, 10.8 Hz), 5.86 (1H, s) ppm; ^{13}C NMR (CDC13, 75 MHz) 8: 14.07, 22.54, 23.76, 23.91, 26.25, 26.95, 27.21, 27.76, 28.91, 28.98, 29.08, 29.41, 31.66, 42.73, 42.90, 53.01, 62.58, 72.42, 78.10, 80.87, 109.77, 124.78, 137.94, 157.28, 171.25, 211.68 ppm; MS (*m*/*z*, %): 482 (2.27), 424 (18.01), 361 (44.30), 97 (45.44), 43 (100); HRMS calcd for $C_{26}H_{43}NO_7$ (M^+): 481.3040, Found: 481.3029.

(4*S*,5*R*,1′*R*,2′*S*,3′*Z*)-4-Methyl-5-(1′,2′-dihydroxy-11′-keto-3′-ene-l′-heptadecyl)-2-oxazolidinone-1-carboxylic acid *γ*-lactone (22). A mixture of **21** (35 mg, 0.073 mmol) and PTS−H_2O (33 mg, 0.174 mmol) in 70% aqueous ethanol (3 mL) was refluxed for 2 h under N_2. After being cooled to room temperature, the mixture was diluted with ether, dried over anhydrous Na_2SO_4, filtered, and evaporated to give a residue, which was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1:1) to afford compound **22** (22 mg, 74%) as a colorless oil. $[\alpha]_D^{20} = +2.6$ (*c* 0.97, $CHCl_3$); IR (film) *ν*: 3516, 3242, 2932, 1761, 1736, 1708, 1467, 1369 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 0.88 (3H, t, *J* = 6.9 Hz), 1.20−1.45 (12H, m), 1.51−1.60 (4H, m), 1.60 (3H, s), 2.16−2.22 (2H, m), 2.39 (4H, t, *J* = 7.4 Hz), 2.94 (1H, s.b), 4.55 (1H, dd, *J* = 4.7, 6.9 Hz), 4.77 (1H, d, *J* = 4.7 Hz), 4.85 (1H, t-like, *J* = 7.9 Hz), 5.43 (1H, t-like, *J* = 10.0 Hz), 5.72 (1H, dt, *J* = 7.3, 10.8 Hz), 6.62 (1H, s) ppm; MS (*m*/*z*, %): 409 (M^+, 15.63), 391 ($M^+ - H_2O$, 8.35), 347 (84.61), 113 (67.64), 57 (52.83), 43 (100).

(4*S*,5*R*,1′*R*,2′*S*,3′*E*)-4-Methyl-5-(1′,2′-dihydroxy-11′-keto-3′-ene-1′-heptadecyl)-2-oxazolidinone-1-carboxylic Acid*γ*-lactone (23). A mixture of **21** (78 mg, 0.162 mmol) and phenyl

disulfide (68 mg, 0.31 mmol) in cyclohexane (15 mL) and 1,4-dioxane (0.9 mL) was irradiated with a 75 W Hg bulb for 24 h under N_2. Evaporation was followed by purification by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1:2) to afford *E*-**21** (62 mg, 79%) as a colorless oil, and *Z*-**21** (13 mg, 17%) was recovered. A mixture of E-**21** (52 mg, 0.108 mmol) and PTS·H_2O (50 mg, 0.263 mmol) in 70% aqueous ethanol (3 mL) was refluxed for 2 h under N_2. After being cooled to room temperature, the mixture was diluted with ether, dried over anhydrous Na_2SO_4, filtered, and evaporated to give a residue, which was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 3:5) to afford compound **23** (36 mg, 81%) as a colorless oil. $[\alpha]_D^{20} = -27.4$ (*c* 1.59, $CHCl_3$); IR (film) ν: 3307, 2930, 1771, 1709, 1459, 1382 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.88 (3H, t, J = 7.0 Hz), 1.23−1.45 (12H, m), 1.51−1.60 (4H, m), 1.61 (3H, s), 2.07 (2H, q, J = 6.8 Hz), 2.39 (4H, t, J = 7.9 Hz), 2.81 (1H, b), 4.47 (1H, dd, J = 4.4, 7.6 Hz), 4.54−4.59 (1H, m), 4.80 (1H, d, J = 4.4 Hz), 5.53 (1H, ddt, J = 1.3, 6.4, 15.5 Hz), 6.01 (1H, dt, J = 6.8, 15.5 Hz), 6.52 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) 6: 14.03, 18.98, 22.50, 23.75, 23.88, 28.50, 28.81, 28.94, 28.95, 31.61, 32.23, 42.70, 42.88, 62.03, 70.40, 81.04, 83.09, 125.00, 137.03, 156.12, 174.79, 211.97 ppm; MS (*m*/*z*, %): 409 (M^+, 1.14), 348 (13.74), 131 (30.16), 113 (61.56), 43 (100); HRMS calcd for $C_{22}H_{35}NO_6$ (M^+): 409.2465, Found: 409.2491

Sphingofungin F (2). To a solution of **23** (8 mg, 0.020 mmol) in ethanol (1 mL) was added 2 N aqueous NaOH (1 mL). The mixture was refluxed for 5 h. After being cooled to room temperature, the mixture was neutralized with acetic acid and evaporated. The residue was purified by chromatography on Dowex-50 H^+ resin (eluent: 1 N NH_3) to give a white solid, which was dissolved in methanol (1 mL). To the mixture was added IRC-76 H^+ resin (50 mg), and the mixture was stirred for 30 min, filtered, and evaporated to give a residue, which was purified by flash chromatography on silica gel (eluent: methanol/chloroform/H_2O = 3:10:1, lower layer) to afford compound **2** (4 mg, 51%) as a white solid. mp: 145−147 °C; $[\alpha]_D^{20} = +0.91$ (*c* 0.22, CH_3OH); IR (film) ν: 3369, 3209, 2930, 2855, 1710, 1630, 1497, 1466, 1404, 1368, 1106, 972 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) 5: 0.89 (3H, t, J = 6.9 Hz), 1.20−1.43 (12H, m), 1.49 (3H, s), 1.45−1.59 (4H, m), 2.02−2.09 (2H, m), 2.43 (4H, t, J = 7.5 Hz), 3.67 (1H, d, J = 7.2 Hz), 3.87 (1H, s), 4.10 (1H, dd, J = 7.2, 7.6 Hz), 5.46 (1H, dd, J = 7.6, 15.4 Hz), 5.77 (1H, dt, J = 6.6, 15.4 Hz) ppm; ^{13}C NMR (CD_3OD, 75 MHz) δ: 14.65, 22.07, 23.86, 25.17, 25.18, 30.29, 30.32, 30.44, 30.47, 33.10, 33.72, 43.78, 43.80, 67.06, 72.81, 75.99, 76.48, 130.50, 135.95, 170.50, 214.67 ppm; MS (*m*/*z*, %): 383 ($M^+ - H_2O$, 0.52), 366 (1.94), 295 (2.13), 256 (14.41), 131 (16.78), 86 (88.42), 85 (100), 73 (36.77), 43 (56.56). HRMS calcd for $C_{21}H_{37}NO_5$ ($M^+ - H_2O$): 383.2671, Found: 383.2678.

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