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PAPER

Taurospongins B and C, new acetylenic fatty acid derivatives possessing a taurine amide residue from a marine sponge of the family Spongiidae

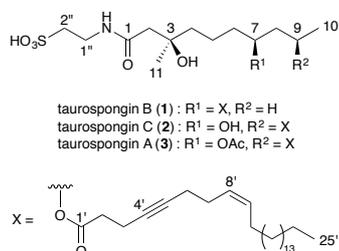
Takaaki Kubota,^a Haruna Suzuki,^a Azusa Takahashi-Nakaguchi,^b Jane Fromont,^c Tohru Gonoï^b and Jun'ichi Kobayashi*^a⁵ Received (in XXX, XXX) Xth XXXXXXXXXX 20XX, Accepted Xth XXXXXXXXXX 20XX

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Two new acetylenic fatty acid derivatives possessing a taurine amide residue, taurospongins B (**1**) and C (**2**), have been isolated from an Okinawan marine sponge of the family Spongiidae. The gross structures of **1** and **2** were elucidated on the basis of their spectral data, especially 2D NMR and ESIMS/MS data. The absolute configurations for **1** and **2** were established by chemical means. Taurospongins B (**1**) and C (**2**) showed inhibitory activity against *Cryptococcus neoformans*.

Introduction

Marine sponges of the family Spongiidae have been demonstrated to be a rich source of unique bioactive meroterpenoids^{1,2} and acetylenic fatty acid derivatives^{3,4}. During our search for bioactive metabolites from marine organisms, we investigated the extract of a sponge family Spongiidae (SS-1202) and resulted in the isolation of two new acetylenic fatty acid derivatives possessing a taurine amide residue, taurospongins B (**1**) and C (**2**). Here we describe the isolation and structure elucidation of **1** and **2**.

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Results and discussion

The sponge family Spongiidae collected at Okinawa, was extracted with MeOH. After evaporation, the MeOH extract was partitioned stepwise between organic solvents (EtOAc and *n*-BuOH) and H₂O. A part of *n*-BuOH soluble materials was fractionated by gel filtration (Sephadex LH-20, MeOH). A fraction eluted in a relatively early stage was purified by C₁₈ column chromatography (MeOH/H₂O) and SiO₂ column chromatography (CH₂Cl/MeOH) to afford taurospongins B (**1**, 1.7 mg, 0.00048%, wet weight) and C (**2**, 4.2 mg, 0.0012%).

Taurospongins B (**1**) was obtained as an optically active colorless amorphous solid. The molecular formula of **1** was revealed to be C₃₈H₆₉NO₇S by HRESIMS data [*m/z* 682.47036 (M-H)⁻, Δ-1.84 mmu]. IR absorptions indicated the existence of hydroxy (3421 cm⁻¹), ester carbonyl (1732 cm⁻¹), and amide carbonyl (1646 cm⁻¹) functionalities. The inspection of the HMQC and HMBC spectra with ¹H and ¹³C NMR data disclosed that **1** consists of ester and amide carbonyls, a triple bond, a double bond, three methyls, twenty seven methylenes, an oxymethine, and an oxygenated quaternary carbon (Table 1). Analysis of the ¹H-¹H COSY and TOCSY spectra of **1** revealed connectivities of C-4 to C-10, C-2' to C-3', C-6' to C-10', C-23' to C-25', and C-1" to C-2". The geometry of a double bond between C-8' and C-9' was assigned as *Z* by the vicinal coupling constant (³*J*_{H-8'/H-9'} = 10.3 Hz). HMBC correlations of H₂-1"/C-1 and H₂-2'/C-1 clarified that *N*-bearing carbon C-1" (δ_C 37.3) and a carbonyl-bearing carbon C-2 (δ_C 48.6) were connected via an amide bond containing a carbonyl carbon C-1 (δ_C 174.6). Linkings of C-2, a methylene carbon C-4, and a methyl carbon C-11 through an oxygenated quaternary carbon C-3 (δ_C 73.4) were inferred from HMBC correlations of H₃-11/C-2, H₂-4/C-3, and H₃-11/C-4. An HMBC correlation of H₂-2'/C-1' revealed that a carbonyl-bearing carbon C-2' (δ_C 36.2) was attached to a carbonyl carbon C-1' (δ_C 174.6).

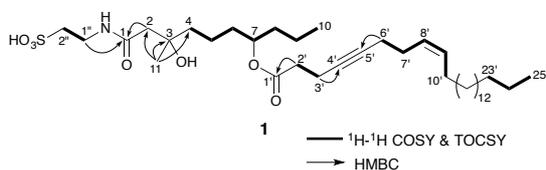
Table 1. ^1H and ^{13}C NMR Data of taurospongins B (**1**) and C (**2**) in CD_3OD .

position	1			2		
	$\delta_{\text{H}}^{\text{a}}$	multi (J in Hz)	$\delta_{\text{C}}^{\text{b}}$	$\delta_{\text{H}}^{\text{a}}$	multi (J in Hz)	$\delta_{\text{C}}^{\text{b}}$
1	-		174.6	-		174.5 ^k
2	2.40	d (14.0)	48.6	2.36 ^c	m	48.4
	2.34	d (14.0)				
3	-		73.4	-		74.2
4	1.59	m ^g	43.8	1.59	m ^g	43.9
	1.53	m ^g		1.52	m ^g	
5	1.44 ^c	m ^g	21.6	1.47 ^c	m ^g	21.8
6	1.61 ^c	m ^g	36.6	1.64 ^c	m ^g	36.7
7	4.98	m	76.2	3.67	m ^g	70.1
8	1.59 ^c	m ^g	38.3	1.85	m ^g	45.3
				1.64	m ^g	
9	1.43 ^c	m ^g	20.5 ^h	5.15	m	71.3
10	0.96 ^d	t (7.4)	15.1 ⁱ	1.30 ^d	d (6.3)	20.7
11	1.25 ^d	s	27.6	1.27 ^d	s	27.7
1'	-		174.6	-		174.3 ^k
2'	2.51 ^c	m	36.2	2.50 ^c	m	36.2
3'	2.48 ^c	m	16.5	2.48 ^c	m	16.4
4'	-		80.2	-		80.1
5'	-		82.2	-		82.2
6'	2.18 ^c	m	20.7 ^h	2.18 ^c	m	20.7
7'	2.23 ^c	m	28.8 ^j	2.23 ^c	m	28.7 ^l
8'	5.44	dt (10.3, 5.6)	130.0	5.44	dt (10.7, 5.4)	130.0
9'	5.45	dt (10.3, 5.6)	132.8	5.46	dt (10.7, 5.4)	132.8
10'	2.09 ^e	m	29.0 ^j	2.09 ^c	q (6.4)	29.0 ^l
11'~22'	1.52~1.15 ^e	m ^g	31.7-31.1 ^f	1.52~1.15 ^e	m	31.7-31.1 ^f
23'	1.33 ^c	m ^g	33.9	1.38 ^c	m	33.9
24'	1.38 ^c	m ^g	24.5	1.33 ^c	m	24.5
25'	0.94	t (7.1)	15.2 ⁱ	0.94	t (7.0)	15.3
1''	3.66	t (6.5)	37.3	3.67	m ^g	37.3
2''	3.02	t (6.5)	52.2	3.03	t (6.6)	52.2

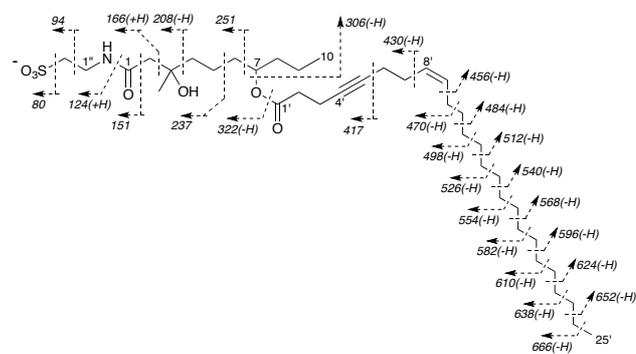
^aRecorded at 600 MHz. ^bRecorded at 150 MHz. ^c2H. ^d3H. ^e24H. ^f12C.

^g J -values were not determined because of overlapping with other signals. ^{h,i,j,k,l} These signals might be exchange.

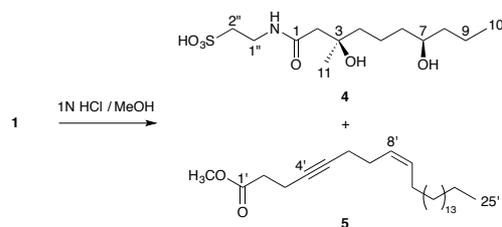
Linkage of C-3' and C-6' by a triple bond between acetylenic carbons C-4' (δ_{C} 80.2) and C-5' (δ_{C} 82.2) was uncovered by HMBC correlations of H_2 -3'/C-4' and H_2 -6'/C-5'. The chemical shift of a proton H-7 (δ_{C} 4.98) of an oxygenated carbon C-7 (δ_{C} 76.2) implied that C-7 was esterified to C-1'. These data and the molecular formula of **1** indicated an attachment of a sulfo group to C-2'' and the connection of C-10' and C-23' by a methylene chain.

**Fig. 2** Selected 2D NMR correlations for taurospongins B (**1**).

The structure of **1** elucidated from the NMR data was also confirmed by a charge-remote fragmentation pattern induced by a sulfo group observed in the FABMS/MS spectrum of **1** (Fig. 3). Thus, the gross structure of taurospongins B (**1**) was elucidated as shown.

**Fig. 3** Fragmentation patterns observed in FABMS/MS spectrum of taurospongins B (**1**) [precursor ion, m/z 682 (M-H)]. The m/z values were indicated in italics.

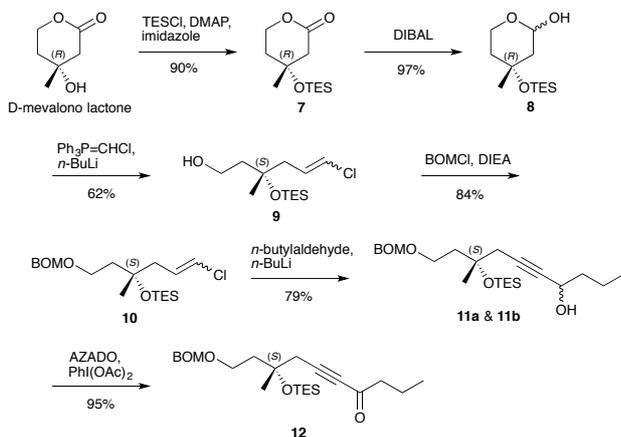
The relative stereochemistry of taurospongins B (**1**) was established by comparison of the NMR data of taurineamide part (**4**) of **1** with its two possible diastereomers (**6a** and **6b**). The taurineamide part (**4**) was obtained by methanolysis of an ester



Scheme 1 Methanolysis of taurospongins B (**1**).

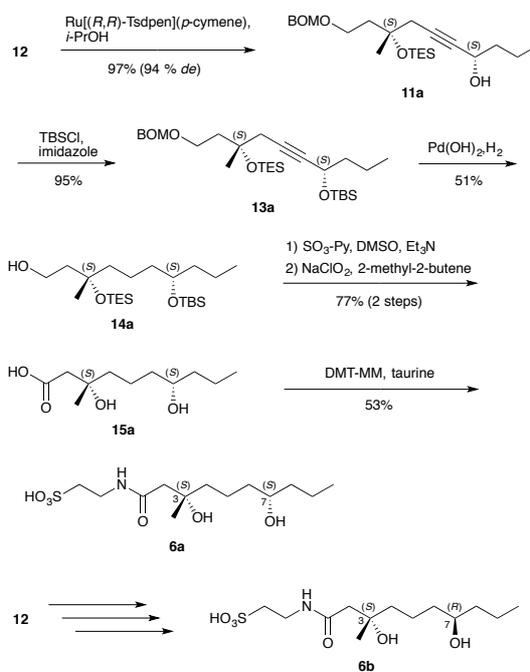
linkage of **1** with an acetylenic fatty acid part (**5**) of **1**⁴ (Scheme 1).

The taurine amides **6a** and **6b** were synthesized from D-mevalono lactone as follows (Schemes 2 and 3). A hydroxy group of D-mevalono lactone was protected by a TES group and then treated with DIBAL to give lactol (**8**), which was coupled with phosphorane by Wittig reaction. After protection of hydroxy group by a BOM group, the resulting chloro-olefin (**10**) was subjected to a coupling reaction with *n*-butylaldehyde to afford a mixture of acetylenic alcohols (**11a** and **11b**), which was converted into an acetylenic ketone (**12**) by oxidation using AZADO⁵.



Scheme 2 Synthesis of **6a** and **6b** (part 1).

The acetylenic ketone (**12**) was derived to chiral acetylenic alcohol (**11a**) by a Noyori asymmetric transfer hydrogenation using Ru[(*S,S*)-Tsdpen](*p*-cymene)⁶. The absolute stereochemistry at C-7 of **11a** was verified by modified Mosher's method⁷ to be *R*-configuration. After the hydroxy group of the **11a** was protected by TBS group, deprotection of BOM group and reduction of the triple bond were accomplished by using Pearlman's catalyst⁸. The resulting primary alcohol (**14a**) was oxidized to carboxylic acid (**15a**) by combination of Parikh-Doering oxidation⁹ and Lindgren-Kraus oxidation¹⁰. Finally, the carboxylic acid was coupled with taurine by amidation using DMT-MM¹¹ to obtain *3S,7R*-isomer (**6a**). The *3S,7S*-isomer (**6b**) was prepared from the acetylenic ketone (**12**) in a similar manner using Ru[(*R,R*)-Tsdpen](*p*-cymene)⁶. Since the ¹H NMR spectra of taurineamide part (**4**) of taurospongins B (**1**) was coincident with that of **6a**, relative relationship for two hydroxy groups of **4**



Scheme 3 Synthesis of **6a** and **6b** (part 2).

were uncovered to be *syn* relationship.

The absolute configuration at C-7 of taurospongins B (**1**) was established by modified Mosher's method⁷. Treatment of taurineamide part (**4**) with (*R*)-(-) and (*S*)-(+)-MTPACl gave (*S*)- and (*R*)-MTPA esters of **4**, respectively. $\Delta\delta$ values obtained from ¹H NMR data of MTPA esters of **4** (Fig. 5) indicated that **4** was an enantiomer of **6a** and the absolute configuration at C-7 of **4** was *R*. Therefore, the absolute configurations at C-3 and C-7 of taurospongins B (**1**) were assigned as both *R*.

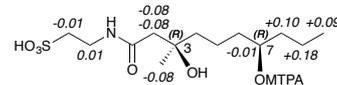


Fig. 5 $\Delta\delta$ values [$\Delta\delta$ (in ppm) = $\delta_S - \delta_R$] obtained for the (*S*)- and (*R*)-MTPA esters of taurineamide part (**4**) of taurospongins B (**1**). $\Delta\delta$ values were indicated in italic.

Taurospongins C (**2**) was obtained as an optically active colorless amorphous solid. The molecular formula of **2** was elucidated as C₃₈H₆₉NO₈S by HRESIMS data [m/z 698.46739 (M-H)⁻, Δ +0.28 mmu]. IR absorptions suggested that **2** possesses hydroxy (3369 cm⁻¹), ester carbonyl (1730 cm⁻¹), and amide carbonyl (1636 cm⁻¹) functionalities. The ¹H and ¹³C NMR data of **2** were almost superimposable to those of taurospongins A (**3**)^{4,12,13}, except for disappearance of signals derived from an acetyl group. In addition, the difference of the molecular formula between **2** and **3** implied that **2** was a 9-*O*-desacetyl form of **3**. To verify the prediction, **2** was derived to 9-*O*-acetyl form by treatment of **2** with acetic anhydride and pyridine. Since the spectral data of 9-*O*-acetyl form of **2** was identical with those of **3**, **2** was assigned as 9-*O*-desacetyl taurospongins A (**3**).

Antimicrobial assay¹⁴ of taurospongins B (**1**), C (**2**), and A (**3**) revealed that **2** and **3** exhibited mild and good antifungal activity,

respectively, against *Cryptococcus neoformans* (MIC, 32 and 1 $\mu\text{g/mL}$), while **1** did not show such activity (MIC, >32.0 $\mu\text{g/mL}$). Taurospongins B (**1**), C (**2**), and A (**3**) were not active against other fungi *Aspergillus niger*, *Trichophyton mentagrophytes*, and *Candida albicans* (MIC, >32 $\mu\text{g/mL}$), and bacteria *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Micrococcus luteus* (IC₅₀, >32 $\mu\text{g/mL}$). Taurospongins B (**1**), C (**2**), and A (**3**) did not show cytotoxicity (IC₅₀ > 10 $\mu\text{g/mL}$) against murine lymphoma L1210 and human epidermoid carcinoma KB cells *in vitro*.

Conclusions

Taurospongins B (**1**) and C (**2**), two new acetylenic fatty acid derivatives possessing a taurine amide residue, have been isolated from an Okinawan marine sponge of the family Spongiidae. The absolute structures of **1** and **2** were established by combination of spectroscopic analysis and synthetic chemistry. Taurospongins C (**2**) and A (**3**) showed mild and good antifungal activity, respectively, against *Cryptococcus neoformans* (MIC, 32 and 1 $\mu\text{g/mL}$).

Experimental section

General experimental procedures

Optical rotations were recorded on a JASCO P-1030 polarimeter. IR spectra were recorded on JASCO FT/IR-230 spectrometer. ¹H and ¹³C NMR spectra were recorded on JEOL ECA400 and JEOL ECA500 spectrometers using 5 mm cell and a Bruker AMX-600 spectrometer using 2.5 mm micro cell. The 7.20 and 77.0 ppm resonances of residual CHCl₃ and CDCl₃, and 3.35 and 49.8 ppm resonances of residual CD₂HOD and CD₃OD were used as internal references for ¹H and ¹³C NMR spectra, respectively. EIMS spectra were recorded on a JEOL JMS-700TZ mass spectrometer. ESIMS spectra were recorded on JEOL JMS-700TZ and Thermo Scientific Exactive mass spectrometers.

Sponge description

The sponge (SS-1202, family Spongiidae) was collected at Unten Port, Okinawa, and kept frozen until used. The sponge was medium brown mound with a spiky, conulose surface, hispid with a fine adherent membrane, and alcohol brown stains. Dermis was unarmored. The sponge has a reticulate fibre skeleton with some pithing of fibres centrally. The reticulation is irregular and all fibres are uncured. Primary fibres are ~50 μm wide. Secondary fibres are ~40 μm wide with finer fibres between as a tertiary skeleton, 10 μm wide. The voucher specimen was deposited at Graduate School of Pharmaceutical Sciences, Hokkaido University.

Extraction and isolation

The sponge of the family Spongiidae (SS-1202, 1.25 kg, wet weight) collected at Okinawa, was extracted with MeOH (2L x 2) to afford the extract (73.3 g), which was partitioned stepwise between organic solvents [EtOAc (500 mL x 3) and *n*-BuOH (500 mL x 3)] and H₂O (500 mL) to give EtOAc-soluble materials (11.8 g) and *n*-BuOH-soluble materials (3.6 g). A part (1.0 g) of *n*-BuOH soluble materials was fractionated by gel filtration (Sephadex LH-20, GE Healthcare; eluent, MeOH). A

fraction was purified by C₁₈ column chromatography (Cosmosil 140 C₁₈ PREP, Nakarai Tesque Inc.; eluent, MeOH/H₂O, 70:30 to 100:0) and SiO₂ column chromatography (Wakosil C-300, Wako Pure Chemical Industries, Ltd.; eluent, CH₂Cl₂/MeOH, 95:5 to 0:100) to afford taurospongins B (**1**, 1.7 mg, 0.00048%, wet weight) and C (**2**, 4.2 mg, 0.0012%).

Taurospongins B (1), colorless amorphous solid; [α]_D²⁵ + 3.4 (c 1.0, MeOH); IR (film) ν_{max} 3421, 1732, 1646, 1456, 1172, 1046 cm⁻¹; ¹H and ¹³C NMR data see Table 1; HRESIMS (neg.) *m/z* 682.47036 [calcd for C₃₈H₆₈NO₇S (M-H)⁻, Δ -1.84 mmu].

Taurospongins C (2), colorless amorphous solid; [α]_D²⁵ + 0.5 (c 1.0, MeOH); IR (film) ν_{max} 3369, 1730, 1636, 1465, 1171, 1044 cm⁻¹; ¹H and ¹³C NMR data see Table 1; HRESIMS (neg.) *m/z* 698.46739 [calcd for C₃₈H₆₈NO₈S (M-H)⁻, Δ +0.28 mmu].

Solvolysis of taurospongins B (1). Taurospongins B (**1**, 1.0 mg, 1.46 μmol) was dissolved in MeOH/1M HCl (10:1, 500 μl). After stirring for 12 h at 80 °C, the mixture was concentrated by Ar blowing. The residue was extracted with CHCl₃, which was concentrated by Ar blowing to afford acetylenic fatty acid part (**5**, 0.5 mg, 1.28 μmol , 88%). The remaining CHCl₃ insoluble material was taurineamide part (**4**, 0.4 mg, 1.23 μmol , 84%).

Taurineamide part (4). ¹H NMR (600 MHz, CD₃OD) δ 3.67 (t, *J* = 6.6 Hz, 2H), 3.58 (m, 1H), 3.03 (t, *J* = 6.6 Hz, 2H), 2.43 (d, *J* = 14.0 Hz, 1H), 2.36 (d, *J* = 14.0 Hz, 1H), 1.66-1.32 (m, 10H), 1.27 (s, 3H), 0.97 (t, *J* = 7.1 Hz, 9H); HRESIMS (neg.) *m/z* 324.14876 [calcd for C₁₃H₂₆NO₆S (M-H)⁻, Δ +0.13 mmu].

(S)-MTPA ester of 4. (*R*)-(-)-MTPACl (1.23 μl) was added to a solution of **4** (0.4 mg, 1.23 μmol) in pyridine (50 μl). After stirring for 1h at rt, (*R*)-(-)-MTPACl (1.23 μl) was added to the mixture additionally. After stirring for 1h at rt, the reaction mixture was concentrated in vacuo. The residue was dissolved with MeOH and passed through an ion-exchange column (Amberlite IR-120 H⁺ form, eluent, MeOH) and concentrated in vacuo. Then, the residue was purified by C18 HPLC (Mightysil RP-18 GP, Kanto Chemical Co., Inc., 4.6 x 250 mm; eluent, CH₃CN/H₂O, 70-100%; flow rate, 1.0 mL/min; UV detection at 230 nm) to afford (*S*)-MTPA ester of **4** (0.4 mg, 0.74 mmol, 60%); ¹H NMR (600 MHz, CD₃OD) δ 7.57 (m, 1H), 7.48 (m, 1H), 5.16 (m, 1H), 3.65 (t, *J* = 6.6 Hz, 2H), 3.59 (s, 3H), 3.02 (t, *J* = 6.6 Hz, 2H), 2.30 (d, *J* = 14.3 Hz, 1H), 2.24 (d, *J* = 14.3 Hz, 1H), 1.59 (m, 2H), 1.24 (m, 2H), 1.80~1.10 (m, 6H), 1.14 (s, 3H), 0.99 (t, *J* = 7.3 Hz, 3H); HRESIMS (neg.) *m/z* 540.18929 [calcd for C₂₃H₃₃NO₈F₃S (M-H)⁻, Δ +0.84 mmu].

(R)-MTPA ester of 4. The (*R*)-MTPA ester of **4** (0.4 mg, 0.74 mmol) was obtained from **4** (0.4 mg, 1.23 μmol) in 60% by using (*S*)-(+)-MTPACl through the same procedure as described for preparation of the (*S*)-MTPA ester of **4**; ¹H NMR (600 MHz, CD₃OD) δ 7.57 (m, 1H), 7.47 (m, 4H), 5.17 (m, 1H), 3.66 (t, *J* = 6.6 Hz, 2H), 3.60 (s, 3H), 3.02 (t, *J* = 6.6 Hz, 2H), 2.38 (d, *J* = 14.3 Hz, 1H), 2.32 (d, *J* = 14.3 Hz, 1H), 1.69 (m, 2H), 1.42 (m, 2H), 1.80~1.10 (m, 6H), 1.22 (s, 3H), 0.90 (t, *J* = 7.3 Hz, 3H); HRESIMS (neg.) *m/z* 540.18851 [calcd for C₂₃H₃₃NO₈F₃S (M-H)⁻, Δ +0.06 mmu].

(R)-4-methyl-4-((triethylsilyloxy)tetrahydro-2H-pyran-2-one (7). Imidazole (1.12 g, 16.45 mmol), DMAP (100.4 mg, 0.82 mmol), and TEA (2.06 mL, 12.27 mmol) were added to a solution of D-mevalonolactone (1.07 g, 8.22 mmol) in DMF (20 mL) at 0 °C. After stirring for 24 h at rt, H₂O was added to the mixture, which was extracted with EtOAc. The organic layer was washed with saturated aqueous CuSO₄, H₂O, and brine, dried with MgSO₄, and concentrated in vacuo. The residue was purified by a SiO₂ column (*n*-hexane/EtOAc, 100:0 to 85:15) to afford **7**

(1.81 g, 7.41 mmol, 90%); yellow oil; $[\alpha]_{\text{D}}^{21}$ -28 (*c* 1.6, CHCl₃); IR (neat) ν_{max} 2957, 2877, 1738, 1458, 1223, 1005, 725 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.58 (m, 1H), 4.34 (m, 1H), 2.67 (brd, *J* = 17.2 Hz, 1H), 2.43 (d, *J* = 17.2 Hz, 1H), 1.84 (m, 2H), 1.39 (s, 3H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.60 (q, *J* = 8.0 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 170.2, 70.4, 66.1, 45.6, 36.9, 29.0, 6.8, 6.3; HRESIMS (pos.) *m/z* 267.13881 [calcd for C₁₂H₂₄O₃NaSi (M+Na)⁺, Δ +0.12 mmu].

(4R)-4-methyl-4-((triethylsilyloxy)tetrahydro-2H-pyran-2-ol

(8). DIBAL (1.04 M in hexane, 8.76 ml, 9.11 mmol) was added to a solution of **7** (1.85 g, 7.57 mmol) in CH₂Cl₂ (20 ml) at -78 °C. After stirring for 1 h at -78 °C, MeOH and saturated aqueous potassium sodium tartrate were added to the mixture, which was allowed to warm to rt with vigorous stirring for 1 h and extracted with EtOAc. The organic layer was washed with H₂O and brine, dried with MgSO₄, and concentrated in vacuo. The residue was purified by a SiO₂ column (*n*-hexane/EtOAc, 100:0 to 85:15) to afford **8** (1.81 g, 7.35 mmol, 97%), which was directly used in the next step; yellow oil; HRESIMS (pos.) *m/z* 269.15447 [calcd for C₁₂H₂₆O₃NaSi (M+Na)⁺, Δ +0.13 mmu].

(S)-6-chloro-3-methyl-3-((triethylsilyloxy)hex-5-en-1-ol (9)

n-BuLi (1.60 M in hexane, 18.6 ml, 29.76 mmol) was added dropwise to a solution of (chloromethyl)triphenylphosphonium chloride (10.33 g, 29.76 mmol) in THF (40 ml) at -78 °C. After stirring for 30 min at -78 °C, a solution of **8** (1.83 g, 7.43 mmol) in THF (3 ml) was added dropwise to the mixture at -78 °C. After stirring for 39 h at -78 °C, saturated aqueous NH₄Cl was added to the mixture, which was extracted with EtOAc. The organic layer was washed with H₂O and brine, dried with MgSO₄, and concentrated in vacuo. The residue was purified by a SiO₂ column (*n*-hexane/EtOAc, 100:0 to 90:10) to afford **9** (1.29 g, 4.63 mmol, 62%), which was directly used in the next step; pale yellow oil; HRESIMS (pos.) *m/z* 301.13601 [calcd for C₁₃H₂₇O₂ClNaSi (M+Na)⁺, Δ -0.10 mmu].

(S)-7-(3-chloroallyl)-9,9-diethyl-7-methyl-1-phenyl-2,4,8-trioxo-9-silaundecane (10)

N,N-diisopropylethylamine (3.15 ml, 18.56 mmol) and benzylchloromethyl ether (1.91 ml, 13.92 mmol) were added to a solution of **9** (1.29 g, 4.63 mmol) in CH₂Cl₂ (32 ml) at 0 °C. After stirring for 12 h at 0 °C, saturated aqueous NH₄Cl was added to the mixture, which was extracted with EtOAc. The organic layer was washed with H₂O and brine, dried with MgSO₄, and concentrated in vacuo. The residue was purified by a SiO₂ column (*n*-hexane/EtOAc, 100:0 to 90:10) to afford **10** (1.56 g, 3.91 mmol, 84%), which was directly used in the next step; pale yellow oil; HRESIMS (pos.) *m/z* 421.19366 [calcd for C₂₁H₃₅O₃ClNaSi (M+Na)⁺, Δ +0.04 mmu].

(8S)-10-((benzyloxy)methoxy)-8-methyl-8-((triethylsilyloxy)dec-5-yn-4-ol (11a and 11b)

n-BuLi (1.60 M in hexane, 6.64 ml, 10.63 mmol) was added dropwise to a solution of **10** (1.41 g, 3.53 mmol) in THF (15 ml) at -78 °C. After stirring for 2 h at -78 °C, *n*-BuLi (1.60 M in hexane, 2.21 ml, 3.54 mmol) was added dropwise at -78 °C additionally. Then a solution of butyraldehyde (0.80 ml, 8.86 mmol) in THF (15 ml) was added dropwise to the mixture. After stirring for 1 h at -78 °C, saturated aqueous NH₄Cl was added to the mixture, which was extracted with EtOAc. The organic layer was washed with H₂O and brine, dried with MgSO₄, and concentrated in vacuo. The residue was purified by a SiO₂ column (*n*-hexane/EtOAc, 100:0 to 90:10) to afford mixture of **11a** and **11b** (1.21 g, 2.78 mmol, 79%), which was directly used in the next step; pale yellow oil; HRESIMS (pos.) *m/z* 457.27449 [calcd for C₂₅H₄₂O₄NaSi (M+Na)⁺, Δ +0.03 mmu].

(S)-10-((benzyloxy)methoxy)-8-methyl-8-((triethylsilyloxy)dec-5-yn-4-one (12)

Iodobenzene diacetate

(1.36 g, 4.23 mmol) and AZADO (42.9 mg, 0.28 mmol) were added to a solution of **11a** and **11b** (1.24 g, 2.82 mmol) in CH₂Cl₂ (4 ml). After stirring for 4 h at rt, CH₂Cl₂ (35 ml) and a mixture of saturated aqueous NaHCO₃ and saturated aqueous Na₂SO₄ (1:1, 30 ml) were added to the mixture, which was extracted with CH₂Cl₂. The organic layer was washed with brine, dried with MgSO₄, and concentrated in vacuo. The residue was purified by a SiO₂ column (*n*-hexane/EtOAc, 100:0 to 90:10) to afford **12** (1.16 g, 2.68 mmol, 95%); pale yellow oil; $[\alpha]_{\text{D}}^{22}$ +5.0 (*c* 1.25, CHCl₃); IR (neat) ν_{max} 3019, 2876, 2211, 1673, 1455, 1377, 1240, 1171, 1114, 1045, 742, 698 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.37~7.26 (m, 5H), 4.75 (s, 2H), 4.60 (s, 2H), 3.72 (m, 2H), 2.61 (d, *J* = 17.1 Hz, 1H), 2.54 (d, *J* = 17.1 Hz, 1H), 2.50 (t, *J* = 7.3 Hz, 1H), 1.96 (ddd, *J* = 13.9, 7.3, 6.8 Hz, 1H), 1.89 (ddd, *J* = 13.9, 7.5, 6.4 Hz, 1H), 1.69 (qt, *J* = 7.3, 7.3 Hz, 2H), 1.37 (s, 3H), 0.95 (qt, *J* = 7.8 Hz, 9H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.60 (q, *J* = 7.8 Hz, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 188.1, 138.0, 128.4, 127.8, 127.7, 94.7, 91.1, 82.6, 73.9, 69.4, 64.1, 47.4, 41.6, 33.8, 28.1, 17.6, 13.5, 7.0, 6.7; HRESIMS (pos.) *m/z* 455.25877 [calcd. for C₂₅H₄₀O₄NaSi (M+Na)⁺, Δ -0.04 mmu].

(4S,8S)-10-((benzyloxy)methoxy)-8-methyl-8-((triethylsilyloxy)dec-5-yn-4-ol (11a)

A solution of **12** (580 mg, 1.34 mmol) in *i*-PrOH (11.6 ml) was added to a solution of [(1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethanediamine]-(*p*-cymene)ruthenium(II) (68.4 mg, 0.11 mmol) in *i*-PrOH (8.29 ml). After stirring for 3 h at rt, the reaction mixture was concentrated in vacuo. The residue was purified by a SiO₂ column (*n*-hexane/EtOAc, 100:0 to 80:20) to afford **11a** (563 mg, 1.30 mmol, 97%, 97:3 dr); pale brown oil; $[\alpha]_{\text{D}}^{23}$ +4.8 (*c* 1.23, CHCl₃); IR (neat) ν_{max} 3441, 2956, 2875, 1455, 1376, 1150, 1111, 1041, 733 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.26 (m, 5H), 4.76 (s, 2H), 4.61 (s, 2H), 4.33 (brt, *J* = 6.5 Hz, 1H), 3.74 (t, *J* = 7.4 Hz, 2H), 2.44 (dd, *J* = 16.4 and 1.5 Hz, 1H), 2.36 (dd, *J* = 16.4 and 1.8 Hz, 1H), 2.03~1.75 (m, 3H), 1.63 (m, 2H), 1.46 (m, 2H), 1.33 (s, 3H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.59 (q, *J* = 7.9 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 137.8, 128.4, 127.9, 127.7, 94.5, 83.4, 82.3, 74.0, 69.3, 64.4, 62.4, 41.2, 40.1, 33.4, 28.0, 18.4, 13.7, 7.0, 6.7; HRESIMS (pos.) *m/z* 457.27512 [calcd for C₂₅H₄₂O₄NaSi (M+Na)⁺, Δ +0.66 mmu].

(S)-MTPA ester of 11a. DMAP (0.2 mg), Et₃N (0.65 μ L), and (*R*)-(-)-MTPACl (0.33 μ L) were added to a solution of **11a** (0.5 mg, 1.15 mmol) in CH₂Cl₂ (30 μ L). After stirring for 3 h at rt, *N,N*-dimethyl 1,3-propanediamine (0.64 μ L) was added to the mixture. After stirring for 15 min at rt, the reaction mixture was concentrated in vacuo. The residue was purified by SiO₂ (hexane-EtOAc, 1:0 to 2:1) to afford (*S*)-MTPA ester of **11a** (0.7 mg, 1.08 mmol, 94%); ¹H NMR (600 MHz, CDCl₃) δ 7.71~7.29 (m, 10H), 5.56 (t, *J* = 6.7 Hz, 1H), 4.73 (s, 2H), 4.59 (s, 2H), 3.71 (t, *J* = 7.3 Hz, 2H), 3.58 (s, 3H), 2.46 (d, *J* = 16.4 Hz, 1H), 2.38 (d, *J* = 16.4 Hz, 1H), 1.93 (m, 1H), 1.86 (m, 1H), 1.73 (m, 2H), 1.35 (m, 2H), 1.31 (s, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.57 (q, *J* = 7.9 Hz, 6H); HRESIMS (pos.) *m/z* 673.31519 [calcd. for C₃₅H₄₉O₆F₃NaSi (M+Na)⁺, Δ +0.92 mmu].

(R)-MTPA ester of 11a. The (*R*)-MTPA ester (0.7 mg, 1.08 mmol) of **11a** was obtained from **11a** (0.5 mg, 1.15 mmol) in 94% by using (*S*)-(-)-MTPACl through the same procedure as described for preparation of the (*S*)-MTPA ester of **11a**; ¹H NMR (600 MHz, CDCl₃) δ 7.70~7.29 (m, 10H), 5.53 (t, *J* = 6.7 Hz, 1H), 4.73 (s, 2H), 4.59 (s, 2H), 3.70 (t, *J* = 7.1 Hz, 2H), 3.54 (s, 3H), 2.42 (d, *J* = 16.4 Hz, 1H), 2.35 (d, *J* = 16.4 Hz, 1H), 1.91 (m, 1H), 1.84 (m, 1H), 1.80 (m, 2H), 1.46 (m, 2H), 1.29 (s, 3H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.92 (t, *J* = 7.8 Hz, 9H), 0.56 (q, *J* = 7.9 Hz, 6H); HRESIMS (pos.) *m/z* 673.31528 [calcd. for C₃₅H₄₉O₆F₃NaSi (M+Na)⁺, Δ +1.01 mmu].

(4R,8S)-10-((benzyloxy)methoxy)-8-methyl-8-

((triethylsilyloxy)dec-5-yn-4-ol (11b)). **11b** (555 mg, 1.28 mmol) was obtained from **12** (580 mg, 1.34 mmol) in 96% (97:3 dr) by using [(1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethanediamine]-(*p*-cymene)ruthenium(II) through the same procedure as described for preparation of **11a**; pale brown oil; $[\alpha]_{\text{D}}^{23} +8.4$ (*c* 1.77, CHCl₃); IR (neat) ν_{max} 3447, 2956, 2875, 1455, 1376, 1150, 1112, 1041, 741 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.26 (m, 5H), 4.76 (s, 2H), 4.61 (s, 2H), 4.33 (brs, 1H), 3.74 (t, *J* = 7.3 Hz, 2H), 2.44 (dd, *J* = 16.4 and 1.8 Hz, 1H), 2.36 (dd, *J* = 16.4 and 1.8 Hz, 1H), 1.98 (m, 1H), 1.87 (m, 2H), 1.63 (m, 2H), 1.46 (m, 2H), 1.33 (s, 3H), 0.94 (t, *J* = 7.8 Hz, 9H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.59 (q, *J* = 7.8 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 137.8, 128.4, 127.9, 127.7, 94.5, 83.4, 82.3, 74.0, 69.2, 64.4, 62.4, 41.2, 40.1, 33.4, 28.0, 18.5, 13.7, 7.1 6.6; HRESIMS (pos.) *m/z* 457.27408 [calcd for C₂₅H₄₂O₄NaSi (M+Na)⁺, Δ -0.38 mmu].

(S)-MTPA ester of 11b. The (*S*)-MTPA ester (0.7 mg, 1.08 mmol) of **11b** was obtained from **11b** (0.5 mg, 1.15 mmol) in 94% through the same procedure as described for preparation of the (*S*)-MTPA ester of **11a**; ¹H NMR (600 MHz, CDCl₃) δ 7.71~7.29 (m, 10H), 5.53 (t, *J* = 6.4 Hz, 1H), 4.72 (s, 2H), 4.58 (s, 2H), 3.69 (t, *J* = 7.3 Hz, 2H), 3.54 (s, 3H), 2.43 (d, *J* = 16.4 Hz, 1H), 2.35 (d, *J* = 16.4 Hz, 1H), 1.89 (m, 1H), 1.83 (m, 1H), 1.81 (m, 2H), 1.46 (m, 2H), 1.29 (s, 3H), 0.93 (t, *J* = 7.8 Hz, 9H), 0.88 (t, *J* = 7.5 Hz, 3H), 0.57 (q, *J* = 7.8 Hz, 6H); HRESIMS (pos.) *m/z* 673.31405 [calcd. for C₃₅H₄₉O₆F₃NaSi (M+Na)⁺, Δ -0.22 mmu].

(R)-MTPA ester of 11b. The (*R*)-MTPA ester (0.7 mg, 1.08 mmol) of **11b** was obtained from **11b** (0.5 mg, 1.15 mmol) in 94% by using (*S*)-(-)-MTPACl through the same procedure as described for preparation of the (*S*)-MTPA ester of **11a**; ¹H NMR (600 MHz, CDCl₃) δ 7.71~7.29 (m, 10H), 5.56 (t, *J* = 6.6 Hz, 1H), 4.73 (s, 2H), 4.58 (s, 2H), 3.71 (t, *J* = 7.3 Hz, 2H), 3.58 (s, 3H), 2.46 (d, *J* = 16.4 Hz, 1H), 2.39 (d, *J* = 16.4 Hz, 1H), 1.92 (m, 1H), 1.85 (m, 1H), 1.73 (m, 2H), 1.36 (m, 2H), 1.32 (s, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.58 (q, *J* = 7.9 Hz, 6H); HRESIMS (pos.) *m/z* 673.31402 [calcd for C₃₅H₄₉O₆F₃NaSi (M+Na)⁺, Δ -0.25 mmu].

(7S,11S)-7,13,13,14,14-pentamethyl-1-phenyl-11-propyl-7-

((triethylsilyloxy)-2,4,12-trioxa-13-silapentadec-9-yne (13a)). Imidazole (175.4 mg, 2.58 mmol) and TBSCl (290.3 mg, 1.94 mmol) were added to a solution of **11a** (560 mg, 1.29 mmol) in CH₂Cl₂ (11 ml). After stirring for 3 h at rt, saturated aqueous NH₄Cl was added to the mixture, which was extracted with CH₂Cl₂. The organic layer was washed with H₂O and brine, dried with MgSO₄, and concentrated in vacuo. The residue was purified by a SiO₂ column (*n*-hexane/EtOAc, 100:0 to 90:10) to afford **13a** (675 mg, 1.23 mmol, 95%); colorless oil; $[\alpha]_{\text{D}}^{24} -14.6$ (*c* 1.17, CHCl₃); IR (neat) ν_{max} 2956, 2876, 1456, 1251, 1111, 1041, 836, 776, 731 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.38~7.26 (m, 5H), 4.75 (s, 2H), 4.60 (s, 2H), 4.33 (brt, *J* = 6.3, 1H), 3.73 (t, *J* = 7.4 Hz, 2H), 2.43 (dd, *J* = 16.4 and 1.5 Hz, 1H), 2.34 (dd, *J* = 16.4 and 1.9 Hz, 1H), 1.98 (m, 1H), 1.86 (m, 1H), 1.61 (m, 2H), 1.42 (m, 2H), 1.33 (s, 3H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.90 (s, 9H), 0.58 (q, *J* = 7.9 Hz, 6H), 0.11 (s, 3H), 0.09 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 137.9, 128.4, 127.9, 127.6, 94.6, 84.0, 81.1, 74.1, 69.2, 64.4, 62.9, 41.1, 41.1, 33.5, 28.0, 25.8, 18.6, 18.2, 13.8, 7.1, 6.7, -4.5, -5.1; HRESIMS (pos.) *m/z* 571.36206 [calcd for C₃₁H₅₆O₄NaSi₂ (M+Na)⁺, Δ +1.13 mmu].

(7S,11R)-7,13,13,14,14-pentamethyl-1-phenyl-11-propyl-7-

((triethylsilyloxy)-2,4,12-trioxa-13-silapentadec-9-yne (13b)). **13b** (674 mg, 1.23 mmol) was obtained from **11b** (554 mg, 1.27 mmol) in 97% through the same procedure as described for preparation of **13a**; colorless oil; $[\alpha]_{\text{D}}^{23} +16.5$ (*c* 1.52, CHCl₃); IR (neat) ν_{max} 2958, 2876, 1456, 1251, 1111, 1041, 836, 776, 731

cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.26 (m, 5H), 4.75 (s, 2H), 4.60 (s, 2H), 4.33 (brt, *J* = 6.5 Hz, 1H), 3.73 (t, *J* = 7.4 Hz, 2H), 2.43 (dd, *J* = 16.3 and 1.8 Hz, 1H), 2.35 (dd, *J* = 16.3 and 1.8 Hz, 1H), 1.98 (m, 1H), 1.86 (m, 1H), 1.62 (m, 2H), 1.42 (m, 2H), 1.33 (s, 3H), 0.94 (t, *J* = 7.8 Hz, 9H), 0.91 (t, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.59 (q, *J* = 7.8 Hz, 6H), 0.12 (s, 3H), 0.10 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 137.9, 128.4, 127.9, 127.6, 94.6, 84.0, 81.1, 74.1, 69.2, 64.3, 62.9, 41.1, 41.1, 33.5, 28.0, 25.8, 18.6, 18.2, 13.8, 7.1, 6.7, -4.5, -5.1; HRESIMS (pos.) *m/z* 571.36052 [calcd for C₃₁H₅₆O₄NaSi₂ (M+Na)⁺, Δ -0.41 mmu].

(3S,7S)-7-((tert-butyltrimethylsilyloxy)-3-methyl-3-

((triethylsilyloxy)decan-1-ol (14a)). 20% Pd(OH)₂/C (13.5 mg) was added to a solution of **13a** (27 mg, 0.049 mmol) in EtOAc (2.5 ml) and the mixture was stirred under H₂ at rt. Additional 20% Pd(OH)₂/C (13.5 mg) and EtOAc (2.5 ml) were added to the mixture every 1 h. After stirring under H₂ for 5 h at rt, the mixture was filtered through a cotton plug, and the filtrate was concentrated in vacuo. The residue was purified by a SiO₂ column (CHCl₃) to afford **14a** (10.9 mg, 0.025 mmol, 51%); colorless oil; $[\alpha]_{\text{D}}^{24} +4.2$ (*c* 1.87, CHCl₃); IR (neat) ν_{max} 3363, 2956, 2932, 2875, 1455, 1253, 1040, 773 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.78 (brq, 5.2 Hz, 2H), 3.63 (brquin, *J* = 5.6 Hz, 1H), 3.18 (brt, *J* = 4.5 Hz, 1H), 1.75 (dt, *J* = 14.5, 5.6 Hz, 1H), 1.70-1.56 (m, 2H), 1.53-1.15 (m, 12H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.89 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.60 (q, *J* = 7.9 Hz, 6H), 0.03 (s, 3H), 0.03 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 77.8, 72.0, 60.0, 43.2, 42.0, 39.4, 37.6, 27.7, 25.9, 20.6, 18.5, 18.1, 14.3, 7.0, 6.7, -4.5; HRESIMS (pos.) *m/z* 455.33454 [calcd for C₂₃H₅₂O₃NaSi₂ (M+Na)⁺, Δ -0.18 mmu].

(3S,7R)-7-((tert-butyltrimethylsilyloxy)-3-methyl-3-

((triethylsilyloxy)decan-1-ol (14b)). **14b** (8.4 mg, 0.019 mmol) was obtained from **13b** (15 mg, 0.027 mmol) in 70% through the same procedure as described for preparation of **14a**; colorless oil; $[\alpha]_{\text{D}}^{24} +2.2$ (*c* 1.39, CHCl₃); IR (neat) ν_{max} 3368, 2955, 2931, 2876, 1461, 1251, 1041, 773 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.79 (2H, brt, *J* = 5.0 Hz), 3.63 (brquin, *J* = 5.6 Hz), 3.18 (brs, 1H), 1.75 (dt, *J* = 14.4, 5.5 Hz, 1H), 1.70-1.17 (m, 12H), 0.96 (9H, t, *J* = 7.9 Hz, TES-Me), 0.89 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.61 (q, *J* = 7.9 Hz, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 77.9, 71.9, 60.0, 43.1, 41.9, 39.4, 37.7, 27.7, 25.9, 20.5, 18.6, 18.1, 14.3, 7.0, 6.8, -4.5; HRESIMS (pos.) *m/z* 455.33408 [calcd for C₂₃H₅₂O₃NaSi₂ (M+Na)⁺, Δ -0.64 mmu].

(3S,7S)-3,7-dihydroxy-3-methyldecanoic acid (15a). DMSO (70.0 μ l) and Et₃N (24.0 μ l) were added to a solution of **14a** (5.0 mg, 0.012 mmol) in CH₂Cl₂ (212.0 μ l). After stirring for 5 min at 0 °C, SO₃-pyr. (19.2 mg) was added to the mixture. After stirring for 1 h at rt, additional SO₃-pyr. (19.2 mg) was added to the reaction mixture. After stirring for 1 h at rt, the mixture was extracted with diethyl ether. The organic layer was washed with H₂O and brine, dried with MgSO₄, and concentrated in vacuo to afford crude aldehyde. Then *t*-BuOH (0.73 ml), NaH₂PO₄ (8.2 mg in 182.0 μ l of H₂O), and 2-methyl-2-butene (2M in THF, 50.4 μ l) were added to the crude aldehyde. After stirring for 5 min at rt, NaClO₂ (7.3 mg) was added to the mixture. After stirring for 15 min at 0 °C, saturated aqueous NaHSO₄ was added to the mixture, which was extracted with EtOAc. The organic layer was washed with H₂O and brine, dried with MgSO₄, and concentrated in vacuo. The residue was purified by a SiO₂ column (*n*-hexane/EtOAc, 100:0 to 90:10) to afford **15a** (2.0 mg, 0.0092 mmol, 77%); colorless oil; $[\alpha]_{\text{D}}^{18} -5.9$ (*c* 2.02, CHCl₃); IR (neat) ν_{max} 3410, 2923, 2853, 1717, 1562, 1456, 1240, 1129, 774 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.05 (brs, 1H), 3.64 (m, 1H), 2.56 (d, *J* = 15.6 Hz, 1H), 2.47 (d, *J* = 15.6 Hz, 1H), 1.61-1.29 (m, 10H), 1.28 (s, 3H), 0.92 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 175.8, 71.5, 71.4, 44.6, 41.6, 39.6, 37.2, 26.7, 19.9,

18.8, 14.1; HRESIMS (pos.) m/z 241.14118 [calcd for $C_{11}H_{22}O_4Na$ (M+Na)⁺, $\Delta+0.15$ mmu].

(3S,7R)-3,7-dihydroxy-3-methyldecanoic acid (15b). **15b** (1.4 mg, 0.0064 mmol) was obtained from **14b** (4.0 mg, 0.0092 mmol) in 70% through the same procedure as described for preparation of **15a**; colorless oil; $[\alpha]_D^{20}$ -4.87 (*c* 1.72, CHCl₃); IR (neat) ν_{max} 3362, 2920, 2850, 1717, 1575, 1456, 1219, 1123, 772 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.20 (brs, 1H), 3.64 (m, 1H), 2.56 (d, *J* = 15.6 Hz, 1H), 2.48 (d, *J* = 15.6 Hz, 1H), 1.62-1.29 (m, 10H), 1.28 (s, 3H), 0.92 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 175.9, 71.6, 71.5, 44.8, 41.6, 39.6, 37.2, 26.6, 19.9, 18.8, 14.1; HRESIMS (pos.) m/z 241.14116 [calcd for $C_{11}H_{22}O_4Na$ (M+Na)⁺, $\Delta+0.13$ mmu].

2-((3S,7S)-3,7-dihydroxy-3-methyldecanamido)ethanesulfonic acid (6a). DMT-MM (95 mg) and Et₃N (400 μ l) were added to a solution of **15a** (25.0 mg, 0.11 mmol) in DMF (5 ml). After stirring for 10 min at rt, taurine (190 mg) was added to the mixture. After stirring for 10 h at rt, the mixture was concentrated in vacuo. The residue was dissolved with MeOH and passed through an ion-exchange column (Amberlite IR-120 H⁺ form, eluent, MeOH) and concentrated in vacuo. The residue was purified by a SiO₂ column (CHCl₃/MeOH, 100:0 to 50:50) to afford **6a** (19.0 mg, 0.058 mmol, 53%); colorless oil; $[\alpha]_D^{20}$ +3.5 (*c* 1.14, MeOH); IR (neat) ν_{max} 3366, 2955, 2871, 2280, 1638, 1555, 1284, 1144, 1059, 938 cm⁻¹; ¹H NMR (600 MHz, CD₃OD) δ 3.67 (brt, *J* = 6.7 Hz, 2H), 3.58 (m, 1H), 3.03 (t, *J* = 6.6 Hz, 2H), 2.43 (d, *J* = 14.0 Hz, 1H), 2.36 (d, *J* = 14.0 Hz, 1H), 1.66-1.32 (m, 10H), 1.27 (s, 3H), 0.97 (t, *J* = 7.1 Hz, 9H); ¹³C NMR (100 MHz, CD₃OD) δ 175.2, 73.9, 72.8, 52.3, 48.3, 44.2, 41.6, 39.6, 37.2, 27.8, 22.1, 20.8, 15.3; HRESIMS (neg.) m/z 324.14903 [calcd for $C_{13}H_{26}NO_6S$ (M-H)⁻, $\Delta+0.40$ mmu].

2-((3S,7R)-3,7-dihydroxy-3-methyldecanamido)ethanesulfonic acid (6b). **6b** (20.5 mg, 0.063 mmol) was obtained from **15b** (24 mg, 0.11 mmol) in 57% through the same procedure as described for preparation of **6a**; colorless oil; $[\alpha]_D^{20}$ -0.4 (*c* 1.28, MeOH); IR (neat) ν_{max} 3439, 2957, 2857, 2279, 1644, 1565, 1282, 1147, 1069, 921 cm⁻¹; ¹H NMR (600 MHz, CD₃OD) δ 3.68 (brt, *J* = 6.6 Hz, 2H), 3.58 (m, 1H), 3.03 (t, *J* = 6.6 Hz, 2H), 2.44 (d, *J* = 14.0 Hz, 1H), 2.38 (d, *J* = 14.0 Hz, 1H), 1.66-1.32 (m, 10H), 1.29 (s, 3H), 0.97 (t, *J* = 7.1 Hz, 9H); ¹³C NMR (100 MHz, CD₃OD) δ 175.4, 74.0, 72.8, 52.3, 48.2, 44.2, 41.6, 39.6, 37.2, 27.8, 22.1, 20.8, 15.3; HRESIMS (neg.) m/z 324.14892 [calcd for $C_{13}H_{26}NO_6S$ (M-H)⁻, $\Delta+0.29$ mmu].

Antimicrobial assay.

Antimicrobial assay of **1-3** against *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Micrococcus luteus*, *Aspergillus niger*, *Candida albicans*, *Cryptococcus neoformans*, and *Trichophyton mentagrophytes* was carried out as previously described.¹⁴ Amphotericin B, micafungin, hygromycin B, and kanamycin showed antifungal activity against *Cryptococcus neoformans* (MIC, <0.05, <0.1, 4.0, and 8.0 μ g/mL, respectively).

Cytotoxic assays.

Human epidermoid carcinoma (KB) and murine leukemia L1210 cells were cultured in an incubator at 37 °C for 48 h in 100 μ L of medium containing various concentrations of test compounds dissolved in 1% DMSO. The IC₅₀ values were obtained by plotting the logarithm of the concentration of the test compound versus the growth rate of the treated cells. Paclitaxel was used as positive control (IC₅₀ <0.005 and <0.1 μ g/mL, respectively).

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Graphical Abstract

