Taurospongin A, a Novel Acetylenic Fatty Acid Derivative Inhibiting DNA Polymerase β and HIV Reverse Transcriptase from Sponge *Hippospongia* sp.

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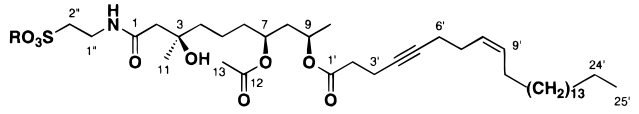
Taurospongin A (**1**), a novel acetylene-containing natural product consisting of a taurine and two fatty acid residues, has been isolated from the Okinawan marine sponge *Hippospongia* sp. and its structure elucidated by spectral data and chemical means. Taurospongin A (**1**) exhibited potent inhibitory activity against DNA polymerase β and HIV reverse transcriptase. The absolute configurations of taurospongin A (**1**) were established to be 3*R*, 7*S*, and 9*R* by synthesis of the MTPA ester of a degradation product of **1**.

During our continuing studies on bioactive substances from Okinawan marine organisms,[2] we recently isolated new sulfonosphingolipid, flavocristamides A and B, that inhibit DNA polymerase α from a marine bacterium *Flavobacterium* sp.[3] Further investigations in search for eukaryotic DNA replication enzyme inhibitors have now resulted in isolation of a novel taurine-containing acetylenic lipid, taurospongin A (**1**), which remarkably inhibits DNA polymerase β and HIV reverse transcriptase, from the Okinawan marine sponge *Hippospongia* sp. This paper describes the isolation and structure elucidation of **1** including the determination of the absolute stereochemistry based on the synthesis of a degradation product of **1**.

The purple-colored sponge *Hippospongia* sp. collected off Okinawa Island was extracted with MeOH, the extract was partitioned between EtOAc and H_2O, and the aqueous phase was further extracted with *n*-BuOH. While the EtOAc-soluble fraction was found to contain a sesquiterpenoid quinone, metachromin A,[4] as a major constituent, the *n*-BuOH-soluble material was subjected to silica gel flash column chromatography ($CHCl_3$/MeOH, 4:1) followed by gel filtration on Sephadex LH-20 ($CHCl_3$/MeOH, 1:1) to give taurospongin A (**1**, 0.02% wet weight).



1 R = H
2 R = Me

The molecular formula of taurospongin A (**1**) was revealed as $C_{40}H_{70}NO_9S$ by negative HRFABMS [*m*/*z* 740.4819 $(M - H)^-$, Δ +4.8 mmu]. The IR absorptions of **1** were suggestive of the presence of hydroxyl (3300 cm^{-1}), acetylene (2370 cm^{-1}), ester carbonyl (1740 cm^{-1}), amide carbonyl (1640 cm^{-1}), and sulfonic acid (1375 cm^{-1}) functionalities. The methyl ester (**2**), prepared from **1** by treatment with diazomethane, was used for the ^{1}H and ^{13}C NMR spectral studies (Table 1), which revealed signals due to three ester or amide carbonyls, one disubstituted double bond, one disubstituted triple bond, one oxygenated quaternary sp^3 carbon, two oxymethines, one methoxy and four other methyl groups, and many sp^3 methylenes. Extensive 2D NMR spectral experiments (^{1}H-^{1}H COSY, HOHAHA, HMQC, and HMBC[5]) were carried out for **2** in C_6D_6 solution to suggest that **2**

Table 1. ^{1}H and ^{13}C NMR Data of Taurospongin A Methyl Ester (2) in C_6D_6

position	^{1}H[a]	*J* (Hz)	^{13}C[b]	HMBC (^{1}H)
1			172.6	NH, 1″, 2a, 2b
2a	1.87 d	14.8	46.1	11
2b	2.02 d	14.8		
3			71.1	2a, 2b, 11
3-OH	4.31 br s			
4(2H)	1.47 m		42.0	2a, 2b, 11
5(2H)	1.50 m		22.0	
6(2H)	1.58 m		35.1	8a, 8b
7	5.17 m		70.8	8a, 8b, 9
8a	1.58 m		41.0	9, 10
8b	1.97 m			
9	5.21 m		68.3	8a, 8b, 10
10(3H)	1.24 d	6.8	20.2	7,[c] 8a, 8b, 9
11(3H)	1.18 s		27.0	2a, 2b
12			170.2	13
13(3H)		1.80 s	20.8	7,[c] 8b
1′			171.3	2′, 3′, 9
2′(2H)	2.41 m		34.5	3′
3′(2H)	2.51 m		15.2	2′
4′			79.0	2′, 3′, 6′
5′			80.9	3′, 6′, 7′
6′(2H)	2.19 m		19.6	7′
7′(2H)	2.29 m		27.3	8′, 9′, 10′[c]
8′	5.53 m		131.3	7′, 10′
9′	5.58 m		128.4	6′,[c] 7′, 10′
10′(2H)	2.07 m		27.7	8′, 9′
11′∼23′(26H)	1.25−1.64 m		29.7 ∼ 32.3	
24′(2H)	1.37 m		23.1	25′
25′(3H)	0.96 t	6.8	14.3	
NH	5.71 m			
1″(2H)	3.30 m		34.0	NH, 2″
2″(2H)	2.74 m		48.5	1″
SO_3Me(3H)	3.20 s		55.0	

[a] 600 MHz. [b] 125 MHz. [c] Correlation through four-bonds.

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(1) (a) Hokkaido University. (b) Nagoya University.

(2) (a) Ishibashi, M.; Kobayashi, J. *Heterocycles* **1997**, *44*, 543−572. (b) Kobayashi, J.; Ishibashi, M. *Heterocycles* **1996**, *42*, 943−970 and references cited therein.

(3) Kobayashi, J.; Mikami, S.; Shigemori, H.; Takao, T.; Shimonishi, Y.; Izuta, S.; Yoshida, S. *Tetrahedron* **1995**, *51*, 10487−10490.

(4) Ishibashi, M.; Ohizumi, Y.; Cheng, J.-F.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1988**, *53*, 2855−2858.

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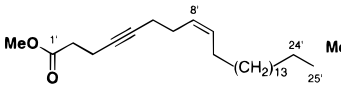
consisted of three elements, i.e., a taurine, a trihydroxyl fatty acid, and an unsaturated fatty acid, as described below.

Amino acid analysis of the acid hydrolysate of **1** revealed the presence of taurine in **1**. The methyl ester **2** was therefore inferred to be a methyl sulfonate ester in the taurine moiety. The ^{1}H NMR spectrum of **2** showed signals assignable to two methylene groups of taurine and the ^{1}H−^{1}H COSY cross peaks were observed for NH/H_2-1″ and H_2-1″/H_2-2″. The HMBC spectrum of **2** showed cross peaks due to ^{1}H−^{13}C long-range correlations for NH/C-1 and H-1″/C-1, thus indicating that the taurine unit was connected to C-1 of trihydroxy fatty acid through an amide bond.

For the trihydroxy fatty acid moiety of **2**, a substructure from C-1 to C-4 with a tertiary methyl group on C-3 oxygenated carbon was suggested from the HMBC correlations observed for H_2-2/C-1, H_2-2/C-3, H_2-2/C-11, H_2-2/C-4, and H_3-11/C-3. The ^{1}H−^{1}H COSY spectrum showed the proton connectivities from H_2-6 to H_3-10. Acetyl and unsaturated acyl groups were shown to be connected on C-7 and C-9 oxymethines, respectively, through ester linkages from the HMBC correlations of **2** for H-7/C-13 (via 4 bonds), H_3-13/C-12, and H-9/C-1′. Thus, another substructure for the C-6 to C-10 moiety was elucidated. The C-4 and C-6 had to be connected through sp^3 methylenes and the HOHAHA spectrum of **2** showed a correlation between H_2-4 and H-7. The number of methylene carbons between C-4 and C-6, however, could not be firmly determined because of overlapping of the methylene signals.

As to the unsaturated fatty acid portion, the ^{1}H−^{1}H COSY spectrum showed a cross peak for H_2-3′/H_2-6′ due to long-range coupling through a triple bond. The relatively high-field resonances of C-3′ (δ_C 15.2) and C-6′ (δ_C 19.6) implied that these methylenes were adjacent to an acetylene group.[6] The ^{1}H−^{1}H COSY revealed the connectivities from H_2-6′ to H_2-10′ through an olefin at C-8′/C-9′ as well as a cross peak for the terminal part, H_2-24′/H_3-25′. The 8′*Z*-configration was deduced from the ^{13}C chemical shifts of the allylic carbons [δ_C 27.3 (C-7′); δ_C 27.7 (C-10′)].[7] Though the C-10′ and C-24′ had to be connected through sp^3 methylene carbons, the number of the methylenes between them was also unknown from spectral data, thus requiring the following chemical degradations.

Methanolysis of **2** (MeOH/1 N HCl, 10:1)[8] afforded two fragments, unsaturated fatty acid methyl ester [**3**, EIMS *m*/*z* 390 (M^+)] and trihydroxy amide [**4**, FABMS *m*/*z* 356 $(M + H)^+$]. Molecular weights of these methanolysis products (**3** and **4**) clearly showed the lengths of the methylene chains. The $\Delta^{8'}$-double bond was further confirmed to be *Z* by the ^{1}H coupling constant for **3** ($J_{8',9'}$= 11.3 Hz). From all of these data the gross structure of taurospongin A was concluded as **1**.



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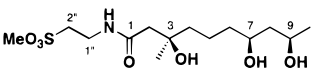

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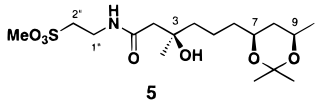

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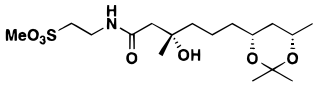
Taurospongin A (**1**) contains three chiral centers at C-3, C-7, and C-9. The relative stereochemistry of 1,3-diol at the C-7/C-9 position was revealed to be *syn* by applying Rychnovsky's ^{13}C-acetonide analysis[9] for the acetonide (**5**: δ_C 19.9, 30.3, and 98.4) prepared from **4**. To elucidate the relative stereochemistry between C-3 and the C-7/C-9 position as well as the absolute stereochemistry of these three chiral centers, two possible diastereomers **6** and **7**, which correspond to the acetonide derivative **5**,



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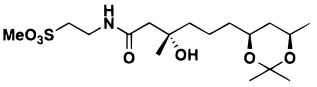

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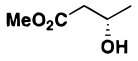
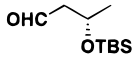
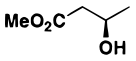
were prepared as optically active forms as follows (Scheme 1). The methoxymethyl (MOM) ether (**9**) derived from (*R*)-3-hydroxy-3-methyl-5-pentanolide (**8**)[10] was reduced with DIBAL to give a lactol, which was subjected to Wittig reaction with (chloromethylene)triphenylphosphorane followed by protection with benzyloxymethyl group to yield a 2:1 mixture of the *E*/*Z* chlorovinyl derivatives **10**. On the other hand, (*S*)-3-[(*tert*-butyldimethylsilyl)oxy]butanal ((*S*)-**12**) was prepared from methyl (*S*)-(+)-3-hydroxybutylate ((*S*)-**11**)[10] in two steps. The



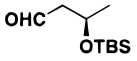
(*S*)-**11**



(*S*)-**12**



(*R*)-**11**



(*R*)-**12**

lithium acetylide generated from *E*/*Z* mixture of **10** (*n*-BuLi, THF, 0 °C, 45 min) was coupled with the aldehyde (*S*)-**12** to afford a 1:1 mixture of the *anti*/*syn* alcohols **13** and **14**. The diastereomeric mixture was separable by silica gel column chromatography, and each diastereomer was then converted into its acetonide **15** and **16**, respectively. Relative stereochemistry of 1,3-diol moiety of **15** and **16** was elucidated from the ^{13}C-acetonide analysis[9] [**15** (*anti*): δ_C 23.8, 29.0, 99.8; **16** (*syn*): δ_C 19.4, 30.1, 99.0]. Since the 1,3-diol moiety at C-7 and C-9 of taurospongin A (**1**) was already revealed as *syn*, the *syn* acetonide **16** was subjected to hydrogenation in the presence of Raney Ni to furnish an alcohol **17**. RuO_4 oxidation[11] of the alcohol **17** afforded an carboxylic acid, which was coupled with taurine through an *N*-hydroxysuccinimide ester.[12] Passing through an ion exchange chromatography (Amberlite IR-122) resulted in the deprotection of MOM ether and acetonide groups, and the resulting sulfonic acid was treated with diazomethane to give trihydroxy amide methyl ester **18**, which was then converted into acetonide **6**. The diastereomeric *syn*

(5) The HMBC data were obtained by combination of three kinds of HMBC spectra, i.e., conventional HMBC, field-gradient HMBC, and D-HMBC (Furihata, K.; Seto, H. *Tetrahedron Lett.* **1995**, *36*, 2817−2820).

(6) Kalinowski, H.-O.; Berger, S.; Braun, S. *Carbon-13 NMR Spectroscopy*; John Wiley & Sons: Chichester, 1984; p 148.

(7) The allylic carbons of *cis*-double bonds are known to resonate approximately at 27 ppm, while those of *trans*-ones at *ca.* 33 ppm: Gunstone, F. D.; Pollard, M. R.; Scrimgeour, C. M.; Vedanayagam, H. S. *Chem. Phys. Lipids* **1977**, *18*, 115−129.

(8) Costantino, V.; Fattorusso, E.; Mangoni, A. *Liebigs Ann.* **1995**, 2133−2136.

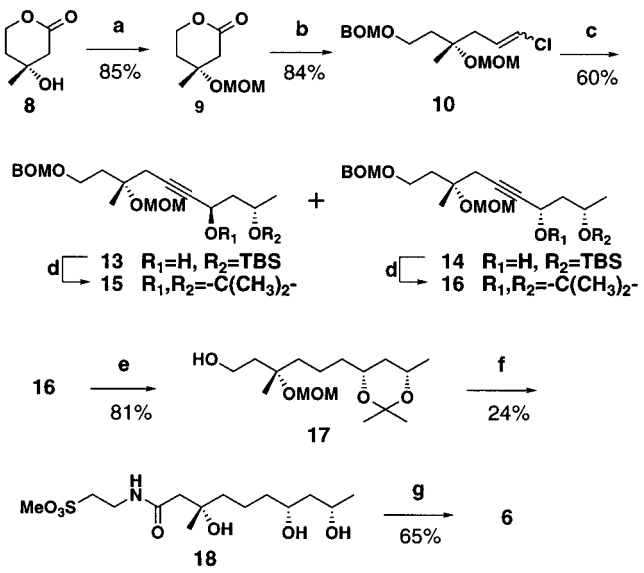
(9) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511−3515.

(10) Chiral precursors **8**, (*S*)-**11**, and (*R*)-**11** were all commercially available from Wako Pure Chemical, Ind., Ltd.

(11) Carlsen, P. H. J; Katsuki, T; Martin, V. S; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

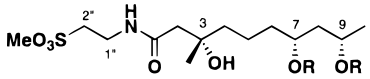
(12) Paquet, A. *Can. J. Chem.* **1979**, *57*, 2775−2778.

Scheme 1[a]



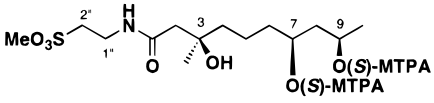
[a](a) MOMCl, NEt(*i*-Pr)$_2$; (b) (1) DIBAL, Et$_2$O; (2) Ph$_3$P=CHCl; (3) BOMCl, NEt(*i*-Pr)$_2$; (c) *n*-BuLi, (*S*)-**12**; (d) (1) *n*-Bu$_4$NF; (2) DMP, PPTS; (e) H$_2$, Raney Ni (W-2); (f) (1) $RuCl_3$, $NaIO_4$; (2) HOSu, DCC; (3) Taurine, TEA; (4) Amberlite IR-122; (5) CH_2N_2; (g) DMP, PPTS

acetonide **7** was also synthesized by coupling of the acetylide from **10** with an enantiomeric aldehyde ((*R*)-**12**), prepared from (*R*)-**11**,[10] followed by the same reactions as described above. The ^{1}H NMR spectra of the diastereomers **6** and **7** could be discriminated from each other particulary by the AB quartet signals due to the C-2 methylene protons (**6**: δ_H 2.28 and 2.41; **7**: δ_H 2.29 and 2.40). The ^{1}H NMR spectrum of the acetonide **5** obtained from natural specimen of taurospongin A (**1**) was identical with that of the synthetic (3*S*,7*R*,9*S*)-derivative **6**. Thus, the relative configuration of **5** was revealed as 3*S**, 7*R**, and 9*S**. Synthetic sample **6**, however, unfortunately had very small optical rotation ([α]$_D$ +0.65°), thus implying that determination of the absolute configurations of **5** based on the sign of the optical rotation was not convincing. This problem could be overcome by preparing Mosher's acid esters[13] from synthetic and natural samples and distinguishing them by NMR spectroscopy. The synthetic triol **18** was treated with (*S*)- and (*R*)-MTPACl to give (*R*)- and (*S*)-bis MTPA esters **19** and **20**, respectively, while the triol **4** from natural specimen was treated with (*R*)-MTPACl to give bis-(*S*)-MTPA ester **21**. The ^{1}H NMR spectra of synthetic



19 R = (*R*)-MTPA

20 R = (*S*)-MTPA



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samples **19** and **20** were easily distinguishable particulary by the methyl proton signals [**19**: δ_H 1.37 (H_3-10) and 1.11 (H_3-11); **20**: δ_H 1.22 (H_3-10) and 1.17 (H_3-11)]. The ^{1}H NMR of bis-(*S*)-MTPA ester **21** from a natural specimen proved to be completely identical with that of synthetic bis-(*R*)-MTPA ester **19**, implying that the synthetic and natural samples (**19** and **21**, respectively) are enantiomers.[14] Thus the absolute configurations of taurospongin A (**1**) were unambiguously established as 3*R*, 7*S*, and 9*R*.

Marine sponges of the genus *Hippospongia* often elaborate various bioactive metabolites including sesquiterpenoid quinones,[4,15] furanoterpenes,[16] and secosterols.[17] Taurospongin A (**1**) consisting of taurine, trihydroxy fatty acid, and unsaturated fatty acid residues appears to belong to an unprecedented class of marine natural products, whereas taurine-bearing mono-fatty acid derivatives were recently isolated from bivalve *Pinna muricata*[18] and protozoan *Tetrahymena thermophila*.[19] The trihydroxy and unsaturated C_{25} fatty acid contained in taurospongin A (**1**) are also new fatty acids, while a C_{25} acetylenic fatty acid with more unsaturations was recently isolated from Australian sponge *Phakellia cardus*.[20] Acetylenic fatty acids mostly bearing bromine atoms were frequently isolated from sponges of the genera *Petrosia*[21] and *Xestspongia*,[22] and they were never obtained so far from *Hippospongia* sp.

Taurospongin A (**1**) exhibited potent inhibitory activity against DNA polymerase *β* and HIV reverse transcriptase with IC_{50} values of 7.0 and 6.5 μM (K_i values of 1,7 and 1.3 μM), respectively.[23] This inhibitory activity has been frequently associated with the sulfonic acid function.[3] Furthermore, **1** showed weak inhibitiory activity against c-erbB-2 kinase (IC_{50} 28 μg/mL), while there was no cytotoxicity (IC_{50} > 10 μg/mL) against murine lymphoma L1210 and human epidermoid carcinoma KB cells in vitro.

Experimental Section

Sponge Material. The sponge (Order Dictyoceratida, Family Spongiidae, *Hippospongia* Schulze, 1879) was collected off Okinawa Island and kept frozen until used. The specimen was a massive, cavernous sponge. Skeleton consists of numerous fine fibers forming a dense network. Primary fibers are present superficially and are lightly cored. Primary fibers are 40 μm wide, and secondary fibers are 8−12 μm. There are no spicules. The voucher specimen (SS-951) was deposited at Faculty of Pharmaceutical Sciences, Hokkaido University.

Extraction and Isolation. The sponge (0.91 kg, wet weight) was extracted with MeOH (1.8 L and 0.7 L). After evaporation under reduced pressure, the residue (91 g) was

(13) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.

(14) Coincidently, the signs of optical rotation of synthetic and natural trihydroxy amides (**18** and **4**, respectively) were opposite (**18**: [α]$^{25}_D$ +5.7°; **4**: [α]$^{27}_D$ −10°).

(15) Luibrand, R. T.; Erdman, T. R.; Vollmer, J. J.; Scheuer, P. J.; Finer, J.; Clardy, J. *Tetrahedron* **1979**, *35*, 609−612.

(16) Kobayashi, J.; Ohizumi, Y.; Nakamura, H.; Hirata, Y. *Tetrahedron Lett.* **1986**, *27*, 2113−2116.

(17) Madaio, A.; Piccialli, V.; Sica, D. *Tetrahedron Lett.* **1988**, *29*, 5999−6000.

(18) Chou, T.; Kuramoto, M.; Otani, Y.; Shinkai, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871−3874.

(19) Kouda, K.; Ooi, T.; Kaya, K.; Kusumi, T. *Tetrahedron Lett.* **1996**, *37*, 6347−6350.

(20) Barrow, R. A.; Capon, R. J. *Aust. J. Chem.* **1994**, *47*, 1901−1918.

(21) Fusetani, N.; Li, H.-Y.; Tamura, K.; Matsunaga, S. *Tetrahedron*, **1993**, *49*, 1203−1210 and references cited therein.

(22) Li, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Chem. Res. (S)* **1995**, 126−127 and references cited therein.

(23) Simbulan, C. M. G.; Taki, T.; Tamiya-Koizumi, K.; Suzuki, M.; Savoysky, E.; Shoji, M.; Yoshida, S. *Biochim. Biophys. Acta* **1994**, *1205*, 68−74.

partitioned between EtOAc (400 mL × 3) and 1 M NaCl (300 mL), and the aqueous portion was subsequently extracted with *n*-BuOH (400 mL × 3). A portion (0.93 g) of the *n*-BuOH-soluble material (7.1 g) was subjected to column chromatography on silica gel (2.3 × 41 cm) with $CHCl_3$/MeOH (80:20). The fraction (47.7 mg) eluting from 240 to 350 mL was further separated by Sephadex LH-20 column (2 × 120 cm) with $CHCl_3$/MeOH (1:1) to afford taurospongin A (**1**, 20 mg; 0.02% wet weight).

NMR Spectroscopy. NMR spectra were recorded at 500 or 600 MHz (^{1}H) and 125 MHz (^{13}C). The ^{1}H and ^{13}C NMR chemical shifts were referenced to solvent signals at 7.20 and 128.0 ppm, respectively, for C_6D_6 or at 7.26 and 77.0 ppm, respectively, for $CDCl_3$. Multiplicities of ^{13}C spectra were assigned by DEPT experiments. For 2D NMR experiments, standard pulse sequences and processing parameters were employed and a total of 256 increments of 1k data points were collected. The HOHAHA and HMQC spectra were in the phase-sensitive mode, while the ^{1}H−^{1}H COSY and HMBC spectra were in the magnitude mode. The HMQC and HMBC spectra were optimized for $^1J_{C-H}$ = 140 Hz and $^{2,3}J_{C-H}$ = 10 Hz, respectively.

Taurospongin A (1). Colorless amorphous solid; $[\alpha]^{27}_D$ +2.4° (*c* 0.20); IR ν_{max} (film) 3320, 2920, 2850, 2370, 1740, 1640, 1240, and 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, t, J = 6.9 Hz), 1.18 (3H, s), 2.04 (3H, s), 2.26 (1H, d, J = 14.3 Hz), 2.35 (1H, d, J = 14.3 Hz), 2.45 (4H, m), 3.02 (2H, m), 3.59 (2H, m), 4.94 (2H, m), 5.39 (2H, m), and 7.56 (1H, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.8, 20.0, 26.8, 34.3, 35.2, 47.1, 50.4, 68.4, 71.1, 127.8, 171.0, 171.6, and 172.3; FABMS (matrix: 3-nitrobenzyl alcohol) *m*/*z* 740 (M − H)$^-$; HRFABMS *m*/*z* 740.4819 (M − H)$^-$, calcd for $C_{40}H_{70}O_9NS$: 740.4771.

Taurospongin A Methyl Ester (2). Taurospongin A (**1**, 10.6 mg, 14.3 μmol) was treated with a 0.6 M diazomethane in Et_2O (2 mL) at rt for 1 h. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel (0.5 × 10 cm) with $CHCl_3$/MeOH (10:1). The fraction (6.5 mg) eluting from 3 to 5 mL was further separated by Sephadex LH-20 column (1.4 × 40 cm) with $CHCl_3$/MeOH (1:1) to afford taurospongin A methyl ester (**2**, 5.8 mg, 54%) together with the starting sulfonic acid (**1**, 3.2 mg, 30%). **2**: colorless oil; $[\alpha]^{27}_D$ −1.4° (*c* 0.78, $CHCl_3$); IR ν_{max} (film) 3370, 2920, 2860, 2360, 1730, 1650, 1250, and 1170 cm^{-1}; ^{1}H and ^{13}C NMR (Table 1); FABMS (matrix: 3-nitrobenzyl alcohol) *m*/*z* 778 (M + Na)$^+$, 756 (M + H)$^+$; HRFABMS *m*/*z* 778.4958 (M + Na)$^+$, calcd for $C_{41}H_{73}O_9NSNa$: 778.4904.

Methanolysis of 2. Methyl ester (**2**, 4.9 mg, 6.6 μmol) was dissolved in MeOH/1 N HCl (10:1, 1 mL) and heated at 80 °C for 12 h in a sealed tube. The solvent was removed by a nitrogen stream, and the residue dissolved in $CHCl_3$−MeOH (1:1, 1 mL) was treated with 0.6 M CH_2N_2 in Et_2O (1 mL) at rt for 1 h. After evaporation of the solvent, the residue was purified on a silica gel column (0.5 × 5 cm) with 0−10% MeOH in $CHCl_3$ to give the unsaturated fatty acid methyl ester (**3**, 2.5 mg, 98%) and the trihydroxy amide (**4**, 0.8 mg, 35%). **3**: Colorless amorphous solid; IR ν_{max} (film) 2920, 2360, and 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, J = 6.8 Hz), 2.02 (2H, m), 2.17 (2H, m), 2.20 (2H, m), 2.47 (2H, m), 2.52 (2H, m), 3.69 (3H, s), 5.38 (1H, dt, J = 11.3 and 6.6 Hz), and 5.43 (1H, dt, J = 11.3 and 6.8 Hz); EIMS *m*/*z* 390 (M$^+$); HREIMS *m*/*z* 390.3517, calcd for $C_{26}H_{46}O_2$ (M$^+$): 390.3498. **4**: Colorless oil; $[\alpha]^{27}_D$ −10° (*c* 0.08, $CHCl_3$); IR ν_{max} (neat) 3360, 2930, 1650, 1350, 1160, and 990 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, d J = 6.1 Hz), 1.24 (3H, s), 2.29 (1H, d, J = 14.6 Hz), 2.45 (1H, d, J = 14.6 Hz), 3.35 (2H, t, J = 5.8 Hz), 3.76 (2H, m), 3.89 (1H, m), 3.93 (3H, s), 4.06 (1H, m), and 6.62 (1H, m); EIMS *m*/*z* 319 (M − 2H_2O)$^+$; FABMS (matrix: glycerol) *m*/*z* 356 (M + H)$^+$; HRFABMS *m*/*z* 356.1753 (M + H)$^+$, calcd for $C_{14}H_{30}O_7NS$: 356.1742.

Acetonide 5. The trihydroxy amide (**4**, 0.7 mg, 2 μmol) was treated with dimethoxypropane (DMP, 0.25 mL, 2 mmol) and pyridinium *p*-toluenesulfonate (PPTS, 3.8 mg, 15.2 μmol) in dry CH_2Cl_2 (1 mL) at rt for 28 h. After evaporation of the solvent, separation with silica gel column (0.5 × 10 cm; $CHCl_3$/MeOH, 95:5) afforded the acetonide (**5**, 0.6 mg, 77%): colorless oil; IR ν_{max} (neat) 3320, 2930, 1650, 1360, 1170, and 990 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (3H, d, J = 6.1 Hz), 1.23 (3H, s,), 1.39 (3H, s), 1.43 (3H, s), 2.28 (1H, d, J = 14.8 Hz), 2.41 (1H, d, J = 14.8 Hz), 3.33 (2H, t, J = 5.8 Hz), 3.66 (1H, br s), 3.77 (2H, m), 3.81 (1H, m), 3.93 (3H, s), 3.97 (1H, m), and 6.60 (1H, m); ^{13}C NMR ($CDCl_3$) δ 19.5, 19.9, 22.2, 26.8, 30.3, 33.8, 36.6, 38.7, 42.2, 46.5, 49.0, 55.6, 65.1, 68.9, 71.5, 98.4, and 172.6; FABMS *m*/*z* 396 (M + H)$^+$; HRFABMS *m*/*z* 396.2064 (M + H)$^+$, calcd for $C_{17}H_{34}O_7NS$: 396.2060.

(*R*)-3-(Methoxymethoxy)-3-methyl-5-pentanolide (9). A solution of (3*R*)-mevalonolactone (**8**,[10] 5.31 g, 40.8 mmol) in CH_2Cl_2−THF (1:1, 50 mL) was treated with *N*,*N*-diisopropylethylamine (23.5 mL, 124 mmol), chloromethyl methyl ether (7.1 mL, 95 mmol), and DMAP (999 mg, 8.16 mmol) at 60 °C under an argon atmosphere for 12 h. After addition of 1 N HCl (75 mL), the mixture was extracted with ethyl acetate (150 mL × 5), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to a silica gel colmun (hexane/EtOAc, 1:1) to give the MOM ether (**9**, 6.03 g, 85%): colorless oil; $[\alpha]^{30}_D$ −52.0° (*c* 1.37, $CHCl_3$); IR ν_{max} (neat) 2976 and 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, s), 1.86 (1H, ddd, J = 5.5, 10.8 and 14.4 Hz), 2.02 (1H, m), 2.40 (1H, d, J = 17.3 Hz), 2.88 (1H, dd, J = 2.3 and 17.3 Hz), 3.35 (3H, s), 4.31 (1H, ddd, J = 3.6, 5.5 and 11.2 Hz), 4.55 (1H, dt, J = 4.1 and 11.2 Hz), 4.68 (1H, d, J = 7.6 Hz), and 4.75 (1H, d, J = 7.6 Hz). Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.97; H, 8.00.

(*S*)-1-[(Benzyloxy)methoxy]-6-chloro-3-[(methoxymethyl)oxy]-3-methyl-5-hexene (10). The lactone (**9**, 6.03 g, 34.6 mmol) was dissolved in dry Et_2O (100 mL), and 0.93 M DIBAL in hexane (40 mL, 37 mmol) was slowly added at −78 °C. The mixture was stirred at rt for 30 min, and then MeOH (0.3 mL) was added. After addition of saturated Rochelle solution (saturated potassium sodium tartrate aqueous solution, 50 mL), the whole was stirred for 1 h. Extraction with EtOAc (100 mL × 5) followed by evaporation of the combined organic solution under reduced pressure afforded a lactol (5.97 g), which was used immediately without purification. A solution of the lactol (5.97 g) in dry THF (50 mL) was added at −78 °C to a dark red solution of triphenyl(chloromethylene)-phosphorane, which was prepared from (chloromethyl)triphenylphosphonium chloride (48.1 g, 139 mmol) in THF (100 mL) and 1.67 M *n*-BuLi in pentane (83 mL, 139 mmol). The mixture was stirred for 17 h at rt. After addition of a saturated NH_4Cl aqueous solution (200 mL), the mixture was extracted with EtOAc (400 mL × 3), washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified with a silica gel column (hexane/EtOAc, 2:1) to yield a chloroolefin as a 2:1 *E*/*Z* mixture (22.2 g), part of which (17.8 g) was dissolved in dry CH_2Cl_2 (80 mL) and treated with *N*,*N*-diisopropylethylamine (9.6 mL, 55 mmol) and benzyl chloromethyl ether (5.8 mL, 42 mmol) at rt for 22 h. After addition of 1 N HCl (40 mL), the mixture was extracted with Et_2O (80 mL × 2), washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to a silica gel colmun (hexane/EtOAc, 8:1) to give the (benzyloxy)methyl ether (**10**, 8.01 g, 84%): colorless oil; $[\alpha]^{23}_D$ −1.7° (*c* 0.84, $CHCl_3$); IR ν_{max} (neat) 1456 and 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$, *: signals for minor isomer) δ 1.23 (3H, s), 1.27 (3H*, s), 2.30 (2H, dd, J = 6.1 and 2.2 Hz), 2.50 (2H*, br d, J = 7.2 Hz), 3.36 (3H, s), 3.38 (3H*, s), 3.68 (2H, m), 4.60 (2H, s), 4.61 (2H*, s), 4.74 (2H, s), 4.75 (2H*, s), 5.86−6.00 (2H, m), 6.13 (1H*, br d, J = 7.1 Hz), and 7.28−7.35 (5H, m). Anal. Calcd for $C_8H_{14}O_4$-Cl: C, 62.09; H, 7.66; Cl, 10.78. Found: C, 62.02; H, 7.60; Cl, 10.80.

(*S*)-3-(*tert*-Butyldimethylsiloxy)butanal ((*S*)-12). The methyl ester ((*S*)-**11**,[10] 4.28 g, 36.3 mmol) dissolved in dry CH_2Cl_2 (25 mL) was treated with *tert*-butyldimethylsilyl chloride (TBSCl, 8.2 g, 54 mmol) and imidazole (4.9 g, 73 mmol) at rt for 14 h. After addition of saturated NH_4Cl aqueous solution (50 mL), the mixture was extracted with Et_2O (100 mL × 3), washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification with a silica gel column (hexane/EtOAc, 25:1) gave methyl (*S*)-3-(*tert*-butyldimethylsiloxy)-butyrate (7.2 g, 85%): colorless oil; $[\alpha]^{27}_D$ +27.3° (*c* 1.13, $CHCl_3$); IR ν_{max} (neat) 1743 and 1085 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.04 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 1.19 (3H, d, J = 6.2), 2.37 (1H, dd, J = 5.3 and 14.5 Hz), 2.48 (1H, dd, J = 7.7 and

14.5 Hz), 3.66 (3H, s), and 4.28 (1H, ddq, J = 5.3, 7.7 and 6.2 Hz). Anal. Calcd for $C_{11}H_{24}O_3Si$: C, 56.85; H, 10.41. Found: C, 56.73; H, 10.29. The silyl ether (6.4 g, 27.6 mmol) was dissolved in dry toluene (90 mL), and 1.01 M DIBAL in toluene (27 mL, 28 mmol) was slowly added to the solution at −78 °C. The mixture was stirred at −78 °C for 10 min. After addition of saturated NH_4Cl aqueous solution (9 mL), the mixture was stirred at rt for 1 h. To the mixture was added Et_2O (200 mL), and stirring was continued for 1.5 h at rt. After addition of $MgSO_4$, the solution was filtered through Celite, washed with Et_2O, and evaporated under reduced pressure to give the aldehyde [(*S*)-**12**, 5.5 g; ^{1}H NMR ($CDCl_3$) δ 0.06 (3H, s), 0.08 (3H, s), 0.87 (9H, s), 1.24 (3H, d, J = 6.2), 2.47 (1H, ddd, J = 1.9, 4.9, and 15.7 Hz), 2.55 (1H, ddd, J = 2.8, 7.0 and 15.7 Hz), 4.35 (1H, ddd, J = 4.9, 6.2, and 7.0 Hz), and 9.80 (1H, dd, J = 1.9 and 2.8 Hz)], which was used immediately without purification.

(3*S*,7*R*,9*S*)- and (3*S*,7*S*,9*S*)-1-[(Benzyloxy)methoxy]-9-(*tert*-butyldimethylsiloxy)-3-(methoxymethoxy)-3-methyl-5-decyn-7-ol (13 and 14). To a solution of chloroolefin (**10**, 3.8 g, 12 mmol) in THF (45 mL) was added 1.67 M *n*-BuLi in pentane (21 mL, 35 mmol) at −78°C. To this mixture was added a solution of the aldehyde ((*S*)-**12**, 5.5 g) in THF (55 mL) at −78°C and stirred for 1 h at −78 °C. After addition of saturated NH_4Cl aqueous solution (150 mL), the mixture was extracted with EtOAc (300 × 3 mL), washed with H_2O and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (hexane/EtOAc, 6:1) to give two diastereomeric acetylenic alcohols [**13** (*anti*), 1.54 g, 27% and **14** (*syn*), 1.89 g, 33%]. **13**: colorless oil; $[\alpha]^{21}_D$ +24.2° (*c* 1.05, $CHCl_3$); IR ν_{max} (neat) 3447, 2234, and 1038 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.09 (3H, s), 0.11 (3H, s), 0.89 (9H, s), 1.19 (3H, d, J = 6.2), 1.35 (3H, s), 1.78 (1H, m), 1.82 (1H, m), 1.95 (1H, dt, J = 14.2 and 7.1 Hz), 2.03 (1H, dt, J = 14.2 and 7.1 Hz), 2.49 (1H, d, J = 16.3 Hz), 2.52 (1H, d, J = 16.3 Hz), 3.22 (1H, br d, 5.2 Hz), 3.37 (3H, s), 3.72 (2H, t, J = 7.1 Hz), 4.24 (1H, m), 4.60 (1H, br m), 4.61 (2H, s), 4.72 (1H, d, J = 7.5 Hz), 4.74 (1H, d, J = 7.5 Hz), 4.75 (2H, s), and 7.28−7.37 (5H, m); FDMS m/z 495 (M + H)$^+$; HRFDMS m/z 495.3171 (M + H)$^+$, calcd for $C_{27}H_{47}O_6Si$: 495.3142. **14**: colorless oil; $[\alpha]^{31}_D$ +22.8° (*c* 1.13, $CHCl_3$); IR ν_{max} (neat) 3447, 2223, and 1038 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.08 (3H, s), 0.08 (3H, s), 0.88 (9H, s), 1.18 (3H, d, J = 6.1), 1.34 (3H, s), 1.73 (1H, ddd, J = 3.7, 6.0 and 13.7 Hz), 1.89 (1H, ddd, J = 7.5, 9.1 and 13.7 Hz), 1.95 (1H, dt, J = 14.4 and 7.2 Hz), 2.03 (1H, dt, J = 14.4 and 7.2 Hz), 2.49 (1H, dd, J = 1.8 and 17.1 Hz), 2.52 (1H, dd, J = 1.8 and 17.1 Hz), 2.82 (1H, br d), 3.37 (3H, s), 3.72 (2H, t, J = 7.2 Hz), 4.04 (1H, m), 4.50 (1H, br m), 4.60 (2H, s). 4.71 (1H, d, J = 7.5 Hz), 4.74 (1H, d, J = 7.5 Hz), 4.75 (2H, s), and 7.27−7.36 (5H, m). Anal. Calcd for $C_{27}H_{46}O_6Si$: C, 65.55; H, 9.37. Found: C, 65.52; H, 9.41.

(3*S*,7*R*,9*S*)- and (3*S*,7*S*,9*S*)-1-[(Benzyloxy)methoxy]-7,9-*O*-isopropylidene-3-(methoxymethoxy)-3-methyl-5-decyne-7,9-diol (15 and 16). The *syn*-alcohol (**14**, 1.8 g, 3.6 mmol) in THF (20 mL) was treated with 1.0 M tetra-*n*-butylammonium fluoride (TBAF) in THF (7 mL, 7 mmol) at rt for 2.5 h. After addition of saturated NH_4Cl aqueous solution (75 mL), the mixture was extracted with EtOAc (200 × 3 mL), washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a crude diol, which was dissolved in CH_2Cl_2 (20 mL) and treated with DMP (5 mL, 40 mmol) and PPTS (305 mg, 1.22 mmol) at rt for 16 h. After addition of saturated $NaHCO_3$ aqueous solution (50 mL), the reaction mixture was extracted with Et_2O (100 mL × 3), washed with H_2O and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a residue, which was purified on a silica gel column (hexane/EtOAc, 4:1) to give the *syn*-acetonide (**16**, 1.4 g, 92%): colorless oil; $[\alpha]^{23}_D$ −16.5° (*c* 0.47, $CHCl_3$); IR ν_{max} (neat) 2234 and 1038 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (3H, d, J = 6.1 Hz), 1.34 (3H, s), 1.43 (3H, s), 1.44 (3H, s), 1.93 (1H, dt, J = 14.2 and 7.2 Hz), 2.02 (1H, dt, J = 14.2 and 7.2 Hz), 2.50 (1H, dd, J = 1.8 and 12.7 Hz), 2.53 (1H, dd, J = 1.8 and 12.7 Hz), 3.36 (3H, s), 3.72 (2H, t, J = 7.2 Hz), 3.95 (1H, ddq, J = 2.6, 11.6 and 6.1 Hz), 4.61 (2H, s), 4.64 (1H, m), 4.71 (1H, d, J = 7.6 Hz). 4.73 (1H, d, J = 7.6 Hz), 4.75 (2H, s), and 7.27−7.35 (5H, m); ^{13}C NMR ($CDCl_3$) δ 19.4, 21.8, 23.7, 30.1, 30.9, 38.6, 39.4, 55.4, 60.4, 63.8, 64.7, 69.3, 76.5, 81.2, 81.4, 91.1, 94.6, 99.0, 127.6, 127.8, 128.4, and 137.9. Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.55; H, 8.63. Found: C, 68.28; H, 8.62. The *anti*-acetonide **15** was prepared from the *anti*-alcohol **13** by the same procedure as above. **15**: colorless oil; $[\alpha]^{21}_D$ −0.5° (*c* 0.89, $CHCl_3$); IR ν_{max} (neat) 2245 and 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ δ 1.19 (3H, d, J = 6.2 Hz), 1.35 (3H, s), 1.36 (3H, s), 1.61 (3H, s), 1.95 (1H, dt, J = 14.2 and 7.1 Hz), 2.02 (1H, dt, J = 14.2 and 7.1 Hz), 2.52 (2H, d, J = 2.1 Hz), 3.37 (3H, s), 3.72 (2H, t, J = 7.1 Hz), 4.20 (1H, m), 4.60 (2H, s), 4.71 (1H, d, J = 7.5 Hz). 4.73 (1H, d, J = 7.5 Hz), 4.74 (1H, m), 4.75 (2H, s), and 7.27−7.36 (5H, m); ^{13}C NMR ($CDCl_3$) δ 21.7, 23.6, 23.8, 29.0, 30.9, 38.6, 38.7, 55.5, 59.8, 61.9, 63.8, 69.3, 76.6, 82.4, 82.8, 91.2, 94.6, 99.8, 127.7, 127.8, 128.4, and 137.9; FDMS m/z 405 (M − CH_3)$^+$; HRFDMS m/z 405.2304 (M − CH_3)$^+$, calcd for $C_{23}H_{33}O_6$: 405.2277.

(3*S*,7*R*,9*S*)-7,9-*O*-Isopropylidene-3-(methoxymethoxy)-3-methyldecane-1,7,9-triol. (17). A solution of the *syn*-acetonide (**16**, 629 mg, 1.5 mmol) in ethanol (6 mL) was stirred under a hydrogen atmosphere in the presence of 0.84 g of Raney Ni (W-2) at rt for 16 h. Insoluble material was removed by filtration through Celite, and the filtrate was concentrated *in vacuo*. The residue was purified on a silica gel column (hexane/EtOAc, 1:1) to afford the alcohol (**17**, 306 mg, 67%): colorless oil; $[\alpha]^{25}_D$ +14.5° (*c* 1.04, $CHCl_3$); IR ν_{max} (neat) 3446 and 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (3H, d, J = 6.0 Hz), 1.26, (3H, s), 1.39 (3H, s), 1.43 (3H, s), 1.70 (1H, ddd, J = 14.6, 6.3, and 5.4 Hz), 1.87 (1H, ddd, J = 14.6, 7.1, and 5.5 Hz), 2.67 (1H, br m), 3.37 (3H, s), 3.79 (3H, m), 3.96 (1H, ddq, J = 12.0, 2.5, and 6.0 Hz), 4.70 (1H, d, J = 7.8 Hz), and 4.71 (1H, d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 19.3, 19.8, 22.2, 23.7, 30.2, 36.6, 38.7, 39.1, 40.8, 55.4, 59.2, 65.0, 68.5, 79.3, 90.6, and 98.3. Anal. Calcd for $C_{16}H_{32}O_5$: C, 63.13; H, 10.59. Found: C, 63.00; H, 10.61.

Methyl 2-(((3*S*,7*R*,9*S*)-3-Methyl-3,7,9-trihydroxydecanoyl)amino)ethanesulfonate (18). To a solution of alcohol (**17**, 229 mg, 0.753 mmol) in CCl_4 (2 mL), MeCN (2 mL), and phosphate buffer (pH 7, 3 mL) were added $NaIO_4$ (669 mg, 3.09 mmol) and $RuCl_3 \cdot n H_2O$ (10 mg) at rt. After stirring at rt for 1 h, H_2O (4 mL) was added, and the aqueous phase was extracted with Et_2O (20 mL × 3), washed with H_2O and saturated NaCl, dried over $MgSO_4$, and evaporated *in vacuo* to give a carboxylic acid, which was used immediately without purification. A solution of the carboxylic acid in dioxane (2 mL) was treated with *N*-hydroxysuccinimide (123 mg, 1.07 mmol) and DCC (175 mg, 0.91 mmol) at rt for 2 h. After removal of the precipitates by filtration, the filtrate was evaporated under reduced pressure to give the *N*-hydroxysuccinimide ester, which was treated with taurine (131 mg, 0.945 mmol) and triethylamine (0.2 mL, 1.4 mmol) in dioxane (2.5 mL) and H_2O (2.5 mL) at rt for 30 min. The mixture was evaporated and extracted with $CHCl_3$. The $CHCl_3$-soluble material was subjected to ion exchange column chromatography (Amberlite IR-122, $CHCl_3$/MeOH, 1:1) to give a sulfonic acid, which was treated with 0.6 M CH_2N_2 in Et_2O at rt. Purification by silica gel column chromatography ($CHCl_3$/MeOH, 9:1) gave the trihydroxy amide (**18**, 64 mg, 24%): colorless oil; $[\alpha]^{25}_D$ +5.7° (*c* 0.6, $CHCl_3$); FABMS m/z 356 (M + H)$^+$; HRFDMS m/z 356.1738 (M + H)$^+$, calcd for $C_{14}H_{30}O_7NS$: 356.1743; IR, ^{1}H NMR, and FABMS spectra were identical with those of **4**.

Methyl 2-(((3*S*,7*R*,9*S*)-7,9-*O*-Isopropylidene-3-methyl-3,7,9-trihydroxydecanoyl)amino)ethanesulfonate (6). A solution of triol (**18**, 31.4 mg, 88.3 μmol) in CH_2Cl_2 (1.5 mL) was treated with DMP (0.5 mL) and PPTS (7 mg, 28 μmol) at rt for 2 h. After addition of saturated $NaHCO_3$ aqueous solution (2 mL), the reaction mixture was extracted with EtOAc (4 mL × 3), washed with H_2O and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a residue, which was purifid on a silica gel column ($CHCl_3$/MeOH, 95:5) to give the acetonide (**6**, 22.7 mg, 62%): colorless oil; $[\alpha]^{28}_D$ +0.65° (*c* 1.23, $CHCl_3$); FDMS m/z 396 (M + H)$^+$; HRFDMS m/z 396.2088 (M + H)$^+$, calcd for $C_{17}H_{34}O_7NS$: 396.2060; IR, ^{1}H and ^{13}C NMR, and FABMS spectra were identical with those of **5**.

Methyl 2-(((3*S*,7*S*,9*R*)-7,9-*O*-Isopropylidene-3-methyl-3,7,9-trihydroxydecanoyl)amino)ethanesulfonate (7). The diastereomeric *syn* acetonide **7** was synthesized by the same procedures as above starting with the coupling of the acetylide derived from **10** with the enantiomeric aldehyde ((*R*)-**12**), prepared from (*R*)-**11**[10] (see Supporting Information). **7**: colorless oil; $[\alpha]^{23}_{D}$ −8.2° (*c* 0.70, $CHCl_3$); IR ν_{max} (neat) 3318, 2941, 1651, 1359, 1164, and 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (3H, d, J = 6.0 Hz), 1.23 (3H, s), 1.39 (3H, s), 1.44 (3H, s), 2.29 (1H, d, J = 14.7 Hz), 2.40 (1H, d, J = 14.7 Hz), 3.34 (2H, t, J = 5.8 Hz), 3.69 (1H, br s), 3.77 (2H, m), 3.82 (1H, m), 3.93 (3H, s), 3.97 (1H, m), and 6.59 (1H, m); ^{13}C NMR ($CDCl_3$) δ 19.5, 19.9, 22.2, 26.6, 30.3, 33.9, 36.6, 38.8, 42.2, 46.6, 49.0, 55.6, 65.1, 68.8, 71.5, 98.4, and 172.6; FABMS *m*/*z* 396 $(M + H)^+$; FDMS *m*/*z* 396 $(M + H)^+$; HRFDMS *m*/*z* 396.2089 $(M + H)^+$, calcd for $C_{17}H_{34}O_7NS$: 396.2060.

Bis-(*S*)-MTPA Ester 21. A solution of the natural specimen-derived triol (**4**, 2.6 mg, 7.3 μmol) in CH_2Cl_2 (40 μmol) was treated with (*R*)-MTPA chloride (7.7 μL, 41.8 μmol) in the presence of DMAP (69 μg, 0.56 μmol) and triethylamine (4.2 μL, 29.4 mmol) at rt for 18 h. After addition of 3-(dimethylamino)propylamine (5 μL, 39 μmol) and evaporation under reduced pressure, the residue was applied on an ion exchange chromatography (Amberlite IR-122, MeOH). The effluent contained the corresponding sulfonic acid, which was treated with 0.6 M CH_2N_2 in Et_2O and purified by silica gel column chromatography ($CHCl_3$/MeOH, 98:2) to give the bis-(*S*)-MTPA ester (**21**, 0.8 mg, 14%): colorless oil; IR ν_{max} (neat) 3396, 2952, 1744, 1654, 1356, 1167, and 991 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (3H, s), 1.37 (3H, d, J = 6.3 Hz), 1.77 (1H, dt, J = 14.1 and 6.4 Hz), 2.07 (1H, dt, J = 14.1 and 6.9 Hz), 2.18 (1H, d, J = 14.8 Hz), 2.27 (1H, d, J = 14.8 Hz), 3.34 (2H, m), 3.54 (6H, s, MeO), 3.76 (2H, m), 3.92 (3H, s), 5.05 (1H, m), 5.15 (1H, m), 6.50 (1H, m), 7.41 (6H, m), and 7.52 (4H, m); FABMS *m*/*z* 788 $(M + H)^+$; HRFABMS *m*/*z* 788.2540 $(M + H)^+$, calcd for $C_{34}H_{44}O_{11}NSF_6$: 788.2539.

(*R*)- and (*S*)-Bis-MTPA Esters 19 and 20. The synthetic triol **18** was treated separately with (*S*)- and (*R*)-MTPA chloride by the same procedures for **21** to afford (*R*)- and (*S*)-bis-MTPA esters **19** and **20**, respectively. **19**: FABMS *m*/*z* 788 $(M + H)^+$; HRFABMS *m*/*z* 788.2529 $(M + H)^+$, calcd for $C_{34}H_{44}O_{11}NSF_6$: 788.2539; IR, ^1H NMR, and FABMS spectra were identical with those of **21**. **20**: colorless oil; IR ν_{max} (neat) 3328, 2928, 1743, 1626, 1360, 1168, and 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (3H, s), 1.22 (3H, d, J = 6.3 Hz), 1.79 (1H, dt, J = 14.1 and 6.3 Hz), 2.06 (1H, dt, J = 14.1 and 6.9 Hz), 2.23 (1H, d, J = 14.8 Hz), 2.30 (1H, d, J = 14.8 Hz), 3.33 (2H, m), 3.53 (3H, s), 3.54 (3H, s), 3.74 (2H, m), 3.92 (3H, s), 5.06 (1H, m), 5.13 (1H, m), 6.44 (1H, m), 7.41 (6H, m), 7.50 (2H, m), and 7.53 (2H, m); FABMS *m*/*z* 788 $(M + H)^+$; HRFABMS *m*/*z* 788.2568 $(M + H)^+$, calcd for $C_{34}H_{44}O_{11}NSF_6$: 788.2539.

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Supporting Information Available: ^1H and ^{13}C NMR spectra including 2D NMR spectra of **2** and experimental data for preparation of **7** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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