Catalytic Asymmetric Syntheses of Antifungal Sphingofungins and Their Biological Activity as Potent Inhibitors of Serine Palmitoyltransferase (SPT)

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Abstract: Unambiguous synthetic routes to sphingofungins B and F and to their stereoisomers have been developed based on the tin(II)-catalyzed asymmetric aldol reaction (Chiral Lewis Acid-Controlled Synthesis (CLAC Synthesis)). Efficient enantioselective synthesis using a catalytic amount of a chiral source as well as the effectiveness of this strategy for the synthesis of the sphingofungin family have been successfully demonstrated. Using the stereoisomers of sphingofungin B synthesized, the relevance of its stereochemistry to its SPT inhibitory activity has been revealed.

Introduction

The sphingofungins are a new family of antifungal agents, isolated by Merck's group in 1992.[1] They are sphingosine-like compounds which potently inhibit serine palmitoyltransferase (SPT), an enzyme catalyzing the initial step in the biosynthesis of sphingolipids (vide infra).[2] Because of their novel polyhydroxyamino acid structures containing five asymmetric centers and of recent interest in the chemistry and biochemistry of sphingolipids,[3] there is a strong requirement for synthesis of these natural products as well as related compounds.

In the initial work, the relative and absolute stereochemistries of sphingofungins A, B, C, and D were determined with the exception of the absolute configuration of the C-14 stereogenic center.[1b] In 1994, Mori et al. reported the first formal synthesis of sphingofungin D from *N*-acetyl D-mannosamine and (*R*)-epoxyoctane.[4] They also prepared its C-14 isomer but could find no difference between two steroisomers on which to base assignment of the natural products stereochemistry. In 1995, Chida and Ogawa et al. reported a total synthesis of sphingofungin D from myo-inositol and (*R*)-epoxyoctane, and they also determined the absolute stereochemistry of C-14.[5] In this paper, we report a general synthetic route to the sphingofungins and their stereoisomers from simple achiral compounds via catalytic asymmetric aldol reactions.[6] The utility of the route has been demonstrated by the catalytic asymmetric synthesis of sphingofungins B and F and of their stereoisomers. Their SPT inhibitory activity and the relevance of the stereochemistry has also been investigated.

Results and Discussion

Synthesis of Sphingofungin B and Its Stereoisomers. Our retrosynthetic analysis for sphingofungin B is shown in Scheme 1. Sphingofungin B consists of three parts; a glycine head part, a triol part containing three contiguous asymmetric centers and a trans olefin, and a hydrophobic side chain. We planned to connect the three parts successively. The final stage was envisaged as an aldol reaction of a glycine enolate with **10**, which would be prepared by alkylation of **13** with **12**. While alkyl bromide **12** would be synthesized from **14**, acetylene **13** would be prepared from **15** whose four stereoisomers can be readily prepared by tin(II)-catalyzed asymmetric aldol reactions using chiral Lewis acid-controlled synthesis (CLAC synthesis).[7] Because the reaction of **10** with **11** can be controlled to afford each of the four stereoisomers selectively and, moreover, amino

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(1) (a) VanMiddlesworth, F.; Giacobbe, R. A.; Lopez, M.; Garrity, G.; Bland, J. A.; Bartizal, K.; Fromtling, R. A.; Polishook, J.; Zweerink, M.; Edison, A. M.; Rozdilsky, W.; Wilson, K. E.; Monaghan, R. L. *J. Antibiot.* **1992**, *45*, 861. Structure elucidation (b) VanMiddlesworth, F.; Dufresne, C.; Wincott, F. E.; Mosley, R. T.; Wilson, K. E. *Tetrahedron Lett.* **1992**, *33*, 297.

(2) Zweerink, M. M.; Edison, A. M.; Well, G. B.; Pinto, W.; Lester, R. L. *J. Biol. Chem.* **1992**, *267*, 25032.

(3) Reviews: (a) Merrill, A. H., Jr.; Sweeley, C. C. In *Biochemistry of Lipids, Lipoproteins and Membranes*; Vance, D. E., Vance, J., Eds; Elsevier Science B. V.: Amsterdam, 1996; pp 309−339. (b) Hannun, Y. A. *Science* **1996**, *274*, 1855. See, also: (c) Hannun, Y. A.; Loomis, C. R.; Merrill, A. H. Jr.; Bell, R. M. *J. Biol. Chem.* **1986**, *261*, 12604. (d) Okazaki, T.; Bell, R. M.; Hannun, Y. A. *J. Biol. Chem.* **1989**, *264*, 19076. (e) Hanada, K., Nishijima, M., Kiso, M., Hasegawa, A., Fujita, S., Ogawa, T., and Akamatsu, Y. *J. Biol. Chem.* **1992**, *267*, 23527. (f) Zhang, H.; Desai, N. N.; Olivera, A.; Seki, T.; Brooker, G.; Spiegel, S. *J. Cell Biol.* **1991**, *114*, 155. (g) Wang, E.; Norred, W. P.; Bacon, C. W.; Riley, R. T.; Merrill, A. H., Jr. *J. Biol. Chem.* **1991**, *266*, 14486. (h) Obeid, L. M.; Linardic, C. M.; Karolak, L. A.; Hannun, Y. A. *Science* **1993**, *259*, 1769. (i) Joseph, C. K.; Wright, S. D.; Bornmann, W. G.; Randolph, J. T.; Kumar, E. R.; Bittman, R.; Liu, J.; Kolesnick, R. N. *J. Biol. Chem.* **1994**, *269*, 17606. (j) Wiegmann, K.; Schutze, S.; Machleidt, T.; Witte, D.; Kronke, M. *Cell* **1994**, *78*, 1005. (k) Miyake, Y.; Koizumi, Y.; Nakamura, S.; Fujita, T.; Kawasaki, T. *Biochem. Biophys. Res. Commun.* **1995**, *211*, 396. (l) Pinto, W. J., Wells, G. W., Lester, R. L. *J. Bacteriol.* **1992**, *174*, 2575.

(4) Mori, K.; Otaka, K. *Tetrahedron Lett.* **1994**, *35*, 9207.

(5) Chida, N.; Ikemoto, H.; Noguchi, A.; Amano, S.; Ogawa, S. *Natural Product Lett.* **1995**, *6*, 295.

(6) Preliminary communications: (a) Kobayashi, S.; Hayashi, T.; Iwamoto, S.; Furuta, T.; Matsumura, M. *Synlett* **1996**, 672. (b) Kobayashi, S.; Matsumura, M.; Furuta, T.; Hayashi, T.; Iwamoto, S. *Synlett* **1997**, 301.

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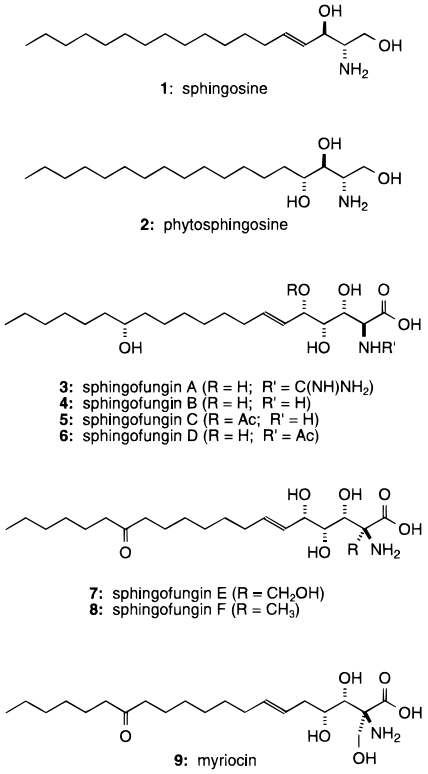
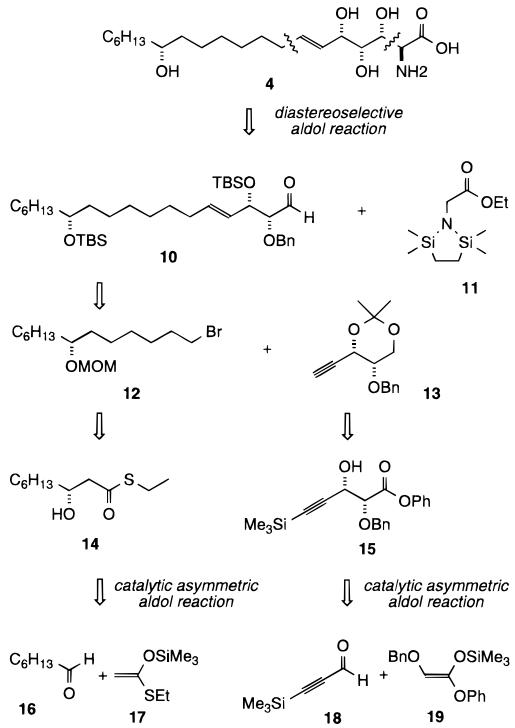
Chart 1. Sphingosine Family



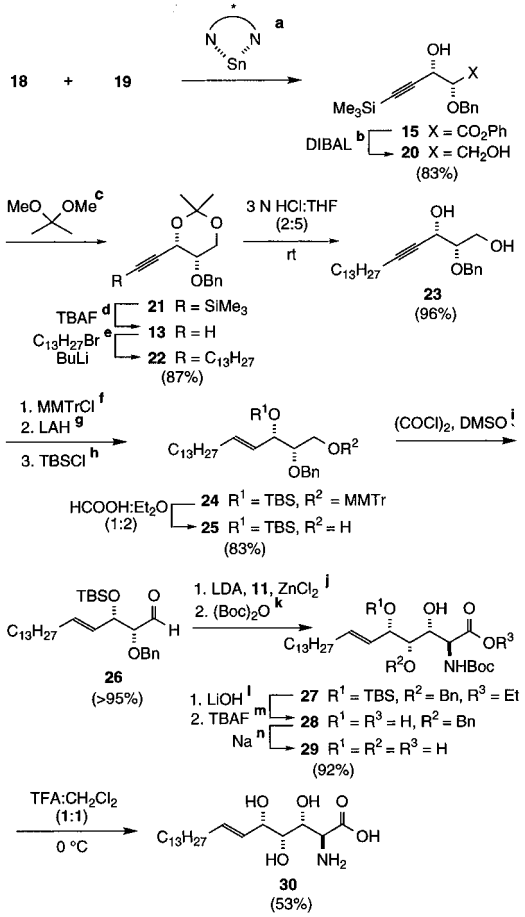
Scheme 1. Retrosynthetic Analysis



acids other than glycine such as serine (sphingofungin E) or alanine (sphingofungin F) could be introduced in this step, this route could be applied to the synthesis of stereoisomers and other members of the sphingofungin family.

At the time this research project was started the absolute configuration of C-14 of sphingofungin B had not yet been determined. We set out to synthesize 14-deoxy sphingofungin B first, as a model study for the synthesis of sphingofungin B as well as to examine the effect of the 14-hydroxyl group on

Scheme 2[a]



[a] (a) $Sn(OTf)_2$ (20 mol %), (*R*)-1-methyl-2-[(*N*-1-naphthylamino)-methyl]pyrrolidine (24 mol %), SnO (20 mol %), C_2H_5CN, −78 °C, slow addition for 4 h, 87%, *syn*/*anti* = 97/3, 91% ee (*syn*); (b) CH_2Cl_2, −78 °C; (c) TsOH (catalyst), DMF, 97%, (d) CH_2Cl_2, 97%; then recrystallized from hexane, 89%; (e) THF−HMPA, −78 °C to room temperature; (f) Et_3N, DMAP (catalyst), CH_2Cl_2, 0 °C; (g) THF, reflux; (h) imidazole, DMF, 98% (three steps); (i) Et_3N, CH_2Cl_2, −50 °C, >95%; (j) THF, −78 °C, 93%, 67% ds; (k) CH_2Cl_2, 85%; (l) THF−H_2O, 0 °C; (m) THF, 93% (two steps); (n) liquid NH_3−THF, −50 °C.

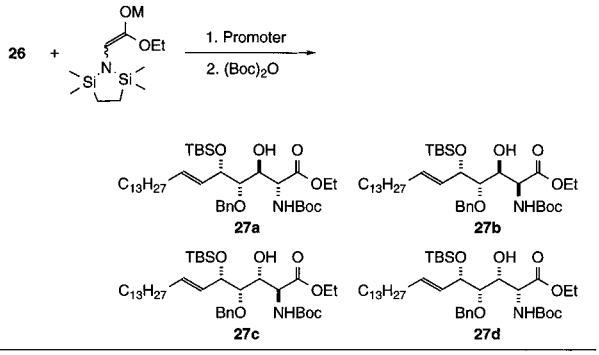
biological activity. The synthesis was performed according to Scheme 2. Phenyl ester **15** was prepared from trimethylsilylpropynal (**18**) and (*Z*)-2-benzyloxy-1-phenoxy-1-trimethylsiloxyethene (**19**) via a tin(II)-catalyzed asymmetric aldol reaction as a key step.[7−9] It should be noted that all the stereoisomers of **15** can be selectively prepared based on this methodology. Phenyl ester **15** was reduced using DIBAL to give diol **20**, which was protected as its acetonide **21**, after which desilylation with tetrabutylammonium fluoride gave **13**. Acetylene **13** was isolated as white crystals and could be purified by recrystallization (>99% de, >99% ee). After introduction of the C-13 side unit giving **22**, the acetonide group was removed under

(7) (a) Kobayashi, S.; Horibe, M. *J. Am. Chem. Soc.* **1994**, *116*, 9805. (b) Kobayashi, S.; Hayashi, T. *J. Org. Chem.* **1995**, *60*, 1098. (c) Kobayashi, S.; Horibe, M.; Matsumura, M. *Synlett* **1995**, 675. (d) Kobayashi, S.; Horibe, M. *Tetrahedron Asym.* **1995**, *6*, 2565. (e) Kobayashi, S.; Horibe, M. *Chem. Lett.* **1995**, 1029. (f) Kobayashi, S.; Horibe, M. *Tetrahedron* **1996**, 52, 7277. (g) Kobayashi, S.; Horibe, M. *Chem. Eur. J.* in press. See, also: (h) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083. (i) Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron* **1994**, *50*, 11623. (j) (g) Kobayashi, S.; Kawasuji, T.; Mori, N. *Chem. Lett.* **1994**, 217.

(8) Kobayashi, S.; Kawasuji, T. *Synlett.* **1993**, 911.

(9) We have previously prepared sphingosine and phytosphingosine using catalytic asymmetric aldol reactions. Kobayashi, S.; Hayashi, T.; Kawasuji, T. *Tetrahedron Lett.* **1994**, *35*, 9573.

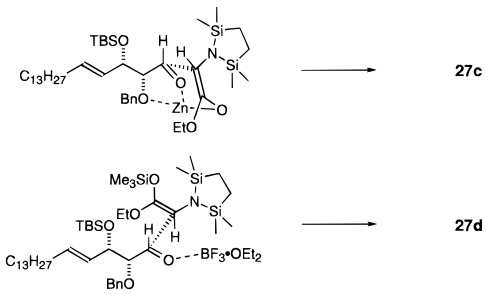
Table 1



Promotor	Additive	M	Temp (°C)	Solvent	Yield (%)	**27a/b/c/d**
LDA	—	Li	-78→ 0	THF	90	22/14/52/12
LDA	$ZnCl_2$	ZnCl	-78→ 0	THF	93	21/9/**67**/3
LDA	Et_2AlCl	$AlEt_2$	-78	THF	74	24/29/12/35
LDA	$Sn(OTf)_2$	SnOTf	-78→ 0	THF	44	19/5/7/69
LDA	$MgCl_2$	MgCl	-78→ 0	THF	60	29/14/41/16
LDA	$CeCl_3$	$CeCl_2$	-78	THF	61	12/23/17/48
LDA	—	Li	-78→ 0	THF-HMPA	79	**68**/14/14/4
BF_3•OEt_2	—	$SiMe_3$	-78	CH_2Cl_2	62	4/5/17/**74**
$SnCl_4$	—	$SiMe_3$	-78	CH_2Cl_2	67	14/3/33/50
$MgBr_2$•OEt_2	—	$SiMe_3$	-78	CH_2Cl_2	58	0/0/**67**/33

acidic conditions to give diol **23**. The primary hydroxyl group of **23** was protected as its mono-*p*-methoxytrityl (MMTr) ether, the acetylene part of **23** was reduced to the trans olefin by lithium aluminum hydride (LAH),[10] and the free secondary alcohol was protected as its *tert*-butyldimethylsilyl (TBS) ether. Deprotection of the MMTr group followed by Swern oxidation gave the key aldehyde **26**.

The aldol reaction of **26** with the glycine enolate derived from **11**[11] was examined under several conditions (Table 1). When the glycine zinc enolate, which was prepared from the glycine lithium enolate and zinc chloride, was used in THF, the desired adduct (**27c**) was obtained in high yield with good selectivity (after protection of the amino group using Boc_2O). It was also found that the four stereoisomers could be easily separated at this stage by silica gel column chromatography. The stereochemical assignments were made by NOE experiments after conversion to δ-lactones (Figure 1).[12] In addition, the isomeric **27a** was obtained in good selectivity when **26** was reacted with the glycine lithium enolate in THF−HMPA. On the other hand, isomeric **27d** was produced with good selectivity when **26** was reacted with the silyl enolate derived from **11** under the influence of BF_3•OEt_2. These selectivities using the zinc enolate and the silyl enol ether/BF_3•OEt_2 can be explained by assuming the following chelation and acyclic transition models, respectively.[13] It should be noted that in both cases, *re* face of the aldehyde **26** reacted selectively.[14]



Hydrolysis of the ethyl ester followed by deprotection of the TBS ether afforded carboxylic acid **28**. The benzyl ether was cleaved under Birch conditions, and finally the Boc group was removed with trifluoroacetic acid (TFA) to give 14-deoxysphingofungin B (**30**).

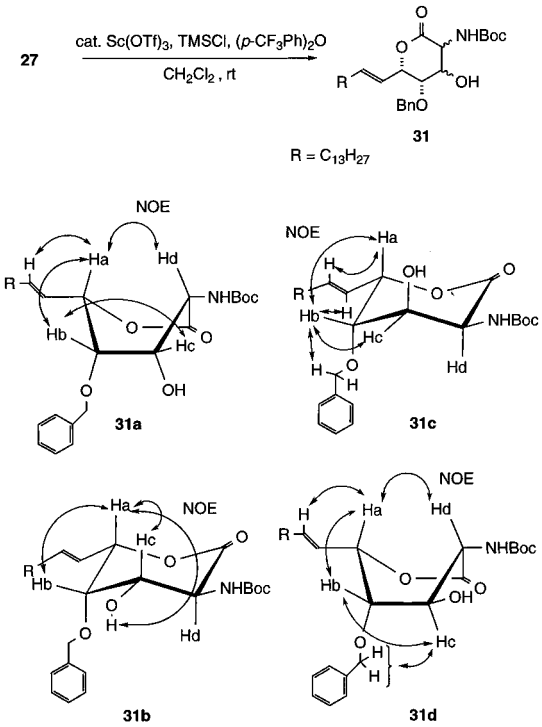
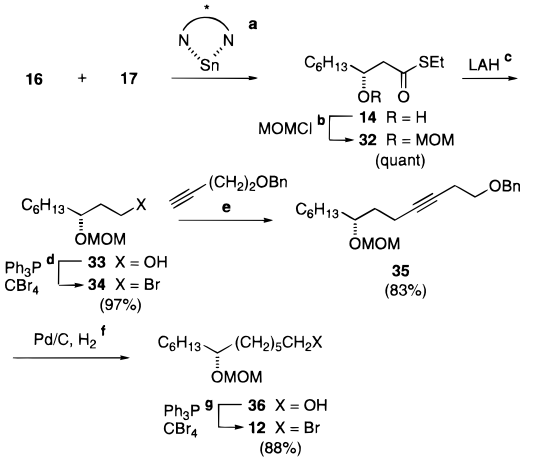


Figure 1.

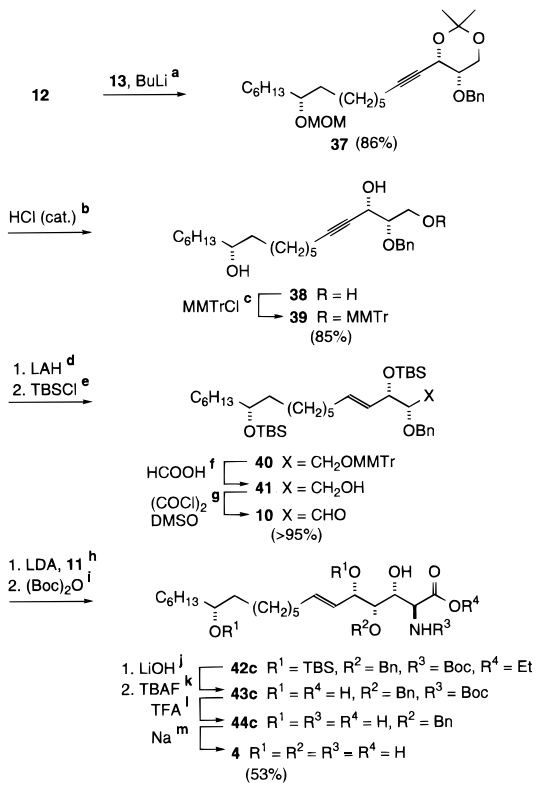
Scheme 3[a]



[a] (a) $Sn(OTf)_2$ (20 mol %), (*S*)-1-methyl-2-[(*N*-1-naphthylamino)-methyl]pyrrolidine (24 mol %), SnO (20 mol %), CH_2Cl_2, −78 °C, slow addition for 4 h, 87%, 94% ee; (b) *i*-Pr_2NEt, CH_2Cl_2; (c) THF, 0 °C, 98%; (d) CH_2Cl_2, 0 °C; (e) BuLi, THF−HMPA, 78 °C to room temperature; (f) EtOH, 96%; (g) CH_2Cl_2, 0 °C.

We next undertook the synthesis of sphingofungin B (Schemes 3 and 4). The chiral hydrophobic chain **12** was prepared according to Scheme 3. The tin(II)-catalyzed asymmetric aldol reaction was a powerful tool again, and the thioester **14** was obtained in 94% ee from the achiral compounds, heptanal (**16**) and 1-ethylthio-1-trimethylsiloxyethene (**17**). The hydroxyl group of **14** was protected as its MOM ether, and the thioester group was reduced using LAH. Alcohol **33** was brominated to give alkyl bromide **34** and the coupling reaction of **34** with 4-benzyloxy-1-butyne proceeded smoothly in THF−HMPA to give alkyne **35**. Reduction of the alkyne of **35** and deprotection of the benzyl ether were carried out in one pot using Pd/C under an H_2 atmosphere. The resulting alcohol (**36**) was brominated

Scheme 4[a]



[a] (a) THF−HMPA, −78 °C to 0 °C; (b) MeOH, 94%; (c) Et_3N, DMAP (catalyst), CH_2Cl_2, 0 °C; (d) LAH, THF, reflux; (e) imid., DMF, 93% (two steps); (f) HCOOH:Et_2O (1:2), 85%; (g) Et_3N, CH_2Cl_2, −50 °C; (h) $ZnCl_2$, THF, −78 °C, 93%, 56% ds; (i) CH_2Cl_2, 61%; (j) THF−H_2O, 0 °C; (k) THF, 60 °C, 96% (two steps); (l) TFA:CH_2Cl_2 (1:1), 0 °C, quant.; (m) liquid NH_3−THF, −50 °C.

with carbon tetrabromide (CBr_4) and triphenylphosphine (Ph_3P) to give the desired chiral hydrophobic chain (**12**) in high yield (Scheme 3). This chiral chain was then coupled with **13** to afford ether **37**, which was treated with concentrated HCl to produce **38**. Triol **38** was converted to aldehyde **10** in five steps (Scheme 4). The primary hydroxyl group of **38** was protected as its MMTr ether, the acetylene was reduced to the trans olefin with LAH, and the free secondary hydroxyl groups were protected as their TBS ethers. The MMTr group was selectively deprotected under mild acidic conditions to give alcohol **41**. Swern oxidation of **41** then gave the key aldehyde **10**.

It was found that the selectivities observed in the aldol reaction of **10** with the glycine enolate derived from **11** was similar to those in the reaction of **26** with the glycine enolate

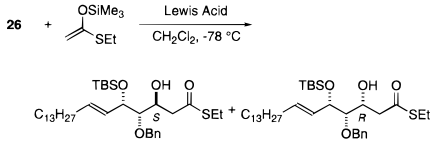
(10) Rossi, R.; Carpita, A. *Synthesis* **1977**, 561.

(11) Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787.

(12) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560.

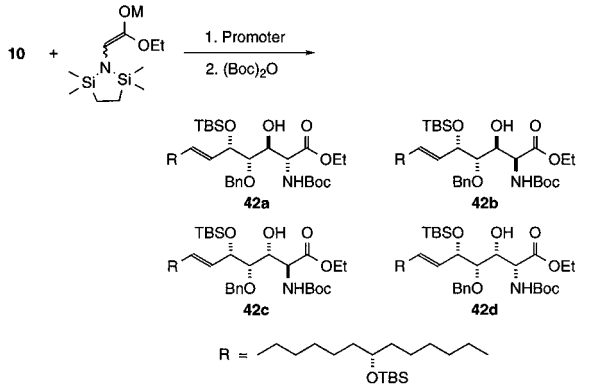
(13) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556 and references therein.

(14) Complete *re* face selectivity was observed in the model reaction of **26** with 1-ethylthio-1-trimethylsiloxyethene under the influence of a Lewis acid.



Lewis Acid	Yield (%)	3*S*/3*R*
$SnCl_4$	82	0/100
BF_3•OEt_2	92	16/84

Table 2



Promotor	Additive	M	Temp (°C)	Solvent	Yield (%)	**42a/b/c/d**
LDA	$ZnCl_2$	ZnCl	-78→ 0	THF	93	35/8/**56**/1
LDA	——	Li	-78→ 0	THF-HMPA	88	**61**/15/19/5
BF_3•OEt_2	——	$SiMe_3$	-78	CH_2Cl_2	70	10/11/27/**52**

(Table 2). When the glycine zinc enolate was used, the desired adduct (**42c**) was obtained in high yield with good selectivity. While the isomeric **42a** was obtained in good selectivity when **10** was reacted with the glycine lithium enolate in THF−HMPA, isomeric **42d** was produced with good selectivity when **10** was reacted with the silyl enolate derived from **11** under the influence of BF_3•OEt_2. The four stereoisomers could be easily separated by silica gel column chromatography. Furthermore, the reactions of **10** with the bislactim ether prepared from either *D*- or *L*-valine and glycine ethyl ester[15] were examined (Table 3). It was found that the tin(II) aza-enolate, which was prepared from the lithium enolate of the *D*-lactim ether and tin(II) chloride, reacted with **10** to afford **46b** in quantitative yield with complete diastereoselectivity. Similarly, *L*-valine was used to obtain **46d** quantitatively. In these reactions, the stereochemistry of the C-2 stereogenic centers of the products were derived from those of the bislactim ether and hence from the *D*- or *L*-valine used. While the adduct predicted by the Felkin-Anh model was obtained using the tin(II) aza-enolate, the adduct predicted by the chelation model was predominantly obtained using the zinc aza-enolate.[16] **46b**−**d** were readily converted to carboxylic acid esters **42b**−**d**.

Hydrolysis of the resulting ester **42c** and deprotection of the TBS groups with tetrabutylammonium fluoride afforded carboxylic acid **43c**. After removal of the Boc group with TFA, the benzyl ether was finally cleaved under Birch conditions. Sphingofungin B (**4**) was obtained after purification using reverse-phase column chromatography.[17] Its spectral and chromatographic properties are identical with those of an authentic sample of the natural product. Similarly, **42a**, **42b**, and **42d** were converted to stereoisomers of **4a**, **4b**, and **4d**, respectively, and by similar routes the stereoisomers **4e**, **4f**, and **4g** were also prepared.

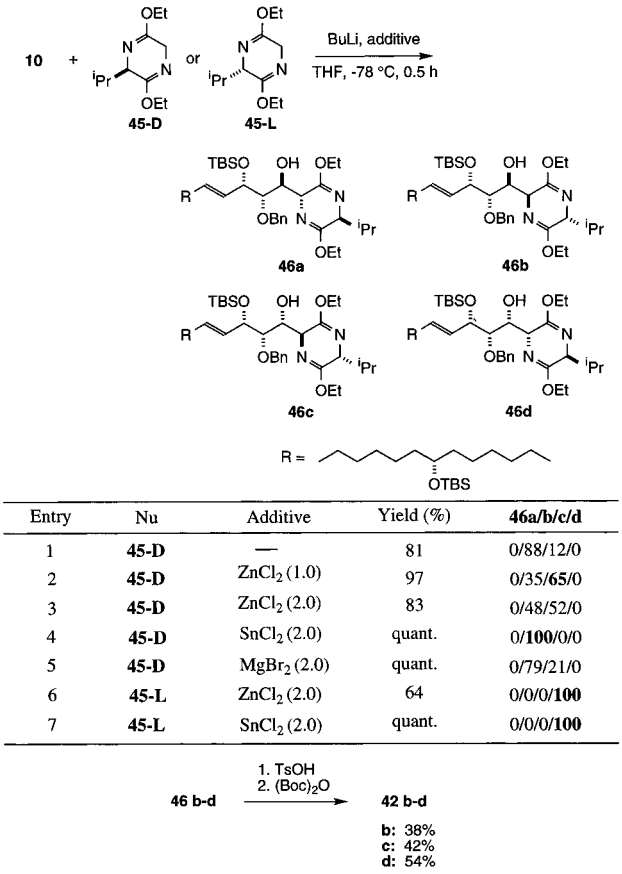
Inhibition of SPT Activity by Stereoisomers of Sphingofungin B. The biosynthesis of sphingolipids starts from the

(15) (a) Schöllkopf, U. *Pure Appl. Chem.* **1983**, *55*, 1799. (b) Schöllkopf, U.; Hartwig, W.; Groth, U.; Westphalen, K. *Liebigs Ann. Chem.* **1981**, 696.

(16) Cf.: Ruiz, M.; Ojea, V.; Quintela, J. M. *Tetrahedron Lett.* **1996**, *37*, 5743.

(17) Kurosawa, K.; Ohfune, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6041. We are grateful to Professor Y. Ohfune for helpful discussion on isolation of sphingofungin B. As for the remote chiral center (C-14) of the synthetic sphingofungin B (**4**), 3% of its epimer was included.

Table 3



Entry	Nu	Additive	Yield (%)	**46a/b/c/d**
1	**45-D**	—	81	0/88/12/0
2	**45-D**	$ZnCl_2$ (1.0)	97	0/35/**65**/0
3	**45-D**	$ZnCl_2$ (2.0)	83	0/48/52/0
4	**45-D**	$SnCl_2$ (2.0)	quant.	0/**100**/0/0
5	**45-D**	$MgBr_2$ (2.0)	quant.	0/79/21/0
6	**45-L**	$ZnCl_2$ (2.0)	64	0/0/0/**100**
7	**45-L**	$SnCl_2$ (2.0)	quant.	0/0/0/**100**

condensation of palmitoyl-CoA with serine, which is catalyzed by serine palmitoyltransferase (SPT).[3a] The fact that cell mutants defective in SPT require exogenous sphingolipids for growth of the cells has revealed that sphingolipids are essential for growth of various types of cells.[3a,3l] Significant roles of sphingolipids have been indicated in various cellular events including proliferation, differentiation, death, and inflammatory responses.[3] Sphingofungin B was reported to inhibit SPT, and it has a striking resemblance to sphingosine and its biosynthetic intermediates. Although the five stereogenic centers of sphingofungin B would be expected to play important roles in its biological activity, the effect of their chirality on activity has not yet been investigated.

Structure−activity relationships of sphingofungin B as an inhibitor of SPT were examined using the synthesized stereoisomers. Natural type sphingofungin B (**4**) inhibited SPT activity with a dose producing 50%-inhibition (ID_{50}) of about 15 nM, confirming it as a potent SPT inhibitor. The C-14 hydroxyl group stereoisomer (**4e**) inhibited SPT activity similar to **4**, whereas dehydroxylation of C-14 (**30**) markedly weakened the observed inhibition (Table 4). In contrast, the C-3 hydroxyl group stereoisomer (**4b**) was about 200-fold less efficient in inhibiting SPT, and the C-2 amino group stereoisomer (**4d**) was 14-fold less efficient than **4** (Table 4). Simultaneous isomerization of both C-2 amino and C-3 hydroxyl groups (**4a**), or both C-4 and C-5 hydroxyl groups (**4g**), further weakened SPT inhibition. It is noted that the enantiomer of sphingofungin B (**4f**) was virtually inactive as an SPT inhibitor (Table 4).

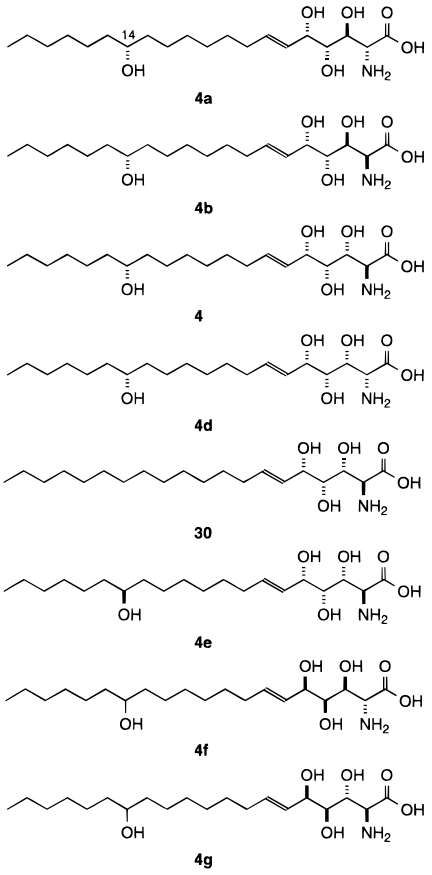
We also examined the effect of these compounds on sphingolipid biosynthesis in intact cells by metabolic labeling of lipids in CHO−K1 cells with radioactive serine and observed that they inhibited sphingolipid biosynthesis in the order (**4**, **4e** ≫ **4b**, **4d**, **30** > **4a**, **4f**, **4g**) similar to that observed under the cell-free SPT assay conditions described above.

Table 4. Inhibition of SPT Activity by Stereoisomers of Sphingofungin B[a]

compd	ID_{50} value for SPT activity/nM
4	16.6 ± 0.8
4e	17.1 ± 0.6
30	3590 ± 150
4d	238 ± 16
4b	3080 ± 360
4a	10000 ± 1000
4f	>10000
4g	>10000

[a] SPT activity of membranes exposed to stereoisomers of sphingofungin B at various concentrations (0−10 μM) was determined as described under Experimental Procedures. The data shown are the mean values ±SD of the ID_{50} values from triplicate experiments.

Chart 2. Sphingofungin B and Stereoisomers



These results indicate that (i) the C-14 hydroxyl group of sphingofungin B is relevant to potent SPT inhibition, but that its stereoconfiguration is not crucial for activity, and that (ii) the stereoconfigurations of the other chiral centers (C-2, -3, -4, and -5) are relevant to activity. The stereochemical requirements of the C-2 amino and C-3 hydroxyl groups for potent activity may suggest that sphingofungin B mimics a transition state intermediate of the SPT reaction.[3a,18]

Synthesis of Sphingofungin F (the Determination of Its Stereochemistry). Our basic strategy shown in Scheme 1 should be useful not only for the synthesis of sphingofungin B and its stereoisomers but also with minor modification for the synthesis of related compounds. Simply changing the amino acid part and the hydrophobic side chain is required. To

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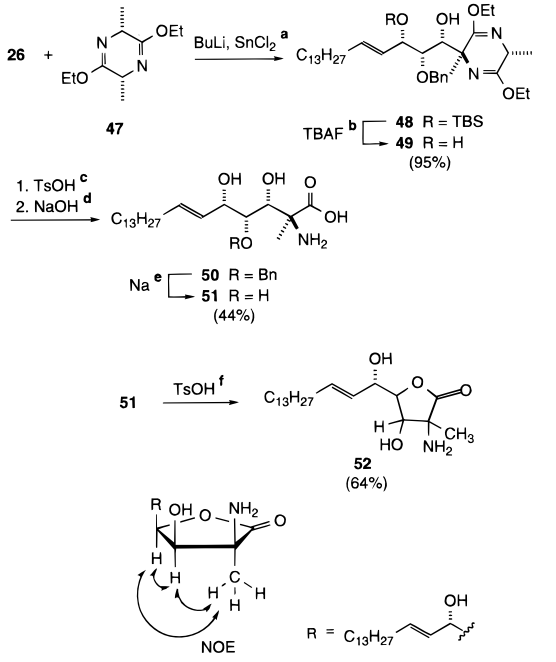
Scheme 5[a]



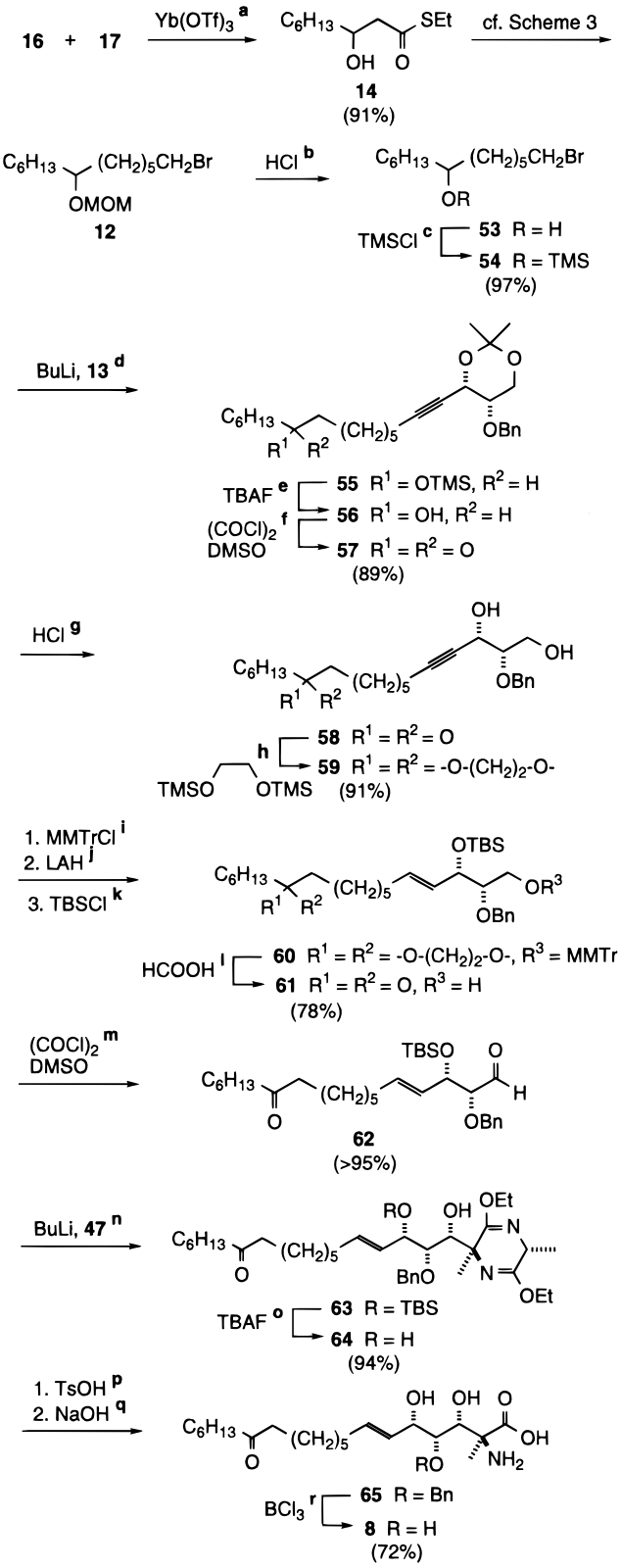
[a] (a) THF −78 °C, 92%; (b) THF; (c) EtOH (70% aqueous), room temperature; (d) 0.5 N NaOH, MeOH, 55% (two steps); (e) liquid NH_3−THF, −50 °C, 44%; (f) EtOH (70% aqueous), 100 °C.

demonstrate the utility of this strategy, we undertook the total synthesis of sphingofungin F (**8**).[19] This compound was isolated from a fermentation of *Poecilomyces variotii*. While it bears a strong structural resemblance to myriocin,[20] its stereochemistry has not yet been determined.

First, the synthesis of 14-deoxy sphingofungin F was carried out (Scheme 5). A key step is the aldol reaction of **26** with an alanine enolate. After several trials, we found a tin(II) aza-enolate of Schölkopf's bislactim ether **47**[14,21] reacted with **26** to afford the desired adduct in 92% yield (diastereomer ratio = 45:42:13:0). After the TBS group of the major stereoisomer was removed, the resulting diol was treated with *p*-toluenesulfonic acid in aqueous ethanol and then NaOH in methanol to afford amino acid **50**. Finally, deprotection of the benzyl ether was performed under Birch conditions to give 14-deoxy sphingofungin F (**51**). ^{1}H and ^{13}C NMR of synthetic **51** were very similar to those of sphingofungin F. The stereochemistry was finally determined by NOE experiments after conversion to lactone **52**. This clarified that the absolute configuration of the contiguous chiral centers of **51** is similar to that of sphingofungin B and myriocin.

We then undertook the synthesis of sphingofungin F. The hydrophobic side chain was prepared according to Scheme 6. The Yb(OTf)$_3$-catalyzed aldol reaction[22] was very useful for the preparation of **14**. The route from racemic **14** to alkyl

Scheme 6[a]



[a] (a) CH_2Cl_2 0 °C; (b) MeOH, 50 °C, quant.; (c) Et_3N, CH_2Cl_2, room temperature; (d) THF−HMPA, 78 °C to 0 °C, 89%; (e) THF, room temperature, quant.; (f) Et_3N, CH_2Cl_2, −78 °C to −50 °C; (g) 3 N HCl, THF, room temperature, 99%; (h) catalyst TMSOTf, CH_2Cl_2, 0 °C; (i) Et_3N, DMAP (catalyst), CH_2Cl_2, 0 °C; (j) THF, reflux; (k) imid., DMF, 91% (three steps); (l) HCOOH:Et_2O (1:2); (m) Et_3N, CH_2Cl_2, −50 °C; (n) **47**, BuLi, $SnCl_2$, THF, −78 °C, 83%; (o) THF; (p) THF−H_2O (7:3), 0 °C; (q) 5 N NaOH, MeOH, room temperature, 58% (two steps); (r) CH_2Cl_2, −78 °C.

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bromide **12** was performed according to Scheme 3 (asymmetric synthesis). After deprotection of the MOM ether of **12**, the resulting alcohol (**53**) was protected as its TMS ether giving **54**. Bromide **54** was then coupled with **13** to afford **55**. The trimethylsilyl group of **55** was deprotected, the resulting alcohol (**56**) was oxidized (**57**), and this ketone was treated with HCl to give diol **58**. After the ketone group of **58** had been protected (**59**), the primary hydroxyl group was protected with MMTrCl. Reduction of the alkyne to the trans olefin was carried out using LAH, and the secondary alcohol was protected as its TBS ether (**60**). Deprotection of the MMTr ether followed by Swern oxidation gave key aldehyde **62**.

The aldol-type reaction of **62** with the tin(II) azaenolate of **47** proceeded smoothly to afford the desired adduct (**63**) in 83% yield with good diastereoselectivity (70:25:5:0, Scheme 6). After deprotection of the TBS group, successive hydrolysis (two steps) of the major diastereomer and finally deprotection of the benzyl ether using BCl_3 worked well to afford sphingofungin F (**8**). Its spectral properties are completely identical with those in the literature.[19] It is now confirmed unambiguously that the structure of sphingofungin F, including the absolute configuration of its chiral centers, is similar to that of sphingofungin B and myriocin.

Conclusions

In summary, we have developed an unambiguous synthetic route to sphingofungins B and F and their derivatives. The synthesis is based on the catalytic asymmetric aldol reaction, and efficient enantioselective synthesis using a catalytic amount of a chiral source as well as the effectiveness of our synthetic strategy for the sphingofungin family (Scheme 1) has been successfully demonstrated. By using the stereoisomers of sphingofungin B, the relevance of the stereochemistry of its chiral centers to SPT inhibitory activity was revealed.

Experimental Section

General Methods. Melting points are uncorrected. IR spectra were recorded on a Horiba FT-300. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNR-EX270L, JNM-LA300, or a JNM-LA400 spectrometer in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) served as internal standard ($\delta = 0$) for ^{1}H NMR, and $CDCl_3$ was used as internal standard ($\delta = 77.0$) for ^{13}C NMR. When CD_3OD was used, CD_3OD served as internal standard ($\delta = 3.3$ for ^{1}H NMR (CH_3OH) and $\delta =$ 49.0 for ^{13}C NMR). Mass spectra were measured on a JEOL DX-303HF spectrometer. HPLC was carried out using a Hitachi LC−Organizer, L-4000 UV Detector, L-6200 Intelligent Pump, and D-2500 Chromato-Integrator. Optical rotations were recorded on a Jasco DIP-360 digital polarimeter. Column chromatography was performed on Silica gel 60 (Merck) or Wakogel B5F. All solvents were purified according to standard procedures.

Membranes were prepared from CHO−K1 cells as described previously.[23] Membranes (1 mg of protein/mL) were incubated in 50 mM Hepes-Na (pH 7.5) containing 5 mM EDTA, 0.1% sucrose monolaurate, and various concentrations of sphingofungin B isomers at 4 °C for 30 min. A concentration of dimethyl sulfoxide, in which sphingofungin B isomers were dissolved, was adjusted to be 1% in the membrane incubation. After the incubation, SPT activity of the membranes were determined as described previously.[20] For examination of sphingolipid synthesis in intact cells, CHO−K1 cells were preincubated in F-12 medium containing various concentrations of sphingofungin B isomers at 37 °C for 1 h. After addition of L-[^{14}C]-serine to the medium, the cells were incubated at 37 °C for 2 h, and lipid extracted from the cells were analyzed as described previously.[24]

Phenyl (2*R*,3*S*)-2-benzyloxy-3-hydroxy-5-trimethylsilylpent-4-ynoate (15): To a mixture of tin(II) trifluoromethansulfonate[25] (834 mg, 2.0 mmol) and tin(II) oxide (269 mg, 2.0 mmol) in propionitrile (20 mL) was added (*R*)-1-methyl-2-[(*N*-1-naphthylamino)methyl]pyrrolidine[26] (576 mg, 2.4 mmol) in propionitrile (20 mL) at room temperature. The solution was cooled to −78 °C, and **18** (1.26 g, 10 mmol) in propionitrile (15 mL) and **19** (3.77 g, 12 mmol) in propionitrile (15 mL) were slowly added over 4 h. After the solution was stirred for 1 h at −78 °C, it was saturated with aqueous $NaHCO_3$ solution which was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with ether. The ethereal extract was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was treated with THF:1 N HCl = 4:1 solution for 30 min. After neutralization using saturated aqueous $NaHCO_3$ solution, the aqueous layer was extracted with ether. The ethereal extract was washed with water and brine, dried over sodium sulfate, and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 20/1) to give **15** (3.21 g, 87%, syn/anti = 97/3, 91% ee (syn)) as a white solid. $[\alpha]_D^{27}$ +28.8 (c = 1.03, $CHCl_3$); IR (neat) 1643, 3379 cm^{-1}; ^{1}H NMR δ 0.02 (s, 9H), 2.91 (d, 1H, J = 8.1 Hz), 4.13 (d, 1H, J = 4.4 Hz), 4.56 (d, 1H, J = 11.9 Hz), 4.69 (dd, 1H, J = 4.4, 8.1 Hz), 4.77 (d, 1H, J = 11.9 Hz), 6.93−7.29 (m, 10H); ^{13}C NMR δ −0.4, 64.0, 73.4, 80.6, 91.7, 102.0, 121.2, 126.1, 128.19, 128.24, 128.4, 129.4, 136.5, 150.1, 168.0. Anal. Calcd for $C_{21}H_{24}O_4Si$: C, 68.45; H, 6.56. Found: C, 68.59; H, 6.51. The enantiomeric excess was determined by HPLC analysis. HPLC (Daicel Chiralcel AD, hexane/*i*-PrOH = 24/1, flow rate = 1.0 mL/min): t_R = 17.5 min (2*S*,3*R*), t_R = 21.2 min (2*R*,3*S*).

(2*S*,3*S*)-2-Benzyloxy-5-trimethylsilylpent-4-yne-1,3-diol (20): To a solution of **15** (3.21 g, 8.7 mmol) in dichloromethane (80 mL) was added diisobutylalminum hydride (1.5 M solution in toluene, 17.4 mL) over 20 min at −78 °C. After stirring for 30 min at −78 °C, the mixture was diluted with 1 N HCl. After the organic layer was separated, the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 6/1) to give **20** (2.01 g, 83%) as a white solid. $[\alpha]^{27}_D$ +13.0 (c = 1.02, C_6H_6); IR (neat) 2171, 3363 cm^{-1}; ^{1}H NMR δ 0.19 (s, 9H), 2.08 (brs, 1H), 2.69 (brs, 1H), 3.63 (ddd, 1H, J = 5.0, 5.0, 5.0 Hz), 3.56 (dd, 1H, J = 5.0, 11.6 Hz), 3.64 (dd, 1H, J = 5.0, 11.6 Hz), 4.30 (brs, 1H), 4.73 (d, 1H, J = 11.4 Hz), 4.83 (d, 1H, J = 11.4 Hz), 7.33−7.38 (m, 5H); ^{13}C NMR δ −0.3, 61.7, 63.2, 73.6, 81.7, 91.5, 103.6, 128.0, 128.1, 128.6, 137.7. Anal. Calcd for $C_{15}H_{22}O_3Si$: C, 64.71; H, 7.96. Found: C, 64.84; H, 7.95.

(4*S*,5*S*)-5-Benzyloxy-4-(2-trimethylsilylethynyl)-2,2-dimethyl-1,3-dioxane (21): To a solution of **20** (2.01 g, 7.2 mmol) in *N*,*N*-dimethylformamide (50 mL) was added a solution of 2,2-dimethoxypropane (2.2 g, 21.6 mmol) in *N*,*N*-dimethylformamide (10 mL) and cat *p*-TsOH at room temperature. After stirring for 10 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with ether. The ethereal extract was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 30/1) to give **21** (2.18 g, 95% (syn); 0.06 g, 3% (anti)) as a white solid. $[\alpha]_D^{26}$ +37.0 (c = 2.13, $CHCl_3$); ^{1}H NMR δ 0.00 (s, 9H), 1.22 (s, 3H), 1.32 (s, 3H), 3.22 (dd, 1H, J = 3.0, 5.9 Hz), 3.64 (dd, 1H, J = 3.0, 12.5 Hz), 3.72 (dd, 1H, J = 3.3, 12.5 Hz), 4.59−4.60 (m, 3H), 7.09−7.24 (m, 5H); ^{13}C NMR δ −0.3, 17.8, 20.3, 61.6, 64.1, 70.9, 71.7,

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91.5, 99.6, 101.4, 127.7, 127.9, 128.3, 138.0. Anal. Calcd for $C_{18}H_{26}O_3Si$: C, 67.88; H, 8.23. Found: C, 68.01; H, 8.16.

(4*S*,5*S*)-5-Benzyloxy-4-ethynyl-2,2-dimethyl-1,3-dioxane (13) (100% ee): To a solution of **21** (2.18 g, 6.8 mmol) in dichloromethane (50 mL) was added a solution of tetrabutylammoniumfluoride (1.96 g, 7.5 mmol) in dichloromethane (10 mL) at room temperature. After having been stirred for 30 min, the reaction was quenched with phosphate buffer (pH = 7), and the aqueous layer was extracted with dichloromethane. The extract was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 6/1) to give **13** (1.62 g, 97%) as white crystals. The crystals were recrystallized from hexane to give optically pure **13** (>99% ee, 1.49 g, 89%). Mp 96−98 °C; $[\alpha]_D^{27}$ +34.3 (c = 1.21, $CHCl_3$); IR (KBr) 2117, 3220 cm^{-1}; ^1H NMR δ 1.43 (s, 3H), 1.54 (s, 3H), 2.57 (d, 1H, J = 2.3 Hz), 3.45 (dd, 1H, J = 3.1, 4.0 Hz), 3.86 (dd, 1H, J = 3.1, 12.5 Hz), 3.93 (dd, 1H, J = 4.0, 12.5 Hz), 4.78−4.80 (m, 3H), 7.26−7.44 (m, 5H); ^{13}C NMR δ 21.0, 27.4, 61.5, 63.6, 70.7, 71.9, 75.0, 80.0, 99.6, 127.8, 128.0, 128.3, 137.9; HRMS calcd for $C_{15}H_{18}O_3$ (M + H) 247.1335, found 247.1338. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.85; H, 7.57. HPLC (Daicel Chiralcel AD, hexane/*i*-PrOH = 50/1, flow rate = 0.5 mL/min): t_R = 22.5 min (4*S*,5*S*), t_R = 26.3 min (4*R*,5*R*).

Ethyl (3*R*)-3-hydroxynonanethioate (14): To a mixture of tin(II) trifluoromethansulfonate (417 mg, 1.0 mmol) and tin(II) oxide (135 mg, 1.0 mmol) in dichloromethane (10 mL) was added (*S*)-1-methyl-2-[(*N*-1-naphthylamino)methyl]pyrrolidine (288 mg, 1.2 mmol) in dichloromethane (10 mL) at room temperature. The solution was cooled to −78 °C, and a solution of **16** (570 mg, 5.0 mmol) and **17** (1.06 mg, 6.0 mmol) in dichloromethane (15 mL) was slowly added over 4 h. After stirring for 1 h at −78 °C, the reaction was quenched with aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with ether. The ethereal extract was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was treated with THF:1 N HCl = 4:1 solution for 30 min, and the mixture was extracted with ether. The ethereal extract was washed with water and brine, dried over sodium sulfate, and concentrated, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 20/1) to give **14** (950 mg, 87%, 94% ee) as a colorless oil. $[\alpha]^{25}_D$ −18.0 (c = 1.15, C_6H_6); IR (neat) 1683.6, 2927.4, 3378.7, 3475.1 cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J = 6.6 Hz), 1.24−1.56 (m, 13H), 2.61−2.81 (m, 3H), 2.91 (q, 2H, J = 7.5 Hz), 4.01−4.08 (m, 1H); ^{13}C NMR δ 14.0, 14.6, 22.5, 23.3, 25.3, 29.1, 31.7, 36.5, 50.6, 68.6, 199.6. Anal. Calcd for $C_{11}H_{22}O_2S$: C, 60.73; H, 10.09; S, 14.46. Found: C, 60.51; H, 10.16; S, 14.68. Enantiomeric excess was determined by HPLC analysis after acetylation of **14**. HPLC (Daicel Chiralcel AS, hexane/*i*-PrOH = 100/1, flow rate = 1.0 mL/min): t_R = 3.6 min (3*S*), t_R = 7.2 min (3*R*).

Ethyl (3*R*)-3-(methoxymethoxy)nonanethioate (32): To a solution of **14** (94% ee, 950.0 mg, 4.35 mmol) in dichloromethane (18 mL) was added a solution of diisopropylethylamine (1.7 g, 13.1 mmol) in dichloromethane (11 mL) and methoxymethyl chloride (1.1 g, 13.1 mmol) in dichloromethane (11 mL) at 0 °C. The solution was warmed to room temperature and stirred for 10 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and the aqueous layer was extracted with dichloromethane. The extract was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 9/1) to give **32** (1.14 g, 100%) as a colorless oil. $[\alpha]^{28}_D$ −0.3 (c = 0.54, C_6H_6); IR (neat) 1689.3, 2927.4 cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J = 5.8 Hz), 1.01−1.46 (m, 11H), 1.48−1.58 (m, 2H), 2.67 (dd, 1H, J = 5.6, 15.0 Hz), 2.83 (dd, 1H J = 7.3, 15.0 Hz), 2.89 (q, 2H, J = 7.4 Hz), 3.35 (s, 3H), 3.99−4.08 (m, 1H), 4.63 (d, 1H, J = 7.3 Hz), 4.66 (d, 1H, J = 7.3 Hz); ^{13}C NMR δ 14.0, 14.7, 22.5, 23.4, 25.0, 29.2, 31.7, 34.7, 49.3, 55.6, 74.6, 95.8, 197.4. Anal. Calcd for $C_{13}H_{26}O_3S$: C, 59.50; H, 9.99; S, 12.22. Found: C, 59.61; H, 10.05; S, 12.09.

(3*R*)-3-(Methoxymethoxy)-1-nonanol (33): To a suspension of lithium aluminum hydride (496.5 mg, 13.1 mmol) in THF (9 mL) was slowly added a solution of **32** (1.14 g, 4.35 mmol) in THF (16 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 1.5 h. The mixture was then cooled to 0 °C and quenched with saturated aqueous sodium sulfate solution. After adding of 1 N HCl aqueous, the suspension was stirred vigorously, and the aqueous layer was extracted with ether. The ethereal extract was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 6/1) to give **33** (869.8 mg, 98%) as a colorless oil. $[\alpha]_D^{25}$ −27.0 (c = 1.67, C_6H_6); IR (neat) 2929.3, 3392.2 cm^{-1}; ^1H NMR δ 0.87 (t, 3H, J = 6.9 Hz), 1.29 (s, 8H), 1.41−1.60 (m, 2H), 2.99 (brs, 1H), 3.40 (s, 3H), 3.66−3.82 (m, 3H), 4.65 (d, 1H, J = 6.9 Hz), 4.69 (d, 1H, J = 6.9 Hz); ^{13}C NMR δ 13.9, 22.4, 25.0, 29.3, 31.6, 34.5, 36.6, 55.5, 59.4, 76.0, 95.6. Anal. Calcd for $C_{11}H_{24}O_3$: C, 64.67; H, 11.84. Found: C, 64.59; H, 11.82.

1-Bromo-(3*R*)-3-(methoxymethoxy)nonane (34): To a solution of **33** (869.8 mg, 4.26 mmol) in dichloromethane (5.0 mL) was quickly added a solution of carbon tetrabromide (2.8 g, 8.51 mmol) in dichloromethane (3.0 mL) and triphenylphosphine (2.2 g, 8.51 mmol) in dichloromethane (3.0 mL) at 0 °C. After stirring for 30 min, the solvent was removed. The residue was then diluted with ether, and the solids were filtered off. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 20/1) to give **34** (1.05 g, 92%) as a colorless oil. $[\alpha]_D^{22}$ −20.9 (c = 0.40, C_6H_6); IR (neat) 1039.4, 2929.3 cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J = 6.9 Hz), 1.29 (s, 8H), 1.42−1.61 (m, 2H), 2.00−2.08 (m, 2H), 3.39 (s, 3H), 3.50 (t, 2H, J = 6.9 Hz), 3.67−3.76 (m, 2H), 4.65 (d, 1H J = 6.9 Hz), 4.69 (d, 1H, J = 6.9 Hz); ^{13}C NMR δ 14.1, 22.6, 25.0, 29.4, 30.1, 31.8, 34.2, 37.8, 55.7, 75.7, 95.7. Anal. Calcd for $C_{11}H_{23}BrO_2$: C, 49.45; H, 8.68; Br, 29.90. Found: C, 49.62; H, 8.49; Br, 29.68.

1-Benzyloxy-(7*R*)-7-(methoxymethoxy)-3-tridecyne (35): To a solution of 4-benzyloxy-1-butyne (818.4 mg, 5.11 mmol) in THF (8.0 mL) was added *n*-BuLi (1.6 M solution in hexane, 4.72 mmol) dropwise over 5 min. The solution was stirred for 15 min, and a mixture of **34** (1.05 g, 3.93 mmol) in THF (6.5 mL) and HMPA (3.2 mL) was added dropwise. After having been stirred for 10 min at −78 °C, the solution was warmed to 0 °C and stirred for further 4 h. The reaction was quenched with water, and the aqueous layer was extracted with ether. The ethereal extract was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 30/1) to give **35** (1.13 g, 83%) as a colorless oil. $[\alpha]_D^{24}$ −9.0 (c = 0.91, C_6H_6); IR (neat) 2927.4 cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J = 5.9 Hz), 1.28 (s, 8H), 1.40−1.49 (m, 2H), 1.68 (dt, 2H, J = 6.9, 13.0 Hz), 2.20−2.27 (m, 2H), 3.37 (s, 3H), 3.55 (t, 2H, J = 7.1 Hz), 3.61−3.67 (m, 1H), 4.54 (s, 2H), 4.65 (s, 2H), 7.25−7.35 (m, 5H); ^{13}C NMR δ 14.1, 14.9, 20.1, 22.6, 25.1, 29.4, 31.8, 33.6, 34.1, 55.5, 68.8, 72.8, 76.3, 76.8, 80.9, 95.5, 127.6, 128.3, 138.1. Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.41; H, 9.95.

(7*R*)-7-(Methoxymethoxy)-1-tridecanol (36): To a solution of **35** (1.13 g, 3.26 mmol) in ethanol (16 mL) was added a catalytic amount of 10% palladium−carbon under argon. The solution was stirred under H_2 at 1 atm for 20 h. Palladium−carbon was then filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 6/1) to give **36** (815.3 mg, 96%) as a colorless oil. $[\alpha]_D^{25}$ −0.1 (c = 1.31, C_6H_6); IR (neat) 2931.3, 3378.7 cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J = 6.6 Hz), 1.11−1.57 (m, 20H), 1.70 (brs, 1H), 3.38 (s, 3H), 3.45−3.54 (m, 1H), 3.64 (t, 2H, J = 6.6 Hz), 4.65 (s, 2H); ^{13}C NMR δ 14.1, 22.6, 25.2, 25.7, 29.5, 29.5, 31.8, 32.7, 34.2, 34.3, 55.4, 62.9, 77.4, 95.3. Anal. Calcd for $C_{15}H_{32}O_3$: C, 69.18; H, 12.39. Found: C, 68.85; H, 12.22.

1-Bromo-(7*R*)-7-methoxymethoxytridecane (12): To a solution of **35** (815.3 mg, 3.13 mmol) in dichloromethane (6.0 mL) was quickly added a solution of carbon tetrabromide (2.08 g, 6.26 mmol) in dichloromethane (4.5 mL) and triphenylphosphine (1.64 g, 6.26 mmol) in dichloromethane (4.5 mL) at 0 °C. After stirring for 30 min, the solvent was removed under reduced pressure. The residue was then diluted with ether, and the solids were filtered off. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 20/1) to give **12** (890.7 mg, 88%) as a colorless oil. $[\alpha]_D^{26}$ −0.06 (c = 0.97, C_6H_6); IR (neat) 2931.3 cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J = 6.4 Hz), 1.18−1.60 (m, 18H), 1.86 (dt, 2H, J = 6.6, 14.4 Hz), 3.38 (s, 3H),

3.41 (t, 2H, J = 5.6, 11.3 Hz), 4.65 (s, 2H); ^{13}C NMR δ 14.1, 22.6, 25.1, 25.2, 28.1, 28.9, 29.5, 31.8, 32.7, 33.9, 34.1, 34.3, 55.5, 77.5, 95.3. Anal. Calcd for $C_{15}H_{31}BrO_2$: C, 55.72; H, 9.66; Br, 24.71. Found: C, 55.96; H, 9.51; Br, 23.47.

(2*S*,3*S*,9′*R*)-3-Benzyloxy-2-(9′-(methoxymethoxy)pentadec-1-ynyl)-2,2-dimethyl-1,3-dioxane (37): To a solution of **13** (646.4 mg, 2.62 mmol) in THF (15.0 mL) at −78 °C was added *n*-BuLi (1.6 M solution in hexane, 2.62 mmol) dropwise over 5 min. The mixture was stirred for 15 min, and a mixture of **12** (890.7 mg, 2.75 mmol) in THF (4.0 mL) and HMPA (1.9 mL) was added dropwise. After stirring for 10 min at −78 °C, the mixture was warmed to 0 °C and stirred for a further 10 h. The reaction was quenched with water, and the aqueous layer was extracted with ether. The ethereal extract was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 9/1) to give **37** (1.10 g, 86%) as a colorless oil. $[\alpha]_D^{24}$ +4.4 (c = 1.06, C_6H_6); IR (neat) 1375.0, 1457.9, 2242.8, 2856.1 cm^{-1}; ^{1}H NMR δ 0.88 (t, 3H, J = 6.4 Hz), 1.28−1.60 (m, 26H), 2.27 (dt, 2H, J = 2.0, 7.1 Hz), 3.33−3.39 (m, 4H), 3.50 (t, 1H, J = 5.6 Hz), 3.82−3.94 (m, 2H), 4.64 (s, 2H), 4.77−4.78 (m, 3H), 7.24−7.44 (m, 5H); ^{13}C NMR δ 14.0, 18.9, 20.3, 22.5, 25.05, 25.14, 27.8, 28.3, 28.9, 29.3, 29.4, 31.7, 34.2, 55.3, 61.7, 63.8, 71.1, 71.7, 76.1, 77.5, 87.3, 95.2, 99.3, 127.5, 127.8, 128.1, 138.1; FABHRMS calcd for $C_{30}H_{48}O_5$ (M + Na) 511.3399, found 511.3396. Anal. Calcd for $C_{30}H_{48}O_5$: C, 73.73; H, 9.90. Found: C, 73.67; H, 9.95.

(2*S*,3*S*,12*R*)-2-Benzyloxyoctadec-4-yne-1,3,12-triol (38): To a solution of **37** (1.10 g, 2.26 mmol) in methanol (35 mL) was added concentrated HCl (0.5 mL), and the mixture was stirred for 30 min at 60 °C. The mixture was cooled to room temperature, then diluted with water (60 mL), and cooled to 0 °C. The mixture was neutralized with potassium carbonate, and the aqueous layer was extracted with ether. The ethereal extract was washed with saturated aqueous $NaHCO_3$ solution, water, and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give **38** (876.4 mg, 96%) as a colorless oil. $[\alpha]_D^{24}$ +0.6 (c = 5.25, C_6H_6); IR (neat) 2337.3, 2927.4, 3371.0 cm^{-1}; ^{1}H NMR δ 0.80 (t, 3H, J = 6.9 Hz), 1.20−1.44 (m, 20H), 1.87 (brs, 1H), 2.14 (t, 2H, J = 5.9 Hz), 2.61 (brs, 1H), 3.08 (brs, 1H), 3.47−3.52 (m, 2H), 3.65 (dd, 1H, J = 5.0, 11.9 Hz), 3.76 (dd, 1H, J = 4.6, 11.5 Hz), 4.40 (m, 1H), 4.63 (d, 1H, J = 11.5 Hz), 4.71 (d, 1H, J = 11.5 Hz), 7.20−7.29 (m, 5H); ^{13}C NMR δ 14.0, 18.6, 22.5, 25.3, 25.5, 28.2, 28.6, 28.9, 29.3, 31.7, 37.1, 37.3, 61.6, 62.9, 71.8, 73.3, 78.2, 82.0, 87.0, 127.9, 128.4, 137.8; FABHRMS calcd for $C_{25}H_{40}O_4$ (M + Na) 427.2824, found 427.2833. Anal. Calcd for $C_{30}H_{48}O_5$: C, 74.22; H, 9.97. Found: C, 74.38; H, 9.88.

(2*S*,3*S*,12*R*)-2-Benzyloxy-1-(4-methoxyphenyldiphenylmethoxy)-octadec-4-yne-3,12-diol (39): To a solution of **38** (876.4 mg, 2.17 mmol) in dichloromethane (12 mL) was added a solution of triethylamine (438.3 mg, 4.3 mmol) in dichloromethane (6.0 mL), and a solution 4-methoxytrityl chloride (1.2 g, 4.3 mmol) in dichloromethane (6.0 mL) at 0 °C. After a catalytic amount of *N*,*N*-(dimethylamino)-pyridine was added, the mixture was stirred for 1 h. The reaction was quenched with water, and the aqueous layer was extracted with dichloromethane. The extract was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give **39** (1.25 g, 85%) as a yellow oil. $[\alpha]_D^{25}$ +8.6 (c = 1.0, C_6H_6); IR (neat) 2233.2, 2923.6, 3423.0 cm^{-1}; ^{1}H NMR δ 0.88 (t, 3H, J = 6.4 Hz), 1.28−1.40 (m, 20H), 2.12 (m, 2H), 2.87 (brs, 1H), 3.32 (dd, 1H, J = 5.0, 9.6 Hz), 3.45 (dd, 1H, J = 4.3, 10.2 Hz), 3.54 (brs, 1H), 3.63 (m, 1H), 3.76 (s, 3H), 4.55 (m, 1H), 4.61 (d, 1H, J = 12.2 Hz), 4.73 (d, 1H, J = 11.6 Hz), 6.79−7.47 (m, 19H); ^{13}C NMR δ 14.0, 18.6, 22.5, 25.4, 25.4, 25.5, 28.3, 28.8, 29.0, 29.3, 31.8, 37.3, 37.4, 55.1, 62.8, 62.9, 71.8, 73.1, 78.2, 81.3, 86.4, 86.5, 113.0, 126.8, 127.7, 127.9, 128.2, 128.3, 130.3, 135.4, 137.9, 144.2, 158.4. Anal. Calcd for $C_{45}H_{56}O_5$: C, 79.84; H, 8.34. Found: C, 79.98; H, 8.33.

(2*S*,3*S*,12*R*)-2-Benzyloxy-3,12-bis(*tert*-butyldimethylsiloxy)-1-(4-methoxyphenyldiphenylmethoxy)-4-octadecene (40): To a suspension of lithium aluminum hydride (244.6 mg, 6.44 mmol) in THF (40 mL) was added a solution of **39** (1.25 g, 1.84 mmol) in THF (40 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 10 min. The mixture was refluxed for 1 h and then cooled to 0 °C. The reaction was quenched with saturated aqueous potassium sodium tartarate solution. After the suspension was stirred vigorously, the aqueous layer was extracted with ether. The ethereal extract was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure to give a yellow oil. To a solution of the yellow oil in DMF (12 mL) was added a solution of imidazole (501.4 mg, 7.36 mmol) in DMF (6.0 mL) and *tert*-butyldimethylsilyl chloride (1.11 g, 7.36 mmol) in DMF (6.0 mL) at 0 °C. After the solution was stirred for 10 h at room temperature, the reaction was quenched with water, and the aqueous layer was extracted with ether. The ethereal extract was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 30/1) to give **40** (1.56 g, 93%, two steps) as a yellow oil. $[\alpha]_D^{26}$ −7.5 (c = 0.97, C_6H_6); IR (neat) 1251.6, 2919.7 cm^{-1}; ^{1}H NMR δ −0.06 (s, 6H), 0.00 (s, 6H), 0.79−0.85 (m, 21H), 1.18−1.35 (m, 18H), 1.83 (m, 2H), 3.04 (dd, 1H, J = 6.3, 9.6 Hz), 3.25 (d, 1H, J = 9.6 Hz), 3.47 (m, 1H), 3.56−3.59 (m, 1H), 3.70 (s, 3H), 4.22 (t, 1H, J = 5.8 Hz), 4.68 (d, 1H, J = 11.9 Hz), 4.75 (d, 1H, J = 11.9 Hz), 5.28 (dd, 1H, J = 6.1, 15.3 Hz), 5.46 (m, 1H), 6.74 (d, 2H, J = 8.6 Hz), 7.11−7.44 (m, 19H); ^{13}C NMR δ −4.8, −4.4, −4.4, 14.1, 18.2, 22.6, 25.3, 25.9, 26.0, 29.1, 29.2, 29.6, 29.7, 31.9, 32.1, 37.2, 55.1, 63.9, 72.3, 73.1, 73.8, 82.7, 86.2, 112.9, 126.4, 127.3, 127.7, 127.7, 128.2, 128.3, 128.5, 129.3, 130.4, 132.0, 135.9, 139.2, 144.7, 158.3; FABHRMS calcd for $C_{57}H_{86}O_5Si_2$ (M + Na) 929.5911, found 929.5905. Anal. Calcd for $C_{57}H_{86}O_5Si_2$: C, 75.44; H, 9.55. Found: C, 75.58; H, 9.49.

(2*R*,3*S*,14*R*)-2-Benzyloxy-3,14-bis(*tert*-butyldimethylsiloxy)octadec-4-ene-1-ol (41): To a solution of **40** (1.56 g, 1.72 mmol) in ether (120 mL) was added 98% formic acid (60 mL). The mixture was stirred for 30 min at 0 °C and then diluted with water (150 mL). The solution was neutralized with potassium carbonate, and the aqueous layer was extracted with ether. The ethereal extract was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 20/1) to give **41** (927.1 mg, 85%) as a colorless oil. $[\alpha]_D^{27}$ +16.5 (c = 1.81, C_6H_6); IR (neat) 1253.5, 2856.1, 2931.3 cm^{-1}; ^{1}H NMR δ 0.03 (s, 6H), 0.04 (s, 6H), 0.86 (t, 3H, J = 6.8 Hz), 0.886 (s, 9H), 0.888 (s, 9H), 1.27−1.39 (m, 20H), 2.04 (dt, 2H, J = 6.8, 13.4 Hz), 2.18 (brs, 1H), 3.45−3.53 (m, 2H), 3.59 (dt, 1H, J = 5.6, 11.5 Hz), 3.75 (dd, 1H, J = 4.6, 11.2 Hz), 4.29 (d, 1H, J = 5.9 Hz), 4.62 (d, 1H, J = 11.6 Hz), 4.75 (d, 1H, J = 11.6 Hz), 5.49 (dd, 1H, J = 6.3, 15.5 Hz), 5.67 (dt, 1H, J = 6.6, 15.5 Hz), 7.16−7.40 (m, 5H); ^{13}C NMR δ −4.9, −4.5, −4.4, 14.1, 18.1, 22.6, 25.3, 25.8, 25.9, 29.2, 29.2, 29.5, 29.7, 31.9, 32.3, 37.1, 61.9, 72.4, 73.0, 74.0, 81.9, 127.8, 127.8, 128.5, 133.1, 138.5; FABHRMS calcd for $C_{37}H_{70}O_4Si_2$ (M + Na) 657.4711, found 657.4714. Anal. Calcd for $C_{37}H_{70}O_4Si_2$: C, 69.97; H, 11.11. Found: C, 69.82; H, 10.97.

(2*R*,3*S*,12*R*)-2-Benzyloxy-3,12-bis(*tert*-butyldimethyisiloxy)octadec-4-enal (10): To a solution of oxalyl chloride (60.9 mg, 0.48 mmol) in dichloromethane (1.5 mL) was added a solution of dimethyl sulfoxide (48.8 mg, 0.62 mmol) in dichloromethane (1.1 mL) dropwise over 15 min at −78 °C. A solution of **41** (151.9 mg, 0.24 mmol) in dichloromethane (1.7 mL) was added, and the mixture was stirred for 10 min at −78 °C and for 1 h at −50 °C. Triethylamine (176.0 mg, 1.67 mmol) was added, and the mixture warmed to 0 °C and stirred for 20 min. The reaction was quenched with saturated aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane. The extract was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 20/1) to give **10** (151.4 mg, quant.) as a colorless oil. ^{1}H NMR δ 0.04 (s, 6H), 0.06 (s, 6H), 0.90−0.91 (m, 21H), 1.30−1.41 (m, 20H), 2.01−2.06 (m, 2H), 3.64 (t, 1H, J = 5.3 Hz), 3.76 (dd, 1H, J = 1.5, 5.0 Hz), 4.43 (t, 1H, J = 5.6 Hz), 4.59 (d, 1H, J = 12.2 Hz), 4.71 (d, 1H, J = 12.2 Hz), 5.57 (dd, 1H, J = 6.6, 15.5 Hz), 5.70 (dt, J = 6.3, 15.5 Hz), 7.28−7.37 (m, 5H), 9.69 (d, 1H, J = 1.5 Hz); ^{13}C NMR δ −5.0, −4.4, 14.1, 18.1, 22.6, 25.3, 25.7, 25.9, 29.0, 29.1, 29.5, 29.7, 31.9, 32.1,

37.1, 72.3, 72.8, 73.8, 86.2, 127.9, 128.1, 128.4, 133.6, 137.4, 202.6; FABHRMS calcd for $C_{37}H_{68}O_4Si_2$ (M + Na) 655.4553, found 655.4559.

Ethyl (2*S*,3*R*,4*S*,5*S*,14*R*)-4-benzyloxy-2-(*tert*-butoxycarbonylamino)-5,14-bis(*tert*-butyldimethylsiloxy)-3-hydroxyeicos-6-enoate (42c): To a solution of diisopropylamine (41.3 mg, 0.41 mmol) in THF (1.9 mL) was added *n*-BuLi (1.6 M solution in hexane, 0.38 mmol) dropwise at 0 °C. The mixture was stirred for 10 min and cooled to −78 °C. A solution of **11** (94.3 mg, 0.38 mmol) in THF (1.8 mL) was then added, and, after stirring for 30 min, a solution of zinc chloride (51.8 mg, 0.38 mmol) in THF (1.0 mL) was added. The mixture was warmed to 0 °C and stirred for a further 30 min. After the mixture was cooled to −78 °C, a solution of **10** (152.0 mg, 0.24 mmol) in THF (1.7 mL) was added. The mixture was stirred for 30 min at −78 °C and for 30 min at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl solution, and the aqueous layer was extracted with ether. The ethereal extract was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give an aldol adduct (163.8 mg, 93%). To a solution of the aldol adduct (163.8 mg, 0.22 mmol) in dichloromethane (1.0 mL) was added a solution of di-*tert*-butyldicarbonate (72.8 mg, 0.33 mmol) in dichloromethane (1 mL) at room temperature. After stirring for 10 h, the reaction was quenched with water, and the aqueous layer was extracted with dichloromethane. The extract was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 20/1) to give **42a**−**d** (113.5 mg, 61%) as a colorless oil. Diastereomers **42a**−**d** could be separated by column chromatography on silica gel (hexane/ethyl acetate = 20/1), and the diastereomer ratio was determined by HPLC analyses. **42a:** ^{1}H NMR δ 0.003 (s, 3H), 0.01 (s, 3H), 0.03 (s, 9H), 0.86−0.88 (m, 21H), 1.23−1.39 (m, 23H), 1.43 (s, 9H), 2.01−2.06 (m, 2H), 3.59−3.66 (m, 2H), 4.02 (d, 1H, J = 8.9 Hz), 4.10 (brs, 1H), 4.16 (dq, 2H, J = 2.3, 7.3 Hz), 4.40 (m, 1H), 4.57 (d, 1H, J = 8.9 Hz), 4.64 (d, 1H, J = 11.6 Hz), 4.70 (d, 1H, J = 11.6 Hz), 5.46 (d, 1H, J = 8.6 Hz), 5.55−5.74 (m, 2H), 7.28−7.36 (m, 5H); ^{13}C NMR δ −5.3, −4.7, −4.4, 14.1, 14.3, 18.0, 18.2, 22.6, 25.3, 25.7, 25.9, 28.3, 29.2, 29.3, 29.5, 29.7, 31.9, 32.3, 37.2, 53.4, 55.7, 61.2, 72.3, 72.9, 73.3, 73.7, 78.9, 79.7, 127.0, 127.8, 128.4, 133.6, 138.1, 155.8, 170.4; FABHRMS calcd for $C_{46}H_{85}NO_8Si_2$ (M + Na) 858.5712, found 858.5706. **42b:** ^{1}H NMR δ −0.02 (s, 6H), 0.03 (s, 6H), 0.86−0.88 (m, 21H), 1.11−1.43 (m, 23H), 1.50 (s, 9H), 2.06−2.08 (m, 2H), 3.35 (dd, 1H, J = 4.0, 9.6 Hz), 3.55−3.69 (m, 1H), 4.12−4.30 (m, 4H), 4.33 (m, 1H), 4.56−4.69 (m, 2H), 5.43 (d, 1H, J = 10.2 Hz), 5.52−5.73 (m, 2H), 7.33−7.36 (m, 5H); ^{13}C NMR δ −5.4, −4.8, −4.4, 14.1, 14.2, 18.0, 18.1, 22.6, 25.3, 25.7, 25.9, 28.4, 29.2, 29.5, 29.7, 31.9, 32.3, 37.2, 53.4, 54.6, 61.3, 72.3, 72.7, 73.5, 73.6, 77.2, 79.6, 126.4, 128.1, 128.5, 128.7, 134.0, 137.8, 156.1, 171.7; FABHRMS calcd for $C_{46}H_{85}NO_8Si_2$ (M + Na) 858.5712, found 858.5713. **42c:** ^{1}H NMR δ 0.01 (s, 3H), 0.02 (s, 3H), 0.03 (s, 6H), 0.88−0.95 (m, 21H), 1.21−1.42 (m, 32H), 1.99−2.04 (m, 2H), 2.66 (d, 1H, J = 8.9 Hz), 3.43 (d, 1H, J = 5.0 Hz), 3.61 (t, 1H, J = 5.5), 3.96 (t, 1H, J = 7.3 Hz), 4.11 (q, 2H, J = 7.0 Hz), 4.27−4.41 (m, 2H), 4.63 (d, 1H, J = 10.7 Hz), 4.89 (d, 1H, J = 10.7 Hz), 5.31 (d, 1H, J = 8.9 Hz), 5.50 (dd, 1H, J = 6.9, 15.5 Hz), 5.66 (dt, J = 6.3, 15.5 Hz), 7.29−7.46 (m, 5H); ^{13}C NMR δ −4.8, −4.4, −4.2, 14.1, 18.07, 18.11, 22.6, 25.3, 25.86, 25.91, 28.2, 29.1, 29.2, 29.5, 29.7, 31.9, 32.3, 37.1, 56.8, 61.2, 70.0, 72.3, 73.9, 74.1, 79.8, 80.6, 127.8, 128.2, 128.4, 129.2, 133.9, 138.0, 155.3, 171.4; FABHRMS calcd for $C_{46}H_{85}NO_8Si_2$ (M + Na) 858.5712, found 858.5704. **42d:** ^{1}H NMR δ 0.03 (s, 9H), 0.04 (s, 3H), 0.86−0.88 (m, 21H), 1.20−1.42 (m, 23H), 1.44 (s, 9H), 1.99−2.04 (m, 2H), 2.76 (d, 1H, J = 5.0 Hz), 3.42 (t, 1H, J = 5.0 Hz), 3.60 (t, 1H, J = 5.4 Hz), 4.27 (q, 2H, J = 7.3 Hz), 4.24 (d, 1H, J = 2.6 Hz), 4.29−4.39 (m, 2H), 4.57 (d, 1H, J = 11.1 Hz), 4.80 (d, 1H, J = 11.1 Hz), 5.33 (d, 1H, J = 8.9 Hz), 5.52 (dd, 1H, J = 6.9, 15.5 Hz), 5.67 (dt, 1H, J = 6.3, 15.5 Hz), 7.29−7.35 (m, 5H); ^{13}C NMR δ −4.8, −4.4, −4.1, 14.1, 18.1, 22.6, 25.3, 25.9, 25.9, 28.3, 29.1, 29.3, 29.5, 29.7, 31.9, 32.3, 37.2, 56.4, 61.3, 69.7, 72.4, 73.6, 74.1, 79.7, 81.6, 127.9, 128.4, 129.0, 133.7, 137.9, 155.9, 171.0; FABHRMS calcd for $C_{46}H_{85}NO_8Si_2$ (M + Na) 858.5712, found 858.5728. HPLC (Shodex SIL-5B, hexane/ethyl acetate = 10/1, flow rate = 1.0 mL/min): t_R = 11.7 min (2*R*,3*S*,4*S*,5*S*,14*R*), t_R = 14.4 min (2*S*,3*S*,4*S*,5*S*,14*R*), t_R = 21.6 min (2*S*,3*R*,4*S*,5*S*,14*R*), t_R = 28.0 min (2*R*,3*R*,4*S*,5*S*,14*R*).

(2*S*,3*R*,4*R*,5*S*,14*R*)-4-Benzyloxy-2-(*tert*-butoxycarbonylamino)-3,5,14-trihydroxyeicos-6-enoic acid (43c): To a solution of **42c** (60.9 mg, 0.073 mmol) in THF (3.0 mL) and water (1.0 mL) was added lithium hydroxide (12.2 mg, 0.29 mmol) at 0 °C. The mixture was stirred for 10 h and was neutralized with a resin (IRC-76). The resin was filtered off, and the filtrate was concentrated under reduced pressure to give a colorless oil of a carboxylic acid. To a solution of the carboxylic acid in THF (1.2 mL) was added tetrabutylammonium fluoride 1.0 N solution in THF (0.29 mmol) at room temperature. After stirring for 48 h at 50 °C, the reaction was quenched with phosphate buffer solution (pH = 7). The aqueous layer was extracted with ether, and the ethereal extract was washed with 10% aqueous citric acid solution, saturated aqueous $NaHCO_3$ solution, and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1) to give **43c** (40.4 mg, 96%, two steps) as a colorless oil. **43c:** ^{1}H NMR (CD_3OD) δ 0.90 (t, 3H, J = 6.4 Hz), 1.30−1.42 (m, 29H), 2.01−2.04 (m, 2H), 3.48 (brs, 1H), 3.60 (brs, 1H), 3.95 (dd, 1H, J = 3.3, 7.3 Hz), 4.27 (d, 1H, J = 7.6 Hz), 4.37 (t, 1H, J = 5.3 Hz), 4.69 (d, 1H, J = 10.8 Hz), 4.77 (d, 1H, J = 10.8 Hz), 5.58 (dd, 1H, J = 6.6, 15.2 Hz), 5.75 (dt, 1H, J = 6.3, 15.2 Hz), 7.22−7.46 (m, 5H); FABHRMS calcd for $C_{32}H_{53}NO_8$ (M + Na) 602.3668, found 602.3663. Similarly, **42a**, **42b**, and **42d** were prepared. **43a:** ^{1}H NMR (CD_3OD) δ 0.90 (t, 3H, J = 6.9 Hz), 1.30−1.39 (m, 29H), 1.98 (brs, 2H), 3.48 (brs, 2H), 3.64 (brs, 1H), 4.14 (brs, 1H), 4.34 (brs, 1H), 4.45−4.60 (m, 2H), 5.52−5.75 (m, 2H), 7.27−7.41 (m, 5H); FABHRMS calcd for $C_{32}H_{53}NO_8$ (M + Na) 602.3668, found 602.3680. **43b:** ^{1}H NMR (CD_3OD) δ 0.89 (t, 3H, J = 6.6 Hz), 1.29−1.45 (m, 29H), 2.02−2.07 (m, 2H), 3.38 (brs, 1H), 3.42 (brs, 1H), 3.47 (brs, 1H), 4.32 (d, 1H, J = 9.2 Hz), 4.41 (t, 1H, J = 5.4 Hz), 4.54 (d, 1H, J = 12.2 Hz), 4.58 (d, 1H, J = 10.2 Hz), 5.62 (dt, 1H, J = 5.6, 9.9 Hz), 5.72 (dd, 1H, J = 5.6 Hz), 7.22−7.46 (m, 5H); FABHRMS calcd for $C_{32}H_{53}NO_8$ (M + Na) 602.3668, found 602.3662. **43d:** ^{1}H NMR (CD_3OD) δ 0.89 (t, 3H, J = 6.9 Hz), 1.29−1.43 (m, 29H), 1.99−2.01 (m, 2H), 3.37 (d, 1H, J = 4.3 Hz), 3.48 (brs, 1H), 4.23 (brs, 1H), 4.33−4.48 (m, 2H), 4.63 (d, 1H, J = 10.9 Hz), 4.78 (d, 1H, J = 11.2 Hz), 5.54 (dd, 1H, J = 6.4, 15.3 Hz), 5.69 (dt, 1H, J = 6.3, 15.2 Hz), 7.22−7.46 (m, 5H); FABHRMS calcd for $C_{32}H_{53}NO_8$ (M + Na) 602.3668, found 602.3680.

(2*S*,3*S*,4*R*,5*S*,14*R*)-2-Amino-4-benzyloxy-3,5,14-trihydroxyeicos-6-enoic acid (44c): To a solution of **43c** (23.0 mg, 0.040 mmol) in dichloromethane (1.5 mL) was added trifluoroacetic acid (1.5 mL) at 0 °C. After stirring for 45 min, the solution was concentrated under reduced pressure, and the residue was diluted with THF (2.0 mL) and water (1.0 mL). NaOH aqueous (1 N, 0.2 mL) was added, and the mixture was stirred for 30 min at 0 °C and neutralized with a resin (IRC-76). The resin was filtered off, and the filtrate was diluted with ether (5.0 mL) and washed with water and brine. The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol = 6/1) to give **44c** (20.0 g, 100%) as a white solid.

(2*S*,3*R*,4*R*,5*S*,14*R*)-2-Amino-3,4,5,14-tetrahydroxyeicos-6-enoic acid (sphingofungin B) (4): To a dark blue solution of sodium-ammonia prepared from excess sodium and liquid ammonia (10 mL) was added a solution of **44c** (20.0 mg, 0.040 mmol) in THF (1.5 mL) at −78 °C. The solution was warmed to −50 °C and was stirred for 1 h. The reaction was quenched with ammonium chloride (254.5 mg, 4.8 mmol). The cooling bath was removed, and after all ammonia was evaporated, the mixture was diluted with water, and the aqueous layer extracted with *n*-butanol. The extract was washed with water and was concentrated under reduced pressure. The residue was purified by Sephadex (LH-20, H_2O to H_2O/methanol = 1/2) and reverse phase column chromatography (Wakogel, LP-60-C18, H_2O to H_2O/methanol = 1/2) to give **4** (8.2 mg, 53%) as a white solid. **4:** ^{1}H NMR (CD_3OD) δ 0.89 (t, 3H, J = 6.4 Hz), 1.18−1.60 (m, 20H), 1.98−2.06 (m, 2H), 3.49 (brs, 1H), 3.60 (d, 1H, J = 6.9 Hz), 3.77 (d, 1H, J = 3.6 Hz), 4.06−4.10 (m, 2H), 5.47 (dd, 1H, J = 7.3, 15.2 Hz), 5.77 (dt, 1H, J = 6.6, 15.2 Hz); ^{13}C NMR δ 14.4, 23.7, 26.79, 26.82, 30.2, 30.4, 30.6,

30.7, 33.1, 33.5, 38.5, 60.8, 69.4, 72.5, 75.2, 76.0, 130.2, 135.5, 172.4; FABHRMS calcd for $C_{20}H_{39}NO_6$ (M + H) 390.2856, found 390.2859. Similary, other stereoisomers, **4a**, **4b**, and **4d**, ware prepared. **4a:** ^{13}C NMR (CD_3OD) δ 14.4, 23.7, 26.8, 30.3, 30.47, 30.56, 30.64, 30.8, 33.1, 38.5, 57.3, 72.5; FABHRMS calcd for $C_{20}H_{39}NO_6$ (M + H) 390.2856, found 390.2868. **4b:** ^{1}H NMR (CD_3OD) δ 0.89 (t, 3H, J = 6.9 Hz), 1.28−1.58 (m,20H), 2.06−2.08 (m, 2H),3.50 (m,2H), 3.92 (brs, 1H), 4.20−4.28 (m,2H), 5.62 (dd, 1H, J = 6.6, 15.5 Hz), 5.77 (dt, 1H, J = 6.3, 15.5 Hz); ^{13}C NMR δ 14.4, 23.7, 26.8, 30.3, 30.6, 30.7, 33.1, 33.5, 38.5, 57.3, 70.3, 72.5, 73.2, 77.1, 131.2, 134.2, 173.3; FABHRMS calcd for $C_{20}H_{39}NO_6$ (M + H) 390.2856, found 390.2844. **4d:** ^{13}C NMR (CD_3OD) δ 14.4, 23.7, 26.8, 30.2, 30.4, 30.6, 30.7, 33.1, 33.5, 38.4, 61.5, 70.0, 72.4, 74.2, 77.6, 130.2, 135.5, 173.0; FABHRMS calcd for $C_{20}H_{39}NO_6$ (M + H) 390.2856, found 390.2865. Stereoisomer **4e** was prepared using ***ent*-12**. Stereoisomer **4f** and 4 g were synthesized using ***ent*-13**. **4e:** ^{1}H NMR (CD_3OD) δ 0.89 (t, 3H, J = 6.4 Hz), 1.18−1.60 (m, 20H), 1.98−2.06 (m, 2H), 3.49 (brs, 1H), 3.60 (d, 1H, J = 6.9 Hz), 3.77 (d, 1H, J = 3.6 Hz), 4.06−4.10 (m, 2H), 5.47 (dd, 1H, J = 7.3, 15.2 Hz), 5.77 (dt, 1H, J = 6.6, 15.2 Hz); ^{13}C NMR δ 14.4, 23.7, 26.79, 26.82, 30.2, 30.4, 30.6, 30.7, 33.1, 33.5, 38.5, 60.8, 69.4, 72.5, 75.2, 76.0, 130.2, 135.5, 172.4; FABHRMS calcd for $C_{20}H_{39}NO_6$ (M + H) 390.2856, found 390.2846. **(2*R*,3*S*,4*S*,5*R*,14*RS*)-2-Amino-3,4,5,14-tetrahydroxyeicos-6-enoic acid (4f):** ^{1}H NMR (CD_3OD) δ 0.89 (t, 3H, J = 6.4 Hz), 1.18−1.60 (m, 20H), 1.98−2.06 (m, 2H), 3.49 (brs, 1H), 3.60 (d, 1H, J = 6.9 Hz), 3.77 (d, 1H, J = 3.6 Hz), 4.06−4.10 (m, 2H), 5.47 (dd, 1H, J = 7.3, 15.2 Hz), 5.77 (dt, 1H, J = 6.6, 15.2 Hz); ^{13}C NMR δ 14.4, 23.7, 26.79, 26.82, 30.2, 30.4, 30.6, 30.7, 33.1, 33.5, 38.5, 60.8, 69.4, 72.5, 75.2, 76.0, 130.2, 135.5, 172.4; FABHRMS calcd for $C_{20}H_{39}NO_6$ (M + H) 390.2856, found 390.2845. **(2*S*,3*R*,4*S*,5*R*,14*RS*)-2-Amino-3,4,5,14-tetrahydroxyeicos-6-enoic acid (4 g):** ^{13}C NMR (CD_3OD) δ 14.4, 23.7, 26.8, 30.3, 30.47, 30.56, 30.64, 30.8, 33.1, 38.5, 57.3, 72.5; FABHRMS calcd for $C_{20}H_{39}NO_6$ (M + H) 390.2856, found 390.2871.

(3*RS*)-*S*-Ethyl 3-hydroxynonanethioate (14): To a solution of ytterbium(III) trifluoromethanesulfonate (129.9 mg, 0.21 mmol) in dichloromethane (30 mL) was added a solution of **16** (2.33 g, 20.4 mmol) in dichloromethane (20 mL) and **17** (4.85 g, 27.5 mmol) in dichloromethane (20 mL) at 0 °C. After stirring for 1 h at 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with dichloromethane. The extract was dried over sodium sulfate and concentrated under reduced pressure. The residue was treated with THF: 1 N HCl = 4:1 solution for 30 min. After hexane was added, the organic layer was separated, and the aqueous layer was extracted with ether. The ethereal extract was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 20/1) to give **14** (4.05 g, 91%) as a colorless oil. ^{1}H NMR δ 0.88 (t, 3H, J = 6.6 Hz), 1.24−1.56 (m, 13H), 2.61−2.81 (m, 3H), 2.91 (q, 2H, J = 7.5 Hz), 4.01−4.08 (m, 1H); ^{13}C NMR δ 14.0, 14.6, 22.5, 23.3, 25.3, 29.1, 31.7, 36.5, 50.6, 68.6, 199.6; IR (neat) 1683.6, 2927.4, 3378.7, 3475.1 cm^{-1}.

(7*RS*)-1-Bromo-7-tridecanol (53): To a solution of **12** (2.24 g, 6.94 mmol) in methanol (21 mL) was added concentrated HCl (0.7 mL), and the solution was stirred for 3 h at 50 °C. The mixture was cooled to room temperature, diluted with water (60 mL), and neutralized with potassium carbonate at 0 °C. The aqueous layer was extracted with ether. The ethereal extract was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1) to give **53** (1.72 g, quant.) as a colorless oil. ^{1}H NMR δ 0.89 (t, 3H, J = 6.9 Hz), 1.29−1.60 (m, 21H), 1.68−2.00 (m, 2H), 3.41 (t, 2H, J = 6.9 Hz), 3.59 (br, 1H); ^{13}C NMR d 14.1, 22.6, 25.4, 25.6, 28.1, 28.8, 29.3, 31.8, 32.7, 34.0, 37.3, 37.5, 71.9; HRMS calcd for $C_{13}H_{27}BrO$ (M^+) 278.1245, found 278.1229.

(7*RS*)-1-Bromo-7-trimethylsiloxytridecane (54): To a solution of **53** (1.94 g, 6.16 mmol) in dichloromethane (21 mL) was added a solution of triethylamine (1.34 g, 12.4 mmol) in dichloromethane (7.0 mL) and trimethylsilyl chloride (1.25 g, 12.3 mmol) in dichloromethane (7.0 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 15 min. The reaction was then quenched with water, and the aqueous layer was extracted with dichloromethane. The extract was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 50/1) to give **54** (2.08 g, 97%) as a colorless oil. IR (neat) 1252.0, 2859.0, 2932.0 cm^{-1}; ^{1}H NMR δ 0.00 (s, 9H), 0.78 (t, 3H, J = 6.4 Hz), 1.17−1.51 (m, 18H), 1.70−1.80 (m, 2H), 3.30 (t, 2H, J = 6.8 Hz), 3.36−3.58 (m, 1H); ^{13}C NMR δ 0.8, 14.4, 22.9, 25.8, 26.0, 28.5, 29.2, 30.0, 32.2, 33.1, 34.3, 37.6, 37.8, 72.9; HRMS calcd for $C_{16}H_{35}BrOSi$ (M^+) 350.1641, found 350.1662.

(16*S*,17*S*)-17-Benzyloxy-16,18-dihydroxyoctadec-14-yn-7-one ethylene acetal (59): To a solution of trimethylsilyl trifluoromethanesulfonate (17.2 mg, 0.08 mmol) in dichloromethane (3.0 mL) was added a solution of 1,2-bis(trimethylsilyloxy)ethane (479.1 mg, 2.3 mmol) in dichloromethane (2.3 mL) and **58** (622.9 mg, 1.55 mmol) in dichloromethane (5.0 mL) at 0 °C. After the mixture was stirred for 1 h, the reaction was quenched with pyridine (0.2 mL) and saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ether. The ethereal extract was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 9/1) to give **59** (649.8 mg, 94%) as a colorless oil. ^{1}H NMR δ 0.88 (t, 3H, J = 6.3 Hz), 1.28−1.59 (m, 20H), 2.04 (br, 1H), 2.22(dt, 2H, J = 1.7, 7.0 Hz), 2.69 (br, 1H), 3.58 (dd, 1H, J = 4.7, 10.3 Hz), 3.79 (ddd, 2H, J = 4.6, 11.6, 27.8 Hz), 3.91 (s, 4H), 4.49 (d, 1H, J = 5.6 Hz), 4.76 (dd, 2H, J = 11.5, 20.1 Hz), 7.26−7.37 (m, 5H); ^{13}C NMR δ 14.0, 18.7, 22.6, 23.6, 23.8, 28.3, 28.8, 29.3, 29.5, 31.8, 37.0, 37.1, 61.7, 63.1, 64.8, 73.4, 78.1, 82.1, 87.4, 111.8, 127.9, 128.0, 128.5, 137.8; FABHRMS calcd for $C_{27}H_{42}O_5$ (M + Na) 469.2930, found 469.2933.

(1′*S*,4′*S*,16*S*,17*S*,18*R*)-17-Benzyloxy-16-(*tert*-butyldimethylsiloxy)-18-(3′,6′-diethoxy-1′,4′-dimethyl-4′H-2,5-diazyl)-18-hydroxyoctadec-14-ene-7-one (63): To a solution of **47** (81.4 mg, 0.41 mmol) in THF (1.5 mL) was added *n*-BuLi (1.6 M solution in hexane, 0.41 mmol) dropwise at −78 °C. The mixture was warmed to 0 °C and stirred for 15 min, and a solution of tin(II) chloride (77.9 mg, 0.41 mmol) in THF (1.5 mL) was added. The mixture was stirred for a further 15 min, and after the solution was cooled to −78 °C, a solution of **62** (106.1 mg, 0.21 mmol) in THF (1.5 mL) was added. The mixture was stirred for 3 h at −78 °C and quenched with phosphate buffer solution (pH = 7). The aqueous layer was extracted with ether. The ethereal extract was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 20/1) to give **63** (98.4 mg, 83%). Diastereomers of **63** could be separated by the column chromatography (silica gel, hexane/ethyl acetate = 20/1). ^{1}H NMR δ 0.00 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 0.91−0.98 (m, 7H), 1.33−1.38 (m, 28H), 1.42 (s, 3H), 1.59−1.64 (br, 3H), 2.07−2.38 (br, 2H), 2.44 (t, 4H, J = 7.5 Hz), 3.17 (d, 1H, J = 8.3 Hz), 3.44 (d, 1H, J = 11.5 Hz), 3.52 (dd, 1H, J = 6.9, 10.6 Hz), 3.87−4.34 (m, 5H), 3.93 (t, 1H, J = 8.1 Hz), 4.96 (d, 1H, J = 11.9 Hz), 5.45 (dd, 1H, J = 8.1, 15.4 Hz), 5.72 (dt, 1H, J = 6.8, 16.5 Hz), 7.24−7.31 (m, 5H); ^{13}C NMR δ −4.5, −4.2, 13.7, 14.0, 14.2, 18.1, 21.8, 22.4, 23.8, 25.9, 28.9, 29.0, 29.1, 31.6, 42.7, 52.2, 60.6, 60.8, 72.7, 73.7, 76.4, 77.1, 82.1, 126.1, 126.6, 127.8, 130.8, 133.7, 139.1, 162.3, 164.5, 211.5; IR (neat) 1687.0, 2856.0, 2929.0 cm^{-1}; FABHRMS calcd for $C_{41}H_{64}N_2O_6$-Si (M + Na) 731.4431, found 731.4420.

(1′*S*,4′*R*,16*S*,17*S*,18*R*)-17-Benzyloxy-18-(3′,6′-diethoxy-1′,4′-dimethyl-4′H-2′,5′-diazyl)-16,18-dihydroxyoctadec-14-ene-7-one (64): To a solution of **63** (68.4 mg, 0.096 mmol) in THF (3.0 mL) was added a solution of tetrabutylammonium fluoride (1 N solution in THF, 0.4 mmol) at room temperature. After stirring for 4 h, the reaction was quenched with phosphate buffer solution (pH = 7). The aqueous layer was extracted with ether, and the ethereal extract was washed with 10% aqueous citric acid solution, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1) to give **64** (54.0 mg, 94%) as a white solid. ^{1}H NMR δ 0.81 (t, 3H, J = 6.6 Hz), 0.99 (t, 3H, J = 7.1 Hz), 1.20−1.49 (m, 22H), 1.94−2.07 (br, 2H), 2.30 (t, 4H, J = 7.5 Hz), 2.72 (br, 1H), 3.13 (d, 1H, J = 6.6 Hz), 3.47 (d, 1H, J = 11.6 Hz), 3.63 (dd, 1H, J = 7.1, 10.7 Hz), 3.69−4.15 (m, 5H), 4.20 (t, 1H, J = 6.9 Hz), 4.48 (d, 1H, J = 11.2 Hz), 5.38 (dd, 1H, J = 7.4, 15.3 Hz), 5.74 (dt, 1H, J = 6.8, 15.2 Hz), 7.17−7.30 (m,

5H); ^{13}C NMR δ 13.9, 14.0, 14.2, 21.7, 22.4, 23.8, 27.2, 28.8, 28.9, 29.0, 29.1, 31.6, 32.4, 42.7, 42.8, 52.4, 60.4, 60.9, 61.0, 74.0, 74.6, 75.0, 82.0, 127.1, 127.5, 128.3, 129.0, 134.6, 138.1, 163.2, 164.5, 211.6; IR (neat) 1689.0, 2855.0, 2929.0, 3361.0 cm^{-1}; FABHRMS calcd for $C_{35}H_{56}N_2O_6$ (M + Na) 623.4036, found 623.4033.

(2*S*,3*S*,4*R*,5*S*)-2-Amino-4-benzyloxy-2-methyl-3,5-dihydroxy-14-oxoeicos-6-enoic acid (65): To a solution of **64** (54.0 mg, 0.09 mmol) in THF (4.0 mL) was added *p*-toluensulfonic acid (171.2 mg, 0.9 mmol) at room temperature. After stirring for 1 h, the mixture was neutralized with a resin (IRA-93ZU). The resin was filtered off, and the filtrate was concentrated under reduced pressure to give a mixture of an ester and a lactone. To a solution ester and lactone in methanol (4.0 mL) was added 1 N NaOH aqueous (4.0 mL) at room temperature. After stirring for 30 min, the solution was neutralized with a resin (IRC-76). The resin was filtered off, and the filtrate was extracted with ether. The ethereal extract was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol = 10/1) to give **65** (25.6 mg, 58%, two steps) as a white solid. $[\alpha]_D^{26}$ +8.2 (c = 0.23, C_6H_6); ^{1}H NMR (CD_3OD) δ 0.88 (t, 3H, J = 3.5 Hz), 1.12−1.56 (m, 19H), 2.03−2.15 (br, 2H), 2.43 (t, 4H, J = 7.2 Hz), 3.77 (dd, 1H, J = 1.8, 7.1 Hz), 3.95 (d, 1H, J = 1.7 Hz), 4.43 (t, 1H, J = 6.9 Hz), 4.55 (d, 1H, J = 10.2 Hz), 5.08 (d, 1H, J = 9.9 Hz), 5.58 (dd, 1H, J = 7.3, 15.5 Hz), 5.76 (dt, 1H, J = 6.4, 14.1 Hz), 7.23−7.52 (m, 5H); ^{13}C NMR (CD_3OD) δ 14.4, 22.0, 23.6, 24.9, 30.0, 30.2, 32.8, 33.4, 43.5, 66.2, 73.0, 76.0, 76.5, 85.5, 129.1, 129.6, 130.0, 130.8, 134.7, 139.5, 214.4; FABHRMS calcd for $C_{28}H_{45}NO_6$ (M + Na) 514.3144, found 514.3159.

(2S,3R,4R,5S)-2-Amino-2-methyl-3,4,5-trihydroxy-14-oxoeicos-6-enoic acid (sphingofungin F) (8): To a solution of **65** (7.3 mg, 0.015 mmol) in dichloromethane (1.0 mL) was added trichloroborane 1 N solution in hexane (0.045 mmol) dropwise at −78 °C. After stirring for 10 min, the reaction was quenched with methanol (1.0 mL). The solution was warmed to room temperature and diluted with water. The aqueous layer was extracted with *tert*-butyl alcohol. The extract was washed with water and was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol = 10/1) to give **8** (4.3 mg, 72%) as a white solid. $[\alpha]_D^{26}$ +0.8 (c = 0.33, MeOH); ^{1}H NMR (CD_3OD) δ 0.89 (t, 3H, J = 6.6 Hz), 1.28−1.55 (m, 19H), 2.05 (br, 2H), 2.44 (t, 4H, J = 7.4 Hz), 3.69 (d, 1H, J = 7.3 Hz), 3.86 (br, 1H), 4.10 (t, 1H, J = 7.3 Hz), 5.47 (dd, 1H, J = 7.8, 15.6 Hz), 5.78 (dt, 1H, J = 6.7, 15.6 Hz); ^{13}C NMR (CD_3OD) δ 14.4, 21.8, 23.6, 24.9, 30.0, 30.2, 32.8, 33.5, 43.5, 67.7, 72.4, 75.7, 76.2, 130.2, 135.7, 214.4; FABHRMS calcd for $C_{21}H_{39}NO_6$ (M + H) 402.2856, found 402.2861.

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Supporting Information Available: Experimental procedures for the synthesis of compounds **22**, **23**, **24**, **25**, **26**, **27a**−**d**, **28**, **29**, **30**, **31c**, **42c** (from **46c**), **46b**−**d**, **48**, **49**, **50**, **51**, **52**, **55**, **56**, **57**, **58**, **60**, **61**, and **62** including spectral data (17 pages). See any current masthead page for ordering and Internet access instructions.

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