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Stereoselective Total Synthesis of (+)-Scyphostatin via a π-Facially Selective Diels−Alder Reaction

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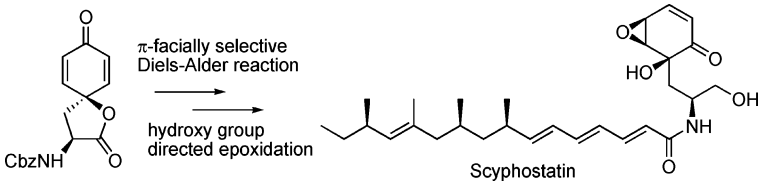

A stereoselective total synthesis of scyphostatin is described. The hydrophilic moiety was stereoselectively synthesized via (i) a highly π-facially selective Diels−Alder reaction of a spirolactone generated from L-tyrosine and (ii) a hydroxy group directed epoxidation as key reactions. The hydrophilic moiety was combined with the hydrophobic side chain in the final stage. Total synthesis was achieved by overcoming the instability of the C5−C6 epoxide ring with carefully executed mild reactions. In the course of this work, it was revealed that we had mistakenly assigned the relative stereochemistry of the C5−C6 epoxide ring of the end product in our previous model study. Revision of the stereochemical assignment in the model study is described. A diastereomer of (+)-scyphostatin epimeric at C5 and C6 (the epoxide region) was also synthesized.

Introduction

Scyphostatin **1**, which was isolated from the mycelial extract of *Dasyscyphus mollissima* by Ogita et al. (Sankyo Co., Ltd., Japan) in 1997, was the first discovered potent small molecule inhibitor of neutral sphingomyelinase (N-SMase) (Scheme 1).[1] Scyphostatin **1** consists of a hydrophobic side chain **2** and a hydrophilic 4,5-epoxy-2-cyclohexen-1-one **3**. Our interest in such amphiphilic natural products has inspired us to carry out synthetic studies on scyphostatin **1**.[2,3] Other groups have also reported synthetic efforts,[4] and various analogues[5] of scyphostatin **1** have been synthesized. Thus far, the total synthesis of scyphostatin **1** has been reported only by Katoh et al.[6] The difficulty lies in the extremely labile nature of the compound, especially in a condensed state, and its highly functionalized

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(2) (a) Takagi, R.; Sasaoka, A.; Kojima, S.; Ohkata, K. *Chem. Commun.* **1997**, 1887. (b) Takagi, R.; Sasaoka, A.; Nishitani, H.; Kojima, S.; Hiraga, Y.; Ohkata, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 925. (c) Nishitani, H.; Sasaoka, A.; Tokumasu, M.; Ohkata, K. *Heterocycles* **1999**, *50*, 35. (d) Tokumasu, M.; Ando, H.; Hiraga, Y.; Kojima, S.; Ohkata, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 489. (e) Hiraga, Y.; Ago, M.; Tokumasu, M.; Kaku, K.; Ohkata, K. *Aust. J. Chem.* **2000**, *53*, 909. (f) Ohmori, N. *Chem. Commun.* **2001**, 1552. (g) Ohmori, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 755.

(3) Our synthetic studies on the hydrophilic moiety of scyphostatin **1**: (a) Takagi, R.; Miyanaga, W.; Tamura, Y.; Ohkata, K. *Chem. Commun.* **2002**, 2096. (b) Miyanaga, W.; Takagi, R.; Ohkata, K. *Heterocycles* **2004**, *64*, 129. (c) Takagi, R.; Tojo, K.; Iwata, M.; Ohkata, K. *Org. Biomol. Chem.* **2005**, *3*, 2031. Our synthetic study on the hydrophobic moiety of scyphostatin **1**: (d) Takagi, R.; Tsuyumine, S.; Nishitani, H.; Miyanaga, W.; Ohkata, K. *Aust. J. Chem.* **2004**, *57*, 439.

(4) Synthetic studies on the hydrophilic moiety of scyphostatin **1**: (a) Gurjar, M. K.; Hotha, S. *Heterocycles* **2000**, *53*, 1885. (b) Katoh, T.; Izuhara, T. *Tetrahedron Lett.* **2000**, *41*, 7651. (c) Izuhara, T.; Katoh, T. *Org. Lett.* **2001**, *3*, 1653. (d) Runcie, K. A.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 3237. (e) Fujioka, H.; Kotoku, N.; Sawama, Y.; Nagatomi, Y.; Kita, Y. *Tetrahedron Lett.* **2002**, *43*, 4825. (f) Izuhara, T.; Yokota, W.; Inoue, M.; Katoh, T. *Heterocycles* **2002**, *56*, 553. (g) Murray, L. M.; O'Brien, P.; Taylor, R. J. K. *Org. Lett.* **2003**, *5*, 1943. (h) Pitsinos, E. N.; Cruz, A. *Org. Lett.* **2005**, *7*, 2245. (i) Katoh, T.; Izuhara, T.; Yokota, W.; Inoue, M.; Watanabe, K.; Nobeyama, A.; Suzuki, T. *Tetrahedron* **2006**, *62*, 1590. (j) Stevenson, N. G.; Savi, C. D.; Harrity, J. P. A. *Synlett* **2006**, 2272. (k) Pitsinos, E. N.; Moutsos, V. I.; Vageli, O. *Tetrahedron Lett.* **2007**, *48*, 1523. Synthetic studies on the hydrophobic moiety of scyphostatin **1**: (l) Hoye, T. R.; Tennakoon, M. A. *Org. Lett.* **2000**, *2*, 1481. (m) Tan, Z.; Negishi, E.-i. *Angew. Chem., Int. Ed.* **2004**, *43*, 2911. (n) McAllister, G. D.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 2551.

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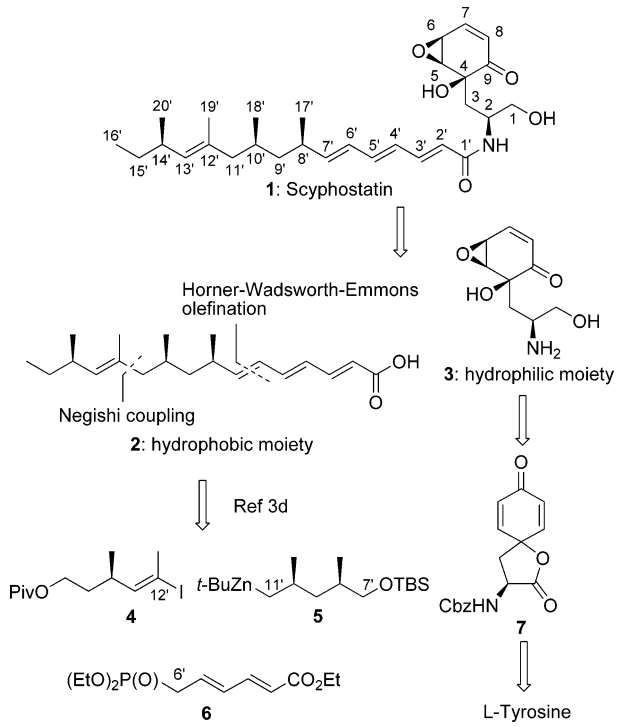
SCHEME 1. Synthetic Plane of Scyphostatin

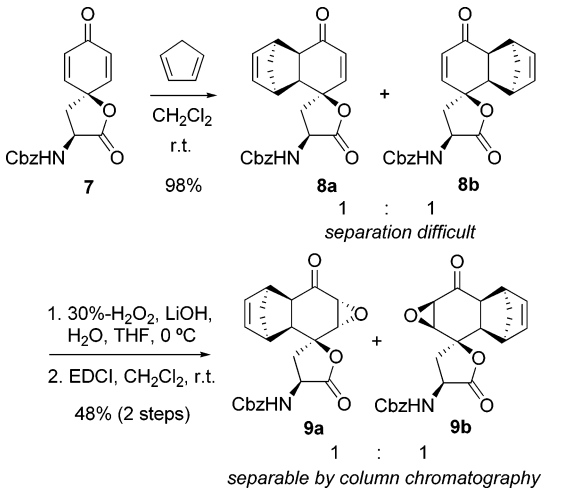


profile.[1b] Our synthetic plan for scyphostatin **1** was to synthesize the hydrophobic carboxylic acid **2** and the hydrophilic cyclohexenone **3** moieties separately and to combine them in a late stage of the total synthesis. The stereoselective synthesis of the hydrophobic carboxylic acid **2** was achieved by the attachment of the three components of vinyl iodide **4**, organozinc compound **5**, and phosphonate **6**.[3d] In this paper, the stereoselective total synthesis of scyphostatin **1** and revision of the stereochemical assignment in our previous model study are described.

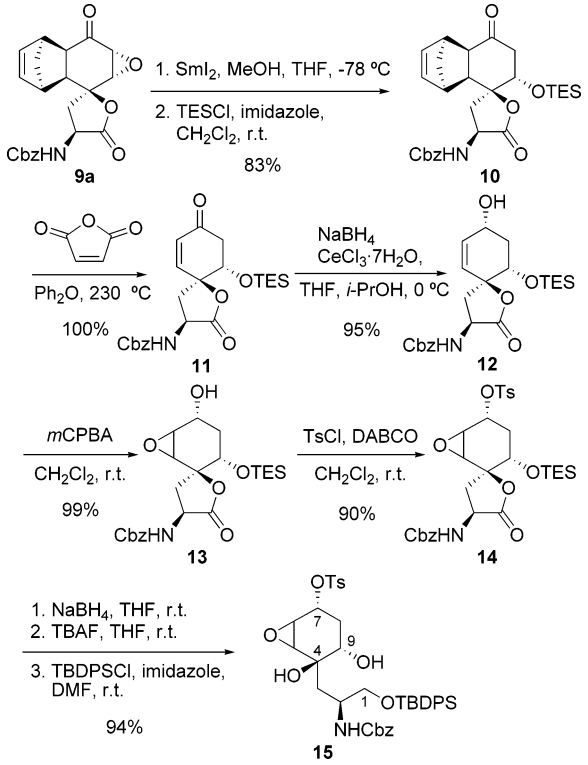
Results and Discussion

L-Tyrosine was selected as the starting material because of the presence of the 6-membered ring and the requisite stereocenter in the appropriate position, and the synthetic route depicted in Scheme 1 was envisioned. On the basis of our model studies,[3a−c] we decided to proceed with the key spirolactone **7**,[7] readily prepared from L-tyrosine. The Diels−Alder reaction of spirolactone **7** with cyclopentadiene proceeded with high π-facial selectivity to give a mixture of *endo* adducts **8a** and **8b** (**8a**:**8b** = 1:1, 98%), resulting from reaction to the face bearing the spiro ring oxygen atom (Scheme 2).[8] Treatment of the mixture of **8a** and **8b** with LiOH/H_2O_2, followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) gave a mixture of only two of the possible epoxides, which were found to be readily separable.[9] Since it was easier to separate **9**, **8** was used routinely as a diastereomeric mixture. Interestingly, the products turned out to result from opposite facial selectivity, i.e., *exo*-epoxide **9a** and *endo*-epoxide **9b** (48%, two steps). The absolute stereochemistry of **8a**,**b** and **9a**,**b** was determined by ^{1}H NMR dif-NOE experiments (Figure 1).

SCHEME 2 π-Facially Selective Diels−Alder Reaction of 7



SCHEME 3. Synthesis of 15 from 9a



Since *exo*-epoxide **9a** met our strategic needs, the synthesis was carried on from this compound (Scheme 3). The reductive cleavage of the epoxide ring with SmI_2,[10] followed by protection

(5) (a) Arenz, C.; Giannis, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1440. (b) Arenz, C.; Gartner, M.; Waschol owski, V.; Giannis, A. *Bioorg. Med. Chem.* **2001**, *9*, 2901. (c) Pitsinos, E. N.; Waschol owski, V.; Karaliota, S.; Rigou, C.; Couladouros, E. A.; Giannis, A. *Chem. Biol. Chem.* **2003**, *4*, 1223. (d) Kenworthy, M. N.; McAllister, G. D.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 6661. (e) Claus, R. A.; Wüstholz, A.; Müller, S.; Bockmeyer, C. L.; Riedel, N. H.; Kinscherf, R.; Deigner, H.-P. *Chem. Biol. Chem.* **2005**, *6*, 726.

(6) Inoue, M.; Yokota, W.; Murugesh, M. G.; Izuhara, T.; Katoh, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 4207.

(7) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477.

(8) (a) Takagi, R.; Miyanaga, W.; Tamura, Y.; Kojima, S.; Ohkata, K. *Heterocycles* **2003**, *60*, 785. (b) Ohkata, K.; Tamura, Y.; Brandon, B. S.; Takagi, R.; Miyanaga, W.; Kojima, S.; Paquette, L. A. *J. Am. Chem. Soc.* **2004**, *126*, 16783.

(9) Both **8a** and **9a** were obtained as colorless oils. In contrast, both **8b** and **9b** were obtained as white crystals. So, both **8b** and **9b** could easily be obtained as single isomers by recrystallization of the diastereomer mixtures. The undesired isomer **8b** in this strategy can easily be recycled by converting it back to **7** by the retro-Diels−Alder reaction.

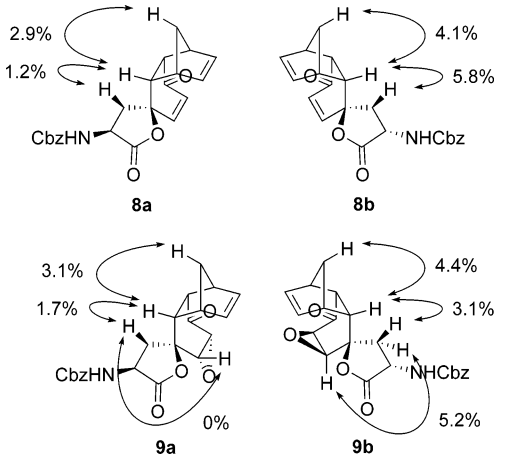


FIGURE 1. Absolute stereochemistry of the cycloaddition products **8** and **9**.

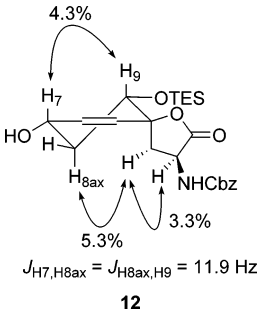


FIGURE 2. Absolute stereochemistry of **12**.

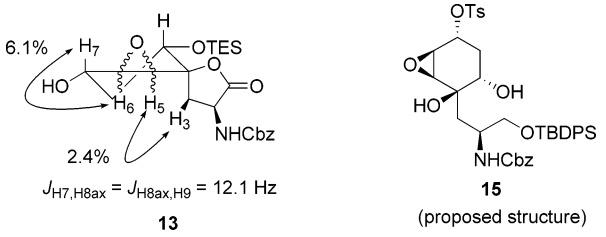
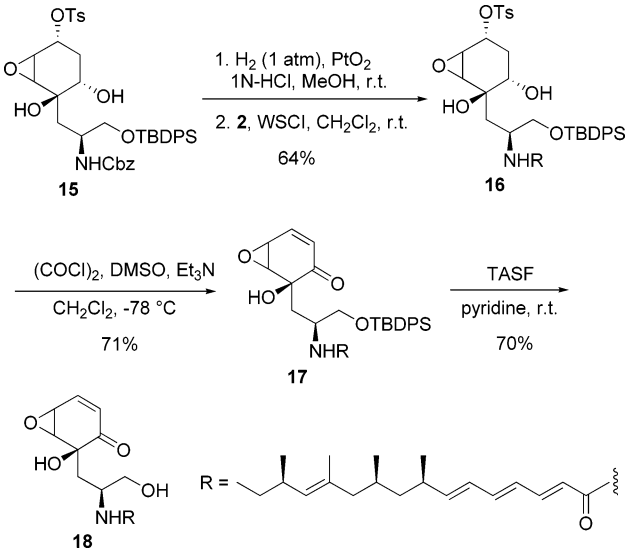


FIGURE 3. NOE experiments on **13** and the proposed structure of **15**.

of secondary hydroxyl group with triethylsilyl (TES) group afforded **10** (83%, two steps). The retro-Diels−Alder product **11** was obtained by heating (230 °C) **10** in the presence of maleic anhydride (100%). Reduction of **11** with $NaBH_4/CeCl_3$ gave **12** as a single isomer (95%). ^{1}H NMR dif-NOE experiments indicated that alcohol **12** was a product of axial attack of the hydride (Figure 2). The epoxidation of alcohol **12** with *m*CPBA gave epoxide **13** as a single isomer (99%). Tosylate **14** was obtained by tosylation of epoxide **13** (90%). The lactone ring of **14** was easily reduced with $NaBH_4$,[11] and the following removal of the TES group (C9) with tetrabutylammonium fluoride (TBAF) and reprotection of the C1-hydroxy group with a *tert*-butyldiphenylsilyl (TBDPS) group gave **15** (94%). The TBDPS protection of the C1-hydroxy group was necessary for the ensuing hydrogenolysis of the benzyloxycarbonyl (Cbz) group. The stereochemistry of the C5−C6 epoxide ring of **15**

(10) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596.
(11) Wipf, P.; Kim, Y. *J. Org. Chem.* **1993**, *58*, 1649.

SCHEME 4. Synthesis of 18 from 15



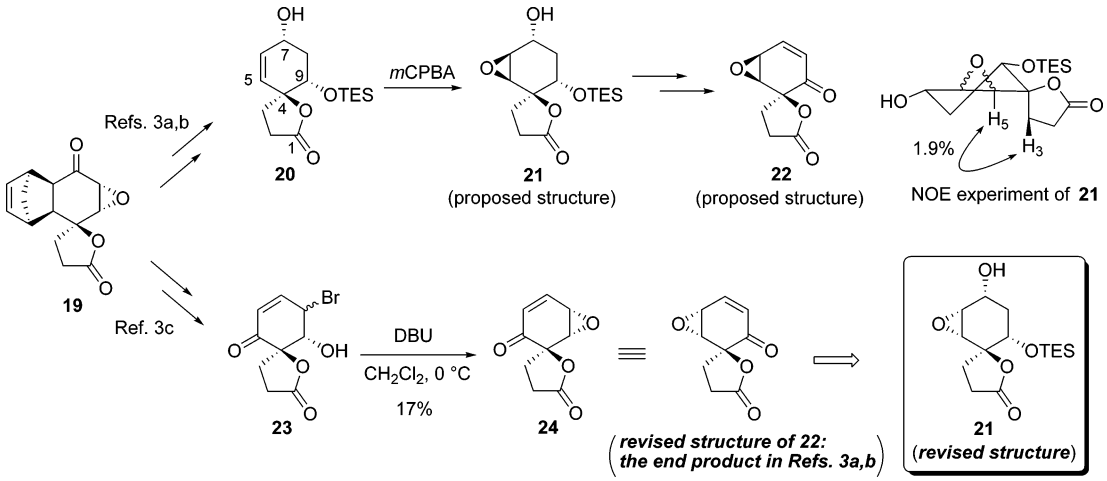
was tentatively assigned to be the same as that in the natural product on the basis of ^{1}H NMR dif-NOE experiments carried out for the assignment of **13**, in which NOE enhancement between H3 and H5 (2.4%) was observed (Figure 3).

The attempt to complete the total synthesis is described in Scheme 4. The removal of the Cbz protecting group by hydrogenolysis was not straightforward and required the use of $Pd(OH)_2/C$ in the presence of 1 N HCl. Although several conditions [Pd/C (100 wt %), MeOH, 72 h; PtO_2 (25 wt %), MeOH/AcOH (1/1), 4 days] were attempted, both the long reaction time and the large amount of the catalyst were necessary, and the C1-silyl protecting group was cleaved off under the reaction conditions. The hydrophilic moiety **15** was combined with the hydrophobic carboxylic acid **2** using the optimized Cbz removal conditions and subsequent amidation (64%, two steps). Swern oxidation of **16** furnished **17** with spontaneous extrusion of the TsO group (71%).[12] Removal of the TBDPS group with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)[13] in pyridine afforded **18** in satisfactory yield (70%).[14] Disappointingly, however, the spectroscopic data [^{1}H and ^{13}C NMR] of **18** were not identical to those of natural scyphostatin.

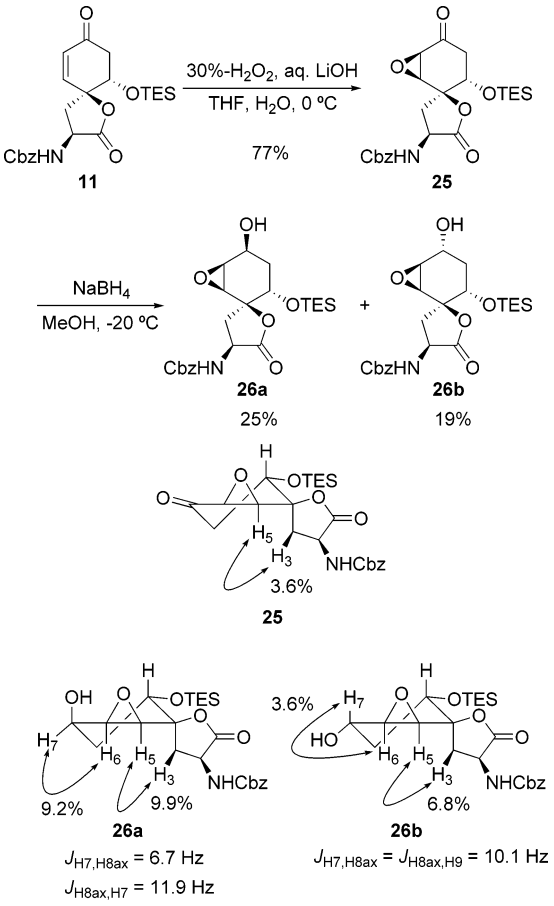
In order to reveal the reason for the spectral difference between **18** and the natural product, we decided to re-examine the stereochemical assignment in our previous model study (Scheme 5). Bromohydrin **23**, obtained from epoxide **19** in the model study,[3c] was converted to **24**, an analogue of the hydrophilic moiety. Since the relative stereochemistry of **19** had been confirmed by X-ray structural analysis,[3b] the relative stereochemistry of **24** was assured. The ^{1}H NMR spectrum of **24** turned out to be identical to that of **22**,[3a,b] the end product in refs 3a,b. Thus, the relative stereochemistry of **22** was the same as that of **24**, and the original stereochemical assignment of epoxide **21**[3a,b] based upon NOE experiments was incorrect. This

(12) Other methods of oxidations (e.g., IBX; Dess−Martin periodinane; TPAP, NMO) of **15** were also attempted. However, the epoxy-cyclohexenone compound was not obtained.
(13) (a) Noyori, R.; Nishida, I.; Sakata, J.; Mishisawa, M. *J. Am. Chem. Soc.* **1980**, *102*, 1223. (b) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436.
(14) When **17** was treated with TBAF in the presence of AcOH (10 equiv) at 0 °C for 3 h, **18** was obtained in 27% yield (conversion yield: 61%) along with recovered **17** (66% recovered).

SCHEME 5. Revision of the Stereochemical Assignment of 22



SCHEME 6. Synthesis of 26a,b



suggested that the C7-hydroxy group had actually directed the epoxidation reaction to occur from the same side as this group, as is the usual case.[15] A similar stereochemical revision has been reported in the assignment of structurally related natural product, calafianin.[16]

As for determination of the absolute stereochemistry in the series involving **13**, we could not resort to X-ray structural analysis due to lack of appropriate single crystals. Therefore, we decided to determine the absolute stereochemistry by comparing the ^{1}H NMR dif-NOE experiments among **13** and its diastereomers (Scheme 6). To this end, **11** was epoxidized to give **25** as a single isomer. The absolute stereochemistry of **25** could not be determined with certainty from NOE experiments, since signal enhancement (3.6%) between H3 and H5 was only slightly larger than that (1.9%) observed for **21**, for which we had mistakenly assigned stereochemistry. The epoxide **25** was then reduced to give a mixture of **26a** and **26b**, diastereomeric in regards with the relative stereochemistry of the epoxide and the C7 hydroxy group. Neither the spectral data of **26a** nor **26b** turned out to be identical to that of **13**, suggesting that we had three different diastereomers in hand. In the NOE experiments of **26a**,**b**, the NOE enhancement between H3 and H5 was clearly larger than that of **13**. Also, the NOE enhancement between H6 and H7 of **13** and **26a** was larger than that of **26b**. This analysis implied that **13** was a product of C7-hydroxy group directed epoxidation as it happened to be in the model system (Figure 4). It followed that **18** was a diastereomer of scyphostatin epimeric at C5 and C6.

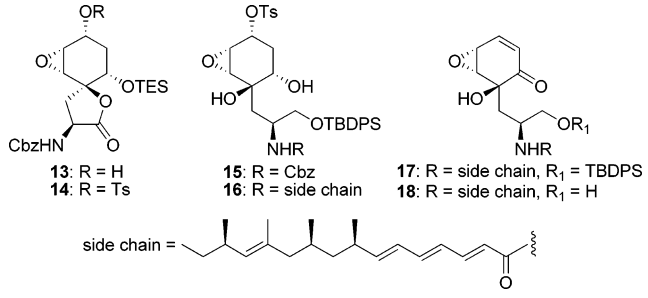


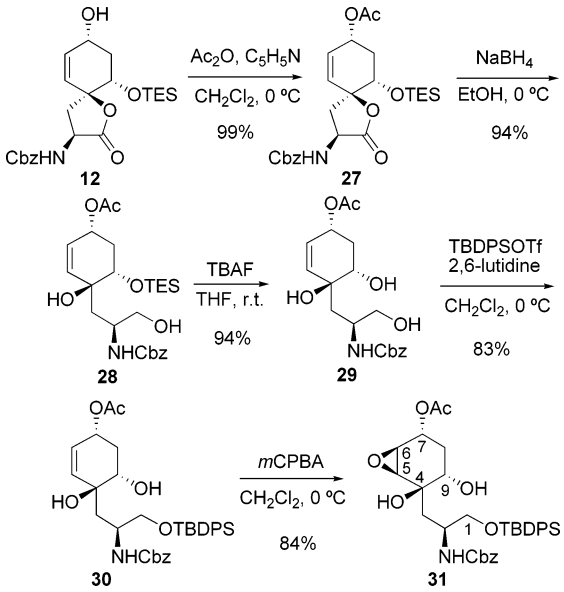
FIGURE 4. Revised structures of **13**−**18**.

In accordance with the results from the stereochemical reexamination, we modified our synthetic strategy. Thus, we decided to utilize the hydroxyl group that is formed upon ring opening of the lactone to direct epoxidation to the opposite side of the ring (Scheme 7). On the basis of the synthetic study of

(15) In the model study (refs 3a,b), we could not obtain the diastereomer epimeric at C5 and C6 (the epoxide region) and thus could not compare the NOE enhancement pattern between the diastereomers. The epoxidation of the C7-OAc protected **20** with *m*CPBA was also examined in order to confirm the stereochemical assignment. Although the yield was low (5% yield), the facial selectivity of the epoxidation was the same as that of **20**.

(16) (a) Encarnación, R. D.; Sandoval, E.; Malmstrøm, J.; Christophersen, C. *J. Nat. Prod.* **2000**, *63*, 874. (b) Ogamino, T.; Obata, R.; Tomoda, H.; Nishiyama, S. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 134.

SCHEME 7. Synthesis of 31 from 12



18, **12** was converted to **30** as follows. The C7-hydroxy group of **12** was protected as an acetate,[17] and then the spirolactone ring was reduced to diol **28**. Removal of the C9-TES group, followed by silylation of the C1-hydroxy group with TBDPSOTf, gave **30**.[18,19] Stereoselective epoxidation by the directing effect of the C4-hydroxy group was thus examined (Table 1). The stereochemistry of the C5−C6 epoxide ring was determined by comparing the ^{1}H NMR dif-NOE experiments between those of **31** and **32**-minor (Figure 5). Treatment of **28** with *m*CPBA

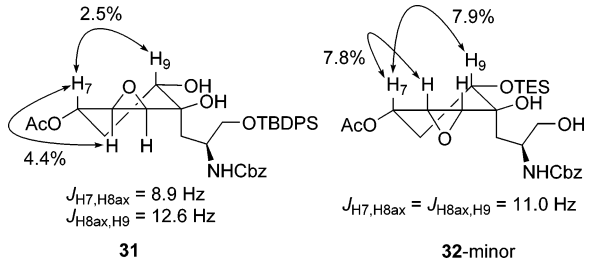
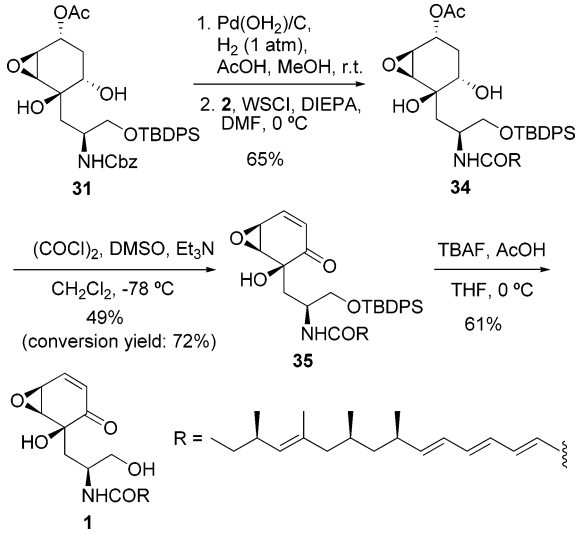


FIGURE 5. Absolute stereochemistry of **31** and **32**-minor.

afforded a mixture of diastereomers **32** (major:minor = 21:1, Table 1, entry 1). Compared to the C5−C6 epoxide ring of **13**−**15**, that of **32** was sensitive to acidic conditions (epoxidation with *m*CPBA; silylation of the C1-hydroxy group with TBDPSOTf; removal of the C9-TES group with AcOH and H_2O; in $CDCl_3$). The formation of the minor isomer was reasoned to be due to the presence of the free primary hydroxyl group. Thus, in order to improve the stereochemistry and the yield of epoxidation with *m*CPBA, the epoxidation of **30**, in which the primary hydroxyl group is protected with a silyl group, was examined (Table 1, entries 2−6). The epoxidation

SCHEME 8. Completion of (+)-Scyphostatin



of **30** gave **31** as a single isomer with diol **33**. As the results indicate, treatment of **30** at 0 °C gave the best result (Table 1, entry 2).

The end game is described in Scheme 8. Removal of the Cbz group by hydrogenolysis was more problematic than in the synthesis of the diastereomer **18** because of the sensitivity of the C5−C6 epoxide ring (Table 2). The hydrogenolysis of **31** with PtO_2 was unsuccessful, even in the presence of AcOH (Table 2, entry 1). When **31** was treated with $Pd(OH)_2$/C in the absence of AcOH, the C5−C6 epoxide ring was cleaved by the intramolecular nucleophilic reaction of the resulting amine (Table 2, entry 2). This could be suppressed by the use of $Pd(OH)_2$/C in the presence of AcOH (Table 2, entries 3, 4). It was revealed that the resulting amine **31′** readily converted to **36** under the reaction conditions. Condensation of amine **31′** and the hydrophobic carboxylic acid **2** with EDCI furnished **34** (69%, two steps). Exposure of epoxide **34** to Swern oxidation conditions furnished **35**, which bears the epoxy-cyclohexenone moiety, with the spontaneous extrusion of the AcO group (49%). Epoxide **34** was also recovered (32%). The C5−C6 epoxide ring seemed to have cleaved under the reaction conditions, and the diluted conditions (0.015 M) were necessary for satisfactory yields.[20] Finally, the treatment of **35** with TBAF in the presence of AcOH gave scyphostatin **1** in 61% yield. Spectroscopic data [^{1}H and ^{13}C NMR, HRMS] of synthetic scyphostatin **1** were identical to those of natural scyphostatin.[1] There was also good agreement obtained in the optical rotation value between those of synthetic and natural scyphostatin.

In summary, the stereoselective total synthesis of (+)-scyphostatin was achieved from L-tyrosine. The high π-facially selective Diels−Alder reaction of spirolactone **7** and a stereoselective epoxidation directed by the C4 hydroxy group were keys to the success. This synthetic study suggested that the high reactivity of the C5−C6 epoxide ring may be the cause of the extremely labile nature of scyphostatin.[21] Also, in the course of this work, it was revealed that we had mistakenly assigned the relative stereochemistry of the C5−C6 epoxide ring of the

(17) Similar to the synthesis of the diastereomer **18**, the tosylation of **12** was also attempted. However, after generation of the tosylate, a subsequent spontaneous reaction with the chloride ion occurred under the reaction conditions.

(18) Kobayashi, S.; Takahashi, Y.; Komano, K.; Alizadeh, B. H.; Kawada, Y.; Oishi, T.; Tanaka, S.; Ogasawara, Y.; Sasaki, S.; Hirama, M. *Tetrahedron* **2004**, *60*, 8375.

(19) TBDPS protection of the C1-hydroxy group of **29** was more difficult than the synthesis of **15**, and a more reactive reagent, TBDPSOTf, was necessary.

(20) When a reaction mixture of 0.023 M was used for the Swern oxidation, **35** (36% yield, conversion yield: 49%) and the recovered **34** (26% recovered) were obtained.

(21) The sensitivity of the cyclohexenone moiety to basic conditions has been mentioned by Katoh et al (ref 6).

TABLE 1. Stereoselective Epoxidation of 28 and 30 by the Directing Effect of the C4-Hydroxy Group

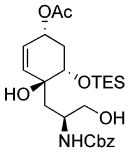
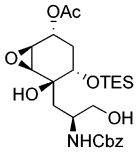
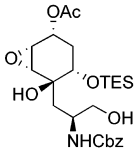
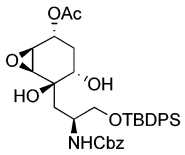
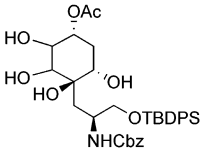
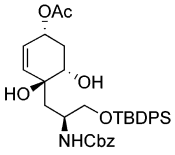
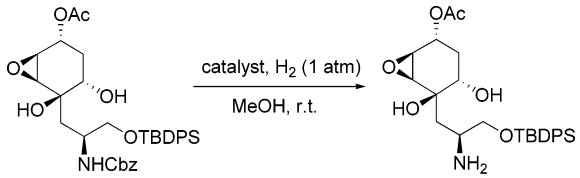
entry	subst.	conditions	product	
1	 **28**	*m*CPBA, CH_2Cl_2 r.t., 21 h	 **32**-major: 82%	 **32**-minor: 4%
2		*m*CPBA, CH_2Cl_2 0 °C, 70 h	 **31**: 84%	 **33**: 7%
3	 **30**	*m*CPBA, CH_2Cl_2 r.t., 17 h	**31**: 59%	**33**: 7%
4		*m*CPBA, pH 7 buffer CH_2Cl_2, r.t., 17 h	**31**: 76%	**33**: 14%
5		*m*CPBA, aq. $NaHCO_3$ CH_2Cl_2, r.t., r.t., 21 h	**31**: 13%	**33**: 13%
6		*m*CPBA, $NaHPO_4 \cdot 12H_2O$ CH_2Cl_2, 0 °C, 61 h	**31**: 52%	**33**: 6%

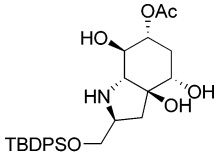
TABLE 2. Hydrogenolysis of 31



31 **31′**

entry	catalyst	conditions	product
1	PtO_2 (9 wt %)	AcOH (3.0 equiv) 5 h	no reaction
2	$Pd(OH)_2/C$ (21 wt %)	5 h	**36** (85%)
3	$Pd(OH)_2/C$ (19 wt %)	AcOH (3.0 equiv) 5 h	**31′**:**36** = 1:1[a]
4	$Pd(OH)_2/C$ (17 wt %)	AcOH (3.0 equiv) 30 min	**31′**[a]

[a] Compound **31′** was used for the next reaction without further purification.



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end product in our previous model study.[3a,b] Our strategy allows for the synthesis of various analogues of scyphostatin, as evident from the synthesis of a diastereomer of (+)-scyphostatin epimeric at C5 and C6 (the epoxide region).

Experimental Section

(4*S*)-4-Benzyloxycarbonylamino-1′,3,4,4′,4′a,8′a-hexahydrospiro[furan-2(5*H*),5′(8′*H*)-1′,4′-methanonaphthalene]-5,8′-dione (8). Cyclopentadiene (171 mg, 2.59 mmol), which was prepared by thermolysis of dicyclopentadiene, was added to a solution of **7**[7] (79.8 mg, 0.26 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. The reaction mixture was stirred at room temperature for 72 h. The solvent was removed in vacuo. The residue was purified by column chromatography (silica gel, EtOAc/hexane 1:1) to give a mixture of **8a** and **8b** (94.8 mg, 98%, **8a**:**8b** = 1:1). The mixture of **8a** and **8b** was separated by preparative TLC (SiO_2, EtOAc/hexane 1:1, multiple developments). **8a**: colorless oil; $[\alpha]_D^{27}$ = +4.2 (*c* 1.69, $CHCl_3$); IR (thin film) 2956, 1675, 1790, 1718, 1529, 1261, 1190 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.30 (d, J = 7.9 Hz, 1 H), 1.45 (d, J = 7.9 Hz, 1 H), 2.43 (t, J = 11.9 Hz, 1 H), 2.76 (dd, J = 10.1, 11.9 Hz, 1 H), 2.89 (bs, 1 H), 3.04 (dd, J = 3.4, 5.0 Hz, 1 H), 3.38 (bs, 2 H), 4.51 (dd, J = 10.1, 11.9 Hz, 1 H), 5.10 (d, J = 12.0 Hz, 1 H), 5.13 (d, J = 12.0 Hz, 1 H), 5.72 (d, J = 6.3 Hz, 1 H), 5.84 (dd, J = 2.1, 5.0 Hz, 1 H), 5.88 (d, J = 10.0 Hz, 1 H), 6.11 (bs, 1 H), 6.46 (d, J = 10.0 Hz, 1 H), 7.31−7.40 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.2, 47.4, 47.5, 47.9, 48.6, 50.6, 51.0, 67.4, 81.3, 128.2 (×2), 128.4, 128.6, (×2) 131.4, 134.6, 135.3, 135.7, 147.4, 155.9, 173.6, 198.9. EI-HRMS *m*/*z*: calcd for $C_{22}H_{21}NO_5$ [M^+], 379.1420; found, 379.1417. **8b**: white crystal; mp 179−181 °C (hexane/*i*-PrOH); $[\alpha]_D^{27}$ +14.1 (*c* 0.507, $CHCl_3$); IR (thin film) 2994, 1765, 1716, 1666, 1520, 1430, 1250, 1200 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (d, J = 8.4 Hz, 1 H), 1.49 (d, J = 8.4 Hz, 1 H), 2.12 (t, J = 12.1 Hz, 1 H), 2.73 (dd, J = 7.3, 12.1 Hz, 1 H), 2.94 (d, J = 8.5 Hz, 1 H), 3.05 (dd, J = 4.0, 8.5 Hz, 1 H), 3.12 (bs, 1 H), 3.41 (bs, 1 H), 4.65−4.74 (m, 1 H), 5.13 (s, 2 H), 5.27 (b, J = 4.9 Hz, 1 H), 5.85−5.90 (m, 2 H), 6.13 (dd, J = 3.1, 5.8 Hz, 1 H), 6.45 (d, J = 10.2 Hz, 1 H), 7.31−7.43 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.8 (×2), 47.2, 47.4, 48.7, 49.7, 50.8, 67.6, 80.7, 128.3 (×2), 128.4, 128.6 (×2), 131.0, 135.0, 135.1, 135.4, 147.8, 155.9, 173.5, 198.7. EI-HRMS *m*/*z*: calcd for $C_{22}H_{21}NO_5$ [M^+], 379.1420; found, 379.1442. Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58. N, 3.69. Found: C, 69.59; H, 5.53; N, 3.43.

(4*S*)-4-Benzyloxycarbonylamino-6′,7′-epoxy-1′,3,4,4′,4′a,6′,7′,8′a-octahydro-spiro[furan2(5*H*),5′(8′*H*)-1′,4′-methanonaphtalene]-5′,8-dione (9). To a solution of a diastereomer mixture of **8a** and **8b** (2.91 g, 7.67 mmol, 1:1) in THF (38 mL) was added a solution of 30% H_2O_2 (4.41 g, 38.9 mmol) and 0.5 M LiOH (8 mL, 4.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 6 h and quenched with saturated $NaHSO_3$ and saturated NH_4Cl. The aqueous layer was extracted with EtOAc. The combined organic

layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) (1.46 g, 7.60 mmol) was added to a solution of the resulting residue in CH_2Cl_2 (76 mL) at room temperature. The reaction mixture was stirred for 18 h, quenched with saturated NH_4Cl, and extracted with CH_2Cl_2. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated. The crude product was purified by column chromatography (silica gel, $CHCl_3$/MeOH, 50/1) to give **9a** and **9b** as pure products (**9a**:**9b** = 1:1, combined yield 1.47 g, 48%). **9a**: colorless oil; $[\alpha]_D^{27}$ = +28.2 (*c* 1.17, $CHCl_3$); IR: (thin film) 2973, 1789, 1716, 1538, 1538, 1454, 1338, 1261, 1199 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.25 (d, J = 7.7 Hz, 1 H), 1.47 (d, J = 7.7 Hz, 1 H), 2.59 (t, J = 12.9 Hz, 1 H), 2.84 (dd, J = 3.1, 10.8 Hz, 1 H), 3.05 (dd, J = 9.4, 12.9 Hz, 1 H), 3.11 (bs, 1 H), 3.13 (d, J = 10.8 Hz, 1 H), 3.15 (s, 1 H), 3.33−3.39 (m, 2 H), 4.44−4.52 (m, 1 H), 5.15 (bs, 2 H), 5.55 (d, J = 6.4 Hz, 1 H), 6.06 (bs, 1 H), 6.13 (bs, 1 H), 7.42−7.31 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.2, 42.9, 43.8, 48.5, 48.7, 50.0 (×2), 55.2, 58.8, 67.5, 81.7, 128.2 (×2), 128.4, 128.6 (×2), 133.7, 135.7, 135.9, 155.8, 172.3, 204.9. EI-HRMS *m*/*z*: calcd for $C_{22}H_{21}NO_6$ [M^+], 395.1369; found 395.1360. Anal. Calcd for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35, N; 3.54. Found: C, 66.71; H, 5.55; N, 3.48. **9b**: white solid; mp 177−179 °C (hexane/*i*-PrOH); $[\alpha]_D^{27}$ +5.16 (*c* 0.53, CH_3CN); IR (thin film) 2969, 2877, 1786, 1716, 1523, 1261, 1203 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (d, J = 8.2 Hz, 1 H), 1.50 (d, J = 8.2 Hz, 1 H), 2.72 (t, J = 12.9 Hz, 1 H), 2.86−3.02 (m, 3 H), 3.12−3.20 (m, 2 H), 3.36 (d, J = 2.9 Hz, 1 H), 3.57 (d, J = 2.9 Hz, 1 H), 4.48−4.56 (m, 1 H), 5.12 (s, 2 H), 5.50 (d, J = 4.9 Hz, 1 H), 5.85 (dd, J = 3.2, 5.5 Hz, 1 H), 6.17 (dd, J = 2.4, 5.5 Hz, 1 H), 7.30−7.43 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.0, 42.3, 44.3, 49.3 (×2), 49.8, 51.2, 54.9, 61.6, 67.7, 82.4, 128.2 (×2), 128.5, 128.6 (×2), 134.3, 135.2, 135.6, 155.8, 172.8, 204.9. EI-HRMS *m*/*z*: calcd for $C_{22}H_{21}NO_6$ [M^+], 395.1369; found, 395.1385. Anal. Calcd for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54. Found: C, 66.87; H, 5.34; N, 3.54.

(1*S*,4*R*,4′*S*,4a*S*,5*S*,6*S*,8a*R*)-4′-Benzyloxycarbonylamino-6-triethylsilyloxy-1,3′,4′,4,4a,6,7,8a-octahydro-spiro[furan-2′(5*H*),5-(8*H*)-1,4-methanonapthalene]-5′,8-dione (10). CH_2I_2 (305 mg, 1.14 mmol) was added to a solution of samarium metal (174 mg, 1.16 mmol) in THF (10 mL). The mixture was stirred at room temperature for 5 h. The resulting deep blue solution was cooled to −78 °C. The solution of SmI_2 was added dropwise to a solution of **9a** (89.1 mg, 0.23 mmol) and MeOH (0.09 mL, 2.0 mmol) in THF (1.0 mL) at −78 °C over 10 min. The reaction mixture was stirred at −78 °C for 1 h. After it was diluted with saturated NH_4Cl, the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 30:1) to give the alcohol (73.8 mg, 83%) as a white crystal: mp 165−167 °C (hexane/$CHCl_3$); $[\alpha]_D^{27}$ −1.73 (*c* 0.525, $CHCl_3$); IR (thin film) 3325, 2965, 1774, 1716, 1701, 1523, 1253, 1218 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (d, J = 8.2 Hz, 1 H), 1.48 (d, J = 8.2 Hz, 1 H), 2.19 (t, J = 11.9 Hz, 1 H), 2.35 (dd, J = 6.6, 18.8 Hz, 1 H), 2.47 (dd, J = 4.8, 18.8 Hz, 1 H), 2.90 (dd, J = 2.3, 9.6 Hz, 1 H), 2.95−3.04 (m, 2 H), 3.26 (bs, 1 H), 3.31 (bs, 1H), 3.58 (bs, 1 H), 4.00 (m, 1 H), 4.50 (td, J = 6.3, 11.9 Hz, 1 H), 5.10 (d, J = 12.8 Hz, 1 H), 5.12 (d, J = 12.8 Hz, 1H), 5.73 (d, J = 6.3 Hz, 1 H), 6.08 (bs, 1 H), 6.18 (m, 1 H), 7.30−7.38 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.0, 44.6, 45.2, 47.1, 48.6, 50.1, 51.4, 51.7, 67.4, 68.2, 85.8, 128.1 (×2), 128.4, 128.6 (×2), 135.1, 135.7, 136.4, 156.0, 174.8, 210.9. EI-HRMS *m*/*z*: calcd for $C_{22}H_{23}NO_6$ [M^+], 397.1525; found, 397.1537. Anal. Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.34; H, 5.92; N, 3.76.

Triethylsilyl chloride (TESCl) (0.55 mL, 3.29 mmol) was added to a solution of the alcohol (872 mg, 2.19 mmol) and imidazole (448 mg, 6.59 mmol) in CH_2Cl_2 (23 mL) at room temperature. The reaction mixture was stirred at room temperature for 14 h. After it was diluted with H_2O, the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc 2:1) to give **10** (1.24 g, 100%) as a colorless oil: $[\alpha]_D^{27}$ −11.6 (*c* 1.12 $CHCl_3$); IR (thin film) 2954, 2877, 1786, 1709, 1523, 1454, 1214, 1095, 1006 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.59 (q, J = 7.5 Hz, 6 H), 0.94 (t, J = 7.5 Hz, 9 H), 1.36 (d, J = 8.2 Hz, 1 H), 1.50 (d, J = 8.2 Hz, 1 H), 2.17 (t, J = 11.4 Hz, 1 H), 2.32 (dd, J = 7.6, 18.8 Hz, 1 H), 2.44 (dd, J = 4.3, 18.8 Hz, 1 H), 2.86 (d, J = 8.8 Hz, 1 H), 2.96 (d, J = 8.8 Hz, 1 H), 3.01 (t, J = 11.4 Hz, 1 H), 3.32 (bs, 2 H), 3.99 (m, 1 H), 4.43 (td, J = 6.9, 11.4 Hz, 1 H), 5.12 (d, J = 12.2 Hz, 1 H), 5.15 (d, J = 12.2 Hz, 1 H), 5.35 (d, J = 6.9 Hz, 1 H), 6.11 (bs, 1 H), 6.21 (bs, 1 H), 7.30−7.40 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.7 (×3), 6.6 (×3), 37.6, 45.4, 45.5, 47.3, 48.9, 50.2, 51.4, 51.6, 67.2, 69.2, 85.6, 128.0 (×2), 128.2, 128.5 (×2), 135.1, 135.9, 136.5, 155.8, 173.9, 210.2. EI-HRMS *m*/*z*: calcd for $C_{28}H_{37}NO_6Si$ [M^+], 511.2390; found, 511.2365. Anal. Calcd for $C_{28}H_{37}NO_6Si$: C, 65.72; H, 7.29; N, 2.74. Found: C, 65.49; H, 7.30; N, 2.95.

(3*S*,5*S*,10*S*)-3-Benzyloxycarbonylamino-10-triethylsilyloxy-1-oxa-spiro[4.5]dec-6-ene-2,8-dione (11). Maleic anhydride (464 mg, 4.73 mmol) was added to a mixture of **10** (1.20 g, 2.35 mmol) in Ph_2O (110 mL) at room temperature. The reaction mixture was heated at 230 °C for 1 h. The reaction mixture was purified by flash column chromatography (silica gel, hexane/EtOAc 10:1) to remove Ph_2O. The residue was purified by column chromatography (silica gel, hexane/EtOAc 2:1) to give **11** (1.05 g, 100%) as a yellow oil: $[\alpha]_D^{27}$ −4.99 (*c* 0.530, $CDCl_3$); IR (thin film) 2958, 2877, 1790, 1716, 1693, 1523, 1454, 1261, 1218, 1164, 1103 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.63 (q, J = 7.8 Hz, 6 H), 0.96 (t, J = 7.8 Hz, 9 H), 2.12 (t, J = 11.1 Hz, 1 H), 2.55 (dd, J = 12.2, 16.7 Hz, 1 H), 2.75 (dd, J = 4.8, 16.7 Hz, 1 H), 3.06 (t, J = 11.1 Hz, 1 H), 4.32 (dd, J = 4.8, 12.2 Hz, 1 H), 4.54 (td, J = 6.0, 11.1 Hz, 1 H), 5.10 (d, J = 12.2 Hz, 1 H), 5.15 (d, J = 12.2 Hz, 1 H), 5.47 (d, J = 6.0 Hz, 1 H), 6.02 (d, J = 10.1 Hz, 1 H), 6.92 (d, J = 10.1 Hz, 1 H), 7.30−7.40 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.7 (×3), 6.6 (×3), 32.4, 43.9, 51.2, 67.3, 72.1, 84.2, 128.1 (×2), 128.3, 128.6 (×2), 129.3, 135.8, 149.3, 155.8, 174.0, 195.9. EI-HRMS *m*/*z*: calcd for $C_{23}H_{31}NO_6Si$ [M^+], 445.1921; found, 445.1915. Anal. Calcd for $C_{23}H_{31}NO_6Si$: C, 62.00; H, 7.01; N, 3.14. Found: C, 61.98; H, 7.14; N, 3.00.

(3*S*,5*S*,8*R*10*S*)-3-Benzyloxycarbonylamino-8-hydroxy-10-triethylsilyloxy-1-oxa-spiro[4.5]dec-6-ene-2-one (12). $NaBH_4$ (26.1 mg, 0.69 mmol) was added to a solution of **11** (310 mg, 0.70 mmol) and $CeCl_3 \cdot 7H_2O$ (261 mg, 0.70 mmol) in *i*-PrOH (3.5 mL) and THF (3.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 40 min. After it was diluted with saturated NH_4Cl, the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc 1:1) to give **12** (295 mg, 95%) as a yellow oil: $[\alpha]_D^{27}$ +0.29 (*c* 0.69, $CHCl_3$); IR (thin film) 3406, 2954, 2877, 1775, 1705, 1527, 1454, 1272, 1230, 1114, 1041 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.63 (q, J = 7.6 Hz, 6 H), 0.96 (t, J = 7.6 Hz, 9 H), 1.66 (q, J = 11.9 Hz, 1 H), 1.80 (d, J = 5.3 Hz, 1 H), 1.98 (t, J = 11.2 Hz, 1 H), 2.25−2.32 (m, 1 H), 2.97 (t, J = 11.2 Hz, 1 H), 3.95 (dd, J = 1.7, 11.9 Hz, 1 H), 4.36−4.43 (m, 1 H), 4.58 (td, J = 6.3, 11.2 Hz, 1 H), 5.10 (d, J = 12.1 Hz, 1 H), 5.15 (d, J = 12.1 Hz, 1 H), 5.30 (d, J = 6.3 Hz, 1 H), 5.68 (d, J = 10.1 Hz, 1 H), 5.81 (d, J = 11.9 Hz, 1H), 7.30−7.41 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.8 (×3), 6.7 (×3), 35.7, 39.5, 51.7, 66.6, 67.2, 71.9, 85.7, 128.1 (×2), 128.3, 128.6 (×2), 130.1, 133.6, 136.0, 155.8, 174.9. EI-HRMS *m*/*z*: calcd for $C_{23}H_{33}NO_6Si$ [M^+], 447.2077; found, 447.2057. Anal. Calcd for $C_{23}H_{33}NO_6Si$: C, 61.72; H, 7.43; N, 3.13. Found: C, 61.85; H, 7.31; N, 3.02.

(3*S*,5*S*,8*R*10*S*)-8-Acetoxy-3-benzyloxycarbonylamino-10-triethylsilyloxy-1-oxaspiro[4.5]dec-6-ene-2-one (27). To a solution

of **12** (2.62 g, 5.85 mmol) in CH_2Cl_2 (58 mL) at 0 °C were added pyridine (2.40 mL, 29.3 mmol), Ac_2O (0.75 mL, 7.9 mmol), and DMAP (75.3 mg, 0.62 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 24 h. After the reaction was quenched with saturated NH_4Cl, the mixture was extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc 4:1 to 2:1) to give **27** (2.83 g, 99%) as a colorless oil: $[\alpha]_D^{27} = +5.02$ (*c* 2.65, $CHCl_3$); IR (thin film) 2958, 2877, 1789, 1735, 1523, 1457, 1373, 1230, 1118, 1037 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.63 (q, J = 7.9 Hz, 6 H), 0.96 (t, J = 7.9 Hz, 9 H), 1.69−1.78 (m, 1 H), 1.99 (t, J = 11.3 Hz, 1 H), 2.07 (s, 3 H), 2.27−2.34 (m, 1 H), 2.99 (t, J = 11.3 Hz, 1 H), 4.00 (d, J = 11.8 Hz, 1 H), 4.57 (td, J = 6.6, 11.3 Hz, 1 H), 5.10 (d, J = 12.2 Hz, 1 H), 5.15 (d, J = 12.2 Hz, 1 H), 5.26 (bs, 1 H), 5.39−5.45 (m, 1 H), 5.72 (d, J = 10.1 Hz, 1 H), 5.78 (d, J = 10.1 Hz, 1 H), 7.32−7.39 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.7 (×3), 6.6 (×3), 21.0, 35.4, 35.6, 51.6, 67.1, 68.5, 71.6, 85.3, 128.0, 128.2, 128.5 (×2), 129.3 (×2), 131.9, 136.0, 155.8, 170.2, 174.8. EI-HRMS *m*/*z*: calcd for $C_{25}H_{35}NO_7Si$ [M^+], 489.2183; found, 489.2182. Anal. Calcd. for $C_{25}H_{35}NO_7Si$: C, 61.32; H, 7.20; N, 2.86. Found C, 61.60; H, 7.36; N, 2.84.

(1*S*,2′*S*,4*R*,6*S*)-4-Acetoxy-1-(2′-benzyloxycarbonylamino-3′-hydroxy-propyl)-6-triethylsilyloxy-2-cyclohexen-1-ol (28). To a solution of **27** (2.75 g, 5.62 mmol) in EtOH (56 mL) at 0 °C was added $NaBH_4$ (412 mg, 10.9 mmol). After the reaction mixture was stirred for 5 h, additional $NaBH_4$ (432 mg, 11.4 mmol) was added. After the mixture was stirred for another 3 h, another amount of $NaBH_4$ (216 mg, 5.72 mmol) was added. After the mixture was stirred for 1 h, the reaction was quenched with saturated NH_4Cl and the mixture extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography (silica gel, hexane/EtOAc 2:1) to give **28** (2.62 g, 94%) as a colorless oil: $[\alpha]_D^{28} = +5.05$ (*c* 2.70, $CHCl_3$); IR (thin film) 3382, 2954, 2877, 1716, 1519, 1457, 1373, 1238, 1114, 1022 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.63 (q, J = 7.9 Hz, 6 H), 0.96 (t, J = 7.9 Hz, 9 H), 1.70 (td, J = 12.8, 15.6 Hz, 1 H), 1.81 (dd, J = 4.6, 15.2 Hz, 1 H), 1.99 (dd, J = 9.1, 15.2 Hz, 1 H), 2.06 (s, 3 H), 2.22 (dddd, J = 1.2, 4.0, 6.7, 12.8 Hz, 1 H), 2.59 (bs, 1 H), 2.88 (s, 1 H), 3.66 (dd, J = 5.5, 11.3 Hz, 1 H), 3.70 (dd, J = 3.4, 11.3 Hz, 1 H), 3.75 (d, J = 4.0, 12.8 Hz, 1 H), 3.88−3.95 (m, 1 H), 5.10 (d, J = 12.2 Hz, 1 H), 5.13 (d, J = 12.2 Hz, 1 H), 5.40 (ddt, J = 2.1, 6.7, 9.8 Hz, 1 H), 5.62 (d, J = 10.4 Hz, 1 H), 5.80 (dd, J = 2.1, 10.4 Hz, 1 H), 5.84 (bs, 1 H), 7.30−7.37 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.9 (×3), 6.8 (×3), 21.1, 35.5, 36.6, 50.4, 53.4, 66.9, 69.1, 74.4, 74.9, 127.4, 128.0 (×2), 128.1, 128.5 (×2), 134.1, 136.3, 157.3, 170.5. EI-HRMS *m*/*z*: calcd for $C_{25}H_{39}NO_7Si$ [M^+], 493.2496; found, 493.2495. Anal. Calcd. for $C_{25}H_{39}NO_7Si$: C, 60.82; H, 7.96; N, 2.84. Found C, 60.66; H, 8.06; N, 2.69.

(1*S*,2′*S*,4*R*,6*S*)-4-Acetoxy-1-(2′-benzyloxycarbonylamino-3′-hydroxy-propyl)-6-hydroxy-2-cyclohexen-1-ol (29). To a solution of **28** (65.3 mg, 0.13 mmol) in THF (1.3 mL) at room temperature was added TBAF (1.0 M in THF, 0.15 mL, 0.15 mmol). After the mixture was stirred for 10 min, the reaction was quenched with saturated NH_4Cl and the mixture extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 15:1) to give **29** (46.3 mg, 94%) as a colorless oil: $[\alpha]_D^{28} = +17.4$ (*c* 1.57, $CHCl_3$); IR (thin film) 3390, 2958, 2877, 1700, 1523, 1457, 1373, 1241, 1052 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.75−1.84 (m, 2 H), 2.05 (s, 3 H), 2.03−2.10 (m, 1 H), 2.07 (dd, J = 8.2, 15.2 Hz, 1 H), 3.18 (bs, 1 H), 3.40 (bs, 1 H), 3.52 (bs, 1 H), 3.60−3.72 (m, 2 H), 3.81 (d, J = 9.1 Hz, 1 H), 3.93−4.00 (m, 1 H), 5.07 (d, J = 12.2 Hz, 1 H), 5.11 (d, J = 12.2 Hz, 1 H), 5.35−5.40 (m, 1 H), 5.67−5.82 (m, 3 H), 7.29−7.37 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 33.1, 37.2, 49.6, 65.9, 67.0, 68.3, 72.8, 73.0, 126.9, 128.0 (×2), 128.2, 128.5 (×2), 134.8, 136.2, 157.0, 170.5. EI-HRMS *m*/*z*: calcd for $C_{19}H_{25}NO_5$ [M^+], 379.1631; found, 379.1613. Anal. Calcd. for $C_{19}H_{25}NO_7$: C, 60.15; H, 6.64; N, 3.69. Found C, 60.03; H, 6.80; N, 3.61.

(1*S*,2′*S*,4*R*,6*S*)-4-Acetoxy-1-(2′-benzyloxycarbonylamino-3′-*tert*-butyldiphenylsilyloxy-propyl)-6-hydroxy-2-cyclohexen-1-ol (30). To a solution of **29** (41.8 mg, 0.12 mmol) in CH_2Cl_2 (0.6 mL) at 0 °C was added 2,6-lutidine (0.14 mL, 1.2 mmol) and TBDPSOTf (0.10 M in CH_2Cl_2, 2.9 mL, 0.29 mmol). After the mixture was stirred for 0.5 h, the reaction was quenched with saturated NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc 2:1) to give **30** (59.4 mg, 83%) as a colorless oil: $[\alpha]_D^{28} = +11.8$ (*c* 2.51, $CHCl_3$); IR (thin film) 3386, 2931, 2857, 1716, 1508, 1427, 1373, 1238, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.06 (s, 9 H), 1.74 (ddd, J = 7.0, 10.4, 13.4 Hz, 1 H), 1.83 (dd, J = 5.2, 15.2 Hz, 1 H), 2.02−2.07 (m, 1 H), 2.04 (s, 3 H), 2.34 (ddd, J = 2.9, 5.4, 13.4 Hz, 1 H), 2.87 (bs, 1 H), 3.41 (bs, 1 H), 3.67 (dd, J = 5.2, 10.4 Hz, 1 H), 3.69−3.74 (m, 1 H), 3.77−3.82 (m, 1 H), 3.90−3.96 (m, 1 H), 5.07 (d, J = 12.2 Hz, 1 H), 5.13 (d, J = 12.2 Hz, 1 H), 5.31 (d, J = 6.1 Hz, 1 H), 5.38 (td, J = 2.9, 7.0 Hz, 1 H), 5.59−5.67 (m, 2 H), 7.30−7.46 (m, 11 H), 7.61−7.66 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 21.1, 26.8 (×3), 32.8, 37.6, 48.9, 66.5, 66.9, 68.2, 72.5, 72.7, 126.9, 127.8 (×2), 128.0, 128.1, 128.5 (×2), 129.8, 132.9, 133.0, 135.1, 135.5 (×4), 135.6 (×4), 136.2, 156.8, 170.3. FAB+-HRMS (NBA) *m*/*z*: calcd for $C_{35}H_{44}NO_7Si$ [M + H], 618.2887; found, 618.2868. Anal. Calcd. for $C_{35}H_{43}NO_7Si$: C, 68.04; H, 7.02; N, 2.27. Found: C, 68.04; H, 7.12; N, 2.27.

(1*R*,2*S*,2′*S*,3*S*,4*R*,6*S*)-4-Acetoxy-1-(2′-benzyloxycarbonylamino-3′-*tert*-butyldiphenylsilyloxy-propyl)-2,3-epoxy-6-hydroxy-2-cyclohexen-1-ol (31). To a solution of **30** (17.8 mg, 29.0 μmol) in CH_2Cl_2 (0.3 mL) at 0 °C was added *m*CPBA (23.0 mg, 87.0 μmol). After the mixture was stirred for 48 h, additional *m*CPBA (23.6 mg, 89.0 μmol) was added. The reaction mixture was stirred at 0 °C for 22 h. After the mixture was diluted with CH_2Cl_2, the reaction was quenched with saturated $Na_2S_2O_3$ and evaporated. The mixture was extracted with CH_2Cl_2. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated. The resulting residue was purified by preparative TLC (silica gel, CH_2Cl_2/MeOH 15:1) to give **31** (15.3 mg, 84%) and **33** (1.4 mg, 7%) as a colorless oil: **31**: $[\alpha]_D^{29} = -9.59$ (*c* 3.26, MeOH); IR (thin film) 3401, 2931, 2857, 1720, 1519, 1427, 1369, 1238, 1110, 1060 cm^{-1}; ^1H NMR (500 MHz, C_5D_5N) δ 1.12 (s, 9 H), 2.02 (s, 3 H), 2.07 (td, J = 8.1, 12.6 Hz, 1 H), 2.51 (ddd, J = 3.5, 8.1, 12.6 Hz, 1 H), 2.58 (dd, J = 3.9, 14.7 Hz, 1 H), 2.77 (dd, J = 8.9, 14.7 Hz, 1 H), 3.41 (d, J = 3.0 Hz, 1 H), 3.80 (d, J = 3.0 Hz, 1 H), 4.07 (dd, J = 6.4, 9.0 Hz, 1 H), 4.24 (dd, J = 4.4, 9.0 Hz, 1 H), 4.37 (dd, J = 3.5, 12.6 Hz, 1 H), 4.74−4.82 (m, 1 H), 5.22 (d, J = 12.6 Hz, 1 H), 5.29 (d, J = 12.6 Hz, 1 H), 5.45 (t, J = 8.1 Hz, 1 H), 7.23−7.45 (m, 11 H), 7.87 (t, J = 7.8 Hz, 4 H), 7.96 (d, J = 6.4 Hz, 1 H); ^{13}C NMR (125 MHz, C_5D_5N) δ 19.5, 20.9, 27.0 (×3), 33.8, 34.5, 50.4, 57.0, 61.2, 66.2, 67.3, 67.7, 68.7, 73.3, 128.0, 128.1, 128.2 (×2), 128.3, 128.7 (×4), 130.1, 130.2, 134.0, 134.1, 136.0 (×4), 138.0, 157.0, 170.1. FAB+-HRMS (NBA) *m*/*z*: calcd for $C_{35}H_{44}NO_8Si$ [M + H], 634.2836; found, 634.2847. Anal. Calcd. for $C_{35}H_{43}NO_8Si$: C, 66.33; H, 6.84; N, 2.21. Found: C, 66.34; H, 6.91; N, 2.17. **33**: colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 9 H), 1.97 (dd, J = 4.9, 15.2 Hz, 1 H), 2.05 (bs, 2 H), 2.10 (s, 3 H), 2.25 (dd, J = 6.7, 15.2 Hz, 1 H), 2.55 (bs, 1 H), 3.70 (dd, J = 4.9, 10.4 Hz, 1 H), 3.72−3.74 (m, 1 H), 3.78−3.84 (m, 3 H), 3.85−3.92 (m, 1 H), 5.06 (d, J = 12.2 Hz, 1 H), 5.12 (m, 1 H), 5.24−5.28 (m, 1 H), 5.32 (d, J = 5.5 Hz, 1 H), 7.31−7.46 (m, 11 H), 7.61−7.67 (m, 4 H). EI-HRMS *m*/*z*: calcd for $C_{35}H_{45}NO_9Si$ [M^+], 651.2864; found, 651.2850.

(1*R*,2*S*,2′*S*,2″*E*,3*S*,4*R*,4″*E*,6*S*,6″*E*,8″*R*,10″*S*,12″*E*,14″*R*)-4-Acetoxy-2,3-epoxy-6-hydroxy-1-[2′-(8″,10″,12″,14″-tetramethyl-hexadeca-2″,4″,6″,12″-tetraenoylamino)-3′-*tert*-butyldiphenyl-

silyloxy-propyl]-2-cyclohexen-1-ol (34). To a solution of **31** (49.6 mg, 78.3 μmol) in MeOH (5.0 mL) at room temperature were added $Pd(OH)_2/C$ (10.2 mg, 17 wt %) and AcOH (0.34 M in MeOH, 0.45 mL, 0.15 mmol). The reaction mixture was stirred at room temperature for 30 min under a hydrogen atmosphere. Then it was diluted with EtOAc, and filtered. The insoluble material was washed with EtOAc. The filtrate was washed with H_2O and brine, dried over Na_2SO_4, and evaporated to give **31′** as a white crystal. **31′**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (s, 9 H), 1.43−1.56 (m, 1 H), 1.74−1.84 (m, 1 H), 2.03−2.19 (m, 2 H), 3.16 (d, J = 3.4 Hz, 1 H), 3.18 (d, J = 3.4 Hz, 1 H), 3.67−3.94 (m, 4 H), 5.04 (t, J = 8.2 Hz, 1 H), 7.39−7.50 (m, 6 H), 7.67−7.73 (m, 4 H).

To a solution of the residue and **2** in DMF (2.0 mL) at 0 °C were added EDCI (20.0 mg, 0.10 mmol) and diisopropylethylamine (DIPEA) (0.53 M in DMF, 0.14 mL, 64 μmol). The reaction mixture was allowed to gradually warm to room temperature, and stirring was continued for 12 h. Then it was quenched with saturated NH_4Cl and extracted with Et_2O. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated. The resulting residue was purified by column chromatography (neutral silica gel, CH_2Cl_2/MeOH 20/1) to give **34** (40.2 mg, 65%) as a colorless oil: $[\alpha]_D^{27}$ = +2.89 (*c* 0.784, CH_3OH); IR (thin film) 3390, 2958, 2927, 1747, 1650, 1604, 1427, 1369, 1234, 1110, 1002 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 0.82 (d, J = 6.6 Hz, 3 H), 0.85 (t, J = 7.3 Hz, 3 H), 0.90 (d, J = 6.7 Hz, 3 H), 1.00 (d, J = 6.6 Hz, 3 H), 1.06 (s, 9 H), 1.13−1.23 (m, 1 H), 1.25−1.39 (m, 4 H), 1.51−1.61 (m, 1 H), 1.53 (d, J = 1.2 Hz, 3 H), 1.79 (dd, J = 7.2, 13.0 Hz, 1 H), 1.89 (dd, J = 7.2, 13.0 Hz, 1 H), 1.97−2.10 (m, 3 H), 2.00 (s, 3 H), 2.20−2.29 (m, 1 H), 2.29−2.40 (m, 1 H), 3.09 (d, J = 3.4 Hz, 1 H), 3.19 (dd, J = 0.5, 3.4 Hz, 1 H), 3.65−3.70 (m, 1 H), 3.66 (dd, J = 3.8, 10.8 Hz, 1 H), 3.79 (dd, J = 5.3, 10.8 Hz, 1 H), 4.29−4.36 (m, 1 H), 4.82 (m, 1 H), 5.05 (t, J = 8.1 Hz, 1 H), 5.70 (dd, J = 8.6, 15.1 Hz, 1 H), 5.98 (d, J = 14.9 Hz, 1 H), 6.15 (dd, J = 10.5, 15.1 Hz, 1 H), 6.27 (dd, J = 11.1, 14.9 Hz, 1 H), 6.53 (dd, J = 10.5, 14.9 Hz, 1 H), 7.14 (dd, J = 11.1, 14.9 Hz, 1 H), 7.33−7.44 (m, 6 H), 7.63−7.70 (m, 4 H); ^{13}C NMR (125 MHz, CD_3OD) δ 12.5, 16.4, 20.0, 20.1, 20.9, 21.5, 21.9, 27.5 (×3), 29.5, 31.7, 34.2, 34.3, 35.4, 36.3, 45.2, 48.8, 49.6, 57.5, 60.9, 67.3, 68.2, 69.4, 73.7, 124.1, 128.8 (×2), 128.9 (×2), 129.5, 130.0, 131.0, 131.1, 133.6, 134.2, 134.5, 134.6, 136.8 (×2), 136.9 (×2), 141.3, 142.2, 146.1, 168.7, 171.8. EI-HRMS *m*/*z*: calcd for $C_{47}H_{67}O_7NSi$ [M^+], 785.4687; found, 785.4720.

***(2′S,2″E,4S,4″E,5S,6S,6″E,8″R,10″S,12″E,14″R)*-4,5-Epoxy-6-hydroxy-6-[2′-(8″,10″,12″,14″-tetramethylhexadeca-2″,4″,6″,-12″-tetraenoylamino)-3′-*tert*-butyldiphenylsilyloxy-propyl]-2-cyclohexen-1-one (35).** $(COCl)_2$ (0.23 M in CH_2Cl_2, 0.30 mL, 69.0 μmol) was slowly added to a solution of DMSO (0.28 M in CH_2Cl_2, 0.40 mL, 0.11 mmol) in CH_2Cl_2 (1.0 mL) at −78 °C. After the mixture was stirred at −78 °C for 30 min, **34** (38.2 mg, 48.6 μmol) in CH_2Cl_2 (1.5 mL) was added at −78 °C. The reaction mixture was stirred at −78 °C for 1 h. To the solution was added Et_3N (0.20 mL, 1.4 mmol) at −78 °C. After the mixture was stirred at −78 °C for 1 h, the reaction was quenched with saturated NH_4Cl, warmed to room temperature, and extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated. The resulting residue was purified by column chromatography (neutral silica gel, CH_2Cl_2/MeOH 20/1) to give recovered **34** (12.1 mg, 32%) and **35** (17.1 mg, 49%) as a colorless oil: $[\alpha]_D^{27}$ = + 12.7 (*c* 1.41, CH_3OH); IR (thin film) 3070, 2958, 2857, 1697, 1647, 1604, 1427, 1110, 1002 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 0.82 (d, J = 6.6 Hz, 3 H), 0.85 (t, J = 7.3 Hz, 3 H), 0.90 (d, J = 7.3 Hz, 3 H), 0.97−1.06 (m, 1 H), 1.00 (d, J = 6.6 Hz, 3 H), 1.02 (s, 9 H), 1.13−1.23 (m, 1 H), 1.25−1.39 (m, 2 H), 1.53 (d, J = 1.2 Hz, 3 H), 1.56−1.63 (m, 1 H), 1.76−1.92 (m, 3 H), 2.13 (dd, J = 2.8, 14.6 Hz, 1 H), 2.21−2.29 (m, 1 H), 2.30−2.40 (m, 1 H), 3.54 (td, J = 1.6, 3.9 Hz, 1 H), 3.56 (dd, J = 6.1, 9.9 Hz, 1 H), 3.62 (dd, J = 5.4, 9.9 Hz, 1 H), 3.64 (d, J = 3.9 Hz, 1 H), 4.15−4.23 (m, 1 H), 4.82−4.85 (m, 1 H), 5.70 (dd, J = 8.6, 15.1 Hz, 1 H), 5.89 (d, J = 15.0 Hz, 1 H), 6.05 (dd, J = 1.6, 9.9 Hz, 1 H), 6.14 (dd, J = 10.7, 15.1 Hz, 1 H), 6.25 (dd, J = 11.2, 14.8 Hz, 1 H), 6.53 (dd, J = 10.7, 14.8 Hz, 1 H), 7.10−7.16 (m, 2 H), 7.32−7.45 (m, 6 H), 7.60−7.67 (m, 4 H); ^{13}C NMR (125 MHz, CD_3OD) δ 12.5, 16.4, 20.0, 20.1, 21.5, 21.9, 27.4 (×3), 29.6, 31.7, 35.4, 36.3, 40.0, 45.3, 47.9, 49.2, 49.6, 58.1, 67.3, 77.4, 123.8, 128.8 (×2), 128.9 (×2), 129.4, 129.9, 130.9, 131.0, 132.0, 133.5, 134.2, 134.4, 134.6, 136.7 (×4), 141.4, 142.5, 146.1, 146.2, 168.5, 199.6. FAB+-HRMS (NBA) *m*/*z*: [M + H] Calcd for $C_{45}H_{62}NO_5Si$, 724.4397; found, 724.4402.

***(2′S,2″E,4S,4″E,5S,6S,6″E,8″R,10″S,12″E,14″R)*-4,5-Epoxy-6-hydroxy-6-[3′-hydroxy-2′-(8″,10″,12″,14″-tetramethylhexadeca-2″,4″,6″,12″-tetraenoylamino)-propyl]-2-cyclohexen-1-one (1).** To a solution of **35** (14.1 mg, 19.5 μmol) in THF (0.5 mL) were added AcOH (0.17 M in THF, 0.17 mL, 29 μmol) and TBAF (0.090 M in THF, 0.33 mL, 30 μmol) at 0 °C. The reaction mixture was allowed to gradually warm to room temperature, and stirring was continued for 9 h. Then it was quenched with saturated NH_4Cl, extracted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, and evaporated. The resulting residue was purified by column chromatography (neutral silica gel, CH_2Cl_2/MeOH 20/1) to give **1** (5.7 mg, 61%) as a colorless amorphous powder: $[\alpha]_D^{28}$ = +61.9 (*c* 0.240, CH_3OH) [lit.[3] $[\alpha]_D^{25}$ = +66.4 (*c* 0.09, MeOH)]; IR (thin film) 3289, 2958, 2923, 1697, 1650, 1608, 1542, 1457, 1376, 1268, 1157, 1002 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 0.82 (d, J = 6.5 Hz, 3 H), 0.85 (t, J = 7.5 Hz, 3 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.99 (d, J = 6.7 Hz, 3 H), 1.01−1.07 (m, 1 H), 1.13−1.23 (m, 1 H), 1.30−1.39 (m, 2 H), 1.53 (d, J = 1.0 Hz, 3 H), 1.55−1.63 (m, 1 H), 1.79 (dd, J = 7.3, 13.4 Hz, 1 H), 1.84−1.92 (m, 2 H), 2.07 (dd, J = 3.4, 14.7 Hz, 1 H), 2.21−2.29 (m, 1 H), 2.29−2.38 (m, 1 H), 3.45 (dd, J = 5.8, 11.0 Hz, 1 H), 3.51 (dd, J = 5.1, 11.0 Hz, 1 H), 3.58 (td, J = 1.7, 3.9 Hz, 1 H), 3.66 (d, J = 3.9 Hz, 1 H), 4.00−4.08 (m, 1 H), 4.84 (m, 1 H), 5.70 (dd, J = 8.7, 15.1 Hz, 1 H), 5.89 (d, J = 15.1 Hz, 1 H), 6.07 (dd, J = 1.5, 9.9 Hz, 1 H), 6.14 (dd, J = 10.7, 15.1 Hz, 1 H), 6.25 (dd, J = 11.2, 14.8 Hz, 1 H), 6.53 (dd, J = 10.7, 14.8 Hz, 1 H), 7.09−7.17 (m, 2 H); ^{13}C NMR (125 MHz, CD_3OD) δ 12.5, 16.4, 19.9, 21.5, 21.9, 29.5, 31.7, 35.4, 36.3, 39.8, 45.2, 48.0, 49.2, 49.6, 58.2, 65.6, 77.5, 123.8, 129.4, 130.0, 132.1, 133.6, 134.2, 141.4, 142.4, 145.9, 146.2, 168.6, 199.6. FAB+-HRMS (NBA) *m*/*z*: [M + H] calcd for $C_{29}H_{44}NO_5$, 486.3219; found, 486.3217.

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Supporting Information Available: General experimental methods, experimental procedures and/or characterization data of **13**−**18**, **23**−**26**, **32**, and **36**, copies of NMR spectra of new compounds, and a comparison table of the NMR data of natural and synthetic scyphostatin and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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