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Concise Asymmetric Total Synthesis of Scyphostatin, a Potent Inhibitor of Neutral Sphingomyelinase

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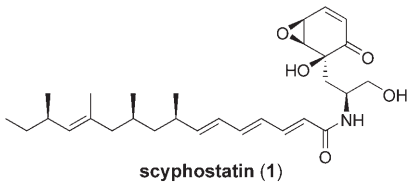
Abstract: The concise asymmetric total synthesis of scyphostatin has been achieved by condensation of the optically active cyclohexane unit, prepared from the commercially available 1,4-cyclohexadiene by our own method, and the side chain, prepared by the method developed by Hoye and Tennakoon (T. R. Hoye, M. A. Tennakoon, *Org. Lett.* **2000**, *2*, 1481–1483). The modification of the epoxy cyclohexenone unit was achieved in a late stage of the total synthesis, and deprotection of the primary alcohol was conducted in the final step. During the synthesis several key reactions were attained: 1) intramolecular bromoetherification of the cyclohexadiene acetal; 2) stereoselective introduction of the tertiary alcohol, 3) deprotection of the acetal function to the aldehyde by combination with silyl triflate/2,4,6-collidine and the one-pot synthesis of the disilyl aldehyde compounds, with different types of silyl groups, from the dihydroxy acetal compounds; and 4) facile deprotection of the 2,4-dimethoxyphenylmethyl (^{2,4}DMPM) protecting group of the primary alcohol.

Keywords: asymmetric synthesis · bromoetherification · cyclic compounds · natural products · scyphostatin

Introduction

Scyphostatin (**1**)[1] was isolated from Dasyscyphus mollissimus SANK-13892 in 1997 and showed the most potent activity ($IC_{50}=1.0$ μM) toward a neutral sphingomyelinase (N-SMase) among the large number of already reported N-SMase inhibitors.[2] N-SMase is the enzyme that accelerates the conversion of sphingomyelin into ceramide. Since the ceramide is believed to be an intracellular lipid second messenger and to play vital roles in the regulation of cell proliferation, modulation of the inflammatory process, and apoptosis,[3] **1** is recognized as a lead compound for the treatment of inflammation and autoimmune diseases. This molecule consists of an epoxy cyclohexenone unit with an amino alcohol moiety and an unsaturated fatty acid side chain, so that **1** is a challenging target compound for many organic chemists in view of not only its biological activity but also its unique structure. Although several synthetic studies toward



scyphostatin (1)

1 have already been reported,[4,5] to the best of our knowledge only two total asymmetric syntheses of **1** have, quite recently, been reported by Katoh and co-workers from D-arabinose derivatives in 22 steps[6] and by Takagi et al. through a spirolactone derivative from tyrosine in 18 steps.[7]

We now present our study on the total asymmetric synthesis of **1**. For the optically active epoxy cyclohexenone unit of **1**, we recently succeeded in the synthesis of model compound **5**, which has the same epoxy cyclohexenone unit of **1**.[8] Thus the intramolecular bromoetherification of the diene acetal **2** gave a cyclohexene eight-membered acetal **3** in a stereoselective manner.[9] Compound **3** was transformed into the allyl alcohol **4**, which was further modified to **5.** In the beginning, we attempted to convert the dimethyl acetal function of **5** into an aldehyde function, which would be used for the further construction of the amino alcohol moiety and the introduction of the fatty acid side chain. However, the conversion of **5** into **6** was unsuccessful, possi-

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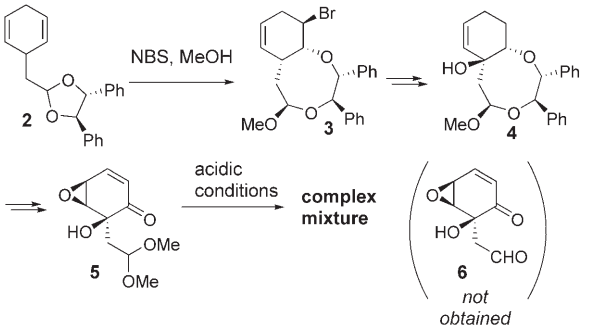
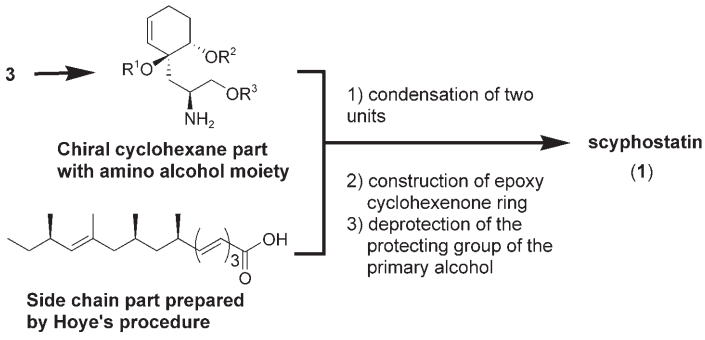
bly as a result of the instability of the epoxy cyclohexenone unit (Scheme 1). We then decided to develop an alternative way to synthesize **1**. As another synthetic plan, we had to consider the instability of **1**, as it is a very unstable com-



Scheme 1. Attempted conversion of **5** into **6**. NBS = *N*-bromosuccinimide.

pound under acidic and basic conditions. For example, the epoxy cyclohexenone unit of **1** has many reactive functional groups, such as the enone, unstable under basic conditions, and the epoxide, unstable under acidic conditions. The primary alcohol of **1** causes an intramolecular nucleophilic attack on the ketone under basic conditions. Furthermore, the trienamide unit of the side chain causes decomposition even under neutral conditions.[1b]

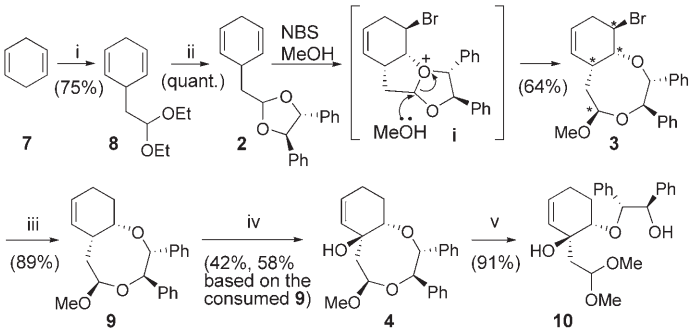
A summary of our total synthesis is depicted in Scheme 2. We first condensed the optically active cyclohexane unit, prepared by our own method, and the side chain prepared by the method developed by Hoye and Tennakoon.[5a] Then modification of the epoxy cyclohexenone unit was achieved in a late stage of the total synthesis, and deprotection of the primary alcohol was conducted in the final step. We then completed the first generation asymmetric total synthesis of **1**. We next improved two reactions, thus giving a more efficient second generation asymmetric total synthesis of **1** in a total of 17 steps.



Scheme 2. Summary of the synthesis of scyphostatin (**1**).

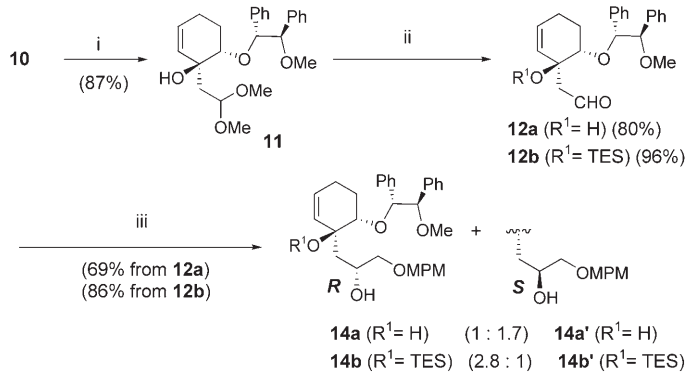
Results and Discussion

Examination of the synthetic route to an epoxy cyclohexenone unit with an amino alcohol moiety: Herein, the studies of the synthetic route to an epoxy cyclohexenone unit with an amino alcohol moiety using cyclohexene eight-membered acetal **4** are described. In a previous study,[9] the cyclohexadiene acetal **2** was prepared by the transacetalization of diethylacetal **8**, obtained from benzoic acid by using a four-step sequence according to a previously reported procedure[10] with (*R,R*)-hydrobenzoin. We then succeeded in synthesizing **8** in only one step. Thus, lithiation of commercially available 1,4-cyclohexadiene (**7**) and successive reaction with bromoacetaldehyde diethyl acetal afforded **8** in a one-pot operation in 75% yield. The transformation of **8** into dimethyl acetal **10** was carried out by our previously reported procedure:[8] 1) Transacetalization of **8** with (*R,R*)-hydrobenzoin, 2) intramolecular bromoetherification of **2** with NBS in the presence of MeOH, 3) radical reduction of **3**, 4) stereoselective oxidation of **9** by using SeO_2, and **5**) acidic treatment of **4** in MeOH (Scheme 3).

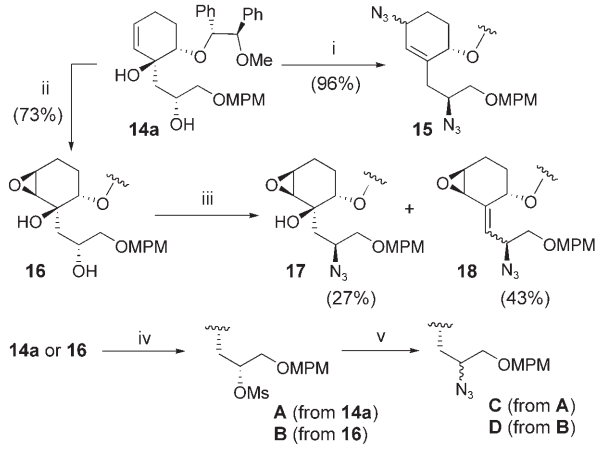


Scheme 3. Synthesis of cyclohexene dimethyl acetal **10**. i) *sec*-BuLi, TMEDA, THF, −78°C, then $BrCH_2CH(OEt)_2$; ii) (*R,R*)-hydrobenzoin, *p*-TsOH, toluene, 50°C; iii) Bu_3SnH, AIBN, benzene, reflux; iv) SeO_2, pyridine, dioxane, 70°C; v) cat. PPTS, MeOH, RT. AIBN = azobisisobutylonitrile, PPTS = pyridinium *p*-toluene sulfonate, TMEDA = *N,N,N′,N′*-tetramethylethylenediamine, *p*-TsOH = *p*-toluenesulfonic acid.

We then examined the construction of the amino alcohol moiety. First, we prepared the *p*-methoxyphenylmethyl (MPM) ether **14a** from **10** by using a three-step sequence (Scheme 4, a series): 1) Methylation of the benzyl alcohol, 2) acid hydrolysis of the acetal, and 3) nucleophilic addition of 4-methoxyphenylmethyloxymethyl lithium from the stannyl compound **13**.[11] The stereochemistry of the secondary alcohols **14a** and **14a′** was determined by using a modified Mosher's method (see the Experimental Section).[12] In this case, the undesired *S* alcohol **14a′** was obtained as a major product. Our study using **14a** is shown in Scheme 5. The Mitsunobu reaction[13] of the secondary alcohol **14a** using DPPA for introduction of the azide group with inversion was unsuccessful and gave a diastereomeric mixture of the allylic azide **15** because of the presence of the reactive allylic tertiary alcohol. We then attempted to first convert the olefin and then introduce a nitrogen atom. In this case, the stereoselective epoxidation[14] of **14a** with $[VO(acac)_2]$ and TBHP proceeded well without any problems to give the epoxy alcohol **16**. However, the following Mitsunobu reaction afforded a low yield of the desired azide **17** accompa-



Scheme 4. Syntheses of MPM ethers **14a** and **14b**. i) MeI, NaH, THF/DMF (1:1), 0 °C; ii) HCO_2H (10%), CH_3CN (90% aq.), RT for **12a** or TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C for **12b**; iii) $MPMOCH_2SnBu_3$ (**13**), *n*-BuLi, THF, −78 °C. DMF = *N*,*N*-dimethylformamide, TESOTf = triethylsilyl trifluoromethanesulfonate.

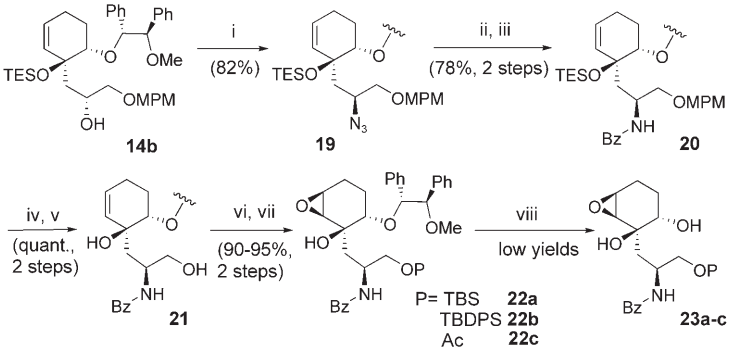


Scheme 5. Introduction of a nitrogen atom into **14a**. i) DPPA, PPh_3, DEAD, THF, RT; ii) TBHP, $[VO(acac)_2]$, toluene, 0 °C; iii) DPPA, PPh_3, DEAD, THF, RT; iv) MsCl, Et_3N, CH_2Cl_2, 0 °C; v) NaN_3 or $TMSN_3$. DEAD = diethyl azodicarboxylate, DPPA = diphenylphosphorylazide, Ms = methanesulfonyl, TBHP = *tert*-butylhydroperoxide, TMS = trimethylsilyl.

Since the presence of the naked tertiary alcohol caused unfavorable side reactions, as shown in Scheme 5 (a series), we next examined a route using the triethylsilyl (TES) ether **14b**, in which the tertiary alcohol was protected as a silyl ether. Compound **14b** was prepared from **10** almost in the same procedure as **14a** shown in Scheme 4. Thus, the deprotection of the acetal function and silylation of the tertiary alcohol of **11** by using our recently developed method,[15] a combination of TESOTf and 2,6-lutidine followed by a work-up with water gave the TES ether aldehyde **12b** in excellent yield. The subsequent nucleophilic addition of the lithiated **13** gave the diastereomixture of **14b** and **14b′**. The stereochemistries of the secondary alcohols were also determined by the modified Mosher's method.[12] To our delight, the ratio of the two alcohols **14b** and **14b′** was reversed compared to the ratio of **14a** and **14a′**, and the desired alcohol **14b** was obtained as the major product. This outcome shows that the silylation of the tertiary alcohol increases the ratio of the desired alcohol.

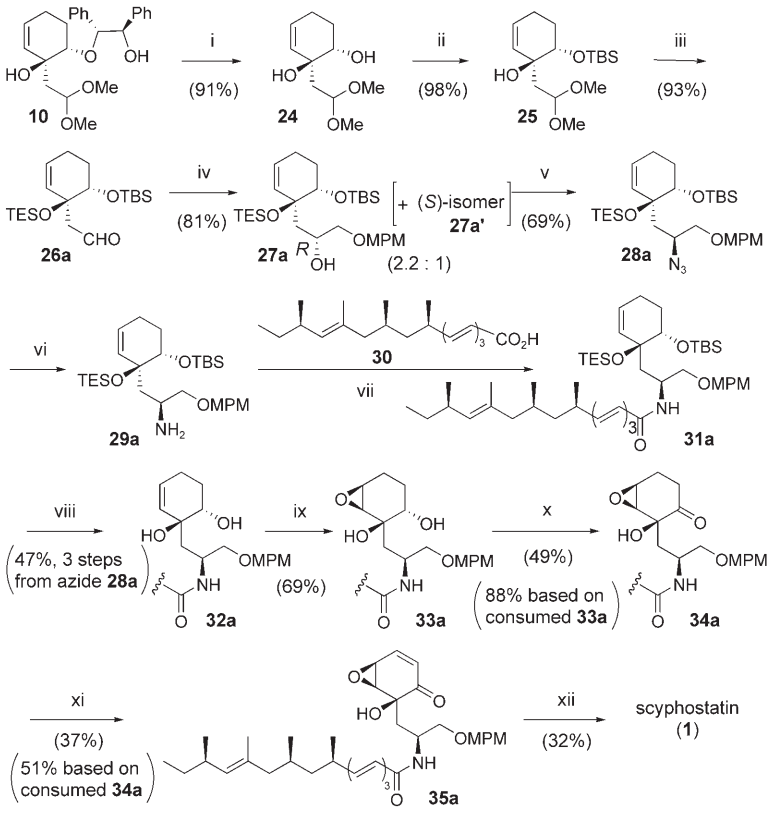
Introduction of a nitrogen atom and its conversion are shown in Scheme 6. The Mitsunobu reaction of **14b** gave the azide **19** in good yield. Formation of an undesirable allylic azide, such as **15**, was not observed. For examination of the synthetic route available for the synthesis of **1**, a benzoyl group was introduced in place of the unsaturated fatty acid side chain. The reduction of **19** using $LiAlH_4$ followed by *N*-acylation gave the benzoate **20**. Deprotection of the MPM and TES ethers gave the diol **21** in two steps. Protection of the primary alcohol with a *tert*-butyldimethylsilyl (TBS), *tert*-butyldiphenylsilyl (TBDPS), or acetyl (Ac) group, respectively, and stereoselective epoxidation of each compound gave the epoxy alcohols **22a–c**. However, the reactions to remove the hydrobenzoin unit of **22a–c** caused several side reactions, such as opening of the oxirane ring, cleavage of the amide bond, deprotection of the primary alcohol, and so on, thus the yields of the desired compounds **23a–c** were low. These results showed that the removal of the hydrobenzoin unit is necessary at an early stage.

nied by the allylic azide **18**, which was obtained by β-elimination of the tertiary alcohol **17**. In another trial using **14a** and **16**, the selective mesylation of the secondary alcohol followed by nucleophilic substitution resulted in low yields of the mixture of the epimeric azide isomers **C** and **D** to our disappointment. Furthermore, the reduction of the azide group of **17** did not afford the desired amino compound possibly as a result of the presence of the tertiary alcohol.



Scheme 6. Introduction of a nitrogen atom into **14b**. i) DPPA, PPh_3, DEAD, THF, RT; ii) $LiAlH_4$, THF, 0 °C; iii) BzCl, Et_3N, CH_2Cl_2, RT; iv) DDQ, CH_2Cl_2, RT; v) TBAF, THF, RT; vi) TBSCl, imidazole, DMF, RT for **22a**; TBDPSCl, imidazole, DMF, RT for **22b**; Ac_2O, pyridine, RT for **22c**; vii) TBHP, $[VO(acac)_2]$, toluene, RT; viii) 1. $[Pd(OH_2)]$, H_2, MeOH, RT, 3.5 atm or 2. liq. NH_3, ca. −78 °C. acac = acetylacetonate, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TBAF = tetra-*n*-butylammonium fluoride, TBDPSCl = *tert*-butyldiphenylsilyl chloride, TBSCl = *tert*-butyldimethylsilyl chloride.

Asymmetric total synthesis of 1; first generation: Based on the results described above, we decided to remove the hydrobenzoin unit before constructing the oxirane ring, forming the amide bond, and deprotecting the primary alcohol. Since the epoxy cyclohexenone unit is considered to be unstable, in other words, very reactive under various reaction conditions, its construction was carried out at a late stage of the total synthesis. Our first generation asymmetric synthesis of **1** is shown in Scheme 7. Birch reduction of the hydrobenzoin unit of **10**, prepared from 1,4-cyclohexadiene (**7**) in six steps (Scheme 2), gave the diol **24**, which was treated with TBSCl/imidazole to afford the hydroxy silyl ether **25**. Deprotection of the acetal function of **25** by our recently developed method[15] gave the disilylated aldehyde **26a** in high yield. Nucleophilic addition of 4-methoxyphenylmethyloxymethyl lithium from the stannyl compound **13** to **26a** gave the two alcohols (*R*)-**27a** and (*S*)-**27a′** in a ratio of 2.2:1 and 81% total yield. The stereochemistry of the two alcohols was determined by the modified Mosher's method[12] (see the Experimental Section). The desired *R* isomer **27a** was converted into amine **29a** through azide **28a** by the Mitsunobu reaction[13] in 69% yield followed by reduction using $LiAlH_4$. Condensation of the amine **29a** and side chain acid **30**, prepared by the method developed by Hoye and Tennakoon,[5a] gave amide **31a**, which was desilylated to give diol **32a** in 47% yield from azide **28a**. Stereoselective epoxidation[14] of **32a** with $[VO(acac)_2]$ and TBHP gave *cis*-epoxy alcohol **33a** in 69% yield as a single isomer. Oxidation of the secondary alcohol of **33a** using TPAP/NMO[16] gave the ketone **34a** in 49% yield (88% based on the consumed **33a**). The treatment of **34a** with LDA and the reaction with *N*-*tert*-butylphenylsulfinimidoyl chloride gave enone **35a** in 37% yield (51% based on consumed **34a**).[17] The addition of [15]crown-5 to the reaction mixture improved the yield. Deprotection of the MPM ether to give the alcohol was successfully done using trityl tetrafluoroborate ($Ph_3C^+BF_4^-$) to afford scyphostatin (**1**) in 32% yield,[18] whereas CAN and DDQ, usually used for the deprotection of the MPM ether,[19] gave a complex mixture as a result of the reaction at the trienamide unit (the same results were obtained in our model study of **35a** with a trienamide unit, as described later in Table 2). The spectroscopic data of synthetic **1** are identical with those previously reported.[1a] As stated above, our first generation synthesis of **1** was attained in 18 steps from the commercially available 1,4-cyclohexadiene (**7**).

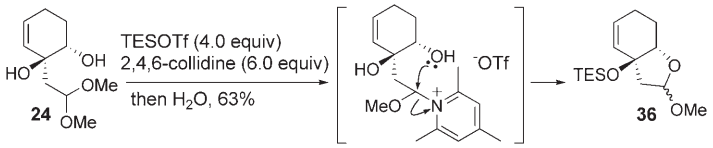


Scheme 7. First generation asymmetric total synthesis of scyphostatin (**1**). i) Ca, EtOH, liq. NH_3, −40°C; ii) TBSCl, imidazole, DMF, RT; iii) TESOTf, 2,4,6-collidine, CH_2Cl_2, 0°C, then H_2O; iv) Bu_3SnCH_2OMPM (**13**), *n*BuLi, THF, −78°C; v) DPPA, PPh_3, DEAD, CH_2Cl_2, RT; vi) $LiAlH_4$, THF, RT; vii) **30**, DCC, DMAP, CH_2Cl_2, 0°C; viii) TBAF, THF, 0°C; ix) TBHP, $[VO(acac)_2]$, toluene, 0°C; x) TPAP, NMO, CH_2Cl_2, 0°C; j) LDA, [15]crown-5, Ph(Cl)S=N*t*Bu, THF, −78°C; xii) $Ph_3C^+BF_4^-$, CH_2Cl_2, 0°C. DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = dimethylaminopyridine, LDA = lithium diisopropylamide, NMO = *N*-methylmorpholine-*N*-oxide, TPAP = tetra-*n*-propylammonium perruthenate.

Studies of the improvements of the first generation asymmetric synthesis: In the first generation asymmetric synthesis described above, some steps (i.e., the conversion of **24** into **26a** and the low-yielding transformation of **35a** to **1**) could be improved by extending our method and searching for more efficient protecting groups and deprotecting conditions.

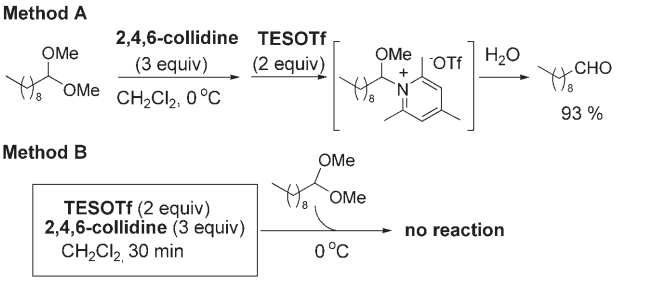
One-pot conversion of dihydroxy acetal 24 into disilyl aldehydes 26a–e: For the first generation asymmetric synthesis outlined above, the secondary alcohol of **24** was protected as a TBS ether to give **25**, and then our deprotection method using acetal groups afforded aldehyde **26a**, both hydroxy groups of which were protected as silyl ethers. Since the second step of the reaction mentioned above, that is, the use of TESOTf/2,4,6-collidine followed by a work-up with water, uses reagents and conditions employed for the silylation of the hydroxy group, we next examined obtaining disilyl

aldehyde **26** directly from **24** in one step by applying our method. However, the treatment of **24** with TESOTf/2,4,6-collidine gave the lactol derivative **36**, in which the tertiary alcohol was protected as a TES ether, in 63% yield (Scheme 8). We already found that the addition of alcohols to the pyridinium-type salt intermediates prepared by the reaction of the acetal groups with the TESOTf/base combination gave mixed acetals in high yields.[15b]



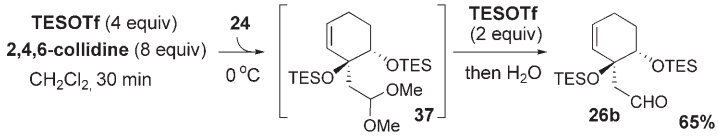
Scheme 8. Treatment of **24** with TESOTf/2,4,6-collidine.

The formation of lactol **36** was rationalized by the intramolecular attack of the naked secondary alcohol on the *N*,*O*-acetal carbon atom of the intermediate. This result suggests that the secondary alcohol moiety must be protected before deacetalization. For our deacetalization method, the order of the addition of the reagents and substrates is very important. When the silyl triflate, such as TESOTf or TMSOTf, is added to the mixture of an acetal and 2,4,6-collidine, we can obtain an aldehyde (Method A in Scheme 9).[15] On the other hand, when an acetal is added to



Scheme 9. Reactivity of the silyl triflate/2,4,6-collidine combination.

the mixture of the silyl triflate and base, no deacetalization is observed (Method B in Scheme 9). However, the combination of the silyl triflate and 2,4,6-collidine is employed for the silylation of alcohols.[19] We then utilized this different reactivity with **24** for the one-pot synthesis of disilyl aldehyde **26b** (Scheme 10). Thus **24** was added to a solution of TESOTf (4.0 equiv) and 2,4,6-collidine (8.0 equiv) in CH_2Cl_2 to give disilyl acetal **37** as an intermediate. Additional

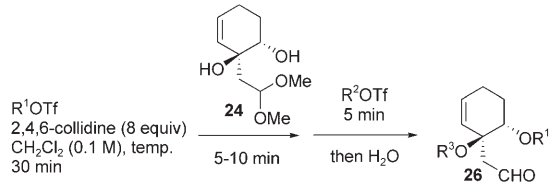


Scheme 10. One-pot synthesis of disilyl aldehyde from dihydroxy acetal **24**.

TESOTf (2.0 equiv) was added to the resulting solution followed by a work-up with water to give the bis(TES) ether aldehyde **26b** in 65% yield from a one-pot operation.

The results shown in Scheme 10 encouraged our efforts toward the one-pot synthesis of the disilyl aldehyde, although the yield of **26b** was moderate. We then studied this conversion in detail (Table 1). At first, the *tert*-butyldimethylsilylation of the secondary alcohol of **24** was performed with the proper amount of TBSOTf and an excess of 2,4,6-collidine (8.0 equiv). Thereafter TESOTf or TMSOTf were added to the reaction mixture and a work-up with water afforded disilyl aldehydes **26**. The reactions in entries 1 and 2 were carried out at 0 °C. The use of 2.0 equivalents of TBSOTf as the first silyl triflate and TESOTf as the second silyl triflate gave the desired **26a** along with bis(TBS) ether **26c** (Table 1, entry 1). The use of more TBSOTf (4.0 equiv) gave only **26c** (Table 1, entry 2). We then studied the reaction using 2.0 equivalents of TBSOTf and 4.0 equivalents of TESOTf at −78 °C, which produced of **26a** in 98% yield (Table 1, entry 3). The reaction using TMSOTf instead of TESOTf afforded the TMS ether **26d** in 94% yield (Table 1, entry 4). The use of triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) instead of TBSOTf at 0 °C gave TIPS ether **26e** in 90% yield (Table 1, entry 5). Based on these results, we developed a one-pot synthesis of different disilyl aldehydes **26a–e** by controlling the amount of silyl triflate, the order of the addition of the reagents, and the reaction temperature.

Table 1. One-pot synthesis of disilyl aldehyde **26**.[a]

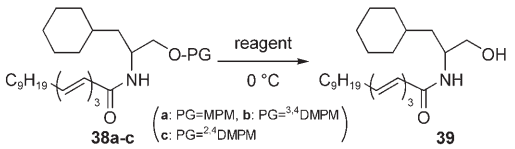


Entry	*T* [°C]	Reagent (equiv) R^1	R^2		Product R^3	Yield [%]
1	0	TBS (2)	TES (4)	**26a**	TES	85
				26c	TBS	13
2	0	TBS (4)	TES (2)	**26c**	TBS	89
3	−78	TBS (2)	TES (4)	**26a**	TES	98
4	−78	TBS (2)	TMS (4)	**26d**	TMS	94
5	0	TIPS (2)	TES (4)	**26e**	TES	90

[a] TIPS = triisopropylsilyl.

Study of the protection and deprotection of the primary alcohol: In the final step of the first generation asymmetric synthesis, the conversion of **35a** into **1** resulted in a low yield (32%; Scheme 7). Especially, reagents such as DDQ or CAN,[19] which are recognized as good reagents for the deprotection of MPM ethers, resulted in decomposition of the compound. We therefore examined the protecting group and deprotection conditions for the primary alcohol of **1** using the MPM-type protecting group (Table 2). We used

Table 2. Examination of protecting group (PG) and deprotection conditions.

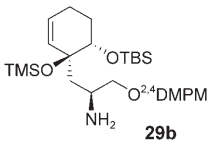


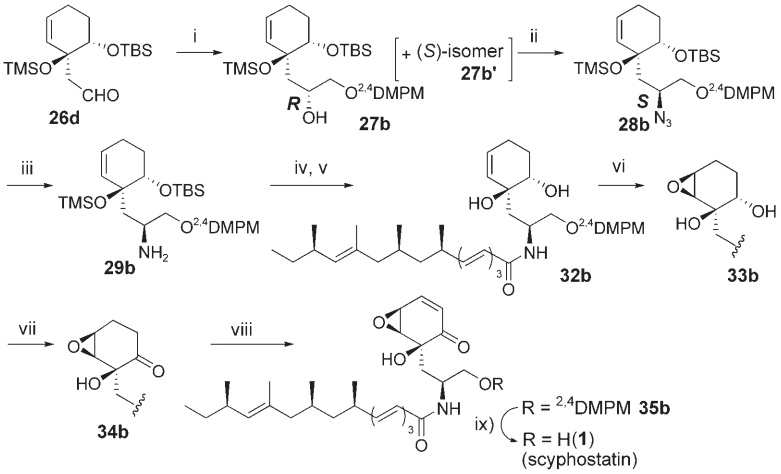
Entry	PG	Reagent	Time	Yield [%]
1	MPM	DDQ	5 min	decomp
2	MPM	DDQ[a]	5 min	decomp
3	MPM	CAN	5 min	decomp
4	MPM	$MgBr{\cdot}OEt_2$[b]	5 min	decomp
5	MPM	$Ph_3C^+BF_4^-$	6 h	67
6	MPM	$Ph_3C^+PF_5^-$	2 h	trace
7	MPM	$Ph_3C^+SnCl_5^-$	3 h	56
8	3,4DMPM	$Ph_3C^+BF_4^-$	2 h	90
9	2,4DMPM	$Ph_3C^+BF_4^-$	<5 min	93
10	2,4DMPM	HPF[4]	30 min	quant.

[a] $NaHCO_3$ was added as an additive. [b] Me_2S was added as an additive. PG = protecting group.

trienamide alcohol **39** as a model compound that has an amino alcohol unit with a highly reactive trienamide component. Treatment of MPM ether **38a** with DDQ, CAN, or $MgBr_2{\cdot}OEt_2$[20] also resulted in decomposition (Table 2, entries 1–4). However, the use of trityl tetrafluoroborate ($Ph_3C^+BF_4^-$)[18] gave the desired product **39** in 67% yield in 6 hours (Table 2, entry 5). The other trityl reagent, trityl pentafluorophosphate ($Ph_3C^+PF_5^-$) produced a trace amount of **39** (Table 2, entry 6), whereas the trityl pentachlorostannane ($Ph_3C^+SnCl_5^-$) afforded **39** in 56% yield (Table 2, entry 7). The use of the 3,4-dimethoxyphenylmethyl (3,4DMPM) group and $Ph_3C^+BF_4^-$ increased the yield to 90% and shortened the reaction time to 2 hours (Table 2, entry 8). The use of the 2,4-dimethoxyphenylmethyl (2,4DMPM) group and $Ph_3C^+BF_4^-$ gave better results: <5 minutes and 93% yield of **39** (Table 2, entry 9). Although HBF_4 also afforded **39** in a quantitative yield, the conditions were strongly acidic (Table 2, entry 10). We then chose 2,4DMPM and $Ph_3C^+BF_4^-$ for the most efficient total synthesis of **1**.

Asymmetric total synthesis of 1: second generation: Since the improvement of some of the drawbacks in the first generation asymmetric synthesis of **1** was carried out, we tried to utilize these results and achieved the second generation asymmetric synthesis of **1** in a total of 17 steps with a higher total yield via **29b**, which has TMS and 2,4DMPM protecting groups. As the silyl group for the protection of the tertiary alcohol, the TMS group was chosen for the higher yield in every step for the synthesis of **1** (compare Scheme 11 (second generation synthesis) to Scheme 7 (first generation synthesis)). Aldehyde **26d** was obtained from commercially available 1,4-cyclohexadiene (**7**) in eight steps (Schemes 3 and 7 and Table 1, entry 4). Nucleophilic addition of the lithium reagent derived from the 2,4-dimethoxyphenylmethyloxymethyl stannyl compound **40**, which was easily prepared by using the procedure developed by Still,[11] to the aldehyde **26d** afforded alcohol (*R*)-**27b** in 56% yield accompanied by its stereoisomeric alcohol (*S*)-**27b′** in 36% yield. The stereochemistry of the two alcohols was determined by the modified Mosher's method[12] (see the Experimental Section). The





Scheme 11. Second generation asymmetric total synthesis of scyphostatin (**1**). i) 2,4DMPMOCH$_2$SnBu$_3$ (**40**); *n*BuLi, THF, −78°C (56%); ii) DPPA, PPh_3, DEAD, THF, RT (75%); iii) $LiAlH_4$, THF, 0°C to RT; iv) **30**, DCC, DMAP, CH_2Cl_2, RT; v) TBAF, THF, RT (59% from azide **28b**); vi) TBHP, [VO(acac)$_2$], toluene, 0°C (73%); vii) DMP, CH_2Cl_2, 40°C (69%, 78% based on the consumed **33b**); viii) Ph(Cl)S=N*t*Bu, LDA, [15]crown-5, THF, −78°C (35%, 82% based on the consumed **34b**); ix) $Ph_3C^+BF_4^-$, CH_2Cl_2, 0°C (66%).

Mitsunobu reaction of **27b** with DPPA[13] afforded azide(*S*)-**28b** in 75% yield, which was reduced by $LiAlH_4$ to afford amino alcohol **29b**. Condensation of the amino group of **29b** with the side chain acid **30**,[5a] followed by desilylation gave dihydroxyamide **32b** in 59% yield from azide **28b**. The stereo- and chemoselective epoxidation of **32b** with [VO(acac)$_2$] and TBHP[14] gave epoxy alcohol **33b** in 73% yield, which was oxidized using Dess–Martin periodinane (DMP)[21] to afford epoxy ketone **34b** in 69% yield (78% based on consumed **33b**). The treatment of **34b** with LDA and reaction with *N*-*tert*-butylphenylsulfinimidoyl chloride[17] gave enone **35b** in 35% yield (82% based on consumed **34b**). Finally, deprotection of 2,4DMPM ether **35b** was successfully carried out by $Ph_3C^+BF_4^-$[18] to afford **1** in 66%

yield. The spectroscopic data of synthetic **1** were identical with those of the authentic compound.

Conclusion

The concise asymmetric total synthesis of scyphostatin (**1**) was achieved from commercially available 1,4-cyclohexadiene in a total of 17 steps. The characteristic points of our synthesis are that 1) the chiral acetal from the optically pure hydrobenzoin works not only as a discrimination tool for two olefins, a source of oxygen atoms, and a protecting group for the alcohol unit, but also as the template for stereoselective oxidation using SeO_2;[8] 2) the silyl triflate/2,4,6-collidine combination works not only for the deprotection of the acetal, but also for the silylation of hydroxy functions to give disilyl aldehyde compounds with different kinds of silyl groups in a one-pot operation; 3) the use of the ^{2,4}DMPM protecting group would be very useful for the syntheses of other unstable compounds; and 4) the asymmetric centers are constructed step-by-step, which allows the syntheses of many stereoisomeric analogues.

Experimental Section

General: All melting points are uncorrected. ^{1}H NMR spectra were recorded at 270 or 300 MHz and ^{13}C NMR spectra were recorded at 67.8 or 75 MHz with $CDCl_3$ as the solvent and $SiMe_4$ as the internal standard. Infrared (IR) absorption spectra (cm^{-1}) were recorded as KBr pellets.

1-(2,2-Diethoxyethyl)-2,5-cyclohexadiene (8): *sec*-BuLi (0.98 M in *n*-hexane/cyclohexane, 3.2 mL, 3.1 mmol) was added slowly to a stirred solution of **7** (0.30 mL, 3.2 mmol) in THF (5 mL) at −78 °C under N_2. After being stirred for 5 min at the same temperature, TMEDA (0.50 mL, 3.3 mmol) was added. The resulting mixture was stirred for an additional 1 h. Bromoacetoaldehyde diethyl acetal (0.40 mL, 2.7 mmol) was added to the reaction mixture. After being stirred for 2 h, the reaction mixture was quenched by addition of saturated $NaHCO_3$. The reaction mixture was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane/Et_2O (10:1) as the eluent to give **8** (0.39 g, 2.0 mmol, 75 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17–1.25 (6H, m), 1.72 (2H, t, J = 5.7 Hz), 2.61–2.66 (2H, m), 2.83–2.94 (1H, m), 3.45–3.71 (4H, m), 4.65 (1H, t, J = 5.7 Hz), 5.65–5.74 ppm (4H, m).

(4*R*,5*R*)-2-(2,5-Cyclohexadienylmethyl)-4,5-diphenyl-1,3-dioxolane (2): *p*-TsOH (0.1 mmol) was added slowly to a stirred solution of **8** (0.31 g, 1.6 mmol) and (*R*,*R*)-hydrobenzoin (0.34 g, 1.6 mmol) in toluene (10 mL) under N_2. The resulting mixture was stirred for 2 h at 70 °C. After being cooled to room temperature, saturated $NaHCO_3$ (aq.) was added to the mixture. The reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane/EtOAc (25:1) as the eluent to give **2** (0.51 g, 1.6 mmol, 100 %) as a colorless oil. $[\alpha]_D^{25}$ = +31.0 (c = 1.00, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 3022, 1605, 1497, 1456 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02 (2H, dd, J = 4.8, 6.7 Hz), 2.6–2.7 (2H, m), 3.1–3.2 (1H, m), 4.77 (2H, s), 5.63 (1H, t, J = 4.8 Hz), 5.7–5.9 (4H, m), 7.2–7.4 ppm (10H, m); elemental analysis (%) calcd for $C_{22}H_{22}O_2$: C 82.99, H 6.96; found: C 82.93, H 7.04.

(1*R*,3*R*,4*R*,6*R*,8*R*,12*R*)-12-Bromo-6-methoxy-3,4-diphenyl-2,5-dioxabicyclo[6.4.0]dodec-9-ene (3): NBS (0.21 g, 1.2 mmol) was added portionwise to a stirred solution of **2** (0.32 g, 1.0 mmol) and MeOH (0.20 mL, 5.0 mmol) in CH_3CN (10 mL) at −40 °C under N_2. The resulting mixture was allowed to warm to room temperature over 6 h with stirring. After saturated $NaHCO_3$ (aq.) was added, The reaction mixture was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane/EtOAc (15:1) as the eluent to give **3** (0.27 g, 0.63 mmol, 64 %) as a colorless oil. $[\alpha]_D^{24}$ = −156.0 (c = 1.62, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 3031, 1495, 1454, 1125 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01 (2H, dd, J = 5.6, 6.3 Hz), 2.5–2.6 (1H, m), 2.8–3.0 (1H, m), 3.29 (3H, s), 3.3–3.5 (1H, m), 4.04 (1H, dd, J = 5.3, 8.9 Hz), 4.31 (1H, dt, J = 7.9, 5.9 Hz), 4.41 (1H, d, J = 9.1 Hz), 4.47 (1H, d, J = 9.1 Hz), 5.24 (1H, dd, J = 5.0, 6.3 Hz), 5.5–5.7 (2H, m), 6.9–7.4 ppm (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.3, 35.4, 37.7, 47.7, 54.9, 81.9, 88.0, 88.5, 105.1, 124.4, 127.3, 127.4, 127.5, 127.7, 127.8, 129.1, 137.9, 138.1 ppm; FAB-MS m/z: 451 [M^++Na]; HR-FAB-MS: calcd for $C_{23}H_{25}O_3BrNa$ [M^++Na]: 451.0885; found 451.0873.

(1*R*,3*R*,4*R*,6*R*,8*S*)-6-Methoxy-3,4-diphenyl-2,5-dioxabicyclo[6.4.0]dodec-9-ene (9): A mixture of **3** (0.91 g, 2.1 mmol), Bu_3SnH (0.86 mL, 3.2 mmol), and a catalytic amount of azobisisobutyronitrile (AIBN) in toluene (21 mL) was refluxed for 1 h under N_2. After being cooled to room temperature, saturated KF (aq.) was added to the mixture. The reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane/EtOAc (10:1) as the eluent to give **9** (0.66 g, 1.9 mmol, 89 %) as colorless crystals. M.p. 162–164 °C (hexane/EtOAc); $[\alpha]_D^{26}$ = −101.2 (c = 1.23, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 3029, 1096, 994 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.7–2.2 (6H, m), 3.2–3.3 (1H, m), 3.29 (3H, s), 3.84 (1H, dt, J = 4.5, 11.4 Hz), 4.42 (1H, d, J = 9.0 Hz), 4.49 (1H, d, J = 9.0 Hz), 5.39 (1H, dd, J = 5.1, 8.1 Hz), 5.63 (2H, d, J = 2.7 Hz), 6.9–7.3 ppm (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.6, 25.7, 35.4, 37.3, 54.8, 79.6, 87.4, 88.7, 105.3, 126.9, 127.3, 127.6, 127.7, 127.9, 129.1, 138.3, 139.5 ppm; elemental analysis (%) calcd for $C_{23}H_{26}O_3$: C 78.83, H 7.48; found: C 78.86, H 7.47.

(1*S*,3*R*,5*R*,6*R*,8*S*)-3-Methoxy-5,6-diphenyl-4,7-dioxabicyclo[6.4.0]dodec-11-en-1-ol (4): A mixture of **9** (71 mg, 0.202 mmol), pyridine (32.6 μL, 0.404 mmol), and SeO_2 (11.4 mg, 0.102 mmol) in 1,4-dioxane (4 mL) was stirred for 1 h at 80 °C under N_2. After being cooled to room temperature, saturated $NaHCO_3$ (aq.) was added to the mixture. The reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane/EtOAc (7:1) as the eluent to give **4** (30.6 mg, 0.084 mmol, 41 %) and recovered **9** (20.6 mg, 29 %). **4**: White crystals; M.p. 159–162 °C (hexane); $[\alpha]_D^{26}$ = −34.3 (c = 1.21, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 3438, 3033, 1096, 994 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.7–1.8 (1H, m), 1.9–2.0 (1H, m), 2.0–2.2 (2H, m), 2.07 (1H, dd, J = 7.2, 15.2 Hz), 2.44 (1H, dd, J = 4.5, 15.2 Hz), 3.32 (3H, s), 4.08 (1H, dd, J = 3.3, 10.8 Hz), 4.51 (1H, d, J = 9.0 Hz), 5.01 (1H, d, J = 9.0 Hz), 5.47 (1H, m), 5.50 (1H, s), 5.73 (1H, dt, J = 3.5, 9.9 Hz), 6.9–7.3 ppm (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.2, 27.3, 41.5, 55.0, 75.7, 84.0, 87.2, 89.0, 106.5, 127.1, 127.5, 127.6, 127.7, 127.9, 128.0, 128.1, 132.5, 137.3, 139.5 ppm; elemental analysis calcd (%) for $C_{23}H_{26}O_4$: C 75.38, H 7.15; found: C 75.43, H 7.12.

(1*S*,6*S*)-1-(2,2-Dimethoxyethyl)-6-[(1*R*,2*R*)-2-hydroxyethoxy-1,2-diphenyl]cyclohex-2-en-1-ol (10): PPTS (10 mg, 0.04 mmol) was added to a stirred solution of **4** (140 mg, 0.39 mmol) in MeOH (4 mL) at room temperature under N_2. The reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with saturated $NaHCO_3$ (aq.) and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane/EtOAc (2:1) as the eluent to give **10** (140 mg, 0.35 mmol, 91 %) as colorless crystals. M.p. 82–84 °C (hexane); $[\alpha]_D^{25}$ = −14.4 (c = 1.19, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 3455, 3031, 1455, 1240 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.4–1.7 (2H, m), 1.90 (1H, dd, J = 3.7, 14.5 Hz), 1.9–2.1 (2H, m), 2.49 (1H, dd, J = 8.6, 14.5 Hz), 3.41 (3H, s), 3.47 (3H, s), 3.80 (1H, dd, J = 4.1, 11.9 Hz), 4.1–4.4 (1H, br s), 4.41 (1H, d, J = 7.2 Hz), 4.68 (1H, d, J = 7.2 Hz), 4.7–5.0 (1H, br s), 4.82 (1H, dd, J = 3.7, 8.6 Hz), 6.9–7.3 ppm (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7, 25.8, 37.9, 52.2, 53.9, 73.5, 80.1, 84.0, 89.3, 102.7, 127.0, 127.4, 127.7, 131.6, 139.6, 139.8 ppm; el-

emental analysis (%) calcd for $C_{24}H_{30}O_5$: C 72.34, H 7.59; found: C 72.39, H 7.61.

(1*S*,2*S*)-2-(2,2-Dimethoxyethyl)cyclohex-3-ene-1,2-diol (24): Ca (49.3 mg, 1.23 mmol) was added to liquid NH_3 (3.0 mL) at −78 °C under N_2. The reaction mixture was allowed to warm to −40 °C to give a clear-blue solution. A solution of **10** (49.0 mg, 0.123 mmol) and EtOH (0.06 mL, 1.23 mmol) in Et_2O (0.5 mL) was added to dropwise to the blue solution at −40 °C under N_2. After being stirred for 30 min, the reaction mixture was quenched with saturated NH_4Cl (aq.) After NH_3 was removed by distillation at atmospheric pressure, The reaction mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane/EtOAc (1:2) as the eluent to give **24** (22.2 mg, 0.110 mmol, 91 %) as a colorless oil. $[\alpha]_D^{28} = -28.3$ ($c = 2.10$, $CHCl_3$): IR (KBr): $\tilde{\nu} = 3340$, 1724, 1380, 1274 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 1.66–1.83 (2H, m), 1.92–2.04 (1H, m), 2.13–2.21 (3H, m), 3.36 (3H, s), 3.44 (3H, s), 3.54 (1H, s), 3.81 (1H, dd, $J = 3.9$, 7.5 Hz), 3.85 (1H, s), 4.76 (1H, dd, $J = 3.9$, 7.5 Hz), 5.51 (1H, dt, $J = 10.0$, 2.1 Hz), 5.74 ppm (1H, dt, $J = 10.0$, 3.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.7$, 25.4, 38.2, 51.8, 53.6, 71.5, 72.4, 102.1, 127.9, 130.8 ppm; FAB-MS *m*/*z*: 225 [M^++Na]; HR-FAB-MS: calcd for $C_{10}H_{18}O_4Na$ [M^++Na]: 225.1103; found 225.1095.

(1*S*,6*S*)-1-(2,2-Dimethoxyethyl)-6-[(1,1-dimethylethyl)(dimethyl)siloxy]-cyclohex-2-en-1-ol (25): Imidazole (71.6 mg, 1.06 mmol) and TBSCl (158.6 mg, 1.06 mmol) were added successively to a solution of **24** (30.4 mg, 0.154 mmol) in DMF (1.5 mL) at room temperature under N_2, and the mixture was stirred for 12 h. The reaction mixture was quenched with addition of water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane/EtOAc (7:1) as the eluent to give **25** (46 mg, 0.14 mmol, 98 %) as a colorless oil. $[\alpha]_D^{25} = -15.5$ ($c = 1.29$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3487$, 2952, 1471, 1253 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.10$ (6H, s), 0.91 (9H, s), 1.56–1.65 (1H, m), 1.77–1.84 (2H, m), 2.09–2.16 (3H, m), 3.35 (3H, s), 3.38 (3H, s), 3.64 (1H, s), 3.77 (1H, dd, $J = 3.3$, 9.6 Hz), 4.78 (1H, dd, $J =$ 5.2, 6.8 Hz), 5.52 (1H, dt, $J = 10.0$, 1.8 Hz), 5.67 ppm (1H, dt, $J = 10.0$, 3.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.8$, 18.0, 23.5, 27.6, 37.7, 52.2, 53.0, 71.9, 74.7, 102.3, 127.6, 131.2 ppm; elemental analysis (%) calcd for $C_{16}H_{32}O_4Si$: C 60.72, H 10.19; found: C 60.64, H 10.00.

(1*S*,6*S*)-1-Triethylsiloxy-6-*tert*-butyldimethylsiloxycyclohex-2-en-1-yl acetaldehyde (26a): 2,4,6-Collidine (62 μL, 0.472 mmol) and TESOTf (71 μL, 0.315 mmol) were successively added to a solution of **25** (24.9 mg, 0.0787 mmol) in dry CH_2Cl_2 (0.78 mL) at 0 °C under N_2. After being stirred at the same temperature for 5 min, the reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography using hexane/EtOAc (25:1) as the eluent to give **26a** (28.1 mg, 0.073 mmol, 93 %) as a colorless oil. $[\alpha]_D^{25} = +36.9$ ($c = 1.60$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 2954$, 1720, 1461, 1253 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.08$ (6H, s), 0.62 (6H, q, $J =$ 7.8 Hz), 0.88 (9H, s), 0.94 (9H, t, $J = 7.8$ Hz), 1.54–1.64 (1H, m), 1.82–1.92 (1H, m), 2.03–2.19 (2H, m), 2.31 (1H, dd, $J = 2.7$, 15.9 Hz), 2.63 (1H, dd, $J = 3.2$, 15.9 Hz), 3.89 (1H, dd, $J = 2.0$, 14.5 Hz), 5.57 (1H, dt, $J = 10.0$, 1.8 Hz), 5.76 (1H, dt, $J = 10.0$, 3.6 Hz), 9.82 ppm (1H, dd, $J = 2.7$, 3.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.0$, 7.2, 18.0, 23.1, 25.9, 28.2, 51.4, 75.8, 129.5, 130.9, 202.6; elemental analysis (%) calcd for $C_{20}H_{40}O_3Si_2$: C 62.44, H 10.48; found: C 62.55, H 10.38 ppm.

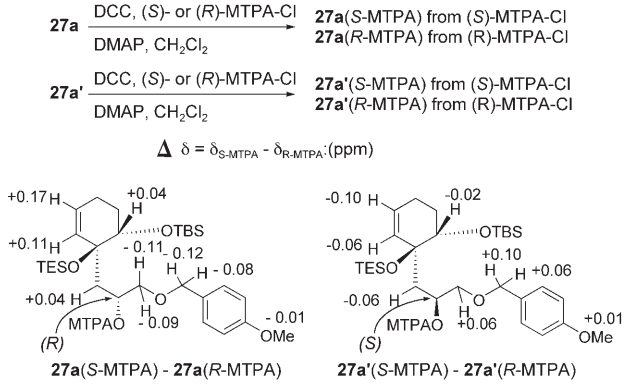
Preparation of $MPMOCH_2SnBu_3$ (13):[11] A mixture of 4-methoxybenzyl alcohol (3.8 mL, 30.4 mmol) and NaH (1.4 g, 60 % in oil, 35.1 mmol) in THF (120 mL) was stirred at room temperature under N_2. After being stirred for 1 h, a solution of tri-*n*-butylstannylmethyl iodide (10.1 g, 23.4 mL) in THF (30 mL) was added slowly to the solution. The resulting mixture was stirred for three days. The reaction mixture was quenched by addition of MeOH. The solution was diluted with Et_2O. The organic layer was washed with water two times. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane/Et_2O (30:1) as the eluent to give **13** (8.8 g, 85 %) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 0.86–0.94 (15H, m), 1.29 (6H, m), 1.49 (6H, m), 3.71 (2H, s), 3.78 (3H, s), 4.34 (2H, s), 6.86 (2H, d, $J = 8.7$ Hz), 7.22 ppm (2H, d, $J = 8.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 8.9$, 13.7, 27.3, 29.1, 55.1, 61.0, 77.4, 113.5, 129.0, 130.9, 158.9 ppm.

(2*R*)-1-[(1*S*,6*S*)-1-Triethylsiloxy-6-*tert*-butyldimethylsiloxycyclohex-2-en-1-yl]-3-[(4-methoxyphenyl)methyloxy]propan-2-ol (27a) and (2*S*)-1-[(1*S*,6*S*)-1-triethylsiloxy-6-*tert*-butyldimethylsiloxy cyclohex-2-en-1-yl]-3-[(4-methoxyphenyl)methyloxy]propan-2-ol (27a′): *n*BuLi (1.56 M in hexane, 0.22 mL) was added dropwise to a solution of $MPMOCH_2SnBu_3$ (**13**; 155.4 mg, 0.352 mmol) in dry THF (1.0 mL) at −78 °C under N_2. After being stirred for 15 min, a solution of **26a** (33.8 mg, 0.088 mmol) in THF (1.0 mL) was added to the reaction mixture. After being stirred for 5 min, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography using hexane/EtOAc (7:1) as the eluent to give **27a** (26.4 mg, 56 %) and **27a′** (12 mg, 25 %).

27a: Colorless oil; $[\alpha]_D^{25} = +33.0$ ($c = 1.25$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3482$, 2945, 1612, 1514, 1461 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.08$ (3H, s), 0.09 (3H, s), 0.62 (6H, q, $J = 7.8$ Hz), 0.83 (9H, s), 0.94 (9H, t, $J =$ 7.8 Hz), 1.58–2.19 (6H, m), 3.30–3.40 (2H, m), 3.80 (3H, s), 3.97 (1H, d, $J = 5.4$ Hz), 4.05 (1H, s), 4.11–4.20 (1H, m), 4.46 (1H, d, $J = 11.7$ Hz), 4.53 (1H, d, $J = 11.7$ Hz), 5.53 (1H, d, $J = 10.2$ Hz), 5.78 (1H, dt, $J = 10.2$, 3.6 Hz), 6.86 (2H, d, $J = 8.4$ Hz), 7.26 ppm (2H, d, $J = 8.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.9$, −4.0, 6.6, 7.0, 17.9, 22.2, 25.7, 26.3, 40.8, 55.1, 67.3, 72.8, 74.5, 76.2, 113.5, 129.1, 129.8, 130.5, 131.0, 159.0 pm; elemental analysis (%) calcd for $C_{29}H_{52}O_5Si_2$: C 64.88, H 9.76; found: C 64.74, H 9.79.

27a′: Colorless oil; $[\alpha]_D^{26} = -12.5$ ($c = 1.39$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3482$, 2931, 1612, 1514, 1463 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.11$ (3H, s), 0.14 (3H, s), 0.62 (6H, q, $J = 7.2$ Hz), 0.91 (9H, s), 0.93 (9H, t, $J =$ 7.2 Hz), 1.62–1.77 (3H, m), 1.98 (1H, dd, $J = 9.0$, 14.7 Hz), 2.07–2.13 (2H, m), 3.35–3.46 (2H, m), 3.80 (3H, s), 3.84 (1H, dd, $J = 4.2$, 10.8 Hz), 4.11–4.18 (1H, m), 4.18 (1H, s), 4.50 (2H, s), 5.62–5.64 (2H, m), 6.86 (2H, d, $J = 8.7$ Hz), 7.26 ppm (2H, d, $J = 8.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.6$, −4.4, 6.6, 6.8, 7.0, 7.1, 18.0, 24.5, 25.7, 25.8, 28.8, 41.8, 55.1, 66.0, 72.7, 74.5, 77.0, 113.5, 127.7, 129.1, 130.6, 133.0, 158.9 ppm; FAB-MS *m*/*z*: 559 [M^++Na]; HR-FAB-MS: calcd for $C_{29}H_{52}O_5Si_2Na$ [M^++Na]: 559.3251; found 559.3265.

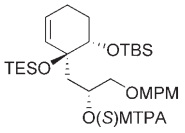
Determination of the absolute configurations of the secondary alcohols of 27a and 27a′: The absolute configurations of the secondary alcohols of **27a** and **27a′** were determined by a modified Mosher's method.[12]



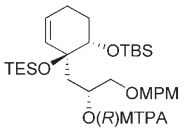
General procedure for the preparation of an MTPA ester: DCC (3.3 mmol), α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl) (4.3 mmol), and DMAP (3.3 mmol) were added successively to a stirred solution of secondary alcohol **27a** or **27a′** (1.0 mmol) in

CH_2Cl_2 (10.0 mL) at room temperature. After being stirred for 30 min, the solvent was removed in vacuo. The residue was purified by column chromatography using hexane/EtOAc (20:1) as the eluent.

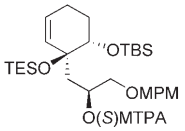
(2*R*)-1-[(1*S*,6*S*)-1-Triethylsiloxy-6-*tert*-butyldimethylsiloxycyclohex-2-en-1-yl]-3-[(4-methoxyphenyl)methyloxy]propan-2-yl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (27a; (*S*)-MTPA): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.07$ (6H, s), 0.62 (6H, q, $J=7.8$ Hz), 0.87 (9H, s), 0.94 (9H, t, $J=7.8$ Hz), 1.37–2.08 (5H, m), 2.15 (1H, dd, $J=4.8$, 15.0 Hz), 3.44 (1H, d, $J=10.8$ Hz), 3.49 (3H, s), 3.56 (1H, dd, $J=2.1$, 10.8 Hz), 3.76 (1H, dd, $J=3.6$, 11.1 Hz), 3.80 (3H, s), 3.99–4.07 (1H, m), 4.32 (1H, d, $J=11.4$ Hz), 4.41 (1H, d, $J=11.4$ Hz), 5.62 (1H, d, $J=10.0$ Hz), 5.69 (1H, d, $J=10.0$ Hz), 6.83 (2H, d, $J=8.4$ Hz), 7.16 (2H, d, $J=8.4$ Hz), 7.27–7.35 (3H, m), 7.57 ppm (2H, d, $J=7.5$ Hz).



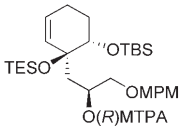
(2*R*)-1-{(1*S*,6*S*)-1-Triethylsiloxy-6-[*tert*-butyldimethylsiloxycyclohex-2-en-1-yl]}-3-[(4-methoxyphenyl)methyloxy]propan-2-yl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (27a; (*R*)-MTPA): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.05$ (6H, s), 0.61 (6H, q, $J=7.8$ Hz), 0.85 (9H, s), 0.94 (9H, t, $J=7.8$ Hz), 1.42–1.72 (3H, m), 1.96–2.00 (2H, m), 2.11 (1H, dd, $J=5.1$, 15.3 Hz), 3.52 (1H, d, $J=10.8$ Hz), 3.56 (3H, s), 3.65 (1H, dd, $J=2.7$, 11.0 Hz), 3.72 (1H, dd, $J=3.6$, 11.0 Hz), 3.81 (3H, s), 4.41 (1H, d, $J=11.4$ Hz), 4.53 (1H, d, $J=11.4$ Hz), 5.44 (1H, dt, $J=10.2$, 3.0 Hz), 5.58 (1H, d, $J=10.2$ Hz), 5.63–5.73 (1H, m), 6.85 (2H, d, $J=8.7$ Hz), 7.23 (2H, d, $J=8.7$ Hz), 7.28–7.37 (3H, m), 7.59 ppm (2H, d, $J=7.5$ Hz).



(2*S*)-1-{(1*S*,6*S*)-1-Triethylsiloxy-6-[*tert*-butyldimethylsiloxycyclohex-2-en-1-yl]}-3-[(4-methoxyphenyl)methyloxy]propan-2-yl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (27a′; (*S*)-MTPA): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.04$ (3H, s), 0.07 (3H, s), 0.57 (6H, q, $J=7.8$ Hz), 0.85 (9H, s), 0.91 (9H, t, $J=7.8$ Hz), 1.50–1.98 (5H, m), 2.03 (1H, dd, $J=4.5$, 10.5 Hz), 3.52–3.54 (1H, m), 3.55 (3H, s), 3.70 (1H, dd, $J=3.6$, 9.6 Hz), 3.79 (1H, dd, $J=2.4$, 11.4 Hz), 3.80 (3H, s), 4.38 (1H, d, $J=11.4$ Hz), 4.52 (1H, d, $J=11.4$ Hz), 5.40 (1H, d, $J=10.0$ Hz), 5.61 (1H, dt, $J=10.0$, 3.6 Hz), 5.70–5.75 (1H, m), 6.84 (2H, d, $J=8.7$ Hz), 7.22 (2H, d, $J=8.7$ Hz), 7.27–7.41 (3H, m), 7.59 ppm (2H, d, $J=7.2$ Hz).



(2*S*)-1-{(1*S*,6*S*)-1-Triethylsiloxy-6-[*tert*-butyldimethylsiloxycyclohex-2-en-1-yl]}-3-[(4-methoxyphenyl)methyloxy]propan-2-yl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (27a′; (*R*)-MTPA): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.07$ (3H, s), 0.09 (3H, s), 0.58 (6H, q, $J=7.5$ Hz), 0.86 (9H, s), 0.91 (9H, t, $J=7.5$ Hz), 1.53–1.94 (5H, m), 2.09 (1H, dd, $J=4.2$, 14.4 Hz), 3.45 (1H, dd, $J=8.1$, 11.4 Hz), 3.51 (3H, s), 3.72 (1H, dd, $J=2.4$, 11.4 Hz), 3.78 (3H, s), 3.84 (1H, dd, $J=3.3$, 9.6 Hz), 4.31 (1H, d, $J=11.7$ Hz), 4.42 (1H, d, $J=11.7$ Hz), 5.49 (1H, d, $J=10.2$ Hz), 5.67 (1H, dt, $J=10.2$, 3.9 Hz), 5.71–5.77 (1H, m), 6.82 (2H, d, $J=8.7$ Hz), 7.16 (2H, d, $J=8.7$ Hz), 7.25–7.42 (3H, m), 7.56 ppm (2H, d, $J=7.5$ Hz).



(2*S*)-2-Azido-1-{(1*S*,6*S*)-1-triethylsiloxy-6-[*tert*-butyldimethylsiloxycyclohex-2-en-1-yl]}-3-[(4-methoxyphenyl)methyloxy]propane (28a): PPh_3 (194.0 mg, 0.738 mmol), DEAD (0.33 mL; 40% in toluene, 0.738 mmol), and DPPA (95 μL, 0.442 mmol) were added successively to a stirred solution of **27a** (207.4 mg, 0.369 mmol) in THF (3.7 mL) at room temperature under Ar. The reaction mixture was stirred at the same temperature for 30 min. After removal of the solvent in vacuo, the residue was purified by column chromatography using hexane/EtOAc (20:1) as the eluent to give **28a** (138.8 mg, 0.247 mmol, 67%) as a colorless oil. $[\alpha]_D^{25}=+19.7$ ($c=0.77$, $CHCl_3$); IR (KBr): $\tilde{\nu}=2952$, 2104, 1612, 1514, 1461 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.08$ (3H, s), 0.11 (3H, s), 0.58 (6H, q, $J=7.8$ Hz), 0.88 (9H, s), 0.92 (9H, t, $J=7.8$ Hz), 1.50–1.65 (3H, m), 1.84–1.92 (3H, m), 1.98–2.12 (1H, m), 3.41 (1H, dd, $J=8.4$, 9.9 Hz), 3.66 (1H, dd, $J=3.3$, 9.9 Hz), 3.81 (3H, s), 3.86 (1H, dd, $J=2.8$, 8.4 Hz), 4.42 (2H, s), 5.48 (1H, d, $J=10.1$ Hz), 5.74 (1H, dt, $J=10.1$, 3.7 Hz), 6.88 (2H, d, $J=8.6$ Hz), 7.28 ppm (2H, d, $J=8.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=-4.1$, −4.0, 6.9, 7.0, 14.1, 18.0, 22.5, 25.8, 27.2, 38.9, 55.1, 58.2, 72.7, 73.6, 74.0, 74.5, 113.6, 113.7, 128.9, 129.0, 129.2, 129.6, 130.1, 131.3, 159.1 ppm; FAB-MS m/z: 584 (M^++Na); HR-FAB-MS: calcd for $C_{29}H_{51}N_3O_4Si_2Na$ [M^++Na]: 584.3316; found 584.3322.

(1*S*,6*S*)-1-{(2*S*)-3-[(4-methoxyphenyl)methyloxy]-2-[(2*E*,4*E*,6*E*,12*E*)-(8*R*,10*S*,14*R*)-8,10,12,14-(tetramethyl)hexadeca-2,4,6,12-tetraenoylamino]propyl}-2-cyclohexene-1,6-diol (32a): A solution of **28a** (138.8 mg, 0.247 mmol) in dry THF (2.4 mL) was added to a solution of $LiAlH_4$ (93.7 mg, 2.47 mmol) in THF (2.4 mL) at 0°C under Ar. After being stirred for 1.5 h at room temperature, the reaction mixture was quenched with water and 15% NaOH (aq.), then the precipitate was filtered through a Celite pad. The filtrate was evaporated in vacuo to give crude **29a**. Side-chain carboxylic acid **30** (86.0 mg, 0.296 mmol), DCC (203.9 mg, 0.988 mmol), and DMAP (120.7 mg, 0.988 mmol) were added to a solution of crude **29a** in CH_2Cl_2 (2.5 mL) at room temperature under Ar. After being stirred for 1 h, the reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo to give crude coupled product **31a**. TBAF (2.47 mL, 1.0 M in THF, 2.47 mmol) was added to crude **31a** in THF (1.2 mL) at room temperature under Ar. After being stirred at room temperature for 10 h, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography using hexane/EtOAc (1:2) as the eluent to give **32a** (97.6 mg, 66%) as a yellow oil. $[\alpha]_D^{24}=+3.13$ ($c=1.53$, $CHCl_3$); IR (KBr): $\tilde{\nu}=3307$, 2923, 1651, 1608, 1514, 1456 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.79$ (3H, d, $J=6.4$ Hz), 0.84 (3H, t, $J=7.3$ Hz), 0.90 (3H, d, $J=6.6$ Hz), 0.99 (3H, d, $J=6.6$ Hz), 1.03 (1H, m), 1.16–1.34 (3H, m), 1.52 (3H, d, $J=1.3$ Hz), 1.55 (1H, m), 1.72–1.80 (2H, m), 1.83–1.92 (3H, m), 1.98–2.09 (2H, m), 2.17 (1H, m), 2.23 (1H, m), 2.32 (1H, m), 3.60 (1H, d, $J=4.2$ Hz), 3.81 (3H, s), 3.92 (1H, dd, $J=2.9$, 8.3 Hz), 4.26 (1H, m), 4.42 (1H, d, $J=11.5$ Hz), 4.50 (1H, d, $J=11.5$ Hz), 4.84 (1H, d, $J=9.4$ Hz), 5.51 (1H, d, $J=10.0$ Hz), 5.67–5.72 (2H, m), 5.76 (1H, d, $J=14.9$ Hz), 6.07 (1H, dd, $J=10.9$, 14.9 Hz), 6.16 (1H, dd, $J=11.4$, 14.7 Hz), 6.27 (1H, d, $J=6.0$ Hz), 6.48 (1H, dd, $J=10.9$, 14.7 Hz), 6.89 (2H, d, $J=9.0$ Hz), 7.22 (1H, dd, $J=11.4$, 14.9 Hz), 7.26 ppm (2H, d, $J=9.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=12.1$, 16.2, 19.5, 21.1, 21.4, 22.9, 25.7, 28.3, 30.6, 34.1, 34.9, 39.1, 44.0, 45.9, 48.3, 55.3, 72.0, 72.3, 72.6, 72.9, 113.9, 121.9, 127.7, 128.3, 129.2, 129.6, 129.8, 131.3, 132.1, 133.1, 140.7, 141.9, 145.7, 159.4, 166.9 ppm; FAB-MS m/z: 594 [M^++H]; HR-FAB-MS: calcd for $C_{37}H_{56}NO_5$ [M^++H]: 594.4158; found 594.4153.

(1*R*,2*S*,3*S*,6*S*)-1,6-Dihydroxy-2,3-epoxy-1-{(2*S*)-3-[(4-methoxyphenyl)methyloxy]-2-[(2*E*,4*E*,6*E*,12*E*)-(8*R*,10*S*,14*R*)-8,10,12,14-(tetramethyl)hexadeca-2,4,6,12-tetraenoylamino]propyl}cyclohexane (33a): A solution of aqueous TBHP (18 μL, 0.147 mmol) in toluene (0.2 mL) was dried with molecular sieves (4 Å) at room temperature under Ar. After being stirred for 20 min, a solution of **32a** (8.7 mg, 0.0147 mmol) and [VO(acac)$_2$] (2.1 mg, 0.008 mmol) in dry toluene (0.5 mL) was added to the above mixture at 0°C. After being stirred for 30 min, the reaction mixture was quenched with saturated $Na_2S_2O_3$ (aq.) and extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography using hexane/EtOAc (3:2) as the eluent to give **33a** (6.1 mg, 69%) as a yellow oil. $[\alpha]_D^{24}=+10.2$ ($c=1.10$, $CHCl_3$); IR (KBr): $\tilde{\nu}=3305$, 2956, 1651, 1606, 1514, 1454 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.79$ (3H, d, $J=6.6$ Hz), 0.83 (3H, t, $J=7.1$ Hz), 0.90 (3H, d, $J=6.8$ Hz), 0.99 (3H, d, $J=6.6$ Hz), 1.12–1.32 (4H, m), 1.52 (3H, s), 1.53–1.67 (4H, m), 1.71–1.78 (1H, m), 1.84–2.08 (4H, m), 2.23 (1H, m), 2.33 (1H, m), 2.81 (1H, d, $J=3.5$ Hz), 3.40 (1H, d, $J=3.5$ Hz), 3.72–3.81 (3H, m), 3.82 (3H, s), 4.21 (1H, m), 4.50 (2H, s), 4.83 (1H, d, $J=9.3$ Hz), 5.70 (1H, dd, $J=8.4$, 14.7 Hz), 5.74 (1H, d, $J=14.8$ Hz), 6.08 (1H, dd, $J=10.8$, 14.7 Hz), 6.16

(1H, dd, J=11.4, 14.6 Hz), 6.23 (1H, d, J=6.5 Hz), 6.47 (1H, dd, J=10.8, 14.6 Hz), 6.90 (2H, d, J=8.6 Hz), 7.22 (1H, dd, J=11.4, 14.8 Hz), 7.28 ppm (2H, d, J=8.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=12.1, 15.9, 18.6, 19.9, 21.1, 21.4, 28.3, 30.5, 32.3, 34.1, 34.9, 38.4, 43.9, 46.1, 48.2, 55.3, 56.1, 57.8, 67.0, 69.9, 71.4, 73.0, 113.9, 121.6, 127.6, 128.3, 129.6, 129.9, 132.1, 133.1, 140.8, 142.2, 145.9, 159.6, 166.9 ppm; FAB-MS m/z: 610 [M^++H]; HR-FAB-MS: calcd for $C_{37}H_{56}NO_6$ [M^++H]: 610.4108; found 610.4092.

(2*S*,3*S*,4*S*)-3,4-Epoxy-2-hydroxy-2-{(2*S*)-3-[(4-methoxyphenyl)methyloxy]-2-[(2*E*,4*E*,6*E*,12*E*)-(8*R*,10*S*,14*R*)-8,10,12,14-(tetramethyl)hexadeca-2,4,6,12-tetraenoylamino]propyl}cyclohexan-1-one (34a): TPAP (1.1 mg, 0,0030 mmol) and NMO (4.6 μL, 0.0224 mmol) were added to a stirred solution of **33a** (9.1 mg, 0.0149 mmol) in CH_2Cl_2 (0.15 mL) at 0°C under Ar. After being stirred for 30 min, the reaction mixture was quenched with saturated $NaHCO_3$ (aq.) and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography using hexane/EtOAc (1:1) as the eluent to give **34a** (4.4 mg, 49%) as a yellow oil, and the substrate **33a** (4.0 mg, 44%) was recovered. $[\alpha]_D^{26}=-7.5$ (c=1.04, $CHCl_3$); IR (KBr): $\tilde{\nu}$=3290, 2923, 1722, 1651, 1610, 1514, 1461 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.77–0.86 (6H, m), 0.90 (3H, d, J=6.8 Hz), 0.99 (3H, d, J=6.3 Hz), 1.10–1.40 (4H, m), 1.52 (3H, s), 1.55 (1H, m), 1.76 (1H, m), 1.87 (1H, m), 2.14 (1H, d, J=2.9 Hz), 2.16 (1H, d, J=2.9 Hz), 2.21 (1H, m), 2.30–2.46 (4H, m), 2.79 (1H, m), 3.36 (1H, d, J=4.1 Hz), 3.39 (1H, m), 3.45 (1H, dd, J=5.3, 9.4 Hz), 3.65 (1H, dd, J=4.4, 9.4 Hz), 3.81 (3H, s), 4.06 (1H, m), 4.13 (1H, brs), 4.38 (1H, d, J=11.2 Hz), 4.43 (1H, d, J=11.2 Hz), 4.84 (1H, d, J=9.8 Hz), 5.69 (1H, dd, J=8.5, 15.2 Hz), 5.71 (1H, d, J=14.9 Hz), 6.06 (1H, d, J=8.5 Hz), 6.08 (1H, dd, J=11.0, 15.2 Hz), 6.16 (1H, dd, J=11.2, 14.9 Hz), 6.48 (1H, dd, J=11.0, 14.9 Hz), 6.78 (2H, d, J=8.5 Hz), 7.19 (1H, dd, J=11.2, 14.9 Hz), 7.24 ppm (2H, d, J=8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=12.1, 16.2, 19.5, 21.1, 22.3, 24.9, 25.6, 28.3, 29.7, 30.5, 31.6, 33.9, 35.1, 46.3, 49.2, 53.0, 60.7, 70.9, 72.9, 77.8, 113.9, 122.2, 127.7, 128.3, 129.6, 129.9, 132.1, 133.1, 140.5, 141.6, 145.6, 159.4, 166.1, 209.9 ppm; FAB-MS m/z: 608 [M^++H]; HR-FAB-MS: calcd for $C_{37}H_{54}NO_6$ [M^++H]: 608.3951; found 608.3937.

(4*S*,5*S*,6*S*)-4,5-Epoxy-6-hydroxy-6-{(2*S*)-3-[(4-methoxyphenyl)methyloxy]-2-[(2*E*,4*E*,6*E*,12*E*)-(8*R*,10*S*,14*R*)-8,10,12,14-(tetramethyl)hexadeca-2,4,6,12-tetraenoylamino]propyl}2-cyclohexen-1-one (35a): LDA in THF (0.25 M) was prepared as follows: *n*BuLi (1.56 M in hexane, 0.78 mL) was added to a solution of diisopropylamine (70.3 μL, 0.5 mmol) in dry THF (1.15 mL) at −78°C for 30 min under Ar. LDA (0.25 M in THF, 0.10 mL) and [15]crown-5 (20 μL, 0.10 mmol) were added to a solution of **34a** (6.1 mg, 0.010 mmol) in THF (0.1 mL) at −78°C under Ar. After being stirred for 10 min, a solution of *N*-*tert*-butylbenzenesulfinimidoyl chloride (22.0 mg, 0.10 mmol) in THF (0.1 mL) was added to the reaction mixture. After being stirred for 30 min, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography using Et_2O as the eluent to give **35a** (2.3 mg, 0.0037 mmol, 38%) as a yellow oil, and the substrate **34a** (1.6 mg, 26%) was recovered. $[\alpha]_D^{25}=+22.3$ (c=0.32, $CHCl_3$); IR (KBr): $\tilde{\nu}$=3320, 2922, 1693, 1651, 1612, 1514, 1454 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.71–0.91 (9H, m), 0.99 (3H, d, J=7.0 Hz), 1.20–1.30 (4H, m), 1.52 (3H, s), 1.55 (1H, m), 1.85–2.05 (4H, m), 2.20 (1H, m), 2.31 (1H, m), 3.46 (1H, dd, J=4.0, 9.0 Hz), 3.53 (1H, m), 3.58 (1H, dd, J=3.5, 9.0 Hz), 3.69 (1H, d, J=4.0 Hz), 3.81 (3H, s), 4.14 (1H, brs), 4.22 (1H, m), 4.42 (2H, s), 4.84 (1H, d, J=9.0 Hz), 5.69 (1H, m) 5.70 (1H, d, J=15.0 Hz), 5.91 (1H, d, J=8.7 Hz), 6.08 (1H, dd, J=11.0, 15.5 Hz), 6.16 (1H, dd, J=10.5, 14.0 Hz), 6.17 (1H, d, J=10.5 Hz), 6.48 (1H, dd, J=11.0, 14.0 Hz), 6.88 (2H, d, J=8.7 Hz), 7.08 (1H, dd, J=3.5, 8.7 Hz), 7.22 (1H, m), 7.23 ppm (2H, d, J=8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=11.9, 14.0, 15.9, 21.0, 22.6, 28.2, 29.2, 29.7, 32.1, 33.5, 34.9, 38.3, 44.9, 47.1, 55.3, 58.9, 65.5, 71.4, 72.9, 106.8, 109.1, 113.9, 121.8, 127.2, 128.0, 128.5, 129.5, 130.3, 132.9, 140.0, 141.9, 143.9, 158.9, 165.6, 197.3 ppm; FAB-MS m/z: 606 [M^++H]; HR-FAB-MS: calcd for $C_{37}H_{52}NO_6$ [M^++H]: 606.3795; found 606.3796.

(4*S*,5*S*,6*S*)-4,5-Epoxy-6-hydroxy-6-{(2*S*)-3-hydroxy-2-[(2*E*,4*E*,6*E*,12*E*)-(8*R*,10*S*,14*R*)-8,10,12,14-(tetramethyl)hexadeca-2,4,6,12-tetraenoylamino]propyl}-2-cyclohexen-1-one (scyphostatin (1)): $Ph_3C^+BF_4^-$ (6.6 mg, 0.0200 mmol) was added to a solution of **35a** (10.1 mg, 0.0167 mmol) in CH_2Cl_2 (0.2 mL) at 0°C under Ar. After being stirred for 5 min, the reaction mixture was quenched with saturated $NaHCO_3$ (aq.) and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography using EtOAc/acetone (4:1) as the eluent to give scyphostatin (**1**) (2.67 mg, 32%) as a yellow oil. $[\alpha]_D^{25}=+60.5$ (c=0.20, MeOH); IR (KBr): $\tilde{\nu}$=3292, 2956, 2923, 1697, 1651, 1606, 1512, 1454 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ=0.83–0.86 (6H, m), 0.91 (3H, d, J=6.7 Hz), 1.00 (3H, d, J=6.8 Hz), 1.04 (1H, m), 1.19 (1H, m), 1.27–1.41 (2H, m), 1.54 (3H, s), 1.58 (1H, m), 1.78 (1H, m), 1.86 (1H, m), 1.88 (1H, m), 2.08 (1H, dd, J=3.7, 14.7 Hz), 2.27 (1H, m), 2.35 (1H, m), 3.46 (1H, dd, J=5.5, 11.0 Hz), 3.52 (1H, dd, J=4.9, 11.0 Hz), 3.59 (1H, m), 3.66 (1H, d, J=3.7 Hz), 4.04 (1H, m), 4.86 (1H, m), 5.71 (1H, m), 5.89 (1H, d, J=15.3 Hz), 6.07 (1H, dd, J=1.3, 9.8 Hz), 6.15 (1H, dd, J=11.6, 14.6 Hz), 6.26 (1H, dd, J=11.0, 15.3 Hz), 6.54 (1H, dd, J=11.0, 14.6 Hz), 7.09–7.18 ppm (2H, m); ^{13}C NMR (125 MHz, CD_3OD): δ=12.9, 16.9, 20.5, 22.0, 22.5, 30.1, 32.2, 36.0, 36.7, 40.3, 46.0, 48.5, 49.8, 50.1, 58.8, 65.9, 78.0, 124.2, 129.9, 130.4, 132.6, 134.5, 134.7, 141.8, 142.9, 146.4, 146.8, 169.0, 200.4 ppm; FAB-MS m/z: 486 [M^++H]; HR-FAB-MS: calcd for $C_{29}H_{44}NO_5$ [M^++H]: 486.3219; found 486.3199. The ^{1}H and ^{13}C NMR, IR, and HR-FAB-MS spectra showed good agreement with those of authentic sample (see the Acknowledgements).

Experiment in Scheme 8: 2,4,6-Collidine (0.18 mL, 1.38 mmol) and TESOTf (0.21 mL, 0.920 mmol) were successively added to a solution of **24** (46.1 mg, 0.230 mmol) in dry CH_2Cl_2 (2.3 mL) at 0°C under N_2. After being stirred at the same temperature for 5 min, the reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography using hexane/EtOAc (25:1) as the eluent to give **36** (41.1 mg, 0.146 mmol, 63%) as a colorless oil. $[\alpha]_D^{22}=+136.5$ (c=0.64, $CHCl_3$); IR (KBr): $\tilde{\nu}$=2875, 1445, 1238 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.57 (6H, q, J=7.9 Hz), 0.93 (9H, t, J=7.9 Hz), 1.80–1.88 (2H, m), 1.95–2.12 (3H, m), 2.33–2.48 (1H, m), 3.35 (3H, s), 4.04 (1H, t, 5.4 Hz), 5.09 (1H, dd, J=3.2, 6.3 Hz), 5.70–5.83 ppm (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ=6.4, 6.9, 21.2, 26.1, 47.8, 55.4, 77.2, 83.4, 104.7, 128.2, 130.6 ppm; FAB-MS m/z: 307 [M^++Na]; HR-FAB-MS: calcd for $C_{15}H_{28}O_3SiNa$ [M^++Na]: 307.1701; found 307.1736.

General procedure for the one-pot synthesis of disilyl aldehydes: Silyl triflate (R^1OTf) was added to a solution of 2,4,6-collidine in dry CH_2Cl_2 at 0 or −78°C under N_2. After being stirred at the same temperature for 30 min, a solution of **24** in dry CH_2Cl_2 was added to the reaction mixture at the same temperature. After being stirred at the same temperature for 5–10 min, silyl triflate (R^2OTf) was added to the reaction mixture at the same temperature. After being stirred at the same temperature for 5 min, the reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography using hexane/EtOAc (25:1) as the eluent to give **26** in the yield shown in Table 1.

(1*S*,6*S*)-1,6-Di(triethylsiloxy)cyclohex-2-en-1-yl acetaldehyde (26b): Colorless oil; $[\alpha]_D^{24}=+38.5$ (c=0.68, $CHCl_3$); IR (KBr): $\tilde{\nu}$=2955, 1715, 1458, 1238 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.61 (12H, q, J=7.9 Hz), 0.94 (9H, t, J=7.9 Hz), 0.95 (9H, t, J=7.9 Hz), 1.57–1.67 (1H, m), 1.84–1.94 (1H, m), 1.99–2.19 (2H, m), 2.33 (1H, dd, J=2.4, 15.9 Hz), 2.59 (1H, dd, J=3.0, 15.9 Hz), 3.90 (1H, dd, J=3.2, 9.2 Hz), 5.59 (1H, dt, J=10.1, 1.8 Hz), 5.78 (1H, dt, J=10.1, 3.6 Hz), 9.79 ppm (1H, t, J=3.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ=4.9, 6.7, 6.8, 7.1, 23.1, 28.3, 51.7, 75.5, 75.7, 129.6, 131.0, 202.3 ppm; FAB-MS m/z: 407 [M^++Na]; HR-FAB-MS: calcd for $C_{20}H_{40}O_3Si_2Na$ [M^++Na]: 407.2414; found 407.2433.

(1*S*,6*S*)-1,6-Di(*tert*-butyldimethylsiloxy)cyclohex-2-en-1-yl acetaldehyde (26c): Colorless oil; $[\alpha]_D^{25}=+64.4$ (c=0.70, $CHCl_3$); IR (KBr): $\tilde{\nu}$=2955, 1717, 1471, 1256 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.07 (3H, s), 0.08 (3H, s), 0.09 (3H, s), 0.11 (3H, s), 0.86 (18H, s), 1.58–1.69 (1H, m), 1.89–2.06 (2H, m), 2.12–2.21 (1H, m), 2.35 (1H, dd, J=2.7, 15.9 Hz), 2.67

(1H, dd, J=2.7, 15.9 Hz), 3.92 (1H, dd, J=2.4, 7.5 Hz), 5.56 (1H, d, J=10.1 Hz), 5.83 (1H, dt, J=10.1, 3.6 Hz), 9.83 ppm (1H, t, J=2.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ=−4.7, −4.2, −2.3, −1.9, 18.0, 18.2, 22.2, 25.8, 25.9, 27.1, 51.7, 74.5, 74.8, 130.2, 130.4, 202.7 ppm; FAB-MS m/z: 407 [M^++Na]; HR-FAB-MS: calcd for $C_{20}H_{40}O_3Si_2Na$ [M^++Na]: 407.2414; found 407.2415.

(1*S*,6*S*)-1-Trimethylsiloxy-6-(*tert*-butyldimethylsiloxy)cyclohex-2-en-1-yl acetaldehyde (26d): Colorless oil; $[\alpha]_D^{25}$=+41.0 (c=1.20, $CHCl_3$): IR (KBr): $\tilde{\nu}$=2929, 1722, 1461, 1251 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.07 (6H, s), 0.12 (9H, s), 0.86 (9H, s), 1.59 (1H, m), 1.84 (1H, m) 1.96–2.17 (2H, m), 2.30 (1H, dd, J=2.6, 15.7 Hz), 2.65 (1H, dd, J=3.0, 15.7 Hz), 3.86 (1H, dd, J=3.3, 9.5 Hz), 5.61 (1H, dt, J=10.0, 1.8 Hz), 5.77 (1H, dt, J=10.0, 3.5 Hz), 9.81 ppm (1H, t, J=3.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ=−4.6, −4.5, 2.4, 18.0, 23.3, 25.8, 28.2, 51.2, 75.4, 76.3, 129.6, 130.7, 202.9 ppm; FAB-MS m/z: 365 [M^++Na], HR-FAB-MS m/z: calcd for $C_{17}H_{34}O_3Si_2Na$ [M^++Na]: 365.1944; found 365.1949.

(1*S*,6*S*)-1-Triisopropylsiloxy-6-triethylsiloxy-cyclohex-2-en-1-yl acetaldehyde (26e): Colorless oil; $[\alpha]_D^{21}$=+15.6 (c=0.52, $CHCl_3$); IR (KBr): $\tilde{\nu}$=2947, 1715, 1462, 1101 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.62 (6H, q, J=7.8 Hz), 0.94 (9H, t, J=7.8 Hz), 1.08 (18H, s), 0.88–1.15 (3H, m), 1.58–1.69 (1H, m), 1.87–1.96 (1H, m), 2.02–2.18 (2H, m), 2.34 (1H, dd, J=2.4, 15.8 Hz), 2.69 (1H, dd, J=3.4, 15.8 Hz), 4.06 (1H, dd, J=3.3, 10.5 Hz), 5.60 (1H, dt, J=9.8, 1.7 Hz), 5.74 (1H, dt, J=9.8, 3.7 Hz), 9.91 ppm (1H, dd, J=2.4, 3.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ=6.8, 7.1, 12.9, 18.15, 18.23, 24.1, 29.4, 51.2, 77.1, 77.2, 128.9, 131.6, 203.1 ppm; FAB-MS m/z: 449 [M^++Na]; HR-FAB-MS: calcd for $C_{23}H_{46}O_3Si_2Na$ [M^++Na]: 449.2844; found 449.2880.

Experiments in Table 2: Compounds **38a–c** were prepared from cyclohexylacetoaldehyde and the corresponding stannyl compound with 4-methoxyphenylmethyloxymethyl (for **38a**), 3,4-dimethoxyphenylmethyloxymethyl (for **38b**), or 2,4-dimethoxyphenylmethyloxymethyl (for **38c**) groups in the same way as compounds **31a** and **31b** (see Schemes 7 and 11, respectively).

MPM ether (38a): White crystals; m.p. 110–112°C; IR (KBr): $\tilde{\nu}$=3273, 2923, 1651, 1612, 1514, 1448 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (3H, t, J=6.2 Hz), 0.85–0.98 (2H, m), 1.08–1.32 (15H, m), 1.35–1.49 (2H, m), 1.52–1.71 (7H, m), 1.74–1.83 (1H, m), 2.12 (2H, dd, J=6.8, 14.3 Hz), 3.47 (2H, t, J=3.1 Hz), 3.81 (3H, s), 4.27 (1H, m), 4.40 (1H, d, J=11.8 Hz), 4.47 (1H, d, J=11.8 Hz), 5.56 (1H, d, J=9.3 Hz), 5.75 (1H, d, J=14.9 Hz), 5.88 (1H, m), 6.07–6.22 (2H, m), 6.49 (1H, dd, J=10.6, 14.9 Hz), 6.68 (2H, d, J=8.7 Hz), 7.22 (1H, m), 7.24 ppm (2H, d, J=8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.1, 22.6, 26.1, 26.2, 26.5, 29.0, 29.2, 29.3, 29.4, 29.5, 31.8, 33.0, 33.6, 34.3, 39.5, 46.5, 55.3, 71.8, 72.9, 76.5, 113.8, 122.8, 127.8, 129.3, 129.8, 130.2, 139.6, 139.9, 141.0, 159.2, 165.5 ppm; FAB-MS m/z: 510 [M^++H]; HR-FAB-MS: calcd for $C_{33}H_{52}NO_3$ [M^++H]: 510.3947; found 510.3946.

3,4-DMPM ether (38b): White crystals; m.p. 74–75°C; IR (KBr): $\tilde{\nu}$=3284, 2923, 1651, 1608, 1514, 1448 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (3H, t, J=7.0 Hz), 0.88–0.99 (2H, m), 1.11–1.32 (15H, m), 1.35–1.46 (3H, m), 1.57–1.70 (6H, m), 1.74–1.83 (1H, m), 2.11 (2H, dd, J=6.9, 14.1 Hz), 3.46 (2H, d, J=4.0 Hz), 3.80 (6H, s), 4.29 (1H, m), 4.39 (1H, d, J=11.5 Hz), 4.47 (1H, d, J=11.5 Hz), 5.57 (1H, d, J=8.8 Hz), 5.76 (1H, d, J=14.7 Hz), 5.83–5.92 (1H, m), 6.06–6.21 (2H, m), 6.48 (1H, dd, J=10.6, 14.5 Hz), 6.80–6.85 (3H, m), 7.22 ppm (1H, dd, J=11.2, 14.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0, 22.6, 26.1, 26.4, 28.9, 29.1, 29.2, 29.3, 29.4, 31.8, 32.9, 33.5, 34.2, 39.5, 46.5, 55.7, 55.8, 71.8, 73.0, 73.1, 110.7, 110.8, 110.9, 120.2, 122.7, 127.6, 129.7, 130.6, 139.5, 139.9, 141.0, 148.5, 148.9, 165.5 ppm; FAB-MS m/z: 540 [M^++H]; HR-FAB-MS: calcd for $C_{34}H_{54}NO_4$ [M^++H]: 540.4053; found 540.4039.

2,4-DMPM ether (38c): White crystals; m.p. 67–68°C; IR (KBr): $\tilde{\nu}$=3284, 2923, 1651, 1612, 1510, 1454 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (3H, t, J=7.1 Hz), 0.85–0.99 (2H, m), 1.11–1.30 (15H, m), 1.38–1.45 (3H, m), 1.57–1.71 (6H, m), 1.74–1.84 (1H, m), 2.12 (2H, dd, J=6.9, 14.1 Hz), 3.49 (2H, d, J=3.3 Hz), 3.79 (6H, s), 4.27 (1H, m), 4.40 (1H, d, J=11.7 Hz), 4.50 (1H, d, J=11.7 Hz), 5.78 (1H, d, J=14.8 Hz), 5.88 (2H, m), 6.06–6.21 (2H, m), 6.42–6.50 (3H, m), 7.17–7.22 ppm (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.9, 22.4, 26.0, 26.3, 28.8, 28.9, 29.0, 29.2, 29.3, 31.6, 32.7, 33.3, 34.0, 39.3, 46.3, 55.0, 67.7, 71.5, 98.2, 98.3, 103.6, 103.7, 118.6, 122.9, 127.7, 129.6, 130.2, 130.3, 139.1, 139.4, 140.5, 158.3, 160.4, 165.3 ppm; FAB-MS m/z: 540 [M^++H]; HR-FAB-MS: calcd for $C_{34}H_{54}NO_4$ [M^++H]: 540.4053; found 540.4058.

General procedure for the deprotection of MPM-type ethers with $Ph_3C^+BF_4^-$: $Ph_3C^+BF_4^-$ (1.1 mmol) was added to a solution of MPM-type ether **38** (1 mmol) in CH_2Cl_2 (10 mL) at 0°C under Ar. After completion of the reaction (TLC check), the reaction mixture was quenched by the addition of saturated $NaHCO_3$ (aq.), and the reaction mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane/EtOAc (10:1) as the eluent to give **39** in the yield shown in Table 2.

Alcohol (39): White crystals; m.p. 84–86°C; IR (KBr): $\tilde{\nu}$=3280, 2923, 1651, 1608, 1539, 1463 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (3H, t, J=7.0 Hz), 0.87–1.00 (2H, m), 1.11–1.32 (17H, m), 1.34–1.44 (2H, m), 1.58–1.83 (6H, m), 2.12 (2H, dd, J=6.8, 14.3 Hz), 3.01 (1H, brs), 3.56 (1H, dd, J=6.2, 10.9 Hz), 3.72 (1H, dd, J=3.1, 10.9 Hz), 4.15 (1H, m), 5.51 (1H, d, J=7.5 Hz), 5.81–5.95 (2H, m), 6.07–6.22 (2H, m), 6.51 (1H, dd, J=10.6, 14.3 Hz), 7.25 ppm (1H, dd, J=10.5, 14.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.1, 22.6, 26.0, 26.2, 26.4, 28.9, 29.2, 29.3, 29.5, 31.8, 32.8, 32.9, 33.7, 34.3, 38.8, 49.8, 67.0, 76.6, 121.9, 127.5, 129.7, 140.2, 140.6, 141.9, 167.2 ppm; FAB-MS m/z: 390 [M^++H]; HR-FAB-MS: calcd for $C_{25}H_{44}NO_2$ [M^++H]: 390.3372; found 390.3390.

Preparation of ^{2,4}DMPMOCH$_2$SnBu$_3$ (40):[11] A mixture of 2,4-methoxybenzyl alcohol (2.54 g, 15.1 mmol) and NaH (0.70 g, 60% in oil, 17.4 mmol) in THF (40 mL) was stirred at room temperature under N_2. After being stirred for 1 h at the same temperature, a solution of tri-*n*-butylstannylmethyl iodide (5.0 g, 11.6 mmol) in THF (8 mL) was added slowly to the solution. The resulting mixture was stirred for three days. The reaction mixture was quenched by addition of MeOH, and the solution was diluted with Et_2O. The organic layer was washed with water two times, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane/Et_2O (30:1) as the eluent to give **40** (3.7 g, 68%) as a colorless oil. IR (KBr): $\tilde{\nu}$=2954, 1614, 1506, 1463 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.85–0.94 (15H, m), 1.28 (6H, m), 1.51 (6H, m), 3.72 (2H, s), 3.87 (3H, s), 3.88 (3H, s), 4.35 (2H, s), 6.83–6.87 ppm (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.0, 13.7, 27.3, 29.1, 55.3, 61.4, 71.5, 98.3, 103.7, 119.7, 129.7, 158.2, 160.2 ppm.

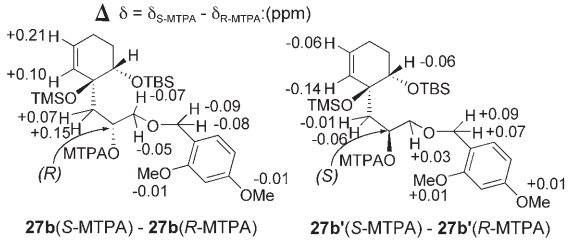
(2*R*)-1-[(1*S*,6*S*)-1-Trimethylsiloxy-6-(*tert*-butyldimethylsiloxy)cyclohex-2-en-1-yl]-3-[(2,4-dimethoxyphenyl)methyloxy]propan-2-ol (27b) and (2*S*)-1-[(1*S*,6*S*)-1-Trimethylsiloxy-6-(*tert*-butyldimethylsiloxy)cyclohex-2-en-1-yl]-3-[(2,4-dimethoxyphenyl)methyloxy]propan-2-ol (27b′): *n*BuLi (1.58 M in hexane, 0.24 mL) was added dropwise to a solution of ^{2,4}DMPMOCH$_2$S*n*Bu$_3$ (**40**; 177.2 mg, 0.376 mmol) in dry THF (0.9 mL) at −78°C under N_2. After being stirred for 15 min, a solution of **26d** (36.1 mg, 0.105 mmol) in THF (0.9 mL) was added to the reaction mixture. After being stirred for 5 min, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography using hexane/EtOAc (10:1) as the eluent to give **27b** (30.8 mg, 0.0588 mmol, 56%) and **27b′** (12 mg, 0.0378 mmol, 25%).

27b: Colorless oil; $[\alpha]_D^{25}$=+26.0 (c=0.67, $CHCl_3$): IR (KBr): $\tilde{\nu}$=3498, 2945, 1614, 1504, 1454 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.11 (3H, s), 0.12 (3H, s), 0.16 (9H, s), 0.88 (9H, s), 1.62 (1H, dd, J=9.5, 14.3 Hz), 0.74 (1H, m), 1.84–1.97 (2H, m), 2.04 (1H, m), 2.14 (1H, m), 3.45 (2H, d, J=5.3 Hz), 3.83 (6H, s), 3.89 (1H, brs), 3.95 (1H, dd, J=2.2, 7.5 Hz), 4.22 (1H, m), 4.57 (2H, s), 5.68 (1H, d, J=10.1 Hz), 5.81 (1H, dt, J=10.1, 3.1 Hz), 6.47 (1H, s), 6.49 (1H, d, J=7.9 Hz), 7.29 ppm (1H, d, J=7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ=−4.8, −4.1, 2.3, 17.9, 22.5, 25.7, 26.6, 40.6, 55.2, 67.2, 67.8, 73.5, 74.9, 98.3, 103.8, 119.3, 129.6, 130.2, 131.1, 158.4, 160.4 ppm; FAB-MS m/z: 547 [M^++Na]; HR-FAB-MS: calcd for $C_{27}H_{48}O_6Si_2Na$ [M^++Na]: 547.2887; found 547.2890.

27b′: Colorless oil; $[\alpha]_D^{26}$=−8.4 (c=0.64, $CHCl_3$): IR (KBr): $\tilde{\nu}$=3512, 2931, 1614, 1508, 1463 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.07 (3H, s), 0.08 (3H, s), 0.11 (9H, s), 0.90 (9H, s), 1.63 (1H, dd, J=2.4, 14.9 Hz), 1.63–1.83 (2H, m), 2.01 (1H, dd, J=9.2, 14.9 Hz), 2.05–2.12 (2H, m),

3.42 (1H, dd, $J=5.5$, 9.7 Hz), 3.47 (1H, dd, $J=6.0$, 9.7 Hz), 3.78 (3H, s), 3.79 (3H, s), 3.83 (1H, dd, $J=3.7$, 10.4 Hz), 4.02 (1H, brs), 4.13 (1H, m), 4.52 (2H, s), 5.65 (2H, dt, $J=10.1$, 2.9 Hz), 6.43 (1H, s), 6.45 (1H, m), 7.25 ppm (1H, d, $J=8.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=-4.6$, −4.4, 2.5, 24.2, 25.8, 28.6, 41.1, 55.3, 66.4, 67.8, 74.9, 76.6, 78.1, 98.3, 103.8, 119.3, 127.9, 130.2, 132.1, 158.4, 160.4 ppm; FAB-MS m/z: 547 [M^++Na]; HR-FAB-MS: calcd for $C_{27}H_{48}O_6Si_2Na$ [M^++Na]: 547.2887; found 547.2889.

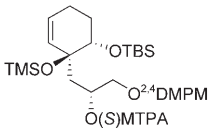
Determination of the absolute configurations of the secondary alcohols of 27b and 27b′: The absolute configurations of the secondary alcohols of **27b** and **27b′** were determined by the modified Mosher's method.[12] Each MTPA ester was synthesized in the same way as **27a** and **27b**.



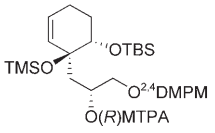
27b(*S*-MTPA) - **27b**(*R*-MTPA) **27b′**(*S*-MTPA) - **27b′**(*R*-MTPA)

General procedure for the preparation of an MTPA ester: DCC (3.3 mmol), MTPA (4.3 mmol), and DMAP (3.3 mmol) were added successively to a stirred solution of secondary alcohol **27b** or **27b′** (1.0 mmol) in CH_2Cl_2 (10.0 mL) at room temperature. After being stirred for 30 min, the solvent was removed in vacuo. The residue was purified by column chromatography using hexane/EtOAc (20:1) as the eluent.

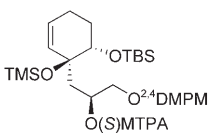
(2*R*)-1-[(1*S*,6*S*)-1-Trimethylsiloxy-6-*tert*-butyldimethylsiloxycyclohex-2-en-1-yl]-3-[(2,4-dimethoxyphenyl)methyloxy]-propan-2-yl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (27b; (*S*)-MTPA): Colorless oil; $[\alpha]_D^{26}=-27.5$ ($c=1.03$, $CHCl_3$); IR (KBr): $\tilde{\nu}=$ 2935, 1745, 1614, 1508, 1463 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.07$ (6H, s), 0.13 (9H, s), 0.87 (9H, s), 1.57 (1H, m), 1.72 (1H, m), 1.74 (1H, dd, $J=4.7$, 15.2 Hz), 2.07 (2H, m), 2.14 (1H, dd, $J=5.7$, 15.2 Hz), 3.49 (3H, s), 3.51 (1H, m), 3.63 (1H, dd, $J=2.4$, 10.6 Hz), 3.73 (1H, m), 3.76 (3H, s), 3.80 (3H, s), 4.40 (1H, d, $J=12.1$ Hz), 4.46 (1H, d, $J=12.1$ Hz), 5.69 (1H, m), 5.72 (1H, m), 5.79 (1H, d, $J=10.1$ Hz), 6.42 (2H, m), 7.17 (1H, d, $J=$ 8.8 Hz), 7.24–7.43 (3H, m), 7.58 ppm (2H, d, $J=7.5$ Hz).



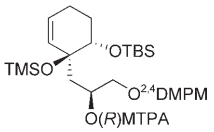
(2*R*)-1-[(1*S*,6*S*)-1-Trimethylsiloxy-6-*tert*-butyldimethylsiloxycyclohex-2-en-1-yl]-3-[(2,4-dimethoxyphenyl)methyloxy]-propan-2-yl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (27b; (*R*)-MTPA): Colorless oil; $[\alpha]_D^{24}=-8.4$ ($c=0.91$, $CHCl_3$); IR (KBr): $\tilde{\nu}=$ 2935, 1745, 1614, 1508, 1463 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.04$ (6H, s), 0.13 (9H, s), 0.84 (9H, s), 1.50 (1H, m), 1.59 (1H, dd, $J=4.9$, 15.2 Hz), 1.71 (1H, dd, $J=4.0$, 13.2 Hz), 1.97–2.06 (2H, m), 2.07 (1H, dd, $J=5.5$, 15.2 Hz), 3.56 (1H, m), 3.57 (3H, m), 3.70 (1H, dt, $J=10.8$, 3.7 Hz), 3.76 (1H, m), 3.77 (3H, s), 3.80 (3H, s), 4.48 (1H, d, $J=11.7$ Hz), 4.55 (1H, d, $J=$ 11.7 Hz), 5.48 (1H, dt, $J=10.0$, 2.9 Hz), 5.69 (1H, d, $J=10.0$ Hz), 5.70 (1H, m), 6.43 (1H, s), 6.44 (1H, d, $J=7.0$ Hz), 7.21–7.37 (4H, m), 7.59 ppm (2H, d, $J=7.5$ Hz).



(2*S*)-1-[(1*S*,6*S*)-1-Trimethylsiloxy-6-*tert*-butyldimethylsiloxycyclohex-2-en-1-yl]-3-[(2,4-dimethoxyphenyl)methyloxy]-propan-2-yl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (27b′; (*S*)-MTPA): Colorless oil; $[\alpha]_D^{25}=+1.8$ ($c=$ 1.30, $CHCl_3$); IR (KBr): $\tilde{\nu}=2933$, 1747, 1614, 1508, 1463 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.07$ (6H, s), 0.12 (9H, s), 0.90 (9H, s), 1.49 (1H, m), 1.70 (1H, m), 1.74 (1H, dd, $J=$ 7.0, 14.8 Hz), 1.89–2.06 (2H, m), 2.10 (1H, dd, $J=5.0$, 14.8 Hz), 3.56 (3H, s), 3.55–3.64 (2H, m), 3.75 (3H, s), 3.77 (1H, dd, $J=2.7$, 8.4 Hz), 3.80 (3H, s), 5.46 (1H, d, $J=11.9$ Hz), 5.49 (1H, d, $J=10.0$ Hz), 5.54 (1H, d, $J=11.9$ Hz), 5.65 (1H, dt, $J=10.0$, 3.5 Hz), 5.73 (1H, m), 6.42 (1H, s), 6.44 (1H, m), 7.22–7.35 (4H, m), 7.59 ppm (2H, d, $J=7.3$ Hz).



(2*S*)-1-[(1*S*,6*S*)-1-Trimethylsiloxy-6-*tert*-butyldimethylsiloxycyclohex-2-en-1-yl]-3-[(2,4-dimethoxyphenyl)methyloxy]-propan-2-yl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (27b′; (*R*)-MTPA): Colorless oil; $[\alpha]_D^{25}=+35.2$ ($c=1.10$, $CHCl_3$); IR (KBr): $\tilde{\nu}=$ 2935, 1745, 1614, 1508, 1463 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.07$ (6H, s), 0.12 (9H, s), 0.90 (9H, s), 1.64 (1H, m), 1.78 (1H, m), 1.80 (1H, dd, $J=7.0$, 14.6 Hz), 1.95–2.15 (2H, m), 2.21 (1H, dd, $J=4.2$, 14.6 Hz), 3.52 (1H, dd, $J=8.0$, 11.2 Hz), 3.54 (3H, s), 3.67 (1H, dd, $J=3.0$, 11.2 Hz), 3.76 (3H, s), 3.80 (3H, s), 3.83 (1H, dd, $J=3.3$, 9.7 Hz), 4.39 (1H, d, $J=12.0$ Hz), 4.45 (1H, d, $J=12.0$ Hz), 5.63 (1H, d, $J=10.2$ Hz), 5.71 (1H, dt, $J=10.2$, 3.3 Hz), 5.76 (1H, m), 6.41 (1H, s), 6.43 (1H, m), 7.17–7.47 (4H, m), 7.57 ppm (2H, d, $J=7.3$ Hz).



(2*S*)-2-Azido-1-[(1*S*,6*S*)-1-trimethylsiloxy-6-*tert*-butyldimethylsiloxycyclohex-2-en-1-yl]-3-[(2,4-dimethoxyphenyl)methyloxy]propane (28b): PPh_3 (122.0 mg, 0.465 mmol), DEAD (0.21 mL, 40% in toluene, 0.465 mmol), and DPPA (50 μL, 0.223 mmol) were added successively to a stirred solution of **27b** (81.4 mg, 0.155 mmol) in THF (1.6 mL) at room temperature under Ar. The reaction mixture was stirred at the same temperature for 30 min. After removal of the solvent in vacuo, the residue was purified by column chromatography using hexane/EtOAc (17:1) as the eluent to give **28b** (64.0 mg, 0.116 mmol, 75%) as a colorless oil. $[\alpha]_D^{25}=+18.8$ ($c=$ 0.77, $CHCl_3$): IR (KBr): $\tilde{\nu}=2933$, 2108, 1614, 1508, 1463 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.08$ (6H, s), 0.10 (9H, s), 0.88 (9H, s), 1.56 (1H, dd, $J=5.5$, 14.6 Hz), 1.63 (1H, m), 1.83 (1H, m), 2.01 (1H, dd, $J=6.8$, 14.6 Hz), 2.02 (1H, m), 2.12 (1H, m), 3.48 (1H, dd, $J=7.9$, 9.9 Hz), 3.66 (1H, dd, $J=3.7$, 9.9 Hz), 3.75 (1H, m), 3.79 (3H, s), 3.80 (3H, s), 3.83 (1H, dd, $J=2.8$, 8.4 Hz), 4.53 (2H, s), 5.57 (1H, d, $J=10.1$ Hz), 5.76 (1H, dt, $J=10.1$, 3.7 Hz), 6.43–6.50 (2H, m), 7.28 ppm (1H, d, $J=8.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=-4.7$, −4.2, 2.4, 2.6, 18.1, 22.8, 25.9, 27.3, 38.4, 55.4, 57.7, 67.7, 73.9, 75.1, 98.3, 103.9, 118.9, 129.8, 129.9, 130.8, 158.3, 160.5 ppm; FAB-MS m/z: 572 [M^++Na]; HR-FAB-MS: calcd for $C_{27}H_{47}N_3O_5Si_2Na$ [M^++Na]: 572.2952; found 572.2939.

(1*S*,6*S*)-1-{(2*S*)-3-[(2,4-Dimethoxyphenyl)methyloxy]-2-[(2*E*,4*E*,6*E*,12*E*)-(8*R*,10*S*,14*R*)-8,10,12,14-(tetramethyl)hexadeca-2,4,6,12-tetraenoylamino]propyl}-2-cyclohexene-1,6-diol (32b): A solution of **28b** (275.8 mg, 0.50 mmol) in dry THF (5.0 mL) was added to a solution of $LiAlH_4$ (190.0 mg, 5.0 mmol) in THF (5.0 mL) at 0°C under Ar. After being stirred for 1.5 h at room temperature, the reaction mixture was quenched with water and 15% NaOH (aq.), then the precipitate was filtered through a Celite pad. The filtrate was evaporated in vacuo to give crude **29b**. Side-chain carboxylic acid **30** (168.0 mg, 0.58 mmol), DCC (412.7 mg, 2.0 mmol), and DMAP (244.3 mg, 2.0 mmol) were added to a solution of crude **29b** in CH_2Cl_2 (2.5 mL) at room temperature under Ar. After being stirred for 1 h, the reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo to give crude coupled product. TBAF (5.0 mL, 1.0 M in THF, 5.0 mmol) was added to the crude coupled product in THF (5.0 mL) at room temperature under Ar. After being stirred for 10 h, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography using hexane/EtOAc (1:2) as the eluent to give **32b** (183.3 mg, 0.295 mmol, 66%) as a yellow oil. $[\alpha]_D^{24}=+9.81$ ($c=2.38$, $CHCl_3$); IR (KBr): $\tilde{\nu}=3305$, 2923, 1591, 1504, 1454 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.80$ (3H, d, $J=6.1$ Hz), 0.84 (3H, t, $J=7.4$ Hz), 0.90 (3H, d, $J=6.7$ Hz), 0.99 (3H, d, $J=6.1$ Hz), 1.02 (1H, m), 1.20 (1H, m), 1.27–1.38 (2H, m), 1.52 (3H, s), 1.56 (1H, m), 1.70–1.76 (2H, m), 1.81 (1H, dd, $J=6.7$, 14.7 Hz), 1.85–1.93 (2H, m), 2.01 (1H, dd, $J=3.7$, 15.3 Hz), 2.07 (1H, m), 2.17 (1H, m), 2.23 (1H, m), 2.32 (1H, m), 3.55 (1H, brs), 3.62 (2H, d, $J=4.3$ Hz), 3.81 (3H, s), 3.82 (3H, s), 3.92 (1H,

d, $J=6.7$ Hz), 4.10 (1H, brs), 4.25 (1H, m), 4.47 (1H, d, $J=11.3$ Hz), 4.52 (1H, d, $J=11.3$ Hz), 4.83 (1H, d, $J=9.2$ Hz), 5.51 (1H, d, $J=9.8$ Hz), 5.65–5.72 (2H, m), 5.75 (1H, d, $J=14.0$ Hz), 6.07 (1H, dd, $J=11.0$, 15.3 Hz), 6.16 (1H, dd, $J=11.0$, 14.6 Hz), 6.39 (1H, d, $J=6.1$ Hz), 6.43–6.50 (3H, m), 7.18–7.24 ppm (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=12.1$, 16.2, 19.5, 21.1, 21.4, 22.9, 25.6, 28.3, 30.5, 34.1, 34.9, 39.2, 44.0, 45.9, 48.3, 49.1, 55.5, 66.1, 72.1, 72.2, 72.4, 98.7, 104.0, 118.5, 122.1, 127.8, 128.2, 129.0, 130.9, 131.5, 132.2, 133.1, 140.5, 141.7, 145.6, 158.8, 161.0, 166.8 ppm; FAB-MS m/z: 624 [M^++H]; HR-FAB-MS: calcd for $C_{38}H_{58}NO_6$ [M^++H]: 624.4264; found 624.4250.

(1*R*,2*S*,3*S*,6*S*)-1,6-Dihydroxy-2,3-epoxy-1-{(2*S*)-3-[(2,4-dimethoxyphenyl)-methyloxy]-2-[(2*E*,4*E*,6*E*,12*E*)-(8*R*,10*S*,14*R*)-8,10,12,14-(tetramethyl)hexadeca-2,4,6,12-tetraenoylamino]propyl}cyclohexane (33b): A solution of aqueous TBHP (0.46 mL, 3.69 mmol) in toluene (3.0 mL) was dried with molecular sieves (4 Å) at room temperature under Ar. After being stirred for 20 min, a solution of **32b** (230.0 mg, 0.369 mmol) and [VO(acac)$_2$] (49.1 mg, 0.185 mmol) in dry toluene (3.0 mL) was added to the above mixture at 0 °C. After being stirred for 30 min, the reaction mixture was quenched with saturated $Na_2S_2O_3$ (aq.) and extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography using hexane/EtOAc (3:2) as the eluent to give **33b** (172.9 mg, 0.269 mmol, 69%) as a yellow oil. $[\alpha]_D^{24}=+19.1$ ($c=0.73$, $CHCl_3$); IR (KBr): $\tilde{\nu}=3330$, 2923, 1651, 1591, 1504, 1454 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.80$ (3H, d, $J=6.7$ Hz), 0.83 (3H, t, $J=7.4$ Hz), 0.90 (3H, d, $J=6.7$ Hz), 0.99 (3H, d, $J=8.6$ Hz), 1.02 (1H, m), 1.20 (1H, m), 1.28–1.35 (2H, m), 1.52 (3H, s), 1.52–1.62 (2H, m), 1.74 (1H, m), 1.84–1.97 (4H, m), 2.05 (1H, d, $J=14.7$ Hz), 2.17 (1H, m), 2.23 (1H, m), 2.32 (1H, m), 2.64 (1H, brs), 2.80 (1H, d, $J=3.1$ Hz), 3.39 (1H, m), 3.75–3.80 (3H, m), 3.81 (3H, s), 3.83 (3H, s), 4.21 (1H, m), 4.51 (1H, d, $J=11.3$ Hz), 4.54 (1H, d, $J=11.3$ Hz), 4.84 (1H, d, $J=9.2$ Hz), 5.70 (1H, dd, $J=8.5$, 15.3 Hz), 5.74 (1H, d, $J=14.7$ Hz), 6.08 (1H, dd, $J=11.0$, 15.3 Hz), 6.16 (1H, dd, $J=11.6$, 14.7 Hz), 6.43 (1H, d, $J=6.7$ Hz), 6.44–6.51 (3H, m), 7.19–7.24 ppm (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=12.1$, 16.2, 18.7, 19.5, 19.9, 21.0, 21.4, 28.3, 30.5, 34.1, 35.0, 38.3, 44.0, 46.1, 48.3, 49.1, 55.4, 56.0, 57.9, 67.6, 68.3, 69.9, 71.4, 98.7, 103.9, 118.6, 121.8, 127.7, 128.2, 131.0, 133.1, 135.5, 140.7, 141.9, 145.7, 158.8, 161.0, 166.9 ppm; FAB-MS m/z: 640 [M^++H]; HR-FAB-MS: calcd for $C_{38}H_{58}NO_7$ [M^++ H]: 640.4213; found 640.4220.

(2*S*,3*S*,4*S*)-3,4-Epoxy-2-hydroxy-2-{(2*S*)-3-[(2,4-dimethoxyphenyl)methyl-oxy]-2-[(2*E*,4*E*,6*E*,12*E*)-(8*R*,10*S*,14*R*)-8,10,12,14-(tetramethyl)hexadeca-2,4,6,12-tetraenoylamino]propyl}cyclohexan-1-one (34b): Dess–Martin periodinane (120.5 mg, 0.284 mmol) was added to a stirred solution of **33b** (90.8 mg, 0.142 mmol) in CH_2Cl_2 (7.0 mL) under N_2. After being stirred at 40 °C for 10 min, the reaction mixture was quenched with saturated $NaHCO_3$ (aq.) and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography using hexane/EtOAc (1:1) as the eluent to give **34b** (62.5 mg, 0.098 mmol, 69%) as a yellow oil, and the substrate **33b** (10.9 mg, 12%) was recovered. $[\alpha]_D^{25}=-6.2$ ($c=2.52$, $CHCl_3$); IR (KBr): $\tilde{\nu}=3290$, 2923, 1720, 1651, 1612, 1508, 1454 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.80$ (3H, d, $J=6.7$ Hz), 0.83 (3H, t, $J=7.4$ Hz), 0.90 (3H, d, $J=6.7$ Hz), 0.99 (3H, d, $J=6.7$ Hz), 1.02 (1H, m), 1.20 (1H, m), 1.25–1.36 (2H, m), 1.52 (3H, s), 1.55 (1H, m), 1.75 (1H, m), 1.88 (1H, m), 2.10 (1H, dd, $J=6.1$, 15.0 Hz), 2.17 (1H, dd, $J=6.7$, 15.0 Hz), 2.24 (1H, m), 2.32 (1H, m), 2.35–2.42 (3H, m), 2.80 (1H, m), 3.49 (1H, dd, $J=4.9$, 9.5 Hz), 3.66 (1H, dd, $J=4.3$, 9.5 Hz), 3.80 (3H, s), 3.81 (3H, s), 4.05 (1H, m), 4.24 (1H, brs), 4.45 (2H, s), 4.84 (1H, d, $J=9.2$ Hz), 5.68 (1H, dd, $J=8.5$, 15.0 Hz), 5.71 (1H, d, $J=15.0$ Hz), 6.07 (1H, dd, $J=11.0$, 15.0 Hz), 6.16 (1H, dd, $J=11.3$, 14.6 Hz), 6.21 (1H, d, $J=7.3$ Hz), 6.43–6.49 (3H, m), 7.18 (1H, d, $J=8.6$ Hz), 7.19 ppm (1H, dd, $J=11.3$, 15.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=12.1$, 16.2, 19.5, 21.1, 21.4, 22.3, 28.3, 29.7, 30.5, 31.7, 34.1, 34.9, 42.5, 44.0, 46.2, 48.3, 53.0, 55.4, 60.7, 68.1, 71.0, 76.8, 98.6, 104.0, 118.5, 122.4, 127.8, 128.2, 130.9, 132.1, 133.1, 140.4, 141.4, 145.5, 158.7, 160.9, 166.1, 209.8 ppm; FAB-MS m/z: 638 [M^++H]; HR-FAB-MS: calcd for $C_{38}H_{56}NO_7$ [M^++H]: 638.4057; found 638.4065.

(4*S*,5*S*,6*S*)-4,5-Epoxy-6-hydroxy-6-{(2*S*)-3-[(2,4-dimethoxyphenyl)methyl-oxy]-2-[(2*E*,4*E*,6*E*,12*E*)-(8*R*,10*S*,14*R*)-8,10,12,14-(tetramethyl)hexadeca-2,4,6,12-tetraenoylamino]propyl}-2-cyclohexen-1-one (35b): LDA in THF (0.25 M) was prepared as follows: *n*BuLi (1.56 M in hexane, 0.78 mL) was added to a solution of diisopropylamine (70.3 μL, 0.5 mmol) in dry THF (1.15 mL) at −78 °C for 30 min. under Ar. LDA (0.25 M in THF, 0.35 mL) and [15]crown-5 (69 μL, 0.348 mmol) were added to a solution of **34b** (7.4 mg, 0.0116 mmol) in THF (0.3 mL) at −78 °C under Ar. After being stirred for 10 min, a solution of *N*-*tert*-butylbenzenesulfinimidoyl chloride (75.1 mg, 0.348 mmol) in THF (0.3 mL) was added to the reaction mixture. After being stirred for 15 min, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography using Et_2O as the eluent to give **35b** (2.6 mg, 0.0058 mmol, 35%) as a yellow oil, and the substrate **34b** (4.3 mg, 58%) was recovered. $[\alpha]_D^{23}=+24.8$ ($c=0.30$, $CHCl_3$); IR (KBr): $\tilde{\nu}=3271$, 2958, 1697, 1651, 1612, 1514, 1461 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.80$ (3H, d, $J=6.1$ Hz), 0.81 (3H, m), 0.90 (3H, d, $J=6.7$ Hz), 0.99 (3H, d, $J=6.7$ Hz), 1.02 (1H, m), 1.16–1.33 (3H, m), 1.61 (3H, s), 1.74 (1H, m), 1.88 (1H, dd, $J=6.7$, 12.8 Hz), 2.01 (2H, m), 2.20 (1H, m), 2.32 (1H, m), 3.50 (1H, dd, $J=4.9$, 9.5 Hz), 3.52 (1H, m), 3.61 (1H, dd, $J=3.7$, 9.5 Hz), 3.69 (1H, d, $J=3.7$ Hz), 3.80 (3H, s), 3.81 (3H, s), 4.22 (1H, m), 4.45 (2H, s), 4.84 (1H, d, $J=9.2$ Hz), 5.68 (1H, dd, $J=9.8$, 14.7 Hz), 5.69 (1H, d, $J=14.7$ Hz), 5.97 (1H, d, $J=9.0$ Hz), 6.04–6.21 (3H, m), 6.41–6.49 (3H, m), 7.07 (1H, dd, $J=4.3$, 9.0 Hz), 7.17 (1H, d, $J=9.2$ Hz), 7.21 ppm (1H, dd, $J=11.6$, 14.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=12.1$, 19.5, 21.1, 21.4, 28.3, 29.7, 30.5, 31.6, 34.1, 35.0, 38.3, 44.0, 45.5, 47.9, 48.3, 53.0, 55.5, 56.3, 68.3, 71.8, 98.6, 114.0, 118.5, 122.2, 127.8, 128.3, 130.5, 130.8, 132.1, 133.1, 140.5, 144.1, 144.6, 145.6, 158.9, 160.9, 165.9, 197.7 ppm; FAB-MS m/z: 636 [M^++H]; HR-FAB-MS: calcd for $C_{38}H_{54}NO_7$ [M^++H]: 636.3900; found 636.3876.

(4*S*,5*S*,6*S*)-4,5-Epoxy-6-hydroxy-6-{(2*S*)-3-hydroxy-2-[(2*E*,4*E*,6*E*,12*E*)-(8*R*,10*S*,14*R*)-8,10,12,14-(tetramethyl)hexadeca-2,4,6,12-tetraenoylamino]propyl}-2-cyclohexen-1-one (scyphostatin (1)): $Ph_3C^+BF_4^-$ (1.8 mg, 0.00564 mmol) was added to a solution of **35b** (3.0 mg, 0.0047 mmol) in CH_2Cl_2 (0.2 mL) at 0 °C under Ar. After being stirred for 5 min, the reaction mixture was quenched with saturated $NaHCO_3$ (aq.) and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography using EtOAc/acetone (4:1) as the eluent to give scyphostatin (**1**; 1.5 mg, 0.00312 mmol, 66%). $[\alpha]_D^{25}=+60.5$ ($c=0.20$, MeOH); IR (KBr): $\tilde{\nu}=3292$, 2956, 2923, 1697, 1651, 1606, 1512, 1454 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): $\delta=0.83$–0.86 (6H, m), 0.91 (3H, d, $J=6.7$ Hz), 1.00 (3H, d, $J=6.8$ Hz), 1.04 (1H, m), 1.19 (1H, m), 1.27–1.41 (2H, m), 1.54 (3H, s), 1.58 (1H, m), 1.78 (1H, m), 1.86 (1H, m), 1.88 (1H, m), 2.08 (1H, dd, $J=3.7$, 14.7 Hz), 2.27 (1H, m), 2.35 (1H, m), 3.46 (1H, dd, $J=5.5$, 11.0 Hz), 3.52 (1H, dd, $J=4.9$, 11.0 Hz), 3.59 (1H, m), 3.66 (1H, d, $J=3.7$ Hz), 4.04 (1H, m), 4.86 (1H, m), 5.71 (1H, m), 5.89 (1H, d, $J=15.3$ Hz), 6.07 (1H, dd, $J=1.3$, 9.8 Hz), 6.15 (1H, dd, $J=11.6$, 14.6 Hz), 6.26 (1H, dd, $J=11.0$, 15.3 Hz), 6.54 (1H, dd, $J=11.0$, 14.6 Hz), 7.09–7.18 ppm (2H, m); ^{13}C NMR (125 MHz, CD_3OD): $\delta=12.9$, 16.9, 20.5, 22.0, 22.5, 30.1, 32.2, 36.0, 36.7, 40.3, 46.0, 48.5, 49.8, 50.1, 58.8, 65.9, 78.0, 124.2, 129.9, 130.4, 132.6, 134.5, 134.7, 141.8, 142.9, 146.4, 146.8, 169.0, 200.4 ppm; FAB-MS m/z: 486 [M^++H]; HR-FAB-MS m/z: 486.3199 (calcd for $C_{29}H_{43}NO_5H$: 486.3219); the ^{1}H and ^{13}C NMR, IR, and HR-FAB-MS spectra showed good agreement with those of the authentic sample.

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