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Selected Paper

Total Synthesis of Stevastelins: Structure Confirmation of Stevastelins B and B3, and Structure Revision of Stevastelin C3

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The total syntheses of stevastelins B, B3, C3, and the 5-deoxy derivative of stevastelin C3, novel cyclic depsipeptides starting from L-quebrachitol, and amino acids are described. Stereoselective introduction of two methyl groups into L-quebrachitol, followed by regioselective cleavage of the cyclohexane ring by way of the Baeyer–Villiger reaction effectively afforded the fatty acid moiety of stevastelins. Introduction of the peptide and subsequent macrolactamization gave stevastelin B. Stevastelins C3 and B3 were also synthesized by a similar way. The direct comparison of synthetic stevastelins with natural compounds revealed that the synthetic stevastelins B and B3 are identical to the natural products, confirming the proposed structures. However, the synthetic stevastelin C3 was found to not be identical with the natural product. To elucidate the structure of stevastelin C3, degradation of the natural product was carried out to show the possibility that the natural product could be a 5-deoxy derivative of the proposed structure. Thus, the 5-deoxy derivative of the fatty acid moiety was prepared and transformed into a macrocycle. The synthetic 5-deoxy compound was fully identical to natural stevastelin C3. Based on these studies, it was shown that the structure of stevastelin C3 should be revised.

Stevastelins A, B (**1**), B3 (**2**), and C3 (**3**) are novel cyclic depsipeptides that were isolated from a culture broth of *Penicilium* sp. NK374186 by Nippon Kayaku group in 1994 (Fig. 1).[1,2] It has been reported that stevastelins show potent immunosuppressive activity by way of blocking human T cell activation without affecting the phosphatase activity of calcineurin. With such a novel mode of action, which is different from that of the well-known immunosuppressants FK506 and cyclosporin A, stevastelins are expected to be new immunosuppressants as well as useful biochemical probes. The structural study by spectral, degradation, and synthetic methods of stevastelin B (**1**), the most abundant congener of the stevastelin family, established that stevastelin B consists of (2*S*,3*S*,4*S*,5*R*)-3,5-dihydroxy-2,4-dimethyloctadecanoic acid, *O*-acetyl-L-serine, L-threonine, and L-valine, and possesses a 15-membered ring structure.[3] Based on spectroscopic analyses of other stevastelins, it has been proposed that stevastelin B3 (**2**) is an isomer of stevastelin B (**1**) with a 13-membered ring structure, and stevastelin C3 (**3**) is a de-*O*-acetyl derivative of stevastelin B3.[1] Their interesting and important mode of action as well as unique structures have attracted synthetic attention, and the total synthesis of stevastelin B[4] and the proposed structure of C3[5] have been reported. The synthetic approach to stevastelin B,[6] and preparation and biological assessment of simple analogues of stevastelins have also appeared.[7] Yamamoto's group reported the first total synthesis of **1**, in which they constructed the 15-membered macrocycle by lactamization between a carboxylic acid at the C-1 and an amino group in valine, and the fatty acid moiety with four contiguous chiral centers was prepared by the combination of Evans asymmetric aldol reaction and Roush asymmetric crotylation starting from tetradecanal.[4] Sarabia's total synthesis of the proposed structure of stevastelin C3 (**3**) employed Yamaguchi's macrolactonization between a hydroxy group at C-3 and a carboxylic acid in serine to construct the 13-membered ring, and the fatty acid was synthesized from tetradecanal by way of Evans asymmetric synthesis methodology and an aldol reaction with a thioester.[5] Recently, Sarabia's group has completed the total synthesis of stevastelins B and B3,[8] in which they utilized a base-induced translactonization of a 15-membered macrocycle (stevastelin B precursor) prepared by macrolactamization between a carboxylic acid at C-1 and an amino group in valine, to a 13-membered one (stevastelin B3 precursor). The Sarabia's group also reported the structure–activity relationship study of stevastelin

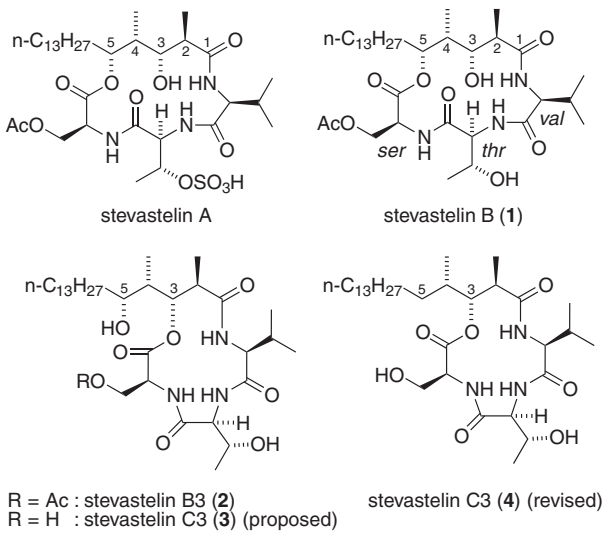

Fig. 1. Structures of stevastelins.

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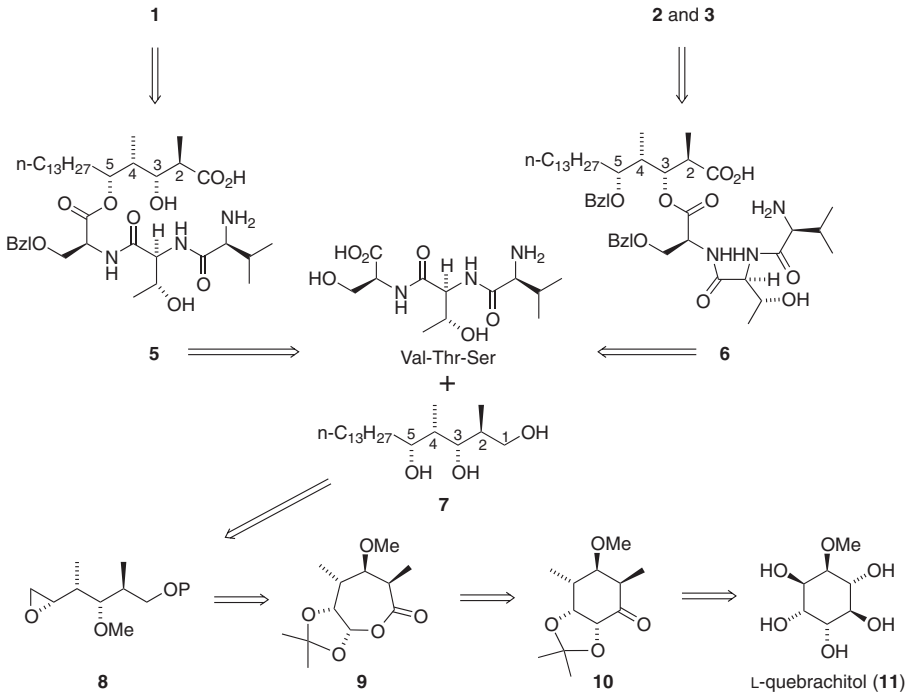


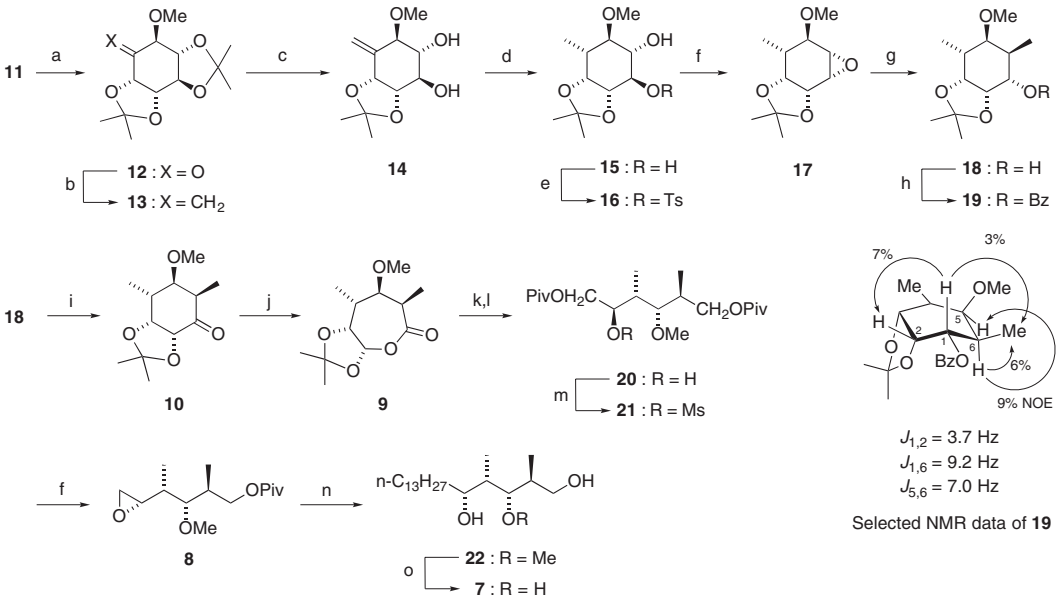
Fig. 2. Retrosynthetic analysis of stevastelins. Bzl = $-CH_2Ph$.

B analogues.[8b] Chakraborty has reported the formal synthesis of stevastelin B3 starting from methyl (*S*)-3-hydroxy-2-methylpropionate.[9] These successful syntheses, however, did not describe the identity of their synthetic compounds with the natural products, providing insufficient information for structure confirmation of the natural products. In this paper, we report a total synthesis of stevastelins B (**1**), B3 (**2**), C3 (**3**), and 5-deoxy derivative of stevastelin C3 (**4**), which resulted in the unambiguous confirmation of the proposed absolute structures of stevastelins B (**1**) and B3 (**2**), and the structure revision of stevastelin C3 to **4** in detail.[10]

Results and Discussion

Synthetic Plan of Stevastelins. Our retrosynthetic analysis (Fig. 2) suggested that stevastelin B (**1**), possessing a 15-membered ring structure, would be obtained by macrolactamization of the amino carboxylic acid **5**, followed by deprotection and acetylation. Stevastelins B3 (**2**) and C3 (**3**), with 13-membered macrocycles, were also expected to derive from another amino carboxylic acid, **6**. The key intermediates **5** and **6** were envisioned to be synthesized by condensation of a tripeptide (Val–Thr–Ser) moiety with the fatty acid precursor **7**. The tripeptide could be prepared from commercially available protected serine, threonine, and valine derivatives. The common precursor **7**, in turn, was planned to be constructed by carbon elongation of the chiral epoxide **8** with a dodecyl group. The epoxide **8** was envisioned to be synthesized by a ring cleavage of the 7-membered lactone **9**, which would derive from regioselective Baeyer–Villiger reaction[11] of the ketone **10**. For preparation of the cyclohexanone **10**, L-quebrachitol (**11**) was chosen as the starting material. L-Quebrachitol (**11**) is a naturally occurring optically active cyclitol, obtained in large quantities from the serum of the rubber tree[12] and has been utilized as a raw material in the preparation of useful chiral building blocks for total syntheses of a variety of natural products.[13]

Preparation of Common Fatty Acid Precursor 7. The cyclitol derivative **13**,[14] prepared stereoselectively from L-quebrachitol (**11**) in the known 3 steps with slight modification, was used as the starting material for the preparation of the fatty acid precursor **7**. Tebbe olefination[15] of the known ketone **12**[16] afforded the *exo*-methylene compound **13** in 64% yield (Scheme 1). Selective removal of the *trans*-*O*-isopropylidene group in **13** gave **14**, whose hydrogenation afforded the diol **15** stereoselectively in 76% yield from **13**. Removal of the isopropylidene group in **13** prior to hydrogenation was required since hydrogenation of **13** was found to proceed very slowly giving the desired product in poor yield. Reaction of **15** with Bu_2SnO[17] followed by treatment with TsCl afforded **16** (82% yield), whose treatment with base cleanly provided the α-epoxide **17** in 93% yield. Reaction of **17** with Me_3Al gave the *trans*-diaxial ring opening product **18** in 93% yield. The structure of **18** was confirmed by the ^1H NMR analysis (coupling constants and NOE experiments) of the derived benzoate **19** as shown in Scheme 1. PCC (pyridinium chlorochromate) oxidation of **18** provided the ketone **10**. From our earlier observations, it was highly anticipated that the Baeyer–Villiger reaction of **10**, possessing a methyl and an oxygen substituent on α- and α'-carbons, respectively, would proceed in a highly regioselective manner.[11,13] Indeed, treatment of **10** with mCPBA afforded the expected product, the 7-membered lactone **9**, as the sole isomer in 81% yield from **18**. Reduction of **9** with $LiAlH_4$ gave a triol, whose selective *O*-acylation afforded the di-*O*-pivalate **20** (65% yield from **9**). The secondary hydroxy group in **20** was mesylated to give **21** in 99% yield, which was further treated with MeONa to give the inverted epoxide **8** in 96% yield. Reaction of **8** with didodecylmagnesium in the presence of CuCN[18] smoothly provided **22** in 87% yield. Deprotection of the *O*-methyl group in **22** by the action of tri-



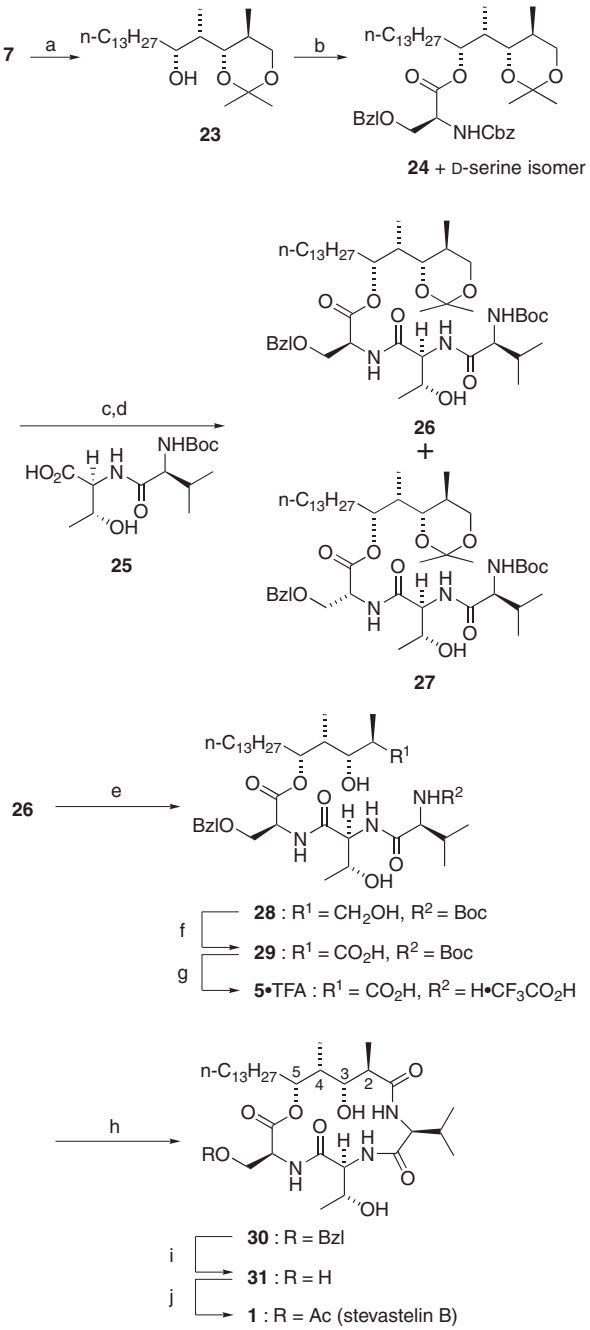
Scheme 1. Ts = $-SO_2C_6H_4$(*p*-Me), Ms = $-SO_2Me$, Bz = –COPh, Piv = $-COCMe_3$. Reagents and conditions: a) see Ref. 16; b) Tebbe reagent, THF; c) *p*-TsOH (cat), MeOH, 0 °C; d) H_2, Raney-Ni, EtOH; e) Bu_2SnO, MeOH, reflux, then TsCl, DMAP, 1,4-dioxane; f) MeONa, MeOH; g) Me_3Al in hexane, CH_2Cl_2; h) BzCl, DMAP, pyridine; i) PCC–Al_2O_3, CH_2Cl_2; j) mCPBA, $KHCO_3$, $(CH_2Cl)_2$; k) $LiAlH_4$, THF; l) PivCl, DMAP, pyridine; m) MsCl, pyridine; n) $(n\text{-}C_{12}H_{25})_2Mg$, CuCN, Et_2O; o) TMSI, CH_2Cl_2.

methylsilyl iodide[19] afforded the precursor of the fatty acid moiety **7** in 93% yield. The spectroscopic data and $[\alpha]_D$ value of **7** showed good accordance with those reported for the authentic compound derived from the natural stevastelin B (**1**) by reductive degradation.[3b]

Total Synthesis of Stevastelin B. Having established the preparation of the common precursor **7** for the synthesis of stevastelins, the total synthesis of stevastelin B, possessing a 15-membered cyclic depsipeptide structure, was first explored. Treatment of **7** with 2-methoxypropene in the presence of camphorsulfonic acid (CSA)[20] afforded the kinetic acetonide **23** in 76% yield (Scheme 2). To introduce a tripeptide into **23**, direct acylation of **23** with Boc–Val–Thr–Ser(Bzl) under various reaction conditions were attempted. However, none of the acylated product was obtained even under Yamaguchi's conditions.[21a] Recognition of the poor reactivity of the hydroxy group in **23**, probably due to steric hindrance, led us to employ the stepwise introduction of the peptide moiety. Although condensation of **23** with Cbz–Ser(Bzl)[22] under Keck conditions[23] using dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) gave no desired product, under Yamaguchi's conditions[21a] the acylated products were successfully afforded. Unfortunately, partial racemization of the serine moiety during the condensation process was observed, and compound **24** and its D-serine isomer were obtained as an inseparable mixture in a ratio of ca. 6:1 (determined with 300 MHz ^{1}H NMR) in 73% yield. Hydrogenolysis of a mixture of **24** and its epimer in the presence of a 10% Pd/C ethylenediamine complex[24] selectively deprotected the *N*-Cbz group to give amines, which, without isolation, were coupled with Boc–Val–Thr (**25**) by the action of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC·HCl) and 1-hydroxybenzotriazole (HOBt) to provide a mixture of **26** and its diastereomer **27** in 95% yield. At this stage, diastereomers were cleanly separated by silica-gel chromatography to give compounds **26** (58% yield from **23**) and **27** (9% from **23**) in pure forms, respectively. Acid hydrolysis of **26** gave the triol **28** in 94% yield. The primary alcohol in **28** was selectively oxidized with TEMPO[25] (2,2,6,6-tetramethyl-1-piperidinyloxy, free radical) to give aldehyde, which was further oxidized by sodium chlorite to afford the carboxylic acid **29**. Treatment of **29** with trifluoroacetic acid (TFA) provided the amino carboxylic acid **5** as its TFA salt. The crucial step, macrolactamization of **5**·TFA, was successfully carried out by Shioiri's protocol[26] using diethylphosphoryl cyanide (DEPC) in DMF under high dilution conditions (0.01 M) to provide the 15-membered macrocycle **30** in 41% yield from **29**. Removal of the *O*-benzyl group in **30** by hydrogenolysis afforded the triol **31**, which was treated with acetic anhydride in pyridine at 0 °C to furnish stevastelin B (**1**) in 67% yield from **30**. Direct comparison of synthetic **1** with natural stevastelin B, kindly provided by Nippon Kayaku Co., Ltd., revealed that the synthetic compound is unambiguously identical to the natural product, therefore confirming the proposed whole structure of stevastelin B (**1**).

Synthesis of Macrocycles Possessing Proposed Structures of Stevastelins B3 and C3: Structure Confirmation of Stevastelin B3. Successful total synthesis of stevastelin B led us to investigate the synthesis of stevastelins B3 (**2**) and C3 (**3**), whose 13-membered structures have not been synthetically confirmed, based on a similar methodology employed for the synthesis of stevastelin B.

Synthesis of stevastelin B3 (**2**) commenced from the acetonide **23** (Scheme 3). Benzylation of the hydroxy group in **23**, followed by acid hydrolysis gave the diol **32**. The primary hydroxy group in **32** was selectively protected as a TES ether to give **33** in 96% yield from **23**. Although coupling of **33** with Cbz–Ser(Bzl) was first attempted under Yamaguchi's conditions, the desired product **34** was not obtained. After several

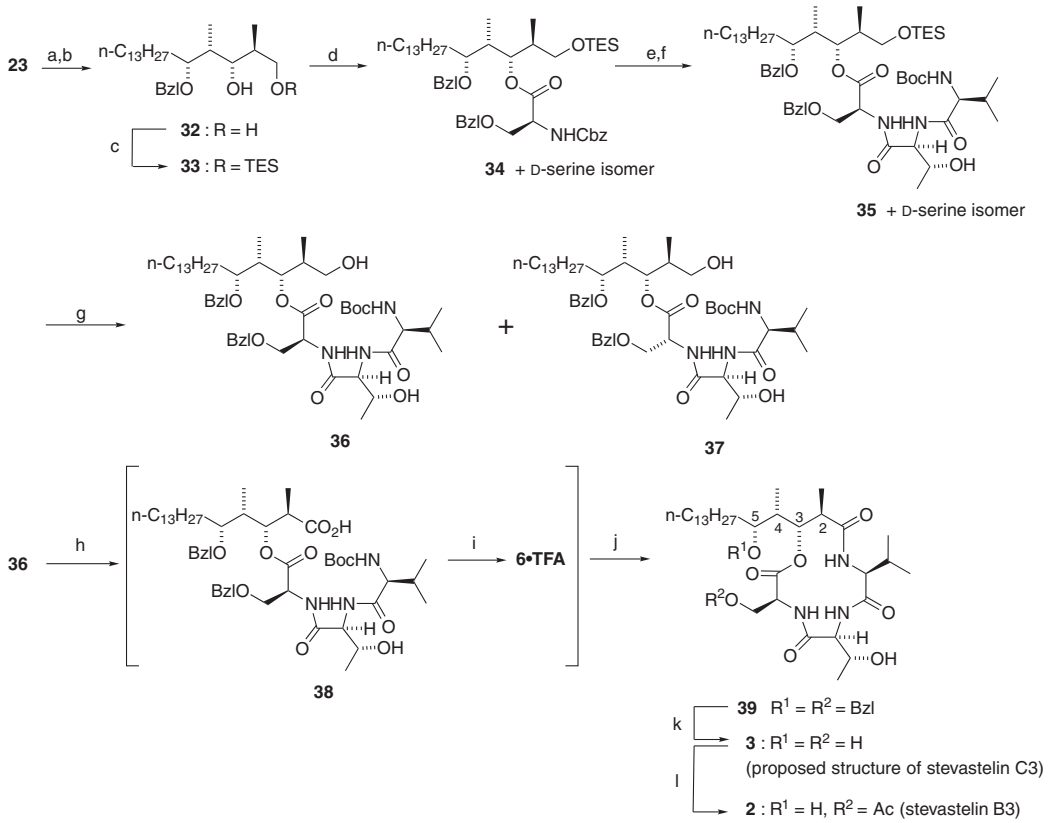


Scheme 2. Cbz = –C(O)OCH$_2$Ph, Boc = –C(O)OCMe$_3$. Reagents and conditions: a) 2-methoxypropene, CSA, CH_2Cl_2; b) 2,4,6-trichlorobenzoyl chloride, Et_3N, Cbz–Ser(Bzl), THF then DMAP, toluene–THF; c) H_2, 10% Pd/C ethylenediamine complex, MeOH; d) Boc–Val–Thr (**25**), WSC·HCl, HOBt, DMF; e) aqueous AcOH; f) TEMPO, KBr, NaOCl, $NaHCO_3$, H_2O–CH_2Cl_2, 0 °C, then $NaClO_2$, $HOSO_2NH_2$, NaH_2PO_4, *t*-BuOH–H_2O; g) TFA, CH_2Cl_2, 0 °C; h) DEPC, Et_3N, DMF; i) H_2, 20% Pd(OH)$_2$/C, MeOH; j) Ac_2O, pyridine, 0 °C.

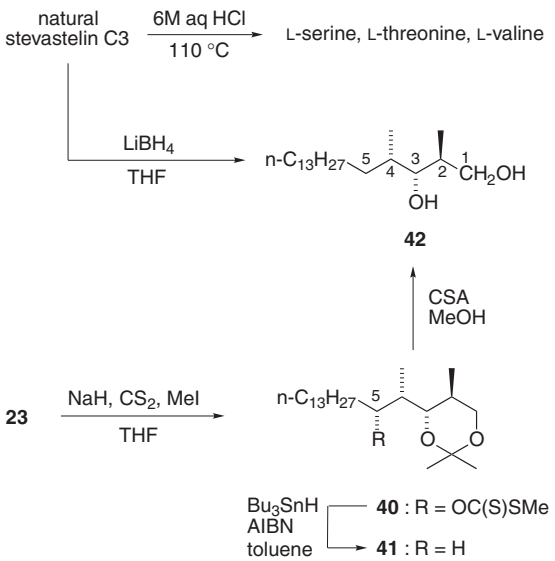
attempts, it was found that the modified Yamaguchi's conditions[21b] and Shiina's method[27] gave a condensate. Racemization of the serine moiety during the coupling process was again observed in this case, and **34** and its diastereoisomer were obtained as an inseparable mixture in a ratio of ca. 1:1 in 77% yield under the modified Yamaguchi's conditions. Shiina's method also provided a 1:1 mixture of **34** and its epimer in 36% yield. To suppress racemization in the serine moiety, various reaction parameters (temperature, solvent, time, amount of reagents, and so on) were examined in the modified Yamaguchi's and Shiina's conditions; however, improved results could not be obtained. Selective deprotection of the *N*-Cbz group in **34** and its diastereomer afforded amines, which, without isolation, were coupled with the dipeptide **25** in the presence of WSC·HCl and HOBt to provide a mixture of **35** and its diastereomer in 94% yield. Removal of the *O*-TES group, followed by chromatographic separation gave diastereomerically pure **36** (45%, 33% overall yield from **33**) and **37** (43%, 31% from **33**). The absolute structures of the amino acids in **36** and **37** were determined by chiral HPLC analyses of hydrolysates of compounds derived from **36** and **37**, respectively (vide infra). The primary hydroxy group in **36** was selectively oxidized to give the carboxylic acid **38**, whose *N*-Boc group was deprotected to generate **6** as its TFA salt. Macrolactamization of **6**·TFA by Shioiri's procedure effectively constructed the 13-membered cyclic structure, and compound **39** was obtained in 29% yield from **36**. Deprotection of the *O*-benzyl group in **39** by hydrogenolysis afforded a compound possessing the proposed structure of stevastelin C3 (**3**) in 74% yield. At this stage, the absolute structures of the amino acids in **3** were confirmed to all be L by chiral HPLC analyses (MCI GEL CRS 10W, Mitsubishi Chemical Industries, Ltd.) of acidic hydrolysates of **3**. Similar HPLC analyses of hydrolysates of a de-*O*-benzyl product of compound **37** (prepared by hydrogenolysis of **37** with H_2, Pd/C in MeOH) showed that the amino acids in **37** were D-serine, L-threonine, and L-valine. The primary hydroxy group in **3** was selectively acetylated to provide stevastelin B3 (**2**) in 38% yield.

The direct comparison of synthetic **2** and **3** with natural stevastelins B3 and C3 revealed that synthetic **2** is unambiguously identical with natural stevastelin B3. Thus, the proposed structure of stevastelin B3 was fully confirmed by this total synthesis. However, spectral data of synthetic **3** were not identical with those of natural stevastelin C3. Further analyses of natural stevastelin C3 and compound **3** by ^{1}H NMR (in DMSO-d_6) revealed that a proton of OH at C-5 ($\delta = 4.31$) and a methine proton attached to C-5 ($\delta = 3.85$) observed in compound **3** were missing in the spectrum of natural stevastelin C3. The signal of a methine carbon bearing an oxygen function ($\delta = 69.0$) observed in the ^{13}C NMR of compound **3** was also missing in the natural product. These results suggested the possibility that the natural product might be a deoxy derivative of the proposed structure. The molecular ion peak of natural stevastelin C3 detected at *m*/*z* 598 ($C_{32}H_{59}N_3O_7 + H$) by FAB-MS also supported the deoxygenated structure [the molecular ion peak of the proposed structure of stevastelin C3 (**3**, $C_{32}H_{59}N_3O_8 + H$) was observed at *m*/*z* 614].

Total Synthesis and Structure Revision of Stevastelin C3. To elucidate the correct structure of stevastelin C3, the natural product was subjected to degradation (Scheme 4). Treatment of natural stevastelin C3 with $LiBH_4$ afforded the diol **42** in 24% yield. The structure of **42** was determined based on spectral analyses, and finally confirmed by comparison with the



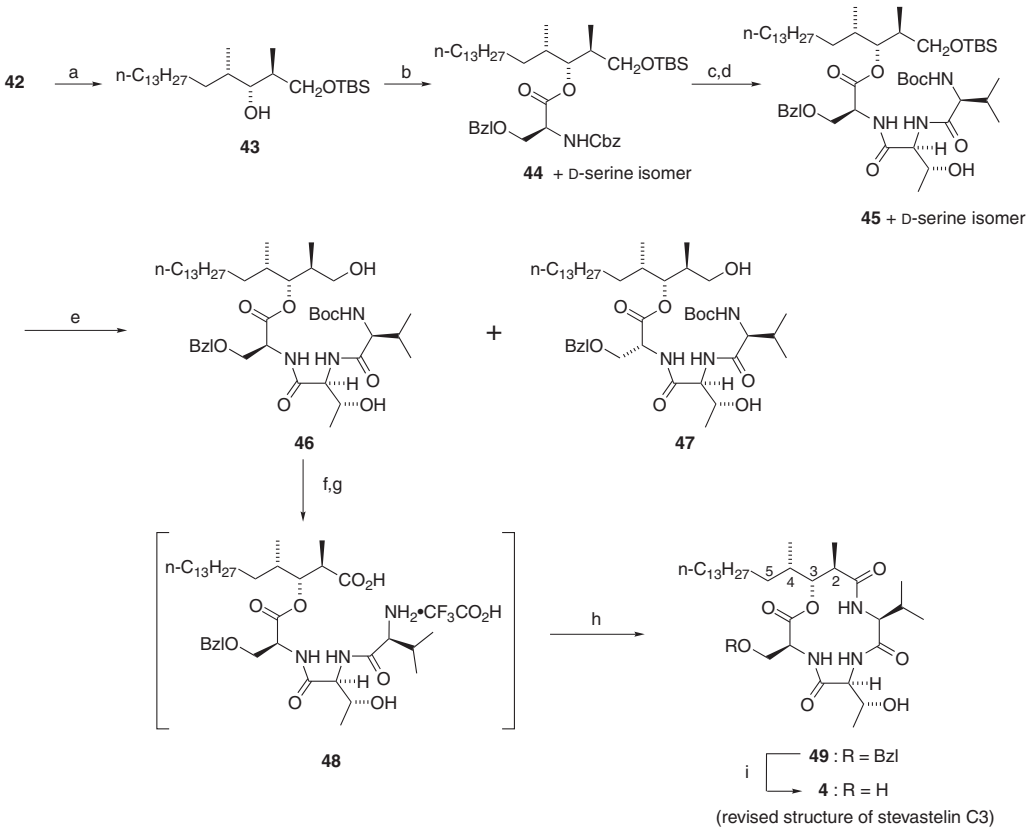
Scheme 3. TES = –$SiEt_3$. Reagents and conditions: a) $(Me_3Si)_2NK$, BzlBr, THF; b) aqueous AcOH; c) TESCl, Et_3N, CH_2Cl_2; d) Cbz–Ser(Bzl), 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, THF; e) H_2, 10% Pd/C ethylenediamine complex, MeOH; f) Boc–Val–Thr (**25**), WSC·HCl, HOBt, DMF; g) AcOH–THF–H_2O; h) TEMPO, KBr, NaOCl, $NaHCO_3$, H_2O–CH_2Cl_2, 0 °C, then $NaClO_2$, $HOSO_2NH_2$, NaH_2PO_4, *t*-BuOH–H_2O; i) TFA, CH_2Cl_2, 0 °C; j) DEPC, Et_3N, DMF; k) H_2, 10% Pd/C, MeOH; l) Ac_2O, pyridine.



Scheme 4.

synthetic specimen (vide infra). On the other hand, acid hydrolysis of natural stevastelin C3, followed by chiral HPLC analysis (MCI GEL CRS 10W) showed that the amino acids constituting stevastelin C3 are the same as those of stevastelins B and B3 (L-serine, L-threonine, and L-valine). From these degradation studies, it was presumed that natural stevastelin C3 is a 5-deoxy derivative of the proposed structure.

With this structural information, we turned to the synthesis of the expected structure of stevastelin C3. The hydroxy group in **23** was deoxygenated via the *S*-methyl dithiocarbonate ester **40** by Barton's method[28] to give **41** in 93% yield from **23**. Acid hydrolysis of **41** gave the diol **42** in 79% yield. The spectral data of **42** were fully identical with those of the diol obtained by reductive degradation of natural stevastelin C3. After selective protection of the primary hydroxy group in **42** as a TBS ether, the resulting secondary alcohol in **43** was acylated with Cbz–Ser(Bzl) under the modified Yamaguchi's conditions to give **44** and its D-serine isomer as an inseparable mixture in a ratio of ca. 1.5:1 in 89% yield (Scheme 5). Condensation of **43** with Cbz–Ser(Bzl) under Yamaguchi's conditions gave a 1:1 mixture of **44** and its epimer in 20% yield and that with Shiina's method also provided a 1:1 mixture in 87% yield. Hydrogenolysis of a mixture of **44** and its diastereomer, followed by condensation with **25**, afforded a mixture of **45** and its D-serine isomer in 92% yield. Treatment of a mixture of **45** and its diastereomer with AcOH–H_2O–THF, followed by chromatographic separation provided diastereomerically pure **46** (38% overall yield from **43**) and **47** (25% from **43**). The absolute configurations of the amino acids in **46** and **47** were confirmed by chiral HPLC analyses of acidic hydrolysates of de-*O*-benzyl products derived from **46** and **47**, respectively.



Scheme 5. TBS = –Si(Me)$_2$(*t*-Bu). Reagents and conditions: a) TBSCl, Et_3N, CH_2Cl_2; b) Cbz–Ser(Bzl), 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, THF; c) H_2, 10% Pd/C ethylenediamine complex, MeOH; d) Boc–Val–Thr (**25**), WSC·HCl, HOBt, DMF; e) AcOH–THF–H_2O; f) TEMPO, KBr, NaOCl, $NaHCO_3$, H_2O–CH_2Cl_2, 0 °C, then $NaClO_2$, $HOSO_2NH_2$, NaH_2PO_4, *t*-BuOH–H_2O; g) TFA, CH_2Cl_2, 0 °C; h) DEPC, Et_3N, DMF; i) H_2, 10% Pd/C, MeOH.

Compound **46** was transformed into the macrocycle **49** via **48** in 28% overall yield by the same procedure as described for preparation of **39** from **36**. Removal of the *O*-benzyl group in **49** furnished **4**, whose spectral data as well as $[\alpha]_D$ value showed good accordance with those of natural stevastelin C3. Based on this synthesis, it was concluded that the true structure of natural stevastelin C3 is **4**.

Conclusion

The total synthesis of stevastelins B, B3, C3, and the 5-deoxy derivative of stevastelin C3 from L-quebrachitol has been accomplished. This study unambiguously confirmed the proposed absolute structure of stevastelins B and B3, and revealed that the structure of stevastelin C3 should be revised to the 5-deoxy structure of the proposed one. Successful synthesis of stevastelins also showed the usefulness of L-quebrachitol as the starting material for chiral syntheses of natural products. The methodology described here is applicable to the synthesis of other stevastelins as well as other cyclic depsipeptides. It is interesting to note that the fatty acid moiety of stevastelin C3 is different from that of stevastelins B and B3, although the stevastelins are produced by the same microorganism.

Experimental

General. Melting points were determined on a Mitamura-Riken micro hot stage and were not corrected. Optical rotations were recorded using a sodium lamp (589 nm) with a JASCO DIP-370 instrument with a 1 dm tube. Infrared (IR) spectra were measured with a JASCO FT/IR-200 spectrometer and were reported in wavenumbers (cm^{-1}). ^1H NMR spectra were recorded at 270 MHz on a JEOL GSX-270, or at 300 MHz on a JEOL Lambda 300 or Varian MVX-300 spectrometer. Chemical shifts are reported as δ values in ppm relative to tetramethylsilane ($\delta = 0$) or chloroform ($\delta = 7.26$). Coupling constants (J) are reported in Hz. Abbreviations used are b (broad peak), s (singlet), d (doublet), t (triplet), q (quartet), and m (complex multiplet). ^{13}C NMR spectra were recorded at 75 MHz on a JEOL Lambda 300 spectrometer. Chemical shifts are reported as δ values in ppm relative to chloroform-*d* ($\delta = 77.00$), DMSO-d_6 ($\delta = 39.52$), or methanol-d_4 ($\delta = 49.00$) as internal references. Mass spectra were measured by a JEOL GC Mate spectrometer in EI (70 eV) or FAB mode. Organic extracts were dried over solid anhydrous Na_2SO_4 and concentrated below 40 °C under reduced pressure. Column chromatography was carried out with silica gel (Merck Kieselgel 60 F_{254}; 230–400 mesh) for purification. Preparative TLC (PLC) was performed with Merck PLC plates (Kieselgel 60 F_{254}, 0.5 mm thickness).

1-Deoxy-2-*O*-methyl-1-methylene-3,4:5,6-bis-*O*-(1-methylethylidene)-L-*chiro*-inositol (13). At 0 °C, a THF solution (240 mL) of 2-*O*-methyl-3,4:5,6-bis-*O*-(1-methylethylidene)-L-*chiro*-1-inosose (**12**) (10.5 g, 38.6 mmol), prepared from L-quebrachitol by the method reported by Paulsen,[16] was dropwise added to a solution of Tebbe reagent[15] [prepared by stirring a mixture of $[Cp_2TiCl_2]$ (25 g, 100 mmol) and Me_3Al (2.0 M solution in toluene, 100 mL, 200 mmol) under Ar at room temperature for 72 h],

and the mixture was stirred at room temperature for 3 h. After dilution of the reaction mixture with Et_2O (250 mL), 1 M aqueous NaOH (200 mL) was slowly added to the resulting mixture at 0 °C. The insoluble material was removed by filtration through Celite. The layers were separated and the organic layer was washed with a 1 M aqueous NaOH solution and dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 200 g, EtOAc/hexane = 1/5 as eluent) to give compound **13** (6.7 g, 64%) as white crystals: $R_f = 0.60$ (EtOAc/toluene = 1/3); mp 93–93.5 °C (from EtOH); $[\alpha]_D^{28}$ +52 (*c* 0.8, $CHCl_3$); IR (neat) 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.40, 1.44, 1.53, 1.59, and 3.46 (5s, each 3H), 3.57–3.61 (m, 2H), 4.01 (m, 1H), 4.32 (m, 1H), 4.77 (d, 1H, $J = 6.4$ Hz), 5.41 and 5.56 (2d, each 1H, $J = 1.5$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.3, 27.0, 27.5, 57.0, 76.1, 77.0, 79.0, 79.2, 80.7, 110.6, 112.5, 118.7, 140.6; FAB-HRMS Calcd for $C_{14}H_{23}O_5$ $(M + H)^+$: 271.1546, Found: *m/z* 271.1537. Found: C, 62.16; H, 7.97%. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20%.

1-Deoxy-2-*O*-methyl-1-methylene-3,4:5,6-bis-*O*-(1-methylethylidene)-L-*chiro*-inositol (14). To a stirred solution of compound **13** (161 mg, 0.593 mmol) in MeOH (3 mL) at 0 °C was added *p*-toluenesulfonic acid monohydrate (*p*-TsOH, 1.1 mg, 5.9 μmol). After being stirred at 0 °C for 5 h, the reaction mixture was neutralized by the addition of triethylamine (0.5 mL) and concentrated to give a residue, which was purified by column chromatography (silica gel, 4 g, EtOAc/toluene = 1/3 as eluent) to give the starting material **13** (16 mg, 10%). Further elution with MeOH/$CHCl_3$ = 1/10 afforded the diol **14** (109 mg, 80%) as a colorless syrup: $R_f = 0.51$ (MeOH/$CHCl_3$ = 1/10); $[\alpha]_D^{26}$ −34 (*c* 1.6, $CHCl_3$); IR (neat) 3450, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.40 and 1.54 (2s, each 3H), 2.54 (m, 2H), 3.42 (dd, 1H, $J = 8.3$ and 8.3 Hz), 3.49 (s, 3H), 3.76–3.88 (m, 2H), 4.08 (dd, 1H, $J = 5.9$ and 6.3 Hz), 4.66 (d, 1H, $J = 5.9$ Hz), 5.42 and 5.49 (2d, each 1H, $J = 1.5$ Hz); FAB-HRMS Calcd for $C_{11}H_{19}O_5$ $(M + H)^+$: 231.1233, Found: *m/z* 231.1236.

3-Deoxy-3-methyl-4-*O*-methyl-1,2-*O*-(1-methylethylidene)-D-*myo*-inositol (15). A mixture of the alkene **14** (6.81 g, 29.6 mmol) and Raney-Ni W-4 (ca. 50 mL) in EtOH (205 mL) was hydrogenated under an atmospheric pressure of H_2 at room temperature for 3 h. The insoluble material was removed by filtration and the filtrate was concentrated to give a residue, which was purified by column chromatography (silica gel, 400 g, acetone/toluene = 1/3 as eluent) to afford compound **15** (6.50 g, 95%) as white crystals: $R_f = 0.45$ (MeOH/$CHCl_3$ = 1/10); mp 131–133 °C (from EtOH); $[\alpha]_D^{27}$ −35 (*c* 1.1, $CHCl_3$); IR (neat) 3450 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.24 (d, 3H, $J = 6.8$ Hz), 1.35 and 1.51 (2s, each 3H), 1.85 (m, 1H), 2.68–2.80 (m, 2H), 3.08 (dd, 1H, $J = 9.3$ and 10.7 Hz), 3.33 (dd, 1H, $J = 9.3$ and 9.8 Hz), 3.58 (s, 3H), 3.64 (dd, 1H, $J = 7.8$ and 9.8 Hz), 3.91 (dd, 1H, $J = 4.9$ and 7.8 Hz), 4.12 (dd, 1H, $J = 3.9$ and 4.9 Hz); ^{13}C NMR (CD_3OD, 75 MHz) δ 14.3, 26.4, 28.8, 39.1, 60.6, 74.7, 76.9, 79.0, 81.4, 84.5, 109.8; FAB-HRMS Calcd for $C_{11}H_{21}O_5$ $(M + H)^+$: 233.1389, Found: *m/z* 233.1407. Found: C, 56.66; H, 8.44%. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68%.

3-Deoxy-3-methyl-4-*O*-methyl-6-*O*-(4-methylphenylsulfonyl)-1,2-*O*-(1-methylethylidene)-D-*myo*-inositol (16). A mixture of **15** (1.70 g, 7.32 mmol) and *n*-Bu_2SnO (2.19 g, 14.6 mmol) in MeOH (200 mL) was heated under reflux for 40 h. The reaction mixture was cooled to room temperature and concentrated to give a residue, which was dissolved in 1,4-dioxane (100 mL). To this solution were added TsCl (1.67 g, 14.6 mmol) and DMAP (179 mg, 1.46 mmol), and the mixture was stirred at room temperature for 48 h. After addition of MeOH (10 mL), the reaction mixture was concentrated to give a residue, which was purified by column chromatography (silica gel, 90 g, EtOAc/toluene = 1/3 as eluent) to give the 6-*O*-tosyl derivative **16** (2.32 g, 82%) as white crystals: $R_f = 0.48$ (acetone/toluene = 1/3); mp 120–122 °C; $[\alpha]_D^{27}$ −62 (*c* 1.4, $CHCl_3$); IR (neat) 3450, 1355, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.21 (d, 3H, $J = 7.0$ Hz), 1.29 and 1.45 (2s, each 3H), 1.82 (ddq, 1H, $J = 4.0$, 11.0, and 7.0 Hz), 2.44 (s, 3H), 3.15 (dd, 1H, $J = 9.2$ and 11.0 Hz), 3.51 (dd, 1H, $J = 9.2$ and 9.9 Hz), 3.60 (s, 3H), 3.97 (dd, 1H, $J = 4.8$ and 7.3 Hz), 4.10 (dd, 1H, $J = 4.0$ and 4.8 Hz), 4.66 (dd, 1H, $J = 7.3$ and 9.9 Hz), 7.27–7.34 (m, 2H), 7.84–7.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.6, 21.6, 25.9, 27.8, 35.3, 60.9, 73.8, 77.0, 77.6, 82.7, 85.9, 109.4, 128.1 (2C), 129.4 (2C), 134.2, 144.5; FAB-HRMS Calcd for $C_{18}H_{27}O_7S$ $(M + H)^+$: 387.1490, Found: *m/z* 387.1477. Found: C, 55.67; H, 6.99%. Calcd for $C_{18}H_{26}O_7S$: C, 55.94; H, 6.78%.

1,2-Anhydro-5-deoxy-5-methyl-6-*O*-methyl-3,4-*O*-(1-methylethylidene)-D-*epi*-inositol (17). To a solution of the 6-*O*-tosyl derivative **16** (2.32 g, 6.01 mmol) in MeOH (45 mL) at 0 °C was added NaOMe in MeOH (4.92 M, 2.50 mL, 12.3 mmol), and the mixture was stirred at room temperature for 16 h. The reaction mixture was neutralized by the addition of acetic acid (0.83 mL, 14.4 mmol) at 0 °C, and then concentrated. The residue was diluted with EtOAc and washed with a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 65 g, EtOAc/hexane = 1/5 as eluent) to give **17** (1.20 g, 93%) as white crystals: $R_f = 0.59$ (acetone/toluene = 1/3); mp 118.0–118.2 °C; $[\alpha]_D^{23}$ −52 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 1.20 (d, 3H, $J = 7.0$ Hz), 1.34 and 1.50 (2s, each 3H), 1.69 (ddq, 1H, $J = 2.9$, 10.3, and 7.0 Hz), 3.20 (dd, 1H, $J = 3.7$ and 3.8 Hz), 3.27 (d, 1H, $J = 10.3$ Hz), 3.30 (d, 1H, $J = 3.8$ Hz), 3.53 (s, 3H), 4.13 (dd, 1H, $J = 2.9$ and 6.4 Hz), 4.39 (dd, 1H, $J = 3.7$ and 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.9, 25.3, 25.7, 35.2, 51.4, 57.1, 57.6, 72.2, 75.9, 76.9, 109.1; FAB-HRMS Calcd for $C_{11}H_{19}O_4$ $(M + H)^+$: 215.1283, Found *m/z* 215.1273. Found: C, 61.43; H, 8.77%. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47%.

4,6-Dideoxy-4,6-dimethyl-5-*O*-methyl-2,3-*O*-(1-methylethylidene)-D-*allo*-inositol (18). To a solution of the epoxide **17** (2.07 g, 9.38 mmol) in CH_2Cl_2 (193 mL) at room temperature under Ar was added Me_3Al (1.0 M solution in hexane, 96.6 mL, 96.6 mmol) via a cannula, and the mixture was stirred at room temperature for 19 h. To the reaction mixture was added H_2O (10 mL) at 0 °C, and the mixture was diluted with EtOAc. The organic layer was washed successively with a 0.5 M aqueous HCl solution, a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a syrup, which was purified by column chromatography (silica gel, 60 g, EtOAc/hexane = 1/6 as eluent) to give the alcohol **18** (2.00 g, 93%) as a colorless syrup: $R_f = 0.47$ (acetone/toluene = 1/5); $[\alpha]_D^{20}$ −2.7 (*c* 1.2, $CHCl_3$); IR (neat) 3460 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99 (d, 3H, $J = 6.9$ Hz), 1.16 (d, 3H, $J = 7.2$ Hz), 1.36 and 1.50 (2s, each 3H), 1.81 (ddq, 1H, $J = 1.5$, 9.6, and 7.2 Hz), 2.13 (d, 1H, $J = 6.3$ Hz), 2.27 (ddq, 1H, $J = 6.9$, 6.0, and 7.3 Hz), 3.33 (dd, 1H, $J = 9.6$ and 6.0 Hz), 3.40 (s, 3H), 3.59 (m, 1H), 4.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.7, 15.0, 24.5, 26.0, 33.5, 34.6, 59.0, 70.8, 74.5, 77.2, 80.3, 108.4; FAB-HRMS calcd for $C_{12}H_{23}O_4$ $(M + H)^+$: 231.1596, Found: *m/z* 231.1602. Found: C, 62.49; H, 9.62%. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63%.

1-*O*-Benzoyl-4,6-dideoxy-4,6-dimethyl-5-*O*-methyl-2,3-*O*-(1-methylethylidene)-D-*allo*-inositol (19). To a solution of com-

pound **18** (99 mg, 0.43 mmol) in pyridine (2 mL) were added benzoyl chloride (0.17 mL, 1.46 mmol) and DMAP (12 mg, 0.098 mmol), and the mixture was stirred at room temperature for 9 h. After addition of MeOH (1 mL) at 0 °C, the reaction mixture was concentrated to give a residue, which was diluted with EtOAc. The organic layer was washed successively with a 1 M aqueous HCl solution, a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a syrup, which was purified by column chromatography (silica gel, 10 g, EtOAc/hexane = 1/10 as eluent) to give the benzoate **19** (92 mg, 64%) as a colorless syrup: $R_f = 0.55$ (EtOAc/hexane = 1/3); $[\alpha]_D^{25}$ −15 (*c* 1.3, $CHCl_3$); IR (neat) 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.01 (d, 3H, $J = 7.3$ Hz), 1.17 (d, 3H, $J = 7.0$ Hz), 1.30 and 1.45 (2s, each 3H), 1.87 (ddq, 1H, $J = 3.7$, 7.0, and 7.0 Hz), 2.67 (ddq, 1H, $J = 7.0$, 9.2, and 7.3 Hz), 3.40 (s, 3H), 3.42 (dd, 1H, $J = 7.0$ and 7.0 Hz), 4.31 (dd, 1H, $J = 3.7$ and 7.3 Hz), 4.54 (dd, 1H, $J = 3.7$ and 7.3 Hz), 5.08 (dd, 1H, $J =$ 3.7 and 9.2 Hz), 7.42–7.60 (m, 3H), 8.08–8.12 (m, 2H). Found: C, 67.98; H, 8.04%. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84%.

(3a*R*,5*R*,6*R*,7*R*,7a*R*)-Tetrahydro-6-methoxy-2,2,5,7-tetramethyl-1,3-benzodioxol-4(3a*H*)-one (10). To a solution of the alcohol **18** (616 mg, 2.67 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added PCC on alumina (1 mmol g^{-1}, 14.4 g, 14.4 mmol). After being stirred at room temperature for 4 h, the reaction mixture was diluted with Et_2O and the insoluble material was removed by filtration through Celite. The filtrate was concentrated to give the crude ketone **10** (610 mg), which was used in the next reaction without further purification. A part of this compound was purified by column chromatography and used as an analytical sample: $R_f =$ 0.67 (acetone/toluene = 1/3); IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.09 (d, 3H, $J = 7.3$ Hz), 1.18 (d, 3H, $J =$ 7.1 Hz), 1.32 and 1.36 (2s, each 3H), 2.29 (ddq, 1H, $J = 7.1$, 4.2, and 10.0 Hz), 2.99 (dq, 1H, $J = 4.6$ and 7.3 Hz), 3.31 (s, 3H), 3.34 (dd, 1H, $J = 4.6$ and 10.0 Hz), 4.29 (dd, 1H, $J = 5.4$ and 4.2 Hz), 4.45 (d, 1H, $J = 5.4$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.7, 13.7, 25.7, 26.9, 32.3, 46.2, 57.2, 70.0, 78.0, 80.4, 109.4, 210.2; FAB-HRMS Calcd for $C_{12}H_{21}O_4$ $(M + H)^+$: 229.1440, Found *m*/*z* 229.1457. Found: C, 62.93; H, 8.54%. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83%.

3,5-Dideoxy-3,5-dimethyl-4-*O*-methyl-1,2-*O*-(1-methylethylidene)-6-*C*-oxo-β-L-mannoseptanose (9). To a solution of the crude ketone **10** (610 mg, 2.67 mmol) in $(CH_2Cl)_2$ (30 mL) at 0 °C were added mCPBA (692 mg, 4.01 mmol) and $KHCO_3$ (401 mg, 4.01 mmol), and the mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with $CHCl_3$ and then washed successively with a 20% aqueous $NaHSO_3$ solution, a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel, 15 g, EtOAc/hexane = 1/7 as eluent) to afford **9** (529 mg, 81% from **18**) as a colorless syrup: $R_f = 0.80$ (acetone/toluene = 1/1); $[\alpha]_D^{24}$ −122 (*c* 1.0, $CHCl_3$); IR (neat) 1755 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (d, 3H, $J = 6.8$ Hz), 1.33 (d, 3H, $J = 6.8$ Hz), 1.35 and 1.56 (2s, each 3H), 1.94 (dq, 1H, $J = 8.5$ and 6.8 Hz), 3.16 (dd, 1H, $J = 4.6$ and 8.5 Hz), 3.31 (dq, 1H, $J = 4.6$ and 6.8 Hz), 3.51 (s, 3H), 4.23 (d, 1H, $J =$ 6.8 Hz), 5.72 (d, 1H, $J = 6.8$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.6, 18.5, 23.9, 25.3, 37.4, 40.9, 61.6, 79.4, 83.1, 99.3, 108.9, 172.5; EI-HRMS Calcd for $C_{12}H_{20}O_5$ M^+: 244.1311, Found *m*/*z* 244.1317. Found: C, 58.93; H, 8.15%. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25%.

1,6-Bis-*O*-(2,2-dimethylpropanoyl)-2,4-dideoxy-2,4-dimethyl-3-*O*-methyl-L-mannitol (20). To a solution of the lactone **9** (708 mg, 2.90 mmol) in THF (28 mL) at 0 °C was added $LiAlH_4$ (547 mg, 14.5 mmol), and the mixture was stirred at room temperature for 2 h. To the ice-cooled reaction mixture was added H_2O (20 mL) dropwise, and then the mixture was diluted with MeOH. The insoluble material was removed by filtration through Celite, and the filtrate was concentrated to give a residue, which was dissolved in pyridine (30 mL). To this solution at 0 °C were added 2,2-dimethylpropanoyl chloride (PivCl, 0.88 mL, 7.2 mmol) and DMAP (354 mg, 2.90 mmol), and the mixture was stirred at room temperature for 2 h. After the addition of MeOH (5 mL) at 0 °C, the reaction mixture was concentrated to give a residue, which was diluted with EtOAc and washed successively with a 1 M aqueous HCl solution, a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 20 g, EtOAc/hexane = 1/6 as eluent) to afford the di-*O*-pivaloyl derivative **20** (679 mg, 65%) as colorless crystals: $R_f = 0.41$ (EtOAc/hexane = 1/3); mp 61.0–62.7 °C; $[\alpha]_D^{24}$ −15 (*c* 1.3, $CHCl_3$); IR (neat) 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (d, 3H, $J =$ 6.8 Hz), 0.90 (d, 3H, $J = 6.8$ Hz), 1.22 and 1.24 (2s, each 9H), 1.78 (ddq, 1H, $J = 9.2$, 2.0, and 6.8 Hz), 2.01 (dddq, 1H, $J = 9.6$, 3.4, 5.6, and 6.8 Hz), 2.63 (bs, 1H), 3.46 (s, 3H), 3.52 (dd. 1H, $J =$ 2.0 and 9.6 Hz), 3.79 (ddd, 1H, $J = 9.2$, 6.3, and 2.9 Hz), 4.08 (dd, 1H, $J = 5.6$ and 10.7 Hz), 4.09 (dd, 1H, $J = 6.3$ and 11.5 Hz), 4.22 (dd, 1H, $J = 10.7$ and 3.4 Hz), 4.34 (dd, 1H, $J = 11.5$ and 2.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.3, 14.2, 27.11 (3C), 27.13 (3C), 35.7, 37.3, 38.8, 60.5, 66.4, 67.5, 71.6, 81.1, 178.5, 178.8; FAB-HRMS Calcd for $C_{19}H_{37}O_6$ $(M + H)^+$: 361.2590, Found *m*/*z* 361.2579. Found: C, 63.19; H, 9.99%. Calcd for $C_{19}H_{36}O_6$: C, 63.30; H, 10.07%.

1,6-Bis-*O*-(2,2-dimethylpropanoyl)-2,4-dideoxy-2,4-dimethyl-5-*O*-methylsulfonyl-3-*O*-methyl-L-mannitol (21). To a solution of the pivalate **20** (655 mg, 1.82 mmol) in pyridine (16 mL) at 0 °C was added MsCl (0.70 mL, 9.08 mmol), and the mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated to give a residue, which was diluted with EtOAc. The organic layer was washed successively with a 1 M aqueous HCl solution, a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 20 g, EtOAc/hexane = 1/7 as eluent) to afford **21** (788 mg, 99%) as a colorless syrup: $R_f =$ 0.16 (EtOAc/hexane = 1/5); $[\alpha]_D^{23}$ −13 (*c* 1.9, $CHCl_3$); IR (neat) 1730, 1360, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.93 (d, 3H, $J = 6.8$ Hz), 0.96 (d, 3H, $J = 7.1$ Hz), 1.23 and 1.24 (2s, each 9H), 2.01 (m, 1H), 2.13 (ddq, 1H, $J = 1.7$, 8.0, and 7.1 Hz), 3.09 (s, 3H), 3.35 (dd, 1H, $J_{3,4} = 1.7$ and 9.0 Hz), 3.48 (s, 3H), 4.08 (dd, 1H, $J = 5.2$ and 10.9 Hz), 4.11 (dd, 1H, $J = 5.0$ and 13.1 Hz), 4.21 (dd, 1H, $J = 3.5$ and 10.9 Hz), 4.69 (dd, 1H, $J =$ 2.0 and 13.1 Hz), 4.91 (ddd, 1H, $J = 2.0$, 5.0, and 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.6, 14.2, 27.1 (3C), 27.2 (3C), 35.9, 37.1, 38.9, 39.3, 60.8, 63.2, 66.0, 80.9, 82.4, 178.0, 178.4; FAB-HRMS Calcd for $C_{20}H_{39}O_8S$ $(M + H)^+$: 439.2365, Found *m*/*z* 439.2373.

1,2-Anhydro-3,5-dideoxy-6-*O*-(2,2-dimethylpropanoyl)-3,5-dimethyl-4-*O*-methyl-L-glucitol (8). To a solution of the mesylate **21** (321 mg, 0.732 mmol) in MeOH (17 mL) at 0 °C was added MeONa in MeOH (4.92 M, 0.45 mL, 2.21 mmol), and the mixture was stirred at room temperature for 3 h. To the reaction mixture was added AcOH (0.17 mL) at 0 °C, and the mixture was concentrated to give a residue, which was purified by column chromatography (silica gel, 15 g, EtOAc/hexane = 1/5 as eluent) to afford **8** (182 mg, 96%) as a colorless syrup: $R_f = 0.55$ (EtOAc/hexane =

1/3); $[\alpha]_D^{24}$ −21 (*c* 2.0, $CHCl_3$); IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (d, 3H, $J = 6.8$ Hz), 1.07 (d, 3H, $J = 7.1$ Hz), 1.22 (s, 9H), 1.44 (ddq, 1H, $J = 3.4$, 7.3, and 6.8 Hz), 2.02 (m, 1H), 2.60 (dd, 1H, $J = 2.7$ and 4.9 Hz), 2.82 (dd, 1H, $J = 3.9$ and 4.9 Hz), 2.95 (ddd, 1H, $J = 2.7$, 3.9, and 7.3 Hz), 3.06 (dd, 1H, $J = 3.4$ and 8.3 Hz), 3.42 (s, 3H), 4.04 (dd, 1H, $J = 6.1$ and 10.7 Hz) and 4.20 (dd, 1H, $J = 3.7$ and 10.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.7, 14.4, 27.2 (3C), 35.6, 38.9, 39.1, 46.8, 55.6, 60.6, 65.9, 84.7, 178.4; EI-HRMS Calcd for $C_{14}H_{27}O_4$ $(M + H)^+$: 259.1909, Found *m/z* 259.1916. Found: C, 65.02; H, 10.15%. Calcd for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14%.

(2*S*,3*S*,4*S*,5*R*)-3-Methoxy-2,4-dimethyl-1,5-octadecanediol (22). To a stirred mixture of the epoxide **8** (532 mg, 2.06 mmol) and CuCN (92 mg, 1.0 mmol) in Et_2O at 0 °C under Ar was added a solution of didodecylmagnesium[18] [1.0 M solution in Et_2O, 10.3 mL, 10.3 mmol; prepared by addition of 1,4-dioxane (1.26 mL, 14.8 mmol) to a 1 M solution of dodecylmagnesium bromide in diethyl ether (15 mL), followed by centrifuging (2500 rpm, 10 min)], and the mixture was stirred at room temperature for 2 h. The reaction mixture was quenched by the addition of a saturated aqueous NH_4Cl solution at 0 °C, and the products were extracted with EtOAc. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 30 g, EtOAc/hexane = 1/7 as eluent) to afford **22** (618 mg, 87%) as a colorless syrup: $R_f = 0.50$ (acetone/toluene = 1/3); $[\alpha]_D^{24}$ +7.5 (*c* 0.9, $CHCl_3$); IR (neat) 3420 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 3H, $J = 6.8$ Hz), 0.94 (d, 3H, $J = 6.8$ Hz), 0.96 (d, 3H, $J = 6.6$ Hz), 1.21–1.34 (m, 22H), 1.45 (m, 2H), 1.71 (ddq, 1H, $J = 1.7$, 4.1, and 6.8 Hz), 1.98 (m, 1H), 3.28 (dd, 1H, $J = 4.1$ and 7.5 Hz), 3.51 (s, 3H), 3.66 (dd, 1H, $J = 5.6$ and 11.0 Hz), 3.71 (dd, 1H, $J = 4.4$ and 11.0 Hz), 3.73 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.2, 14.0, 14.4, 22.6, 26.2, 29.3, 29.6, 29.7, 31.9, 35.0, 37.5, 39.3, 60.4, 65.1, 74.6, 88.8; FAB-HRMS Calcd for $C_{21}H_{45}O_3$ $(M + H)^+$: 345.3369, Found *m/z* 345.3374. Found: C, 73.15; H, 12.75%. Calcd for $C_{21}H_{44}O_3$: C, 73.20; H, 12.87%.

(2*S*,3*S*,4*S*,5*R*)-2,4-Dimethyl-1,3,5-octadecanetriol (7). To a solution of the methyl ether **22** (443 mg, 1.28 mmol) in CH_2Cl_2 (22 mL) at −18 °C under Ar was added iodotrimethylsilane[19] [prepared by heating a mixture of hexamethyldisilane (2.05 mL, 10 mmol) and iodine (2.5 g, 10 mmol) at 65 °C for 1.5 h]. After being stirred at room temperature for 2 h, to the reaction mixture was added MeOH at 0 °C. The mixture was diluted with EtOAc and washed successively with a 20% aqueous $Na_2S_2O_3$ solution, a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 7 g, EtOAc/hexane = 1/2 as eluent) to afford **7** (394 mg, 93%) as an amorphous solid: $R_f = 0.42$ (acetone/toluene = 1/3); mp 54.5–56.0 °C; $[\alpha]_D^{22}$ +17 (*c* 1.3, $CHCl_3$), {lit.,[3] $[\alpha]_D^{20}$ +14.1 (*c* 1.23, $CHCl_3$)}; IR (neat) 3250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75 (d, 3H, $J = 6.8$ Hz), 0.88 (t, 3H, $J = 6.8$ Hz), 0.92 (d, 3H, $J = 7.1$ Hz), 1.22–1.69 (m, 25H), 1.89 (m, 1H), 2.83 and 3.39 (2bs, each 1H), 3.63–3.73 (m, 2H), 3.76 (dd, 1H, $J = 1.5$ and 9.5 Hz), 3.87 (m, 1H), 4.39 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 4.0, 13.1, 14.1, 22.6, 26.0, 29.3, 29.6, 29.6, 31.9, 35.4, 37.2, 37.7, 69.1, 77.7, 83.5; FAB-HRMS Calcd for $C_{20}H_{43}O_3$ $(M + H)^+$: 331.3212, Found *m/z* 331.3201. Found: C, 72.53; H, 12.52%. Calcd for $C_{20}H_{42}O_3$: C, 72.67; H, 12.81%. The ^1H NMR data were identical to those reported for the authentic compound derived from natural stevastelin B by reductive degradation.[3]

(α*R*,β*S*,4*S*,5*S*)-β,2,2,5-Tetramethyl-α-tridecyl-1,3-dioxane-4-ethanol (23). To a solution of the triol **7** (267 mg, 0.808 mmol) in CH_2Cl_2 (28 mL) at room temperature were added 2-methoxypropene (0.155 mL, 1.62 mmol) and CSA (19 mg, 0.081 mmol), and the mixture was stirred at room temperature for 5 min. To the reaction mixture at 0 °C was added Et_3N (4 mL), and the mixture was diluted with EtOAc. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 30 g, EtOAc/hexane = 1/14 as eluent) to afford **23** (229 mg, 76%) as a colorless syrup: $R_f = 0.68$ (EtOAc/hexane = 1/3); $[\alpha]_D^{21}$ +35 (*c* 1.2, $CHCl_3$); IR (neat) 3540 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.71 (d, 3H, $J = 6.6$ Hz), 0.88 (t, 3H, $J = 6.7$ Hz), 0.93 (d, 3H, $J = 7.1$ Hz), 1.22–1.34 (m, 24H), 1.37 and 1.48 (2s, each 3H), 1.68 and 1.92 (2m, each 1H), 3.39 (bs, 1H), 3.53 (dd, 1H, $J = 11.3$ and 11.4 Hz), 3.70 (dd, 1H, $J = 5.3$ and 11.4 Hz), 3.73 (dd, 1H, $J = 2.0$ and 10.4 Hz), 3.77 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 4.8, 12.0, 14.1, 19.2, 22.7, 26.2, 29.3, 29.6, 29.7, 30.5, 31.9, 35.0, 36.8, 66.1, 76.7, 81.4, 98.2; EI-HRMS Calcd for $C_{23}H_{46}O_3$ M^+: 370.3447, Found *m/z* 370.3444. Found: C, 74.52; H, 12.48%. Calcd for $C_{23}H_{46}O_3$: C, 74.54; H, 12.51%.

An Inseparable Mixture of *N*-[(Phenylmethoxy)carbonyl]-*O*-(phenylmethyl)-L-serine (1*R*)-1-[(1*S*)-1-[(4*S*,5*S*)-2,2,5-Trimethyl-1,3-dioxan-4-yl]ethyl]tetradecyl Ester (24) and Its D-Serine Isomer. To a solution of *N*-[(phenylmethoxy)carbonyl]-*O*-(phenylmethyl)-L-serine [Cbz–Ser(Bzl),[22] 244 mg, 0.741 mmol] in THF (2 mL) under Ar at 0 °C were added 2,4,6-trichlorobenzoyl chloride (0.116 mL, 0.742 mmol) and Et_3N (0.104 mL, 0.742 mmol). After being stirred at room temperature for 1 h, the reaction mixture was diluted with toluene (7 mL) and centrifuged (3000 rpm, 10 min). The supernatant layer was added to a solution of the alcohol **19** (55 mg, 0.15 mmol) in toluene (5.5 mL) at 0 °C under Ar via a cannula. To this mixture under Ar at 0 °C was added a solution of DMAP (14.5 mg, 0.119 mmol) in toluene (2 mL) dropwise over 1.5 h, and the resulting mixture was further stirred at 0 °C for 40 min. To the reaction mixture was added a 1 M aqueous citric acid solution, and the products were extracted with EtOAc. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 5 g, EtOAc/hexane = 1/14 as eluent) to afford an inseparable mixture (ca. 6:1) of **24** and its D-serine isomer (74 mg, 73%) as a colorless syrup: $R_f = 0.60$ (EtOAc/hexane = 1/3); IR (neat) 3300–3500, 1730, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz for the major isomer **24**) δ 0.67 (d, 3H, $J = 6.6$ Hz), 0.88 (t, 3H, $J = 6.8$ Hz), 0.90 (d, 3H, $J = 6.8$ Hz), 1.18–1.60 (m, 24H), 1.30 and 1.36 (2s, each 3H), 1.78–1.87 (m, 2H), 3.48 (dd, 1H, $J = 11.0$ and 11.5 Hz), 3.57 (dd, 1H, $J = 1.0$ and 10.0 Hz), 3.67 (dd, 1H, $J = 4.9$ and 11.5 Hz), 3.72 (dd, 1H, $J = 3.2$ and 9.3 Hz), 3.92 (dd, 1H, $J = 2.7$ and 9.3 Hz), 4.44–4.51 (m, 3H), 5.03 (m, 1H), 5.12 (s, 2H), 5.68 (bd, 1H, $J = 8.5$ Hz), 7.24–7.37 (m, 10H); FAB-HRMS Calcd for $C_{41}H_{64}NO_7$ $(M + H)^+$: 682.4683, Found *m/z* 682.4689.

Boc–Thr(Bzl)–OBzl. To a solution of [*N*-(1,1-dimethylethoxy)carbonyl]-*O*-(phenylmethyl)-L-threonine [Boc–Thr(Bzl); purchased from Peptide Institute, Inc., Osaka, Japan] (1.00 g, 3.23 mmol) in DMF (15 mL) at 0 °C were added Et_3N (0.45 mL, 3.23 mmol) and benzyl bromide (0.383 mL, 3.23 mmol), and the mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with EtOAc, and washed successively with a 1 M aqueous citric acid solution, a saturated aqueous $NaHCO_3$

solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 20 g, EtOAc/hexane = 1/8 as eluent) to afford the title compound (1.10 g, 85%) as a colorless syrup: $R_f = 0.61$ (EtOAc/hexane = 1/3); $[\alpha]_D^{23}$ −18 (*c* 0.7, $CHCl_3$); IR (neat) 3450, 1750, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (d, 3H, $J = 6.6$ Hz), 1.44 (s, 9H), 4.14 (dq, 1H, $J = 2.2$ and 6.6 Hz,), 4.34 (dd, 1H, $J = 2.2$ and 9.7 Hz), 4.26 and 4.47 (2d, each 1H, $J = 11.7$ Hz), 5.12 (s, 2H), 5.30 (d, 1H, $J = 9.7$ Hz), 7.15–7.33 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.1, 28.1, 58.2, 66.9, 70.7, 74.4, 79.6, 127.4, 128.2, 128.32, 128.35, 129.2, 135.2, 137.7, 156.0, 170.8; FAB-HRMS Calcd for $C_{23}H_{30}NO_5$ $(M + H)^+$: 400.2124, Found *m/z* 400.2113. Found: C, 68.90; H, 7.26; N, 3.45%. Calcd for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.51%.

Boc–Val–Thr(Bzl)–OBzl. Boc–Thr(Bzl)–OBzl (1.10 g, 2.75 mmol) was dissolved in TFA (5 mL) at 0 °C, and the solution was stirred at room temperature for 1 h. The reaction mixture was concentrated to give a residue, which was dissolved in HCl in 1,4-dioxane (6 M solution, 1 mL). The mixture was concentrated and dried in vacuo to afford Thr(Bzl)–OBzl HCl salt (985 mg). To a solution of [*N*-(1,1-dimethylethoxy)carbonyl]-L-valine (Boc–Val; purchased from Peptide Institute, Inc., Osaka, Japan) (1.50 g, 6.88 mmol) in DMF (10 mL) at −18 °C were added a solution of Thr(Bzl)–OBzl HCl salt (985 mg, 2.75 mmol) in DMF (10 mL), WSC·HCl (1.60 g, 10.3 mmol), and HOBt (2.79 g, 20.6 mmol), and the mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with EtOAc, and washed successively with a 1 M aqueous citric acid solution, a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 35 g, EtOAc/hexane = 1/8 as eluent) to afford the title compound (992 mg, 72%) as an amorphous solid: $R_f = 0.25$ (EtOAc/hexane = 1/3); $[\alpha]_D^{22}$ −9 (*c* 1.6, $CHCl_3$); IR (neat) 3310, 1740, 1710, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.91 and 0.96 (2d, each 3H, $J = 6.6$ Hz), 1.20 (d, 3H, $J = 6.2$ Hz), 1.43 (s, 9H), 2.10 (m, 1H), 4.00 (m, 1H), 4.18 (dq, 1H, $J = 2.2$ and 6.2 Hz), 4.28 and 4.50 (2d, each 1H, $J = 11.9$ Hz), 4.69 (dd, 1H, $J = 2.2$ and 9.2 Hz), 5.07 (d, 2H, $J = 11.9$ Hz), 5.10 (m, 2H), 6.45 (d, 1H, $J = 9.2$ Hz), 7.21–7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.1, 17.6, 19.1, 28.2, 31.1, 56.6, 59.7, 67.1, 70.7, 74.1, 79.6, 127.6, 127.6, 128.2, 128.3, 128.4, 128.4, 135.1, 137.6, 155.6, 170.0, 171.6; FAB-HRMS Calcd for $C_{28}H_{39}N_2O_6$ $(M + H)^+$: 499.2808, Found *m/z* 499.2834. Found: C, 67.05; H, 7.61; N, 5.58%. Calcd for $C_{28}H_{38}N_2O_6$: C, 67.45; H, 7.68; N, 5.62%.

Boc–Val–Thr (25). A mixture of Boc–Val–Thr(Bzl)–OBzl (85 mg, 0.17 mmol) and 10% Pd on carbon (32 mg) in EtOH (2 mL) was stirred under an atmospheric pressure of H_2 at room temperature for 4 h. The insoluble material was removed by filtration and the filtrate was concentrated to give **25** (39 mg, 72%) as an amorphous solid. This compound was used for the next reaction without further purification: $R_f = 0.47$ (MeOH/$CHCl_3$ = 1/2); $[\alpha]_D^{22}$ −2.5 (*c* 1.1, MeOH); ^1H NMR (MeOH-d_4, 300 MHz) δ 0.94 and 0.98 (2d, each 3H, $J = 6.8$ Hz), 1.18 (d, 3H, $J = 6.3$ Hz), 1.45 (s, 9H), 2.08 (dqq, 1H, $J = 3.4$, 6.8, and 6.8 Hz), 3.94 (bd, 1H, $J = 3.4$ Hz), 4.30 (dq, 1H, $J = 2.9$ and 6.3 Hz), 4.42 (bd, 1H, $J = 2.9$ Hz); ^{13}C NMR (MeOH-d_4, 75 MHz) δ 18.6, 19.8, 20.4, 28.7, 31.7, 58.9, 61.7, 68.6, 80.6, 158.0, 173.4, 174.8; FAB-HRMS Calcd for $C_{14}H_{27}N_2O_6$ $(M + H)^+$: 319.1869, Found *m/z* 319.1849.

***N*-[(1,1-Dimethylethoxy)carbonyl]-L-valyl-L-threonyl-*O*-(phenylmethyl)-L-serine (1*R*)-1-[(1*S*)-1-[(4*S*,5*S*)-2,2,5-Trimethyl-1,3-dioxan-4-yl]ethyl]tetradecyl Ester (26) and Its D-Serine Isomer (27).** A mixture of the acetonide **24** and its D-serine isomer (ca. 6:1, 23 mg, 0.034 mmol) in MeOH (4.5 mL) was stirred in the presence of 10% Pd on a carbon ethylenediamine complex[24] (23 mg) under an atmospheric pressure of H_2 at room temperature for 1 h. The insoluble material was removed by filtration and the filtrate was concentrated to give a crude amine, which was dissolved in DMF (1.9 mL). To this solution at 0 °C were added the dipeptide **25** (17 mg, 0.053 mmol), WSC·HCl (32 mg, 0.17 mmol), and HOBt (23 mg, 0.17 mmol), and the whole mixture was stirred at room temperature for 14 h. The reaction mixture was diluted with EtOAc and washed successively with a 1 M aqueous citric acid solution, a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 5 g, acetone/toluene = 1/10 as eluent) to first afford **27** (3.7 mg, 13%) as a colorless syrup: $R_f = 0.50$ (acetone/toluene = 1/4); $[\alpha]_D^{22}$ −23 (*c* 0.7, $CHCl_3$); IR (neat) 3300, 1740, 1715, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.66 and 0.85 (2d, each 3H, $J = 6.6$ Hz), 0.88 (t, 3H, $J = 6.8$ Hz), 0.90 (d, 3H, $J = 6.8$ Hz), 0.96 (d, 3H, $J = 6.6$ Hz), 1.14–1.70 (m, 24H), 1.17 (d, 3H, $J = 6.3$ Hz), 1.33 and 1.39 (2s, each 3H), 1.43 (s, 9H), 1.70–1.92 (m, 2H), 2.17 (m, 1H), 3.35 (bs, 1H), 3.48 (dd, 1H, $J = 11.5$ and 11.0 Hz), 3.56 (dd, 1H, $J = 1.5$ and 10.0 Hz), 3.68 (dd, 1H, $J = 11.5$ and 5.1 Hz), 3.73 (dd, 1H, $J = 3.4$ and 9.5 Hz), 3.92 (dd, 1H, $J = 3.7$ and 9.5 Hz), 3.97 (m, 1H), 4.28–4.44 (m, 2H), 4.52 (s, 2H), 4.70 (m, 1H), 4.97 (m, 1H), 5.03 (bd, 1H, $J = 7.6$ Hz), 6.87 (bd, 1H, $J = 6.8$ Hz), 7.18–7.40 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.1, 12.1, 14.1, 17.6, 18.5, 18.8, 19.3, 22.7, 24.7, 28.3, 29.35, 29.44, 29.5, 29.6, 31.1, 31.9, 36.8, 53.3, 57.8, 60.2, 66.2, 67.1, 69.1, 73.4, 74.4, 78.9, 80.3, 98.0, 127.8, 127.8, 128.4, 137.3, 156.0, 169.8, 170.9, 172.4; FAB-HRMS Calcd for $C_{47}H_{82}N_3O_{10}$ $(M + H)^+$: 848.6001, Found *m/z* 848.6017. Found: C, 66.59; H, 9.57; N, 5.10%. Calcd for $C_{47}H_{81}N_3O_{10}$: C, 66.56; H, 9.63; N, 4.95%.

Further elution gave **26** (22.9 mg, 80%) as a colorless syrup: $R_f = 0.45$ (acetone/toluene = 1/4); $[\alpha]_D^{22}$ +2.3 (*c* 1.2, $CHCl_3$); IR (neat) 3290, 1740, 1710, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.67 (d, 3H, $J = 6.6$ Hz), 0.88 (t, 3H, $J = 6.9$ Hz), 0.89 (d, 3H, $J = 6.6$ Hz), 0.89 and 0.93 (2d, each 3H, $J = 6.7$ Hz), 1.18 (d, 3H, $J = 6.6$ Hz), 1.21–1.60 (m, 24H), 1.33 and 1.37 (2s, each 3H), 1.44 (s, 9H), 1.78–1.87 (m, 2H), 2.12 (m, 1H), 3.29 (bs, 1H), 3.48 (dd, 1H, $J = 11.2$ and 11.2 Hz), 3.57 (dd, 1H, $J = 1.7$ and 11.2 Hz), 3.67 (dd, 1H, $J = 3.6$ and 9.4 Hz), 3.68 (m, 1H), 3.92 (dd, 1H, $J = 3.3$ and 9.4 Hz), 3.96 (m, 1H), 4.33 (m, 1H), 4.45 (dd, 1H, $J = 2.8$ and 7.4 Hz), 4.50 (s, 2H), 4.69 (ddd, 1H, $J = 3.3$, 3.6, and 8.3 Hz), 4.98–5.05 (m, 2H), 6.82 (bd, 1H, $J = 7.4$ Hz), 7.19 (bd, 1H, $J = 8.3$ Hz), 7.24–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.6, 12.2, 14.1, 17.6, 18.0, 18.7, 19.2, 22.7, 24.9, 28.3, 29.3, 29.4, 29.5, 29.59, 29.62, 30.5, 30.8, 31.4, 31.9, 36.8, 52.9, 56.9, 60.0, 66.1, 68.9, 69.5, 73.4, 75.1, 78.8, 80.0, 97.9, 127.0, 127.6, 127.8, 128.4, 129.5, 137.3, 155.8, 169.6, 170.3, 172.2; FAB-HRMS Calcd for $C_{47}H_{82}N_3O_{10}$ $(M + H)^+$: 848.6001, Found *m/z* 848.6011. Found: C, 66.55; H, 9.59; N, 5.08%. Calcd for $C_{47}H_{81}N_3O_{10}$: C, 66.56; H, 9.63; N, 4.95%.

***N*-[(1,1-Dimethylethoxy)carbonyl]-L-valyl-L-threonyl-*O*-(phenylmethyl)-L-serine (1*R*)-1-[(1*R*,2*S*,3*S*)-2,4-Dihydroxy-1,3-dimethylbutyl]tetradecyl Ester (28).** A solution of the acetonide **26** (55 mg, 0.065 mmol) in acetic acid (3.5 mL) and H_2O (1.5 mL) was stirred at room temperature for 10 h. The reaction mixture was diluted with H_2O, and to this solution was added solid $NaHCO_3$ (6.8 g) at 0 °C. The products were extracted with EtOAc, and the organic layer was washed with a saturated aqueous $NaHCO_3$

solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 1 g, acetone/toluene = 1/4 as eluent) to afford **28** (50 mg, 94%) as a colorless syrup: $R_f = 0.40$ (acetone/toluene = 1/2); $[\alpha]_D^{22}$ −10 (*c* 0.75, $CHCl_3$); IR (neat) 3300, 1740, 1700, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79 (d, 3H, $J = 7.1$ Hz), 0.87 (t, 3H, $J = 7.1$ Hz), 0.90 and 0.92 (2d, each 3H, $J = 6.6$ Hz), 0.93 (d, 3H, $J = 6.6$ Hz), 1.16 (d, 3H, $J = 6.6$ Hz), 1.21–1.35 (m, 22H), 1.44 (s, 9H), 1.55 (m, 1H), 1.80 (m, 4H), 2.13 (m, 1H), 3.25–3.60 (m, 5H), 3.69 (dd, 1H, $J = 3.7$ and 9.4 Hz), 3.89 (dd, 1H, $J = 3.9$ and 9.4 Hz), 3.99 (dd, 1H, $J = 5.4$ and 8.1 Hz), 4.33 (m, 1H), 4.46 (dd, 1H, $J = 1.7$ and 7.6 Hz), 4.51 (s, 2H), 4.65 (ddd, 1H, $J = 3.7$, 3.9, and 7.8 Hz), 5.06 (m, 1H), 5.13 (d, 1H, $J = 8.1$ Hz), 6.99 (bd, 1H, $J = 7.6$ Hz), 7.25–7.37 (m, 5H), 7.48 (bd, 1H, $J = 7.8$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.3, 14.0, 14.1, 17.7, 18.2, 19.3, 22.7, 25.5, 28.3, 29.3, 29.5, 29.6, 29.7, 30.7, 31.9, 32.0, 37.9, 38.3, 53.2, 57.2, 60.1, 66.7, 67.8, 69.3, 73.4, 78.4, 79.6, 80.2, 127.7, 127.9, 128.4, 137.1, 156.0, 169.9, 170.7, 172.4; FAB-HRMS Calcd for $C_{44}H_{78}N_3O_{10}$ $(M + H)^+$: 808.5688, Found *m/z* 808.5697.

***N*-[(1,1-Dimethylethoxy)carbonyl]-L-valyl-L-threonyl-*O*-(phenylmethyl)-L-serine (1*R*)-1-[(1*R*,2*R*,3*R*)-3-Carboxy-2-hydroxy-1-methylbutyl]tetradecyl Ester (29).** To a solution of the triol **28** (47 mg, 0.058 mmol) in CH_2Cl_2 (9 mL) at 0 °C were added TEMPO (1.24 g L^{-1} solution in CH_2Cl_2; 0.073 mL), KBr (5.96 g L^{-1} solution in H_2O; 0.115 mL), NaOCl (0.35 M solution in H_2O; 0.02 mL), and $NaHCO_3$ (50 g L^{-1} solution in H_2O; 0.02 mL). After being stirred at 0 °C for 1 h, to the reaction mixture was added a 20% aqueous $Na_2S_2O_3$ solution. The products were extracted with $CHCl_3$, and the organic layer was washed with a 20% aqueous $Na_2S_2O_3$ solution and then dried. Removal of the solvent gave a crude aldehyde (47 mg), which was dissolved in *t*-BuOH (3.7 mL) and H_2O (0.9 mL). To this solution were added $NaH_2PO_4 \cdot 2H_2O$ (36 mg, 0.23 mmol), $HOSO_2NH_2$ (28 mg, 0.29 mmol), and $NaClO_2$ (31 mg, 0.35 mmol), and the mixture was stirred at room temperature for 1 h. To the reaction mixture at 0 °C was added a 1 M aqueous citric acid solution, and the products were extracted with $CHCl_3$. The organic layer was washed with a 1 M aqueous citric acid solution and then dried. Removal of the solvent gave **29** (47 mg, 100% crude yield) as a colorless syrup, which was used in the next reaction without further purification: $R_f = 0.31$ (MeOH/$CHCl_3$ = 1/10); $[\alpha]_D^{23}$ −5 (*c* 0.76, $CHCl_3$); IR (neat) 3310, 1735, 1715, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3H, $J = 6.3$ Hz), 0.89 (d, 3H, $J = 6.3$ Hz), 0.96 (d, 3H, $J = 7.3$ Hz), 0.96 (d, 3H, $J = 7.3$ Hz), 1.10–1.35 (m, 28H), 1.43 (s, 9H), 1.57 (m, 2H), 1.91 (m, 1H), 2.10 (m, 1H), 2.68 (m, 1H), 3.65 (m, 1H), 3.72 (m, 1H), 3.88 (m, 1H), 4.04 (dd, 1H, $J_{\alpha,\beta} = 5.9$ and 8.3 Hz), 4.32 (m, 1H), 4.46–4.51 (m, 3H), 4.68 (m, 1H), 5.06 (m, 1H), 5.24 (bd, 1H, $J = 8.3$ Hz), 7.26–7.35 (m, 6H), 7.42 (bd, 1H, $J = 8.3$ Hz); FAB-HRMS Calcd for $C_{44}H_{76}N_3O_{11}$ $(M + H)^+$: 822.5480, Found *m/z* 822.5486.

***N*-[(2*R*,3*R*,4*R*,5*R*)-3,5-Dihydroxy-2,4-dimethyl-1-oxooctadecyl]-L-valyl-L-threonyl-*O*-(phenylmethyl)-L-serine (3→1^5)-Lactone (30).** To a solution of the carboxylic acid **29** (47 mg, 0.058 mmol) in CH_2Cl_2 (6 mL) under Ar at 0 °C was added TFA (1.1 mL). After being stirred at 0 °C for 1 h, the reaction mixture was concentrated and dried in vacuo to give **5**·TFA, which was dissolved in DMF (58 mL). To this solution under Ar at 0 °C were added diethylphosphoryl cyanide (DEPC, 0.0431 mL, 0.288 mmol) and Et_3N (0.0445 mL, 0.317 mmol), and the mixture was stirred at 0 °C for 30 min, then at room temperature for 16 h. The reaction mixture was diluted with EtOAc and washed successively with a 1 M aqueous citric acid solution, a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 1 g, acetone/toluene = 1/6 as eluent) to afford **30** (16.7 mg, 41% from **29**) as a colorless syrup: $R_f = 0.53$ (acetone/toluene = 1/1); $[\alpha]_D^{21}$ −33 (*c* 0.8, $CHCl_3$); IR (neat) 3310, 1730, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, 3H, $J = 6.8$ Hz), 0.98 (d, 3H, $J = 7.2$ Hz), 0.99 and 1.04 (2d, each 3H, $J = 6.6$ Hz), 1.12 (d, 3H, $J = 6.6$ Hz), 1.18 (d, 3H, $J = 7.4$ Hz), 1.21–1.33 (m, 22H), 1.51 (m, 1H), 1.63 (m, 1H), 1.80 (m, 1H), 2.06 (m, 1H), 2.52 (m, 1H), 3.26 and 3.33 (2bs, each 1H), 3.57 (dd, 1H, $J = 4.3$ and 8.4 Hz), 3.89 (dd, 1H, $J = 6.3$ and 9.9 Hz), 4.00 (dd, 1H, $J = 4.7$ and 9.9 Hz), 4.12 (dd, 1H, $J = 7.4$ and 9.0 Hz), 4.35–4.45 (m, 2H), 4.49 (m, 1H), 4.50 and 4.58 (2d, each 1H, $J = 11.1$ Hz), 4.90 (m, 1H), 6.80 (bd, 1H, $J = 7.1$ Hz), 7.19 (bd, 1H, $J = 7.4$ Hz), 7.24–7.35 (m, 5H), 7.54 (bd, 1H, $J = 7.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 15.9, 16.0, 16.0, 16.2, 18.8, 19.2, 19.4, 22.7, 26.1, 29.4, 29.5, 29.6, 29.6, 30.2, 31.3, 31.9, 39.6, 45.8, 53.2, 58.0, 62.0, 65.2, 67.4, 69.2, 73.5, 79.9, 128.0, 128.5, 137.6, 169.6, 170.9, 172.7, 176.7; FAB-HRMS Calcd for $C_{39}H_{66}N_3O_8$ $(M + H)^+$: 704.4850, Found *m/z* 704.4873.

Stevastelin B (1). A mixture of the macrocycle **30** (5.1 mg, 0.0073 mmol) and 20% $Pd(OH)_2$ on carbon (6 mg) in MeOH (1 mL) was stirred at room temperature under an atmospheric pressure of H_2 for 2 h. The insoluble material was removed by filtration, and the filtrate was concentrated to give **31**, which was used in the next reaction without further purification: $R_f = 0.42$ (MeOH/$CHCl_3$ = 1/10); $[\alpha]_D^{23}$ −51 (*c* 0.1, MeOH), IR (neat) 3350, 1740, and 1655 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 0.74 (d, 3H, $J = 7.1$ Hz), 0.83 (d, 3H, $J = 6.3$ Hz), 0.86 (t, 3H, $J = 6.6$ Hz), 0.89 (d, 3H, $J = 6.8$ Hz), 1.00 (d, 3H, $J = 6.3$ Hz), 1.12 (d, 3H, $J = 7.3$ Hz), 1.15–1.30 (m, 22H), 1.43 (m, 1H), 1.56 (m, 1H), 1.76 (m, 1H), 2.08 (ddq, 1H, $J = 6.3$, 6.8, and 11.0 Hz), 2.18 (m, 1H), 3.50 (m, 1H), 3.61 (m, 1H), 3.69 (m, 1H), 3.99 (dd, 1H, $J = 10.3$ and 11.0 Hz), 4.18 (ddq, 1H, $J = 2.2$, 4.4, and 6.3 Hz), 4.27 (dd, 1H, $J = 9.8$ and 2.2 Hz), 4.47 (m, 1H), 4.55 (m, 1H), 4.88 (m, 1H), 4.98 (d, 1H, $J = 4.4$ Hz), 5.25 (d, 1H, $J = 5.9$ Hz), 7.64 (d, 1H, $J = 8.3$ Hz), 7.87 (d, 1H, $J = 10.3$ Hz), 8.31 (d, 1H, $J = 9.8$ Hz); FAB-HRMS Calcd for $C_{32}H_{60}N_3O_8$ $(M + H)^+$: 614.4380 Found *m/z* 614.4408.

To a solution of the crude alcohol **31** in pyridine (0.9 mL) at 0 °C was added acetic anhydride (0.010 mL, 0.11 mmol), and the mixture was stirred at 0 °C for 2 h. To the reaction mixture was added MeOH at 0 °C, and the resulting mixture was concentrated to give a residue, which was purified by column chromatography (silica gel, 0.6 g, MeOH/$CHCl_3$ = 1/60 as eluent) to afford **1** (3.2 mg, 67% from **30**) as an amorphous solid: $[\alpha]_D^{21}$ −51 (*c* 0.25, $CHCl_3$), {natural stevastelin B, $[\alpha]_D^{17}$ −48 (*c* 0.1, $CHCl_3$) (measured in our laboratory)}; ^1H NMR (DMSO-d_6, 300 MHz) δ 0.73 (d, 3H, $J = 7.1$ Hz, 4-Me), 0.82 (d, 3H, $J = 6.1$ Hz, val-Me), 0.85 (t, 3H, $J = 6.3$ Hz, $-(CH_2)_{11}CH_3$), 0.88 (d, 3H, $J = 6.6$ Hz, val-Me), 1.00 (d, 3H, $J = 6.1$ Hz, thr-Me), 1.13 (d, 3H, $J = 7.6$ Hz, 2-Me), 1.23 (m, 22H, $-(CH_2)_{11}CH_3$), 1.43 and 1.53 (2m, each 1H, H-6 and H-6′), 1.72 (m, 1H, H-4), 1.98 (s, 3H, OAc), 2.10 (m, 1H, val-βH), 2.19 (m, 1H, H-2), 3.61 (m, 1H, H-3), 3.94 (dd, 1H, $J = 7.1$ and 10.7 Hz, ser-βH), 3.98 (dd, 1H, $J = 10.3$ and 11.0 Hz, val-αH), 4.18 (m, 1H, thr-βH), 4.27 (bd, 1H, $J = 9.1$ Hz, thr-αH), 4.40 (dd, 1H, $J = 6.6$ and 10.7 Hz, ser-β'H), 4.73 (ddd, 1H, $J = 6.6$, 7.1, and 8.1 Hz, ser-αH), 4.90 (d, 1H, $J = 4.4$ Hz, thr-OH), 4.92 (m, 1H, H-5), 5.52 (d, 1H, $J = 5.1$ Hz, 3-OH), 7.81 (d, 1H, $J = 8.1$ Hz, ser-NH), 7.93 (d, 1H, $J = 10.3$ Hz, val-NH), 8.32 (d, 1H, $J = 9.1$ Hz, thr-NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.5

(4-CH_3), 13.9 (18-C), 16.4 (2-CH_3), 19.0 (val-CH_3), 19.4 (val-CH_3), 20.5 (thr-CH_3), 20.6 (COCH_3), 22.1, 25.4, 28.69, 28.73, 28.9, 28.99, 29.04, 29.8 and 31.3 (7–17-C, val-βC), 31.7 (6-C), 40.0 (4-C), 46.3 (2-C), 49.9 (ser-αC), 57.7 (thr-αC), 61.2 (val-αC), 62.4 (ser-βC), 66.8 (thr-βC), 75.3 (3-C), 78.8 (5-C), 169.4, 170.1, 170.4, 171.3 and 174.9 (ser-CO, thr-CO, val-CO, 1-C, O*C*OCH$_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 3H, $J = 6.6$ Hz, –$(CH_2)_{11}CH_3$), 1.03 (d, 3H, $J = 6.3$ Hz, 4-Me), 1.05 (d, 6H, $J = 6.6$ Hz, val-Me$_2$), 1.14 (d, 3H, $J = 6.3$ Hz, thr-Me), 1.25 (m, 22H, –$(CH_2)_{11}CH_3$), 1.31 (d, 3H, $J = 7.4$ Hz, 2-Me), 1.40–1.78 (m, 2H, H-6 and H-6′), 1.84 (m, 1H, H-4), 2.06 (s, 3H, OAc), 2.13 (m, 1H, val-βH), 2.66 (m, 1H, H-2), 2.97 and 3.39 (2bs, each 1H, 2 × OH), 3.64 (m, 1H, H-3), 3.97 (dd, 1H, $J = 6.9$ and 6.9 Hz, val-αH), 4.21 (m, 1H, ser-αH), 4.44 (m, 1H, thr-βH) 4.48 (m, 1H, thr-αH), 4.49 (dd, 1H, $J = 5.5$ and 11.3 Hz, ser-βH), 4.65 (dd, 1H, $J = 7.2$ and 11.3 Hz, ser-β'H), 4.86 (m, 1H, H-5), 6.71 (bs, 1H, thr-NH), 7.20 (bs, 1H, val-NH), 7.51 (bs, 1H, ser-NH); FAB-HRMS Calcd for $C_{34}H_{62}N_3O_9$ $(M + H)^+$: 656.4486, Found m/z 656.4477. The ^{1}H and ^{13}C NMR data were fully identical with those of natural stevastelin B.[2]

(2*S*,3*S*,4*R*,5*R*)-2,4-Dimethyl-5-(phenylmethoxy)-1,3-octadecanediol (32). To a solution of the alcohol **23** (169 mg, 0.456 mmol) in THF (13 mL) at 0 °C under Ar were added potassium bis(trimethylsilyl)amide (KHMDS, 0.5 M solution in toluene, 2.73 mL, 1.37 mmol) and BzlBr (0.081 mL, 0.68 mmol), and the mixture was stirred at 0 °C for 10 min. To the reaction mixture was added a saturated aqueous NH_4Cl solution at 0 °C, and the products were extracted with EtOAc. The organic layer was washed successively with a saturated aqueous NH_4Cl solution, a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a crude benzyl ether (210 mg), which was used in the next reaction without further purification. A part of this compound was purified by column chromatography and used as an analytical sample: $[\alpha]_D^{27}$ +21 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.70 (d, 3H, $J = 6.6$ Hz), 0.88 (t, 3H, $J = 6.8$ Hz), 1.00 (d, 3H, $J = 6.8$ Hz), 1.15–1.73 (m, 24H), 1.35 and 1.42 (2s, each 3H), 1.88 (m, 2H), 3.33 (m, 1H), 3.51 (dd, 1H, $J = 11.5$ and 11.2 Hz), 3.61 (dd, 1H, $J = 10.3$ and 1.5 Hz), 3.70 (dd, 1H, $J = 11.5$ and 4.9 Hz), 4.50 (s, 2H), 7.22–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.7, 12.3, 14.1, 18.9, 22.7, 24.7, 29.4, 29.6, 29.6, 29.7, 29.7, 29.9, 30.6, 30.7, 31.9, 36.6, 66.4, 72.1, 74.1, 81.9, 97.8, 127.3, 127.8, 128.3, 139.8; FAB-HRMS Calcd for $C_{30}H_{53}O_3$ $(M + H)^+$: 461.3995, Found m/z 461.3976. Found: C, 78.09; H, 11.29%. Calcd for $C_{30}H_{52}O_3$: C, 78.21; H, 11.38%.

A solution of the crude benzyl ether (210 mg, 0.456 mmol) in acetic acid (25.2 mL) and H_2O (6.3 mL) was stirred at room temperature for 14 h. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 5 g, EtOAc/hexane = 1/2 as eluent) to afford **32** (188 mg, 98% from **23**) as a colorless syrup; $[\alpha]_D^{27}$ −44 (*c* 1.1, $CHCl_3$); IR (neat) 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.74 (d, 3H, $J = 6.8$ Hz), 0.88 (t, 3H, $J = 6.6$ Hz), 0.95 (d, 3H, $J = 7.1$ Hz), 1.15–1.35 (m, 22H), 1.42–1.95 (m, 4H), 3.50–3.75 (m, 5H), 4.11 (bs, 1H), 4.42 (d, 1H, $J = 11.2$ Hz), 4.68 (d, 1H, $J = 11.2$ Hz), 7.25–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 5.1, 13.6, 14.1, 22.7, 25.7, 29.4, 29.5, 29.6, 29.6, 29.7, 29.8, 30.3, 31.9, 36.2, 37.5, 69.0, 70.9, 82.9, 85.5, 127.8, 127.9, 128.6, 139.8; FAB-HRMS Calcd for $C_{27}H_{49}O_3$ $(M + H)^+$: 421.3682, Found m/z 421.3690. Found: C, 76.85; H, 11.15%. Calcd for $C_{27}H_{48}O_3$: C, 77.09; H, 11.50%.

(2*S*,3*S*,4*R*,5*R*)-2,4-Dimethyl-5-(phenylmethoxy)-1-[(triethylsilyl)oxy]-3-octadecanol (33). To a solution of the alcohol **32** (188 mg, 0.448 mmol) in CH_2Cl_2 (5.7 mL) at 0 °C were added chlorotriethylsilane (TESCl, 0.180 mL, 1.07 mmol) and Et_3N (0.378 mL, 2.69 mmol), and the mixture was stirred at room temperature for 1 h. To the reaction mixture was added H_2O at 0 °C, and the products were extracted with $CHCl_3$. The organic layer was washed with brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 7 g, EtOAc/hexane = 1/19 as eluent) to afford **33** (236 mg, 98%) as a colorless syrup; $[\alpha]_D^{21}$ −10 (*c* 0.5, $CHCl_3$); IR (neat) 3500 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.62 (q, 6H, $J = 7.9$ Hz), 0.79 (d, 3H, $J = 6.8$ Hz), 0.88 (t, 3H, $J = 6.6$ Hz), 0.98 (t, 9H, $J = 7.9$ Hz), 0.99 (d, 3H, $J = 6.8$ Hz), 1.17–1.40 (m, 22H), 1.66 (m, 2H), 1.72–1.86 (m, 2H), 3.51 (m, 1H), 3.58 (m, 1H), 3.68 (m, 2H), 4.03 (d, 1H, $J < 1$ Hz), 4.45 and 4.61 (2d, each 1H, $J = 11.2$ Hz), 7.25–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 4.2, 6.7, 7.6, 13.2, 14.1, 22.7, 25.1, 29.4, 29.6, 29.7, 30.0, 30.5, 31.9, 37.6, 37.9, 67.8, 71.7, 77.4, 83.4, 127.5, 127.8, 128.4, 138.7; FAB-HRMS Calcd for $C_{33}H_{63}O_3Si$ $(M + H)^+$: 535.4547, Found m/z 535.4545. Found: C, 73.97; H, 11.43%. Calcd for $C_{33}H_{62}O_3Si$: C, 74.09; H, 11.68%.

An Inseparable Mixture of (3*S*,6*S*,7*S*)-10,10-Diethyl-7-methyl-6-[(1*S*,2*R*)-1-methyl-2-(phenylmethoxy)pentadecyl]-4-oxo-3-[(phenylmethoxy)methyl]-5,9-dioxa-2-aza-10-siladodecanoic Acid Phenylmethyl Ester (34) and Its (3*R*)-Isomer. To a solution of the alcohol **33** (73 mg, 0.14 mmol), Cbz–Ser(Bzl) (179 mg, 0.54 mmol) and DMAP (50 mg, 0.41 mmol) in THF (7.3 mL) under Ar at 0 °C were added 2,4,6-trichlorobenzoyl chloride (0.11 mL, 0.68 mmol) and Et_3N (0.096 mL, 0.68 mmol). After being stirred at 0 °C for 1.5 h, to the reaction mixture was added a saturated aqueous NH_4Cl solution at 0 °C. The products were extracted with EtOAc and the organic layer was washed successively with a saturated aqueous NH_4Cl solution, a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 10 g, EtOAc/hexane = 1/30 as eluent) to afford a mixture (ca. 1:1) of **34** and its (3*R*)-isomer (89 mg, 77%) as a colorless syrup; IR (neat) 3500–3250, 1730, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.56 (q, 3H, $J = 7.8$ Hz), 0.56 (q, 3H, $J = 8.1$ Hz), 0.90 (m, 18H), 1.20–1.35 (m, 22H), 1.61 (m, 2H), 2.01 (m, 2H), 3.22–3.38 (m, 2H), 3.60 (d, 0.5H, $J = 4.6$ and 9.8 Hz), 3.61 (dd, 0.5H, $J = 5.4$ and 9.8 Hz), 3.70 and 3.72 (2dd, each 0.5H, $J = 3.2$ and 9.5 Hz), 3.91 (dd, 1H, $J = 2.7$ and 9.5 Hz), 4.29 and 4.36 (2d, each 1H, $J = 11.5$ Hz), 4.44 (d, 1H, $J = 11.2$ Hz), 4.51 (m, 2H), 5.10 (m, 3H), 5.62 and 5.64 (2d, each 0.5H, $J = 8.1$ Hz), 7.20–7.40 (m, 15H); FAB-HRMS Calcd for $C_{51}H_{80}NO_7Si$ $(M + H)^+$: 846.5704, Found m/z 846.5721. Found: C, 72.12; H, 9.24; N, 1.50%. Calcd for $C_{51}H_{79}NO_7Si$: C, 72.38; H, 9.41; N, 1.66%.

An Inseparable Mixture of *N*-[(1,1-Dimethylethoxy)carbonyl]-L-valyl-L-threonyl-*O*-(phenylmethyl)-L-serine (1*S*,2*S*,3*R*)-2-Methyl-1-[(1*S*)-1-methyl-2-[(triethylsilyl)oxy]ethyl]-3-(phenylmethoxy)hexadecyl Ester (35) and Its D-Serine Isomer. A mixture of **34** and its D-serine isomer (25 mg, 0.029 mmol) in MeOH (2.5 mL) was stirred in the presence of 10% Pd on a carbon ethylenediamine complex (21 mg) under an atmospheric pressure of H_2 at room temperature for 1 h. The insoluble material was removed by filtration, and the filtrate was concentrated to give a crude amine, which was dissolved in DMF (3.4 mL). To this solution at 0 °C were added the dipeptide **25** (14 mg, 0.044 mmol), WSC·HCl (13 mg, 0.070 mmol), and HOBt (9.5 mg, 0.070 mmol), and the whole mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with EtOAc and washed successively with a saturated aqueous NH_4Cl solution, a saturated aque-

ous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 1 g, acetone/toluene = 1/20 as eluent) to afford a mixture (ca. 1:1) of **35** and its epimer (27.8 mg, 94%) as a colorless syrup; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.55 (q, 3H, J = 7.8 Hz), 0.56 (q, 3H, J = 7.8 Hz), 0.88–1.00 (m, 24H), 1.16 (d, 1.5H, J = 6.3 Hz), 1.17 (d, 1.5H, J = 6.2 Hz), 1.20–1.35 (m, 22H), 1.44 (s, 9H), 1.57 (m, 2H), 1.88–2.25 (m, 3H), 3.22–3.35 (m, 2H), 3.43 (bs, 1H), 3.59 (dd, 1H, J = 9.8 and 4.6 Hz), 3.67 (dd, 0.5H, J = 9.8 and 3.7 Hz), 3.71 (dd, 0.5H, J = 9.8 and 3.7 Hz), 3.88 (dd, 1H, J = 9.8 and 3.7 Hz), 3.96 (m, 1H), 4.25–4.58 (m, 6H), 4.66 (m, 1H), 4.98–5.10 (m, 2H), 6.86 (bd, 0.5H, J = 7.3 Hz), 6.90 (bd, 0.5H, J = 7.3 Hz), 7.15–7.40 (m, 11H); MS (FAB) m/z 1013 (M + H).

***N*-[(1,1-Dimethylethoxy)carbonyl]-L-valyl-L-threonyl-*O*-(phenylmethyl)-L-serine (1*S*,2*S*,3*R*)-1-[(1*S*)-2-Hydroxy-1-methylethyl]-2-methyl-3-(phenylmethoxy)hexadecyl Ester (36) and Its D-Serine Isomer (37).** To a solution of a mixture (ca. 1:1) of the *O*-TES ether **35** and its D-serine isomer (24 mg, 0.065 mmol) in THF (1.0 mL) at 0 °C were added acetic acid (1.0 mL) and H_2O (0.34 mL), and the mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with H_2O, and to this solution was added solid $NaHCO_3$ (1.8 g) at 0 °C. The products were extracted with EtOAc, and the organic layer was washed with a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 2 g, acetone/toluene = 1/8 as eluent) to first afford **37** (9.0 mg, 43%) as a colorless syrup; $[\alpha]_D^{23}$ −29 (*c* 1.6, $CHCl_3$); IR (neat) 3300, 1730, 1715, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 3H, J = 6.8 Hz), 0.91 (d, 3H, J = 6.6 Hz), 0.91 (d, 3H, J = 6.6 Hz), 0.96 (d, 3H, J = 6.8 Hz), 0.96 (d, 3H, J = 6.8 Hz), 1.16 (d, 3H, J = 6.3 Hz), 1.19–1.35 (m, 22H), 1.44 (s, 9H), 1.38–1.67 (m, 2H), 1.84 (m, 1H), 2.02 (m, 1H), 2.18 (m, 1H), 2.46 (bs, 1H), 3.26 (m, 1H), 3.32–3.55 (m, 2H), 3.61 (bs, 1H), 3.67 (dd, 1H, J = 3.7 and 9.5 Hz), 3.93 (dd, 1H, J = 3.7 and 9.5 Hz), 3.98 (m, 1H), 4.37 (m, 2H), 4.37 (d, 1H, J = 11.0 Hz), 4.48 (d, 1H, J = 12.0 Hz), 4.50 (d, 1H, J = 11.0 Hz), 4.53 (d, 1H, J = 12.0 Hz), 4.68 (ddd, 1H, J = 3.7, 3.7, and 7.8 Hz), 5.02 (m, 1H), 5.07 (d, 1H, J = 8.1 Hz), 7.03 (d, 1H, J = 7.3 Hz), 7.18–7.40 (m, 10H), 7.42 (d, 1H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.2, 14.1, 14.3, 17.6, 18.6, 19.3, 22.6, 25.0, 28.2, 29.3, 29.6, 29.7, 29.8, 30.4, 31.9, 36.9, 37.1, 53.3, 57.7, 60.2, 63.6, 66.7, 69.1, 71.7, 73.5, 78.5, 80.3, 80.8, 127.5, 127.6, 127.7, 127.9, 128.3, 128.4, 137.0, 138.6, 156.1, 170.4, 170.9, 172.5; FAB-HRMS Calcd for $C_{51}H_{84}N_3O_{10}$ (M + H)$^+$: 898.6157, Found m/z 898.6181. Found: C, 68.18; H, 9.43; N, 4.53%. Calcd for $C_{51}H_{83}N_3O_{10}$: C, 68.20; H, 9.31; N, 4.68%.

Further elution gave **36** (9.4 mg, 45%) as a colorless syrup; $[\alpha]_D^{23}$ −27 (*c* 0.7, $CHCl_3$); IR (neat) 3300, 1740, 1715, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 3H, J = 6.6 Hz), 0.89 (d, 3H, J = 6.6 Hz), 0.93 (d, 3H, J = 6.6 Hz), 0.93 (d, 3H, J = 6.6 Hz), 1.00 (d, 3H, J = 6.3 Hz), 1.17 (d, 3H, J = 6.3 Hz), 1.15–1.35 (m, 22H), 1.35–1.63 (m, 2H), 1.43 (s, 9H), 1.90 (m, 1H), 2.03 (m, 1H), 2.14 (m, 1H), 2.44 (bs, 1H), 3.21 (m, 1H), 3.35–3.57 (m, 3H), 3.66 (dd, 1H, J = 3.2 and 9.5 Hz), 3.86 (dd, 1H, J = 3.7 and 9.5 Hz), 3.97 (m, 1H), 4.32 (d, 1H, J = 11.5 Hz), 4.34 (m, 1H), 4.44 (m, 1H), 4.45 (d, 1H, J = 11.5 Hz), 4.48 (bs, 2H), 4.68 (ddd, 1H, J = 3.2, 3.8, and 8.3 Hz), 4.96–5.13 (m, 2H), 6.97 (d, 1H, J = 7.6 Hz), 7.20–7.42 (m, 10H), 7.37 (d, 1H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.1, 14.1, 14.2, 17.6, 18.2, 19.3, 22.7, 24.5, 28.3, 29.4, 29.6, 29.7, 29.9, 30.1, 30.6, 31.9, 37.1, 53.1, 56.9, 60.2, 63.9, 66.6, 69.3, 71.7, 73.4, 77.9, 80.2, 81.0, 127.5, 127.7, 127.7, 127.9, 128.3, 128.5, 137.1, 138.7, 155.9, 170.4, 170.8, 172.4; FAB-HRMS Calcd for $C_{51}H_{84}N_3O_{10}$ (M + H)$^+$: 898.6157, Found m/z 898.6154. Found: C, 68.21; H, 9.38; N, 4.47%. Calcd for $C_{51}H_{83}N_3O_{10}$: C, 68.20; H, 9.31; N, 4.68%.

Cyclo[(2*R*,3*R*,4*S*,5*R*)-3-hydroxy-2,4-dimethyl-5-(phenylmethoxy)octadecanoyl-L-valyl-L-threonyl-*O*-(phenylmethyl)-L-seryl] (39). To a solution of the diol **36** (9.3 mg, 0.010 mmol) in CH_2Cl_2 (1.7 mL) at 0 °C were added TEMPO (1.24 g L^{-1} solution in CH_2Cl_2; 0.013 mL), KBr (5.96 g L^{-1} solution in H_2O; 0.021 mL), NaOCl (0.35 M solution in H_2O; 0.036 mL), and $NaHCO_3$ (50 g L^{-1} solution in H_2O; 0.036 mL). After being stirred at 0 °C for 1.5 h, to the reaction mixture was added a 20% aqueous $Na_2S_2O_3$ solution. The products were extracted with $CHCl_3$, and the organic layer was washed with a 20% aqueous $Na_2S_2O_3$ solution, and then dried. Removal of the solvent gave a crude aldehyde (9.3 mg), which was dissolved in *t*-BuOH (1.49 mL) and H_2O (0.37 mL). To this solution were added $NaH_2PO_4 \cdot 2H_2O$ (6.5 mg, 0.041 mmol), $HOSO_2NH_2$ (5.0 mg, 0.052 mmol), and $NaClO_2$ (5.6 mg, 0.062 mmol), and the mixture was stirred at 0 °C for 20 min. To the reaction mixture at 0 °C was added a 1 M aqueous citric acid solution, and the products were extracted with $CHCl_3$. The organic layer was washed with a 1 M aqueous citric acid solution and then dried. Removal of the solvent gave the crude carboxylic acid **38**, which was dissolved in CH_2Cl_2 (1.4 mL). To this solution under Ar at −18 °C was added TFA (0.28 mL), and the mixture was stirred at −18 °C for 1 h. The reaction mixture was concentrated and dried in vacuo to give the crude amino carboxylic acid **6**·TFA, which was dissolved in DMF (5.2 mL). To this solution under Ar at 0 °C were added DEPC (0.0039 mL, 0.026 mmol) and Et_3N (0.0039 mL, 0.028 mmol), and the mixture was stirred at 0 °C for 30 min, and then at room temperature for 14 h. The reaction mixture was diluted with EtOAc and washed successively with a 1 M aqueous HCl solution, a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 1 g, acetone/toluene = 1/12 as eluent) to afford **39** (2.4 mg, 29% from **36**) as a colorless syrup; $[\alpha]_D^{25}$ −39 (*c* 0.2, $CHCl_3$); IR (neat) 3450, 1740, 1670 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.59 (d, 3H, J = 6.8 Hz, 4-Me), 0.85 (t, 3H, J = 6.3 Hz, –$(CH_2)_{11}$-CH_3), 0.86 (d, 3H, J = 5.9 Hz, val-Me), 0.92 (d, 3H, J = 6.6 Hz, val-Me), 0.98 (d, 3H, J = 7.3 Hz, 2-Me), 1.07 (d, 3H, J = 6.1 Hz, thr-Me), 1.10–1.58 (m, 23H, –$(CH_2)_{11}CH_3$ and H-6), 1.67 (m, 1H, H-6′), 1.87–2.12 (m, 2H, H-4 and val-βH), 2.59 (m, 1H, H-2), 3.60 (dd, 1H, J = 2.2 and 9.8 Hz, ser-βH), 3.71 (m, 1H, H-5), 3.86 (dd, 1H, J = 3.4 and 9.8 Hz, ser-β'H), 3.91–4.09 (m, 2H, val-αH and thr-βH), 4.39 and 4.57 (2d, each 1H, J = 11.7 Hz, OCH_2Ph), 4.43–4.65 (m, 2H, OCH_2Ph), 4.80 (m, 1H, ser-αH), 4.96 (m, 1H, H-3), 5.21 (d, 1H, J = 4.6 Hz, thr-OH), 7.17–7.42 (m, 10H, Ph), 7.49 (d, 1H, J = 10.0 Hz, val-NH), 7.81 (m, 2H, thr-NH and ser-NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 9.7, 13.7, 14.0, 19.0, 19.2, 21.0, 22.1, 25.0, 28.7, 29.0, 29.2, 30.4, 31.3, 37.1, 41.5, 51.7, 59.4, 61.7, 65.3, 70.3, 72.6, 77.9, 78.9, 127.4, 127.5, 127.5, 127.7, 128.2, 138.1, 139.0, 169.5, 170.5, 170.9; FAB-HRMS Calcd for $C_{46}H_{72}N_3O_8$ (M + H)$^+$: 794.5320, Found m/z 794.5298.

Macrocycle Possessing a Proposed Structure of Stevastelin C3 (3). A mixture of the macrocycle **39** (2.5 mg, 0.0031 mmol) and 10% Pd on carbon (4 mg) in MeOH (1 mL) was stirred at room temperature under an atmospheric pressure of H_2 for 3 h. The insoluble material was removed by filtration, and the filtrate was concentrated to give a residue, which was purified by column chromatography (silica gel, 0.3 g, MeOH/$CHCl_3$ = 1/30 as elu-

ent) to afford **3** (1.4 mg, 74%) as an amorphous solid; $[\alpha]_D^{25}$ −55 (*c* 0.34, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.52 (d, 3H, J = 6.9 Hz, 4-Me), 0.86 (t, 3H, J = 6.9 Hz, –$(CH_2)_{12}CH_3$), 0.88 (d, 3H, J = 6.0 Hz, val-Me), 0.93 (d, 3H, J = 6.6 Hz, val-Me), 1.07 (d, 3H, J = 6.3 Hz, thr-Me), 1.09 (d, 3H, J = 7.2 Hz, 2-Me), 1.14–1.41 (m, 24H, –$(CH_2)_{12}CH_3$), 1.66 (m, 1H, H-4), 2.04 (m, 1H, val-βH), 2.86 (m, 1H, H-2), 3.54 (m, 1H, ser-βH), 3.85 (m, 1H, H-5), 3.92 (m, 1H, ser-βH), 4.03 (m, 2H, val-αH and thr-βH), 4.13 (dd, 1H, J = 9.9 and 2.4 Hz, thr-αH), 4.31 (d, 1H, J = 5.7 Hz, 5-OH), 4.60 (m, 1H, ser-αH), 4.91 (m, 1H, H-3), 5.03 (dd, 1H, J = 4.8 and 5.1 Hz, ser-OH), 5.14 (d, 1H, J = 4.8 Hz, thr-OH), 7.54 (d, 1H, J = 9.9 Hz, val-NH), 7.84 (d, 1H, J = 9.9 Hz, ser-NH), 7.88 (d, 1H, J = 9.0 Hz, thr-NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 9.3, 13.7 and 14.0 (2-CH_3, 4-CH_3, 18-C), 19.0, 19.3 and 21.0 [val-$(CH_3)_2$, thr-CH_3], 22.1, 25.8, 28.7, 28.9, 29.0, 29.1, 29.1, 29.2, 31.3 and 35.0 (6–17-C, val-βC), 39.3 (4-C), 41.3 (2-C), 53.7 (ser-αC), 59.5 (val-αC), 60.9 (ser-βC), 61.7 (thr-αC), 65.3 (thr-βC), 69.0 (5-C), 79.4 (3-C), 169.9, 170.4, 170.7 and 170.9 (ser-CO, thr-CO-, val-CO, 1-C); FAB-HRMS Calcd for $C_{32}H_{60}N_3O_8$ $(M+H)^+$: 614.4380, Found m/z 614.4407.

Chiral HPLC Analysis of Amino Acids in Compound 3. Compound **3** (0.5 mg) in aqueous HCl (6 M; 1 mL) was heated to 110 °C for 21 h in a sealed tube. Removal of the solvent left a residue, which was dissolved in an aqueous $CuSO_4$ (0.5 mM) solution. The resulting solution was subjected to HPLC analysis using a chiral column (MCI GEL CRS 10W, 4.6 × 50 mm, Mitsubishi Chemical Industries Limited) at room temperature, and the amino acids were detected by UV (254 nm). HPLC was carried out with an aqueous $CuSO_4$ (0.5 mM) solution as the mobile phase at a flow rate of 1.0 mL min^{-1} (condition A) or with an aqueous $CuSO_4$ (0.1 mM) solution at a flow rate of 0.5 mL min^{-1} (condition B). Under condition A, the retention time of L-valine was 8.1 min (D-valine 5.0 min). Under condition B, retention times of L-serine and L-threonine were 8.2 and 8.9 min, respectively (D-serine 7.0 min; D-threonine 7.3 min; D-allothreonine 11.2 min; and L-allothreonine 14.5 min). These analyses revealed that the amino acids in compound **3** were L-serine, L-valine, and L-threonine.

By similar experiments, the structures of the amino acids in natural stevastelins C3, B3, compounds **37**, **46**, and **47** were assigned. For compounds **37**, **46**, and **47**, de-*O*-benzyl products prepared by hydrogenolysis (H_2, 10% Pd/C in MeOH) were subjected to the analyses.

Stevastelin B3 (2). To a solution of the alcohol **3** (3.0 mg, 0.0050 mmol) in pyridine (0.6 mL) at 0 °C was added acetic anhydride (0.22 M solution in pyridine; 0.023 mL). After being stirred at room temperature for 5 h, to the reaction mixture was added MeOH at 0 °C. The resulting mixture was diluted with EtOAc and washed successively with a 1 M aqueous HCl solution, a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 0.9 g, MeOH/$CHCl_3$ = 1/100 as eluent) to afford **2** (1.2 mg, 38%) as an amorphous solid; $[\alpha]_D^{26}$ −53 (*c* 0.1, $CHCl_3$), {natural stevastelin B3, $[\alpha]_D^{25.5}$ −51 (*c* 0.255, $CHCl_3$) (measured in our laboratory)}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.54 (d, 3H, J = 6.8 Hz, 4-Me), 0.85 (t, 3H, J = 6.6 Hz, –$(CH_2)_{12}CH_3$), 0.90 (d, 3H, J = 6.8 Hz, val-Me), 0.93 (d, 3H, J = 6.6 Hz, val-Me), 1.08 (d, 3H, J = 6.1 Hz, thr-Me), 1.12 (d, 3H, J = 6.8 Hz, 2-Me), 1.17–1.35 (m, 24H, –$(CH_2)_{12}CH_3$), 1.72 (m, 1H, H-4), 2.01 (s, 3H, OAc), 2.05 (m, 1H, val-βH), 2.90 (m, 1H, H-2), 3.84 (m, 1H, H-5), 4.01 (m, 2H, val-αH and thr-βH), 4.13 (m, 1H, thr-αH), 4.18 (m, 1H, ser-βH), 4.35 (m, 1H, ser-βH), 4.40 (d, 1H, J = 5.4 Hz, 3-OH), 4.92 (m, 2H, 3-H and ser-αH), 5.24 (d, 1H, J = 4.4 Hz, thr-OH), 7.50 (m, 1H, ser-NH), 7.67 (d, 1H, J = 10.2 Hz, val-NH), 7.72 (d, 1H, J = 9.0 Hz, thr-NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 9.2 (4-CH_3), 13.8 (2-CH_3), 13.9 (18-C), 19.0 (val-CH_3), 19.2 (val-CH_3), 20.7 ($CO\mathit{C}H_3$), 20.9 (thr-CH_3), 22.1, 25.7, 28.7, 29.0, 29.1, 29.1, 31.3 and 34.9 (6–17-C, val-βC), 39.1 (4-C), 41.1 (2-C), 50.2 (ser-αC), 59.4 (thr-αC), 61.6 (val-αC), 63.2 (ser-βC), 65.2 (thr-βC), 69.0 (5-C), 80.2 (3-C), 168.7, 170.1, 170.5, 170.7 and 170.8 (ser-CO, thr-CO, val-CO, 1-C, $O\mathit{C}OCH_3$); FAB-HRMS Calcd for $C_{34}H_{62}N_3O_9$ $(M+H)^+$: 656.4486, Found m/z 656.4494, {natural stevastelin B3, Calcd for $C_{34}H_{62}N_3O_9$ $(M+H)^+$: 656.4486, Found m/z 656.4490 (measured in our laboratory)}. The ^{1}H and ^{13}C NMR data were fully identical with those of natural stevastelin B3.

(4*R*,5*S*)-2,2,5-Trimethyl-4-[(1*S*)-1-methylpentadecyl]-1,3-dioxane (41). At 0 °C, a THF (4 mL) solution of the alcohol **23** (123 mg, 0.332 mmol) was added dropwise to a suspension of NaH (127 mg, 3.32 mmol, washed with hexane) in THF (1 mL), and the mixture was stirred at room temperature for 3 h. To this suspension were added CS_2 (1.2 mL, 19.9 mmol) and MeI (0.414 mL, 6.65 mmol) at 0 °C. After being stirred at room temperature for 22 h, to the reaction mixture was added H_2O at 0 °C. The products were extracted with Et_2O, the organic layer was washed with H_2O, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 3 g, EtOAc/hexane = 1/30 as eluent) to afford the dithiocarbonate ester **40** (153 mg, 100%) as a yellow syrup; $[\alpha]_D^{21}$ +22 (*c* 0.6, $CHCl_3$); IR (neat) 1225, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.70 (d, 3H, J = 6.6 Hz), 0.88 (t, 3H, J = 6.9 Hz), 0.98 (d, 3H, J = 7.2 Hz), 1.16–1.38 (m, 22H), 1.34 and 1.41 (2s, each 3H), 1.71 (m, 2H), 1.83 (dddq, 1H, J = 11.1, 5.4, 10.2, and 6.6 Hz), 2.08 (m, 1H), 2.54 (s, 3H), 3.51 (dd, 1H, J = 11.1 and 11.4 Hz), 3.62 (dd, 1H, J = 10.2 and 1.5 Hz), 3.69 (dd, 1H, J = 5.4 and 11.4 Hz), 5.80 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.6, 12.3, 14.1, 18.5, 18.7, 22.7, 25.1, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 29.7, 30.6, 31.1, 31.9, 36.8, 66.1, 75.3, 87.4, 98.0, 215.6; FAB-HRMS Calcd for $C_{25}H_{49}O_3S_2$ $(M+H)^+$: 461.3123, Found m/z 461.3118. Found: C, 65.37; H, 10.31%. Calcd for $C_{25}H_{48}O_3S_2$: C, 65.17; H, 10.50%.

To a solution of the dithiocarbonate ester **40** (153 mg, 0.332 mmol) in toluene (6 mL) under Ar at 130 °C were added a solution of AIBN (818 mg, 4.99 mmol) and *n*-Bu_3SnH (1.34 mL, 4.49 mmol) in toluene (17 mL) via a cannula. After being stirred at 130 °C for 7 h, the reaction mixture was concentrated to give a residue, which was purified by column chromatography (silica gel, 7 g, EtOAc/hexane = 1/40 as eluent) to afford **41** (110 mg, 93% from **23**) as a yellow syrup; $[\alpha]_D^{21}$ +22 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.70 (d, 3H, J = 6.8 Hz), 0.85 (d, 3H, J = 6.6 Hz), 0.88 (t, 3H, J = 6.3 Hz), 1.22–1.32 (m, 26H), 1.35 and 1.40 (2s, each 3H), 1.60 (m, 1H), 1.83 (dddq, 1H, J = 11.2, 4.9, 10.3, and 6.8 Hz), 3.42 (dd, 1H, J = 10.3 and 2.0 Hz), 3.48 (dd, 1H, J = 11.2 and 11.5 Hz), 3.69 (dd, 1H, J = 11.5 and 4.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.3, 12.7, 14.1, 19.0, 22.7, 26.5, 27.4, 29.4, 29.6, 29.7, 29.8, 30.8, 31.9, 33.2, 33.6, 66.4, 76.7, 97.9; FAB-HRMS Calcd for $C_{23}H_{47}O_2$ $(M+H)^+$: 355.3576, Found m/z 355.3596. Found: C, 77.92; H, 12.99%. Calcd for $C_{23}H_{46}O_2$: C, 77.90; H, 13.07%.

(2*S*,3*R*,4*S*)-2,4-Dimethyl-1,3-octadacanediol (42). To a solution of the acetonide **41** (110 mg, 0.309 mmol) in MeOH (11.0 mL) at 0 °C was added CSA (72 mg, 0.309 mmol), and the mixture was stirred at room temperature for 23 h. The reaction mixture was quenched by the addition of a saturated aqueous $NaHCO_3$ solution at 0 °C, and the products were extracted with EtOAc. The organic

layer was washed with a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 3 g, EtOAc/hexane = 1/12 as eluent) to afford the 5-deoxy diol **42** (77 mg, 79%) as a white solid; mp 43.0–44.8 °C, $[\alpha]_D^{21}$ +10 (*c* 1.74, $CHCl_3$); IR (neat) 3320 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79 (d, 3H, J = 7.1 Hz, 2-Me), 0.86 (d, 3H, J = 7.1 Hz, 4-Me), 0.87 (t, 3H, J = 7.0 Hz, $-(CH_2)_{12}CH_3$), 1.15–1.42 (m, 24H, $-(CH_2)_{12}$-CH_3), 1.60 (m, 3H, H-4, H-5, and H-5′), 1.85 (dddq, 1H, J = 9.0, 7.8, 3.4, and 7.1 Hz, H-2), 2.12–3.18 (m, 2H, 2 × OH), 3.46 (dd, 1H, J = 9.0 and 2.4 Hz, H-3), 3.63 (dd, 1H, J = 10.7 and 7.8 Hz, H-1), 3.71 (dd, 1H, J = 10.7 and 3.4 Hz, H-1′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.2, 13.5, 14.1, 22.7, 27.4, 29.4, 29.7, 29.9, 31.9, 34.0, 35.1, 37.3, 68.8, 80.3; FAB-HRMS Calcd for $C_{20}H_{43}O_2$ $(M + H)^+$: 315.3263, Found m/z 315.3283. Found: C, 76.14; H, 13.13%. Calcd for $C_{20}H_{42}O_2$: C, 76.37; H, 13.46%.

Compound 42 from Natural Stevastelin C3. To a solution of natural stevastelin C3 (3.2 mg, 0.0054 mmol) in THF (1 mL) at 0 °C was added $LiBH_4$ (1 mg, 0.046 mmol), and the mixture was stirred at 80 °C for 1 h. The reaction mixture was quenched by the addition of H_2O at 0 °C, and then diluted with EtOAc. The organic layer was washed with H_2O, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 0.3 g, EtOAc/hexane = 1/12 as eluent) to afford **42** (0.4 mg, 24%) as a white solid. ^1H NMR spectra were fully identical with those of **42** prepared from **23**.

(2*S*,3*R*,4*S*)-1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2,4-dimethyl-3-octadacanol (43). To a solution of the diol **42** (87 mg, 0.276 mmol) in CH_2Cl_2 (4.3 mL) at 0 °C were added Et_3N (0.155 mL, 1.10 mmol) and TBSCl (166 mg, 1.10 mmol), and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc and washed successively with a saturated aqueous NH_4Cl solution, a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 3 g, EtOAc/hexane = 1/50 as eluent) to afford the *O*-TBS ether **43** (115 mg, 97%) as a colorless syrup; $[\alpha]_D^{24}$ +16 (*c* 1.7, $CHCl_3$); IR (neat) 3510 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.08 (s, 6H), 0.77 (d, 3H, J = 7.2 Hz), 0.87 (d, 3H, J = 6.6 Hz), 0.88 (t, 3H, J = 6.6 Hz), 0.90 (s, 9H), 1.10–1.46 (m, 26H), 1.52 (m, 1H), 1.80 (dddq, 1H, J = 8.7, 8.4, 3.9, and 7.2 Hz), 3.42 (ddd, 1H, J = 8.7, 2.7, and 2.7 Hz), 3.59 (dd, 1H, J = 9.9 and 8.4 Hz), 3.76 (dd, 1H, J = 9.9 and 3.7 Hz), 3.76 (d, 1H, J = 2.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.6, −5.6, 12.4, 13.3, 14.1, 18.1, 22.7, 25.8, 27.6, 29.4, 29.7, 30.0, 31.9, 34.1, 35.3, 37.3, 69.5, 79.6; FAB-HRMS Calcd for $C_{26}H_{57}O_2Si$ $(M + H)^+$: 429.4128, Found m/z 429.4132. Found: C, 72.94; H, 12.97%. Calcd for $C_{26}H_{56}O_2Si$: C, 72.82; H, 13.16%.

An Inseparable Mixture of (3*S*,6*R*,7*S*)-7,10,10,11,11-Pentamethyl-6-[(1*S*)-1-methylpentadecyl]-4-oxo-3-[(phenylmethoxy)methyl]-5,9-dioxa-2-aza-10-siladodecanoic Acid Phenylmethyl Ester (44) and Its (3*R*)-Isomer. To a solution of the *O*-TBS ether **43** (34.6 mg, 0.0807 mmol), Cbz–Ser(Bzl) (53.1 mg, 0161 mmol), and DMAP (19.7 mg, 0.161 mmol) in THF (3.46 mL) under Ar at 0 °C were added 2,4,6-trichlorobenzoyl chloride (0.038 mL, 0.242 mmol) and Et_3N (0.057 mL, 0.403 mmol), and the mixture was stirred at 0 °C for 1.5 h. To the reaction mixture was added a saturated aqueous NH_4Cl solution at 0 °C, and the products were extracted with EtOAc. The organic layer was washed successively with a saturated aqueous NH_4Cl solution, a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 7 g, EtOAc/hexane = 1/40 as eluent) to afford a mixture (ca. 1.5:1) of **44** and its (3*R*)-isomer (53.4 mg, 89%) as a colorless syrup; IR (neat) 3440, 3340, 1730, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz for the major isomer **44**) δ 0.01 (s, 6H), 0.78–0.97 (m, 18H), 1.10–1.35 (m, 24H), 1.75 (m, 1H), 1.93 (m, 1H), 3.33 (m, 1H), 3.57 (m, 1H), 3.71 (m, 1H), 3.92 (m, 1H), 4.42–4.60 (m, 3H), 4.91 (m, 1H), 5.12 (s, 2H), 5.66 (d, 1H, J = 8.8 Hz), 7.22–7.43 (m, 10H); FAB-HRMS Calcd for $C_{40}H_{74}NO_6Si$ $(M + H)^+$: 740.5285, Found m/z 740.5285.

An Inseparable Mixture of *N*-[(1,1-Dimethylethoxy)carbonyl]-L-valyl-L-threonyl-*O*-(phenylmethyl)-L-serine (1*R*,2*S*)-1-[(1*S*)-2-[(1,1-Dimethylethyl)dimethylsilyl]oxy-1-methylethyl]-2-methylhexadecyl Ester (45) and Its D-Serine Isomer. A mixture (ca. 1.5:1) of **44** and its D-serine isomer (53 mg, 0.072 mmol) in MeOH (5.3 mL) was stirred in the presence of 10% Pd on a carbon ethylenediamine complex (45 mg) under an atmospheric pressure of H_2 at room temperature for 1 h. The insoluble material was removed by filtration and the filtrate was concentrated to give a crude amine, which was dissolved in DMF (4.4 mL). To this solution at 0 °C were added the dipeptide **25** (46 mg, 0.144 mmol), WSC·HCl (33 mg, 0.173 mmol), and HOBt (23 mg, 0.173 mmol), and the whole mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with EtOAc and washed successively with a saturated aqueous NH_4Cl solution, a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 1 g, acetone/toluene = 1/20 as eluent) to afford a mixture (ca. 1.5:1) of the *O*-TBS ether **45** and its epimer (60 mg, 92%) as a colorless syrup; ^1H NMR ($CDCl_3$, 300 MHz for the major isomer, **45**) δ 0.01 (s, 6H), 0.75–0.97 (m, 24H), 1.10–1.40 (m, 25H), 1.17 (d, 3H, J = 6.3 Hz), 1.43 (s, 9H), 1.80–2.00 (m, 2H), 2.12 (m, 1H), 3.30 (dd, 1H, J = 10.3 and 7.1 Hz), 3.48 (bs, 1H), 3.55 (dd, 1H, J = 3.2 and 10.3 Hz), 3.68 (m, 1H), 3.90 (dd, 1H, J = 3.4 and 9.3 Hz), 3.97 (m, 1H), 4.34 (dq, 1H, J = 2.7 and 6.3 Hz), 4.42–4.59 (m, 3H), 4.68 (m, 1H), 4.89 (dd, 1H, J = 8.8 and 3.2 Hz), 5.07 (m, 1H), 6.87 (d, 1H, J = 7.6 Hz), 7.15–7.40 (m, 6H); FAB-HRMS Calcd for $C_{50}H_{92}N_3O_9Si$ $(M + H)^+$: 906.6602, Found m/z 906.6597.

***N*-[(1,1-Dimethylethoxy)carbonyl]-L-valyl-L-threonyl-*O*-(phenylmethyl)-L-serine (1*R*,2*S*)-1-[(1*S*)-2-Hydroxy-1-methylethyl]-2-methylhexadecyl Ester (46) and Its D-Serine Isomer (47).** A solution of a mixture (ca. 1.5:1) of **45** and its D-serine isomer (60 mg, 0.067 mmol) in acetic acid (8.4 mL), H_2O (3.6 mL), and THF (1.8 mL) was stirred at room temperature for 12 h. The reaction mixture was diluted with H_2O, and to this solution was added solid $NaHCO_3$ (15 g) at 0 °C. The products were extracted with EtOAc, and the organic layer was washed with a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 4 g, acetone/toluene = 1/7 as eluent) to first afford **47** (16 mg, 30%) as a colorless syrup. $[\alpha]_D^{24}$ −29 (*c* 0.6, $CHCl_3$); IR (neat) 3300, 1740, 1720, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (d, 3H, J = 6.8 Hz), 0.88 (t, 3H, J = 6.1 Hz), 0.91 (d, 3H, J = 6.6 Hz), 0.95 (d, 3H, J = 6.8 Hz), 0.96 (d, 3H, J = 7.3 Hz), 1.16 (d, 3H, J = 6.3 Hz), 1.11–1.33 (m, 26H), 1.44 (s, 9H), 1.73 (m, 1H), 1.82 (m, 1H), 2.18 (m, 1H), 2.43 (m, 1H), 3.34–3.63 (m, 3H), 3.68 (dd, 1H, J = 3.4 and 9.5 Hz), 3.94 (dd, 1H, J = 2.9 and 9.5 Hz), 3.98 (m, 1H), 4.32–4.49 (m, 2H), 4.49 (d, 1H, J = 12.2 Hz), 4.54 (d, 1H, J = 12.2 Hz), 4.72 (ddd, 1H, J = 2.9, 3.4, and 8.1 Hz), 4.86 (dd, 1H, J = 2.9 and 9.0 Hz), 5.04 (d, 1H, J = 7.3 Hz), 6.98 (d, 1H, J = 7.3 Hz), 7.22–7.39 (m, 5H), 7.41 (d, 1H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.2,

14.1, 14.2, 17.6, 18.6, 19.3, 22.7, 27.1, 28.2, 29.4, 29.7, 30.4, 31.9, 33.8, 33.9, 36.9, 53.3, 57.7, 60.3, 64.1, 66.7, 69.2, 73.5, 80.3, 80.4, 127.9, 127.9, 128.4, 137.0, 156.0, 170.7, 171.1, 172.6; FAB-HRMS Calcd for $C_{44}H_{78}N_3O_9$ $(M+H)^+$: 792.5738, Found m/z 792.5755. Found: C, 66.36; H, 9.68; N, 5.12%. Calcd for $C_{44}H_{77}N_3O_9$: C, 66.72; H, 9.80; N, 5.30%.

Further elution gave **46** (24 mg, 46%) as a colorless syrup; $[\alpha]_D^{21}$ −27 (*c* 1.0, $CHCl_3$); IR (neat) 3300, 1740, 1690, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (d, 3H, $J = 6.8$ Hz), 0.88 (t, 3H, $J = 6.3$ Hz), 0.89 (d, 3H, $J = 6.3$ Hz), 0.93 (d, 3H, $J = 7.1$ Hz), 0.96 (d, 3H, $J = 7.3$ Hz), 1.10–1.32 (m, 26H), 1.18 (d, 3H, $J = 6.3$ Hz), 1.43 (s, 9H), 1.72 (m, 1H), 1.89 (m, 1H), 2.12 (dqq, 1H, $J = 7.1$, 5.4, and 6.3 Hz), 2.49 (m, 1H), 3.35–3.60 (m, 3H), 3.69 (dd, 1H, $J = 3.2$ and 9.5 Hz), 3.91 (dd, 1H, $J = 3.4$ and 9.5 Hz), 3.99 (dd, 1H, $J = 5.4$ and 8.1 Hz), 4.35 (dq, 1H, $J =$ 2.4 and 6.3 Hz), 4.47 (dd, 1H, $J = 2.4$ and 7.3 Hz), 4.52 (s, 2H), 4.71 (ddd, 1H, $J = 3.2$, 3.4, and 8.3 Hz), 4.90 (dd, 1H, $J = 2.4$ and 9.5 Hz), 5.11 (d, 1H, $J = 8.1$ Hz), 7.00 (d, 1H, $J = 7.3$ Hz), 7.26–7.40 (m, 5H), 7.38 (d, 1H, $J = 8.3$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.0, 14.0, 14.1, 17.7, 18.2, 19.2, 22.7, 27.2, 28.3, 29.3, 29.7, 30.6, 31.9, 33.7, 33.9, 36.9, 53.0, 57.0, 60.1, 64.3, 66.7, 69.3, 73.5, 79.7, 80.2, 127.8, 127.9, 128.4, 137.0, 155.9, 170.7, 170.7, 172.4; FAB-HRMS Calcd for $C_{44}H_{78}N_3O_9$ $(M+H)^+$: 792.5738, Found m/z 792.5748. Found: C, 66.39; H, 9.77; N, 5.12%. Calcd for $C_{44}H_{77}N_3O_9$: C, 66.72; H, 9.80; N, 5.30%.

Cyclo[(2*R*,3*R*,4*S*)-3-hydroxy-2,4-dimethyloctadecanoyl-L-valyl-L-threonyl-*O*-(phenylmethyl)-L-seryl] (49). To a solution of the diol **46** (16 mg, 0.020 mmol) in CH_2Cl_2 (3.1 mL) at 0 °C were added TEMPO (1.24 g L^{-1} solution in CH_2Cl_2; 0.025 mL), KBr (5.96 g L^{-1} solution in H_2O; 0.039 mL), NaOCl (0.35 M solution in H_2O; 0.068 mL), and $NaHCO_3$ (50 g L^{-1} solution in H_2O; 0.068 mL). After being stirred at 0 °C for 1 h, to the reaction mixture was added a 20% aqueous $Na_2S_2O_3$ solution. The products were extracted with $CHCl_3$, and the organic layer was washed with a 20% aqueous $Na_2S_2O_3$ solution, and then dried. Removal of the solvent gave a crude aldehyde (16 mg), which was dissolved in *t*-BuOH (2.5 mL) and H_2O (0.6 mL). To this solution were added $NaH_2PO_4 \cdot 2H_2O$ (12 mg, 0.078 mmol), $HOSO_2NH_2$ (9.5 mg, 0.098 mmol), and $NaClO_2$ (11 mg, 0.117 mmol), and the mixture was stirred at 0 °C for 30 min. To the reaction mixture at 0 °C was added a 1 M aqueous citric acid solution, and the products were extracted with $CHCl_3$. The organic layer was washed with a 1 M aqueous citric acid solution, and then dried. Removal of the solvent gave a crude carboxylic acid, which was dissolved in CH_2Cl_2 (2.4 mL). To this solution under Ar at −18 °C was added TFA (0.474 mL), and the mixture was stirred at −18 °C for 1 h. The reaction mixture was concentrated and dried in vacuo to give crude **48**·TFA, which was dissolved in DMF (9.8 mL). To this solution under Ar at 0 °C were added DEPC (0.0088 mL, 0.058 mmol) and Et_3N (0.0096 mL, 0.069 mmol), and the mixture was stirred at 0 °C for 30 min, and then at room temperature for 13 h. The reaction mixture was diluted with EtOAc and washed successively with a 1 M aqueous HCl solution, a saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 1 g, acetone/toluene = 1/10 as eluent) to afford **49** (3.7 mg, 28% from **46**) as a colorless syrup; $[\alpha]_D^{26}$ −64 (*c* 0.1, $CHCl_3$); IR (neat) 3390, 3270, 1740, 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77 (d, 3H, $J = 6.8$ Hz, 4-Me), 0.79 (d, 3H, $J = 6.9$ Hz, 2-Me), 0.83 (d, 3H, $J = 7.1$ Hz, val-Me), 0.88 (t, 3H, $J = 6.1$ Hz, $-(CH_2)_{12}CH_3$), 0.99 (d, 3H, $J = 6.3$ Hz, val-Me), 1.10–1.80 (m, 28H, thr-Me, H-5, and $-(CH_2)_{12}CH_3$), 1.90–2.25 (m, 2H, H-4 and val-βH), 2.31 (m, 1H, H-5′), 2.79 (m, 1H, H-2), 3.74–3.88 (m, 2H, thr-αH and ser-βH), 4.00–4.20 (m, 2H, val-αH and ser-β'H), 4.46 (d, 1H, $J = 10.7$ Hz, OCH*H*Ph), 4.50 (m, 1H, thr-βH), 4.55 (d, 1H, $J = 10.7$ Hz, OC*H*HPh), 4.58–4.68 (m, 2H, ser-αH and H-3), 5.64 (d, 1H, $J = 9.0$ Hz, val-NH), 7.08 (d, 1H, $J = 7.3$ Hz, thr-NH), 7.17–7.42 (m, 6H, Ph and ser-NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 15.6, 18.4, 19.7, 20.6, 22.7, 26.4, 27.3, 29.4, 29.6, 29.7, 29.9, 31.9, 32.9, 34.8, 41.0, 53.4, 65.9, 70.0, 74.1, 82.8, 128.2, 128.6, 128.7, 137.3, 169.5, 172.9, 173.5; FAB-HRMS Calcd for $C_{39}H_{66}N_3O_7$ $(M+H)^+$: 688.4901, Found m/z 688.4904.

Stevastelin C3, Revised Structure (4). A mixture of the macrocycle **49** (1.4 mg, 0.002 mmol) and 10% Pd on carbon (4.6 mg) in MeOH (0.3 mL) was stirred at room temperature under an atmospheric pressure of H_2 for 3 h. The insoluble material was removed by filtration, and the filtrate was concentrated to give a residue, which was purified by column chromatography (silica gel, 0.3 g, MeOH/$CHCl_3$ = 1/30 as eluent) to afford **4** (1.0 mg, 83%) as an amorphous solid; $[\alpha]_D^{25}$ −67 (*c* 0.13, MeOH), {natural stevastelin C3, $[\alpha]_D^{27}$ −66 (*c* 0.305, MeOH) (measured in our laboratory)}; ^1H NMR (DMSO-d_6, 300 MHz) δ 0.59 (d, 3H, $J = 6.8$ Hz, 4-Me), 0.85 (t, 3H, $J = 6.8$ Hz, $-(CH_2)_{12}CH_3$), 0.87 (d, 3H, $J = 6.3$ Hz, val-Me), 0.92 (d, 3H, $J = 6.6$ Hz, val-Me), 1.07 (d, 3H, $J = 6.3$ Hz, thr-Me), 1.10 (d, 3H, $J = 7.6$ Hz, 2-Me), 1.13–1.30 (m, 25H, H-5 and $-(CH_2)_{12}CH_3$), 1.49 (m, 1H, H-5′), 1.74 (m, 1H, H-4), 2.05 (m, 1H, val-βH), 2.74 (m, 1H, H-2), 3.54 (m, 1H, ser-βH), 3.92 (m, 1H, ser-βH), 4.03 (m, 2H, val-αH and thr-βH), 4.13 (dd, 1H, $J = 10.3$ and 2.4 Hz, thr-αH), 4.61 (m, 2H, ser-αH and H-3), 5.04 (dd, 1H, $J = 5.1$ and 4.9 Hz, ser-OH), 5.16 (d, 1H, $J = 4.6$ Hz, thr-OH), 7.52 (m, 1H, val-NH), 7.85 (m, 2H, ser-NH and thr-NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 13.9 (2-CH_3 and 18-C), 15.4 (4-CH_3), 18.9 and 19.3 (val-CH_3), 21.0 (thr-CH_3), 22.1, 25.9, 28.7, 28.9, 29.0, 29.2, 31.3, 32.3 (5–17-C, val-βC), 34.4 (4-C), 42.1 (2-C), 53.7 (ser-αC), 59.5 (thr-αC), 61.00 (ser-βC), 61.02 (val-αC), 65.2 (thr-βC), 80.5 (3-C), 170.0, 170.4 and 170.8 (ser-CO, thr-CO, val-CO, 1-C); FAB-HRMS Calcd for $C_{32}H_{60}N_3O_7$ $(M+H)^+$: 598.4431, Found m/z 598.4422. The ^1H and ^{13}C NMR data were fully identical with those of natural stevastelin C3.

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