Total Synthesis of (+)-Paniculide A via a Catalytic Asymmetric Diels–Alder Reaction of a 3-Borylpropenoic Acid Derivative

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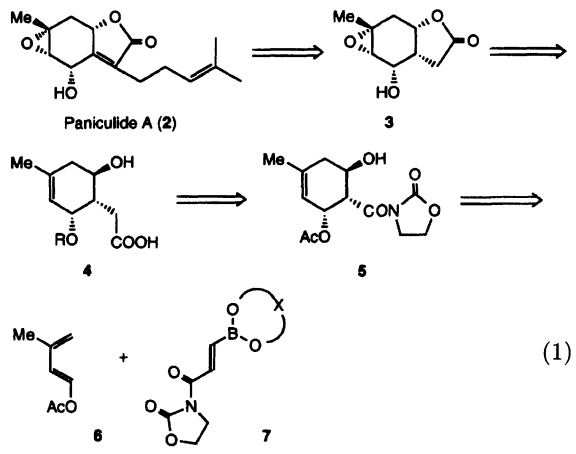
(+)-Paniculide A, a highly oxidized sesquiterpene, has been synthesized enantioselectively starting from a cycloadduct, which was prepared from 3-(3-borylpropenoyl)-1,3-oxazolidin-2-one and 1-acetoxy-3-methyl-1,3-butadiene by a catalytic asymmetric Diels–Alder reaction.

The synthesis of optically active compounds is an important issue in modern organic chemistry. During the course of our studies on the catalytic asymmetric Diels–Alder reactions,[1] we reported on the utility of 3-(3-borylpropenoyl)-1,3-oxazolidin-2-one as a synthetic equivalent of β-hydroxyacrylic acid. With a catalytic amount of a titanium reagent prepared in situ from dichlorodiisopropoxytitanium and a tartrate-derived chiral 1,4-diol **1**, 3-(3-borylpropenoyl)-1,3-oxazolidin-2-ones react smoothly with various dienes in the presence of Molecular Sieves (MS) 4A to afford the adducts in high yield with high optical purity.[2] This method provides an efficient synthetic route for the preparation of various optically active cyclohexenol derivatives, since the boryl groups of the adducts can be easily converted to a hydroxyl group with retention of the configuration. This method was considered to provide a useful synthetic tool for the preparation of highly oxygenated natural products.

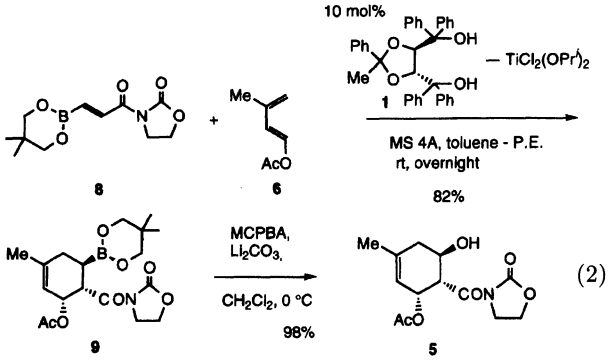


(1)

Paniculide A (**2**), a sesquiterpene isolated by Overton et al. from callus cultures derived from hypocotyl and stem tissues of *Andrographis paniculata* Nees,[3] has been a synthetic target in a number of laboratories due to the highly oxygenated cyclohexane system.[4—8] In this paper, we describe the first asymmetric total synthesis of paniculide A (**2**) by applying the catalytic asymmetric Diels–Alder reaction. The retrosynthetic analysis is shown in Scheme 1. Thus, disconnection of a side chain leads to an epoxy lactone **3** which is a known synthetic intermediate to (±)-paniculide A (**2**).[4] The epoxy lactone **3** could be prepared from a hydroxy acid **4** using intramolecular Mitsunobu reaction[9] and epoxidation. The hydroxy acid **4** could be obtained by a one-carbon elongation of **5**, which could be prepared by the oxidation of the boryl group of the Diels–Alder adduct between **6** and **7**.

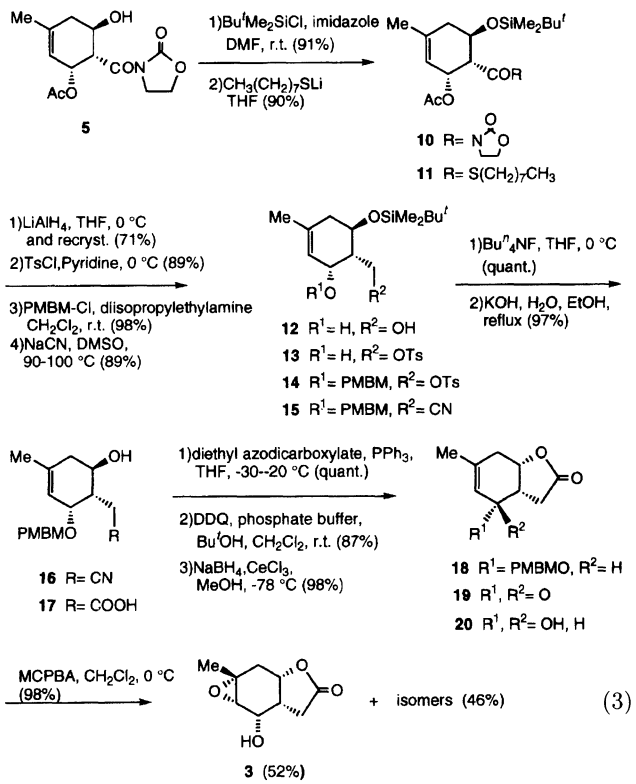
Results and Discussion

The starting material was prepared by a catalytic asymmetric Diels–Alder reaction of (*E*)-3-[3-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)propenoyl]-1,3-oxazolidin-2-one (**8**) with 1-acetoxy-3-methyl-1,3-butadiene (**6**) using a catalytic amount of the chiral titanium reagent in toluene-petroleum ether (PE) in the presence of MS 4A, as previously reported.[2] The reaction proceeded smoothly to afford the adduct **9** in 82% yield with 94% ee, as determined by a 500 MHz ^{1}H NMR analysis of the 3,3,3-trifluoro-2-methoxy-2-phenylpropionate (MTPA) ester of the alcohol **5**. Treatment of the adduct with *m*-chloroperbenzoic acid (MCPBA) at 0 °C to room temperature afforded the alcohol **5** in good yield; however, upon a scale-up, the reaction proved to be somewhat capricious, and the alcohol **5** was obtained with a considerable amount of an epoxide. To prevent the epoxidation of a double bond, **9** was treated with MCPBA at 0 °C in the presence of Li_2CO_3, expecting that selective oxidation of the boryl group may be enhanced by a nucleophilic attack of the *m*-chloroperbenzoate anion to the boryl group. Consequently, **5** could be obtained reproducibly on the gram scale in high yield (98%) (Eq. 2).



(2)

The resulting hydroxyl group was protected as a *t*-butyldimethylsilyl (TBS) ether in 91% yield. Conversion of the 1,3-oxazolidin-2-one derivative **10** to a thioester **11** under the standard conditions[1c] (90%), followed by reduction with $LiAlH_4$ at 0 °C, afforded a diol **12**. After recrystallization from hexane, the optically pure diol **12** could be obtained in 71% yield from the thioester **11**. The optical purity of **12** was confirmed by a 270 MHz ^1H NMR analysis of the bis-MTPA ester of **12**. Tosylation of the diol **12** with 1.2 equiv of *p*-toluenesulfonyl chloride at 0 °C afforded a monotosylate **13** in 89% yield. To protect the residual secondary hydroxyl group as a (*p*-methoxybenzyloxy)methyl (PMBM) ether,[10] **13** was treated with excess PMBM chloride[11] and diisopropylethylamine in CH_2Cl_2 to give the PMBM ether **14** in 98% yield. **14** was then converted to a nitrile **15** in 89% yield by the reaction with NaCN in dimethyl sulfoxide at 90—100 °C. After removing the TBS group using tetrabutylammonium fluoride, **16** was hydrolyzed with KOH to give a hydroxy acid **17**. Lactonization of **17** with the inversion of the hydroxyl center was accomplished by employing an intramolecular Mitsunobu reaction, furnishing a lactone **18** in quantitative yield.



(3)

To introduce an epoxy group stereoselectively, deprotection of the PMBM group of the lactone **18** was examined. Transformation of the PMBM ether **18** to the alcohol **20**, however, did not proceed successfully by the standard oxidative procedures (e.g., DDQ, CAN). The thus-obtained alcohol **20** proved to be a mixture of α and β-epimers, and, in some cases, over oxidation to an enone **19** or rearrangement to the epimeric tertiary alcohols occurred during the deprotection. Ultimately, this goal was accomplished through a two-step process: The lactone **18** was treated with excess DDQ to afford an enone **19** in 87% yield; then, the resulting enone was stereoselectively reduced with $NaBH_4$ and $CeCl_3$[13] in MeOH at −78 °C to afford the alcohol **20** in 98% yield as a 84 : 16 diastereomer mixture. The major isomer proved to be the α-alcohol, but was difficult to be separated by chromatography. Treatment of the mixture of the alcohols with MCPBA in CH_2Cl_2 at 0 °C afforded a mixture of diastereoisomers (98%), from which 52% of the desired epoxy lactone **3** was isolated. The configuration of the epoxy lactone **3** was confirmed by a 2D-NOESY experiment, as shown in Fig. 1. This compound was identical in all respects (^1H NMR, IR, TLC mobility) with the compound previously reported by Smith.[4]

Transformation of **3** to paniculide A was performed through the same series of reactions as reported in the literature.[4] Silylation of the secondary hydroxyl group with triethylsilyl chloride (TESCl) in CH_2Cl_2 afforded a silyl ether **21** in quantitative yield. The silyl ether **21** was lithiated with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) instead of lithium diisopropylamide (LDA) in the Smith's procedure and then treated with 5-iodo-2-methyl-2-pentene (**22**),[12] furnishing an alkylated lactone **23** in 64% yield. Treatment of **23** with 3 molar equiv of potassium bis(trimethylsilyl)amide at −100 °C followed by the addition of diphenyl diselenide to the anion gave a selenide **24** in 58% yield (83% yield on the basis of the recovered starting material). Conversion of **24** to paniculide A (**2**) was accomplished by a slight modification of the method of Smith. Thus, reaction **24** with H_2O_2 and pyridine in CH_2Cl_2 gave a silyl ether of paniculide A **25** which was used for the next reaction without further purification. The crude

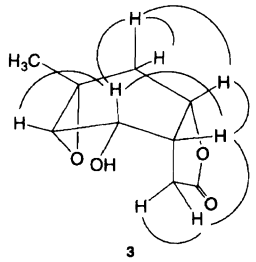


Fig. 1. 2D-NOESY of **3** (500 MHz).

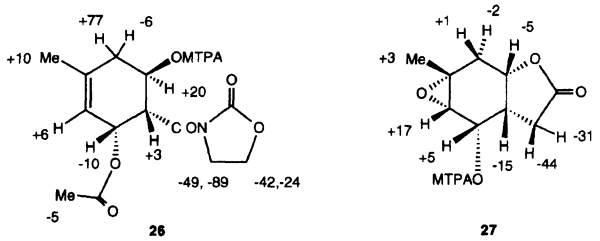
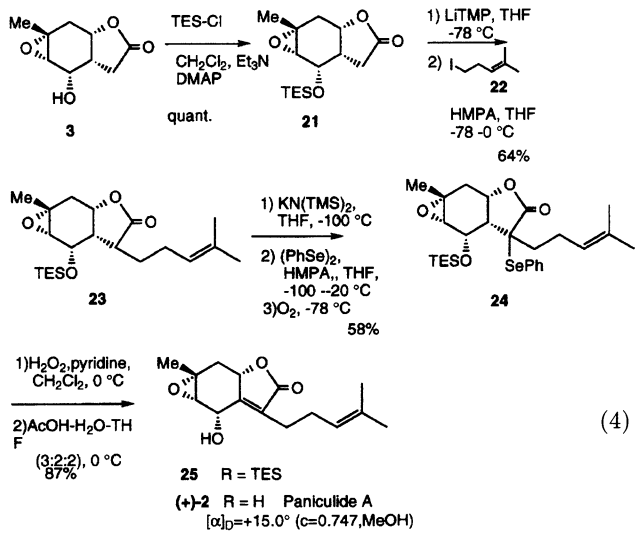


Fig. 2. $\Delta\delta$ Values (Hz) obtained for the MTPA esters of **5** and **3**.

25 was deprotected with AcOH–tetrahydrofuran–H_2O (3:2:2) at 0 °C to give (+)-paniculide A (**2**) in 87% yield from **24**. Analytically pure (+)-paniculide A (**2**) was obtained as colorless crystals (mp 118.8—121.1 °C) by recrystallization from Et_2O.



(4)

The thus-obtained synthetic (+)-paniculide A exhibited the expected spectral data, which were identical to those reported for the natural[3] and the racemic ones.[4] Since the data of optical rotation of natural paniculide A have not been reported, we determined the absolute configuration of our synthetic (+)-paniculide A (**2**) by applying the modified Mosher's method[14] to **5** and **3**. Alcohols **5** and **3** were converted to the corresponding (*R*) and (*S*)-MTPA esters, **26R** and **26S**,[2] **27R** and **27S**, respectively. The proton signals of each compound were assigned and $\Delta\delta[\delta(S)-\delta(R)]$ was calculated for each proton (Fig. 2). The protons with $\Delta\delta>0$ were located on the right side of the MTPA plane, and those with $\Delta\delta<0$ on the left side. The above NMR study indicated that the absolute configuration of compounds **5** and **3** were as depicted in Eq. 3. The absolute configuration is also consistent with the sense of the asymmetric Diels–Alder reaction previously reported.[2] Consequently, the absolute stereochemistry of (+)-paniculide A was determined to be as depicted in structure **2**. In addition, from the ^{1}H NMR study of **27R** and **27S**, it was noted that the epoxy lactone **3** was optically pure (>98% ee), which implied that synthetic (+)-paniculide A was likewise optically pure. In conclusion, the first asymmetric total synthesis of (+)-paniculide A was accomplished in 19 steps with an overall yield of 7% based on the initial dienophile, (*E*)-3-[3-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)propenoyl]-1,3-oxazolidin-2-one (**8**).

Experimental

General Methods. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a JEOL JNM-EX 270 (270 MHz) or a Bruker AM 500 (500 MHz) NMR spectrometer; ^{1}H NMR chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane; ^{13}C NMR chemical shifts are referenced in $CDCl_3$ and MeOH-d_4 to the solvent (77.0 and 49.0 ppm, respectively). IR spectra were measured with a Horiba FT-200. Optical rotations were measured with a JASCO DIP-1000. High-resolution mass spectra were measured for the new compounds with a JEOL JMS-SX 102A spectrometer operating at 70 eV. Elemental analyses were performed using a Carlo Erba EA1108. Melting points were recorded on a Mettler FP800 and are uncorrected. Toluene and petroleum ether (PE) were distilled and stored over MS 4A. CH_2Cl_2 was distilled from P_2O_5, then from CaH_2, and dried over MS 4A. *N*,*N*-Dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and hexamethylphosphoric triamide (HMPA) were distilled under reduced pressure from CaH_2 and dried over MS 4A. Triethylamine, diisopropylamine, 2,2,6,6-tetramethylpiperidine, and pyridine were freshly distilled from CaH_2. MeOH was distilled from magnesium methoxide and dried over MS 3A. Tetrahydrofuran (THF) was freshly distilled from sodium diphenylketyl. Column chromatography was carried out on silica gel (Merck, 7734, 70—230 mesh). Flash column chromatography was performed employing 25—55 mm silica gel (Fuji Davison, BM-300). Reactions were monitored by thin-layer chromatography (TLC) using pre-coated silica-gel plates (Merck Kieselgel 60F-254). All reactions were performed under an argon atmosphere unless otherwise noted.

(2*R*,3*R*)-1,1,4,4-Tetraphenyl-2,3,*O*-(1-phenylethylidene)-1,2,3,4-butanetetrol (**1**),[1a] dichlorodiisopropoxytitanium,[2] (*p*-methoxybenzyloxy)methyl (PMBM) chloride[11] and 5-iodo-2-methyl-2-pentene (**22**)[12] were prepared according to literature methods.

Preparation of 3-[[(1*S*,2*R*,6*R*)-2-Acetoxy-4-methyl-6-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3-cyclohexene-1-yl]carbonyl]-1,3-oxazolidin-2-one (9).[2] The chiral diol **1** (1.5 g, 2.84 mmol) was added to a toluene solution (15 mL) of dichlorodiisopropoxytitanium (610 mg, 2.57 mmol) at room temperature, and the reaction mixture was stirred for 1 h. MS 4A (4.9 g); toluene (120 mL) were then added to this solution and the mixture was cooled to 0 °C. After the boronate **8** (5.8 g, 23 mmol) was added to the mixture, PE (135 mL) and 1-acetoxy-3-methyl-1,3-butadiene (**6**) (29 g, 0.23 mol) were added. After stirring overnight at room temperature, the reaction was quenched with pH 7 phosphate buffer. The mixture was filtered through Celite and the organic materials were extracted three times with EtOAc. The combined extracts were dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography (EtOAc : hexane=2 : 3) to give the adduct **9** (7.17 g, 82 %) as a colorless oil.

Preparation of 3-[[(1*S*,2*R*,6*R*)-2-Acetoxy-6-hydroxy-4-methyl-3-cyclohexene-1-yl]carbonyl]-1,3-oxazolidin-2-one (5). To a solution of the adduct **9** (7.0 g, 18.5 mmol) in CH_2Cl_2 (80 mL) at 0 °C was added Li_2CO_3 (683 mg, 9.2 mmol). Then, a solution of MCPBA (8.69 g, 55% purity, 27.7 mmol) in CH_2Cl_2 (140 mL) was added over 1 h at 0 °C and the suspension was stirred at 0 °C for 2.25 h. After the addition of 2-methyl-2-butene (16.4 mL), the reaction mixture was stirred at 0 °C for 22 h to quench any excess MCPBA. The suspension was filtered and concentrated under reduced pressure. Flash column chromatography (MeOH : ether=5 : 95) gave the alcohol **5** (5.14 g, 98%). **5**: 94% ee; IR (neat) 3458, 2922, 1776, 1728,

1699, 1390, 1232, 1117, 1092, 1039, 1020, and 976 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.79 (3H, s), 1.99 (3H, s), 2.12 (1H, dd, J=10.3, 17.6 Hz), 2.49 (1H, dd, J=5.9, 17.6 Hz), 2.75 (1H, bs), 3.82—3.92 (1H, m), 3.91 (1H, dd, J=3.9, 10.7 Hz), 4.03 (1H, ddd, J=6.8, 8.8, 10.7 Hz), 4.36—4.51 (2H, m), 4.50 (1H, ddd J=5.9, 10.3, 10.7 Hz), 5.43—5.49 (1H, m), and 5.78 (1H, dd J=3.9, 4.9 Hz); ^{13}C NMR ($CDCl_3$) δ=20.94, 23.11, 37.83, 42.55, 51.11, 62.23, 63.63, 68.02, 117.84, 140.34, 153.32, 170.80, and 171.86. These spectral data of **5** agreed with those of the literature.[2] The optical purity was determined by analyzing the 500 MHz ^1H NMR of the MTPA ester of **5** in the same manner as previously reported.[2]

Preparation of 3-[[(1*R*,2*R*,6*R*)-2-Acetoxy-6-*t*-butyldimethylsiloxy-4-methyl-3-cyclohexene-1-yl]carbonyl]-1,3-oxazolidin-2-one (10). To a DMF solution (35 mL) of **5** (5.11 g, 18.1 mmol) was added imidazole (9.24 g, 136 mmol) and *t*-butyldimethylsilyl (TBS) chloride (8.72 g, 57.9 mmol). After the mixture was stirred for 22.5 h at room temperature, the reaction was quenched with a pH 7 phosphate buffer, and the organic materials were extracted three times with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. After removing of the solvent under reduced pressure, the crude product was purified by flash column chromatography (EtOAc : hexane=1 : 4) to afford the TBS ether **10** (6.55 g, 90%) as a colorless oil. **10**: $[\alpha]_D^{26}$ −163.66° (*c* 1.08, CH_2Cl_2); IR (neat) 2954, 2929, 2856, 1780, 1730, 1705, 1389, 1252, 1232, 1105, 1086, and 839 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.05 (3H, s), 0.11 (3H, s), 0.83 (9H, s), 1.76 (3H, s), 2.00 (3H, s), 2.09 (1H, dd, J=9.2, 17.5 Hz), 2.38 (1H, dd, J=6.3, 17.5 Hz), 3.82—3.97 (2H, m), 4.08 (1H, dd, J=3.6, 10.9 Hz), 4.31—4.50 (3H, m), 5.42 (1H, d, J=5.3 Hz), and 5.70 (1H, dd, J=3.6, 5.3 Hz); ^{13}C NMR ($CDCl_3$) δ=−5.12, −4.38, 17.81, 21.10, 23.18, 25.66, 40.09, 42.68, 49.90, 61.91, 64.94, 67.66, 117.72, 139.87, 153.58, 170.80, and 170.98. HRMS Found: m/z 397.1920. Calcd for $C_{19}H_{31}O_6NSi$: M, 397.1921.

Preparation of *S*-Octyl (1*R*,2*R*,6*R*)-2-Acetoxy-6-*t*-butyldimethylsiloxy-4-methyl-3-cyclohexene-1-carbothioate (11). To a solution of 1-octanethiol (3.11 g, 21.3 mmol) in THF (140 mL) was added a solution of Bu^nLi in hexane (1.6 M, 13.2 mL, M=mol dm^{-3}) dropwise at 0 °C. After stirring at 0 °C for 1 h, the resulting suspension was added dropwise to a solution of **10** (6.5 g, 16.4 mmol) in THF (70 mL) at −30 °C. The reaction mixture was stirred for 15 min; then, pH 7 phosphate buffer was added. The aqueous solution was extracted three times with EtOAc. The combined extracts were washed with brine dried over Na_2SO_4 and concentrated in vacuo to give a crude product. Flash column chromatography (EtOAc : hexane=4 : 96) gave the thioester **11** (6.7 g, 90%) as a colorless oil. **11**: $[\alpha]_D^{28}$ −157.09° (*c* 1.178, CH_2Cl_2); IR (neat) 2956, 2927, 2856, 1747, 1707, 1682, 1369, 1230, 1101, 1082, 1018, 839, and 777 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.06 (3H, s), 0.09 (3H, s), 0.85 (9H, s), 0.88 (3H, t, J=6.3 Hz), 1.20—1.41 (10H, m), 1.49—1.60 (2H, m), 1.73 (3H, s), 2.01 (3H, s), 2.02 (1H, dd, J=8.9, 17.5 Hz), 2.36 (1H, dd, J=5.9, 17.5 Hz), 2.74—2.90 (2H, m), 2.92 (1H, dd, J=4.0, 10.6 Hz), 4.42(1H, ddd, J=5.9, 8.9, 10.6 Hz), 5.46 (1H, d, J=4.9 Hz), and 5.61 (1H, dd, J=4.0, 4.9 Hz); ^{13}C NMR ($CDCl_3$) δ=−5.30, −4.31, 14.05, 17.88, 21.08, 22.59, 23.13, 25.66, 28.81, 29.02, 29.06, 29.09, 29.29, 31.75, 40.09, 59.53, 65.25, 68.25, 118.04, 139.28, 170.26, and 196.91. HRMS Found: m/z 456.2728. Calcd for $C_{24}H_{44}O_4SiS$: M, 456.2730.

Preparation of (1*R*,2*R*,6*R*)-6-*t*-Butyldimethylsiloxy-2-hydroxy-4-methyl-3-cyclohexene-1-methanol (12). To a suspension of $LiAlH_4$ (819 mg, 21.6 mmol) in THF (50 mL) was added a THF solution (40 mL) of **11** (3.28 g, 7.2 mmol) at 0 °C; the mixture was stirred for 21 h. After saturated aqueous Na_2SO_4 was added dropwise until hydrogen evolution ceased, saturated aqueous potassium sodium tartrate (5 mL) was added. The resulting suspension was then diluted with isopropyl alcohol. Inorganic materials were removed by filtration and washed with portion of hot isopropyl alcohol. The filtrate was concentrated in vacuo and the crude product was purified by flash column chromatography (EtOAc : hexane=3 : 7) to give the diol **12** (1.82 g, 93%) as colorless crystals. This product was recrystallized from hexane to afford the optically pure **12** (1.39 g, 71%). **12**: >98% ee; mp 71.0—71.4 °C (hexane); $[\alpha]_D^{29}$ −151.90° (*c* 0.546, CH_2Cl_2); IR (KBr) 3498, 2956, 2927, 2885, 2856, 1255, 1086, 1018, 945, 926, 901, 854, 837, and 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.09 (3H, s), 0.10 (3H, s), 0.89 (9H, s), 1.65—1.76 (1H, m), 1.70 (3H, s), 2.00 (1H, dd, J=8.9, 17.2 Hz), 2.23 (1H, dd, J=5.3, 17.2 Hz), 2.40 (2H, bs), 3.86 (1H, dd, J=5.6, 10.9 Hz), 3.94 (1H, dd, J=5.3, 10.9 Hz), 4.08 (1H, ddd, J=5.3, 8.9, 10.6 Hz), 4.38 (1H, dd, J=4.3, 4.3 Hz), and 5.52 (1H, bs); ^{13}C NMR ($CDCl_3$) δ=−4.94, −4.20, 17.92, 23.22, 25.77, 40.95, 47.41, 62.97, 66.88, 68.36, 122.64, and 137.16. Found: C, 62.08; H, 10.64%. Calcd for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36%.

The optical purity of **12** was determined by analyzing the 270 MHz ^1H NMR of the bis-(*R*)-MTPA ester of **12**. Conversion of **12** to the bis-MTPA ester is as follows: To a pyridine solution (2 mL) of the diol **12** (9 mg) were added 3 drops of (+)-MTPA-Cl and a catalytic amount of 4-(dimethylamino)pyridine at room temperature. After the mixture was stirred for 24 h, the reaction was quenched with saturated aqueous NH_4Cl and the organic materials were extracted with Et_2O. The organic phase was washed with brine and dired over Na_2SO_4. After the evaporation of the solvent, the crude product was purified by flash column chromatography to afford the bis-MTPA ester quantitatively.

Determination of the Optical Purity of 12. Signals of one of the methylene protons (CH_2OMTPA) of the bis-(*R*)-MTPA ester, which was prepared from the racemic sample, appeared at 4.70 (1H, dd, J=4.9, 10.7 Hz) and 4.79 (1H, dd, J=4.9, 10.7 Hz) ppm. Only the signal at 4.79 ppm was observed in the spectrum of the bis-(*R*)-MTPA ester, which was prepared from the optically active product **12**.

Preparation of [(1*R*,2*R*,6*R*)-6-*t*-Butyldimethylsiloxy-2-hydroxy-4-methyl-3-cyclohexene-1-yl]methyl *p*-Toluenesulfonate (13). To a solution of **12** (2.3 g, 8.5 mmol) in pyridine (30 mL) was added *p*-toluenesulfonyl chloride (1.93 g, 10.1 mmol) at 0 °C; the solution was stirred for 18 h. The reaction was quenched at 0 °C with saturated aqueous NH_4Cl. The aqueous phase was extracted three times with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography (EtOAc : hexane=1 : 4) gave the tosylate **13** (3.22 g, 89%) as a colorless oil and recovered **12** (0.12 g, 5%). **13**: $[\alpha]_D^{25}$ −109.49° (*c* 1.748, CH_2Cl_2); IR (neat) 3440, 2954, 2929,

2858, 1362, 1255, 1178, 1090, 957, 843, 816, and 779 cm^{-1}; ^1H NMR ($CDCl_3$) δ=−0.06 (3H, s), 0.00 (3H, s), 0.78 (9H, s), 1.68 (3H, s), 1.87—2.01 (3H, m), 2.19 (1H, dd, J=5.6, 17.2 Hz), 2.44 (3H, m), 3.84 (1H, ddd, J=5.6, 9.2, 10.9 Hz), 4.20 (1H, d, J=9.6 Hz), 4.28 (1H, dd, J=5.0, 9.6 Hz), 4.34 (1H, dd, J=4.0, 4.2 Hz), 5.55 (1H, bs), 7.34 (2H, d, J=8.3 Hz), and 7.79 (2H, d, J=8.3 Hz); ^{13}C NMR ($CDCl_3$) δ=−5.19, −4.17, 17.77, 21.58, 23.11, 25.61, 40.70, 45.99, 63.97, 65.21, 69.47, 121.98, 127.92, 129.83, 132.58, 136.84, and 144.83. HRMS Found: m/z 369.1218. Calcd for $C_{21}H_{34}O_5SiS$−Bu^t: M−Bu^t, 369.1192.

Preparation of [(1*R*,2*R*,6*R*)-6-*t*-Butyldimethylsiloxy-2-(4-methoxybenzyloxy)methoxy-4-methyl-3-cyclohexene-1-yl]methyl *p*-Toluenesulfonate (14). To a solution of **13** (3.13 g, 7.3 mmol) in CH_2Cl_2 (56 mL) were added diisopropylethylamine (7.8 mL, 44.8 mmol) and PMBM chloride (5.9 mL, 36.4 mmol). After the solution was stirred for 3 h at room temperature, diisopropylethylamine (4.7 mL, 27 mmol) and PMBM chloride (3.5 mL, 21.6 mmol) were added. The resulting solution was stirred for 13 h. Diethylamine (6 mL) was then added and the mixture was stirred for 30 min. To this solution was added a pH 7 phosphate buffer, and the aqueous solution was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a crude product. Purification by flash column chromatography (acetone : hexane=5 : 95) gave the PMBM ether **14** (4.15 g, 98%) as a colorless oil. **14**: $[\alpha]_D^{27}$ −110.89° (c 0.571, CH_2Cl_2); IR (neat) 2954, 2929, 2856, 1514, 1365, 1250, 1178, 1097, 1036, 958, 841, 816, and 777 cm^{-1}; ^1H NMR ($CDCl_3$) δ=−0.01 (3H, s), 0.03 (3H, s), 0.81 (9H, s), 1.69 (3H, s), 1.92 (1H, dd, J=8.9, 17.2 Hz), 1.97—2.08 (1H, m), 2.22 (1H, dd, J=5.9, 17.2 Hz), 2.42 (3H, s), 3.81 (3H, s), 3.89 (1H, ddd, J=5.9, 8.9, 10.2 Hz), 4.18 (1H, d, J=9.2 Hz), 4.23 (1H, dd, J=4.0, 4.6 Hz), 4.28 (1H, dd, J=5.3, 9.2 Hz), 4.46 (1H, d, J=11.2 Hz), 4.53 (1H, d, J=11.2 Hz), 4.69 (1H, d, J=6.6 Hz), 4.74 (1H, d, J=6.6 Hz), 5.62 (1H, bs), 6.88 (2H, d, J=8.6 Hz), 7.28 (2H, d, J=8.6 Hz), 7.31 (2H, d, J=8.3 Hz), and 7.77 (2H, d, J=8.3 Hz); ^{13}C NMR ($CDCl_3$) δ=−5.12, −4.15, 17.79, 21.55, 23.17, 25.63, 40.38, 45.29, 55.24, 65.54, 69.02, 69.79, 93.68, 113.77, 121.04, 127.98, 129.56, 129.76, 129.96, 132.79, 136.80, 144.62, and 159.16.

Preparation of (1*R*,2*S*,6*R*)-6-*t*-Butyldimethylsiloxy-2-(4-methoxybenzyloxy)methoxy-4-methyl-3-cyclohexene-1-acetonitrile (15). To a solution of **14** (4.15 g, 7.2 mmol) in DMSO (33 mL) was added NaCN (0.55 g, 95% purity, 10.7 mmol), and the solution was heated to 90—100 °C for 9 h. The reaction mixture was poured into ice-cold water and the organic materials were extracted three times with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (EtOAc : hexane=7 : 93) to give the nitrile **15** (2.76 g, 89%) as a colorless oil. **15**: $[\alpha]_D^{27}$ −183.85° (c 0.864, CH_2Cl_2); IR (neat) 2954, 2931, 2891, 2858, 2249, 1514, 1250, 1099, 1034, 839, and 777 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.086 (3H, s), 0.093 (3H, s), 0.90 (9H, s), 1.72 (3H, s), 1.92—2.05 (2H, m), 2.29 (1H, dd, J=5.6, 17.2 Hz), 2.47 (1H, dd, J=10.6, 16.5 Hz), 2.71 (1H, dd, J=4.6, 16.5 Hz), 3.80 (3H, s), 3.89 (1H, ddd, J=5.6, 8.9, 10.2 Hz), 4.30 (1H, dd, J=4.3, 4.3 Hz), 4.57 (2H, s), 4.79 (1H, d, J=6.8 Hz), 4.87 (1H, d, J=6.8 Hz), 5.66 (1H, bs), 6.88 (2H, d, J=8.6 Hz), and 7.30 (2H, d, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ=−4.90, −4.11, 16.12, 17.88, 23.18, 25.72, 40.49, 43.22, 55.20, 67.24, 69.38, 71.45, 93.50, 113.77, 119.61, 120.68, 129.60, 129.78, 137.38, and 159.21. HRMS Found: m/z 374.1779. Calcd for $C_{24}H_{37}O_4NSi$−Bu^t: M−Bu^t, 374.1788.

Preparation of (1*S*,2*S*,6*R*)-6-Hydroxy-2-(4-methoxybenzyloxy)methoxy-4-methyl-3-cyclohexene-1-acetonitrile (16). To a solution of **15** (2.76 g, 6.4 mmol) in THF (150 mL) was added Bu_4^nNF (9.65 mL of a 1 M solution in THF, 9.65 mmol) at 0 °C, and the mixture was stirred at 0 °C for 4 h. The reaction was quenched with pH 7 phosphate buffer and the aqueous layer was extracted three times with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash column chromatography (EtOAc : hexane=2 : 3) to give the alcohol **16** (2.03 g) quantitatively as a colorless oil. **16**: $[\alpha]_D^{28}$ −214.79° (c 0.635, CH_2Cl_2); IR (neat) 3464, 2935, 2912, 2249, 1612, 1514, 1250, 1176, 1159, 1097, 1032, and 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.73 (3H, s), 1.90—2.04 (2H, m), 2.26 (1H, bs), 2.38 (1H, dd, J=5.6, 17.5 Hz), 2.58 (1H, dd, J=9.6, 16.8 Hz), 2.75 (1H, dd, J=5.0, 16.8 Hz), 3.80 (3H, s), 3.92 (1H, ddd, J=5.6, 8.9, 10.2 Hz), 4.27 (1H, dd, J=4.3, 4.3 Hz), 4.55 (2H, s), 4.77 (1H, d, J=6.9 Hz), 4.86 (1H, d, J=6.9 Hz), 5.66 (1H, bs), 6.88 (2H, d, J=8.6 Hz), and 7.29 (2H, d, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ=15.87, 23.04, 39.91, 42.50, 55.20, 66.38, 69.36, 71.77, 93.39, 113.78, 119.68, 120.70, 129.61, 137.22, and 159.19. HRMS Found: m/z 317.1626. Calcd for $C_{18}H_{23}O_4N$: M, 317.1627.

Preparation of (1*S*,2*S*,6*R*)-6-Hydroxy-2-(4-methoxybenzyloxy)methoxy-4-methyl-3-cyclohexene-1-acetic Acid (17). To a solution of **16** (2.03 g, 6.4 mmol) in EtOH (13 mL) was added an aqueous solution of KOH (10.4 mL of a 17% solution in H_2O, 35.3 mmol), and the solution was heated to reflux for 12 h. After concentration of the reaction mixture under reduced pressure, the residue was brought to pH 2 at 0 °C with 1 M H_2SO_4. The resulting mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The crude product was purified by recrystallization from Et_2O to afford the hydroxy acid **17** (2.09 g, 97%) as colorless crystals. **17**: Mp 113.4—114.7 °C (Et_2O); $[\alpha]_D^{27}$ −181.71° (c 0.607, MeOH); IR (KBr) 3201, 2958, 2935, 2910, 2249, 1680, 1514, 1284, 1275, 1248, 1173, 1163, 1097, 1034, 1007, and 812 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.72 (3H, s), 1.98 (1H, dd, J=8.9, 17.5 Hz), 2.14—2.25 (1H, m), 2.40 (1H, dd, J=5.6, 17.5 Hz), 2.60 (1H, dd, J=6.3, 16.5 Hz), 2.69 (1H, dd, J=6.6, 16.5 Hz), 3.80 (3H, s), 3.97 (1H, ddd, J=5.6, 8.9, 10.2 Hz), 4.19 (1H, dd, J=3.6, 4.0 Hz), 4.49 (1H, d, J=11.5 Hz), 4.54 (1H, d, J=11.5 Hz), 4.69 (1H, d, J=6.9 Hz), 4.80 (1H, d, J=6.9 Hz), 5.61 (1H, bs), 6.87 (2H, d, J=8.6 Hz), and 7.26 (2H, d, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ=23.15, 33.16, 39.86, 42.21, 55.26, 67.53, 69.22, 73.44, 93.33, 113.82, 121.13, 129.60, 129.74, 137.04, 159.23, and 178.78. HRMS Found: m/z 318.1443. Calcd for $C_{18}H_{24}O_6$−H_2O: M−H_2O, 318.1467. Found: C, 64.32; H, 7.24%. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19%.

Preparation of (3a*R*,4*S*,7a*S*)-3a,4,7,7a-Tetrahydro-4-(4-methoxybenzyloxy)methoxy-6-methyl-2(3*H*)-benzofuranone (18). To a solution of **17** (2.09 g, 6.2 mmol) and Ph_3P (3.26 g, 12.4 mmol) in THF (53 mL) was

added a THF solution (12 mL) of diethyl azodicarboxylate (2.17 g, 12.4 mmol) dropwise over a period of 35 min at −30 °C. The mixture was stirred at −30—−20 °C for 1 h 40 min. After the addition of pH 7 phosphate buffer, the organic materials were extracted three times with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude products were purified by flash column chromatography (EtOAc : hexane = 1 : 4) to give the lactone **18** (1.98 g) quantitatively as colorless crystals. **18**: Mp 31.0—31.5 °C; $[\alpha]_D^{27}$ −51.47° (*c* 0.748, CH_2Cl_2); IR (KBr) 2941, 2937, 1774, 1514, 1250, 1174, 1047, 1034, and 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.78 (3H, s), 2.27 (1H, dd, *J*=5.9, 17.1 Hz), 2.43 (1H, dd, *J*=2.9, 17.1 Hz), 2.54 (1H, dd, *J*=9.8, 18.1 Hz), 2.68 (1H, dd, *J*=5.4, 18.1 Hz), 2.90—3.02 (1H, m), 3.81 (3H, s), 4.22 (1H, bs), 4.55 (2H, s), 4.75 (1H, d, *J*=6.8 Hz), 4.81 (1H, d, *J*=6.8 Hz), 4.89 (1H, ddd, *J*=2.9, 5.9, 7.8 Hz), 5.66 (1H, bs), 6.89 (2H, d, *J*=8.3 Hz), and 7.26 (2H, d, *J*=8.3 Hz); ^{13}C NMR ($CDCl_3$) δ=23.20, 30.64, 33.19, 37.29, 55.22, 69.45, 71.14, 77.23, 93.10, 113.80, 122.93, 129.43, 129.51, 135.60, 159.26, and 177.03. HRMS Found: *m/z* 318.1454. Calcd for $C_{18}H_{22}O_5$: M, 318.1467. Found: C, 67.80; H, 6.95%. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97%.

Preparation of (3a*S*,7a*S*)-3,3a,7,7a-Tetrahydro-6-methyl-2,4-benzofurandione (19). To a solution of **18** (0.9 g, 2.8 mmol) in CH_2Cl_2 (80 mL) were added 0.2 M pH 7 phosphate buffer (8 mL), Bu^tOH (8 mL), and DDQ (2.56 g, 11.3 mmol). The mixture was stirred for 16.5 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$; the mixture was then diluted with CH_2Cl_2. The resulting suspension was filtered through a Celite pad and the filtrate was extracted twice with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated. The crude product was chromatographed on a silica gel (acetone : CH_2Cl_2 = 5 : 95) and then recrystallized from Et_2O to give the enone **19** (410 mg, 87%) as colorless crystals. **19**: Mp 123.6—129.9 °C (Et_2O); $[\alpha]_D^{27}$ −60.43° (*c* 0.775, CH_2Cl_2); IR (KBr) 2950, 1767, 1662, 1439, 1225, 1169, 1142, 1051, 978, 920, and 816 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.04 (3H, s), 2.69—2.89 (2H, m), 2.83 (1H, dd, *J*=9.3, 17.6 Hz), 3.03 (1H, dd, *J*=2.4, 17.6 Hz), 3.05 (1H, ddd, *J*=2.4, 5.4, 9.3 Hz), 5.04 (1H, ddd, *J*=2.4, 4.9, 5.4 Hz), and 6.07 (1H, bs); ^{13}C NMR ($CDCl_3$) δ=24.46, 32.15, 33.44, 43.40, 125.97, 158.01, 174.61, 194.84, and 205.88. HRMS Found: *m/z* 166.0629. Calcd for $C_9H_{10}O_3$: M, 166.0630. Found: C, 65.22; H, 6.23%. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07%.

Preparation of (3a*R*,7a*S*)-3a,4,7,7a-Tetrahydro-4-hydroxy-6-methyl-2(3*H*)-benzofuranone (20). To a suspension of anhydrous $CeCl_3$ (594 mg, 2.41 mmol) in MeOH (16 mL) was added the enone **19** (400 mg, 2.41 mmol); the mixture was stirred for 2 h to become a solution. The solution was cooled to −78 °C and $NaBH_4$ (96 mg, 90% purity, 2.28 mmol) was added in portions over a 10-min period. After the mixture was stirred at −78 °C for 20 min, the reaction mixture was diluted with EtOAc and quenched with pH 7 phosphate buffer. The organic materials were extracted five times with EtOAc and the extracts were dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by flash column chromatography (acetone : CH_2Cl_2 = 1 : 9) to afford the alcohol **20** (395 mg, 98%, the α-isomer : the β-isomer = 84 : 16) as a colorless oil. The ratio of the α and β-isomers was determined by 270 MHz ^1H NMR. **20**: ^1H NMR ($CDCl_3$) δ=1.77 (3H, s), 2.24—2.88 (6H, m), 4.03 (0.16H, bs), 4.27, (0.84H, bs), 4.88 (1H, ddd, *J*=2.9, 6.4, 6.8 Hz), and 5.67 (1H, bs).

Preparation of (3a*R*,4*S*,5*S*,6*R*,7a*S*)-5,6-Epoxy-3a,4,5,6,7,7a-hexahydro-4-hydroxy-6-methyl-2(3*H*)-benzofuranone (3). To a solution of the alcohol **20** (395 mg, 2.35 mmol) in CH_2Cl_2 (20 mL) was added a solution of MCPBA (1.1 g, 3.54 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After the mixture was stirred at 0 °C for 38 h, the reaction was quenched with 2-methyl-2-butene (0.6 mL) and stirred for 2 h at room temperature. After evaporation of the solvent, the crude residue was purified by flash column chromatography (acetone : CH_2Cl_2 = 1 : 4) to afford the epoxy alcohol **3** (224 mg, 52%) and the mixture of its stereoisomers (199 mg, 46%). **3**: >98% ee; mp 116.1—119.2 °C; $[\alpha]_D^{28}$ −12.23° (*c* 1.00, MeOH); IR (KBr) 3429, 2956, 2926, 1749, 1196, 1101, 1057, 1018, 987, and 843 cm^{-1}; ^1H NMR (acetone-d_6) δ=1.29 (3H, s), 2.13 (2H, d, *J*=3.4 Hz), 2.36 (1H, dd, *J*=11.7, 18.6 Hz), 2.83 (1H, dd, *J*=5.9, 18.6 Hz), 3.01—3.15 (1H, m), 3.08 (1H, s), 4.32 (1H, dd, *J*=4.4, 6.8 Hz), 4.50 (1H, d, *J*=4.4 Hz), and 4.73 (1H, dt, J_d=10.3 Hz, J_t=3.4 Hz); ^{13}C NMR (CD_3OD) δ=22.14, 32.15, 32.45, 37.02, 58.49, 63.50, 67.17, 78.00, and 180.18. Found: C, 58.83; H, 6.49%. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57%. The relative stereochemistry was determined by 500 MHz NMR 2D-NOESY (Fig. 1).

By the same procedure described in the synthesis of the MTPA ester of **12**, the epoxy alcohol **3** was converted to the (*R*)- and (*S*)-MTPA esters, **27R** and **27S**, respectively.

Preparation of (3a*S*,4*S*,5*S*,6*R*,7a*S*)-5,6-Epoxy-3a,4,5,6,7,7a-hexahydro-6-methyl-4-triethylsiloxy-2(3*H*)-benzofuranone (21). To a solution of triethylsilyl chloride (0.11 mL, 0.66 mmol), triethylamine (0.11 mL, 0.79 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (4.2 mg) in CH_2Cl_2 (1.5 mL) was added the epoxy alcohol **3** (90 mg, 0.49 mmol) at 0 °C. After the mixture was stirred for 30 min at room temperature, the reaction was quenched with diluted aqueous NH_4Cl. The crude product was extracted three times with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (EtOAc : hexane = 1 : 4) to afford the silyl ether **21** (146 mg) quantitatively as colorless crystals. **21**: Mp 45.5—46.6 °C; $[\alpha]_D^{30}$ +4.01° (*c* 1.128, CH_2Cl_2); IR (KBr) 2956, 2939, 2912, 2877, 1751, 1201, 1099, 1074, 1063, 1020, 818, 744, and 729 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.62 (6H, q, *J*=7.6 Hz), 0.97 (9H, t, *J*=7.6 Hz), 1.35 (3H, s), 1.96 (1H, dd, *J*=4.9, 16.1 Hz), 2.31 (1H, d, *J*=16.1 Hz), 2.42 (1H, dd, *J*=11.2, 18.6 Hz), 2.85—2.98 (1H, m), 3.03 (1H, s), 3.09 (1H, dd, *J*=5.9, 18.6 Hz), 4.20 (1H, d, *J*=6.8 Hz), and 4.70 (1H, ddd, *J*=1.5, 4.9, 10.3 Hz); ^{13}C NMR ($CDCl_3$) δ=4.62, 6.62, 21.85, 30.86, 31.68, 36.52, 56.82, 62.30, 67.08, 75.06, and 176.73. HRMS Found: *m/z* 269.1218. Calcd for $C_{15}H_{26}O_4Si$−Et: M−Et, 269.1209. Found: C, 60.29; H, 9.06%. Calcd for $C_{15}H_{26}O_4Si$: C, 60.37; H, 8.78%.

Preparation of (3*S*,3a*S*,4*S*,5*S*,6*R*,7a*S*)-5,6-Epoxy-3a,4,5,6,7,7a-hexahydro-6-methyl-3-(4-methyl-3-pentenyl)-4-triethylsiloxy-2(3*H*)-benzofuranone (23). To a solution of 2,2,6,6-tetramethylpiperidine (0.11 ml, 0.65 mmol) in THF (1.5 mL) was added Bu^nLi (0.34 ml of a 1.6 M hexane solution, 0.54 mmol) dropwise at −20 °C,

and the mixture was stirred for 15 min. A THF solution (2 mL) of **21** (124 mg, 0.42 mmol) was added to the above solution dropwise at −78 °C over a period of 30 min. After stirring for 1 h, a THF solution (1.5 mL) of 5-iodo-2-methyl-2-pentene (**22**) (227 mg, 1.08 mmol) and HMPA (0.07 mL) was added in one portion. The reaction mixture was stirred at −78 °C for 1 h and then the reaction temperature was raised to 0 °C over a period of 4 h. The reaction was quenched with pH 7 phosphate buffer and the organic materials were extracted three times with Et_2O. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated. The crude residue was purified by flash column chromatography (EtOAc : hexane=15 : 85) to give **23** (101 mg, 64%) as a colorless oil. **23**: $[\alpha]_D^{26}$ −39.77° (*c* 1.115, CH_2Cl_2); IR (neat) 2956, 2935, 2916, 2877, 1763, 1379, 1194, 1099, 1074, 1057, 1018, 1003, 812, and 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.65 (6H, q, J=7.8 Hz), 0.99 (9H, t, J=7.8 Hz), 1.34 (3H, s), 1.60 (3H, s), 1.58—1.69 (2H, m), 1.67 (3H, s), 1.94 (1H, dd, J=5.4, 16.1 Hz), 2.00—2.18 (2H, m), 2.28 (1H, d, J=16.1 Hz), 2.58 (1H, ddd, J=5.4, 6.8, 10.3 Hz), 2.98 (1H, s), 3.12 (1H, dt, J_d=5.4, J_t=6.4 Hz), 4.26 (1H, d, J=6.8 Hz), 4.60 (1H, ddd, J=1.0, 5.4, 10.3 Hz), and 5.09 (1H, t, J=7.3 Hz); ^{13}C NMR ($CDCl_3$) δ=4.78, 6.78, 17.59, 21.93, 24.66, 25.64, 31.74, 33.89, 41.98, 42.82, 56.75, 62.23, 67.76, 73.37, 123.43, 132.17, and 179.12. HRMS Found: m/z 380.2391. Calcd for $C_{21}H_{36}O_4Si$: M, 380.2383.

Preparation of (3*S*,3a*S*,4*S*,5*S*,6*R*,7a*S*)-5,6-Epoxy-3a,4,5,6,7,7a-hexahydro-6-methyl-3-(4-methyl-3-pentenyl)-3-phenylseleno-4-triethylsiloxy-2(3*H*)-benzofuranone (24). To a solution of potassium bis(trimethylsilyl)amide (1.56 mL of a 0.5 M toluene solution, 0.78 mmol) in THF (1 mL) was added a THF solution (1.5 mL) of **23** (97 mg, 0.26 mmol) dropwise at −100 °C. After stirring for 10 min, a solution of diphenyl diselenide (399 mg, 1.28 mmol) and HMPA (0.16 mL) in THF (0.84 mL) was added dropwise at −100 °C. The mixture was stirred at −100 °C for 1.5 h and the temperature was raised to −20 °C over a period of 1 h. After additional stirring at −20 °C for 45 min, the reaction mixture was cooled to −78 °C, and oxygen was bubbled into the solution for 1 h. The reaction was quenched with pH 7 phosphate buffer. The organic materials were extracted three times with Et_2O and the combined extracts were washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by flash column chromatography (EtOAc : hexane=1 : 9) to afford the starting material **23** (28 mg, 29%) and the selenide **24** (81 mg, 58%) as colorless crystals. **24**: Mp 96.3—97.1 °C (hexane); $[\alpha]_D^{26}$ −36.43° (*c* 1.615, CH_2Cl_2); IR (KBr) 2960, 2943, 2912, 2879, 1751, 1190, 1134, 1111, 982, 957, 914, and 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.62 (6H, q, J=7.8 Hz), 0.94 (9H, t, J=7.8 Hz), 1.36 (3H, s), 1.67 (3H, s), 1.70 (3H, s), 1.87—2.10 (3H, m), 2.13—2.31 (2H, m), 2.45 (1H, dd, J=3.9, 7.3 Hz), 2.62—2.79 (1H, m), 2.97 (1H, d, J=2.9 Hz), 4.40 (1H, dd, J=2.9, 3.9 Hz), 4.49 (1H, ddd, J=6.8, 7.3, 7.3 Hz), 5.11 (1H, t, J=6.8 Hz), 7.28—7.45 (3H, m), and 7.63 (2H, d, J=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ=4.76, 6.76, 17.92, 22.37, 25.12, 25.66, 30.87, 32.83, 48.63, 54.25, 54.77, 59.71, 66.45, 72.62, 123.67, 126.11, 129.04, 129.79, 131.99, 137.79, and 175.47. HRMS Found: m/z 536.1869. Calcd for $C_{27}H_{40}O_4SeSi$: M, 536.1861. Found: C, 60.82; H. 7.59%. Calcd for $C_{27}H_{40}O_4SeSi$: C, 60.54; H, 7.53%.

Preparation of (+)-Paniculide A (2). To a solution of **24** (26 mg, 0.049 mmol) and pyridine (18 mL, 0.22 mmol) in CH_2Cl_2 (2 mL) was added H_2O_2 (29 mg of 30% H_2O_2 in 24 mL H_2O) at 0 °C. After stirring for 30 min at room temperature, the reaction mixture was diluted with Et_2O and washed with brine. The organic layer was dried over Na_2SO_4 and evaporated. The residue was directly used for the next reaction.

The crude product (24 mg) was dissolved in an ice-cold mixture of AcOH–THF–H_2O (3 : 2 : 2, v/v/v) and the solution was stirred at 0 °C for 5.5 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (EtOAc : hexane=2 : 3) to afford (+)-paniculide A (**2**) (11 mg, 87%) as colorless crystals. **2**: Mp 118.8—121.1 °C (Et_2O); $[\alpha]_D^{29}$ +14.98° (*c* 0.747, MeOH); IR ($CHCl_3$) 3370—3600, 3004—2860, 1753, 1682, 1443, 1383, 1342, 1105, 1057, 1007, 864, 719, and 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.45 (3H, s), 1.58, (3H, s), 1.77 (3H, s), 1.85 (1H, dd, J=10.3, 14.6 Hz), 2.10—2.34 (2H, m), 2.48—2.67 (4H, m), 3.26 (1H, d, J=2.4 Hz), 4.72 (1H, dd, J=8.3, 10.3 Hz), 4.94 (1H, d, J=11.2 Hz) and 5.20 (1H, t, J=7.8 Hz); ^{13}C NMR ($CDCl_3$) δ=17.79, 23.47, 23.63, 25.63, 26.02, 36.46, 58.53, 64.57, 68.38, 75.20, 122.84, 129.11, 135.49, 158.33, and 173.37. HRMS Found: m/z 264.1358. Calcd for $C_{15}H_{20}O_4$: M, 264.1362. Found: C, 68.23; H, 7.61%. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63%. These spectral data of (+)-**2** agreed with those of the literature.[3,4]

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