Total Synthesis of (−)-Heliannuol E

Kenji Sato, Tomoyuki Yoshimura, Mitsuru Shindo, and Kozo Shishido*

Institute for Medicinal Resources, University of Tokushima, 1-78 Sho-machi, Tokushima 770-8505, Japan

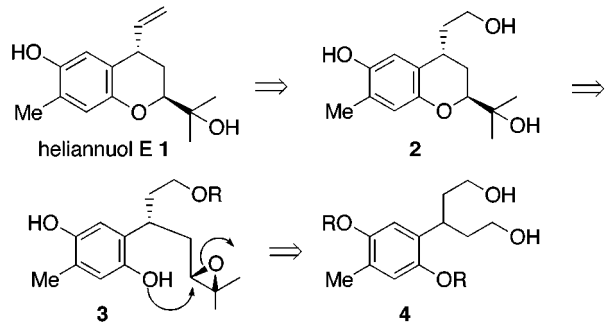
Shishido@ph2.tokushima-u.ac.jp

Received July 27, 2000

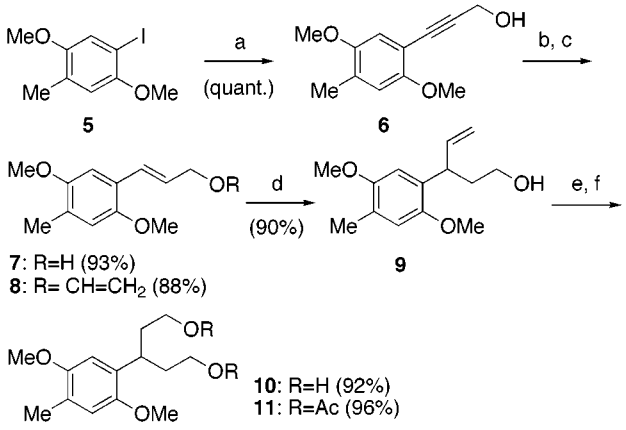
Heliannuol E (**1**)[1] is a novel heliannane-type sesquiterpenoid, which was isolated from the extracts of *Helianthus annuus* L. cv. SH-222 by Macías and co-workers in 1999. The gross structure and relative stereochemistry were assigned on the basis of extensive spectral studies, including $^1H-^1H$ COSY, $^1H-^{13}C$ HETCOR, and NOE experiments. However, the absolute stereochemistry of the two stereogenic centers at C_2 and C_4 has never been established. On the basis of the bioassay results, it would appear that heliannuol E is intricately involved in the allelopathic action[2] of cultivated sunflowers. Its irregular terpenoid structure and significant biological activity thus prompted our interest in a total synthesis of this compound. Our strategy is illustrated in Scheme 1. We thought that heliannuol E might be derived from a selective dehydration of the triol **2**, which could be constructed by a 6-exo cyclization[3] of the configurationally defined epoxy hydroquinone **3**. The epoxide **3** in turn would be prepared through a chemoenzymatic desymmetrization[4] of *σ*-symmetrical 3-aryl-1,5-pentanediol **4** or the corresponding diacetate.

3-Arylpropargyl alcohol **6**, prepared by Sonogashira coupling[5] of the iodide **5**[6] with propargyl alcohol (Scheme 2), was reduced with $LiAlH_4$ to give the cinnamyl alcohol **7**. Reductive Claisen rearrangement[7] of the vinyl ether **8** using $^iBu_3Al$ provided the alkenyl alcohol **9**, which was subjected to sequential hydroboration−oxidation and acetylation to furnish the diol **10** and the diacetate **11** in good overall yield. Next we tried to determine the optimum conditions for the desymmetrization of the required substrates **10** and **11** by a chemoenzymatic reaction. After several attempts to find the most suitable

Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) propargyl alcohol, $(Ph_3P)_2PdCl_2$, CuI, Et_2NH, benzene, rt (room temperature); (b) $LiAlH_4$, THF, rt; (c) CH_2=CHOEt, $Hg(OAc)_2$, reflux; (d) $^iBu_3Al$, CH_2Cl_2, rt; (e) BH_3·SMe_2, THF, 0 °C, and then NaOH, H_2O_2, rt; (f) Ac_2O, pyridine, rt.

enzyme, lipase AK,[8] originating from *Pseudomonas fluorescens* mediated transesterification of **10** using vinyl acetate as an acetyl donor in Et_2O at room temperature, was found to produce the monoacetate (+)-**12** in 34% yield with 78% ee (Sheme 3), which was determined by HPLC on a Chiralcel OD column. Hoping to improve the ee and chemical yield, we then examined the asymmetric hydrolysis of the diacetate **11**. Upon treatment with lipase AK in phosphate buffer for 3.5 days, **11** gave the enantiomeric monoacetate (−)-**12** with 89% ee in 75% yield. To establish the absolute configuration of (−)-**12**, it was converted into the diastereomeric amides **14** via condensation of the carboxylic acid **13** with (*R*)- and (*S*)-phenylglycine methyl ester (PGME) by a conventional five-step sequence as shown in Scheme 4. The positive and negative values are oriented systematically on the right and left side of PGME plane, respectively, and the absolute configuration was determined to be *S*. [9]

Chain elongation of the monoacetate (*S*)-**12** by sequential oxidation, Wittig olefination, and reductive deacetylation gave the alcohol **16** (Scheme 5), which was protected as the *tert*-butyldiphenylsilyl (TBDPS) ether and

(1) Macías, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. *Tetrahedron Lett.* **1999**, *40*, 4725−4728.

(2) A definition of allelopathy: The inhibition of growth in one species of plants by chemicals produced by another species. (a) Rice, E. L. *Allelopathy*, 2nd ed.; Academic Press: New York, 1984. (b) Macías, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G.; Fronczek, F. R. *Tetrahedron Lett.* **1993**, *34*, 1999−2002. (c) Macías, F. A.; Molinillo, J. M. G.; Varela, R. M.; Torres, A.; Fronczek, F. R. *J. Org. Chem.* **1994**, *59*, 8261−8266.

(3) For the 7-exo cyclization of a phenolic epoxide leading to the total synthesis of (±)-heliannuol D, see: Vyvyan, J. R.; Looper, R. E. *Tetrahedron Lett.* **2000**, *41*, 1151−1154. For the competitive 7-exo and 8-endo cyclization leading to the total syntheses of (−)-heliannuol D and (+)-heliannuol A, see: Takabatake, K.; Nishi, I.; Shindo, M.; Shishido, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1807−1808.

(4) Faber, K. In *Biotransformations in Organic Chemistry*; Springer-Verlag: Berlin, Heidelberg, **1997**.

(5) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467−4470. (b) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 672−630.

(6) Hubig, S. M.; Jung, W.; Kochi, J. K. *J. Org. Chem.* **1994**, *59*, 6233−6244.

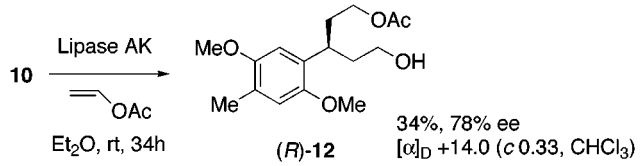
(7) (a) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *20*, 3985−3988. (b) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Bull. Soc. Chem. Jpn.* **1984**, *57*, 446−451. (c) Mori, I.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron* **1984**, *40*, 4013−4018.

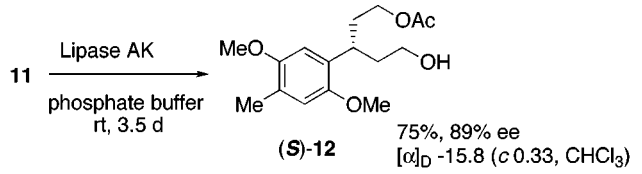
(8) (a) Shishido, K.; Haruna, S.; Yamamura, C.; Iitsuka, H.; Nemoto, H.; Shinohara, Y.; Shibuya, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2617−2622. (b) Bando, T.; Shishido, K. *Heterocycles* **1997**, *46*, 111−114.

(9) Yabuuchi, T.; Kusumi, T. *J. Org. Chem.* **2000**, *65*, 397−404.

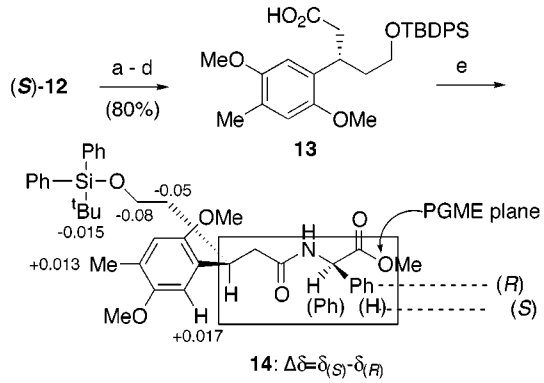
10.1021/jo0011437 CCC: $20.00
Published on Web 12/09/2000

Scheme 3





Scheme 4[a]

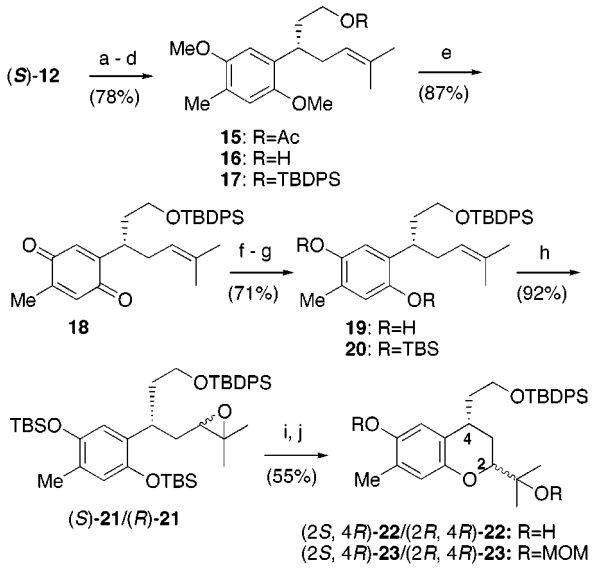


[a] Reagents and conditions: (a) TBDPSCl, imidazole, 4-DMAP, CH_2Cl_2, rt; (b) $LiAlH_4$, THF, rt; (c) Dess−Martin periodinate, CH_2Cl_2, rt; (d) PDC, DMF, rt; (e) (*R*)- or (*S*)-phenylglycine methyl ester, PyBOP, HOBT, ET_3N, CH_2Cl_2, 0 °C.

oxidized with CAN to provide the quinone **18**. Reduction of the quinone with $Na_2S_2O_4$ followed by protection of the phenolic hydroxyl groups as di-*tert*-butyldimethylsilyl (TBS) ether produced **20** in good overall yield. Attempted diastereoselective dihydroxylation employing AD-mix-α[10] for the construction of the other stereogenic center present in **1** yielded the diol as a 1:1 mixture. Discouraged by this result, we next turned our attention to the direct epoxidation of **20**. Treatment with *m*CPBA in CH_2Cl_2 and phosphate buffer provided an inseparable mixture of the epoxides (*S*)-**21**/(*R*)-**21** in a 1:1 ratio in 92% yield. The crucial cyclization leading to the compound with a basic carbon skeleton of **1** was realized by treating the mixture with basic conditions (K_2CO_3 in MeOH) to give an inseparable mixture of (2*S*,4*R*)-**22**/(2*R*,4*R*)-**22** in 85% yield. Since the introduction of a vinyl functionality at the benzylic position by sequential desilylation and dehydration of **22** proved to be troublesome, the two hydroxyl groups were protected as MOM ethers. Fortunately, the di-MOM ethers could be separated by a preparative HPLC to give (2*S*,4*R*)-**23** and (2*R*,4*R*)-**23** in 30% and 28% yield, respectively. At this stage, the stereochemistry of (2*R*,4*R*)-**23** was determined by NOE experiments as shown in Figure 1.

The desired isomer (2*S*,4*R*)-**23** was desilylated with tetra-*n*-butylammonium fluoride to give the primary alcohol **24** (Scheme 6), which was sequentially treated under the conditions for dehydration developed by Grieco[11] and with 6 N HCl to provide, via the selenide **25**,

Scheme 5[a]



[a] Reagents and conditions: (a) Dess−Martin oxdn, CH_2Cl_2, rt; (b) $Ph_3P^{+i}PrI^-$, ^{t}BuOK, THF, rt; (c) $LiAlH_4$, THF, rt; (d) TBDPSCl, imidazole, 4-DMAP, CH_2Cl_2, rt; (e) CAN, MeCN, H_2O, 0 °C; (f) $Na_2S_2O_4$, THF, H_2O, 0 °C; (g) TBSCl, imidazole, CH_2Cl_2, rt; (h) *m*CPBA, phosphate buffer, 0 °C; (i) K_2CO_3, MeOH, rt; (j) MOMCl, ^{i}Pr$_2$NEt, rt.

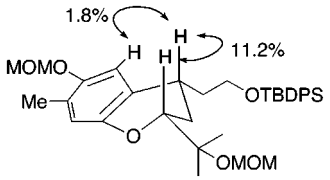
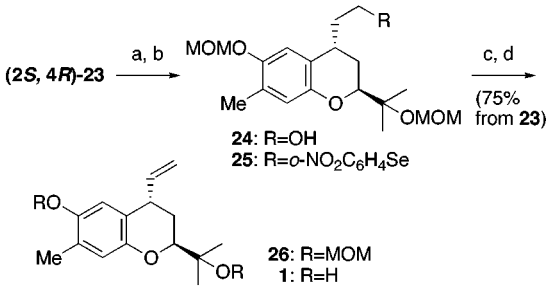


Figure 1. NOE for (2*R*,4*R*)-**23**.

Scheme 6[a]



[a] Reagents and conditions: (a) ^{n}Bu$_4$NF, THF, rt; (b) *o*-$NO_2C_6H_4SeCN$, ^{n}Bu$_3$P, THF, rt; (c) H_2O_2, THF, rt; (d) 6N HCl, THF, rt.

heliannuol E (**1**) in 68% overall yield from (2*S*,4*R*)-**23** for the four steps. ^{1}H and ^{13}C NMR, IR, and mass spectral data as well as optical rotation, $[\alpha]_D$ −69.8 (*c* 0.1, $CHCl_3$) [for the natural **1**[1], $[\alpha]_D$ −68.6 (*c* 0.1, $CHCl_3$)], were indistinguishable from those of the natural product. In conclusion, the first total synthesis of a novel heliannane sesquiterpenoid (−)-heliannuol E has been accomplished and the absolute configurations of the two stereogenic centers were determined to be 2*S* and 4*S*, respectively. The synthetic route developed here holds considerable promise for the synthesis of related natural products.

(10) Kolb, H. C.; Vannieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

(11) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485−1486.

Experimental Section

General Methods. ^{1}H NMR were measured in $CDCl_3$ solution and referenced to TMS (0.00 ppm) using Bruker AM400, JEOL GSX400 (400 MHz), and JEOL AL300 (300 MHz) spectrophotometers, unless otherwise noted. ^{13}C NMR were measured in $CDCl_3$ solution and referenced to $CDCl_3$ (77.0 ppm) using Bruker AM400 (100 MHz), JEOL GSX400 (100 MHz), and JEOL AL300 (75 MHz) spectrometers. IR spectra were recorded on JASCO FT/IR-410 spectrometer. Mass spectra were obtained on a JEOL GX303. Column chromatography was performed on silica gel, Fuji Silysia Chemical BW-127ZH (100−270 mesh). Thin-layer chromatography was performed on precoated plates (0.25 mm, silica gel Merck Kieselgel 60 F_{245}). Melting points were measured with a Büchi 535 melting point apparatus and are uncorrected. All reactions were performed in oven-dried glassware under positive pressure of argon, unless otherwise noted. Reaction mixtures were stirred magnetically. Solutions of alkyllithium reagents were transferred by syringe or cannula and were introduced into reaction vessels through rubber septa.

3-(2,5-Dimethoxy-4-methylphenyl)-2-propyn-1-ol (6). To a flask charged with bis(triphenylphosphine)palladium(II) chloride (1.45 g, 2.06 mmol) and copper iodide (2.62 g, 13.7 mmol) was added a solution of 1-iodo-2,5-dimethoxy-4-methylbenzene[6] (19.1 g, 68.7 mmol) in benzene (400 mL), and the mixture was then cooled to 0 °C. To the resulting red solution were added diethylamine (36.5 mL, 481 mmol) and propargyl alcohol (20.0 mL, 343 mmol). After being stirred for 20 h at 25 °C, the reaction was quenched with 30 mL of saturated NH_4Cl solution and extracted with ether. The combined organic layer was washed with brine, dried over Na_2SO_4. Removal of the solvent and column chromatography (silica gel, hex/AcOEt = 75/25) gave the alcohol **6** (14.2 g, quantitative) as colorless crystals: mp 85−87 °C; IR ($CHCl_3$) 1216, 2222, 3605 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) δ 2.22 (3H, s), 3.77 (3H, s), 3.84 (3H, s), 4.53 (2H, s), 6.69 (1H, s), 6.84 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6 (q), 51.6 (q), 55.8 (q), 56.3 (q), 82.0 (s), 90.7 (s),108.7 (s) 113.9 (d), 114.9 (d), 129.0 (s), 151.3 (s), 154.0 (s); MS (EI) *m*/*z* 206 (base peak, M^+); HRMS calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0949.

3-(2,5-Dimethoxy-4-methylphenyl)-2*E*-propenol (7). To a suspension of lithium aluminum hydride (22.5 g, 0.593 mol) in THF (2.0 L) at 0 °C was added a solution of **6** (122.3 g, 0.593 mol) in THF (400 mL) dropwise. After the reaction mixture was stirred for 2 h at room temperature, water was added. The resulting mixture was filtered through a short pad of Celite and washed with ether, and the filtrate was dried over Na_2SO_4. Removal of the solvent and column chromatography (silica gel, hex/AcOEt = 75/25) gave **7** (120.1 g, 98%) as a pale yellow oil: IR ($CHCl_3$) 973, 1045, 1218, 3607 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) δ 2.20 (3H, s), 3.80 (3H, s), 3.81 (3H, s), 4.32 (2H, d, J = 6.2 Hz), 6.34 (1H, dt, J = 16.0, 6.2 Hz), 6.70 (1H, s), 6.90 (1H, d, J = 16.0 Hz), 6.91 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3 (q), 55.8 (q), 56.2 (q), 64.0 (t), 108.6 (d), 114.4 (d), 123.3 (s), 126.1 (d), 127.2 (s), 128.1 (d), 150.6 (s), 151.8 (s); MS (EI) *m*/*z* 208 (base peak, M^+); HRMS calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1086.

1-(2,5-Dimethoxy-4-methylphenyl)-3-(ethenyloxy)-1*E*-propene (8). A mixture of **7** (19.1 g, 91.7 mol), mercury(II) acetate (8.80 g, 27.5 mmol), and freshly distilled ethyl vinyl ether (1.2 L) was refluxed for 24 h under argon atmosphere. The mixture was poured into 5% KOH solution (300 mL), extracted with hexane, and dried over anhydrous potassium carbonate. Removal of the solvent and column chromatography (silica gel, hex/AcOEt = 95/5) gave **8** (18.9 g, 88%) as a pale yellow oil: IR (neat) 1046, 1211, 1509, 1615, 1634 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (3H, s), 3.79 (3H, s), 3.80 (3H, s), 4.05 (1H, dd, J = 6.8, 0.9 Hz), 4.28 (1H, dd, J = 14.1, 0.9 Hz), 4.40 (2H, d, J = 5.9 Hz), 6.28 (1H, dt, J = 16.4, 5.9 Hz), 6.52 (1H, dd, J = 14.1, 6.8 Hz), 6.69 (1H, s), 6.91 (1H, s), 6.95 (1H, d, J = 16.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3 (q), 55.8 (q), 56.2 (q), 69.4 (t), 87.1 (t), 108.6 (d), 114.5 (d), 123.0 (s), 123.7 (d), 127.6 (s), 128.2 (d), 150.8 (s), 151.4 (d), 151.8 (s); MS (EI) *m*/*z*: 234 (M^+), 83 (base peak); HRMS calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1261.

3-(2,5-Dimethoxy-4-methylphenyl)-4-penten-1-ol (9). A solution of triisobutylaluminum (0.96 M in hexane, 10 mL, 9.6 mmol) was added to a solution of **8** (4.8 mmol, 1.12 g) in CH_2Cl_2 at 25 °C and then stirred for 2.5 h. The mixture was diluted with ether (200 mL) and poured into 1 M HCl (60 mL). The separated organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a crude mixture. Column chromatography (silica gel, hex/AcOEt = 95/5) gave **9** (1.04 g, 92%) as a pale yellow oil: IR (neat) 1046, 1210, 1397, 1465, 1504, 1636, 3387 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) δ 1.74 (1H, dddd, J = 13.2, 9.1, 4.8, 4.8 Hz), 2.08 (1H, m), 2.20 (3H, s), 3.44 (1H, ddd, J = 11.4, 5.0, 4.8 Hz), 3.58 (1H, ddd, J = 11.4, 10.0, 5.0 Hz), 3.77 (3H, s), 3.80 (3H, s), 3.98 (1H, dt, J = 8.2, 6.8 Hz), 5.09 (1H, d, J = 10.5 Hz), 5.12 (1H, d, J = 17.3 Hz), 6.05 (1H, ddd, J = 17.3, 10.5, 6.8 Hz), 6.62 (1H, s), 6.71 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3 (q), 37.5 (t), 37.8 (d), 56.0 (q), 56.6 (q), 60.7 (t), 110.6 (d), 114.1 (t), 114.5 (d), 125.3 (s), 129.5 (s), 141.4 (d), 150.5 (d), 152.2 (s); MS (EI) *m*/*z* 236 (M^+), 191 (base peak); HRMS calcd for $C_{14}H_{20}O_3$ 236.1368, found 236.1398.

3-(2,5-Dimethoxy-4-methylphenyl)pentane-1,5-diol (10). BH_3**.**SMe_2 (90%, 9.05 mL, 85.9 mmol) was added dropwise to a stirred solution of **9** (26.0 g, 110 mmol) in dry THF (650 mL) at 0 °C. After 30 min, the solution was warmed to room temperature. After being stirred for 1.5 h, NaOH(aq) (3 N, 48.8 mL) was added dropwise at 0 °C, followed by addition of 35% aqueous H_2O_2 (14.2 mL). After being stirred for 1.5 h at room temperature, the mixture was diluted with ether, washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Column chromatography (silica gel, hex/AcOEt = 75/25) gave **10** (26.0 g, 93%) as colorless prisms: mp 67.7−68.6 °C (benzene/hexane); IR ($CHCl_3$) 1046, 1214, 1423, 1522, 3684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72−1.85 (4H, m and OH × 2 D_2O exchangeable), 1.93−2.04 (2H, m), 2.21 (3H, s), 3.36−3.43 (3H, m), 3.52−3.57 (2H, dt, J = 10.5, 4.9 Hz), 3.78 (3H, s), 3.80 (3H, s), 6.63 (1H, s), 6.72 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1 (q), 29.8 (d), 38.9 (t), 56.0 (q), 56.7 (q), 60.8 (t), 109.8 (d), 114.6 (d), 125.3 (s), 129.7 (s), 151.0 (s), 152.6 (s); MS (EI) *m*/*z* 254 (base peak, M^+); HRMS calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1526. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.91; H, 8.69.

3-(2,5-Dimethoxy-4-methylphenyl)pentamethylene Diacetate (11). A solution of **10** (21.5 g, 84.6 mmol) in pyridine (10 mL) and acetic anhydride (10 mL) was stirred for 2 h at room temperature and then concentrated in vacuo. To the residue was added water (50 mL), followed by extraction with CH_2Cl_2 (100 mL). The organic phase was washed with 5% aqueous HCl (2 × 50 mL), saturated $NaHCO_3$(aq), and brine and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (silica gel, hex/AcOEt = 95/5) provided **11** (27.2 g, 95%) as a colorless oil: IR (neat) 1045, 1241, 1467, 1506, 1737, 2954 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98 (4H, dt, J = 7.2, 6.9 Hz), 1.99 (6H, s), 2.19 (3H, s), 3.19 (1H, quint, J = 7.2 Hz), 3.73 (3H, s), 3.77 (3H, s), 3.93 (4H, t, J = 6.9 Hz), 6.58 (1H, s), 6.65 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1 (q), 20.9 (q), 32.7 (d), 34.1 (t), 56.0 (q), 56.1 (q), 66.4 (t), 110.5 (d), 114.2 (d), 125.3 (s), 128.5 (s), 151.3 (s), 151.8 (s), 171.0 (s); MS (EI) *m*/*z* 338 (M^+, base peak); HRMS calcd for $C_{18}H_{26}O_6$ 338.1729, found 338.1713.

(3*R*)-5-Hydroxy-3-(2,5-dimethoxy-4-methylphenyl)pentyl Acetate ((*R*)-12). To a solution of **10** (30 mg, 0.10 mmol) in dry ether (0.6 mL) were added lipase AK (15 mg) and vinyl acetate (0.02 mL), and the mixture was stirred at room temperature for 14 h. After filtration and removal of the solvent, the resulting oil was chromatographed (silica gel, hex/AcOEt = 75/25) to afford the enantiomerically enriched monoacetate ((*R*)-**12**) (12 mg, 34%). $[\alpha]_D$ = +14.0 (*c* 0.33, $CHCl_3$) (78% ee: Daicel, Chiral Cel OD (0.46 × 25 cm), 5% ^{i}PrOH/hex (v/v); flow rate, 0.5 mL/min; retention time, 25.72 min for (*R*), 27.95 min for (*S*); eluent detection monitored by UV absorbance at 220 nm); IR (neat) 1046, 1240, 1467, 1508, 1735, 2954, 3685 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) δ 1.66 (1H, m), 1.92−2.08 (3H, m), 1.99 (3H, s), 2.20 (3H, s), 3.34 (2H, ddd, J = 12.4, 7.2, 6.8 Hz), 3.49 (1H, m), 3.78 (6H, s), 3.95 (2H, m), 6.60 (1H, s), 6.70 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0 (q), 20.8 (q), 30.8 (d), 34.2 (t), 39.2 (t), 56.0 (q), 56.4 (q), 60.6 (t), 63.1 (q), 109.7 (d), 114.5 (d), 125.3 (s), 129.0 (s), 151.1 (s), 152.4 (s), 171.0 (s); MS (FAB) *m*/*z*: 296 (M^+, base peak); HRMS calcd for $C_{16}H_{24}O_5$ 296.1624, found 296.1613.

(3*S*)-5-Hydroxy-3-(2,5-dimethoxy-4-methylphenyl)pentyl Acetate ((*S*)-12). Lipase AK (8.2 g) was added to **11** (33.2 g, 98.1 mmol) dispersed in 0.1 M phosphate buffer (pH 7, 1.66 L), and the reaction mixture was stirred for 3.5 days at room

temperature while pH was kept constantly by addition of 1 N NaOH by means of a pH-check sheet. The mixture was filtered through a short pad of Celite and then extracted with AcOEt. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (silica gel, hex/AcOEt = 85/15) gave (*S*)-**12** (21.8 g, 75%) as a colorless oil: $[\alpha]_D = -15.8$ (*c* 0.33, $CHCl_3$) (89% ee); IR (neat) 1046, 1240, 1467, 1508, 1735, 2954, 3685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3 + D_2O$) δ 1.66 (1H, m), 1.92−2.08 (3H, m), 1.99 (3H, s), 2.20 (3H, s), 3.34 (2H, ddd, J = 12.4, 7.2, 6.8 Hz), 3.49 (1H, m), 3.78 (6H, s), 3.94 (1H, ddd, J = 11.8, 7.2, 5.8 Hz), 3.94 (1H, ddd, J = 11.8, 6.8, 6.4 Hz), 6.60 (1H, s), 6.70 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0 (q), 20.8 (q), 30.8 (d), 34.2 (t), 39.2 (t), 56.0 (q), 56.4 (q), 60.6 (t), 63.1 (q), 109.7 (d), 114.5 (d), 125.3 (s), 129.0 (s), 151.1 (s), 152.4 (s), 171.0 (s); MS (EI) *m*/*z* 296 (M^+, base peak); HRMS calcd for $C_{16}H_{24}O_5$ 296.1624, found 296.1639.

(3*S*)-5-(*tert*-Butyldiphenylsiloxy)-3-(2,5-dimethoxy-4-methylphenyl)pentanoic acid (13). Imidazole (14 mg, 0.202 mmol), *tert*-butyldiphenylchlorosilane (14 mg, 0.202 mmol), and 4-(dimethylamino)pyridine (0.3 mg, 2.5 μmol) were added to a solution of the alcohol (*S*)-**12** (50 mg, 0.169 mmol) in dry CH_2Cl_2 (1 mL). After being stirred at room temperature for 1 h, the mixture was quenched with saturated $NaHCO_3$(aq) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by column chromatography (silica gel, hex/AcOEt = 97/3) to give acetoxy silyl ether (90 mg, 100%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (9H, s), 1.89−2.12 (4H, m), 1.98 (3H, s), 2.20 (3H, s), 3.47 (1H, m), 3.60 (2H, t, J = 9.3 Hz), 3.68 (3H, s), 3.72 (3H, s), 3.93 (2H, t, J = 9.6 Hz), 6.58 (1H, s), 6.63 (1H, s), 7.31−7.41 (4H, m), 7.55−7.64 (6H, m). To a suspension of lithium aluminum hydride (21 mg, 0.169 mol) in THF (0.60 mL) at 0 °C was added a solution of the acetoxy silyl ether (90 mg, 0.169 mol) in THF (0.60 mL). After the reaction mixture was stirred for 3 h at room temperature, water was added. The crude product was filtered through a short pad of Celite with ether, and the filtrate was concentrated. Column chromatography (silica gel, hex/AcOEt = 97/3) provided an alcohol (89 mg, quantitative) as a light yellow oil: ^1H NMR (300 MHz, $CDCl_3 + D_2O$) δ 1.02 (9H, s), 1.92−2.16 (4H, m), 2.21 (3H, s), 3.30 (1H, m), 3.34−3.48 (2H, m), 3.60 (2H, t, J = 6.5 Hz), 3.72 (6H, s), 6.58 (1H, s), 6.68 (1H, s), 7.30−7.40 (4H, m), 7.53−7.64 (6H, m). To a solution of the alcohol (87 mg, 0.177 mmol) in CH_2Cl_2 (1.0 mL) was added, via cannula, a suspension of Dess−Martin periodinate (115 mg, 0.268 mmol) in CH_2Cl_2 (0.8 mL) at room temperature. The reaction mixture was stirred for 2 h and then diluted successively with saturated $NaHCO_3$ solution, saturated $Na_2S_2O_3$(aq), and CH_2Cl_2 and stirred for 30 min. The mixture was extracted with CH_2Cl_2. The combined organic solution was washed with saturated $NaHCO_3$(aq) and brine, dried over $MgSO_4$, filtered, and concentrated. Column chromatography (silica gel, hex/AcOEt = 97/3) provided an aldehyde (70 mg, 82%) as a clear oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (9H, s), 1.86−2.04 (2H, m), 2.20 (3H, s), 2.67 (2H, dd, J = 10.9, 2.5 Hz), 3.59 (2H, t, J = 6.4 Hz), 3.71 (6H, s), 3.80 (1H, m), 6.61 (1H, s), 6.65 (1H, s), 7.31−7.41 (4H, m), 7.55−7.64 (6H, m), 9.62 (1H, d, J = 2.5 Hz). To a solution of pyridinium dichromate (83 mg, 0.22 mmol) in DMF (0.7 mL) was added a solution of the aldehyde (35 mg, 73.0μmol) in DMF (0.3 mL). After being stirred for 14 h at room temperature, the reaction mixture was poured into water. The mixture was extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude carboxylic acid **13** (30 mg) was used to the next reaction without further purification.

General Procedure for the Condensation of Phenylglycine Methyl Ester (PGME) with Carboxylic Acid. To a stirred solution of a mixture of the carboxylic acid (1 equiv) and PGME (1.2 equiv) in DMF was successively added (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP, 1.2 equiv), 1-hydroxybenzotriazole (HOBT, 1.2 equiv), and triethylamine (1.2 equiv) at 0 °C. After the reaction was completed, the mixture was diluted with AcOEt, washed with 5% HCl(aq) and saturated $NaHCO_3$(aq), and dried over Na_2SO_4. Removal of the solvent and column chromatography (silica gel, hex/AcOEt = 80/20) afforded the amide.

(2*S*,3′*S*)-*N*-(5′-(*tert*-Butyldiphenylsiloxy)-3′-(2″,5″-dimethoxy-4″-methylphenyl)pentylcarbonyl)phen-ylglycine Methyl Ester (*S*-14) and (2*R*,3′*S*)-*N*-(5′-(*tert*-Butyldiphenylsiloxy)-3′-(2″,5″-dimethoxy-4″-methylphenyl)-pentylcarbonyl)phenylglycine Methyl Ester ((*R*)-14). According to the general procedure, the crude carboxylic acid (15 mg, ca. 0.030 mmol) was converted into the amide (9.0 mg, 70% from the alcohol), a colorless oil, after purification by column chromatography (silica gel, hex/AcOEt = 4/1): for (*S*)-14, ^1H NMR (400 MHz, $CDCl_3$) δ 0.997 (9H, s), 1.913 (2H, dd, J = 6.8, 4.0 Hz), 2.208 (3H, s), 2.630 (2H, m), 3.520 (1H, m), 3.537 (2H, m), 3.591 (3H, s), 3.675 (3H, s), 3.675 (3H, s), 5.446 (1H, d, J = 6.8 Hz), 6.536 (1H, s), 6.629 (1H, s), 6.994−7.626 (15H, m); for (*R*)-14, ^1H NMR (400 MHz, $CDCl_3$) δ: 1.013 (9H, s), 1.918 (2H, dd, J = 6.8, 4.0 Hz), 2.199 (3H, s), 2.631 (2H, m), 3.520 (1H, m), 3.545 (2H, m), 3.591 (3H, s), 3.675 (3H, s), 3.675 (3H, s), 5.435 (1H, d, J = 6.8 Hz), 6.577 (1H, s), 6.589 (1H, s), 7.098−7.610 (15H, m).

(*S*)-3-(2,5-Dimethoxy-4-methylphenyl)-6-methyl-5-heptenyl Acetate (15). To a solution of alcohol (*S*)-**12** (15.0 g, 50.9 mmol) in CH_2Cl_2 (200 mL) was added, via cannula, a suspension of Dess−Martin periodinate (25.9 g, 61.1 mmol) in CH_2Cl_2 (200 mL) at room temperature. The reaction mixture was stirred for 2.5 h and then diluted with saturated $NaHCO_3$(aq) (50 mL), saturated $Na_2S_2O_3$(aq) (50 mL), and CH_2Cl_2 (100 mL) and stirred for 30 min. The mixture was extracted with CH_2Cl_2, and the organic phase was washed with saturated $NaHCO_3$(aq) and brine, dried over $MgSO_4$, filtered, and concentrated. Column chromatography (silica gel, hex/AcOEt = 95/5) provided an aldehyde (13.8 g, 94%) as a colorless oil: $[\alpha]_D = -17.3$ (*c* 1.20, $CHCl_3$); IR (neat) 1044, 1211, 1466, 1506, 1735, 2953 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.92−2.11 (2H, m), 2.00 (3H, s), 2.19 (3H, s), 2.73 (2H, m), 3.59−3.69 (1H, m), 3.76 (3H, s), 3.77 (3H, s), 6.61 (1H, s), 6.67 (1H, s), 9.64 (1H, t, J = 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0 (q), 20.8 (q), 31.3 (d), 33.3 (t), 49.1 (t), 55.8 (q), 56.0 (q), 62.6 (t), 110.9 (d), 114.2 (d), 125.8 (s), 127.7 (s), 150.9 (s), 151.7 (s), 171.0 (s), 202.1 (d); MS (EI) *m*/*z*: 294 (M^+, base peak); HRMS calcd for $C_{16}H_{22}O_5$ 294.1467, found 294.1463. To isopropyltriphenylphosphonium iodide (92.3 g, 0.214 mol) suspended in dry THF (200 mL) at room temperature under nitrogen was added *t*-BuOK (23.8 g, 0.214 mol) in THF (100 mL). After the mixture was stirred for 30 min, the aldehyde (18.2 g, 61.2 mmol) in THF (60 mL) was added. After 3.5 h, water was added and the resulting mixture was poured into ether−brine. The mixture was extracted with ether. The combined organic solution was washed with brine, dried over $MgSO_4$. Removal of the solvent and column chromatography (silica gel, hex/AcOEt = 95/5) afforded the olefin **15** which was used to the next reaction without further purification: $[\alpha]_D = -3.11$ (*c* 0.96, $CHCl_3$); IR (neat) 1047, 1505, 2932 cm^{-1}; ^1H NMR (400 MHz + D_2O, $CDCl_3$) δ 1.55 (3H, s), 1.65 (3H, s), 1.83−2.05 (2H, m), 1.98 (3H, s), 2.19 (3H, s), 2.28 (2H, dd, J = 7.0, 7.0 Hz), 3.13 (1H, m), 3.74 (3H, s), 3.78 (3H, s), 5.07 (1H, tm, J = 7.0 Hz), 6.61 (1H, s), 6.66 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1 (q), 17.8 (q), 20.9 (q), 25.7 (q), 33.1 (t), 34.0 (t), 35.6 (d), 56.1 (q), 56.2 (q), 63.4 (t), 110.5 (d), 114.3 (d), 122.7 (d), 124.7 (s), 130.5 (s), 132.4 (s), 151.2 (s), 151.8 (s), 171.0 (s); MS (EI) *m*/*z* 320 (M^+), 179 (base peak); HRMS calcd for $C_{19}H_{28}O_4$ 320.1988, found 320.2001.

(*S*)-3-(2,5-Dimethoxy-4-methylphenyl)-6-methyl-5-hepten-1-ol (16). To a suspension of lithium aluminum hydride (1.16 g, 30.6 mmol) in THF (300 mL) at 0 °C was added dropwise a solution of crude acetate **15** (27.1 g, 61.2 mmol) in THF (240 mL). After the mixture was stirred for 1.5 h at room temperature, water was added. The crude product was filtered through a short pad of Celite with ether, and the filtrate was concentrated. Column chromatography (silica gel, hex/AcOEt = 95/5) provided alcohol **16** (15.7 g, 92% from the aldehyde) as a light yellow oil: $[\alpha]_D = -2.71$ (*c* 1.0, $CHCl_3$); IR (neat) 1047, 1240, 1465, 1504, 2932, 3389 cm^{-1}; ^1H NMR (400 MHz + D_2O, $CDCl_3$) δ 1.52−1.60 (1H, m), 1.60 (3H, s), 1.65 (3H, s), 2.04 (1H, dddd, J = 13.1, 7.2, 6.9, 6.8 Hz), 2.20 (3H, s), 2.33 (2H, ddd, J = 13.4, 7.6, 6.8 Hz), 3.23 (1H, ddd, J = 11.2, 7.2, 5.8 Hz), 3.31 (1H, ddd, J = 11.2, 7.6, 5.5 Hz), 3.49 (1H, m), 3.78 (3H, s), 3.81 (3H, s), 5.08 (1H, t, J = 7.2 Hz), 6.63 (1H, s), 6.70 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9 (q), 17.7 (q), 25.5 (q), 34.00 (d), 34.04 (t), 38.3 (t), 55.8 (q), 56.4 (q), 60.7 (t), 109.8 (d), 114.4 (d), 122.9 (d), 124.5 (s), 130.8 (s), 132.0 (s), 150.9 (s), 152.1 (s); MS (EI) *m*/*z*

278 (M^+), 179 (base peak); HRMS calcd for $C_{17}H_{26}O_3$ 278.1882, found 278.1896.

(*S*)-7-(*tert*-Butyldiphenylsiloxy)-5-(2,5-dimethoxy-4-methylphenyl)-2-methyl- 2-heptene (17). Imidazole (110 mg, 1.61 mmol), *tert*-butyldiphenylchlorosilane (192 mg, 0.70 mmol), and 4-(dimethylamino)pyridine (0.3 mg, 2.5 μmol) were added to a solution of the alcohol **16** (157 mg, 0.56 mmol) in dry CH_2Cl_2 (3 mL). After being stirred at room temperature for 1 h, the mixture was quenched with H_2O and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give a residue which was purified by column chromatography (silica gel, hex/AcOEt = 98/2) to give silyl ether **17** (285 mg, 98%) as a colorless oil; $[\alpha]_D = -2.58$ (*c* 1.2, $CHCl_3$); IR (neat) 1048, 1210, 1465, 1503, 2930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (9H, s), 1.52 (3H, s), 1.63 (3H, s), 1.82−1.96 (2H, m), 2.20 (3H, s), 2.23 (2H, m), 3.21 (1H, m), 3.54 (2H, dd, J = 10.8, 5.5 Hz), 3.68 (3H, s), 3.72 (3H, s), 5.07 (1H, t, J = 7.2 Hz), 6.59 (1H, s), 6.63 (1H, s), 7.28−7.43 (6H, s), 7.56−7.70 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1 (q), 17.8 (q), 18.4 (s), 25.8 (q), 26.8 (q), 34.0 (t), 35.3 (d), 37.2 (t), 56.09 (q), 56.14 (q), 59.7 (t), 110.9 (d), 114.2 (d), 123.2 (d), 124.2 (s), 127.46 (d), 127.49 (d), 127.56 (d), 129.3 (d), 129.4 (d), 129.5 (d), 131.5 (s), 132.0 (s), 134.2 (s), 135.5 (d), 151.3 (s), 151.6 (s); MS (EI) *m*/*z* 516 (M^+), 447 (base peak); HRMS calcd for $C_{33}H_{44}O_3Si$ 516.3060, found 516.3070.

(*S*)-2-(1-(2-(*tert*-Butyldiphenylsiloxy)ethyl)-4-methyl-3-pentenyl)-5-methyl- *p*-benzoquinone (18). To a solution of **17** (820 mg, 1.59 mmol) in acetonitrile (16 mL) was added aqueous cerium ammonium nitrate (2.0 g, 3.65 mmol) portionwise over 5 min at 0 °C. After being stirred for 15 min at 0 °C, the reaction mixture was extracted with ether (2 × 10 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, hex/AcOEt = 95/5) to give **18** (741 mg, 87%) as a brown oil; $[\alpha]_D = +0.72$ (*c* 0.83, $CHCl_3$); IR (neat) 1110, 1247, 1655, 2853, 3071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (9H, s), 1.56 (3H, s), 1.64 (3H, s), 1.72−1.96 (2H, m), 2.02 (3H, s), 2.16 (2H, dd, J = 7.2, 6.8 Hz), 3.02 (1H, m), 3.54 (2H, dd, J = 8.0, 8.0 Hz), 4.69 (1H, t, J = 7.2 Hz), 6.40 (1H, s), 6.52 (1H, s), 7.34−7.47 (6H, m), 7.61−7.70 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3 (q), 17.8 (q), 19.0 (q), 25.7 (q), 26.8 (q), 32.7 (t), 35.2 (d), 35.7 (t), 61.8 (t), 121.2 (d), 127.6 (d), 129.5 (d), 132.1 (d), 133.57 (s), 133.60 (s), 133.7 (s), 133.8 (d), 135.4 (d), 144.8 (s), 151.8 (s), 187.2 (s), 188.1 (s); MS (EI) *m*/*z* 486 (M^+), 351 (base peak); HRMS calcd for $C_{31}H_{38}O_3Si$ 486.259, found 486.2593.

(*S*)-2-(1-(2-(*tert*-Butyldiphenylsiloxy)ethyl)-4-methyl-3-pentenyl)-5-methyl- hydroquinone (19). To a solution of **18** (741 mg, 1.52 mmol) in THF (15 mL) was added aqueous sodium hydrosulfite (1.32 g, 7.62 mmol) portionwise over 10 min at 0 °C. After being stirred for 10 min at 0 °C, the reaction mixture was extracted with ether (2 × 10 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, hex/AcOEt = 90/10) to give **19** (741 mg, 88%) as a light yellow oil: $[\alpha]_D = -10.4$ (*c* 1.35, $CHCl_3$); IR (neat) 1111, 1144, 1186, 2853, 3071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ + D_2O) δ 1.08 (9H, s), 1.21−1.30 (1H, m), 1.60 (3H, s), 1.70 (3H, s), 1.85−1.96 (1H, m), 2.18 (3H, s), 2.29 (2H, dd, J = 9.3, 6.8 Hz), 3.02 (1H, m), 3.51 (1H, ddd, J = 11, 10.9, 3.5 Hz), 3.63 (1H, ddd, J = 11, 5.4, 3.0 Hz), 5.10 (1H, t, J = 7.2 Hz), 6.49 (1H, s), 6.73 (1H, s), 7.34−7.47 (6H, m), 7.61−7.70 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.5 (q), 17.9 (q), 19.1 (s), 25.8 (q), 26.8 (q), 33.6 (d), 33.7 (t), 38.2 (t), 62.2 (t), 113.0 (d), 119.0 (d), 122.3 (s), 122.9 (s),127.7 (s), 129.3 (s), 129.8 (d), 129.9 (d) 133.0 (d), 135.57 (s), 135.61 (s), 135.7 (d), 147.8 (s), 148.5 (s); MS (EI) *m*/*z* 488 (M^+), 353 (base peak); HRMS calcd for $C_{31}H_{40}O_3Si$ 488.2745, found 488.2761.

(*S*)-5-(2,5-Bis(*tert*-butyldimethylsiloxy)-4-methylphenyl)-7-*tert*-butyldiphenylsiloxy-2-methyl-2-heptene (20). Imidazole (110 mg, 1.61 mmol), *tert*-butyldimethylchlorosilane (384 mg, 1.40 mmol), and 4-(dimethylamino)pyridine (0.3 mg, 2.5 μmol) were added to a solution of **19** (150 mg, 0.55 mmol) in dry CH_2Cl_2 (3 mL). After being stirred at room temperature for 1 h, the mixture was quenched with H_2O and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give a residue which was purified by column chromatography (silica gel, hex/AcOEt = 9/1) to give **20** (302 mg, 95%) as a yellow oil: $[\alpha]_D = -13.8$ (*c* 1.0, $CHCl_3$); IR (neat) 1120, 1146, 1192, 2968, 3049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.126 (3H, s), 0.136 (3H, s), 0.144 (3H, s), 0.151 (3H, s), 0.94 (9H, s), 1.00 (9H, s), 1.01 (9H, s), 1.49 (3H, s), 1.61 (3H, s), 1.85−1.96 (2H, ddd, J = 10.8, 7.2, 6.8 Hz), 2.11 (3H, s), 2.16 (2H, m), 3.01−3.15 (1H, m), 3.55−3.65 (2H, m), 4.99 (1H, dd, J = 7.0, 6.6 Hz), 6.50 (2H, s), 7.24−7.44 (6H, m), 7.58−7.62 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.4 (q), −4.1 (q), 16.5 (q), 17.9 (q), 18.2 (q), 19.1 (s), 25.8 (q), 26.8 (q), 33.6 (d), 33.7 (t), 38.4 (t), 62.2 (t), 116.8 (d), 119.0 (d), 121.2 (s), 123.0 (d), 127.5 (d), 127.7 (d), 128.3 (s), 129.8 (d), 129.9 (d), 132.6 (s), 132.9 (s), 133.0 (d), 135.5 (s), 135.7 (d), 147.8 (s), 148.5 (d); MS (EI) *m*/*z* 716 (M^+), 73 (base peak); HRMS calcd for $C_{43}H_{68}O_3Si_3$ 716.4476, found 716.4491.

(3*S*,5*S*)- and (3*R*,5*S*)-7-*(tert*-Butyldiphenylsiloxy)-3-(2,5-di-*tert*-butyldimethylsiloxy-4-methyl phenyl)-2-methyl-2,3-epoxyheptane (21). To a solution of **20** (45 mg, 58.2 μmol) in ether (0.8 mL) and 0.1 M phosphate buffer (0.8 mL) was added *m*-chloroperbenzoic acid (*m*CPBA, 14 mg, 83.6 μmol) at 0 °C. After being stirred for 25 min at 0 °C, the reaction mixture was extracted with ether (2 × 5 mL). The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated. Column chromatography (silica gel, hex/AcOEt = 4/1) provided a diastereomeric mixture of **21** (40 mg, 92%) as a yellow oil: IR (neat) 1114, 1144, 1188, 2950, 3055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.12 (6/2H, s), 0.13 (6/2H, s), 0.15 (6/2H, s), 0.17 (6/2H, s), 0.99 (9/2H, s), 1.01 (9/2H, s), 1.05 (18/2H, s), 1.07 (18/2H, s), 1.18 (3H, s), 1.20 (3/2H, s), 1.23 (3/2H, s), 1.57−2.01 (4H, m), 2.15 (3H, s), 2.64 (1/2H, dd, J = 6.7, 6.6 Hz), 2.86 (1/2H, dd, J = 7.2, 6.8 Hz), 3.35−3.40 (1H, m), 3.49−3.58 (1H, ddd, J = 10.5, 7.2, 5.5 Hz), 3.58−3.64 (1H, m), 6.47 (1/2H, s), 6.49 (1/2H, s), 6.67 ((1/2H, s), 6.70(1/2H, s), 7.30−7.41 (6H, m), 7.59−7.68 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.4 (q), −4.3 (q), −4.1 (q), −4.0 (q), 16.5 (q), 16.6(q), 17.9 (q), 18.2 (q), 19.1 (s), 19.2 (s),25.8 (q), 26.8 (q), 26.9 (q), 33.6 (d), 33.7 (t), 38.4 (t), 62.2 (t), 62.4 (t), 116.8 (d), 119.0 (d), 121.2 (s), 123.0 (d), 127.5 (d), 127.7 (d), 128.3 (s), 129.8 (d), 129.9 (d), 132.6 (s), 132.9 (s), 133.0 (d), 135.5 (s), 135.7 (d), 147.7 (s), 147.8 (s), 148.5 (s).

(2*S*,4*R*)- and (2*R*,4*R*)-4-(2-(*tert*-Butyldiphenylsiloxy)-ethyl)-3,4-dihydro-6-hydroxy-2-(1-hydroxy-1-methyl)ethyl-7-methyl-2*H*-1-benzopyran (22). To a solution of **21** (45 mg, 0.056 mmol) in MeOH (0.2 mL) was added K_2CO_3 (54 mg, 0.89 mmol). The mixture was stirred at 50 °C for 12 h. The mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo to give a crude mixture that was purified by column chromatography (silica gel, hex/AcOEt = 8/2), giving an inseparable diastereomeric mixture of the benzopyran **22** (25 mg, 85%) as a light yellow oil: IR (neat) 1110, 1210, 3585 cm^{-1}; ^1H NMR (300 MHz + D_2O, $CDCl_3$) δ 1.09 (9H, s), 1.18 (3H, s), 1.23 (3H, s), 1.26 (1H, m), 1.67−1.77 (2H, m), 1.85 (1H, ddd, J = 10.2, 6.5, 6.3 Hz), 2.16 (3H, s), 3.00 (1H, m), 3.68 (1H, dd, J = 6.9, 6.9 Hz), 3.79 (2H, t, J = 6.0 Hz), 6.34 (1H, s), 6.60 (1H, s), 7.36−7.46 (6H, m), 7.66−7.72 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.6 (q), 19.2 (s), 24.1 (q), 25.8 (q), 26.2 (t), 29.7 (d), 40.2 (t), 60.9 (t), 72 (s), 77.4 (d), 115.1 (d), 118.4 (d), 123.5 (s), 124 (s), 127.7 (d), 129.7 (d), 129.8 (d), 133.7 (s), 133.9 (s), 135.6 (s), 147.3 (s), 147.7 (s); MS(EI) *m*/*z*: 504 (M^+), 41 (base peak); HRMS calcd for $C_{31}H_{40}O_4Si$ 504.2696, found 504.2725.

(2*S*,4*R*)-4-(2-(*tert*-Butyldiphenylsiloxy)ethyl)-3,4-dihydro-6-(methoxymethyl)-2-(1-(methoxymethyl)-1-methylethyl)-7-methyl-2*H*-1-benzopyran (23). Chloromethyl methyl ether (0.4 mL) was added to a solution of **22** (18.1 mg, 35.9 μmol) in dry diisopropylethylamine (0.7 mL). After being stirred at room temperature for 17 h, the reaction mixture was diluted with CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, and evaporated. Purification by column chromatography (15% EtOAc/hex) provided **23** (31 mg, 65%) as a diastereomeric mixture. The isomers were separated with preparative HPLC (Hibar RT 250-25LiChrosorbSi 60 (7 μm), hex/AcOEt = 95/5 (v/v), flow rate 10 mL/min), as a yellow oil. (2*S*,4*R*)-**23** (retention time 39.50 min): $[\alpha]_D = -13.0$ (*c* 1.2, $CHCl_3$); IR (neat) 1039, 1149, 1498, 2931 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (9H, s), 1.25 (3H, s), 1.30 (3H, s), 1.63−1.93 (4H, m), 2.18(3H, s), 3.03 (1H, m), 3.33 (3H, s), 3.47 (3H, s), 3.74−3.80 (3H, m), 4.73 (1H, d, J = 7.2 Hz), 4.78 (1H, d, J = 7.2 Hz), 5.04 (1H, d, J = 6.3 Hz), 5.07 (1H, d, J = 6.3 Hz), 6.64 (1H, s), 6.78 (1H, s), 7.38−7.43 (6H, m), 7.57−7.69(4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0 (q), 19.2 (s), 21.7 (q), 23.5 (q), 25.7 (t), 26.9 (q), 30.2 (d), 40.3 (t), 55.2 (q),

56.0 (q), 61.3 (t), 76.8 (d), 77.2 (s), 91.2 (t), 95.5 (t), 115.8 (d), 118.6 (d), 123.9 (s), 127.2 (s), 127.7 (d), 129.6 (d), 133.9 (s), 135.6 (d), 148.9 (s), 149.2 (s); MS (EI) *m*/*z* 592 (M^+), 57 (base peak); HRMS calcd for $C_{35}H_{48}O_6Si$ 592.3220, found 592.3213. (2*R*,4*R*)-**23** (retention time 44.14 min): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.27 (3H, s), 1.33 (3H, s), 1.60 (2H, m), 2.10−2.26 (2H, m), 2.17 (3H, s), 2.31 (1H, m), 3.08 (1H, m), 3.34 (3H, s), 3.48 (3H, s), 3.75 (1H, d, J = 11.2 Hz), 3.82 (2H, t, J = 6.5 Hz), 4.74 (1H, d, J = 7.5 Hz), 4.82 (1H, d, J = 7.5 Hz), 5.06 (1H, d, J = 6.5 Hz), 5.10 (1H, d, J = 6.5 Hz), 6.67 (1H, s), 6.87 (1H, s), 7.35−7.48 (6H, m), 7.66−7.75 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9 (q), 19.2 (s), 21.6 (q), 23.5 (q), 26.8 (q), 28.7 (t), 31.8 (d), 37.7 (t), 55.2 (q), 56.0 (q), 61.7 (t), 91.3 (t), 95.7 (t), 113.5 (d), 118.8 (d), 124.1 (s), 127.6 (s), 129.6 (d), 133.8 (s), 135.6 (d), 149.3 (s), 150.0 (s); MS (EI) *m*/*z* 592 (M^+), 69 (base peak); HRMS calcd for $C_{35}H_{48}O_6Si$ 592.3220, found 592.3208.

(2*S*,4*R*)-3,4-Dihydro-4-(2-hydroxyethyl)-6-(methoxymethyl)-2-(1-(methoxymethyl)-1-methylethyl)-7-methyl-2*H*-1-benzopyran (24). To a stirred solution of (2*S*,4*R*)-**23** (36 mg, 0.061 mmol) in THF (1 mL) was added 1 M tetrabutylammonium fluoride in THF (0.1 mL) at 0 °C. After being stirred for 2.5 h at room temperature, the reaction mixture was poured into water and extracted with ether. The combined organic layer was dried over $MgSO_4$ and evaporated. Purification by column chromatography (silica gel, hex/AcOEt = 60/40) afforded **24** (20 mg, 93%) as a colorless oil: $[\alpha]_D$ = −31.9 (*c* 0.69, $CHCl_3$); IR (neat) 1075, 1150, 3433 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + D_2O) δ 1.30 (3H, s), 1.37 (3H, s), 1.72−2.03 (4H, m), 2.18 (3H, s), 2.97 (1H, m), 3.38 (3H, s), 3.48 (3H, s), 3.78 (2H, dd, J = 6.3, 6.3 Hz), 3.84 (1H, dd, J = 11.7, 1.2 Hz), 4.78 (1H, d, J = 7.2 Hz), 4.83 (1H, d, J = 7.2 Hz), 5.10 (2H, s), 6.65 (1H, s), 6.78 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0 (q), 21.6 (q), 23.6 (q), 25.9 (q), 30.6 (d), 40.2 (t), 55.2 (q), 55.9 (q), 76.7 (d), 77.3 (s), 91.3 (t), 95.4 (t), 115.5 (s), 118.7 (s), 123.5 (s), 127.2 (s), 149.0 (s), 149.1 (s); MS (EI) *m*/*z*: 354 (M^+), 45 (base peak); HRMS calcd for $C_{19}H_{30}O_6$ 354.2042, found 354.2034.

(2*S*,4*S*)-3,4-Dihydro-4-(2-((2-nitrophenyl)seleno)ethyl)-6-(methoxymethyl)-2-(1-(methoxymethyl)-1-methylethyl)-7-methyl-2*H*-1-benzopyran (25). A solution of alcohol **24** (20 mg, 0.056 mmol) in THF (0.5 mL) containing *o*-nitrophenyl selenocyanate (16 mg, 0.115 mmol) under nitrogen was treated with tributylphosphine (20 mg, 0.115 mmol) at room temperature. After the reaction was stirred for 3.5 h, the solvent was removed in vacuo. Purification by column chromatography (silica gel, hex/AcOEt = 92/8) afforded the crude product which was used to the next reaction without further purification.

(2*S*,4*S*)-3,4-Dihydro-4-ethenyl-6-(methoxymethyl)-2-(1-(methoxymethyl)-1-methylethyl)-7-methyl-2*H*-1-benzopyran (26). A solution of **25** (40 mg, 0.056 mmol) in THF (1.0 mL) was treated dropwise with 35% H_2O_2 (0.14 mL, 1.49 mmol) at room temperature. After the reaction was stirred for 2.5 h, the solvent was removed in vacuo. The residue was extracted with ether, washed with brine, and evaporated. Purification by column chromatography (silica gel, hex/EtOAc = 95/5) afforded **26** (20 mg, 91%) as a colorless oil: $[\alpha]_D$ = −52.4 (*c* 0.45, $CHCl_3$); IR (neat) 1075, 1150, 3433 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + D_2O) δ 1.29 (3H, s), 1.35 (3H, s), 1.88 (1H, ddd, J = 13.0, 10.1, 5.4 Hz), 1.94 (1H, ddd, J = 13.0, 2.8, 2.8 Hz), 2.19 (3H, s), 3.37 (3H, s), 3.48 (3H, s), 3.49 (1H, m), 3.7 (1H, dd, J = 11.7, 1.8 Hz), 4.78 (1H, d, J = 7.2 Hz), 4.83 (1H, d, J = 7.2 Hz), 4.90 (1H, d, J = 17 Hz), 5.07 (1H, d, J = 10.8 Hz), 5.10 (2H, s), 5.99 (1H, ddd, J = 17.0, 10.8, 6.3 Hz), 6.67 (1H, s), 6.72 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0 (q), 21.7 (q) 23.5 (q), 27.1 (t), 38.2 (d), 55.2 (q), 55.9 (q), 76.8 (d), 77.1 (s), 91.3 (d), 95.4 (t), 115.6 (t), 116.2 (d), 118.7 (s), 120.4 (s), 127.6 (s), 142.3 (d), 149.0 (s), 150.0 (s); MS (EI) *m*/*z* 336 (M^+, base peak); HRMS calcd for $C_{19}H_{28}O_5$ 336.1937, found 336.1945.

Heliannuol E (1). To a solution of **26** (20 mg, 0.056 mmol) in THF (1.0 mL) was added dropwise 6 N HCl (3.5 mL, 1.49 mmol) at room temperature. After the mixture was stirred for 24 h, H_2O was added and the solution was extracted with ether, washed with brine, and evaporated. Purification by column chromatography (silica gel, hex/AcOEt = 90/10) afforded **1** (10 mg, 89%) as a colorless oil: $[\alpha]^{27}_D$ = −69.8 (*c* 0.11, $CHCl_3$) [lit.[1] $[\alpha]_D$ = −68.6 (*c* 0.1, $CHCl_3$)]; IR (neat) 1196, 1636, 3374 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, s), 1.28 (3H, s), 1.85 (1H, ddd, J = 12.6, 2.9, 2.2 Hz), 1.89 (1H, ddd, J = 12.6, 10.1, 5.4 Hz), 2.18 (3H, s), 3.46 (1H, m), 3.72 (1H, dd, J = 10.1, 2.9 Hz), 4.90 (1H, d, J = 17 Hz), 5.05 (1H, d, J = 10.1 Hz), 5.96 (1H, ddd, J = 17.0, 10.1, 6.3 Hz), 6.48 (1H, s), 6.66 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7 (q), 24.2 (q) 25.0 (q), 27.5 (t), 37.9 (d), 71.9 (s), 77.5 (d), 115.8 (t), 115.9 (d), 118.5 (d), 120.7 (s), 124.5 (s), 142.1 (d), 147.4 (s), 148.3 (s); MS (EI) *m*/*z* 248 (M^+, base peak), 233 $(M - Me)^+$ (17.8), 230 $(M - H_2O)^+$ (62.4), 215 $(M - H_2O - Me)^+$ (49.3).

Acknowledgment. We are grateful to Professor Francisco Macías, University of Cádiz, for valuable discussions and Dr. Yoshihiko Hirose, Amano Pharmaceutical Co., Ltd., for providing lipase AK. This work was supported by Grants-in-Aid for Scientific Research (No. 11557172) from the Ministry of Education, Science, Sports, and Culture, Government of Japan.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **6**−**11**, (*R*)-**12**, (*R*)-**14** (^{1}H NMR only), (*S*)-**14** (^{1}H NMR only), **15**−**21**, (2*S*,4*R*)-**22**, (2*R*,4*R*)-**22** (^{1}H NMR only), (2*S*,4*R*)-**23**, (2*R*,4*R*)-**23**, **24**−**26**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0011437