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A Short and Efficient Synthetic Strategy for the Total Syntheses of (*S*)-(+)- and (*R*)-(–)-Plakolide A

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Concise and efficient total syntheses of anticancer agents (*S*)-(+)-Plakolide A and (*R*)-(–)-Plakolide A were accomplished in eight steps and an overall yield of 39 % starting from geraniol. The key steps in our strategy are Sharpless asymmetric epoxidation, double elimination, and Stille coupling reactions.

Introduction

Plakolide A is an α-exomethylene-γ-disubstituted-γ-lactone isolated recently from a shallow-water marine sponge of the genus *plakortis* collected from La Palma Islands, and it was found to exhibit inducible nitric oxide synthase (iNOS) activity in a cell-based assay (IC_{50} value of 0.2 $\mu g\,mL^{-1}$).[1] It exhibited 72 h cytotoxicity against the cultured P-388 marine lymphoma and A-549 human lung adenocarcinoma cell lines with IC_{50} values of 1.1 and 5.0 $\mu g\,mL^{-1}$, respectively. It also showed cytotoxicity against PANC-1 human pancreatic carcinoma and NCI/ADR human breast carcinoma cell lines with IC_{50} values of 3.8 and 3.7 $\mu g\,mL^{-1}$, respectively. Persuasive data mainly based upon extensive investigation of the structure by its synthesis, specific rotation, and CD spectrum led to the revision of the stereochemistry of the lactone at C4.[2a]

So far only one total synthesis of Plakolide A on the basis of the self-reproduction method developed by Seebach has been reported in the literature.[2b] The interesting pharmacological activity and unique structural features prompted us to devise a new, short, and efficient strategy for the total syntheses of both (*S*)-(+)- and (*R*)-(–)-Plakolide A starting from the simple and readily available geraniol (Figure 1).

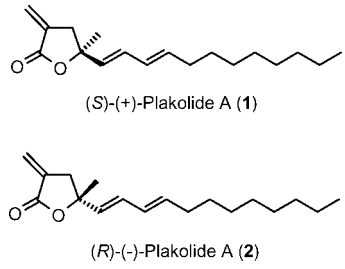

Figure 1. (*S*)-(+)-Plakolide A and (*R*)-(–)-Plakolide A.

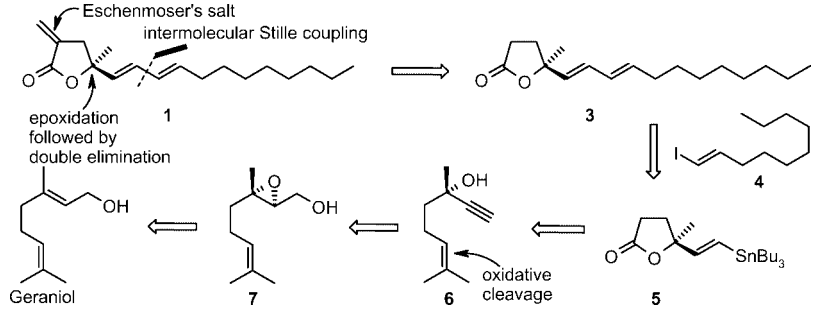

Figure 2. Retrosynthetic analysis of (*S*)-(+)-Plakolide A (**1**).

Our retrosynthetic strategy is outlined in Figure 2. The target molecule was anticipated to be derived from vinyl stannane derivative **5** via a lactol that could be obtained

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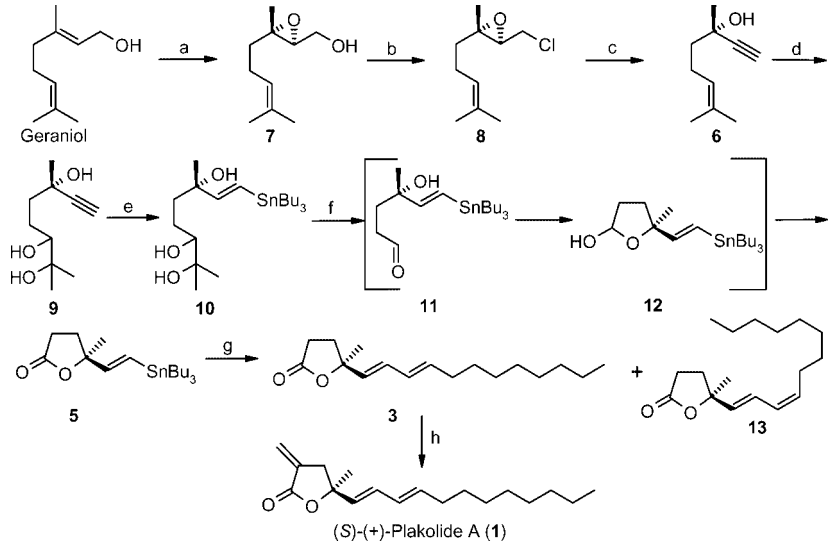

Scheme 1. Synthesis of (*S*)-(+)-Plakolide A (**1**). Reagents and conditions: (a) L-(+)-DIPT, Ti(O*i*Pr)$_4$, TBHP, MS 4 Å, CH_2Cl_2, –23 °C, 6 h, 95%; (b) PPh_3, CCl_4, reflux, 6 h, 93%; (c) *n*-BuLi, THF, –40 °C, 1 h, 85%; (d) OsO_4, NMO, acetone/water (1:4), room temp., 12 h, 92%; (e) Bu_3SnH, AIBN, toluene, 110 °C, 6 h, 90%; (f) (1) silica gel supported $NaIO_4$, CH_2Cl_2, 1 h; (2) PDC, CH_2Cl_2, 4 h, 84% over two steps; (g) **4**, Pd(PPh$_3$)$_4$, LiCl, CuCl, DMSO, room temp. to 60 °C, 26 h, 83% for **3** and 9% for **13**; (h) (1) LDA, THF, –78 °C, 15 min, (2) Eschenmoser's salt, –78 °C to room temp., 6 h, (3) CH_3I, CH_3OH, room temp., 18 h, 82%.

from propargyl alcohol **6**. Alcohol **6** could be obtained from epoxy alcohol **7** in two discrete steps, namely chlorination followed by a double elimination reaction. Epoxy alcohol **7** could be generated by Sharpless epoxidation of geraniol.

Results and Discussion

Our synthesis of the main core commenced with commercially available geraniol, which was subjected to Sharpless asymmetric epoxidation to yield epoxide **7** {$[a]_D^{25}$ = –5.1 (*c* = 3.0, $CHCl_3$), ref.[3] $[a]_D^{25}$ = –5.3 (*c* = 3.0, $CHCl_3$)} in ≥95% *ee* (Scheme 1).[4] Chlorination[5] with refluxing CCl_4 and PPh_3 gave chloroepoxide **8**. A double elimination reaction[6] effected by treatment with *n*BuLi in THF at –40 °C furnished propargyl alcohol **6** in 79% overall yield. Dihydroxylation of olefin **6** with OsO_4 and NMO in acetone and water at ambient temperature gave triol **9** as a diastereomeric mixture (1:1) in 92% yield. Required vinyl stannane **10** (1:1 diastereomeric mixture) was easily obtained from **9** by radical hydrostannylation.[7] Oxidative cleavage[8] of the diol with the use of $NaIO_4$-impregnated silica gel in dichloromethane and treatment of the resulting lactol with PDC in the same pot afforded required lactone **5** in 84% overall yield. Its ^{1}H- and ^{13}C-NMR spectra were in good agreement with the assigned structure; elemental analysis confirmed the chemical composition of **5**.

With lactone vinyl stannane **5** in hand, vinyl iodide side chain **4** was constructed from nonan-1-al by Takai olefination.[9] Subsequent coupling of these entities was achieved through a cuprous chloride accelerated Stille coupling under conditions reported by Corey and coworkers.[10] The expected coupled products (*E*,*E*)-**3** and (*E*,*Z*)-**13** were obtained in a 9:1 ratio by using Pd(PPh$_3$)$_4$ in DMSO. The products were easily separated by flash chromatography on silica gel. Finally, treatment of the (*E*,*E*)-**3** with LDA and Eschenmoser's salt[11] furnished (*S*)-(+)-Plakolide A (**1**). Product **1** exhibited spectroscopic and physical properties identical to those of an authentic sample; the sign of optical rotation was different {$[a]_D^{25}$= +43.2 (*c* = 1.5, MeOH), ref.[1] $[a]_D^{25}$ = –41.0 (*c* = 0.12, MeOH)}. This reconfirmed the observation of Matsuo et al. that natural Plakolide A is not (*S*)-(+)-Plakolide A (**1**) but rather (*R*)-(–)-Plakolide A (**2**).[2]

With the exact same approach, the natural enantiomer (*R*)-(–)-Plakolide A (**2**) was synthesized from geraniol as well by using D-(–)-DIPT for the Sharpless epoxidation and following the same protocol to that described in Scheme 1. We arrived at (*R*)-(–)-Plakolide A (**2**) {$[a]_D^{25}$ = –42.4 (*c* = 1.2, MeOH), ref.[1] $[a]_D^{25}$ = –41.0 (*c* = 0.12, MeOH)}in eight steps with an overall 41% yield.

Conclusions

Starting from readily available geraniol and following a practical sequence of reactions, we developed efficient synthetic routes to enantiopure (*S*)-(+)-Plakolide A (**1**) and (*R*)-(–)-Plakolide A (**2**). In terms of brevity and efficiency, the described methods compare well with the reported route, and they are expected to be attractive alternatives to the existing method for the total synthesis of the title compounds. The obvious and noteworthy advantages of our protocol lie in high overall yields, ready access to the disubstituted γ-lactone moiety with high enantioselectivity, and various possibilities of side chain modifications.

Experimental Section

General Remarks: Air- and/or moisture-sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in oven/flame-dried glassware. All anhydrous solvents were distilled prior to use: THF, benzene, toluene, and diethyl ether from Na and benzophenone; CH_2Cl_2 from CaH_2; MeOH, EtOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60–120 mesh). Specific optical rotations $[\alpha]_D$ are given in 10^{-1} °$cm^2 g^{-1}$. ^1H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane. The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad.

(2*S*,3*S*)-3-Methyl-3-[(4-methylpent-3-enyl)oxiran-2-yl]methanol (7): A stirred mixture of activated 4 Å molecular sieves (5.0 g) and dichloromethane (30 mL) was cooled to –10 °C. L-(+)-Diisopropyl tartrate (0.86 mL, 4.1 mmol), freshly distilled titanium isopropoxide (1.20 mL, 4.1 mmol), and *tert*-butyl hydroperoxide (5 M in decane, 9.72 mL, 48.6 mmol) were added sequentially. After stirring for 10 min, the mixture was cooled to –23 °C and freshly distilled geraniol (5.0 g, 32.4 mmol) in dichloromethane (10 mL) was added at a rate sufficient to ensure that the temperature remained below –20 °C. The mixture was stirred at –23 °C for an additional 6 h and water (10 mL) was then added with vigorous stirring. After 30 min, aqueous NaOH (3 M, 20 mL) was added, and the mixture was stirred at room temp. for an additional 30 min and filtered through Celite. The filtrate was stirred vigorously with 10% citric acid (30 mL) at room temp. for 2 h. After the organic layer was separated, the aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layer was washed with brine (40 mL), dried with Na_2SO_4, and concentrated in vacuo. Bulb-to-bulb distillation (100 °C, 0.1 Torr) of the crude product yielded epoxide **7** (5.24 g, 95%) as a colorless liquid. R_f = 0.6 (ethyl acetate/light petroleum ether, 3:7). $[\alpha]_D^{25}$ = –5.1 (c = 3.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.07 (t, J = 7.08 Hz, 1 H), 3.81 (dd, J = 12.13, 4.29 Hz, 1 H), 3.66 (dd, J = 12.13, 6.70 Hz, 1 H), 2.96 (dd, J = 6.70, 4.29 Hz, 1 H), 2.07 (dt, J = 7.59, 7.08 Hz, 2 H), 1.69 (m, 1 H), 1.68 (s, 3 H), 1.61 (s, 3 H), 1.48 (m, 1 H), 1.30 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 132.0, 123.4, 63.1, 61.3, 61.1, 38.5, 25.7, 23.7, 17.6, 16.7 ppm. IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3418, 1672, 1452, 1384, 1094, 864 cm^{-1}. $C_{10}H_{18}O_2$ (170.25): calcd. C 70.60, H 10.58; found C 70.82, H 10.46.

(2*R*,3*S*)-3-(Chloromethyl)-2-methyl-2-(4-methylpent-3-enyl)oxirane (8): A stirred mixture of epoxy alcohol **7** (4.2 g, 24.7 mmol), PPh_3 (7.76 g, 29.6 mmol), and $NaHCO_3$ (0.42 g, 10 wt.-%) in CCl_4 (50 mL) was heated at reflux, under a nitrogen atmosphere, for 6 h. After completion of the reaction, CCl_4 was removed under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/light petroleum ether, 4:96) to furnish epoxy chloride **8** (4.3 g, 93%) as a colorless liquid. R_f = 0.5 (ethyl acetate/light petroleum ether, 1:9). $[\alpha]_D^{25}$ = +9.95 (c = 2.9, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.08 (t, J = 7.1 Hz, 1 H), 3.69 (dd, J = 11.4, 5.8 Hz, 1 H), 3.41 (dd, J = 11.4, 7.3 Hz, 1 H), 3.01 (dd, J = 7.3, 5.8 Hz, 1 H), 2.09 (dt, J = 7.5, 7.1 Hz, 2 H), 1.68 (m, 1 H), 1.68 (s, 3 H), 1.44 (m, 1 H), 1.32 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 132.0, 123.2, 61.7, 61.3, 42.0, 38.2, 25.5, 23.6, 17.5, 16.1 ppm. IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 1653, 1451, 1385, 1263, 1113, 1072, 914, 860 cm^{-1}. $C_{10}H_{17}ClO$ (188.69): calcd. C 63.65, H 9.00; found C 63.78, H 9.14.

(*S*)-3,7-Dimethyloct-6-en-1-yn-3-ol (6): To a stirred solution of epoxy chloride **8** (3.5 g, 18.5 mmol) in dry THF (25 mL) at –40 °C, under an argon atmosphere, was added *n*BuLi (34.77 mL, 55.6 mmol) dropwise, and the mixture was allowed to stir for an additional 1 h. The mixture was quenched with an aqueous solution of NH_4Cl (20 mL), and THF was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate (2 × 50 mL), dried with Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/light petroleum ether, 3:97) to afford propargyl alcohol derivative **6** (2.2 g, 85%) as a colorless liquid. R_f = 0.5 (ethyl acetate/light petroleum ether, 1:19). $[\alpha]_D^{25}$ = –13.24 (c = 0.65, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.15 (t, J = 7.2 Hz, 1 H), 2.43 (s, 1 H), 2.17 (m, 2 H), 1.7 (m, 2 H), 1.65 (s, 3 H), 1.49 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 132.3, 123.8, 87.7, 71.4, 68.1, 43.2, 29.8, 25.7, 23.5, 17.7 ppm. IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3398, 3308, 2110, 1672, 1451, 1376, 1121, 908 cm^{-1}. $C_{10}H_{16}O$ (152.23): calcd. C 78.90, H 10.60; found C 79.06, H 10.78.

(6*S*)-2,6-Dimethyloct-7-yne-2,3,6-triol (9): Osmium tetroxide (catalytic) was added to a stirred mixture of carbinol **6** (2.20 g, 14.5 mmol) and NMO (50% aqueous solution, 6.77 mL, 28.9 mmol) in acetone/water (1:4, 10 mL) at 0 °C. The mixture was stirred overnight at room temp. After completion of the reaction, it was quenched with a saturated solution of sodium sulfite (10 mL). The mixture was stirred vigorously for 1 h. Acetone was removed under reduced pressure, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo to leave a residue, which on silica gel column chromatography (ethyl acetate/light petroleum ether, 7:3) furnished **9** (1:1 diastereomeric mixture) (2.6 g, 92%) as a viscous liquid. R_f = 0.3 (ethyl acetate). ^1H NMR (200 MHz, $CDCl_3$): δ = 3.44 (m, 1 H), 2.46 (s, 1 H), 2.01–1.69 (m, 4 H), 1.54 (s, 1.5 H), 1.53 (s, 1.5 H), 1.24 (s, 3 H), 1.20 (s, 1.5 H), 1.19 (s, 1.5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 88.0/87.6, 78.8/78.1, 73.3, 71.7/71.4, 67.5, 40.9/40.2, 30.5/29.5, 26.7, 26.4/26.4, 23.4/23.3 ppm. IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3397, 3307, 2109, 1452, 1374, 1167, 1071, 945 cm^{-1}. $C_{10}H_{18}O_3$ (186.25): calcd. C 64.49, H 9.74; found C 64.56, H 9.82.

(6*S*,*E*)-2,6-Dimethyl-8-(tributylstannyl)oct-7-ene-2,3,6-triol (10): To a stirred solution of **9** (2.4 g, 12.9 mmol) in toluene (30 mL) was added *n*Bu_3SnH (4.0 mL, 15.5 mmol) and AIBN (30 mg) at room temp. The reaction mixture was degassed with argon and gently heated at reflux with stirring for 6 h. The solvent was removed, and the residue was purified by silica gel column chromatography (ethyl acetate/light petroleum ether, 2:3) to give **10** (1:1 diastereomeric mixture) (5.5 g, 90%) as a colorless liquid. R_f = 0.6 (ethyl acetate/light petroleum ether, 7:3). ^1H NMR (200 MHz, $CDCl_3$): δ = 6.12 (d, J = 19.3 Hz, 0.5 H), 6.12 (d, J = 19.3 Hz, 0.5 H), 6.0 (d, J = 19.3 Hz, 0.5 H), 5.95 (d, J = 19.3 Hz, 0.5 H), 3.35 (dd, J = 6.9, 2.3 Hz, 0.5 H), 3.35 (dd, J = 6.8, 2.1 Hz, 0.5 H), 1.88–1.57 (m, 4 H), 1.54–1.25 (m, 18 H), 1.19 (s, 1.5 H), 1.18 (s, 1.5 H), 1.14 (s, 1.5 H), 1.12 (s, 1.5 H), 0.93 (s, 1.5 H), 0.89 (s, 1.5 H), 0.89 (t, J = 7.48 Hz, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.7/154.2, 123.8/123.3, 79.1/78.5, 74.6/73.2, 39.3/38.8, 29.3/29.2, 29.1, 28.9, 27.8/27.8, 27.2, 26.5/26.4, 26.1/26.0, 23.2/23.1, 13.7, 9.5 ppm. IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3393, 1641, 1599, 1463, 1376, 1166, 1071, 994 cm^{-1}. $C_{22}H_{46}O_3Sn$ (477.31): calcd. C 55.36, H 9.70; found C 55.49, H 9.88.

(*S*,*E*)-5-Methyl-5-[2-(tributylstannyl)vinyl]dihydrofuran-2(3*H*)-one (5): To a vigorously stirred suspension of silica gel supported $NaIO_4$ reagent (12.0 g) in CH_2Cl_2 (50 mL) was added a solution of triol **10** (2.0 g, 4.2 mmol) in CH_2Cl_2 (20 mL). After completion of the reaction, PDC (2.02 g, 5.4 mmol) was added at 0 °C. The reaction mixture was stirred at room temp. for an additional 4 h period and filtered through a pad of silica gel, which was washed with

CH_2Cl_2 (2 × 50 mL), and the solvent was then evaporated. Silica gel column chromatography (ethyl acetate/light petroleum ether, 1:19) of the residue afforded lactone **5** (1.4 g, 84% over two steps) as a colorless liquid. R_f = 0.4 (ethyl acetate/light petroleum ether, 1:9). $[a]_D^{25}$ = –8.17 (*c* = 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 6.27 (d, *J* = 19.3 Hz, 1 H), 5.92 (d, *J* = 19.3 Hz, 1 H), 2.52 (dt, *J* = 6.8, 2.2 Hz, 2 H), 2.28–1.97 (m, 2 H), 1.60–1.21 (m, 18 H), 0.90 (m, 14 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 176.5, 148.6, 127.0, 86.6, 33.8, 29.0, 28.7, 27.1, 26.3, 13.6, 9.4 ppm. IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 1768, 1463, 1377, 1262, 1143, 1073, 992 cm^{-1}. $C_{19}H_{36}O_2Sn$ (415.20): calcd. C 54.96, H 8.70; found C 55.14, H 8.93.

(*S*)-5-[(1*E*,3*E*)-Dodeca-1,3-dienyl]-5-methyldihydrofuran-2(3*H*)-one (3) and (*S*)-5-[(1*E*,3*Z*)-Dodeca-1,3-dienyl]-5-methyldihydrofuran-2(3*H*)-one (13): A 50-mL two-necked round-bottom flask was charged with LiCl (0.59 g, 13.8 mmol) and flame dried under high vacuum. With cooling, $Pd(PPh_3)_4$ (0.27 g, 0.23 mmol) and CuCl (1.27 g, 13.8 mmol) were added, and the mixture was degassed (4×) under high vacuum with an Ar purge. DMSO (20 mL) was introduced with concomitant stirring, followed by the addition of vinyl iodide **4** (0.60 g, 2.3 mmol) and vinyl stannane **5** (1.40 g, 3.4 mmol). The resulting mixture was rigorously degassed (4×) under high vacuum with an Ar purge. The reaction mixture was stirred at room temp. for 2 h, and then heated to 60 °C for 24 h. After completion of the reaction, as monitored by TLC, the reaction mixture was cooled, diluted with ethyl acetate (50 mL), and washed with a mixture of brine (40 mL) and 5% aqueous NH_4OH (20 mL). The aqueous layer was further extracted with ethyl acetate (2 × 50 mL), and the combined organic layers were washed with water (50 mL) and then brine (50 mL), dried with Na_2SO_4, and concentrated. The crude product was purified by flash silica gel column chromatography (benzene/light petroleum ether, 1:1) to obtain (*E*,*E*)-**3** (0.496 g, 83%) and (*E*,*Z*)-**13** (0.054 g, 9%) as colorless liquids. R_f = 0.5 (benzene/light petroleum ether, 4:1). Data for (*E*,*E*)-**3**: $[a]_D^{25}$ = –2.42 (*c* = 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 6.14 (dd, *J* = 15.2, 10.1 Hz, 1 H), 5.92 (dd, *J* = 15.0, 10.1 Hz, 1 H), 5.67 (dt, *J* = 15.0, 6.8 Hz, 1 H), 5.51 (d, *J* = 15.2 Hz, 1 H), 2.54–2.45 (m, 2 H), 2.20–1.93 (m, 4 H), 1.45 (s, 3 H), 1.30 (m, 2 H), 1.17–1.26 (br. m, 12 H), 0.81 (t, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 176.5, 137.0, 132.0, 129.4, 128.8, 85.2, 34.4, 32.7, 31.9, 29.5, 29.3, 29.2, 29.1, 28.9, 26.7, 22.7, 14.1 ppm. IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3020, 1768, 1658, 1523, 1457, 1420, 1378, 1073, 992, 929, 669 cm^{-1}. Data for (*E*,*Z*)-**13**: $[a]_D^{25}$ = +9.37 (*c* = 0.65, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 6.52 (dd, *J* = 15.3, 11.0 Hz, 1 H), 5.94 (t, *J* = 10.0 Hz, 1 H), 5.67 (d, *J* = 15.4 Hz, 1 H), 5.5 (dt, *J* = 10.8, 7.6 Hz, 1 H), 2.58 (m, 2 H), 2.25–2.08 (m, 4 H), 1.53 (s, 3 H), 1.42–1.25 (m, 14 H), 0.88 (t, *J* = 6.4 Hz, 3 H) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3019, 1770, 1651, 1460, 1419, 1378, 1289, 1141, 1073, 987, 949, 932, 667 cm^{-1}. $C_{17}H_{28}O_2$ (264.40): calcd. C 77.22, H 10.67; found C 77.04, H 10.82.

(*S*)-(+)-Plakolide A (1): To a stirred solution of diisopropylamine (0.17 mL, 1.3 mmol) in anhydrous THF (20 mL) at –20 °C was added *n*BuLi (1.6 M in hexane, 0.78 mL, 1.3 mmol). The solution was stirred for 15 min whilst the cooling bath was maintained at –78 °C. Lactone **3** (0.3 g, 1.1 mmol) in THF (5 mL) was added, and the reaction mixture was stirred for 15 min followed by the addition of dimethyl(methylene)ammonium iodide (0.44 g, 2.4 mmol) in THF (5 mL). The reaction mixture was stirred for 6 h and gradually warmed to room temp. The solvent was removed under reduced pressure, and the residue was dissolved in methanol (10 mL). To this solution was added an excess amount of methyl iodide (0.17 mL, 2.8 mmol), and the resulting mixture was stirred at room temp. for 18 h. The solvent was removed under reduced pressure to give a solid residue that was washed with an aqueous $NaHCO_3$ solution (20 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (2 × 25 mL). The combined organic layer was dried with Na_2SO_4, and solvent was removed in vacuo to afford a crude residue, which on purification by silica gel column chromatography (ethyl acetate/light petroleum ether, 1:19) furnished **1** (0.26 g, 82%) as a colorless liquid. R_f = 0.3 (ethyl acetate/light petroleum ether, 1:9). $[a]_D^{25}$ = +43.2 (*c* = 1.5, MeOH). ^1H NMR (200 MHz, $CDCl_3$): δ = 6.22 (dd, *J* = 15.1, 10.1 Hz, 1 H), 6.23 (t, *J* = 2.7 Hz, 1 H), 5.99 (dd, *J* = 15.0, 10.1, Hz, 1 H), 5.76 (dt, *J* = 15.0, 6.8 Hz, 1 H), 5.61 (d, *J* = 15.2 Hz, 1 H), 5.61 (t, *J* = 2.4 Hz, 1 H), 2.93 (dt, *J* = 16.6, 2.6 Hz, 1 H), 2.79 (dt, *J* = 16.6, 2.6 Hz, 1 H), 2.07 (dt, *J* = 7.2, 6.9 Hz, 2 H), 1.53 (s, 3 H), 1.40–1.25 (m, 12 H), 0.88 (t, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.78, 137.37, 135.31, 132.20, 129.67, 128.68, 122.26, 82.37, 40.79, 32.65, 31.85, 29.42, 29.23, 29.18, 29.09, 27.10, 22.64, 14.08 ppm. IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 1762, 1664, 1624, 1458, 1377, 1281, 1051, 990, 940 cm^{-1}. $C_{18}H_{28}O_2$ (276.41): calcd. C 78.21, H 10.21; found C 78.36, H 10.42.

(2*R*,3*R*)-3-Methyl-3-[(4-methylpent-3-enyl)oxiran-2-yl)methanol (Enantiomer of 7): The same procedure as that for **7** starting from geraniol (6.0 g, 38.9 mmol) gave the enantiomer of **7** (6.5 g, 98%) as a colorless oil. $[a]_D^{25}$ = +5.2 (*c* = 1.65, $CHCl_3$). $C_{10}H_{18}O_2$ (170.25): calcd. 70.60, H 10.58; found C 70.82, H 10.46.

(2*S*,3*R*)-3-(Chloromethyl)-2-methyl-2-(4-methylpent-3-enyl)oxirane (Enantiomer of 8): The same procedure as that for **8** starting from the enantiomer of **7** (5.5 g, 32.3 mmol) furnished the enantiomer of **8** (5.6 g, 91%) as a colorless liquid. $[a]_D^{25}$ = –10.26 (*c* = 2.1, $CHCl_3$). $C_{10}H_{17}ClO$ (188.69): calcd. C 63.65, H 9.00; found C 63.78, H 9.14.

(*R*)-3,7-Dimethyloct-6-en-1-yn-3-ol (Enantiomer of 6): The same procedure as that for **6** starting from the enantiomer of **8** (3.8 g, 20.1 mmol) furnished the enantiomer of **6** (2.6 g, 84%) as a colorless liquid. $[a]_D^{25}$ = +12.64 (*c* = 2.1, $CHCl_3$). $C_{10}H_{16}O$ (152.23): calcd. C 78.90, H 10.60; found C 79.06, H 10.78.

(6*R*)-2,6-Dimethyloct-7-yne-2,3,6-triol (Enantiomer of 9). The same procedure as that for **9** starting from the enantiomer of **6** (3.2 g, 21.0 mmol) afforded the enantiomer of **9** (3.6 g, 93%) as colorless oil. $C_{10}H_{18}O_3$ (186.25): calcd. C 64.49, H 9.74; found C 64.56, H 9.82.

(6*R*,*E*)-2,6-Dimethyl-8-(tributylstannyl)oct-7-ene-2,3,6-triol (Enantiomer of 10): The same procedure as that for **10** starting from the enantiomer of **9** (2.0 g, 10.7 mmol) gave the enantiomer of **10** (1:1 diastereomeric mixture; 4.7 g, 91%) as a colorless liquid. $C_{22}H_{46}O_3Sn$ (477.31): calcd. C 55.36, H 9.70; found C 55.49, H 9.88.

(*R*,*E*)-5-Methyl-5-[2-(tributylstannyl)vinyl]-dihydrofuran-2(3*H*)-one (Enantiomer of 5): The same procedure as that for **5** starting from the enantiomer of **10** (2.8 g, 5.9 mmol) furnished the enantiomer of **5** (2.03 g, 83%) as a colorless oil. $[a]_D^{25}$ = +9.55 (*c* = 1.3, $CHCl_3$). $C_{19}H_{36}O_2Sn$ (415.20): calcd. C 54.96, H 8.70; found C 55.14, H 8.93.

(*R*)-5-[(1*E*,3*E*)-Dodeca-1,3-dienyl]-5-methyldihydrofuran-2(3*H*)-one (Enantiomer of 3) and (*R*)-5-[(1*E*,3*Z*)-Dodeca-1,3-dienyl]-5-methyldihydrofuran-2(3*H*)-one (Enantiomer of 13): The same procedure as that for **3** starting from the enantiomers of **5** (1.18 g, 2.85 mmol) and **4** (0.5 g, 1.9 mmol) afforded the enantiomers of **3** (0.42 g, 84%) and **13** (0.045 g, 9%), respectively, as colorless liquids. (*E*,*E*) Isomer: $[a]_D^{25}$ = +2.68 (*c* = 1.8, $CHCl_3$). (*E*,*Z*) Isomer: $[a]_D^{25}$ = –10.74 (*c* = 1.4, $CHCl_3$). $C_{17}H_{28}O_2$ (264.40): calcd. C 77.22, H 10.67; found C 77.04, H 10.82.

(*R*)-(–)-Plakolide A (2). The same procedure as that for **1** starting from the enantiomer of **3** (0.2 g, 0.76 mmol) gave **2** (0.17 g, 83% yield) as a colorless liquid. $[\alpha]_D^{25}$ = –42.4 (*c* = 1.2, CH_3OH). ^1H NMR (200 MHz, $CDCl_3$): δ = 6.21 (dd, *J* = 15.1, 10.1 Hz, 1 H), 6.23 (t, *J* = 2.7 Hz, 1 H), 5.98 (dd, *J* = 15.0, 10.1 Hz, 1 H), 5.76 (dt, *J* = 15.0, 6.9 Hz, 1 H), 5.6 (d, *J* = 15.1 Hz, 1 H), 5.60 (t, *J* = 2.5 Hz, 1 H), 2.92 (dt, *J* = 16.6, 2.5 Hz, 1 H), 2.78 (dt, *J* = 16.6, 2.5 Hz, 1 H), 2.07 (dt, *J* = 7.3, 6.9 Hz, 2 H), 1.53 (s, 3 H), 1.38–1.25 (m, 12 H), 0.88 (t, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.53, 137.32, 135.41, 132.28, 129.73, 128.80, 122.19, 82.80, 40.90, 32.74, 31.94, 29.52, 29.32, 29.26, 29.18, 27.21, 22.72, 14.19 ppm. IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 1766, 1660, 1463, 1279, 1105, 1051 cm^{-1}. $C_{18}H_{28}O_2$ (276.41): calcd. C 78.21, H 10.21; found C 78.36, H 10.42.

Supporting Information (see footnote on the first page of this article): ^1H- and ^{13}C-NMR spectra of all compounds.

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