found to racemize very rapidly at ambient temperature, and thus NMR data were obtained on the racemates.

The magnitude of the lanthanide induced shift of epoxides **1–10** and arene oxides **11–14** is expressed in terms of the parameter G, the gradient of the initial straight line section of a plot of observed induced shift vs. mole ratio of shift reagent to substrate, obtained from eq 1–3,[14] where $\Delta\delta_{lim}$ is the limiting shift of the

$$G = \Delta\delta_{lim}\frac{KS}{1 + KS} \quad (1)$$

$$K = A/(S - A)(C - A) \quad (2)$$

$$\Delta\delta_{obs} = \Delta\delta_{lim}A/S \quad (3)$$

1:1 complex ($\Delta\delta_{lim} = \delta_{adduct} - \delta_{substrate}$), K is the equilibrium constant for the complex, S is the initial concentration of epoxide, A is the concentration of complex, and C is the concentration of added shift reagent. Values of $\Delta\delta_{lim}$ and K were determined by fitting the data of observed induced shifts ($\Delta\delta_{obs}$) as a function of the concentration of added shift reagent into eq 2 and 3 with a least-squares curve fitting routine of the MLAB program[29] in an interative mode. For each compound, five to eight concentrations up to a 0.8 M ratio, at which point the plots of $\Delta\delta_{lim}$ vs. the concentration ratio had begun to curve, were examined. Initial volumes of 0.70 mL increased to 0.85 mL in the course of adding the shift reagent, and appropriate corrections were made for the volume changes.

Registry No. **1a**, 105205-70-7; **1b**, 52485-73-1; **2a**, 20780-54-5; **2b**, 20780-53-4; **3a**, 66701-19-7; **3b**, 62137-64-8; **4a**, 24825-01-2; **4b**, 58800-12-7; **5a**, 58717-28-5; **5b**, 58680-03-8; **6a**, 77550-46-0; **6b**, 95911-24-3; **7a**, 68906-81-0; **7b**, 68906-75-2; **8a**, 89618-18-8; **8b**, 89618-17-7; **9a**, 89772-83-8; **9b**, 78549-58-3; **10a**, 89618-15-5; **10b**, 89618-16-6; **11a**, 74444-65-8; **11b**, 74444-64-7; **12a**, 72010-12-9; **12b**, 72010-13-0; **13a**, 100017-09-2; **13b**, 100017-08-1; **14a**, 94729-53-0; **14b**, 94729-54-1; (±)-**15**, 84608-95-7; (±)-**16**, 92343-85-6; (±)-**17**, 66226-25-3; (±)-**18**, 66239-76-7; (±)-**19**, 105307-18-4; Eu(hfc)$_3$, 34788-82-4; Eu(tfc)$_3$, 34830-11-0.

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Synthesis of (-)- and (+)-Frontalin

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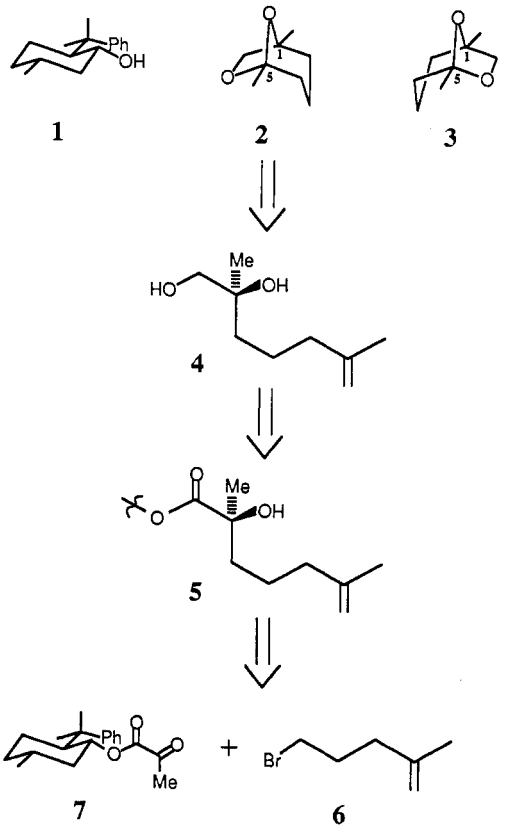
Recently we reported[1] on the high level of induction obtained in the Grignard additions to and in ene reactions of the glyoxylate ester of 8-phenylmenthol (**1**). We now report the application of this method for absolute stereochemical control in the separate syntheses of each of the enantiomers of frontalin.

Frontalin, first isolated by Kinzer,[2] is a component of the aggregation pheromone of the southern pine beetle *Dendroctonus frontalis* Zimmerman, and western pine beetle, *Dendroctonus brevicomis* Le Conte. Through unambiguous syntheses of both enantiomers and biological testing, Mori[3] has shown that the absolute configuration of the biologically active species **2** is 1*S*,5*R*. Its antipode **3** was found to be inactive. Other syntheses and studies[4] of frontalin have also been published.

Scheme I



(*S*)-(-)-Frontalin (2). Although frontalin contains two asymmetric centers, only the stereochemistry of C1 needs to be specifically addressed in the planning stages of a synthesis since the correct configuration at C5 is dictated by that of C1 during the formation of the bicyclic, ketal system. Thus, tertiary alcohol **4** (Scheme I), which contains suitable functionality for elaboration to (*S*)-frontalin, represents an ideal precursor. In turn, **4** could be obtained from hydroxy ester **5** by reduction, itself the product of addition of the Grignard reagent prepared from bromide **6** to the pyruvate ester **7** of 8-phenylmenthol.[5,6]

In the event, conversion of **6** to the Grignard reagent followed by reaction with the ester **7** at −78 °C provided

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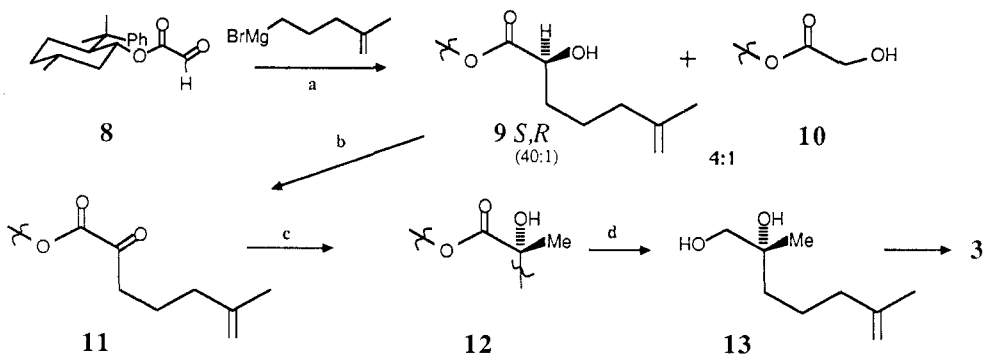
Scheme II[a]



[a] Key: (a) $LiClO_4$, Et_2O, −78 °C; (b) PDC, CH_2Cl_2, room temperature; (c) MeMgBr, Et_2O, −78 °C; (d) $LiAlH_4$, THF; (e) O_3, CH_2Cl_2; Me_2S.

the hydroxy ester **5** in a 62% isolated yield as a single diastereomer.[7] Reduction of hydroxy ester **5** with lithium aluminum hydride resulted in release of the auxiliary **1** and formation of the requisite diol **4**. The optical rotation of **4**, $[\alpha]_D$ −2.4° (lit.[4b] $[\alpha]_D$ −2.0° for *S*, $[\alpha]_D$ +2.4° for *R*), was consistent with an optical purity of 100% and confirmed our assignment of an *S* configuration at C2 in ester **5**. Treatment of diol **4** with ozone at −78 °C followed by a reductive workup with dimethyl sulfide provided (*S*)-frontalin in a 60% yield after distillation. The spectra of this sample were identical to those given in the literature.[3,4] Moreover, the optical rotation, $[\alpha]_D$ −54.8° (lit.[4b] $[\alpha]_D$ −54.4°), confirmed an optical purity of 100%.

(*R*)-(+)-Frontalin (3). Reversing the order of addition of the substituents in the formation of the tertiary alcohol **4** employed above for the synthesis of (*S*)-(−)-frontalin would lead to the opposite absolute stereochemistry and ultimately to the synthesis of (*R*)-frontalin (Scheme II). Thus, the addition of the Grignard of **6** complexed[8] with lithium perchlorate to the parent glyoxylate **8** afforded **9*S*** with a selectivity of 40:1 over **9*R*** (*R*) as well as the hydroxyacetate ester **10** (addition:reduction = 4:1). Oxidation[10] of hydroxy ester **9a** provided keto ester **11** (as well as minor amounts of 8-phenylmenthone and unreacted hydroxy ester). Addition of methylmagnesium bromide to **11** at −78 °C provided the tertiary hydroxy ester **12** as a single diastereomer. Reduction of **12** with lithium aluminum hydride provided the auxiliary **1** and the requisite diol **13** with an optical rotation, $[\alpha]_D$ +2.4°, equal in magnitude but opposite in sign to that obtained for its enantiomer **4** in the *S* series. (*R*)-Frontalin (**3**) was prepared from diol **13** by the same procedure as that in the *S* series, providing material with an optical rotation ($[\alpha]_D$ +54.3°) equal in magnitude but opposite in sign from that obtained in the *S* series, indicating an optical purity of 100%.

In summary, a synthesis of both enantiomers of frontalin has been completed that is amenable to the synthesis of multigram quantities. We anticipate that 8-phenylmenthol (**1**) will continue to prove to be very useful as a synthetic tool in providing intermediates of high optical purity for use in the synthesis of a wide range of natural products. Indeed, we are currently employing its use in the synthesis of iridoid terpenes.

Experimental Section

Materials. Ether and tetrahydrofuran (THF) were distilled prior to use from a deep blue solution resulting from benzophenone and sodium. Methylene chloride and dimethyl sulfide were distilled from calcium hydride. Skelly-B (hexane) was stirred with sulfuric acid and then solid sodium carbonate and distilled before use. All other solvents and reagents were used as obtained from commercial sources.

Procedures. Reactions were routinely run under a dry nitrogen atmosphere with magnetic stirring. Organic solutions of products were dried with molecular sieves prior to concentration in vacuo. Crude products were routinely passed through short columns of silica gel with an appropriate mixture of hexane and ethyl acetate. A Waters system with a 6000A pump and U6K injector was used for analytical (3.8 mm × 30 cm μ-Porasil column) and semipreparative (two 1 cm × 60 cm Porasil A columns or one 7.8 mm × 30 cm μ-Porasil column) HPLC. TLC was performed on precoated silica gel 60 plates from EM reagents. A Perkin-Elmer 144 polarimeter was used to obtain optical rotations using a 1-cm^3 cell with a 1-dm path length.

Spectra. ^1H NMR data were obtained on a Nicolet NT-360 (361-MHz) instrument. ^{13}C NMR data were obtained on a Varian FT-80A (20-MHz) or a Nicolet NT-360 (90-MHz) instrument. Both ^1H and ^{13}C NMR spectra were obtained with $CDCl_3$ as the solvent and are reported (ppm) downfield from Me_4Si as internal standard. Except for ester **5**, assignments are not provided for the 8-phenylmenthol subunit in the carbon spectra since the absorptions for the chiral auxiliary are relatively constant. IR spectra were obtained on dilute dichloromethane solutions on a Perkin-Elmer 298 instrument.

(1*S*)-(−)-Frontalin (2). A solution of 170 mg (1.07 mmol) of diol **4** in 40 mL of CH_2Cl_2 was cooled to −78 °C, and ozone in oxygen was passed through the solution until a blue color persisted, after which excess ozone was removed by passing dry N_2 through the solution. Dimethyl sulfide (0.40 g, 6.5 mmol) was then added, and the reaction was maintained at −78 °C for 5 min and then warmed to −10 °C. The reaction was held for 70 min at −10 °C, 0.01 mL of 12 N HCl was added, and the reaction was allowed to warm slowly to room temparature. After 1.5 h, the reaction was concentrated and the residue partitioned between 5 mL of Et_2O and 3 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with two 5-mL portions of Et_2O, and the combined organic layers were dried and concentrated, affording 170 mg. The sample was vacuum distilled (35 mmHg), providing 91 mg (60%) of frontalin **2**. Additional purification by GLC (94 °C, Carbowax 20M) provided 57 mg of optically pure frontalin **2**: ^{13}C NMR (90 MHz) δ 108.0 (s, C5), 80.0 (s, C1), 74.2 (t, C7), 34.5 (t, C4), 33.9 (t, C2), 24.7 (q, C10), 23.0 (q, C9), 18.0 (t, C3); ^1H NMR (361 MHz) δ 3.92 (d, J = 7.4 Hz, 1 H), 3.46 (dd, J = 1.8, 7.4 Hz, 1 H), 1.97–1.8 (m, 1 H), 1.7–1.5 (m, 5 H), 1.44 (s, 3 H), 1.33 (s, 3 H); $[\alpha]_D$ −54.8° (*c* 0.52, Et_2O) [lit.[4j] $[\alpha]_D$ −54.4° (*c* 1.33, Et_2O)].

(1*R*)-(+)-Frontalin (3). By the same procedure employed for the preparation of (−)-frontalin, 160 mg (1.01 mmol) of diol

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13 was converted to 55 mg (39%) of optically pure 3 with proton and carbon spectral data identical with those obtained for the (+) enantiomer: $[\alpha]_D$ +54.3° (c 0.3, Et_2O) [lit.[4b] $[\alpha]_D$ +54.3° (c 3.39, Et_2O)].

(−)-(2*S*)-2,6-Dimethyl-6-heptene-1,2-diol (4). To 70 mg (1.7 mmol) of $LiAlH_4$ in 10 mL of THF was added dropwise (ca. 8 min) a solution of 0.67 g (1.7 mmol) of ester 5 in 5 mL of THF. The reaction was stirred for 19 h at room temperature, and then 0.5 mL of saturated aqueous Na_2SO_4 was added followed after 10 min by anhydrous Na_2SO_4. This mixture was stirred for 20 min after which the salts were removed by filtration and washed with EtOAc. Concentration of the combined organics afforded 0.69 g. Separation by flash column chromatography (10:1 Skelly-B–EtOAc, and then EtOAc) provided 0.27 g (99%) of optically pure diol 4 and 0.40 g (100%) of alcohol 1: ^{13}C NMR (90 MHz) δ 145.6 (s, C6), 110.1 (t, C7), 73.0 (s, C2), 69.8 (t, C1), 38.3 (t, C3 or C5), 38.2 (t, C3 or C5), 23.2 (t, C4), 22.3 (q, C6 methyl), 21.7 (q, C2 methyl); ^1H NMR (361 MHz) δ 4.70 (d, J = 12.2 Hz, 2 H), 3.46 (d, J = 11.0 Hz, 1 H), 3.40 (d, J = 11.0 Hz, 1 H), 3.10 (s, 1 H), 2.72 (s, 1 H), 2.06–1.98 (m, 2 H), 1.72 (s, 3 H), 1.52–1.43 (m, 4 H), 1.16 (s, 3 H); IR 3590, 3420, 2940, 1460, 1375, 1115, 1045, 890 cm^{-1}; $[\alpha]_D$ −2.4° (c 0.7, CH_2Cl_2) [lit.[4b] $[\alpha]_D$ −2.0° (c 0.98, CH_2Cl_2)].

(1*R*)-8-Phenylmenthyl (2*S*)-2-Hydroxy-2,6-dimethyl-6-heptenoate (5). In a 15-mL flask was placed 90 mg (3.6 mmol) of magnesium, which was covered with 2 mL of Et_2O. A few drops of dibromoethane and bromide 6 were added. When the reaction was initiated, a solution of 0.29 g (1.8 mmol) of bromide 6 in 3 mL of Et_2O was added at such a rate that a vigorous reflux was maintained. After the reaction had cooled, the Grignard solution was added via a syringe to a solution of 0.45 g (1.5 mmol) of pyruvate in 10 mL of Et_2O at −78 °C. After 7 h at −78 °C, the reaction was poured into 25 mL of saturated aqueous NH_4Cl. The aqueous layer was extracted with three 25-mL portions of Et_2O, and the combined organics were washed with 25 mL of saturated aqueous NH_4Cl and 10 mL of water. Concentration of the organic layer afforded 0.48 g of 5 as an oil. semipreparative HPLC (20:1 Skelly-B–EtOAc) provided 0.36 g (62%) of the adduct 5 as a single diastereomer. In addition, 65 mg (R:S = 10:1) of the lactate ester and 0.11 g of the pyruvate ester were recovered: ^{13}C NMR (90 MHz) δ 176.3 (s, C1), 150.9 (s, C'11), 145.3 s, C6), 128.2 (d, C'12), 125.5 (d, C'13 and C'14), 110.2 (t, C7), 76.9 (d, C'1), 74.4 (s, C2), 49.9 (d, C'2), 41.7 (t, C'6), 40.0 (s, C'7), 39.7 (t, C3), 37.9 (t, C5), 34.5 (t, C'4), 31.3 (d, C'5), 27.6 (q, C'9 or C'10), 27.1 (t, C4), 26.5 (t, C'3), 25.3 (q, C'9 or C'10), 22.2 (q, C6 methyl), 21.7 (q, C'8), 21.6 (q, C2 methyl); ^1H NMR (361 MHz) δ 7.35–7.1 (m, 5 H), 4.9 (dt, J = 4.8, 11.0 Hz, 1 H), 4.68 (d, J = 12.9 Hz, 2 H), 2.72 (s, 1 H), 2.14–0.9 (m, 14 H), 1.7 (s, 3 H), 1.32 (s, 3 H), 1.22 (s, 3 H), 1.18 (s, 3 H), 0.86 (d, J = 6.6 Hz, 3 H); IR 3540, 2960, 2920, 1715, 1460, 1180 cm^{-1}.

(1*R*)-8-Phenylmenthyl Lactate: ^{13}C NMR (90 MHz) δ 173.7 (s, C1), 151.9, 128.1, 125.4, 75.8, 67.5 (d, C2, *R*), 66.3 (d, C2, *S*), 50.1, 41.6, 39.7, 34.5, 31.4, 28.4, 26.6, 24.7, 21.7, 20.3 (q, C3, *S*), 19.2 (q, C3, *R*); ^1H NMR (361 MHz) δ 7.35–7.1 (m, 5 H), 4.9 (dt, J = 4.8, 11.0 Hz, 1 H), 3.82 (q, J = 7.0 Hz, 1 H), 1.30 (s, 3 H), 1.21 (s, 3 H), 1.18 (s, 3 H), 0.88 (d, J = 6.6 Hz, 3 H).

(1*R*)-8-Phenylmenthyl (2*S*,2*R*)-2-Hydroxy-6-methyl-6-heptenoate (9a and 9b). In a 15-mL flask was placed 0.20 g (8.3 mmol) of magnesium, which was covered with 5 mL of Et_2O. A few drops of dibromoethane and bromide 6 were added. When the reaction had been initiated, a solution of 0.68 g (4.2 mmol) of bromide 6 in 20 mL of Et_2O was added at such a rate that a vigorous reflux was maintained. After the reaction had cooled, 0.67 g (6.3 mmol) of $LiClO_4$ was added, and stirring was continued for 45 min. The Grignard reagent solution was then added via a syringe to a solution of 1.0 g (3.5 mmol) of glyoxylate 8 in 40 mL of Et_2O at −78 °C. After 5 h at −78 °C, the reaction was poured into 25 mL of saturated aqueous NH_4Cl and the aqueous layer was extracted with three 25-mL portions of Et_2O. The combined organics were washed with 25 mL of saturated aqueous NH_4Cl and 10 mL of water. Concentration afforded 1.1 g of an oil. Analytical HPLc (15:1 Skelly-B–EtOAc) and ^{13}C NMR of the crude reaction mixture revealed an *S* to *R* ratio of 40 to 1 and an addition to reduction ratio of 4 to 1 (all resolved). Semipreparative HPLC (10:1 Skelly-B–EtOAc) provided 0.44 g (34%) of the *S* adduct 9a as a single diastereomer and 0.12 g of the hydroxyacetate ester 10.

2*S* (9a): ^{13}C NMR (90 MHz) δ 174.6 (s, C1), 151.7, 145.2 (s, C6), 128.0, 125.2, 110.1 (t, C7), 75.6, 69.8 (d, C2), 50.4, 41.6, 39.4, 37.4 (t, C5), 34.5, 33.6 (t, C3), 31.3, 29.2, 26.3, 23.4 (t, C4), 22.6, 22.3 (q, C6 methyl), 21.7; ^1H NMR (361 MHz) δ 7.4–7.1 (m, 5 H), 4.86 (dt, J = 4.4, 11.0 Hz, 1 H), 4.66 (d, J = 20.3 Hz, 2 H), 3.25–3.18 (m, 1 H), 1.68 (s, 3 H), 1.28 (s, 3 H), 1.18 (s, 3 H), 0.88 (d, J = 6.6 Hz, 3 H); IR 3520, 2960, 2920, 1720, 1495, 1455, 1390, 1370, 1225, 1100, 1030, 980 cm^{-1}.

2*R* (9b): ^{13}C NMR (90 MHz) δ 173.2 (s, C1), 151.9, 145.3 (s, C6), 128.1, 125.4, 110.1 (t, C7), 75.9, 71.2 (d, C2), 50.1, 41.7, 39.7, 37.4 (t, C5), 34.5, 33.0 (t, C3), 31.4, 28.6, 26.6, 24.4 (t, C4), 22.9, 22.2 (q, C6 methyl), 21.7; ^1H NMR (361 MHz) δ 7.35–7.1 (m, 5 H), 4.92 (dt, J = 4.4, 11.0 Hz, 1 H), 4.65 (d, J = 14.7 Hz, 2 H), 3.76–3.66 (m, 1 H), 2.19–2.08 (m, 1 H), 2.08–1.88 (m, 2 H), 1.88–1.74 (m, 2 H), 1.74–0.95 (m, 11 H), 1.66 (s, 3 H), 1.31 (s, 3 H), 1.20 (s, 3 H), 0.88 (d, J = 6.6 Hz, 3 H); IR 3560, 2980, 2920, 1720, 1455, 1440, 1235, 1105 cm^{-1}.

(1*R*)-8-Phenylmenthyl Hydroxyacetate (10): ^{13}C NMR (90 MHz) δ 172.3 (s, C1), 151.6, 128.0, 125.3, 75.2, 60.5 (t, C2), 50.4, 41.7, 39.5, 34.6, 31.3, 29.2, 26.4, 23.4, 21.8; ^1H NMR (361 MHz) δ 7.35–7.1 (m, 5 H), 4.94 (dt, J = 4.4, 11.0 Hz, 1 H), 3.6 (d, J = 16.5 Hz, 1 H), 3.23 (d, J = 16.5 Hz, 1 H), 1.34 (s, 3 H), 1.21 (s, 3 H), 0.88 (d, J = 6.6 Hz, 3 H); IR 3550, 2920, 1728, 1455, 1440, 1230, 1085 cm^{-1}.

(1*R*)-8-Phenylmenthyl 2-Keto-6-methyl-6-heptenoate (11). To 2.8 g (7.5 mmol) of pyridinium dichromate and 0.29 g (1.5 mmol) of PTFA in 9 mL of CH_2Cl_2 was added a solution of 1.1 g (3.0 mmol) of hydroxy ester 9a in 6 mL of CH_2Cl_2. After 9 days the reaction was diluted with 10 mL of Et_2O and filtered through a pad of alumina. The sample was concentrated, and the residue was taken up in Skelly-B and passed through a short column of silica. Concentration followed by semipreparative HPLC (10:1 Skelly-B–EtOAc) provided 0.69 g of an inseparable mixture of keto ester 11 and 8-phenylmenthone (ca. 20%). In addition, 0.23 g (8%) of the hydroxy ester 9a was recoverd: ^{13}C NMR (90 MHz) δ 193.7 (s, C2), 159.1 (s, C1), 151.1, 144.7 (s, C6), 128.1, 125.5, 110.8 (t, C7), 76.7, 50.4, 41.5, 39.7, 38.3 (t, C3 or C5), 36.8 (t, C3 or C5), 34.4, 31.4, 28.5, 26.6, 24.6 (t, C4), 22.1 (q, C6 methyl), 21.7, 20.7; ^1H NMR (361 MHz) δ 4.95 (dt, J = 4.4, 11.0 Hz, 1 H), 4.7 (d, J = 23.9 Hz, 2 H), 1.7 (s, 3 H), 1.32 (s, 3 H), 1.22 (s, 3 H), 0.90 (d, J = 6.6 Hz, 3 H); IR 2950, 2920, 1735, 1720, 1450, 1390, 1370, 1085, 1045, 910 cm^{-1}.

(1*R*)-8-Phenylmenthyl (2*R*)-2-Hydroxy-2,6-dimethyl-6-heptenoate (12). To 0.71 g of keto ester 11 (containing ca. 20% of 8-phenylmenthone) in 40 mL of Et_2O cooled to −78 °C was added 0.69 mL of a 2.8 M ethereal solution of MeMgBr, and the reaction was held at −78 °C for 6 h. The reaction was poured into a mixture of 25 mL of saturated aqueous NH_4Cl and 25 mL of Et_2O, and the aqueous layer was extracted with four 20-mL portions of Et_2O. Concentration of the combined organic layers afforded 0.79 g of an oil. Semipreparative HPLC (20:1 Skelly-B–EtOAc) provided 0.43 g (34% from 9a) of the adduct 13 as a single diastereomer: ^{13}C NMR (90 MHz) δ 175.7 (s, C1), 151.5, 145.3 (s, C6), 128.3, 125.4, 110.1 (t, C7), 76.8, 74.6 (s, C2), 49.8, 41.5, 39.8, 39.4 (t, C3), 37.7 (t, C5), 34.6, 31.3, 27.4, 26.9 (t, C4), 26.2, 25.8, 22.2 (q, C6 methyl), 21.7 (q, C2 methyl and C'8); ^1H NMR (361 MHz) δ 7.35–7.15 (m, 5 H), 4.85 (dt, J = 4.8, 11.0 Hz, 1 H), 4.64 (d, J = 16.6 Hz, 2 H), 2.20–2.11 (m, 1 H), 2.02 (s, 1 H), 1.98–1.88 (m, 3 H), 1.67 (s, 3 H), 1.65–0.90 (m, 10 H), 1.32 (s, 3 H), 1.22 (s, 3 H), 1.20 (s, 3 H), 0.88 (d, J = 6.6 Hz, 3 H); IR 3560, 2960, 2920, 1715, 1465, 1375, 1185 cm^{-1}.

(2*R*)-(−)-2,6-Dimethyl-6-heptene-1,2-diol (13). By the same procedure utilized in the reduction of 5, 0.51 g (1.3 mmol) of 13 provided 0.19 g (91%) of optically pure diol 13 with proton and carbon NMR and IR spectral data identical with that of 4: $[\alpha]_D$ +2.4° (c 0.8, CH_2Cl_2) [lit.[4b] $[\alpha]_D$ +2.4° (c 1.12, CH_2Cl_2)].

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