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Total Partial Synthesis of (3*S*, 6*S*)-(+)-3,7-Dimethyl-6-hydroxy-3-acetoxyocta-1,7-diene and (3*S*, 6*S*)-(−)-3,7-Dimethylocta-1,7-diene-3,6-diol from Geraniol†

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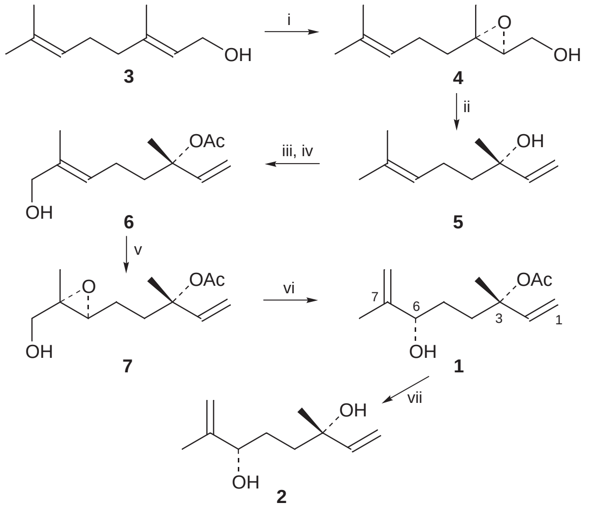
The synthesis of (3*S*, 6*S*)-(+)-3,7-dimethyl-6-hydroxy-3-acetoxyocta-1,7-diene and (3*S*, 6*S*)-(−)-3,7-dimethylocta-1,7-diene-3,6-diol *via* the rearrangement of the chiral 2,3-epoxy alcohol, with the system Ph_3P, pyridine, I_2 and H_2O, is described.

Compound **1**,[1] a novel monoterpenoid, has been isolated from *Mutisia spinosa* (Compositae) and compound **2** has been isolated from *Cinnamonum camphora*.[2] The absolute configurations at C-3 and C-6 of **1** and **2** have not been determined. Photooxidation of linalyl acetate and linalool[4] gave **1** and **2**, respectively. However the authors obtained an isomeric mixture. To our knowledge, the asymmetric synthesis of **1** and **2** has not been reported. Herein we report the total synthesis of (3*S*, 6*S*)-(+)-**1** and (3*S*, 6*S*)-(−)-**2** from geraniol **3** (Scheme 1).



Scheme 1 *Reagents*: i, ref. 5(*b*), 91%; ii, Ph_3P, I_2, pyridine, Et_2O–CH_3CN (5:3), 0 °C, 1 h, then 1 equiv. H_2O, 38 °C, 10 h, 98%, iii, Ac_2O, Et_3N, r.t., 10 h, 70%; iv, SeO_2, ButOOH, CH_2Cl_2, r.t., 2 h, 51%; v, $Ti(OPr^i)_4$, Bu^tOOH, L-(+)-DET, CH_2Cl_2, 4 Å M.S., CaH_2, silica gel, −40 to 20 °C, 5 h, 78%; vi, Ph_3P, I_2, pyridine, Et_2O–CH_3CN (5:3), 0 °C, 1 h, then 1 equiv. H_2O, 38 °C, 6 h, 90%; vii, K_2CO_3, MeOH, r.t., 2 h, 96%.

Geraniol **3** was epoxized by Sharpless asymmetric epoxidation [L-(+)-DET was employed].[5] By our method,[6] rearrangement of epoxide **4** gave linalool **5** in 98% yield and > 95% e.e.[7] Epoxide **4** was iodinated with Ph_3P (3 equiv.), pyridine (4 equiv.) and I_2 (1.5 equiv.) in dry diethyl ether and CH_3CN, then the iodide was converted to linalool **5** by addition of 1 equiv. H_2O.

Linalool **5** was protected with Ac_2O, Et_3N and DMAP,[8] then SeO_2 oxidation gave the allylic alcohol **6**.[9] Sharpless asymmetric epoxidation[5] of the allylic alcohol **5** with L-(+)-DET led to the (6*S*, 7*S*)- and (6*R*, 7*R*)-epoxy alcohols in a ratio of *ca.* 10:1. Rearrangement of epoxy alcohol **7** gave the title compound **1** in 90% yield. Treatment of **1** with K_2CO_3 in MeOH give the diol **2** in 96% yield. As the authors did not report the optical rotation of natural **1** and **2**, we could not determine the absolute configuration of C-3 and C-6.

Experimental

IR spectra were recorded on a Nicolet FT 170SX as liquid films, ^1H NMR spectra were recorded on a Bruker AC-80 or Bruker AM-400 spectrometer and ^{13}C NMR spectra were recorded on a 100 MHz spectrometer in $CDCl_3$ solution using TMS as internal reference. IR spectra were obtained using a FT 170SX (film) spectrophotometer. Mass spectra were measured on a VG ZAB-HS spectrometer by direct inlet at 70 eV, and signals are given in *m/z* with relative intensity (%) in parentheses. Optical rotation measurements were carried out on a Jasco 20C polarimeter.

Rearrangement of Compound **4** *to* **5**.—To a stirred solution of epoxy alcohol **1** (500 mg, 2.94 mmol) in dry Et_2O–CH_3CN (5:3, 16 mL) was added sequentially Ph_3P (2.31 g, 8.82 mmol), pyridine (0.94 mL, 11.76 mmol), I_2 (1.12 g, 4.41 mmol) at 0 °C. After stirring for 2 h at 0 °C, H_2O (53 μL, 2.94 mmol) was added to the system. The reaction mixture was refluxed for 10 h at 38 °C, then 20% $Na_2S_2O_3$ (aq) (2 mL) and saturated $NaHCO_3$ (aq) (2 mL) were added to quench the reaction and the organic layer extracted with ether (3 × 50 mL). The combined ether extracts were washed with 5% HCl (4 × 10 mL), saturated $NaHCO_3$ (10 mL), H_2O and brine, then dried. Evaporation of the solvent gave the residue, which was flash chromatographed eluting with light petroleum–ethyl acetate (6:1 v/v) to afford **4** (445 mg, 98%) as a colorless oil. $[\alpha]_D^{20}$ + 21.2 (*c* 0.6, $CHCl_3$); δ_H(400 MHz) ($CDCl_3$): 5.91 (1H, dd, $J = 17.3$, 10.7 Hz, CH=), 5.21 (1H, d, $J = 17.3$ Hz,CH=), 5.11 (1H, t $J = 6.7$ Hz CH=), 5.07 (1H, d, $J = 10.7$ Hz, CH=), 2.08–1.94 (2H, m, CH_2), 1.68 (3H, s, CH_3), 1.65 (3H, s, CH_3), 1.58–1.50 (2H, m, CH_2), 1.28 (3H, s, CH_3).

Acetylation and SeO_2 *Oxidation of Linalool* **5**.—A mixture of linalool (445 mg, 2.9 mmol), triethylamine (0.61 mL, 4.35 mmol), acetic anhydride (0.41 mL, 4.35 mmol) and DMAP (28 mg, 0.23 mmol) was stirred at r.t. for 10 h. The mixture was extracted with ether (3 × 50 mL) and the organic layer was washed with 5% HCl (4 × 5 mL), saturated $NaHCO_3$ (10 mL), H_2O and brine, then dried. Evaporation of the solvent gave the residue, which was flash chromatographed eluting with light petroleum–ethyl acetate (15:1 v/v) to afford linalyl acetate (400 mg, 70%) as a colorless oil. A solution of linalyl acetate (400 mg, 2.04 mmol) in 5 mL CH_2Cl_2 was added to a solution of SeO_2 (113 mg, 1.02 mmol) and Bu^tOOH (70%, 1.13 mL, 4.08 mmol) in 15 mL CH_2Cl_2 and the reaction mixture was stirred at r.t. for 2 h. The mixture was extracted with ether (3 × 50 mL) and the organic layer washed with 10% KOH (4 × 5 mL), saturated $NaHCO_3$ (10 mL), H_2O and brine, then dried. Evaporation of the solvent gave the residue which was flash chromatographed eluting with light petroleum–ethyl acetate (6:1 v/v) to afford linalyl acetate

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(210 mg, 51%) as a colorless oil. $[\alpha]_D^{21}$ + 8.61 (*c* 2.4, $CHCl_3$); δ_H(80 MHz) ($CDCl_3$): 5.90 (dd, *J* = 17.0, 10.8 Hz, 1H, CH=), 5.30 (t, *J* = 6.4 Hz, 1H, CH=), 4.00 (s, 2H, CH_2), 2.02 (s, 3H, CH_3), 2.18–1.92 (m, 2H, CH_2), 1.74–1.59 (m, 2H, CH_2), 1.65 (s, 3H, CH_3), 1.28 (s, 3H, CH_3).

Epoxidation of **6** *to* **7**.—To a mixture of $Ti(OP^i{}_4)_4)$ (0.3 mL, 1 mmol), CaH_2 (15 mg), 4 Å molecular sieves (40 mg) and silica gel H (20 mg) in 8 mL dry CH_2Cl_2 was added L-(+)-DET (0.21 mL, 1.2 mmol) under Ar at −20 °C. After 10 min, the allylic alcohol **6** (210 mg, 1 mmol) was added. The reaction mixture was stirred for another 10 min and Bu^tOOH (1.1 mL, 3.16 M in toluene, 2 mmol) was added at −40 °C. After 8 h at −20 °C, 2 mL 10% aqueous tartaric acid was added. After stirring for 1 h, the mixture was extracted with ether (3 × 50 mL) and the organic layer was washed with 10% KOH (2 × 10 mL), saturated $NaHCO_3$ (10 mL), H_2O and brine, then dried. Evaporation of the solvent gave the residue, which was flash chromatographed eluting with light petroleum–ethyl acetate (4:1 v/v) to afford epoxy alcohol **7** (177 mg, 77%) as a colorless oil. $[\alpha]_D^{24}$ − 6.4 (*c* 0.75, $CHCl_3$). IR: 3454, 3089, 2974, 2934, 1736, 1643, 1247, 1027, 927, 875 cm^{-1}. EIMS: *m/z* 197(0.2%, M − 31), 153 (0.4), 137(2), 111(6), 94(20), 79(27), 71(30), 55(24), 43(100). δ_H (400 MHz, $CDCl_3$): 5.91 (dd, *J* = 17.3 10.8 Hz, 1H, CH=), 5.15 (d, *J* = 17.3 Hz, 1H, CH=), 5.11 (d, *J* = 10.8 Hz, 1H, CH), 3.66 (d, *J* = 12.1 Hz, 1H, OCH), 3.54 (d, *J* = 12.1 Hz, OCH) 3.01 (t, *J* = 6.4 Hz, 1H epoxy H), 2.00 (s, 3H, CH_3), 2.03–1.95 (m, 1H, CH), 1.91–1.84 (m, H, CH), 1.65–1.59 (m, 1H, CH), 1.56–1.47 (m, 1H, CH), 1.55 (s, 3H, CH_3), 1.30 (s, 3H, CH_3).

(+)-3,7-*Dimethyl*-6-*hydroxy*-3-*acetoxyocta*-1,7-*diene* (**1**).—To a solution of epoxy alcohol **7** (140 mg, 0.61 mmol) in dry Et_2O-CH_3CN (5:3, 8 mL) was added sequentially Ph_3P (482 mg, 3 mmol), pyridine (0.2 mL, 2.45 mmol) and I_2 (234 mg, 0.92 mmol) at 0 °C. After stirring for 2 h at 0 °C, H_2O (11 µL, 0.61 mmol) was added to the system. The reaction mixture was refluxed for 6 h at 38 °C, then 20% $Na_2S_2O_3$ (aq) (2 mL) and saturated $NaHCO_3$ (aq) (2 mL) were added to quench the reaction and the organic layer extracted with ether (3 × 50 mL). The combined ether extracts were washed with 5% HCl (4 × 10 mL), saturated $NaHCO_3$ (10 mL), H_2O and brine, then dried. Evaporation of the solvent gave the residue, which was flash chromatographed eluting with light petroleum–ethyl acetate (6:1 v/v) to afford **1** (118 mg, 91%) as a colorless oil.$[\alpha]_D^{24}$ + 6.0 (*c* 0.80, $CHCl_3$). IR: 3435, 3075, 2974, 2941, 1736, 1647, 1251, 1020, 901 cm^{-1}. EIMS: *m/z* 152(0.4%, M − HOAc), 137(4), 109(5), 93(7), 71(58), 67(65), 55(23), 43(100). δ_H (400 MHz, $CDCl_3$): 5.93 (dd, *J* = 17.4, 10.9 Hz, 1H, CH=), 5.14 (d, *J* = 17.4 Hz, 1H, CH=), 5.11 (d, *J* = 10.9 Hz, 1H, CH=), 4.93, 4.84 (s, 2H, CH_2=), 4.03 (t, *J* = 6.4 Hz 1H, CHO), 2.00 (s, 3H, CH_3, 2.05–1.92 (m, 2H, CH_2), 1.82–1.77 (m, 2H, CH_2), 1.70 (s, 3H, CH_3), 1.53 (s, 3H, CH_3). δ_C(100 MHz, $CDCl_3$): 169.93, 147.06, 141.51, 113.28, 111.29, 82.73, 75.77, 35.65, 28.68, 23.63, 22.33, 17.33.

(−)-3,7-*Dimethylocta*-1,7-*diene*-3,6-*diol* (**2**).—A mixture of **1** (15 mg, 0.064 mmol) in methanol (1 mL) and anhydrous K_2CO_3 (8 mg) was stirred at r.t. for 2 h. The reaction mixture was diluted with Et_2O (30 mL), washed (2 × 5 mL H_2O, 5 mL brine), dried (anhydrous $MgSO_4$), and purified by column chromatography to yield **2** (12 mg, 96%). $[\alpha]_D^{21}$ − 7.53 (*c* 1.30, $CHCL_3$). IR: 3358, 3085, 2973, 2948, 2869, 1649, 1450, 1057, 999, 921, 899 cm^{-1}. EIMS: *m/z* 155(0.2%, M − 15), 137(4), 109(4), 96(4), 82(22), 71(61), 67(75), 55(39), 43(100), 41(56). δ_H (400 MHz $CDCl_3$): 5.90 (dd, *J* = 17.2, 10.7 Hz, 1H, CH=), 5.22 (d, *J* = 17.2 Hz, 1H, CH=) 5.06 (d, *J* = 10.7 Hz, 1H, CH=), 4.95, 4.84 (s, 2H, CH_2=), 4.06 (t, *J* = 6.3 Hz, 1H, CHO), 2.17 (bs, 2H, 2OH), 1.71 (s, 3H, CH_3), 1.76–1.54 (m, 4H, $2CH_2$), 1.29 (s, 3H, CH_3). δ_C(100 MHz, $CDCl_3$) 147.34, 145.01, 111.76, 110.83, 75.60, 72.86, 37.66, 29.10, 27.88, 17.84.

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