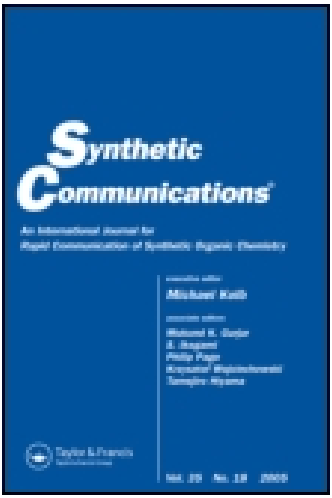

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# ASYMMETRIC SYNTHESIS OF 7-EPI-γ-EUDESMANOL

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# ASYMMETRIC SYNTHESIS OF 7-*EPI*-$\gamma$-EUDESMANOL

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## ABSTRACT

A facile and efficient asymmetric synthesis of 7-*epi*-$\gamma$-eudesmanol (**1**) starting from (−)-dihydrocarvone is described.

Naturally occurring eudesmane sesquiterpenoids have drawn considerable attention due to their wide spectrum of biological activities, such as antifeedant, cell growth inhibitory, plant growth regulation, and so on.[1–3]

7-*epi*-$\gamma$-Eudesmanol (**1**), a novel eudesmane derivative, was isolated recently from a traditional herbal plant, *Laggera alate*, by Ramanoelina and co-workers.[4]

In continuation of our on going project on the synthesis of bioactive sesquiterpenoids, we report the asymmetric synthesis of **1**.

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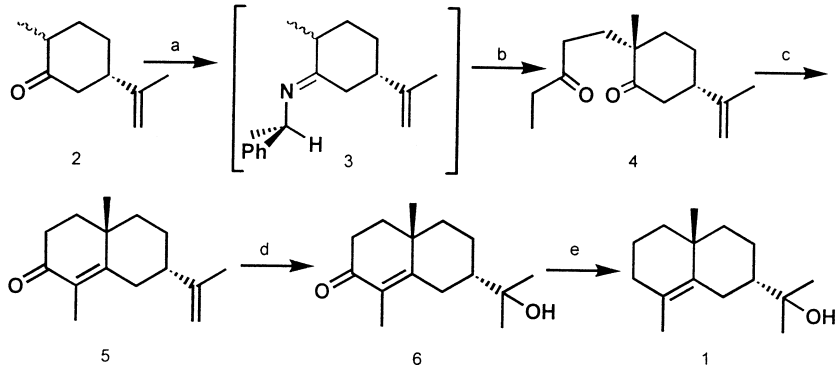


***Scheme 1.*** a) (*R*)-(+)-α-Phenylethylamine, toluene, reflux; b) i) EVK, THF, r.t.; ii) 50% HOAc, r.t.; c) NaOMe/MeOH, reflux; d) 10% $H_2SO_4$, THF, reflux; e) $AlCl_2H$, ether, 0°C.

Our synthesis started from (−)-dihydrocarvone (**2**). Asymmetric Micheal condensation of chiral imine **3** prepared in situ by the condensation of (*R*)-(+)-α-phenylethylamine (from Aldrich, 99% ee) with **2**, with ethyl vinyl ketone (EVK) to give dione **4**[5] in 77% yield, which was subjected to Robinson annulation by treatment with NaOMe in MeOH to afford the key intermediate 7-*epi*-α-cyperone (**5**) in 95% yield (de >95%, determined by GC). Selective hydration of **5** by 10% $H_2SO_4$ in THF gave **6** in 85% yield (based on recovered starting material), which was deoxygenated reductively with $AlCl_2H$[6] to give the title compound **1**. The synthetic **1** have shown identical spectral data with those of reported for the natural product.[4] The overall yield of the synthesis from **2** is 47%. During our synthetic work, we produced the key intermediate **5** in an excellent diasoselectivity. It can be changed into many other eudesmane-typed compounds by functional group transformation, so what we do is to give a general synthetic route of this kind of natural products in an much efficient and simple way.

## EXPERIMENTAL

For column chromatography, silica gel (200–300 mesh) and light petroleum ether (PE, b.p. 60–90°C) was used. IR spectra were recorded on a Nicolet FT-170SX spectrometer as liquid films. $^1$H NMR spectra were taken on a Bruker AM-400 spectrometer with TMS as an internal standard and $CDCl_3$ as solvent. Mass spectra were determined on a VG

ZAB-HS spectrometer (EI, 70 eV). Elemental analysis was performed on an Italian 1106 analyzer.

### (2S,5S)-2-Methyl-2-(3-pentanonyl)-5-isopropenylhexanone (4)

A mixture of (–)-dihydrocarvone (**2**) (0.94 g, 6.18 mmol) and (*R*)-(+)-α-phenylethylamine (0.8 g, 1.05 equiv.) in toluene (15 mL) was heated at refluxing temperature under argon atmosphere with azeotropic removal of water for 24 h. The resulting mixture was cooled in an ice bath and ethyl vinyl ketone (0.55 g, 1.05 equiv.) was added with a syringe under argon. The mixture was stirred and heated at 40°C under argon for 24 h. To the yellow solution, cooled in an ice bath, was added a 50% aq. Acetic acid (4 mL) and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was poured into brine and extracted with ether (3 × 20 mL). The organic layer was washed with 10% hydrochloric acid (2 × 15 mL), water (20 mL), and brine (2 × 15 mL), and dried ($MgSO_4$). After evaporation of the solvents under reduced pressure, the oily residue was chromatographed on silica gel, eluting with PE:ether (15:1) to give diketone **4** (1.12 g, 77% from **2**) as a light yellow oil. (Found: C, 76.04; H, 10.16. $C_{15}H_{24}O_2$ requires C, 76.23; H, 10.23); $[\alpha]_D^{10}$ −92.8 (*c* 1.2, $CHCl_3$); $\nu/cm^{-1}$ 1715, 1423, 1362, 899; $\delta_H$(400 MHz) 0.95(s, 3H, 2-Me), 0.98(t, 7.3 Hz, 3H, $MeCH_2$), 1.69(s, 3H, MeC=C), 4.67(br, s, 1H, C=$CH_2$), 4.72(br, s, 1H, C=$CH_2$); *m*/*z* 236($M^+$, 4), 207(1), 152(11), 109(18), 81(28), 67(61), 57(100).

### (+)-7-*epi*-α-Cyperone (5)

To a solution of diketone **4** (1.00 g, 4.24 mmol) in dry methanol (15 mL) was added a 25% sodium methoxide in methanol (1 mL) under argon, and the mixture was refluxed for 5 h. After being cooled, the resulting pink solution was neutralized with acetic acid. After removal of the solvent, the residue was dissolved in water (15 mL) and extracted with ether (3 × 20 mL). The organic phases were washed with brine (2 × 10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography to yield **5** (878 xmg, 95%) as a light yellow oil. (Found: C, 82.41; H, 10.09. $C_{15}H_{22}O$ requires C, 82.52; H, 10.16%), $[\alpha]_D^{10}$ + 169.9 (*c* 0.8, $CHCl_3$); $\nu/cm^{-1}$ 3004, 1716, 901; $\delta_H$(400 MHz) 1.20(s, 3H, 10-Me), 1.68(s, 3H, 11-Me), 1.77(s, 3H, 4-Me), 4.57(br, s, 1H, 12-H), 4.60(br, s, 1H, 12-H); *m*/*z* 218 ($M^+$, 32), 200(19), 175(42), 147(74), 91(100).

### 3-Oxo-7-*epi*-γ-eudesmanol (6)

To a solution of **5** (800 mg, 3.67 mmol) in THF (15 mL) was added 10% aq. $H_2SO_4$ (10 mL) and the mixture was refluxed for 4 h. After being cooled, the heterogeneous mixture was extracted with ether (3 × 20 mL), washed with saturated $NaHCO_3$ (2 × 10 mL), water (2 × 10 mL), and brine (2 × 10 mL), and dried ($MgSO_4$). The solvent was removed and the crude product was purified by silica gel chromatography to yield **6** (322 mg, 85%, based on recovered material) as a colorless oil, 450 mg of **5** was recovered. **6**: (Found: C, 76.11; H, 10.14, $C_{15}H_{24}O_2$ requires C, 76.23; H, 10.23%), $[\alpha]_D^{10} + 33.1$ (*c* 0.7, $CHCl_3$); $\nu/cm^{-1}$ 3444(OH), 1645, 1379, 1084; $\delta_H$(400 MHz) 1.15, 1.20, 1.22(s, 3H each, 11-Me × 2, 10-Me), 1.78(s, 3H, 4-Me); *m*/*z* 236($M^+$, 1), 218(3), 177(16), 165(23), 149(35), 137(20), 123(23), 109(26), 67(26), 43(100).

### 7-*epi*-γ-Eudesmanol (1)

To a solution of $AlCl_2H$[6] in dry ether (1 M, 20 mL) was added a solution of **7** (120 mg, 0.51 mmol) in dry ether (2 mL) dropwise at 0°C under argon. The resulting mixture was stirred at this temperature for an additional 2 h. The mixture was poured into crushed ice, extracted with ether (3 × 20 mL), washed with water (2 × 10 mL), sat. aq. $NaHCO_3$ (2 × 10 mL), and brine (2 × 10 mL), and dried ($MgSO_4$). After removal of the solvents, the oily residue was chromatographed on silica gel eluting with PE:ether (10:1) to give **1** (87 mg, 77%) as a colorless oil. (Found: C, 80.96; H, 11.70. $C_{15}H_{26}O$ requires C, 81.02; H, 11.78%); $[\alpha]_D^{10} -30.1$ (*c* 0.7, $CHCl_3$); (lit.[4] $[\alpha]_D^{25} -23.3$, *c* 1.2, $CHCl_3$); $\nu$/max 3375(OH), 2927, 1458, 1378; $\delta_H$(400 MHz) 1.07(s, 3H, 10-Me), 1,17(s, 3H, 11-Me), 1.23(s, 3H, 11-Me), 1.66(s, 3H, 4-Me); $\delta_C$(400 MHz) 18.92, 19.61, 22.57, 25.37, 25.94, 27.86, 29.79, 32.71, 34.42, 38.11, 39.44, 44.14, 74.50, 125.89, 134.99; *m*/*z* 222($M^+$, 2), 204(4), 189(5), 149(100), 112(10), 91(10), 59(27), 43(30).

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