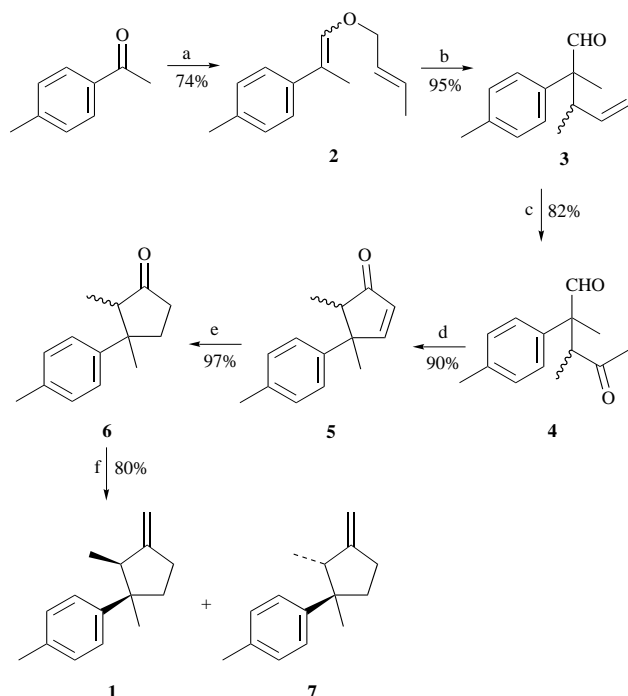


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A short and efficient total synthesis of (\pm)-laurene using a Wittig olefination–Claisen rearrangement–Wacker oxidation protocol is described.

Laurene **1**, a sesquiterpene isolated from *Laurentia glandulifera*¹ is structurally related to the cuparane class of sesquiterpenes. Like other members of this class, laurene has significant steric crowding around a compact cyclopentane ring. Several strategies² have been adopted for the synthesis of this sterically congested molecule. We report herein a short and efficient synthesis of (\pm)-laurene (Scheme 1) adopting the Wittig olefination methodology³ developed in our laboratory.



Scheme 1 Reagents and conditions: a, $\text{CH}_3(\text{H})\text{C}=\text{C}(\text{H})\text{CH}_2\text{OCH}_2\text{P}^+\text{Ph}_3\text{Cl}^-$, $\text{Bu}^-\text{O}^-\text{K}^+$, THF, 0 °C; b, toluene reflux, 18 h; c, PdCl_2 (10 mol%), CuCl_2 (10 mol%), O_2 , $\text{H}_2\text{O}:\text{DME}$ (1:9), room temp., 2 h; d, 5% aq. methanolic KOH, room temp., 2 h; e, 5% Pd/C ethyl acetate, H_2 (1 atm pressure), room temp., 8 h; f, Zn, CH_2Br_2 , TiCl_4 , THF, 0 °C, 12 h

On treating a suspension of 4-methylacetophenone (1.0 equiv.) and but-2-enyloxymethylenetriphenylphosphonium chloride³ (1.0 equiv.) in dry THF with potassium *tert*-butoxide (1.5 equiv.) the allyl vinyl ether **2** was obtained in 74% yield. This allyl vinyl ether **2**, on heating in refluxing toluene for 18 h, smoothly underwent Claisen rearrangement to yield the unsaturated aldehyde **3** in 95% yield. The ¹H NMR spectrum of this aldehyde showed it to be a 3:2 mixture of diastereomers. Wacker oxidation⁴ (10 mol% PdCl_2 , 10 mol% CuCl_2 , oxygen atmosphere) of this diastereomeric mixture of the aldehyde **3** in $\text{H}_2\text{O}:\text{DME}$ (1:9) at ambient temperature furnished the keto aldehyde **4** as a mixture of diastereomers (1:1) in 82% yield. A

(1:1) diastereomeric mixture of cyclopent-2-enone **5** was obtained in good yield (90%) when the keto aldehyde **4** was treated with KOH (5% in aqueous methanol) at ambient temperature for 2 h. Hydrogenation of the cyclopent-2-enone **5** over 5% Pd/C at ambient temperature afforded the cyclopentanone **6** as a mixture of diastereomers (1:1) in 97% yield. On subjecting this cyclopentanone **6** to Lambardo methylenation conditions⁵ (Zn, TiCl_4 , CH_2Br_2 , room temp., 12 h) a 1:1 mixture of (\pm)-laurene **1** and (\pm)-epilaurene **7** was obtained in 80% yield.

Experimental

General

All solvents were distilled before use. Dry THF was prepared by distillation over benzophenone and sodium under an argon atmosphere, and toluene was distilled and stored over sodium wire. All the anhydrous reactions were carried out under an argon atmosphere. IR Spectra were recorded on a Perkin-Elmer model 1600 series FTIR instrument. ¹H NMR Spectra [ppm, TMS internal standard; *J* values in Hz] in CDCl_3 were recorded on a JEOL FX90Q instrument and a Bruker AC-200 instrument. Elemental analysis was obtained on a HOSLI semiautomatic C, H analyser. Silica gel (100–200) mesh was used for column chromatography.

1-But-2-enyloxy-2-(4-methylphenyl)-2-methylethene **2**

But-2-enyloxymethylenetriphenylphosphonium chloride (4.98 g, 13 mmol) and 4-methylacetophenone (1.34 g, 10 mmol) were suspended in dry THF (20 cm^3). Potassium *tert*-butoxide (1.5 g, 13 mmol) in *tert*-butyl alcohol (10 cm^3) was added to it at 0 °C in a dropwise manner. The mixture was stirred at 0 °C for 1 h. Then the reaction mixture was diluted with water and extracted with diethyl ether (3 \times 50 cm^3). The combined ether extracts were washed with water, dried over anhyd. Na_2SO_4 and concentrated. The crude product on purification by column chromatography using hexane as eluent furnished pure **2** (*E*:*Z* 1:1) (1.49 g, 74%) as a colourless liquid (Found: C, 83.04; H, 9.07; $\text{C}_{14}\text{H}_{18}\text{O}$ requires C, 83.12; H, 8.97%); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 1638, 1500, 1435, 1371, 950 and 795; $\delta_{\text{H}}(90 \text{ MHz}; \text{CDCl}_3)$ 1.82 (3 H, d, *J* 5.1, C=C-CH₃), 2.21, 2.62, (3 H, s, *E* and *Z* C=C-CH₃), 2.25 (3 H, s, Ar-CH₃), 4.50 (2 H, m, O-CH₂-CH=), 5.96 (2 H, m, CH=CH), 6.45, 6.68 (1 H, s, *E* and *Z* O-CH=C), 7.4 to 7.91 (4 H, m, Ar-H).

2-(4-Methylphenyl)-2,3-dimethylpent-4-enal **3**

Colourless oil 95% bp 162 °C/8 Torr (Found: C, 83.19; H, 8.85. $\text{C}_{14}\text{H}_{18}\text{O}$ requires C, 83.12; H, 8.97%); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 2710.1, 1724.3 and 1636.9; $\delta_{\text{H}}(90 \text{ MHz}; \text{CDCl}_3)$ 0.76 (2 H, d, *J* 7.7, CH-CH₃), 1.00 (1 H, d, *J* 7.7, CH-CH₃), 1.34 (2 H, s, C-CH₃), 1.52 (1 H, s, C-CH₃), 2.53 (3 H, s, Ar-CH₃), 3.08 (1 H, m, CH-CH₃), 5.10 (2 H, m, CH=CH₂), 5.29 to 5.95 (1 H, m, CH=CH₂), 7.23 (4 H, s, Ar-H), 9.63 (1 H, s, CHO).

2-(4-Methylphenyl)-2,3-dimethyl-4-oxovaleraldehyde **4**

In a solution of unsaturated aldehyde **3** (0.8 g, 4 mmol) in aqueous dimethoxyethane (10 cm^3 , 1:9) was suspended PdCl_2 (0.071 g, 0.4 mmol) and CuCl_2 (0.05 g, 0.4 mmol). This mixture

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was stirred at room temp. under an oxygen atmosphere. On completion of reaction (TLC check, 3 h), the mixture was diluted with water and extracted with diethyl ether ($3 \times 25 \text{ cm}^3$). The combined ether layer was washed with water and dried over anhyd. Na_2SO_4 . The ether layer was concentrated and the crude product was purified by column chromatography using hexane–ethyl acetate (20:1) as eluent to obtain pure **4** (0.707 g, 82%) as a colourless oil, bp $97\text{--}99^\circ\text{C}/0.2 \text{ Torr}$ (Found: C, 77.14; H, 8.19. $\text{C}_{14}\text{H}_{18}\text{O}_2$ requires C, 77.03; H, 8.31%); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 2748, 1732 and 1725; $\delta_{\text{H}}(90 \text{ MHz}; \text{CDCl}_3)$ 0.95, 1.14 (3 H, d, J 7.7, $\text{CH}-\text{CH}_3$), 1.59, 1.64 (3 H, s, $\text{C}-\text{CH}_3$), 2.28 (3 H, s, COCH_3), 2.35 (3 H, s, $\text{Ar}-\text{CH}_3$), 3.34 (1 H, m, $\text{CH}-\text{CH}_3$), 7.25 (4 H, s, $\text{Ar}-\text{H}$), 9.57 (1 H, s, CHO).

4-(4-Methylphenyl)-4,5-dimethylcyclopent-2-enone **5**

Colourless oil, 90% (Found: C, 83.81; H, 8.13. $\text{C}_{14}\text{H}_{16}\text{O}$ requires C, 83.96; H, 8.05%); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 1715.6, 1588.8, 1513.6 and 1453.5; $\delta_{\text{H}}(90 \text{ MHz}; \text{CDCl}_3)$ 0.63, 1.18 (3 H, d, J 7.2, $\text{CH}-\text{CH}_3$), 1.41, 1.68 (3 H, s, $\text{C}-\text{CH}_3$), 2.32 (3 H, s, $\text{Ar}-\text{H}$), 2.45 (1 H, m, $\text{CH}-\text{CH}_3$), 6.52 (1 H, t, J 5.1, $\text{CO}-\text{CH}=\text{CH}$), 7.38 (4 H, m, $\text{Ar}-\text{H}$), 7.8, 8.0 (1 H, d, J 5.1, $\text{COCH}=\text{CH}$).

3-(4-Methylphenyl)-2,3-dimethylcyclopentanone **6**

Colourless oil, 97% (Found: C, 83.25; H, 8.91. $\text{C}_{14}\text{H}_{18}\text{O}$ requires C, 83.12; H, 8.97%); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 1740.6, 1515.0 and 1454.9; $\delta_{\text{H}}(90 \text{ MHz}; \text{CDCl}_3)$ 0.79, 1.07 (3 H, d, J 6.9, $\text{CH}-\text{CH}_3$), 1.21, 1.43 (3 H, s, $\text{C}-\text{CH}_3$), 1.28 (1 H, m, $-\text{CH}_2-$), 1.71 (1 H, m, $-\text{CH}_2-$), 2.08 (2 H, m, COCH_2), 2.27 (3 H, s, $\text{Ar}-\text{CH}_3$), 2.59 (1 H, m, $\text{CO}-\text{CH}-\text{CH}_3$), 7.24 (4 H, m, $\text{Ar}-\text{H}$).

Laurene **1** and epilaurene **7**

To a stirred suspension of Zn powder (5.6 g, 85.6 mmol) in THF (16 cm^3), a 1 M solution of titanium tetrachloride in dichloromethane (14 cm^3) and dibromomethane (3.2 cm^3 , 45 mmol) were added successively at 0°C and the stirring was continued for 15 min at room temp. To this mixture was added a

solution of ketone **6** (0.08 g, 0.4 mmol) in THF (2 cm^3) and the reaction mixture was stirred at ambient temperature for 12 h. It was then diluted with diethyl ether (10 cm^3) and treated with 10% HCl (5 cm^3). The mixture was extracted with diethyl ether and the extract was washed with NaHCO_3 and brine. The ether layer was dried over anhyd. Na_2SO_4 and concentrated. The crude product was purified by column chromatography using pentane as eluent to give a mixture of **1** and **7** (1:1) (0.063 g, 80%) as a colourless oil, bp $87\text{--}89^\circ\text{C}/10 \text{ Torr}$ (Found: C, 89.67; H, 10.00. $\text{C}_{15}\text{H}_{20}$ requires C, 89.94; H, 10.06%); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 1654.1, 1519.0 and 1447.8; $\delta_{\text{H}}(200 \text{ MHz}; \text{CDCl}_3)$ 0.73, 1.02 (3 H, d, J 7.3, $\text{CH}-\text{CH}_3$), 1.1, 1.61 (3 H, s, $\text{C}-\text{CH}_3$), 1.6 to 2.05 (2 H, m, CH_2-C), 2.39 (3 H, s, $\text{Ar}-\text{CH}_3$), 2.5 to 2.91 (3 H, m, $\text{CH}-\text{CH}_3$, $\text{C}=\text{C}-\text{CH}_2$), 5.0 (2 H, br s, $\text{C}=\text{CH}_2$), 7.35 (4 H, m, $\text{Ar}-\text{H}$).

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