The first synthesis of (–)-4-(1,5-dimethylhex-4-enyl)-2-methylphenol

Shaojun Shan and Chengyong Ha*

Guangzhou Institute of Chemistry, Chinese Academy of Sciences, PO. Box 1122, Guangzhou 510650, P. R. China

The first synthesis of (–)-4-(1,5-dimethylhex-4-enyl)-2-methylphenol from (+)-citronellal is described.

Keywords: (+)-citronellal, (–)-4-(1,5-dimethylhex-4-enyl)-2-methylphenol, enantiospecific synthesis, iostephane heterophylla

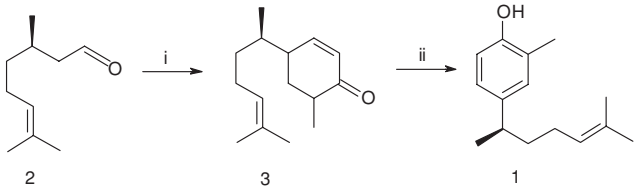
(–)-4-(1,5-dimethylhex-4-enyl)-2-methylphenol **1** was isolated in optically active form from Iostephane heterophylla.[1] The phenol **1** is a new naturally occurring bisabolene previously synthesised as a racemic mixture.[2] We now report the first enantiospecific synthesis of (–)-**1** from (+)-citronellal. The synthesis described here is short and efficient. The synthetic route to (–)-**1** is outlined in Scheme 1.

The key intermediate **3** was obtained from commercially available citronellal **2** following a reported procedure.[3] The ketone **3** was exposed[4] to $PdCl_2$ in *t*-butanol containing 4 equivalent of Na_2CO_3 at 80 °C to afford (–)-**1** in 68%.

Thus, the first enantiospecific synthesis of (–)-4-(1, 5-dimethylhex-4-enyl)-2-methylphenol has been achieved from readily available (+)-citronellal. The two reaction steps are very simple and the conditions are mild. The reactions proceed with excellent yields and are easy to perform

Experimental

4-(1,5-dimethyl-4-hexenyl)-6-methyl-2-cyclohexen-1-one (**3**) : To an ice cooled mixture of piperidine (1.12 g, 15 mmol) and anhydrous K_2CO_3 (0.35 g, 2.5 mmol) was added dropwise (+)-citronellal (1.54 g, 10 mmol, ee>96%). After stirring for additional 2 h, the solution was filtered. The residue was washed with anhydrous ether and added to the original filtrate. After drying the extract and removal of the solvent, freshly distilled methyl isopropenyl ketone (1.00 g, 12 mmol) was added to the above residue dropwise in a N_2 atmosphere with stirring for 0.5 h at 0 °C. The reaction mixture was then kept in a N_2 atmosphere at room temperature for 24 h. The resulting mixture was refluxed with glacial acetic acid (0.8 ml) for 4 h. It was then poured into water, extracted with ether and the ethereal layer washed with 5% hydrochloric acid and then with water. The organic layer was dried and the solvent removed. The residue was chromatographed on silica gel eluting with petroleum ether–acetone (100:2) to afford ketone **3** (1.65g, 75%). IR (film): 2964, 2921, 1678, 1629, 1454, 979 cm^{-1}; ^1H NMR ($CDCl_3$): δ6.80–6.70 (m, 1H), 6.10 (dd, J_{trans}=10.2 Hz, J_{cis}=2.4 Hz, 1H), 5.07 (t, *J* =6Hz, 1H), 2.62–2.53 (m, 2H), 1.98–1.70 (m, 3H), 1.66 (s,3H), 1.64–1.06 (m, 4H), 1.58 (s, 3H), 1.10 (d, *J* =6.8Hz, 3H), 0.91 (d, *J* =4Hz, 3H); ^{13}C NMR ($CDCl_3$): 200.7, 145.6, 131.1, 124.2, 121.0, 39.9, 37.3, 36.8, 36.0, 34.9, 33.9, 25.5, 20.4, 19.4, 17.5 ppm; MS (*m*/*z*): 220 (M^+, 1), 205 (3), 177 (9), 149 (6), 137 (16), 136 (13), 135 (10), 123 (13), 121 (16), 109 (41), 95 (42), 69 (84), 55 (34), 41 (100).



Scheme 1 Reagents and conditions: (i) 1) piperidine, K_2CO_3, 2) methyl isopropenyl ketone, 75%; (ii) $PdCl_2$, Na_2CO_3, *t*-butanol, 68%.

(–)-4-(1,5-dimethylhex-4-enyl)-2-methylphenol (**1**): A mixture of ketone **3** (1.10 g, 5 mmol), $PdCl_2$ (0.87 g, 5 mmol) and anhydrous Na_2CO_3 (2.76 g, 20 mmol) in *t*-butanol (100 ml) was refluxed for 10 h. The solution was then filtered and after drying and removal of the solvent, the residue was chromatographed on silica gel eluting with petroleum ether–AcOEt (100:4) to afford (–)-**1** (0.74g, 68%) as a colourless oil. $[\alpha]_D^{25}$ –46 (c 0.5, CH_3OH) [lit.[1] $[\alpha]_D$ –60 (c 1, CH_3OH)]; ee=96%; IR (film): 3428, 2960, 2925, 2856, 1610, 1508, 1455, 1376, 1261, 1118; ^1H NMR ($CDCl_3$): δ6.91 (s, 1H), 6.88 (d, *J*=2Hz, 1H), 6.69 (d, *J*=8Hz, 1H), 5.08 (t, *J*=7.2Hz, 1H), 4.5 (br s, OH), 2.59–2.30 (m, 1H), 2.22 (s, 3H), 1.86 (q, *J*=7.2Hz, 2H), 1.66 (s, 3H), 1.56–1.26 (m, 2H), 1.51 (s, 3H), 1.19 (d, *J*=6.8Hz, 3H); ^{13}C NMR ($CDCl_3$): 151.8, 139.9, 131.3, 129.6, 125.4, 124.6, 123.3, 114.7, 38.6, 29.7, 26.2, 25.7, 22.6, 17.6, 15.8 ppm; MS (*m*/*z*): 218 (M^+, 31), 203 (3), 161 (25), 148 (55), 135 (100), 121 (22), 91 (15), 69 (16), 55 (12).

The ee of (**1**) was determined by HPLC analysis (CHIRALCEL 01); hexane/*i*-PrOH= 100/5; flow rate 1.0ml min^{-1}

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* Correspondence.