

# A short and facile synthesis of lactarochromal and the corresponding acid†

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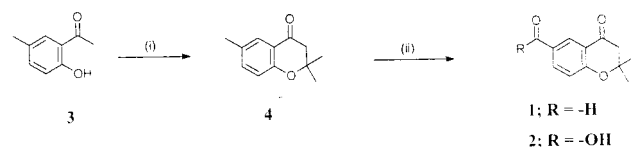
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Lactarochromal (**1**), a metabolite of *Lactarius deliciosus* and the corresponding acid (**2**), also a natural product from *Chrysothamnus viscidiflorus* have been synthesized starting from *p*-cresol.

**Keywords:** lactarochromal, *p*-cresol

Lactarochromal (**1**), a metabolite of the fungus *Lactarius deliciosus*, was isolated by Ayer and Trifonov,<sup>1</sup> and characterized on the basis of spectroscopic data. The corresponding acid (**2**) has been reported as a natural product from *Chrysothamnus viscidiflorus*.<sup>2</sup> Since structure (**1**) was based only on spectral data, synthetic support to confirm the assigned structure seemed desirable. Herein, we report a short and facile synthesis of (**1**) and the corresponding acid (**2**) starting from *p*-cresol (Scheme 1).

*p*-Cresyl acetate, prepared by acetylation of *p*-cresol with acetic anhydride in presence of pyridine, was subjected to Fries reaction as described in literature<sup>3</sup> to afford 2'-hydroxy-5'-methylacetophenone (**3**). The latter was condensed with acetone in presence of piperidine and pyridine to give 2,2,6-trimethyl-4-chromanone (**4**). Finally, oxidation of aromatic methyl group of (**4**) was accomplished using potassium persulfate and Cu(II) ions in aqueous acetonitrile<sup>4</sup> to furnish lactarochromal (**1**) and the corresponding acid (**2**). The melting point and spectral data (IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and MS) of our synthetic (**1**) were in good agreement with the published data.<sup>1</sup> The acid (**2**) was characterized by spectral data which agreed well with the reported<sup>2</sup> data. It is noteworthy that we obtained the acid (**2**) as a crystalline solid in contrast to the naturally occurring material which has been reported as an oil.



**Scheme 1** Reagents and conditions: (i) acetone, piperidine, pyridine, reflux, 72 h, (ii) K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>-Cu(II), CH<sub>3</sub>CN, H<sub>2</sub>O, 75–80°C, 1 h.

## Experimental

Melting points were determined by capillary method and are uncorrected. Column chromatography was performed on silica gel (60–120 mesh size, Macherey Nagel & Co) and TLC on precoated plastic sheets Polygram SIL G<sub>uv</sub> 254 (Macherey Nagel & Co, Duren, Germany). IR spectra were recorded on a Shimadzu FTIR-8001 (KBr pellet or neat). <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Varian instrument in CDCl<sub>3</sub> solution, and chemical shifts were recorded in ppm units using SiMe<sub>4</sub> as internal standard. Mass spectra were measured on Varian MAT 371 and Jeol D-300 Mass spectrometers at 70 eV.

**2,2,6-Trimethyl-2H-1-benzopyran-4-one (4):** A mixture of 2'-hydroxy-5'-methylacetophenone **3** (1 g, 6.66 mmol), acetone (2.5 ml), piperidine (0.56 ml, 6.66 mmol) and pyridine (2.5 ml) was heated at reflux for 72 h. The mixture was then cooled, concentrated under reduced pressure and poured into a mixture of 2N NaOH

(25 ml) and ice. The resultant solution was extracted with ethyl acetate, washed with water, dried over anhydrous MgSO<sub>4</sub> and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (petroleum ether-diethyl ether, 19:1) to afford **4** (0.98 g, 77 %) as a light yellow oil. IR ν<sub>max</sub> (neat) 1700, 1610, 1565, 1475, 1440, 1270 cm<sup>-1</sup>; δ<sub>H</sub> (200 MHz, CDCl<sub>3</sub>) 1.44 (s, 6 H, 2 × CH<sub>3</sub>), 2.3 (s, 3 H, CH<sub>3</sub>), 2.72 (s, 2 H, CH<sub>2</sub>), 6.82 (d, 1 H, *J* = 8.5 Hz, H-8), 7.28 (dd, 1 H, *J* = 8.5, 2.0 Hz, H-7), 7.65 (d, 1 H, *J* = 2.0 Hz, H-5); EIMS *m/z* (intensity %): 190 (M<sup>+</sup>) (70), 175 (M<sup>+</sup> - CH<sub>3</sub>) (100), 134 (50), 133 (28), 107 (16), 106 (44), 105 (28).

**Lactarochromal (1) and the corresponding acid (2):** Compound **4** (0.4 g, 2.106 mmol) in acetonitrile (15 ml) was added to a solution of potassium persulfate (1.25 g, 4.2 mmol) in water (15 ml) and copper sulfate (0.127 g, 5 mmol). The resulting solution was stirred at 75–80°C for 1 h and then cooled. The cold mixture was extracted with diethyl ether (3 × 50 ml). The diethyl ether extract was extracted with 60 % sodium bicarbonate solution (3 × 30 ml). Acidification of the bicarbonate extract with dilute HCl gave a colourless crystalline solid **2** (0.09 g, 19 %), m.p. 182°C, IR ν<sub>max</sub> (KBr) 3000, 1710, 1610, 1565, 1475, 1440, 1270 cm<sup>-1</sup>; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 1.49 (s, 6 H, 2 × CH<sub>3</sub>), 2.85 (s, 2 H, CH<sub>2</sub>), 7.0 (d, 1 H, *J* = 8.5 Hz, H-8), 8.19 (dd, 1 H, *J* = 8.5, 2.0 Hz, H-7), 8.63 (d, 1 H, *J* = 2.0 Hz, H-5); δ<sub>C</sub> (50 MHz, CDCl<sub>3</sub>) 26.2 (2 × CH<sub>3</sub>), 48.2 (CH<sub>2</sub>), 80.4 (C), 119.2 (CH), 119.8 (C), 121.5 (C), 129.8 (CH), 137.1 (CH), 163.2 (C), 170.8 (C), 191.2 (C); EIMS *m/z* (intensity %): 220.1 (M<sup>+</sup>) (48), 205.1 (M<sup>+</sup> - CH<sub>3</sub>) (100), 175.1 (10), 165 (44), 164 (40), 149.1 (12), 136 (15), 119 (14).

The ether extract was washed with water, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The crude solid product was further purified using a silica gel column (petroleum ether-diethyl ether, 9:1) to give a colourless crystalline solid **1** (0.26 g, 61 %), m.p. 91°C (lit.<sup>1</sup> m.p. 89–91°C); IR ν<sub>max</sub> (KBr) 1700, 1610, 1565, 1475, 1440, 1270 cm<sup>-1</sup>; δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 1.48 (s, 6 H, 2 × CH<sub>3</sub>), 2.76 (s, 2 H, CH<sub>2</sub>), 7.03 (d, 1 H, *J* = 8.8 Hz, H-8), 8.00 (dd, 1 H, *J* = 8.8, 2.0 Hz, H-7), 8.32 (d, 1 H, *J* = 2.0 Hz, H-5), 9.89 (s, 1 H, CHO); δ<sub>C</sub> (125.5 MHz, CDCl<sub>3</sub>) 26.5 (2 × CH<sub>3</sub>), 48.4 (CH<sub>2</sub>), 80.6 (C), 119.6 (CH), 119.8 (C), 129.8 (C), 131.1 (CH), 134.8 (CH), 164.3 (C), 190.1 (CH), 191.1 (C); EIMS *m/z* (intensity %): 204.1 (M<sup>+</sup>) (66), 189 (M<sup>+</sup> - CH<sub>3</sub>) (100), 149. (50), 148 (48), 147 (14), 119 (16).

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