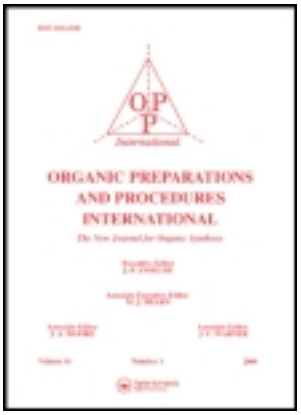

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OPPI BRIEF

A One-pot Synthesis of 6-Isopropyl-7-methoxy-1-tetralone and 6-Isopropyl-7-methoxy-2-tetralone

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6-Isopropropyl-7-methoxy-1-tetralone[1] (**2**) and 6-isopropyl-7-methoxy-2-tetralone[2] (**4**) have been claimed to be potential intermediates for the synthesis of natural products related to diterpenes *miltirone* (**5**) and *carnosic acid* (**6**), respectively. *Miltirone*, a tanshinone (*ortho*-quinone diterpene), isolated from S. *miltiorrhiza*[3] and other species,[4] has previously been synthesized[5,6] and is cytotoxic against a number of cultured tumor cell lines.[7] *Carnosic acid*, a naturally occurring *catechol-type* polyphenolic diterpene, is obtained[8] from *Rosmarinus officinalis* (rosemary) leaves and has also been synthesized previously.[9,10] *Carnosic acid* is known to possess potent anti-oxidant activity as well as anti-cancer and anti-viral properties.[11–13]

In 1990, a four-step synthesis of tetralone **2** from 2-isopropylphenol in an overall yield of 24% was reported[1] and the preparation of tetralone **4** from 2,7-dimethoxynaphthalene was accomplished in six steps with an overall yield of 39%.[2]

A concise and high-yield approach to tetralones **2** and **4** would be useful for the scale-up preparation of the previously mentioned and related natural products. In addition, the synthesis of these two tetralones in high yields would be advantageous for pre-clinical and clinical evaluations of **5** and **6**. Our experience in the studies on the synthesis of α,β-substituted tetralones[14,15] encouraged us to develop a concise approach for the tetralones **2** and **4**. The present article describes for the first time a short approach for the tetralones **2** and **4** in high yields.

To a mixture of polyphosphoric acid (PPA) and isopropanol (*i*-Pr^{i}OH) previously heated to 75°C–80°C, was added commercially available 7-methoxy-1-tetralone (**1**) and

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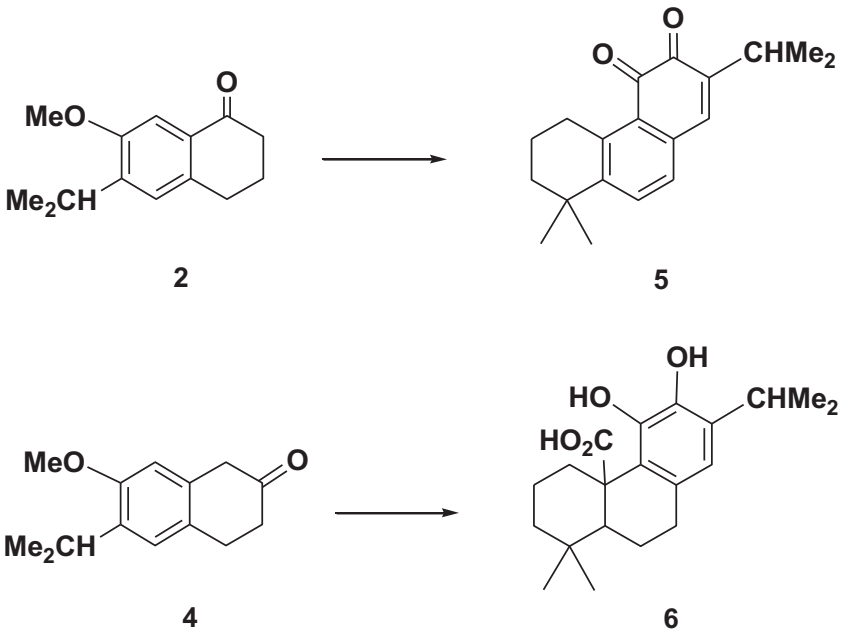
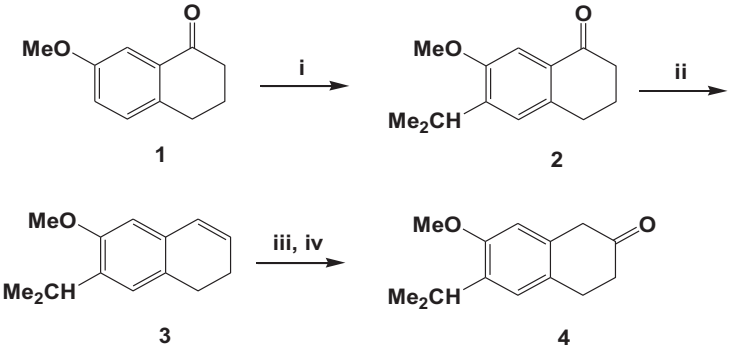


the resulting mixture was heated under reflux for 5 h to yield the tetralone **2** in 85% yield (*Scheme 1*). The same experiment carried out using conc. sulfuric acid or boron trifluoride etherate did not afford **2** in acceptable yield. The spectral data of tetralone **2** agreed with the published data.[1]



Reagents and conditions: (i) Pr^{i}OH, PPA, 5h reflux; (ii) 2,4-PD, PTSA, Tol, 16h reflux; (iii) MCPBA, $CHCl_3$, 0°C/ 12h; (iv) H_2SO_4 10% en EtOH, 3h reflux.

Scheme 1

The conversion of tetralone **2** into the olefin **3** was achieved in 90% yield by heating in toluene under reflux with 2,4-pentanediol (2,4-PD)[16] and a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH). Epoxidation of the olefin was performed with *m*-chloroperoxybenzoic (MCPBA) and the resulting epoxide was, without purification, heated

under reflux with a 10% solution of sulfuric acid (10%) in ethanol to afford the tetralone **4** in 69% yield (overall yield 53% from **1** to **4**). The spectral data of **4** matched with that reported.[2] In conclusion, a concise approach to 6-isopropyl-7-methoxy-1-tetralone (**2**) and 6-isopropyl-7-methoxy-2-tetralone (**4**) has been developed in very high overall yields of 85% (for **2**) and of 53% (for **4**), respectively.

Experimental Section

Infrared spectra were recorded on a Nicolet-Fourier Transform (FT) Instrument and ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AM-300 spectrometer in $CDCl_3$. Chemical shifts are expressed in δ (ppm). Mass spectra (MS) were determined on a DuPont 21-492B. Column chromatography was carried out with indicated solvents on silica gel 60 (0.04–0.063 mm) (Merck). The organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. Thin layer chromatography (TLC) plates were coated with silica gel 60 F_{254}, layer thickness 0.2 mm and the spots were visualized using ultraviolet light. Elemental analyses were performed on a Carlo-Erba 1108 Elemental Analyzer.

6-Isopropyl-7-methoxy-1-tetralone (2)

To a preheated (75°C–80°C) solution of commercially available polyphosphoric acid (6 ml, 126 mmol) and isopropanol (1 ml) was added in portions the tetralone **1** (0.49 g, 2.8 mmol) maintaining the temperature (75°C–80°C). The resulting solution, which initially developed a blue color, was heated under reflux for 5 h. The progress of the reaction was monitored by TLC (hexane-Et_2O 9:1). The reaction mixture was cooled, diluted with water (15 ml), and extracted with chloroform (30 ml). The organic extracts were washed with brine, dried and evaporated *in vacuo* to afford an oil, which was chromatographed (hexane:Et_2O 9:1) to afford tetralone **2** (0.51 g, 85%) as a pale yellow oil; R_f 0.79 (hexane:Et_2O 8:2); IR (cm^{-1}): 3019, 1674 (CO), 1601; MS (*m/z*): 219 (MH^+); ^{1}H NMR: δ 7.44 (s, 1H) (H at C-8), 7.04 (s, 1H) (H at C-5), 3.84 (s, 3H) (H at C-11), 3.38–3.24 (m, 1H) (H at C-12), 2.87 (t, 2H, $J = 6$ Hz) (H at C-2), 2.59 (t, 2H, $J = 6$ Hz, H-4), 2.09 (q, 2H, H-3), 1.19 (d, 6H, $J = 6.$ Hz) (H at C-13 and H-14); ^{13}C NMR: δ 198.28 (CO), 155.81 (C-7), 143.88 (C-6), 137.28 (C-9), 130.95 (C-10), 128.31 (C-8), 107.15 (C-5), 55.50 (OMe), 38.86 (C-2), 29.02 ($CHMe_2$), 26.96 (C-4), 23.61 (C-3), 22.35 (2Me).

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.29; H, 8.49

7-Methoxy-6-isopropyl-1,2-dihydronaphthalene (3)

To a solution of the tetralone **2** (0.42 g, 1.93 mmol) in toluene (40 ml) in a flask fitted with a Dean-Stark trap was added a catalytic amount of *p*-toluenesulfonic acid (0.014 g, 0.074 mmol), 2,4-pentanediol (1 ml, 9.22 mmol) and the resulting solution was heated under reflux for 16 h. The reaction mixture was cooled, quenched with an aqueous solution of $NaHCO_3$ (8 ml, 5%), and extracted with ether (25 ml). The organic extracts were washed with brine, dried and evaporated *in vacuo*. The resulting brown oil was chromatographed (hexane) to afford the compound **3** (0.35 g, 90%) as a pale yellow oil; R_f 0.81 (hexane:Et_2O 9:1); IR (cm^{-1}): 3031, 2598, 1597, 1486, 1462; MS (*m/z*): 202 (M^+); ^{1}H NMR: δ 6.98 (s, 1H) (H at C-8), 6.59 (s, 1H) (H at C-5), 6.44 (d, 1H, $J = 7.98$ Hz) (H at C-1), 6.05–5.99

(m, 1H, H-2), 3.84 (s, 3H) (H at C-11), 3.37–3.28 (m, 1H, H-12), 2.76 (t, 2H, $J = 8.16$ Hz, H-4), 2.37–2.27 (m, 2H, H-3), 1.24 (dd, 6H, $J = 6.89$ Hz, H-13, H-14); ^{13}C NMR: δ 155.28 (C-7), 135.35 (C-9), 132.26 (C-10), 128.08 (C-2), 127.67 (C-1), 127.21 (C-6), 125.30 (C-8), 108.58 (C-5), 55.55 (OMe), 26.79 (C-4), 26.52 (C-3), 23.57 (Me_2CH), 22.79 (2 Me).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.35; H, 9.13.

6-Isopropyl-7-methoxy-2-tetralone (4)

To a suspension of *m*-CPBA (0.60 g, 3.48 mmol) in dichloromethane (5 ml), cooled to 0°C, was added a solution of alkene **3** (0.30g 1.49 mmol) in dichloromethane (2 ml) and the mixture was stirred for 16 h at room temperature. Then an aqueous solution of $NaHCO_3$ (5 ml, 5%) was added and the mixture was stirred for 30 min. The organic layer was separated, washed with water, dried, and evaporated to afford a solid (0.36 g), which was dissolved in a 10% ethanolic solution of sulfuric acid (5 ml) and heated under reflux for 3 h. The reaction mixture was cooled, diluted with water (10 ml), and extracted with chloroform (25 ml). The organic extracts were washed with brine, dried and evaporated to afford an oil which, on chromatographic purification (hexane:Et_2O 9:1), gave tetralone **4** (0.22 g, 69%) as a pale yellow oil, R_f 0.61 (hexane:Et_2O 8:2); IR (cm^{-1}):1732 (CO); MS (*m/z*) 218 (M^+); ^{1}H NMR: δ 7.03 (s, 1H, H-5), 6.58 (s, 1H, H-8), 3.78 (s, 3H, H at C-11), 3.53 (s, 2H, H-1), 3.33–3.24 (m, 1H, H-12), 2.99 (t, 2H, $J = 6.57$ Hz, H-3), 2.54 (t, 2H, $J = 6.36$ Hz, H-4), 1.22 (d, 6H, $J = 6.93$ Hz, H-13, H-14); ^{13}C NMR: δ 211.33 (CO), 155.68 (C-7), 135.61 (C-6), 131.13 (C-9), 128.16 (C-10), 125.42 (C-8), 110.40 (C-5), 55.54 (OMe), 44.77 (C-1), 38.76 ($CHMe_2$), 27.75 (C-3), 26.46 (C-4), 23.04 (Me).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.25; H, 8.45.

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