A convenient synthesis of 6-methoxy-4-isopropyl-1-tetralone

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The transformation of 7-methoxy-1-tetralone into 6-methoxy-4-isopropyl-1-tetralone has been achieved in three steps.

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The synthesis of the title compound **7** and its transformation into the sesquiterpene (±)-cadinene dihydrochloride **5** have been reported[1,2] by Dev and collaborators. An alternative synthesis of this tetralone was also reported[3] by Bardhan and Mukerjee. The reported syntheses of the tetralone **7** involve many steps and complicated experimental procedures. As a part of our synthetic studies on sesquiterpenes[4] we required a convenient preparation of this tetralone. We now report a short synthetic sequence for the preparation of the tetralone **7**.

Treatment of the commercially available 7-methoxy-1-tetralone **1** with isopropylmagnesium chloride in presence of cerium chloride[5] afforded the tertiary alcohol **2** in 91% yield. In the absence of cerium chloride a mixture (40 : 60) of alcohols **2** and **3** (as detected by GC.MS) was obtained. The separation of these alcohols by column chromatography was not successful. Dehydration of alcohol **2** with *p*-toluenesulfonic acid yielded the unsaturated compound **4** in 82%. Catalytic hydrogenation of **4** with 10% Pd/C proceeded smoothly to afford the tetralin **6** in 95% yield. Its transformation to the desired tetralone **7** was achieved by oxidation[6] with chromic acid in acetic acid.

The complete disappearance of the signals of benzyl protons at δ 2.71 ppm (m, 2H, at C-4) indicated that oxidation took place exclusively at C-4 yielding the tetralone **7**. Its spectral data (IR, MS, NMR ^{1}H and ^{13}C NMR) are in full accord with the structure **7**. It was also characterised by its 2,4-dinitrophenylhydrazone, which melted at 184–185°C and was identical with that of reported.[3]

In conclusion we have developed a convenient route to the tetralone **7**. The present approach has the merit of relative brevity and offers advantages in ease of manipulation.

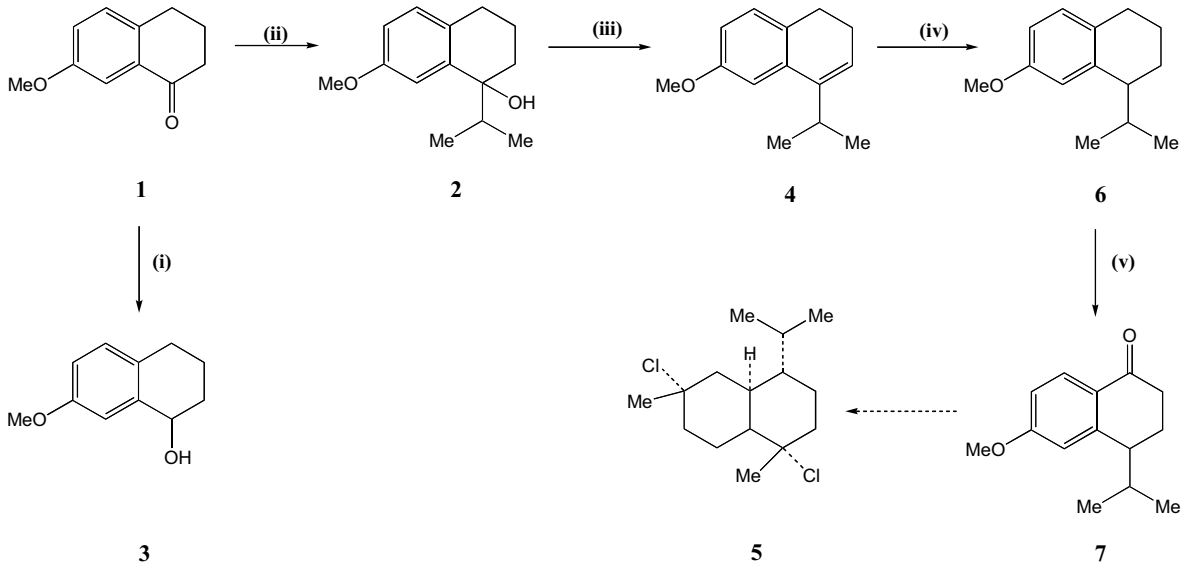
Experimental

Unless otherwise stated IR spectra were taken on Nicolet FT IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM 300 spectrometer in $CDCl_3$ as a solvent. Mass spectra were carried out on Dupont 21-492B. For column chromatography, silica gel 60 (Merck) was used. Reaction progress was monitored by TLC on silica gel plates (Fluka Kieselgel 60 F_{254}) and spots were located by exposing the plate to UV light. Microanalyses were carried out in the Chemistry Department, IVIC, Caracas.

1-Isopropyl-3,4-dihydro-7-methoxynaphthalene **(4)**: Dry tetrahydrofuran (15 ml) was added under argon to a flask cooled in ice bath containing anhydrous cerium chloride (2.12 g, 8.6 mmol) with vigorous stirring. The ice bath was removed and the suspension was stirred overnight under argon at room temperature. The flask was again immersed in ice bath and a solution 2M of isopropylmagnesium chloride (4.28 ml, 8.6 mmol) was added. After stirring at 0°C for 1 h, the tetralone **1** (1 g, 5.7 mmol) dissolved in dry tetrahydrofuran (10 ml) was added dropwise and the stirring was continued for 2 h. The reaction mixture was treated with 10% acetic acid and extracted with ether. The combined extracts were washed with brine and 10% sodium bicarbonate solution and dried. The solvent was removed to give the alcohol **2** (1.17 g) in 91% yield. The crude alcohol did not show the presence of tetralone **1** in TLC.

IR: 3439 cm^{-1} (OH); MS (*m/z*): 220 (M), 203 (M-OH), 202 (M-H_2O), 177 (M-C_3H_7); ^{1}H NMR: δ 7.03 (d,1H, *J* = 2.7 Hz, H-8), 6.97 (d, 1H, *J* = 8.4 Hz, H-5), 6.71 (dd, 1H, *J* = 2.7 Hz and *J* = 8.4 Hz, H-6), 3.76 (s, 3H, OMe), 2.59 (m, 2H, H-4), 2.32 (sept, 1H, *J* = 6.91 Hz, H-13), 1.73 (m, 4H, H-2 and H-3), 1.06 (d, 3H, *J* = 6.9 Hz, H-11 Me), 0.64 (d, 3H, *J* = 6.9 Hz, H-12 Me); ^{13}C NMR: δ 158.09 (C-7), 142.68 (C-9), 130.05 (C-10), 129.72 (C-5), 113.24 (C-6), 110.80 (C-8), 74.48 (C-1), 55.22 (C-14), 37.48 (C-2), 30.86 (C-13), 29.44 (C-4), 19.28 (C-3), 18.33 (C-11), 16.32 (C-12). The alcohol was used for dehydration without further purification.

To the alcohol **2** 1.51 g (6.8 mmol) dissolved in benzene (18 ml) was added *p*-toluenesulfonic acid 80 mg (0.44 mmol) and heated under reflux for 4 h. The reaction mixture was diluted with brine and



Reagents: (i) i-Pr MgCl, THF, 0°C; (ii) i-Pr MgCl, $CeCl_3$, THF, 0°C; (iii) p-TsOH, C_6H_6; (iv) H_2, Pd/C 10%, 1 atm; (v) 10% aq. CrO_3 – AcOH.

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the layers were separated. The organic extract was washed with 10% sodium bicarbonate solution, brine and dried ($MgSO_4$). The solvent was removed and the residue passed through a column of silica gel in hexane as the eluent to give the compound **3** (1.13 g) in 82% yield. IR: 1605 cm^{-1} (C =C); MS (*m/z*): 202 (M), 159 (M- C_3H_7); ^1H NMR: δ 7.13 (d, 1H, *J* = 8 Hz, H-5), 6.98 (d, 1H, *J* = 2.6 Hz, H-8), 6.75 (dd, 1H, *J* = 2.6 Hz and *J* = 8 Hz, H-6), 5.97 (t, 1H, *J* = 4.6 Hz, H-2), 3.87 (s, 3H, OMe), 2.96 (sept, 1H, *J* = 6.7 Hz, H-13), 2.70 (t, 2H, *J* = 7.7 Hz, H-4), 2.27 (m, 2H, H-3), 1.23 (d, 6H, *J* = 6.7 Hz, H-11 Me and H-12 Me); ^{13}C NMR: δ 158.32 (C-7), 142.51 (C-9), 136.11 (C-1), 129.32 (C-10), 128.07 (C-5), 122.10 (C-2), 110.44 (C-8), 109.54 (C-6), 55.28 (C-14), 28.30 (C-13), 27.64 (C-4), 23.57 (C-3), 22.30 (C-13 and C-12); (Found: C 83.37; H 9.15; $C_{14}H_{18}O$ requires: C 83.12; H 8.97%).

1-Isopropyl-1,2,3,4-tetrahydro-7-methoxynaphthalene **(6)**: The compound **4** 1.57 g (7.8 mmol) was dissolved in absolute ethanol (3 ml) and stirred for 6 h with Pd/C 10% (220 mg) under hydrogen (1 atm) at ambient temperature. The filtered solution was concentrated to give a yellow oil which was passed through a column of silica gel (eluent hexane) to obtain **6 (**1.52 g) as a colourless oil in 95% yield. MS (*m/z*): 204 (M), 161 (M- C_3H_7); ^1H NMR: δ 6.99 (d,1H, *J* = 8.3 Hz, H-5), 6.79 (d,1H, *J* = 2.5 Hz, H-8), 6.69 (dd, 1H, *J* = 2.5 Hz and *J* = 8.3 Hz, H-6), 3.79 (s, 3H, OMe), 2.71 (m, 2H, H-4), 2.26 (m, 1H, H-1), 1.77 (m, 5H, H-13, H-2 and H-3), 1.05 (d, 3H, *J* = 6.8 Hz, H-12 Me), 0.77 (d, 3H, *J* = 6.8 Hz, H-11); ^{13}C NMR: δ 157.43 (C-7), 141.51 (C-9), 130.42 (C-10), 129.61 (C-5), 113.68 (C-8), 110.98 (C-6), 55.17 (C-14), 43.71 (C-1), 31.53 (C-13), 29.18 (C-4), 23.12 (C-3), 21.74 (C-11), 21.28 (C-12), 17.28 (C-2); (Found: C 82.57; H 10.03; $C_{14}H_{20}O$ requires: C 82.30; H 9.87%).

1-Keto-4-isopropyl-1,2,3,4-tetrahydro-6-methoxynaphthalene **(7)**: To a solution of **6** (461 mg, 2.3 mmol) in acetic acid (60 ml) was added dropwise 11 ml of 10% aqueous CrO_3 acetic acid solution (prepared by dissolving 5.25 gr of CrO_3 in 47.5 ml of acetic acid and 2.5 ml of water). The reaction mixture was stirred for 3 h at a temperature between 15–20°C with an ice bath. The progress of the reaction was monitored by tlc. It was then diluted with water and extracted with ether. The ether extract was washed with water, sodium bicarbonate solution, brine, dried ($MgSO_4$) and concentrated. The residue obtained was chromatogrphed over silica gel. Elution with hexane: ether (8 : 2) afforded the compound **7** as a yellow oil **(**301 mg) in 60% yield. IR: 1674 cm^{-1} (C=O); MS (*m/z*): 218 (M), 175 (M- C_3H_7), 147 (M-C_3H_7-CO); ^1H NMR: δ 7.93 (d, 1H, *J* = 8.7 Hz, H-8), 6.76 (dd,1H, *J* = 2.5 Hz and *J* = 8.7 Hz, H-7), 6.67 (d, 1H, *J* = 2.5 Hz, H-5), 3.79 (s, 3H, OMe), 2.55 (m, 3H, H-2 and H-4), 2.01 (m, 3H, H-3 and H-13), 0.92 (d, 3H, *J* = 6.7 Hz, H-11 Me), 0.91 (d, 3H, *J* = 6.7 Hz, H-12 Me); ^{13}C NMR: δ 197.00 (C-1), 162.70 (C-6), 149.39 (C-10), 129.52 (C-8), 125.71 (C-9), 113.09 (C-5), 111.95 (C-7), 54.97 (C-14), 44.82 (C-4), 34.71 (C-2), 29.65 (C-13), 23.90 (C-3), 21.22 (C-11), 19.41 (C-12); (Found: C 77.22; H 8.43; $C_{14}H_{18}O_2$ requires: C 77.03; H 8.31%).

Its 2,4-dinitrophenylhydrazone. m.p. 184–185°C (from ethanol) (lit[3].187) (Found: C, 60.56; H, 5.67. $C_{20}H_{22}N_4O_5$ requires C, 60.30; H, 5.52%).

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