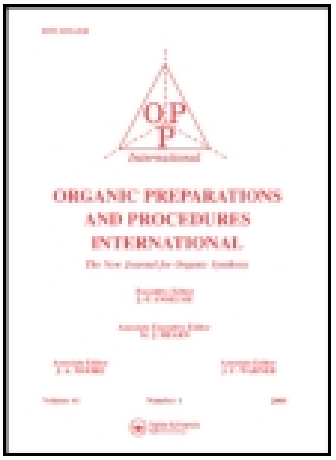

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Elvia V. Cabrera [a], Jennifer L. Sanchez [b] & Ajoy K. Banerjee [b]

[a] Department of Chemistry, Faculty of Sciences, University of Zulia, Maracaibo, Venezuela

[b] Chemistry Center, Venezuelan Institute of Scientific Research (IVIC), Caracas, Venezuela

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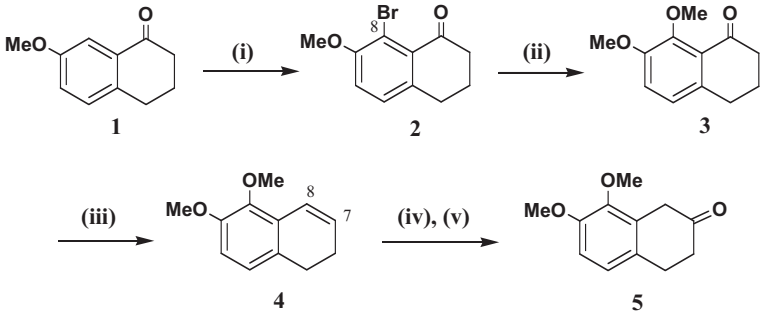
A Practical Synthesis of 7,8-Dimethoxy-2-tetralone

Elvia V. Cabrera,[1] Jennifer L. Sanchez,[2] and Ajoy K. Banerjee[2]

[1]Department of Chemistry, Faculty of Sciences, University of Zulia, Maracaibo, Venezuela
[2]Chemistry Center, Venezuelan Institute of Scientific Research (IVIC), Caracas, Venezuela

Much interest has been shown recently in 2-tetralones bearing hydroxy, methyl and methoxy substituents in the aromatic ring because of their high reactivity and importance as raw materials for the synthesis of natural products.[1,2] Among the methoxy-substituted compounds, 7,8-dimethoxy-2-tetralone (**5**) has drawn the attention of organic chemists for a long time due to its importance as an intermediate in the synthesis of analgesics, morphines[3] and steroids.[4] Recently tetralone **5** has been synthesized by Gorka *at al*.[5] in ten steps with an overall yield of 18%. In addition, tetralone **5** had also been prepared by other authors.[6,7] but most of the published syntheses report low yields of tetralone **5** and use starting materials that are not easily accessible. In connection with our studies on substituted tetralones,[8,9] we devised a concise route for the synthesis of tetralone **5** (*Scheme 1*).



Reagents: (i) NBS, CH_3CN, rt; (ii) NaOMe, CuBr, DMF-H_2O, reflux; (iii) 2,4-pentanediol, *p-TsOH,* reflux; (iv) MCPBA, CH_2Cl_2, 0ºC; (v) H_2SO_4 (10%), EtOH

Scheme 1

Submitted April 7, 2011.
Address correspondence to Ajoy K. Banerjee, Centro de Química, IVIC, Apartado-21827 Caracas-1020 A, Venezuela. E-mail: abanerje@ivic.gob.ve or aabanerje@gmail.com

The commercially available 7-methoxy-1-tetralone (**1**) was brominated with *N*-bromosuccinimide (NBS) in acetonitrile to yield the known[10] bromotetralone **2**, as a colorless solid in 96% yield. Though the bromination of tetralone **1** was carried out according to a literature procedure, the yield (96%) obtained by us was superior to that reported (70%).[10] A higher yield (92%) of bromotetralone **2** was also reported by Tsotinis *at al*.[11] who carried out the bromination of tetralone **1** by the published method.[10] Bromotetralone **2** was subjected to methoxylation[12] by heating at 110°C with a mixture of excess cupric bromide, a solution of sodium methoxide (25%) in methanol and dimethylformamide:water (95:5) to give tetralone **3** in 72% yield. The use of a low concentration of sodium methoxide in methanol and dimethylformamide with water was essential for the methoxylation of the tetralone **2**. The use of a more concentrated solution of sodium methoxide in methanol and dimethylformamide[13] led to the formation of many uncharacterized secondary products and only 8% of the tetralone **3**. The conversion of the tetralone **3** into the olefin **4** in 98% yield was accomplished[14] by heating under reflux with 2,4-pentanediol and a catalytic amount of *p*-toluenesulfonic acid (p-TsOH). Epoxidation of the olefin was performed with *m*-chloroperoxybenzoic acid (MCPBA) and without purification, the resulting epoxide was heated under reflux with ethanolic sulfuric acid (10%) to afford tetralone **5** in 53% yield (overall yield 36% from **1** to **5**), mp.74–76°C. The spectral data agreed with the published data.[5]

In conclusion, a concise approach to 7,8-dimethoxy 2-tetralone **(5)** has been developed in a very high overall yield (36%). To the best of our knowledge this is the first report of the synthesis of tetralone **5** with a high overall yield. The starting material is commercially available. Most of the intermediates were sufficiently stable to permit isolation. The present method can be utilized in the synthesis of tetralone **5** in gram quantities for the synthesis of bioactive compounds.

Experimental Section

Unless otherwise stated all melting points are uncorrected and were determined on an Electrothermal melting point apparatus. Infrared (IR) spectra were recorded on a Nicolet-Fourier Transform (FT) Instrument and NMR (^{1}H and ^{13}C) spectra were determined on a Bruker AM-300 spectrometer in $CDCl_3$. Chemical shifts (δ) are expressed in ppm. Mass spectra (MS) were determined on a Dupont 21-492B. Column chromatography was carried out on silica gel 60 (Merck). Thin layer chromatography (TLC) plates were coated with silica gel and the spots were visualized using ultraviolet light. Elemental analyses were performed on a Carlo-Erba 1108 elemental analyser.

7,8-Dimethoxy-1-tetralone (3)

A solution of the bromotetralone **2** (500 mg, 2.47 mmol) in 8 mL DMF:H_2O (95:5) was heated at 80°C for 30 min. To this was added a solution of 25% NaOMe (720 mg of Na in 7.8 mL MeOH) in four portions. The temperature of the resulting solution was raised to 110°C, the catalyst CuBr (56 mg, 0.392 mmol) was added and then the reaction mixture was heated under reflux for 3 h. The progress of the reaction was monitored by TLC (7:3 hexane:ether, R_f 0.17). The reaction was cooled, filtered, diluted with

water and extracted with $CHCl_3$. The organic extract was washed with a diluted solution of hydrochloric acid (5%), brine, dried and evaporated *in vacuo* to afford an oil which was chromatographed (8:2 hexane:ether) to give tetralone **3** (291 mg, 72%) as a pale brown oil; IR (cm^{-1}): 1680 (CO); MS (m/z): 207 (M^{+1}); ^1H NMR: δ 6.97 (d, 1H, J = 8.3 Hz) (H at C-5), 6.87 (d, 1H, J = 8.3 Hz) (H at C-6), 3.79 (s, 3H, OMe), 3.76 (s, 3H, OMe), 2.78 (t, 2H, J = 6.1 Hz) (2H at C-2), 2.41 (t, 2H, J = 6.5 Hz) (2H at C-4), 1.98–1.93 (m, 2H at C-3); ^{13}C NMR: δ 197.54 (C-1), 151.93 (C-7), 149.62 (C-8), 137.39 (C-10), 126.99 (C-9), 123.79 (C-5), 117.24 (C-6), 61.04 (C-12), 56.23 (C-11), 40.73 (C-2), 29.79 (C-3), 23.08 (C4).

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.09; H, 6.98

1,2-Dimethoxy-$\Delta^{7,8}$-dihydronaphthalene (4)

To a solution of the tetralone **3** (1.00 g, 4.85 mmol) in toluene (97 mL) was added a catalytic amount of *p*-toluenesulfonic acid (34 mg, 0.18 mmol) and 2,4-pentanediol (2.2 mL, 20.29 mmol) and the mixture was heated under reflux for 24 h using a Dean-Stark apparatus. The reaction mixture was cooled, quenched with an aqueous solution of $NaHCO_3$ (5%) and extracted with ether. The organic extract was washed with brine, dried and evaporated *in vacuo*. The resulting brown oil was chromatographed (hexane) to afford compound **4** (903 mg, 98%) as a faint yellow oil; IR (cm^{-1}): 2934, 2831 and 1572; MS (m/z): 190 (M^+); ^1H NMR: δ 6.84 (t, 1H, J = 1.6 Hz) (H at C-8), 6.81 (d, 1H, J = 8 Hz) (H at C-4), 6.70 (d, 1H, J = 8 Hz) (H at C-3), 6.11 (dt, J = 4.4 Hz and J = 9 Hz) (H at C-7), 3.83 (s, 3H, OMe), 3.81 (s, 3H, OMe), 2.73 (t, J = 8 Hz) (H at C-5), 2.31–2.25 (m, 2H) (2H at C-6); ^{13}C NMR: δ 152.08 (C-1), 144.63 (C-2), 129.18 (C-3), 128.73 (C-9), 127.77 (C-10), 122.65 (C-1), 121.87 (C-7), 110.31 (C-4), 61.04 (C-11), 55.68 (C-12), 27.01 (C-5), 23.28 (C-6).

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.99; H, 7.61.

7,8-Dimethoxy-2-tetralone (5)

To a suspension of MCPBA (1.5 g, 7.85 mmol) in dichloromethane (16 mL), cooled at 0°C, was added a solution of the compound **4** (653 mg, 3.44 mmol) in dichloromethane (5 mL) and the mixture was stirred for 16 h at room temperature. To the reaction mixture was then added a solution of sodium bicarbonate (10 mL, 5%) and the resulting solution was stirred for 2 h at room temperature. The organic layer was separated, washed with water, dried and evaporated to afford a solid (670 mg) which was dissolved in ethanolic sulfuric acid (5 mL, 10%) and heated under reflux for 3 h. The reaction was cooled, diluted with water and extracted with chloroform. The organic extract was washed with brine, dried and evaporated *in vacuo* to afford a solid which on chromatographic purification (1:1 hexane:ether) yielded the tetralone **2** (374 mg, 53%) as a crystalline solid, mp. 73–75°C (petroleum ether) (lit.[5] 73–74°C). IR (cm^{-1}): 1713 (CO); MS (m/z): 206 (M^+); ^1H NMR: δ 6.86 (d, 1H, J = 9 Hz), 6.75 (d, 2H, J = 9 Hz) (H at C-5 and C-6), 3.81 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.54 (s, 2H) (H at C-1), 2.97 (t, 2H, J = 7 Hz) (H at C-4), 2.50 (t, 2H, J = 7 Hz) (H at C-3); ^{13}C NMR: 210.43 (C-2), 151.20 (C-7), 146.22 (C-8), 129.79 (C-11), 126.45 (C-12), 123.47 (C-6), 60.37 (C-10), 55.83 (C-9), 38.69 (C-1), 38.50 (C-3), 28.63 (C-4).

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.01; H, 6.92

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