Transformation of 5-methoxy-1-tetralone into 8-methoxy-1-tetralone

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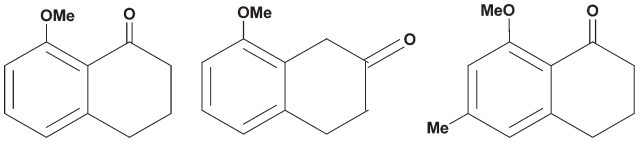
The transformation of 1-hydroxy-5-methoxtetralin into 4-hydroxy-8-methoxy-1-tetralone was accomplished in three steps (benzoylation, oxidation and alkaline hydrolysis). Treatment of the corresponding ketotosylate with sodium iodide and zinc dust in dimethoxyethane yielded the 8-methoxy-1-tetralone in 22% yield. The ketotosylate also underwent detosylation with sodium cyanoborohydride but afforded tetraol in 45% yield which on oxidation was converted into the required tetralone in 87% yield.

Keywords: 5-methoxy-1-tetralone, cyclisation, 8-methoxy-1-tetralone, bromination, aromatisation

8-Methoxy1-tetralone **1** is a valuable starting material in the synthesis of ARQ-501, which is a fully synthetic version of β-lapachone and a promising anticancer agent currently in multiple Phase II clinical trials.[1] ARQ-501 is also effective against human ovarian cancer and prostrate cancer xenografs in mice.[2] Tetralone **1** can also be used in the synthesis of previously reported tetralone[3] **2** and tetralone[4] **3**. Tetralone **2** is an important starting material in the synthesis of compounds for the study of dopamine (DA) and serotin (5-HT) receptors. Tetralone **3** can be considered to provide an easy access to diospyrol,[5] a very potent anthelmintic drug from *Diospyros mollis (Ebenaceae)*



1 **2** **3**

8-Methoxy-1-tetralone has been synthesised by the three routes.[6–8] Except for the first route,[6] tetralone **1** was obtained in very poor yield by the other published procedures.[7,8] The first route[6], though it affords an acceptable yield (41%) of tetralone **1**, utilises a starting material whose preparation involves seven steps which consume a considerable amount of time. In relation of our studies on the synthesis[9] of substituted 1-tetralones and because of the notable biological activities of tetralone **1** we have devised a concise and convenient approach for the synthesis of the tetralone **1**. The synthetic route is described in Scheme 1.

Results and discussion

5-Methoxy-1-tetralone **4** was considered to be promising starting material for the synthesis of the 8-methoxy-1-tetralone **1**. The synthetic route is shown in Scheme 1.

The known alcohol[10] **5** was treated with benzoyl chloride (BzCl) and pyridine (Py). The resulting derivative **6** (81%) on oxidation[11] with pyridinium dichromate (PDC) and *t*-butylhydroperoxide (TBHP) (70% in water) produced the ketobenzoate **7** (75%). Alkaline hydrolysis of **7** yielded the ketoalcohol **8** (95%) which on tosylation with *p*-toluenesulfonyl chloride (TsCl) and pyridine (Py) yielded the ketotosylate **9** (12%), naphthol[12] **10** (31%) and tosylate **11** (30%). The spectroscopic data gave strong support to their structures. Detosylation[13] of **9** on heating under reflux with sodium iodide (NaI) and zinc (Zn) in dimethoxyethane (DME) furnished tetralone **1** in 22% yield. The ketotosylate **9** on heating with with sodium cyanoborohydride ($NaBH_3CN$) and hexamethylphosphoramide (HMPA) underwent detosylation[14] yielding the tetraol **12** (45%) as a brown oil. The other products could not be identified. Tetraol **12** on oxidation[15] with Jones reagent produced tetralone **1** in 87% yields.

We consider it worthwhile to provide a mechanism for the formation of the naphthol **10** and the the tosylate **11** and this is depicted in Scheme 2. The tosylate **9** with pyridine forms an enolate anion and the tosylate a good leaving undergoes base promoted E_2 elimination yielding the intermediate **9a** which produces naphthol **10** and its derivative **11**.

In order to improve the yield of the tetralone **1**, an alternative route was tried and this is depicted in Scheme **3**. The ketoalcohol **8** was heated under reflux with ethylene glycol and catalytic amount of p-toluenesulfonic acid expecting to obtain the ketal **13**. The resulting product which was a mixture of several compounds as evidenced by TLC was subjected to chromatographic purification. To our surprise the naphthol **10** was the only product that could be isolated and formed the major component. We believe that during ketalisation the ketoalcohol **8** underwent acid-catalysed dehydration affording the naphthol **10**. We failed to isolate and identify the compound **13**. Similar experience was also met during the ketalisation of the ketobenzoate **7**. Therefore we were forced to abandon our plan to achieve the transformation of the compound **13** to the tetralone **1** by tosylation, detosylation with lithium aluminium hydride and dekealisation successively. It is known[16] that aromatisation reactions involving tetralones are very common but we never thought that it would be impossible to isolate the compound **13** even in poor yield.

In conclusion a new synthesis of 8-methoxy-1-tetralone has been achieved from 5-methoxy-1-tetralone. Although the yield by the present procedure is not high when compared to the published method[6] it is superior to the other methods.

In addition, the present procedure is easily reproducible because it does not involve any complicated experimental procedure.

Experimental

Unless otherwise stated, all melting points are uncorrected on an electrothermal melting point apparatus, infrared (IR) spectra were taken on a Nicolet Fourier Transform (FT) instrument. Only selected absorbances (υ_{max} in cm^{-1}) were recorded. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer in $CDCl_3$. ^1H NMR spectra are reported as follows: chemical shift in ppm (δ), integration, multiplicities (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened and coupling constant (*J*) in Hz. ^{13}C NMR spectra are reported in ppm (δ). Mass spectra (MS) were determined on a Dupont 21-492B. Column chromatography was carried out on silica gel 60 (Merck). The expression workup indicates that the solution was diluted with water, extracted with Et_2O or $CHCl_3$, washed with brine,

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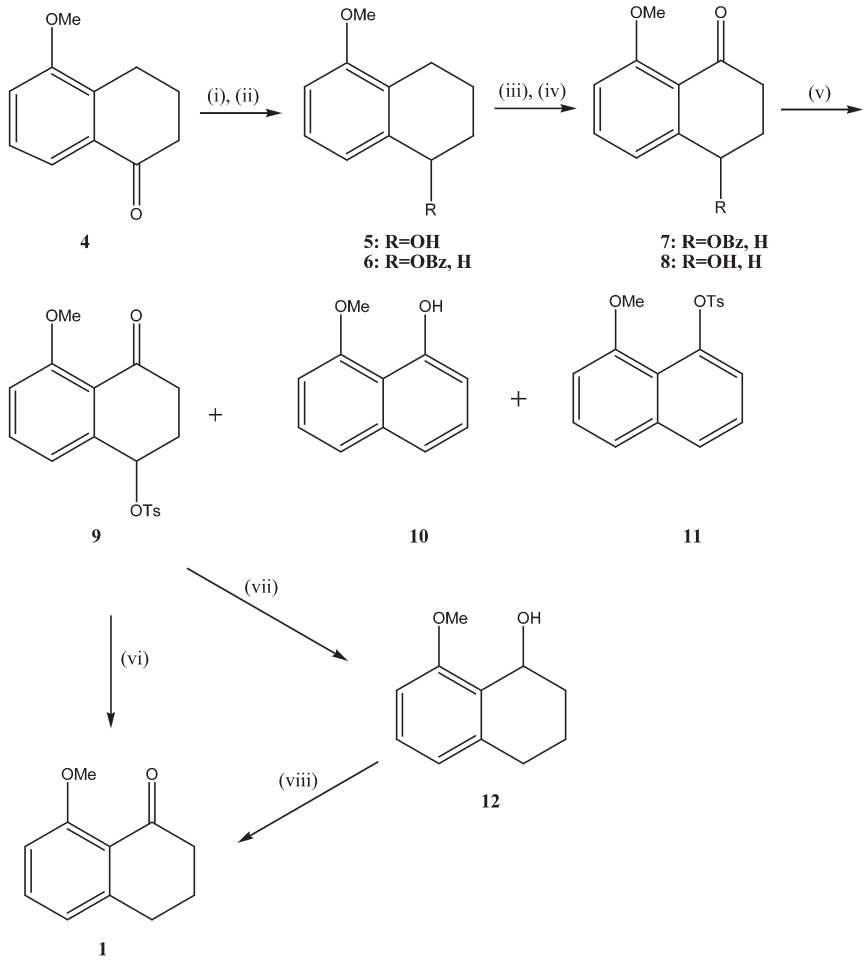
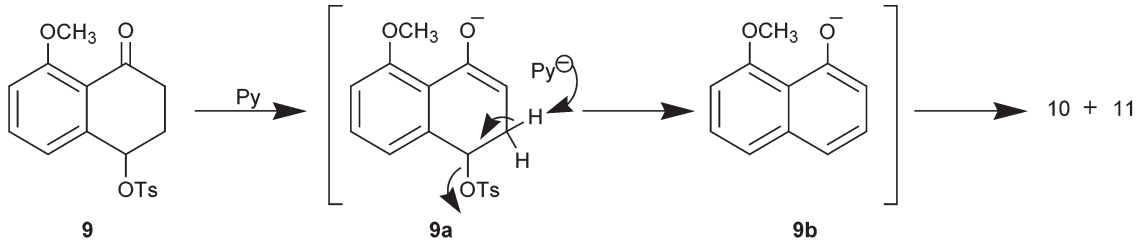


Reagents: (i) $NaBH_4$; (ii) BzCl, Py; (iii) PDC, TBHP; (iv) K_2CO_3, EtOH; (v) TsCl, Py; (vi) NaI, Zn, DME; (vii) $NaBH_3CN$, HMPA, (viii) CrO_3, H_2SO_4.

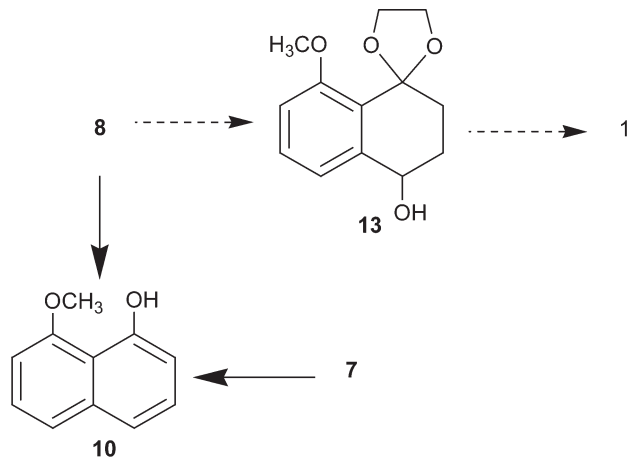
Scheme 1



Scheme 2

dried ($MgSO_4$) and evaporated under reduced pressure. TLC plates were coated with silica gel and the spots were located by exposure to UV light. Microanalyses were performed on a Carlo-Erba model 1108 elemental analyser, IVIC, Caracas.

1-Benzoyloxy-5-methoxytetralin (**6**): A solution of alcohol **5** (2.27 g, 12.7 mmol) in dry Py (25 mL) and BzCl (7.71 g, 58.3 mmol) was stirred for 20 h at room temperature. The reaction mixture was diluted with water and extracted with Et_2O. The organic extract was washed with dilute HCl, aqueous $NaHCO_3$, brine, dried and evaporated to yield a dense material which was chromatographed over silica gel. Evaporation of the hexane eluate afforded the benzoate **6** (2.91 g, 81%), m.p. 53–55 °C; IR υ_{max} (cm^{-1}): 1713 (CO); MS(*m/z*): 282 (M^+), 160 (M^+ -C_6H_5COOH); ^1H $\delta_{(ppm)}$: 8.05 (dd, 2H, *J* = 7.01, *J* = 1.5), 7.54 (tt, 1H, *J* = 6.7) (H-16), 7.42 (t, 2H, *J* = 7.5) (H-15, H-17), 7.18 (t, 1H, *J* = 7.9) (H-7), 6.98 (d,1H, *J* = 7.7) (H-8), 6.79 (d, 1H, *J* = 8) (H-6), 6.24 (t,1H,*J* = 4.2) (H-1), 3.83 (s, 3H,OMe), 2.91–2.64 (m, 2H) (H-4), 2.08–1.87 (m, 4H) (H-2, H-3); ^{13}C $\delta_{(ppm)}$: 166.16 (C-12), 156.98 (C-5), 135.73 (C-9), 132.77 (C-16), 130.66 (C-13), 129.67 (C-14, C-18), 128.22 (C-15, C-17), 127.07 (C-7), 126.34 (C-10), 121.40 (C-8), 109.07 (C-6) , 70.58 (C-1), 55.30 (C-11), 28.70 (C-2),



Scheme 3

22.77 (C-4), 18.27 (C-3) (Found: C, 76.75; H, 6.43. $C_{18}H_{18}O_3$ requires: C, 76.57; H, 6.43%).

4-Benzoyloxy-8-methoxy-1-tetralone (**7**): To a solution of the benzoate **6** (202 mg, 0.72 mmol) in dry C_6H_6 (12 mL) at 0 °C was added at 0 °C Celite (602 mg), PDC (1.03 mg, 2.73 mmol) and TBHP (70%) (1.74 mL, 8.41 mmol). The whole operation was done with a period of 15 min and then the mixture was stirred at room temperature for 24 hr. The mixture was diluted with Et_2O (20 mL) and then filtered through a column of celite. The column of the Celite was eluted with Et_2O (3 x 10 mL). The combined filtrate was evaporated and the residue was washed with Et_2O to obtain the ketobenzoate **7** (159 mg, 75%), m.p. 95–96° C; IR υ_{max} (cm^{-1}): 1720, 1678 (CO); MS(*m/z*): 296 (M^+), 175 (M^+ -C_6H_5COOH); ^1H $\delta_{(ppm)}$: 8.03 (dd, 2H, *J* = 9.6 Hz, *J* = 1.9 Hz) (H-14, 18), 7.59–7.38 (m, 4H) (H-6, 15, 16, 17), 7.12 (d, 1H, *J* = 7.5 Hz) (H-5), 7.01 (d, 1H, *J* = 8.4 Hz), 6.31 (t, 1H, *J* = 4.7 Hz), 3.92 (s, 3H, OMe), 3.03–2.92 (m, 1H) , 2.71–2.66 (m, 1H) (H-2), 2.48–2.34 (m,2H) (H-3); ^{13}C $\delta_{(ppm)}$: 192.02 (C-1), 165.08 (C-8), 143.05 (C-10), 134.66 (C-6), 133.26 (C-16), 129.91 (C-13), 129.72 (C-14, C-18), 128.44 (C-15, C-17), 121.47 (C-5), 120.34 (C-9), 112.67 (C-7), 70.35 (C-4), 56.17 (C-11), 35.74 (C-2), 27.96 (C-3) (Found: C, 72.72; H, 5.56. $C_{18}H_{16}O_4$ requires C, 72.96; H, 5.44%).

4-Hydroxy-8-methoxy-1-tetralone (**8**): To a solution of the ketobenzoate **7** (974 mg, 3.29 mmol) dissolved in EtOH (60 mL) was added K_2CO_3 (2.14 g, 7.24 mmol) and stirred at room temperature for 24 h. The alkaline solution was concentrated, diluted with water and extracted with $CHCl_3$. The organic extract was washed with brine, dried ,.evaporated under reduced pressure and chromatographed. The chromatographic purification (hexane:ether 1:1) afforded the ketoalcohol **8** (599 mg, 95%); IR υ_{max} (cm^{-1}): 3411 (OH), 1611 (CO); MS (*m/z*): 192 (M^+), 174 (M^+ - H_2O); ^1H $\delta_{(ppm)}$: 7.49 (t, 1H, *J* = 8) (H-6), 7.16 (d, 1H, *J* = 7.6) (H-5), 6.93 (d, 1H, *J* = 8.4) (H-7), 3.87 (s, 3H, OMe), 2.91–2.81 (m, 1H), 2.59–2.48 (m, 1H) (H-2), 2.33–2.23 (m, 1H), 2.16–2.04 (m, 1H) (H-3), 1.83 (s, 1H, OH); ^{13}C $\delta_{(ppm)}$: 196.67 (C-1), 159.94 (C-8), 147.94 (C-10), 134.72 (C-6), 120.41 (C-5), 118.76 (C-9), 111.75 (C-7), 68.31 (C-4), 56.05 (C-11), 36.33 (C-2), 31.21 (C-3) (Found: C, 68.55; H, 6.41. $C_{11}H_{12}O_3$ requires C, 68.73; H, 6.29%).

Tosylation of the ketoalcohol (**8**): To a solution of the ketoalcohol **8** (793 mg, 4.13 mmol) in dry Py (25 mL), cooled at 0 °C, was added TsCl (4.88 g, 25.88 mmol), stirred at room temperature for 48 h, poured on ice and extracted with Et_2O. The organic extract was dried and evaporated to obtain a dense liquid which was purified by chromatography. Hexane elute yielded (i) 4-Toluene-p-sulfonoxy-8-methoxy-1-tetralone **9**: 428 mg (30%). It was contaminated with other products and had a tendency of decomposition as evidenced in TLC and therefore it was used directly for the next step. (ii) 1-Hydroxy-8-methoxynaphthalene **10**: 222 mg (31%), m.p. 43–45 °C (lit.[12] m.p. 44–46 °C); IR υ_{max} (cm^{-1}) 3355 (OH); MS (*m/z*): 174 (M^+); ^1H $\delta_{(ppm)}$:9.31 (s,1H,OH), 7.42–7.21 (m, 4H) (H-3,4,5,6), 6.87 (dd,1H, *J* = 8.7 Hz, *J* = 1.47 Hz) (H-7), 6.77 (dd, 1H, *J* = 7.88 Hz, *J* = 0.57 Hz) (2-H), 4.03 (s, 3H, OMe); ^{13}C $\delta_{(ppm)}$: 156.10 (C-1), 154.42 (C-8), 136.68 (C-10), 127.66 (C-6), 125.53 (C-3), 121.80 (C-4), 118.80 (C-5), 115.01 (C-9), 110.75 (C-2), 103.83 (C-7), 56.04 (C-11) (Found: C, 75.69; H, 5.87. $C_{11}H_{10}O_2$ requires C, 75.84; H, 5.79%). (iii) 1-Toluene-p-sulfonoxy8-methoxynaphthalene **11**: 405 mg (30%), m.p. 121–123 °C; MS(*m/z*): 329 (M^{+1}); ^1H $\delta_{(ppm)}$: 7.74–7.66 (m, 3H) (H-3, 13, 17), 7.41–7.32 (m, 2H) (H-4,5), 7.30–7.22 (m, 3H) (H-6,14, 16), 6.89-6.81 (m, 2H) (H-2, 7), 3.91 (s, 3H, OMe), 2.45 (s, 3H,Me); ^{13}C $\delta_{(ppm)}$: 155.39 (C-1), 145.27 (C-12), 144.65 (C-8), 136.95 (C-15), 133.92 (C-10), 129.40 (C-14, C-16), 128.41 (C-13, C-17), 127.41 (C-3), 126.83 (C-6), 125.41(C-4, C-5), 120.31(C-9), 119.63 (C-7), 106.42 (C-2), 55.53 (C-11), 21.62 (C-18) (Found: C, 65.59; H, 5.02. $C_{18}H_{16}O_4S$ requires C, 65.85; H, 4.91%).

8-Methoxy-1-tetralone (**1**): *Method A:* To a solution of the ketotosylate **9** (40 mg, 0.12 mmol) dissolved in HMPA (2 mL) was added $NaBH_3CN$ (0.6 mL, 8.73 mmol), refluxed at 70 °C for 6 h and stirred at room temperature for 18 h. The reaction mixture was diluted with water and extracted with Et_2O. The organic extract was washed, dried and evaporated to obtain an oil which on preparative chromatographic purification (eluant hexane) yielded tetraol **12** (9.5 mg, 45%); IR υ_{max}(cm^{-1}): 3452 (OH); MS (*m/z*): 179 (M^{+i});^1H $\delta_{(ppm)}$ 9.25 (s,1H, 1-H), 7.41–7.26 (m, 1H, 7-H), 6.88–6.85 (dd, 1H, *J* = 8.71 Hz, *J* = 1.47, 6-H), 6.77–6.75 (d, 1H, *J* = 7.81 Hz, 5-H), 3.98 (s, 3H, OMe), 1.59 (s, 1H, OH). As the tetraol **12** was obtained in small amounts, the, reactions were repeated to prepare additional amounts of tetraol. To a solution of tetraol **12** (80 mg, 0.45 mmol) in Me_2CO (5 mL) at 0 °C, was added Jones reagent (2 mL). The mixture was stirred at room temperature for 30 min and 2-propanol (4 mL) was added. The resulting dark blue solution was diluted with water and extracted with Et_2O. The organic extract was washed, dried, evaporated and chromatographed. Elotion with hexane:Et_2O (7:3) yielded the tetralone **1** (69 mg, 87%); υ_{max}(cm^{-1}) 1674 (CO); MS (*m/z*): 176 (M^+); ^1H $\delta_{(ppm)}$: 7.38 (dd, 1H, *J* = 8.01 Hz, *J* = 7.9 Hz, 6-H), 6.82–6.78 (m, 2H, 5-H, 7-H), 3.87 (s, 3H, OMe), 2.89 (t, 2H, *J* = 6 Hz, 2-H), 2.60 (t, 2H, *J* = 6 Hz, 4-H), 2.07–2.01 (m, 2H, 3-H); ^{13}C $\delta_{(ppm)}$: 156.10 (C-1), 154.42 (C-8), 136.68 (C-10), 127.66 (C-6); 125.53 (C-3), 121.80 (C-4), 118.80 (C-5), 115.01 (C-9), 110.75 (C-2), 103.83 (C-7), 56.04 (C-11) (Found: C, 74.82; H, 6.95. $C_{11}H_{12}O_2$ requires C 74.97; H, 6.86%).

Method B: To a solution of the ketotosylate **9** (343 mg, 0.99 mmol) in DME (15 mL) was added NaI (811 mg, 5.41 mmol) and Zn dust (3.33 g, 50.98 mmol). The mixture was stirred and heated under reflux for 8 h. The progress of the reaction was monitored by TLC. After removal of the zinc, the solution was diluted with water and extracted with Et_2O. The organic extract was washed, dried and evaporated to obtain a brown oil which was chromatographed (hexane: ether 7:3) to obtain the tetralone **1** (37 mg, 21%) whose spectroscopic data were identical with the tetralone **1** obtained by Method A.

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