Transformation of 5,8-dimethyl-1-tetralone: synthesis of ar-occidol

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Reduction of 5,8-dimethyl-1-tetralone **1** with sodium borohydride in methanol followed by methylation of the resulting alcohol with methyl iodide and sodium hydride yielded a methyl ether. This was oxidised with potassium permanganate and acetonitrile to give 4-methoxy-5,8-dimethyle-1-tetralone. Methoxycarbonylation of the ketone with dimethylcarbonate (DMC) in the presence of sodium hydride in dimethoxyethane (DME) afforded β-ketoester **5** which on heating with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane underwent aromatisation and elimination to furnish a naphthalene. The mesyl derivative the phenol on hydrogenation produced methyl 5,8-dimethyl-2-naphthoate. The transformation of naphthoate into ar-occidol was accomplished by a Grignard reaction with methyllithium in ether.

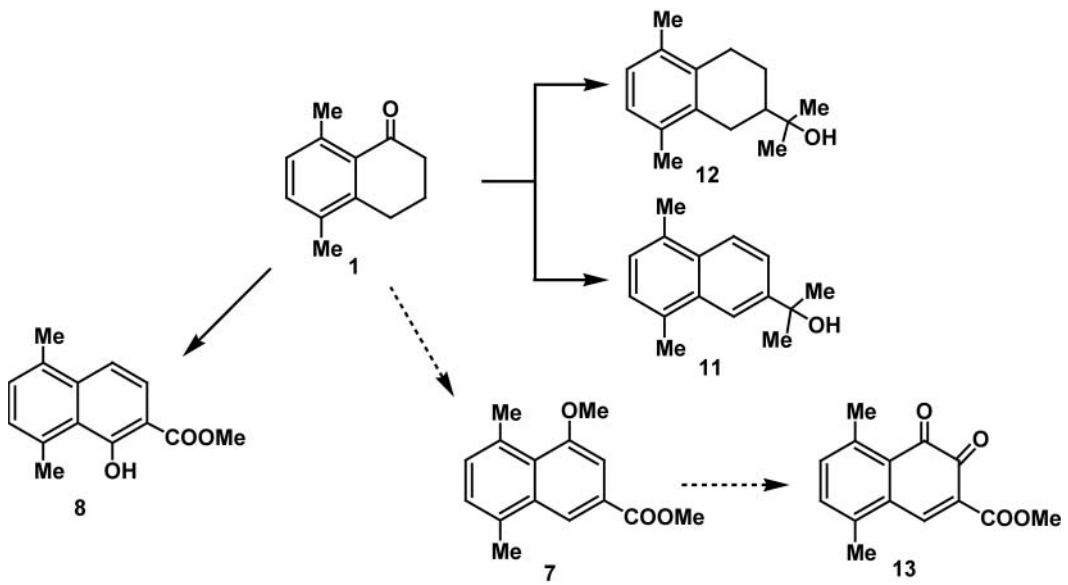
Keywords: reduction, methylation, methoxycarbonylation, aromatisation, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, methyllithium

The importance of the substituted 1-tetralone in the synthesis of natural products and other synthetic products has recently been described.[1] The previously reported[2,3] 5,8-dimethyltetetralone **1** has been utilised for the synthesis of bicyclic sesquiterpene occidol **12** and the ar-occidol[5] **11**, the aromatic analogue of occidol (Scheme 1). Having observed the utility of the tetralone **1** in the synthesis of sesquiterpenes and as a part of a program aimed at expanding the synthetic utility[6] of 1-tetralone, we tried to achieve the transformation of the tetralone **1** into the compound **7** whose conversion into the emmotin-H **13** can easily be performed following the published procedure[7].Emmotin H **13** is an aromatic sesquiterpene which has been isolated[8] from the trunk wood of *Emmotunitens* (Icacinaceae). Unfortunately the synthetic route led the formation of the phenol **8** instead of the desired ester **7**. The phenol **8** proved to be a potential intermediate for the synthesis of ar-occidol **11**. The details of our synthetic endeavours are described below (Scheme 2).

Results and discussion

In order to achieve the goal, the tetralone **1** was reduced with sodium borohydride to obtain the alcohol **2** which on methylation with methyl iodide and sodium hydride in tetrahydrofuran yielded the oily compound **3**. The tetralone **4**, obtained by the oxidation [9] of **3** with potassium permanganate and acetonitrile was treated with dimethyl carbonate in the presence of sodium hydride in 1,2-dimethoxyethane. The resulting ketoester **5**, obtained in 40% yield, displayed absorption at 1744 and 1683 cm^{-1} in the IR spectrum indicating the presence of an ester and a carbonyl group respectively. Its mass spectrum exhibited a parent peak at *m/z* 261 (M^+–1). The NMR spectrum of the compound **5** in chloroform was complicated because of the probable contamination by the enol tautomer **6**. The presence of the signal in the ^{1}H NMR spectrum at δ 12.34 (s, OH) indicated the presence of the enol ester **6**. Its ^{13}C NMR spectrum in chloroform also confirmed the presence of a tautomeric mixture of keto and enol esters.

The signals at δ 193.60 and 173.02 in the ^{13}C NMR spectrum correspond to the C-1 and C-11 respectively of the ketoester **5** whereas the signals at δ 170.99 and 164.52 correspond to the C-11 and C-1 of the enol ester **6**. The formation of keto-enol ester in solution prevented the reduction of the carbonyl group of the keto-ester **5**. Therefore it was subjected to dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone



Scheme 1

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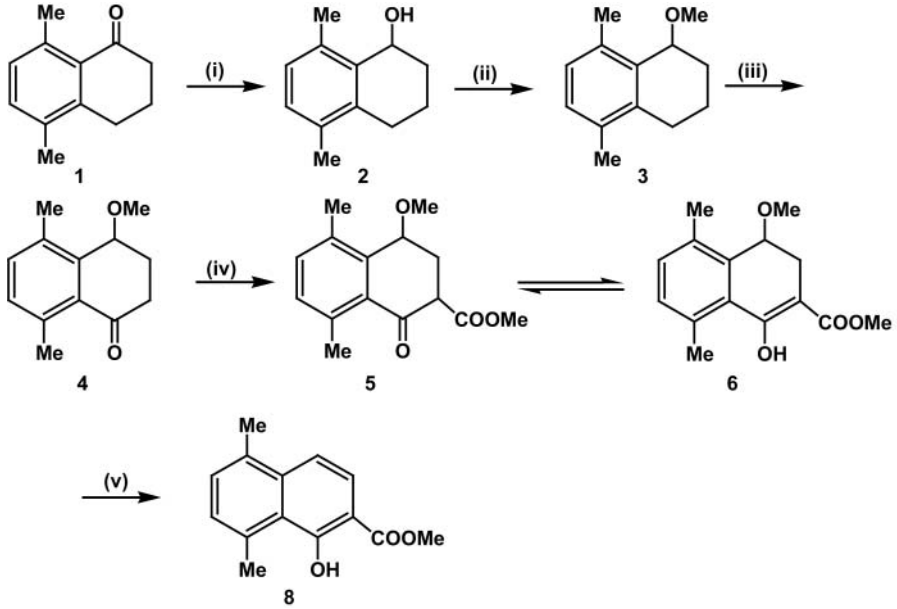


Reagents: (i) $NaBH_4$, ethanol, rt (ii) MeI, NaH, THF (iii) $KMnO_4$, MeCN
(iv) DMC, DME, NaH (v) DDQ, dioxane

Scheme 2

(DDQ) in dioxane. To our surprise instead of the expected ester **7**, a phenol was obtained in 32% yield as pale yellow solid, the spectroscopic data of which led to the assignment of structure **8**. The rest of the material, which contained several products as shown by TLC, could not be identified.

As the phenol **8** is not an appropriate intermediate for the synthesis of emmotin-H **13** attempts were made to transform it to ar-occidol **11** which is an aromatic analogue of naturally occurring bicyclic sesquiterpene occidol. An alternative synthesis of ar-occidol has already been reported[5]. In order to achieve the synthesis of ar-occidol (Scheme 3) the phenol **8** was converted to its mesyl derivative **9** which was hydrogenated[10] with Pd-C (10%) in diethylamine and ethylacetate at room temperature and atmospheric pressure to obtain the ester **10**. This was identified by comparison of its spectra (IR and NMR) with the literature data.[5] Reaction of the ester **10** with methyllithium furnished ar-occidol **11** whose spectra (IR and NMR) when compared with the data reported[5] confirmed its structure.

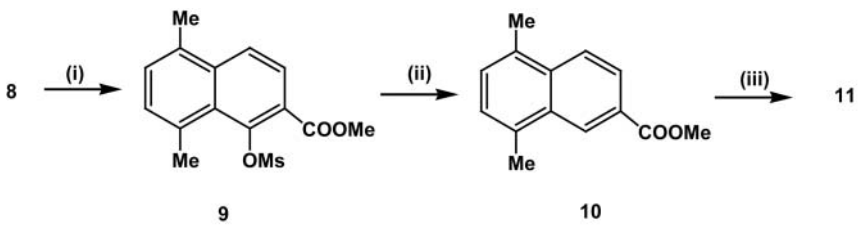
In conclusion a new approach for the synthesis of ar-occidol **11** has been developed.

Experimental

Unless otherwise stated, all melting points are uncorrected and were determined on an Electrothermal melting point apparatus. IR spectra were taken on a Nicolet Fourier transform (FT) instrument and NMR spectra were recorded on a Bruker AM-300 spectrometer in $CDCl_3$. 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 ether or chloroform, washed with brine, 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 carried out in the Chemistry Department, IVIC, Caracas.

1-Methoxy-5,8-dimethyl-1,2,3,4-tetrahydronaphthalene (**3**): To a solution of tetralone **1** (2g, 0.011 mmol) in ethanol (30 mL) was added dropwise a solution of the sodium borohydride (560 mg, 0.014 mol) in ethanol (60 mL). The mixture was stirred for 20 h at room temperature, diluted with cold water and extracted with chloroform. The workup afforded alcohol **2** as oil (1.96g, 97%); IR υ_{max} (cm^{-1}): 3406 (OH); MS (*m/z*): 158 (M^+-H_2O) (100%).

A solution of the alcohol **2** (2g, 0.011 mol) in THF (40 mL) was added dropwise to a suspension of sodium hydride (4.31 g, 0.17 mole) (60%, m/v) under nitrogen. The mixture was warmed for 10 min, followed by the addition of methyl iodide (15 mL, 0.24 mol) and then heated under reflux for 6 h. The mixture was cooled, diluted with water and extracted with ether. The workup followed by chromatographic purification (hexane:ether 8:2) yielded the product **3** (1.91, 88%); IR υ_{max} (cm^{-1}): 2973, 1082; MS(*m/z*): 158 (M^+-MeOH) (100%). 143 (M^+-MeOH-Me) (38%); ^1H $\delta_{(ppm)}$: 2.55 (s,3H), 2.63 (s,3H) (H-5, H-8), 3.71 (s, 3H, OMe), 4.58 (s,1H) (H-1), 7.06 (s,1H), 7.15 (s,1H) (H-6, H-7); ^{13}C $\delta_{(ppm)}$: 17.79 (Me-5), 18.90 (Me-8), 21.20 (C-4), 26.44 (C-3), 30.18 (C-2), 56.02 (OMe), 73.40 (C-1), 127.58 (C-6), 129.22 (C-7), 130.07 (C-5), 137.63 (C-8), 138.43 (C-9, C-10) (Found: C, 82.32; H, 9.71. $C_{13}H_{18}O$ requires C, 82.06; H, 9.54%).



Reagents: (i) MsCl, CH_2Cl_2, Et_3N (ii) H_2, Pd/C, Et_2NH, AcEt (iii) MeLi, Et_2O

Scheme 3

4-Methoxy-5,8-dimethyl-1-tetralone (**4**): To a solution of the compound **3** (200 mg, 1 mmol) in acetonitrile (25 mL) was added potassium permanganate (1 g, 6.3 mmol) portionwise during a period of 5 min. The mixture was stirred vigorously at room temperature for 24 h. The reaction mixture was filtered and the residue was washed with chloroform. To the combined extract was added hydrazine hydrochloride, diluted with water and extracted with chloroform. The organic extract was washed, dried and evaporated to obtain a viscous oil which on chromatographic purification (hexane:ether 9:1) afforded the oily tetralone **4** (128 mg, 63%); IR υ_{max}(cm^{-1}): 1685 (CO), 1080; MS (*m/z*): 205 $(M^+)^{+1}$ (11%), 173 $(M^+\text{-MeOH})^{+1}$ (100%); ^1H $\delta_{(ppm)}$: 2.24 (s, 3H), 2.32 (s, 3H) (5-Me, 8-Me), 3.39 (s,3H, OMe), 4.49 (s, 1H, H-4), 7.16 (s, 1H), 7.63 (s, 1H) (H-6,H-7); ^{13}C $\delta_{(ppm)}$: 18.51 (5-Me), 20.91 (8-Me), 24.67 (C-2), 32.41 (C-3), 56.68 (OMe), 71.76 (C-4), 124.88 (C-7), 131.92 (C-10), 136.52 (C-6), 137.28 (C-8, C-9); 138.08 (C-5), 198.59 (C-1) (Found: C, 76.67; H, 8.04. $C_{13}H_{16}O_2$ requires C, 76.44; H, 7.90%).

5,8-Dimethyl-4-methoxy-2-methoxycarbonyl-α-tetralone (**5**): To a solution of the ketone **4** (600 mg, 2.3 mmol) in dimethoxyethane (10 mL) was added sodium hydride (340 mg, 60% dispersion in mineral oil), and dimethyl carbonate (3.91 g, 0.044 mol). The resulting mixture was subjected to microwave irradiation apparatus with a power 280W for 1h, cooled, acidified with acetic acid, diluted with water and extracted with ether. The ether extract was washed, dried and evaporated to give a pale yellow oil which on chromatographic purification (hexane:ether 9:1) afforded ketoester **5** (308mg, 40%); IR υ_{max} (cm^{-1}): 1744 (ester CO), 1683 (CO); MS (*m/z*) 261 (M^+-1) (100%), 229 (M^+-1-MeOH) (50%), 197 (M^+-1-2MeOH) (30%); ^1H $\delta_{(ppm)}$: 2.33 (s, 3H), 2.37 (s, 3H) (5,8-Me), 3.29 (s, 3H,OMe), 3.81 (s, 3H, OMe) (4,8-OMe), 4.51–4.48 (dd, 1H, *J* = 2 Hz) (C-2),7.09 (s, 1H), 7.59 (s,1H) (C-6, C-7), 12.34 (s, 1H, C-1); ^{13}C $\delta_{(ppm)}$ (keto form **5**): 18.38 (5-Me), 24.92 (8-Me), 28.09 (C-3), 51.59 (11-OMe), 52.21 (C-2), 55.75 (4-OMe), 69.99 (C-4), 133.80 (C-6), 136.42 (C-7), 136.62 (C-9), 137.12 (C-5), 138.11 (C-10), 138.65 (C-8), 173.02 (C-11), 193.60 (C-1); (enol form **6**): 18.58 (8-Me), 21.11 (5-Me), 48.86 (C-3), 51.59 (11-OMe), 55.75 (4-OMe), 69.99 (C-4), 93.23 (C-2), 123.06 (C-6), 125.37 (C-5), 129.39 (C-7), 130.88 (C-9), 132.17 (C-8), 137.44 (C-10), 164.52 (C-1), 170.99 (C-11) (Found: C, 68.99; H, 7.16. $C_{15}H_{18}O_4$ requires C, 68.68; H, 6.92%).

5,8-Dimethyl-2-methoxycarbonyl-1-hydroxynaphthalene (**8**): To a suspension of DDQ (332 mg, 1.3 equiv) in dry dioxane (20 mL) was added the keto-enol ester **5** and **6** (260 mg, 1 mmol) and the mixture was heated under reflux for 50 h. under an inert atmosphere. The solution was cooled and filtered. The filtrate was washed with a solution of sodium bicarbonate (5%), brine, dried and evaporated. The resulting material on chromatographic purification (hexane:ether 9:1) afforded the naphthol **8** (74 mg, 32%), m.p. 71–72 °C IR (film) υ_{max} (cm^{-1}): 3419 (OH), 1662 (CO); MS (*m/z*): 230 (M^+) (72%), 198 (M^+-MeOH) (100%); ^1H $\delta_{(ppm)}$ 2.48 (s,3H), 2.61 (s, 3H) (Me at C-8 and C-5), 3.97 (s, 3H, OMe), 7.26 (s,1H), 8.05 (s, 1H) (H-6, H-7); 7.34 (d, 1H, *J* = 9.03 Hz), 7.69 (d, 1H, *J* = 9.03 Hz) (H-3, H-4), 11.89 (s, 1H, OH); ^{13}C $\delta_{(ppm)}$: 19.36 (s, 3H), 21.31 (s, 3H) (5-Me, 8-Me), 52.17 (OMe), 105.35 (C-2), 114.74 (C-4), 120.85 (C-7), 122.93 (C-3), 124.90 (C-5), 132.34 (C-6), 133.83 (C-9), 134.48 (C-8), 135.12 (C-10), 160,63 (C-1), 171.50 (C-11) (Found: C, 73.24; H, 6.31. $C_{14}H_{14}O_3$ requires C, 73.02; H, 6.13 %).

5,8-Dimethyl-2-methoxycarbonyl-1-mesylnaphthalene (**9**): To a solution of compound **8** (48.7 mg, 0.211 mmol) in THF (11 mL) was added Et_3N (0.05 mL, 0.36 mmol), cooled in an ice-bath and then added mesyl chloride (0.3 mL, 0.358 mmol). The solution was stirred for 16 h at room temperature, diluted with water and extracted with ether. The extract was washed with a solution of sodium carbonate solution (5%), brine, dried and evaporated. The material obtained on purification by preparative TLC over silica gel (eluant hexane-ether 8:2) yielded the mesylate **9** (55mg, 84%), m.p. 78–79 °C; IR υ_{max} (cm^{-1}) 1724 (CO); MS (*m/z*): 308 (45%), 229 (M^+-SO_2Me) (100%); ^1H $\delta_{(ppm)}$: 2.51 (s,3H), 2.64 (s, 3H) (5-Me, 8-Me), 3.42 (s, 3H, $MeSO_3$-), 3.95 (s, 3H, OMe), 7.91–7.85 (**st**. 2H, *J* = 9.06 Hz) (4-H, 3-H), 7.28 (s, 1H), 8.01 (s, 1H) (H-7) (H-6); ^{13}C $\delta_{(ppm)}$: 19.35 (5-Me), 22.04 (8-Me), 39.6 (1-SO_3Me), 120.98 (C-4), 121.06 (C-2), 123.11 (C-7), 124. 86 (C-6), 128.71 (C-9), 131.94 (C-3), 134.15 (C-5), 134.34 (C-8), 137.54 (C-10), 144.92 (C-1), 165.76 (C-11) (Found: C, 58.72; H, 5.36. $C_{15}H_{16}O_5S$ requires C, 58.94; H, 5.19%).

5,8-Dimethyl-2-methoxycarbonylnaphthalene (**10**): To the mesylate **9** (28.2 mg, 0.092 g, mmol) dissolved in ethyl acetate (10 mL) and diethylamine (0.1 mL, 0.19 mmol) was added 10% Pd-C (10 mg). The mixture was hydrogenated for 10 h at room temperature and under atmospheric pressure. The catalyst was removed by filtration and the filtrate was extracted with ether, washed, dried and evaporated to obtain a brown oil which on purification by preparative TLC over silica gel (eluant hexane-ether 1:1) yielded the ester **10** (19.4 mg, 99%); IR υ_{max} (cm^{-1}) 1720 (CO); MS (*m/z*): 214 (M^+) (100%); ^1H $\delta_{(ppm)}$: 2.46 (s, 3H), 2.65 (s, 3H) (5,8-Me), 3.95 (s, 3H, OMe), 7.25 (s,1H), 7.55 (s,1H) (6-H), (7-H), 8.01–7.93 (d, 2H, q_{AB}, *J* = 8.8 Hz) (3-H, 4-H), 8.48 (s, 1H) (1-H); ^{13}C $\delta_{(ppm)}$: 19.11 (5-Me), 21.47 (8-Me), 52.05 (2-OMe), 124.17 (C-3, C-4), 126.24 (C-2), 126.50 (C-6), 127.05 (C-9), 130.84 (C-1), 131.26 (C-7),132.99 (C-5), 134.03 (C-10), 135.97 (C-8), 167.38 (C-11) (Found: C, 78.72; H, 6.75. $C_{14}H_{14}O_2$ requires C, 78.48; H, 6.59%).

Ar-Occidol [1-Methyl-1-(5,8-dimethyl-2-naphthyl)ethanol] (**11**): A solution of the ester **10** (20 mg, 0.09 mmol) in THF (3 mL) was added over a period of 5 min to a stirred methyl-lithum solution (1.38 M, 2 mL) under an argon atmosphere. The resulting solution was then heated for 2 h, cooled, diluted with water and extracted with ether. The extract was washed, dried, evaporated and purified by preparative TLC over silica gel (eluant ether:hexane 2:8) to afford ar-occidol **11** (14 mg, 72%); IR $\upsilon_{(max)}$ (cm^{-1}): 3601–3150 (OH), 1600 (aromatic); MS (*m/z*): 214 (M^+) (86%), 199 (M^+-CH_3) (67%), 196 (M^+-H_2O) (69%), 181 (M^+-H_2O-CH_3); ^1H $\delta_{(ppm)}$: 7.91–7.89 (d, 1H, *J* = 8.8 H_z, 4-H), 7.82–7.81 (d, 1H, *J* = 1.9 Hz, 1-H), 7.57–7.53 (dd, 1H, *J* = 1.9 Hz, 8.8 Hz, 3-H), 7.45 (s, 1H, 6-H), 7.12 (s, 1H, 7-H), 2.63 (s, 3H, 5-Me), 2.44 (s, 3H, 8-Me), 1.65 (s, 6H, 11-Me); ^{13}C $\delta_{(ppm)}$: 19.12 (Me-5), 21.59 (Me-8), 31.68 (2xMe-11), 72.67 (C-11), 122.35 (C-4), 122,40 (C-3), 124.05 (C-1), 125.49 (C-7), 128.80 (C-6), 129.75 (C-8), 133.67 (C-5), 133.77 (C-10), 135.38 (C-9), 146.16 (C-2).

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References

1 Po.S. Poon, A.K. Banerjee, W.J. Vera, H.D. Mora, M.S. Laya, L. Bedoya, E.V. Cabrera and C. Melean. *J.Chem. Res.*, 2008, 181
2 A.K. Banerjee, W. Vera and M.S. Laya. *Synth Commun*., 2004, **34**, 2301.
3 R.B. Mane and A.J. Kadam. *Collect Czech. Chem Commun.*, 1999, **64**, 533
4 P.A. Reddy and G.S.K. Rao, *Indian J Chem*., 1980, **19B**, 753.
5 T.P. Veluchamy and G.S.K. Rao, *Indian J Chem*., 1983, **22B**,824.
6 A.K. Banerjee and Po.S. Poon, *Arkivoc*, 2009, **13**, 108.
7 T.P. Veluchamy, D. Murali and G.S.K. Rao, *Indian J. Chem*., 1986, **25B**, 1247.
8 A.B. De Oliveira, G.G. De Oliveira, T.M.C. Liberalli, O.R. Gottlieb and M.T. Magalhaces, *Phytochemistry*, 1976, **15**, 1267.
9 A. Shaabani, F. Tavaso-Red and D. Lee, *Synth. Commun*., 2005, **35**, 571.
10 A. Mori, T. Mizusaki, T. Ikawa, T. Maegawa, Y. Monguchi and H. Sajiki, *Tetrahedron*, 2007, **63**, 63270.