Wittig reaction on 5,8-dimethyl-2-tetralone. A total formal synthesis of Emmotin-G methyl ether

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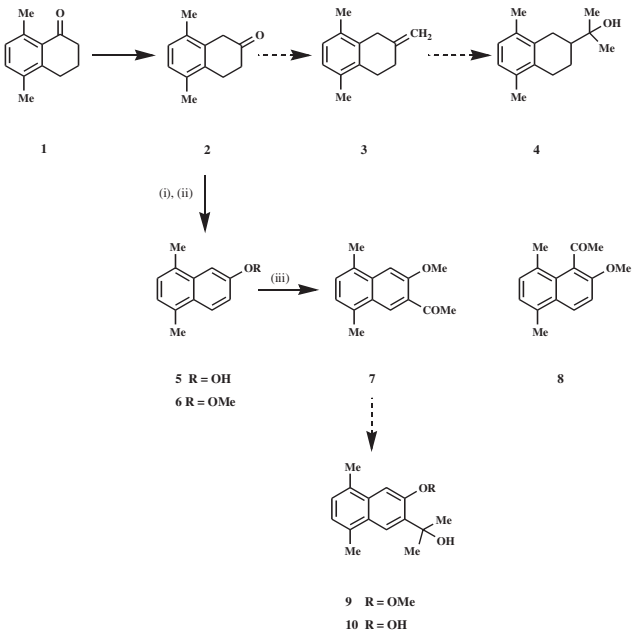
The conversion of tetralone **2** to 6-methoxy-7-acetyl-1,4-dimethylnaphthalene **7**, a precursor for Emmotin-G methyl ether is described.

Keywords: Wittig reaction, polyphosphoric acid, Emmotin-G methyl ether

Recently we have accomplished a concise and convenient synthesis[1] of 5,8-dimethyl-2-tetralone **2** from the known[2] tetralone **1**. Tetralone **1** was prepared in our laboratory with some modifications.[1] Bachute *et al.*,[3] have already reported the synthesis of tetralone **2** by a very different route. It appeared to us that tetralone **2** might serve as a useful intermediate for the synthesis of Occidol **4** which belongs to the eudesmane class of sesquiterpenes.[2]

Tetralone **2** was subjected to Wittig reaction with $Ph_3P{=}CH_2$ and we expected to obtain compound **3** which on successive reactions involving hydroboration, oxidation, esterification and Grignard reaction with methyllithium would lead the formation of occidol **4**. To our surprise the reaction of tetralone **2** with the Wittig reagent ($Ph_3P{=}CH_2$) carried out by refluxing $Ph_3P^+MeBr^-$ and sodamide in toluene afforded 60% of naphthol **5** (Scheme 1) along with several unidentified products. The identity of naphthol **5** was confirmed by its spectroscopic data (IR, MS, ^{1}H NMR and ^{13}C NMR). The same reaction was repeated with sodium hydride and dimethylsulfoxide at room temperature for 24 hr to obtain only naphthol **5** (48%). The experiment was repeated by changing solvents, temperature, hydrides, amount of $Ph_3P{=}CH_2$ but the desired product **3** was not obtained. In each of the experiments, naphthol **5** was the only product that could be isolated, in variable yield. The situation was not anticipated when the present scheme was devised. It is necessary to provide here the reasons for the formation of naphthol **5** and this is explained in Scheme 2.



Scheme 1 Reagent: (i) $Ph_3P{=}CH_2$, $NaNH_2$, C_6H_5Me; (ii) Me_2SO_4, NaOH; (iii) Ac_2O-PPA.

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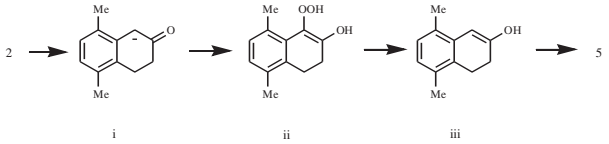

Scheme 2

We believe that 5,8-dimethyl groups of tetralone **2** inhibits the enolisation to give $\Delta^{1,2}$ enol because this brings the alkene proton into closer proximity with the methyl group. Thus it is reasonable to think that enolisation takes places to the 2 (3) position yielding the enol $\Delta^{2,3}$ (i) (Scheme 2). As this reaction was not carried out in nitrogen, the air probably provided oxygen to form[4] the hydroperoxide intermediate (ii) which underwent elimination yielding naphthol **5** and thus no Wittig product **3** was obtained. The isolation of naphthol **5** (60%) by heating tetralone **2** with sodamide and toluene confirmed our assumption.

Naphthol **5** was methylated with dimethylsulphate and sodium hydroxide to obtain the compound **6**. This on acylation with polyphosphoric acid and acetic anhydride yielded a crystalline solid material which was assigned to structure **7** instead of **8** on the basis of spectral data (IR, MS, ^{1}H NMR and ^{13}C NMR). In ^{1}H NMR the compound **7** showed singlets at δ 8.11 (s, 1H) and 7.12 (s, 1H) which correspond to the protons at C-8 and C-5. If the acylated product is assigned to structure **8** the protons at C-7 and C-8 would appear as doublets. As these were not detected in the NMR spectrum we remained confident of the structural assignment **7** of the acylated product. This acylated product **7** had already been synthesised[5] by a different route. Its ^{1}H NMR data satisfactorily match our data.

In addition the ^{13}C NMR spectra provided strong support in favour of the structure of compound **7.**

Transformation of acylated product **7** to Emmotin-G methyl ether **9** has been reported.[5] This is a methyl derivative of Emmotin-G **10** which is a naturally occurring rearranged sesquiterpene, that had been isolated from the trunk wood of *Emmotum nitens*[6,7] and synthesised by Rao.[8] As the acylated product **7** has been converted[5] to Emmotin-G methyl ether **9** our alternative approach to the product **7** constitutes a total formal synthesis of Emmotin-G methyl ether.

In conclusion it has been shown that Wittig reaction of a β-tetralone yields a β-naphthol instead of alkene. This unexpected observation led accidentally to a precursor for Emmotin-G methyl ether whose transformation to Emmotin-G can be accomplished easily.

Experimental

For general experimental details see ref. **9.**

5,8-Dimethyl-β-naphthol **5**: A solution of $Ph_3P^+MeBr^-$ (4.14 g) and sodamide (10 ml suspension in toluene, 50% w/v) was heated under reflux for 6 h, and cooled to room temperature. Tetralone **2** (501 mg) in toluene (25 ml) was added to the resulting yellow solution. The mixture was heated under reflux for 24 h, cooled, water was added to destroy the excess sodamide, and the product was extracted with ether. The workup followed by chromatographic purification

(hexane-diethyl ether 8:2) yielded a liquid material which on further purification by preparative layer chromatography (hexane-diethyl ether 9:1) yielded naphthol **5**; (302 mg, 60%), m.p. 102–105°C, m/z 172 (M^+); ν_{max} 3350 (OH), 1611 cm^{-1} (C=C); ^1H: δ 2.51 (s, 3H, 5-Me), 2.58 (s, 3H, 8-Me), 7.13–7.17 (dd, 1H, *J*=8.7 Hz and *J*=2.5 Hz, 3-H), 7.19 (bs, 1H, 6-H), 7.31 (d, *J*=2.5 Hz, 1-H), 7.47 (bs, 1H, 7-H), 7.71 (d, 1H, *J*=8.7, 4-H), ^{13}C: δ 159 (C2), 134.08 (C9), 133.95 (C5), 133.39 (C10), 133.16 (C4) 130.96 (C7), 130.64 (C8), 126.47 (C6), 118.64 (C3), 107.87 (C1), 22.81 (C12) and 20.71 (C11). (Found: C, 83.92; H, 7.13. $C_{12}H_{12}O$ requires C, 83.69 %; H, 7.02%).

To a suspension of sodamine in toluene (20 ml, 50% W/V) was added dropwise a solution of tetralone **2** (910 mg) in dry toluene (50 ml) and the mixture was heated under reflux for 24 h. The workup by the usual procedure afforded an oil which on purification by preparative layer chromatography (hexane-diethyl ether 8:2) yielded β-naphthol **5** (540 mg, 60%), m.p. 102–105°C whose spectral data were identical to β-naphthol **5** obtained by the procedure (A).

5,8-Dimethyl-2-methoxynaphthalene **6**: Freshly distilled dimethyl sulfate (20 ml) and aqueous solution of sodium hydroxide (20 ml, 10%) was added to a solution of naphthol **5** (502 mg) in ethanol (166 ml, 95%). The resulting solution was stirred at room temperature for 1.5 h and heated at 80°C for 1 h. Workup followed by purification by preparative layer chromatography (hexane-diethyl ether 9:1) afforded compound **6** (270 mg, 50%), m.p. 95–97°C; *m/z* 186 (M^+). ^1H: δ 2.37 (s, 3H), 2.39 (s, 3H) (5,8-Me), 3.88 (s, 3H, OMe), 7.01–7.04 (m, 3H, 1-H and 3-H), 7.49 (bs, 1H,7-H), 7.48 (bs, 1H, 6-H) and 7.59 (d, 1H, *J*=9.5 Hz, 4-H). ^{13}C: δ 19.91 (5-Me), 20.19 (8-Me), 55.23 (2-OMe), 105.01 (C-1), 117.61 (C-3), 126.41 (C-6), 127.17 (C-7), 127.80 (C-8), 128.35 (C-4), 132.99 (C-9), 133.30 (C-10), 136.01 (C-5), 157.04 (C-2) (Found: C, 84.11; H, 7.73. $C_{13}H_{14}O$ requires C, 83.83 %; H, 7.58%).

6-Methoxy-7-acetyl-1,4-dimethylnaphthalene **7**: A mixture of the methoxynaphthalene **6** (270 mg), polyphosphoric acid (2.28 g) and freshly distilled acetic anhydride (0.2 ml) was heated for 2 h at 45°C. The workup followed by purification by preparative chromatography (hexane-diethyl ether 9:1) gave **7** (100 mg, 30%); m.p. 107–110°C; *m/z* 228 (M^+) and 213 (M^+-Me); ν_{max} 1678 (CO) cm^{-1}; ^1H: δ 2.42 (s, 3H), 2.45 (s, 3H) (1-Me and 4-Me), 2.71 (s, 3H, COMe), 4.01 (s, 3H, 6-OMe), 7.11 (s, 1H, 5-H), 7.52 (bs, 1H, 2-H), 7.60 (bs, 1H, 3-H) and 8.11 (s, 1H, 8-H). ^{13}C : δ 19.88 (4-Me), 20.38 (1-Me), 31.56 (MeCO), 55.42 (6-OMe), 105.45 (C5), 125.98 (C8), 126.77 (C7), 128.56 (C3), 129.22 (C4), 130.39 (C2), 134.01 (C9), 135.12 (C10), 138.57 (C1), 155.26 (C6) and 200.37 (C11) (Found: C, 79.17; H, 7.18. $C_{15}H_{16}O_2$ requires C, 78.92 %; H, 7.06%).

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