A NEW SYNTHESIS OF OCCIDOL

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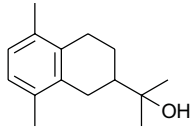
Sodium borohydride reduction of 5,8-dimethyl-3,4-dihydronaphthalen-1-(2*H*)-one (**4**) yielded 5,8-dimethyl-1,2,3,4-tetrahydro-1-naphthol (**5**). The tetralol **5** on Vilsmeier–Haack reaction with *N*,*N*-dimethylacetamide yielded 1-(5,8-dimethyl-3,4-dihydro-2-naphthyl)-ethan-1-one (**7**) which on hydrogenation over Pd/C afforded 1-(5,8-dimethyl-1,2,3,4-tetrahydro-2-naphthyl)ethan-1-one (**8**). The tetralol **5** on Vilsmeier–Haack formylation gave 5,8-dimethyl-3,4-dihydro-2-naphthaldehyde (**9**) which on reduction with lithium aluminium hydride followed by oxidation with the Jones reagent furnished 5,8-dimethyl-1,2,3,4-tetrahydro-2-naphthoic acid (**11**). The acid **11** on treatment with excess of methyllithium yielded (±)-occidol (**1**); with two moles of methyllithium it yielded ketone **8**, which on reaction with methyllithium furnished (±)-occidol (**1**).

Key words: Occidol; Sesquiterpenoids; Total synthesis; Vilsmeier–Haack reaction; 1,2,3,4-Tetrahydronaphthalenes.

Occidol (**1**), which occurs in the essential oil of *Thuja* species[1,2], incorporates a rearranged sesquiterpene skeleton and belongs to the eudesmane class of sesquiterpenes. Occidentalol[2,3] (**2**), an eudesmane-based sesquiterpene, which co-occurs with occidol in *Thuja occidentalis* and *Thuja koraiensis* is believed to be the precursor of the latter[1]. A biogenetic skeletal rearrangement is implied in this transformation.



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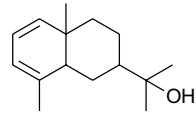

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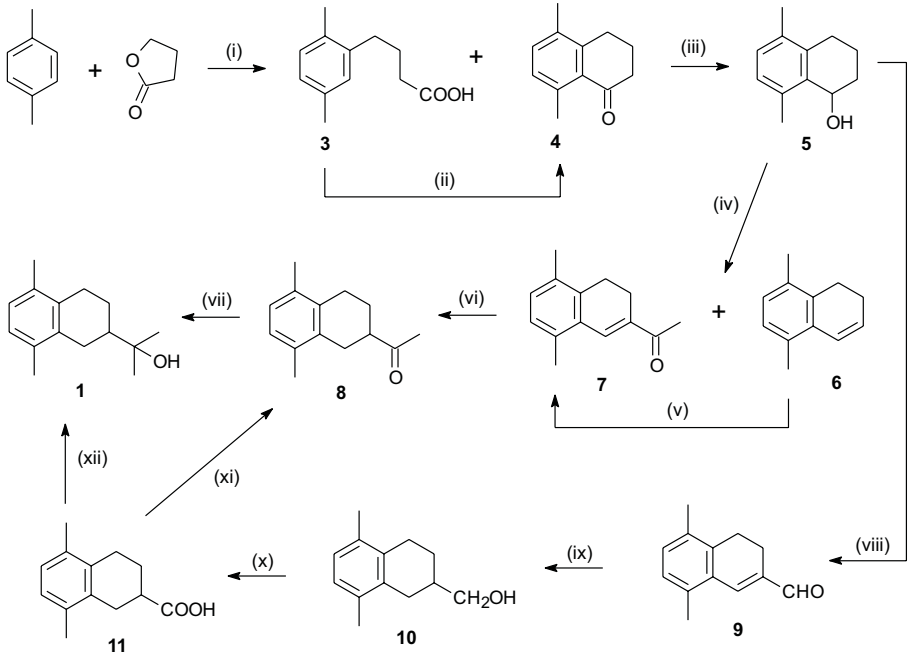
Several syntheses[4–11] of occidol have been reported. Biogenetically unusual features of occidol have aroused a lot of interest in its synthetic endeavours. We report here a new synthesis of occidol shown in Scheme 1.

The Vilsmeier–Haack reaction using *N*,*N*-dimethylacetamide is a key step in this synthesis.



(i) $AlCl_3$, 90 °C; (ii) PPA, 95 °C; (iii) $NaBH_4$, EtOH; (iv) CH_3CONMe_2, $POCl_3$, 100 °C; (v) PPA-AcOH, 95 °C; (vi) H_2, Pd/C; (vii) MeLi, Et_2O, r.t.; (viii) DMF, $POCl_3$, 100 °C; (ix) $LiAlH_4$, Et_2O, reflux; (x) Jones reagent, acetone, 15-20 °C; (xi) 2 equivalents of MeLi, Et_2O, r.t.; (xii) high excess of MeLi, Et_2O, r.t.

SCHEME 1

The approach started with 5,8-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (**4**), which was prepared in one step by Friedel–Crafts alkylation of *p*-xylene with butano-4-lactone[12]. The minor product, 4-(2,5-dimethylphenyl)butanoic acid (**3**) was cyclized with polyphosphoric acid (PPA) to yield additional tetralone **4**. The tetralone **4** on reduction with sodium borohydride yielded 5,8-dimethyl-1,2,3,4-tetrahydro-1-naphthol (**5**). The Vilsmeier–Haack reaction of tetralol **5** using *N*,*N*-dimethylacetamide[13] gave the unsaturated methyl ketone **7** along with a small amount of 5,8-dimethyl-1,2-dihydronaphthalene (**6**) formed by dehydration of **5**. Reactions of the olefin **6** with acetic acid and PPA are reported[14] to give conjugated methyl ketones.

Catalytic hydrogenation of **7** with Pd/C gave saturated ketone **8**. In order to correlate the structure of **8**, the compound was prepared by another

route. Tetralol **5** was converted into 5,8-dimethyl-3,4-dihydro-2-naphthaldehyde (**9**) using the Vilsmeier–Haack reaction[9]. The aldehyde **9** was reduced with lithium aluminum hydride[15] to 1-(5,8-dimethyl-1,2,3,4-tetrahydro-2-naphthyl)methan-1-ol (**10**), which was oxidized to 5,8-dimethyl-1,2,3,4-tetrahydro-2-naphthoic acid (**11**) by the Jones reagent[16]. The acid **11** was converted into occidol in one step by reaction with excess of methyllithium[17]. The major component was occidol (**1**) and the minor component was ketone **8**. Spectral data of **1** agreed with those reported for occidol.

The acid **11** was also converted into ketone **8** by the reaction with two moles of methyllithium[18]. This ketone has already been converted into occidol by Nakazuki *et al.*[19]. We have converted this ketone into occidol by reaction with methyllithium.

EXPERIMENTAL

Melting and boiling points are uncorrected. Analytical and preparative thin-layer chromatography (TLC) was carried out on glass plate precoated with silica gel G (Merck). Materials were detected by visualization under an iodine chamber. Column chromatography was performed with silica gel (Merck) (60–120 mesh). IR spectra (wavenumbers are given in cm^{-1}) were recorded on a Perkin–Elmer 783 spectrophotometer and ^1H NMR spectra on a Bruker AC-200 (200 MHz) machine. The chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz.

5,8-Dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (**4**)

Anhydrous aluminum chloride (167 g, 1.25 mol) was added in portions during 2 h to a stirred mixture of *p*-xylene (106 g, 1.0 mol) and butano-4-lactone (43 g, 0.5 mol) at room temperature. The reaction mixture was heated at 90 °C for 6 h, cooled and decomposed with 15% ice-cold hydrochloric acid. The organic layer was separated and aqueous layer extracted with diethyl ether. The combined organic extracts were consecutively washed with a sodium hydrogencarbonate solution, water and then dried with anhydrous sodium sulfate. The residue after evaporation was distilled under vacuum to yield pure tetralone **4** (45 g, 52%), b.p. 160–162 °C/1 595 Pa (ref.[20] gives b.p. 145 °C/1 320 Pa). IR (neat): 1 670 (C=O), 1 605. ^1H NMR ($CDCl_3$): 2.07 quintet, 2 H, J = 7 (CH_2); 2.58 t, 2 H, J = 7 (CH_2); 2.90 t, 2 H, J = 7 (CH_2); 2.3 s, 3 H (CH_3); 2.60 s, 3 H (CH_3); 6.92 and 6.94 AB quartet, 2 H, J = 8.5 (Ar-H).

The alkaline extract was acidified with concentrated hydrochloric acid to yield 4-(2,5-dimethylphenyl)butanoic acid (**3**) (19 g, 20%), b.p. 150–153 °C/1 064 Pa (ref.[20] gives b.p. 188–192 °C/2 127 Pa). IR (neat): 3 400–2 900 (COOH), 1 715 (C=O).

5,8-Dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (**4**)

To a well stirred polyphosphoric acid[21], prepared from phosphorus pentoxide (150 g) and orthophosphoric acid (80 ml), was added **3** (15 g, 78 mmol) at 95 °C. The reaction mixture was heated at this temperature for 2 h, cooled and, after addition of ice-cold water, ex-

tracted with diethyl ether. The ether extract was successively washed with a 10% sodium hydroxide solution, water and dried with anhydrous sodium sulfate. Removal of ether furnished **4** (11.5 g, 85%).

5,8-Dimethyl-1,2,3,4-tetrahydro-1-naphthol (**5**)

To a stirred solution of **4** (14 g, 79.5 mmol) in ethanol (100 ml) was added sodium borohydride (5 g, 132 mmol) in small portions[9]. The reaction mixture was left overnight at room temperature, most of the solvent was removed under vacuum and saturated aqueous solution of ammonium chloride (100 ml) was added. After 30 min, the mixture was extracted with diethyl ether. The ether extract was washed with water and dried with anhydrous sodium sulfate. Removal of solvent yielded **5** (13.7 g, 97%), m.p. 89 °C (petroleum ether) (ref.[9] gives m.p. 88–89 °C). IR (KBr): 3 360 (broad, OH).

1-(5,8-Dimethyl-3,4-dihydronaphtyl)ethan-1-one (**7**)

A) Phosphorus oxychloride (1.0 ml, 10.71 mmol) was added dropwise to a stirred solution of **5** (1.0 g, 5.6 mmol) in dry *N*,*N*-dimethylacetamide (10 ml) at 100 °C. The reaction mixture was stirred at this temperature for 3 h, cooled and poured onto crushed ice (50 g). The complex formed during the reaction was hydrolyzed by addition of sodium acetate (2 g, 24.3 mmol), the solution was extracted with diethyl ether, the ether extract washed with water and dried with anhydrous sodium sulfate. The residue after evaporation (0.7 g) was purified by TLC (silica gel G, petroleum ether–ethyl acetate, 9 : 1). The yield of **7** was 0.2 g (18%). IR (neat): 1 675, 1 650, 1 600. ^{1}H NMR ($CDCl_3$): 2.3 s, 3 H (Ar-CH_3); 2.38 s, 3 H (Ar-CH_3); 2.43 s, 3 H ($COCH_3$); 2.53 t, 2 H (CH_2); 2.77 t, 2 H (CH_2); 6.85 and 6.91 AB quartet, 2 H, J = 8.5 (Ar-H); 7.64 s, 1 H (vinylic proton). The yield of olefin **6** was 0.4 g (45%). IR (neat): 1 612.

B) To a well stirred solution of PPA, prepared from phosphorus pentoxide (2.5 g) and orthophosphoric acid (1.7 ml), was added a mixture of **6** (0.6 g, 3.8 mmol) and acetic acid (0.6 ml, 10 mmol) in one lot. The mixture was stirred at 95 °C for 4 h and after cooling added to crushed ice (25 g) and extracted with diethyl ether. The ether extract was washed with water and dried with anhydrous sodium sulfate. Removal of the solvent gave the crude product which was purified by TLC (silica gel G, petroleum ether–ethyl acetate, 9 : 1) to give **7** (0.12 g, 16%).

1-(5,8-Dimethyl-1,2,3,4-tetrahydro-2-naphthyl)ethan-1-one (**8**)

A solution of **7** (0.05 g, 0.25 mmol) in ethanol (5 ml) was shaken with Pd/C (0.02 g, 10%) in hydrogen atmosphere for 3 h. The catalyst was filtered off and the filtrate was evaporated under vacuum to give **8** (0.045 g, 90%). IR (neat): 1 705 (C=O). ^{1}H NMR ($CDCl_3$): 1.7 m, 2 H (CH_2); 2.2 s, 3 H ($COCH_3$); 2.25 s, 6 H (CH_3); 2.62 m, 4 H (CH_2); 3.00 m, 1 H (CH); 6.77 and 6.83 AB quartet, 2 H, J = 8.5 (Ar-H).

5,8-Dimethyl-3,4-dihydro-2-naphthaldehyde (**9**)

To a stirred solution of **5** (6 g, 34 mmol) in dry *N*,*N*-dimethylformamide (15 ml), phosphorus oxychloride (6 ml, 64.31 mmol) was added dropwise at 100 °C. The reaction was carried out as described for **7**. The crude product obtained was purified by chromatography on silica gel (150 g). Elution with petroleum ether furnished olefin **6** (0.6 g) and with petroleum

ether–chloroform (9 : 1) the desired aldehyde **9** (4.4 g, 69%), m.p. 75–76 °C (petroleum ether) (ref.[9] gives b.p. 165–170 °C/1 197 Pa). IR (KBr): 2 712 (CHO), 1 670 (C=O). ^{1}H NMR ($CDCl_3$): 2.34 s, 3 H (CH_3); 2.42 s, 3 H (CH_3); 2.54 t, 2 H (CH_2); 2.82 t, 2 H (CH_2); 6.88 and 6.92 AB quartet, 2 H, J = 8.5 (Ar-H); 7.53 s, 1 H (vinylic proton); 9.7 s, 1 H (CHO). For $C_{13}H_{14}O$ (186.2) calculated: 83.83% C, 7.57% H; found: 83.55% C, 7.44% H.

1-(5,8-Dimethyl-1,2,3,4-tetrahydro-2-naphthyl)methan-1-ol (**10**)

To a stirred solution of **9** (1.5 g, 8.06 mmol) in dry diethyl ether, lithium aluminum hydride was added (0.8 g, 21 mmol) in three lots at 0–10 °C. After the addition, the reaction mixture was refluxed for 6 h. The excess of lithium aluminum hydride was decomposed by addition of ethyl acetate to the cooled reaction mixture, followed by aqueous tartaric acid for decomposition of the complex formed. The mixture was then extracted with diethyl ether, the extract was washed with water and dried with anhydrous sodium sulfate. Removal of the solvent gave alcohol **10** as an oil (1.4 g, 91%), b.t. 150–156 °C/266 Pa. IR (neat): 3 370 (broad, OH). ^{1}H NMR ($CDCl_3$): 2.1 m, 2 H (CH_2); 2.22 s, 3 H (CH_3); 2.78 m, 5 H (2 × CH_2 and CH); 3.7 d, 2 H, J = 6 (CH_2OH); 6.86 and 6.9 AB quartet, 2 H, J = 8.5 (Ar-H). For $C_{13}H_{18}O$ (190.3) calculated: 82.05% C, 9.53% H; found: 81.92% C, 9.30% H.

5,8-Dimethyl-1,2,3,4-tetrahydro-2-naphthoic Acid (**11**)

To a stirred solution of **10** (1.2 g, 6.3 mmol) in acetone (10 ml) was added during 30 min the Jones reagent (5.5 ml), prepared from chromium trioxide (26.72 g) and concentrated sulfuric acid (23 ml) and diluted to 100 ml. The reaction mixture was stirred at 15–20 °C for 4 h and then sodium disulfite was added to decompose excess of the Jones reagent (brown colour disappears). The product was extracted with diethyl ether and the acid was extracted with 10% sodium hydroxide solution. Acidification of the alkaline extract gave the desired acid **11** (0.875 g, 68%), m.p. 132–133 °C (ethanol) (ref.[9] gives m.p. 134–135 °C). IR (KBr): 3 400–3 000 (COOH), 1 700 (C=O).

1-(5,8-Dimethyl-1,2,3,4-tetrahydro-2-naphthyl)ethan-1-one (**8**)

A solution of the acid **11** (0.41 g, 2 mmol) in diethyl ether (10 ml) was added during 15 min to a stirred solution of methyllithium, prepared from lithium (0.07 g, 10 mmol) and methyl iodide (0.32 ml, 5 mmol) in dry ether (60 ml). The reaction mixture was stirred at room temperature for 4 h and kept at this temperature overnight. It was decomposed by pouring into a cold saturated ammonium chloride solution (20 ml) and extracted with diethyl ether. The ether extract was washed successively with a saturated sodium hydrogencarbonate solution, water and dried with anhydrous sodium sulfate. Removal of solvent furnished the ketone **8** (0.39 g, 96%), b.t. 140–145 °C/268 Pa (ref.[19] gives b.p. 120–140 °C/67 Pa). IR and NMR spectra were identical in all respects with the products obtained in the earlier experiment.

1-Methyl-1-(5,8-dimethyl-1,2,3,4-tetrahydro-2-naphthyl)ethan-1-ol (**1**)

A) To a stirred solution of methyllithium, prepared from lithium (0.03 g, 4.3 mmol) and methyl iodide (0.15 ml, 2.4 mmol) in dry ether (40 ml), a solution of **8** (0.35 g, 1.75 mmol) in diethyl ether (5 ml) was added during 15 min. The reaction was carried out as described

above to give the crude product which was purified by TLC (silica gel G, petroleum ether–ethyl acetate, 9 : 1). The yield of pure occidol (**1**) was 0.30 g (79%), m.p. 97–98 °C (petroleum ether) (ref.[9] gives m.p. 99–100 °C). IR (KBr): 3 420 (broad, OH). ^{1}H NMR ($CDCl_3$): 1.23 s, 6 H (CH_3); 1.4 bs, 1 H (OH); 2.15 s, 3 H (Ar-CH_3); 2.2 s, 3 H (Ar-CH_3); 1.6 m, 2 H (CH_2); 2.1 m, 1 H (CH); 2.65 m, 4 H (CH_2); 6.73 and 6.77 AB quartet, 2 H, J = 8.5 (Ar-H). For $C_{15}H_{22}O$ (218.3) calculated: 82.53% C, 10.15% H; found: 82.48% C, 9.92% H.

B) To a stirred solution of methyllithium, prepared from lithium (0.29 g, 41.7 mmol) and methyl iodide (1.34 ml, 21.5 mmol) in dry ether (80 ml), a solution of **11** (0.61 g, 3 mmol) in diethyl ether (10 ml) was added during 15 min. The reaction was carried out as described above to give the crude product which was purified by TLC (silica gel G, petroleum ether–ethyl acetate, 9 : 1). The yield of pure **1** was 0.51 g (77%).

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