



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/lcyc20>

Formal Total Synthesis of (±)-Occidol

William J. Vera^a & Ajoy K. Banerjee^a

^a Centro de Química, Instituto Venezolano de Investigaciones Científicas (IVIC), Caracas, Venezuela

Version of record first published: 16 Feb 2007.

To cite this article: William J. Vera & Ajoy K. Banerjee (2006): Formal Total Synthesis of (±)-Occidol, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 36:20, 3091-3094

To link to this article: <http://dx.doi.org/10.1080/00397910600775663>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.tandfonline.com/page/terms-and-conditions>

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae, and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand, or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Formal Total Synthesis of (\pm)-Occidol

William J. Vera and Ajoy K. Banerjee

Centro de Química, Instituto Venezolano de Investigaciones Científicas
(IVIC), Caracas, Venezuela

Abstract: The conversion of tetralone **1** to methylketone **7**, a valuable intermediate of occidol **8**, has been accomplished in four steps (reduction, mesylation, cyanation, and Grignard reaction with methylmagnesium bromide).

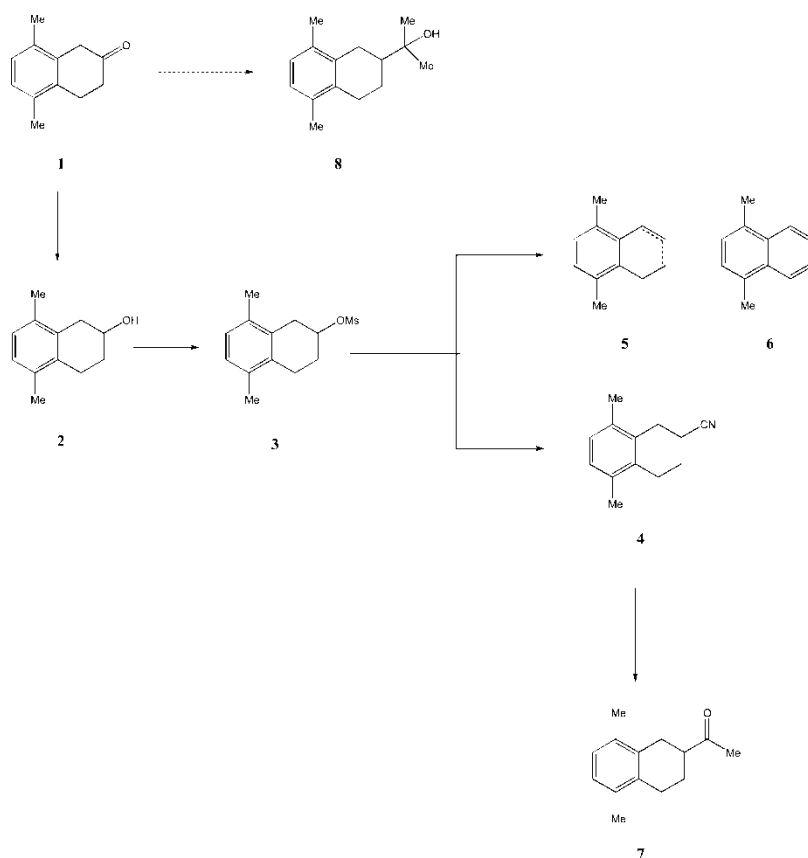
Keywords: Cyanation, Grignard reaction, occidol, tetralones

Occidol **8**, a principal constituent of essential oil of Thuja species,^[1] belongs to the eudesmane class of sesquiterpenes. Several syntheses of occidol **8** have been accomplished by a variety of methods.^[2] In some of these approaches, substituted α -tetralones have been smoothly converted to occidol **8**. To date, no attempt has been made to synthesize occidol from substituted β -tetralones. The recently reported^[3] 5,8-dimethyl β -tetralone **1** prompted us to study its conversion to occidol **8**.

Tetralone **1** was reduced with sodium borohydride to an oily alcohol **2**, which was converted to its mesylate derivative **3** by adopting standard procedures. The conversion to the nitrile derivative was accomplished by heating^[4] with sodium cyanide and hexamethyl-phosphoramide. The nitrile **4** was formed along with products **5** and **6**.

Received in U.S.A. March 9, 2006

Address correspondence to Ajoy K. Banerjee, Centro de Química, Instituto Venezolano de Investigaciones Científicas (IVIC), Apartado 21827, Caracas, 1020, Venezuela. E-mail: abanerje@ivic.ve



The separation of **4** from the reaction mixture by silica-gel chromatography was successful; however, compounds **5** and **6** could not be separated because of their close R_f values. The nitrile **4**, on heating with methylmagnesium bromide in ether (3M) at 50°C for 72 h, produced methylketone **7** in 80%. The IR and ^1H NMR spectral data compared to literature values^[2] confirmed the assigned structure. The one-step conversion of **7** to occidol **8** has already been reported,^[2] so this synthesis constitutes the formal total synthesis of **8**.

EXPERIMENTAL

Unless otherwise stated, IR spectra were taken on Nicolet FT instrument. ^1H and ^{13}C NMR spectra were recorded on Bruker AM 300-MHz instrument in CDCl_3 . Mass spectra were run on gas chromatograph Hewlett Packard 5890 Quadrapol 5972 Series S. Melting points were recorded on an

electrothermal melting-point apparatus. The solution is diluted with water, extracted with ether, washed with brine, dried (MgSO_4), and evaporated under reduced pressure. Column chromatography was performed on silica gel (Merck grade 60, 70–230 mesh). The spectral and analytical data of all new compounds have been reported in the Experimental section. Microanalyses were carried out at the Chemistry Department, IVIC, Caracas.

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

Sodium borohydride (980 mg, 26 mmol) in ethanol (70 mL) was added to a solution of **1** (2.26 g, 13 mmol) in ethanol (70 mL). The mixture was stirred for 2 h at room temperature, decomposed with acetic acid, diluted with water, and extracted with diethyl ether. The organic layer was washed, dried, and purified on silica gel (hexane–diethyl ether 4:6) to obtain **2** (2.17 g, 95%); m/z 176 (M^+) and 158 ($\text{M}^+ - \text{H}_2\text{O}$); ν_{max} 3375 cm^{-1} (OH); ^1H : δ 1.85–1.78 (m, 2H, CH_2), 2.21 (s, 3H, C5-Me), 2.26 (s, 3H, C8-Me), 3.1–2.5 (m, 4H, C1-2H, C4-2H), 4.13–4.10 (m, 1H, CHOH), 6.79 (bs, 1H, C-6) and 6.84 (bs, 1H, C-7); ^{13}C : δ 136.7 (C-10), 135 (C-9), 130.5 (C-8), 129.6 (C-5), 128.3 (C-6), 126.8 (C-7), 67.8 (C-2), 35.6 (C-1), 31.4 (C-3), 27.5 (C-4), 19.4 (C-12) and 19.2 (C-11). (Found: C, 82.15; H, 9.37. $\text{C}_{12}\text{H}_{16}\text{O}$ requires C, 81.77%; H, 9.15%.)

5,8-Dimethyl-1,2,3,4-tetrahydro-2-cyanonaphthalene **4**

Mesylchloride (1.2 mL, 14.5 mmol) was added to a solution of **2** (2.17 g, 12.3 mmol) in pyridine (12 mL). The resulting brown solution was stirred at room temperature for 24 h, diluted with water, and extracted with ether. The organic extract was washed with a 5% solution of copper sulfate, washed with brine, dried, and evaporated to give **3** (2.41 gr, 77%); m/z 254 (M^+), 175 ($\text{M}^+ - \text{MeSO}_2$) and 158 ($\text{M}^+ - \text{MeSO}_2\text{OH}$); ^1H : δ 2.15–2.22 (m, 2H, CH_2), 2.26 (s, 3H), 2.33 (s, 3H) (C-5, C-8), 2.81–3.03 (m, 4H) (C-1 and C-4), 3.09 (s, 3H, MeSO_3), 5.16–5.28 (m, 1H, CHOSO_2Me), 6.86 (bs, 1H), and 6.92 (bs, 1H) (C-6 and C-7); ^{13}C : δ 136.5 (C-10), 135.5 (C-9), 130.2 (C-8), 129.7 (C-5), 128.7 (C-6), 126.9 (C-7), 78.5 (C-2), 38.7 (C-13), 33.5 (C-3), 28.9 (C-1), 26.4 (C-4), 19.4 (C-12) and 19.3 (C-11).

The mesylate **3** (2.0 g, 7.9 mmol), powdered sodium cyanide (1.16 g, 23.7 mmol), and hexamethylphosphoramide (28 mL) was heated at 120°C for 72 h under argon. The reaction mixture was diluted with water, extracted with ether, dried and evaporated. The resulting material was purified on silica gel by eluting with hexane to afford a mixture of **5** and **6** (641 mg, 38%); m/z 158 (M^+) and 156 (M^+).

Further elution (hexane–diethyl ether 8:2) yielded **4** (521 mg, 36%), mp $107\text{--}110^\circ\text{C}$; m/z 185 (M^+), 170 ($\text{M}^+ - \text{Me}$), 158 ($\text{M}^+ - \text{HCN}$) and 143

(M^+ -HCN-Me); ν_{\max} 2234 cm^{-1} (CN); ^1H : δ 1.99–2.07 (m, 2H, CH_2), 2.21 (s, 3H), 2.28 (s, 3H) (C-5 and C-8), 2.77–3.06 (m, 5H) (C-1, C-4 and CHCN), 6.80 (bs, 1H), 6.87 (bs, 1H); (aromatic protons) ^{13}C : δ 136.3 (C-10), 135.8 (C-9), 134.3 (C-8), 128.7 (C-6), 127.9 (C-5), 127.3 (C-7), 122.3 (C-13), 29.6 (C-1), 27.6 (C-3), 25.9 (C-2), 20.7 (C-12), 19.3 (C-11). (Found: C, 84.68; H, 8.38. $\text{C}_{13}\text{H}_{15}\text{N}$ requires C, 84.32%; H, 8.10%.)

5,8-Dimethyl-1,2,3,4-tetrahydro-2-naphthyl-ethan-1-one 7

A solution of methylmagnesium bromide in dry ether (1.8 mL, 3M) was added dropwise to a solution of **4** (502 mg, 2.7 mmol) in tetrahydrofuran (11 mL). The reaction mixture was heated at 50°C for 72 h, and then hydrochloric acid (10%) was cautiously added and extracted with ether. The organic extract was washed, dried, evaporated, and chromatographed on silica gel (hexane–diethyl ether 8:2) to obtain **7** (441 mg, 80%); m/z 202 (M^+); 187 (M^+ -Me), 144 (M^+ -Me-COMe); ν_{\max} 1708 cm^{-1} (CO); ^1H : 1.81–1.71 (m, 2H, CH_2), 2.23 (s, 3H, MeCO), 2.28 (s, 6H; Me), 2.91–2.73 (m, 5H) (C-1, C-2, and C-4), 6.81 (bs, 1H, Ar-H), 6.86 (bs, 1H, Ar-H); ^{13}C : δ 211.3 (C-13), 136.5 (C-10), 135.5 (C-9), 134.9 (C-8), 134.1 (C-5), 128.4 (C-6), 127.1 (C-7), 48.4 (C-2), 29.4 (C-3), 28.1 (C-14), 27.8 (C-1), 25.2 (C-4), 19.4 (C-12) and 19.2 (C-11). (Found: C, 83.38; H, 9.15. $\text{C}_{14}\text{H}_{18}\text{O}$ requires C, 83.12%; H, 8.97%.)

REFERENCES

1. Reddy, P. A.; Rao, G. S. K. A simple synthesis of methyl 5,8-dimethyl-1,2,3,4-tetrahydro-2-naphthoate and its conversion into (\pm)-occidol. *Ind. J. Chem.* **1980**, *19B*, 753.
2. Mane, R. B.; Kadam, A. J. A new synthesis of occidol. *Collect. Czech. Chem. Commun.* **1999**, *64*, 527.
3. Banerjee, A. K.; Vera, W.; Laya, M. S. A new synthesis of 5,8-dimethyl-2-tetralone—a potential intermediate for the synthesis of ring A aromatic sesquiterpenes: Novel transformation during acetoxylation of 5,8-dimethyldihydronaphthalene. *Synth. Commun.* **2004**, *34*, 2301.
4. Shaw, J. E.; Hsia, D. Y.; Parries, G. S.; Sawyer, T. K. Reaction of alkali metal cyanides with alkyl halides in HMPA or HMPA containing crown ether. *J. Org. Chem.* **1978**, *43*, 1017.