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An Alternative Synthesis of 8-Methylene-4,4,8a-trimethyl-7-oxo-octahydronaphthalene

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Summary. An alternative synthesis of 8-Methylene-4,4,8a-trimethyl-7-oxo-octahydronaphthalene, which is a potential synthon for the preparation of several terpenoid compounds, is described.

Keywords. Dehydration; Selective oxidation; Reduction; Hydrogenation; Elimination.

Eine Alternativsynthese für 8-Methylen-4,4,8a-trimethyl-7-oxo-octahydronaphthalin

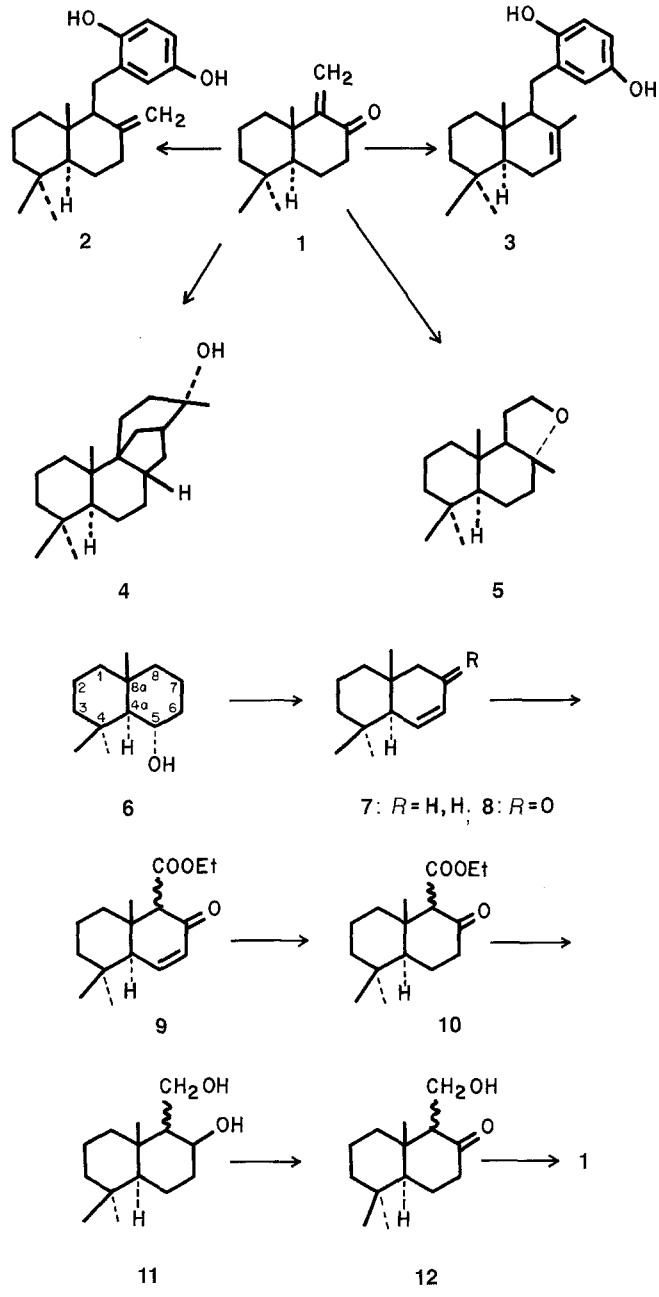
Zusammenfassung. Es wird eine alternative Synthese von 8-Methylen-4,4,8a-trimethyl-7-oxo-octahydronaphthalin, welches ein potentielles Synthon für terpenoide Verbindungen darstellt, beschrieben.

Introduction

The utility of the title compound (**1**) in the synthesis of zonarol (**2**) and isozonarol (**3**) [1], 2-desoxystemodinone (**4**) [2], and the perfumary agent (±)-Ambrox® (**5**) [3] has been reported. Recently, an efficient synthesis of compound **1** has been reported [4]. In connection with our work on terpenoid compounds as well as considering the importance of **1** for the synthesis of terpenoid compounds, an alternative synthesis was sought. The topic of this paper is to discuss possible methods of preparation of **1**.

Results and Discussions

The already reported alcohol **6** [5] was selected as a reference material for our synthetic work. Upon dehydration with *p*-toluenesulfonic acid adsorbed on silica gel [6], olefin **7** was obtained in 90% yield. Its structure was confirmed by ^{1}H NMR spectroscopic data which showed a broad signal centered at $\delta = 5.42$ ppm (2H). Allylic oxidation of **7** [7] with chromium trioxide and 3,5-dimethyl pyrazole afforded the α,β-unsaturated ketone **8** in 88% yield. Treatment of **8** with sodium hydride and diethyl carbonate in 1,2-dimethoxyethane furnished **9** whose ^{1}H NMR spectrum was rather complicated, probably because of contamination with a small amount of the enol tautomer. An examination of a molecular model of **8** indicates the preferential approach of the ester group from the β-side of the molecule to yield



β-ketoester **9**. No conclusive evidence was available to confirm this assumption. The catalytic hydrogenation of **9** with *Adam's* catalyst (PtO_2) in methanol yielded the saturated keto ester **10** in 50% yield, showing two overlapping spots in the TLC probably due to a mixture of two keto esters. Its ^1H NMR spectrum was also difficult to interpret because of the presence of a small amount of the enol tautomer. A similar observation has been noted previously [8,9]. However, completion of the synthesis of the target molecule did not require the separation of the mixture, and thus **10** was used directly for the next step. The yield of **10** was not very satisfactory, probably owing to steric hindrance.

Reduction of **10** with lithium aluminum hydride in tetrahydrofuran provided diol **11** which upon selective oxidation with sodium hypochlorite in acetic acid [10] afforded compound **12** in excellent yield. An alternative method for the preparation of **12** by means of a ketalization of the keto ester **10**, lithium aluminum hydride reduction, and deketalization was also tried. However, the yield of the resulting compound **12** was not satisfactory. Treatment of **12** with tosyl chloride and pyridine afforded the tosyl derivative which in turn underwent smooth elimination upon treatment with 1,5-diazabicyclo[5.4.0]-unedec-5-ene (*DBN*) [2] to yield the target molecule **1** in 72% yield. A moderate yield of **1** was also obtained by heating **12** in either with 1,3-dicyclohexylcarbodiimide [11]. **1** was characterized by its spectroscopic data and was found to be identical with the compound reported in Refs. [2,4].

The presented method for the synthesis of **1** avoids the synthesis of a cyclic ester like **10** *via* polyene cyclization [4]. It proceeds *via* intermediates which can also be utilized for the synthesis of several diterpenoids and sesquiterpenoids. It should be mentioned that the synthesis of the target molecule (by short or multiple steps) is never as important as the chemistry learned along the way. The suitable use of known reactions like selective dehydration, oxidation of secondary alcohols in the presence of primary alcohols, and the direct conversion of a primary alcohol to a methylene group are the salient features of the present method. This information adds special merit to the present synthesis.

Experimental

Unless stated otherwise, IR spectra were taken on a Nicolet FT instrument. NMR spectra were recorded on a Varian A-90 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were run on a Dupont 21–492B apparatus. The expression "workup" indicates that 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 60 (Merck). Microanalyses were carried out in the Chemistry Department, IVIC, Caracas; experimental and calculated values (C, H) agreed satisfactorily.

4,4,8aβ-Trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene (**7**, $C_{13}H_{22}$)

To the catalyst (prepared from 4.24 g *p*-TsOH and 200 g SiO_2) suspended in 200 ml toluene, 6 g of **6** in 50 ml toluene were added. The mixture was stirred for 2 h, applied to a chromatographic column, and eluted with 200 ml toluene. Evaporation of toluene afforded an oily material which was chromatographed (hexane:ether = 6 : 4) to obtain 4.89 g (90%) **7**.

IR: ν_{max} = 1612 cm^{-1} (C=C); ^1H NMR: δ = 0.92 (s, 3H), 0.99 (s, 3H), 1.14 (s, 3H, 4,4,8a-Me), 1.21–2.12 (m, 11H), 5.23 (br s, 2H, C-5 and C-6) ppm; MS: *m/z*= 178 (M^+), 163 (M^+-Me).

4,4,8aβ-Trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene-7-one (**8**, $C_{13}H_{20}O$)

To a suspension of 2.95 g of chromic anhydride in 45 ml of dichloromethane, 2.95 g 3,5-dimethylpyrazole were added rapidly at −25°C under nitrogen. The reaction mixture was stirred for 35 min and treated with 500 mg of olefin **7** in 3 ml of dichloromethane. The resulting dark solution was stirred for 6 h at −25°C, a solution of 40 ml of sodium hydroxide (10%) was added. Workup followed by chromatographic purification (hexane:ether= 8:2) yielded 474 mg (88%) of ketone **8**.

IR: ν_{max} = 1650 cm^{-1} (CO); ^1H NMR: δ = 0.94 (s, 3H), 0.98 (s, 3H), 1.21 (s, 3H, 4,4,8a-Me), 1.28–2.46 (m, 9H), 5.52 (s, 1H), 5.72 (s, 1H, C-5 and C-6) ppm; MS: *m/z*= 192 (M^+). The reaction was repeated several times to accumulate sufficient material.

Ethyl-4,4,8aβ-trimethyl-7-oxo-trans-perhydronaphthalene-8-carboxylate (**10**, $C_{16}H_{24}O_3$)

A mixture of 2 g of ketone **8**, 500 mg of sodium hydride (50% dispersion), 4.82 g of diethyl carbonate, and 20 ml of dry 1,2-dimethoxyethane was stirred and heated at 80–85°C for 2 h under nitrogen. The mixture was cooled, and a little amount of absolute ethanol was added to destroy an excess of sodium hydride. A solution of 6 ml of cold water was carefully added to the reaction mixture under nitrogen. The resulting solution was extracted with ether, washed subsequently with 5% aqueous sodium hydrogen carbonate and brine, dried, and evaporated to dryness. The resulting keto ester **9** (2.25 g; IR: ν_{max} = 1650 (CO) and 1725 (ester CO) cm^{-1}) appeared to be unstable and thus was used without purification for the next step.

A solution of 2.25 g of ketoester **9** in 30 ml of methanol was hydrogenated over 50 mg of PtO_2 for 30 min. Workup afforded a reddish oily material which upon filtration through a column of neutral alumina (hexane:diethyl=ether 4:6) yielded ketoester **10** (1.37 g, 50%).

IR: ν_{max} = 1712 and 1745 cm^{-1} (ketonic and ester CO); MS: *m/z*= 266 (M^+), 251 (M^+-Me), 192 (M^+-EtCOOH).

4,4,8aβ-Trimethyl-8-hydroxymethylene-7-oxo-trans-perhydronaphthalene (**12**, $C_{14}H_{24}O_2$)

To 1 g of ketoester **10** in 25 ml of tetrahydrofuran, 300 mg of lithium aluminum hydride were added. The mixture was heated under reflux for 10 h, cooled, and cautiously diluted with water to destroy an excess hydride. The precipitate was filtered, and the filtrate was dried. Removal of the solvent afforded diol **11** (765 mg).

IR: ν_{max} = 3450 cm^{-1} (OH); MS: *m/z*= 266 (M^+), 194 (M-MeOH). The diol was used without purification for the next step.

To a solution of 762 mg of diol **11** in 5 ml of glacial acetic acid, 3 ml of 1.88 *M* NaClO were added very slowly. The solution was stirred for 1 h at room temperature, followed by the addition of 2 ml of isopropanol and then 50 ml of water. The solution was extracted with dichloromethane, washed with aqueous sodium bicarbonate solution, dried, and evaporated. After column chromatography on Florisil (hexane:ethyl acetate=2:1) afforded 714 mg (85%) of **12**.

IR: ν_{max} = 3455 (OH), 1710 (CO) cm^{-1}; ^1H NMR: δ = 0.91 (s, 3H), 1.08 (s, 3H), 1.22 (s, 3H, 4,4,8a-Me), 1.25–2.12 (m, 11H), 3.65 (m, OH, exchangeable by D_2O), 3.95 (m, 2H, CH_2OH) ppm; MS: *m/z*= 224 (M^+), 194 (M^+-2Me), 163 (M^+-2Me-CH_2OH).

8-Methylene-4,4,8a-trimethyl-7-oxo-trans-perhydronaphthalene (**1**, $C_{14}H_{22}O$)

Method A: To a solution of 500 mg of **2** in 10 ml of dry pyridine cooled in ice-bath, 250 mg of *p*-toluenesulfonyl chloride were added. The solution was kept at 0°C for 24 h then poured on ice and extracted with ether. The usual workup afforded the tosyl derivative whose IR spectrum gave no evidence of a hydroxyl group. To a solution of this material in 10 ml of toluene, 500 mg of 1,5-diazabicyclo[5.4.0]-undec-5-ene (*DBN*) were added, and the mixture was left at room temperature for 17 h. The workup yielded an oily material which after chromatographic purification (eluant: toluene) gave 330 mg (72%) of the target compound **12**.

IR: ν_{max} = 1710 cm^{-1} (CO); ^1H NMR: δ = 0.92 (s, 3H), 0.98 (s, 3H), 1.01 (s, 3H, 4,4,8a-Me), 1.26–2.38 (m, 11H), 5.08 (d,1H), 5.42 (d, 1H, C-8), ppm; MS: *m/z*= 206 (M^+), 191 (M^+-Me).

Method B: To a solution of 300 mg of alcohol **12** in 20 ml of dry ether, 600 mg of dicyclohexylcarbodiimide and 20 mg of cuprous chloride were added, and the mixture was then refluxed for

3 h. The resulting dark material was filtered, and the residue was washed with ether. The combined filtrate was dried and evaporated to obtain an oily material which after chromatographic purification on Florisil (eluant: toluene) yielded 143 mg (52%) of **1**. Its spectroscopic data were identical with those of the specimen prepared by *Method A*.

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