Convenient and Practical Synthesis of (*R*)-(+)-4-Methyl-2-cyclohexen-1-one

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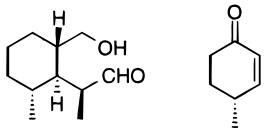
In our efforts toward the synthesis of the cyclohexane unit **1** of tetronasin, optically pure (*R*)-(+)-4-methyl-2-cyclohexen-1-one (**2**) was required as a starting material. Optically active 4-methyl-2-cyclohexen-1-one is useful as a chiral building block.[1−4] In case of (*S*)-(−)-4-methyl-2-cyclohexen-1-one, this compound is available from (*S*)-(+)-carvone[1] or 4-methylcyclohexanone.[4] (*R*)-(+)-4-methyl-2-cyclohexen-1-one has been prepared by various methods[2,3] reported in the literature utilizing starting materials such as (*R*)-(+)-3-methylcyclohexanone and (*R*)-(+)-pulegone (**3**). However, these methods are not suitable for the preparation of optically active (*R*)-(+)-4-methyl-2-cyclohexen-1-one in large scale. Herein we would like to report the convenient and practical preparation of (*R*)-(+)-4-methyl-2-cyclohexen-1-one from (*R*)-(+)-pulegone.

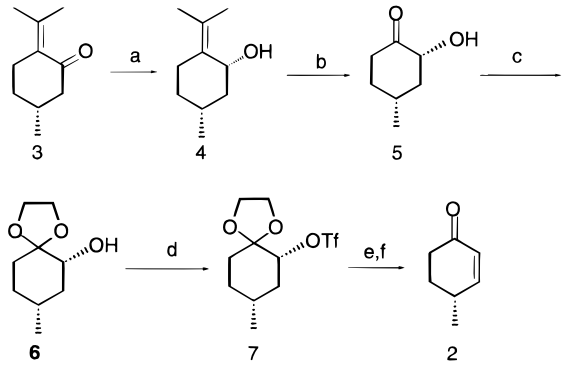


1 **2**

The previously reported method[3] utilizing (*R*)-(+)-pulegone seems to give good optical rotation for (*R*)-(+)-4-methyl-2-cyclohexen-1-one. However, it is rather unsuitable for large scale because it employs the inconvenient Shapiro reaction for the introduction of the double bond and suffers from low yield as a result of selective ozonolysis between *endo* and *exo* double bonds of an intermediate compound. In contrast, we could prepare (*R*)-(+)-4-methyl-2-cyclohexen-1-one practically in large scale by employing a new and simple reaction pathway from (*R*)-(+)-pulegone. Furthermore, in our method there is only one double bond in the intermediate so that there is no need to pay attention to the selective ozonolysis of double bonds. And the subsequent elimination of hydroxy group provides the double bond of enone. The other manipulations are the simple protection and deprotection of the carbonyl group in the reaction pathway (see Scheme 1).

Commercially available (*R*)-(+)-pulegone of technical grade with 85% purity was reduced with $NaBH_4$ to yield alcohol **4**[5] in 87% yield and subsequent ozonolysis at −78 °C in CH_2Cl_2 and methanol provided the hydroxy ketone **5** in 81% yield. The presence of methanol was found to be critical. The use of CH_2Cl_2 alone gave unfavorable side products. Compound **5** was converted to ketal **6** in 92% yield by transketalization[6] using ethylene glycol and 2-ethyl-2-methyl-1,3-dioxolane in the presence of catalytic amount of camphorsulfonic acid at room temperature for 1.5 h. It is advisable that compounds **4** and **5** be used immediately after preparation because of their unstability. Mosher's method[7] using 2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid (MTPA) esters was used to confirm the configuration of the hydoxyl group as *R*. Spectral data of ^1H NMR indicates that only one enantiomer of compound **6** was obtained. The resulting hydroxyl group of **6** was converted to trifluoromethanesulfonate ester **7** in 95% yield by treating with trifluoromethanesulfonic anhydride and pyridine in CH_2Cl_2 at −23 °C. The consequent elimination of trifluoromethanesulfonate group of compound **7** with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) at 50 °C in 1 h and hydrolysis under acidic condition in 10 min furnished the desired (*R*)-(+)-4-methyl-2-cyclohexen-1-one (**2**) in 68% yield (two steps). Thus, the overall yield from crude pulegone became 45%.

Scheme I[a]



[a] Reagents: (a) $NaBH_4$, MeOH, 0 °C; (b) O_3, CH_2Cl_2:MeOH 1:1, Sudan Red; CH_3SCH_3; (c) $HOCH_2CH_2OH$, $CH_3C(OCH_2CH_2O)$-CH_2CH_3, CSA, rt; (d) $(CF_3SO_2)_2$, Py, CH_2Cl_2, −23 °C; (e) DBU, 50 °C; (f) aqueous THF, H_2SO_4.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, on a commercially available spectrometer. Unless otherwise indicated in a specific experiment, all of the chemicals used were reagent grade and no additional purification has been done. Technical grade (*R*)-(+)-pulegone was purchased from Aldrich Chemical Co. and used without further purification.

(2*R*,4*R*)-(−)-Isopropylidene-4-methyl-2-cyclohexanol (4). To a solution of (*R*)-(+)-pulegone (20.0 g, 131 mmol) in MeOH (100 mL) was added $NaBH_4$ (6.46 g, 170 mmol) at 0 °C. After stirring for 1 h at room temperature, the resulting solution was treated with water and extracted with ether (2 × 100 mL). The extracts were dried over anhydrous $MgSO_4$, and evaporation of solvent provided the crude syrup, which was used for the next step. However, the crude product was purified by column chromatography (SiO_2, hexane:ether = 4:1) to give 17.6 g (87%) of pure alcohol as a colorless solid: mp 30−31 °C; $[\alpha]^{20}_D = -99.6°$ (*c* 6.00, $CHCl_3$).

(2*R*,4*R*)-2-Hydroxy-4-methylcyclohexanone (5). To a solution of **4** (16.6 g, 108 mmol) in methylene chloride and methanol (1:1, 100 mL) was added 0.10% Sudan Red 7B in solution of dichloromethane (3.5 mL). The red solution was cooled to −78 °C and ozonized until the red color began to

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lighten. The solution was rapidly purged with N_2 for 30 min. The solution was treated with dimethyl sulfide (10 equiv) and allowed to warm to room temperature overnight. The solvent was removed *in vacuo* to give crude syrup, which was purified by column chromatography (silica gel, hexane:ethyl acetate = 4:1) to provide 11.2 g (81%) of pure hydroxy ketone as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.04 (d, J = 6.4 Hz, 3H), 1.29 (q, J = 12.3 Hz, 1H), 1.39 (m, 1H), 2.05 (m, 2H), 2.38−2.48 (m, 2H), 2.51 (m, 1H), 3.58 (d, J = 3.3 Hz, 1H), 4.16 (m, 1H); ^{13}C NMR δ 211.62, 74.26, 44.54, 38.41, 35.46, 30.20, 20.93; IR (neat) 3485, 1725 cm^{-1}; $[\alpha]^{20}_D = +16.6°$ (*c* 2.20, $CHCl_3$); HRMS 128.0837 calcd for $C_7H_{12}O_2$ 128.0344 (obsd).

(6*R*,8*R*)-8-Methyl-1,4-dioxaspiro[4.5]decan-6-ol (6). To a solution of hydroxy ketone **5** (9.20 g, 71.9 mmol) in 2-ethyl-2-methyl-1,3-dioxolane (100 mL) and ethylene glycol (45 mL) was added camphorsulfonic acid (1.40 g, 6.03 mmol) at room temperature under nitrogen. The solution was stirred for 1 h at room temperature. The resulting solution was poured into aqueous $NaHCO_3$ to neutralize, and the product was extracted with ether (3 × 100 mL). The combined extracts were washed with water and brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave crude product, which was purified by column chromatography (SiO_2, hexane:ethyl acetate = 2:1) to get pure 11.4 g (92%) of ketal as a colorless oil: bp 72−73 °C/0.1 mmHg: ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J = 6.4 Hz, 3H), 1.19 (m, 1H), 1.22 (q, J = 12.1 Hz, 1H), 1.41 (td, J = 13.6, 4.1 Hz, 1H), 1.52−1.61 (m, 2H), 1.78 (ddd, J = 2.8, 3.5, 13.5 Hz, 1H), 1.92 (m, 1H), 2.03 (d, J = 7.0 Hz, 1H), 3.63 (m, 1H), 3.96−4.09 (m, 4H); ^{13}C NMR δ 109.45, 72.66, 65.48, 65.18, 40.71, 32.33, 30.67, 29.94, 21.56; IR (neat) 3474, 2971 cm^{-1}; $[\alpha]^{20}_D = +5.0°$ (*c* 6.50, $CHCl_3$): HRMS 172.1099 calcd for $C_9H_{16}O_3$ 172.1099 (obsd).

(*R*)-4-Methyl-2-cyclohexen-1-one (1). To a solution of hydroxy ketal **6** (10.0 g, 58.7 mmol) in CH_2Cl_2 (100 mL) were added pyridine (9.50 mL, 117 mmol) and trifluoromethanesulfonic anhydride (10.4 mL, 61.6 mmol) at −23 °C under the nitrogen atmosphere. After 30 min, water was added to the solution and the separated dichloromethane layer was dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give crude triflate. For the characterization, a small amount of the triflate was purified through column chromatography.

^{1}H NMR ($CDCl_3$) δ 0.97 (d, J = 6.3 Hz, 3H), 1.24 (m, 1H), 1.51 (td, J = 13.7, 4.0 Hz, 1H), 1.57−1.65 (m, 2H) 1.69 (q, J = 11.9 Hz, 1H), 1.79 (ddd, J = 2.7, 3.7, 13.2 Hz, 1H), 2.02 (m, 1H), 3.91−4.03 (m, 3H), 4.08 (m, 1H), 4.77 (dd J = 4.9, 11.9 Hz, 1H); ^{13}C NMR δ 118.11, 106.94, 88.65, 66.00, 65.53, 37.95, 34.40, 30.91, 30.71, 21.09.

The crude triflate was dissolved in DBU (13 mL, 88.0 mmol) and stirred for 1 h at 50 °C under the nitrogen atmosphere. Then water (10 mL) was added to the reaction mixture. The reaction mixture was extracted with ether (3 × 20 mL). The ethereal extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give crude syrupy product of (*R*)-8-methyl-1,4-dioxaspiro[4.5]decen-6-ene, which was used for hydrolysis without any further purification. This crude ketal was dissolved in a solution of 15% aqueous sulfuric acid (15 mL) and tetrahydrofuran (20 mL) and stirred at room temperature for 10 min. The reaction mixture was extracted with dichloromethane (3 × 15 mL) and dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give crude product, which was distilled at 75−76 °C (20 mmHg) to furnish 4.15 g of pure product (65% for three steps); $[\alpha]^{20}_D = +113°$ (*c* 1.41, $CHCl_3$)[lit.[3] $[\alpha]^{22}_D$ +105° (*c* 9.2, $CHCl_3$)].

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **2**, **5**, **6**, and **7** are provided (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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