New Synthesis of *trans*-γ-Irone

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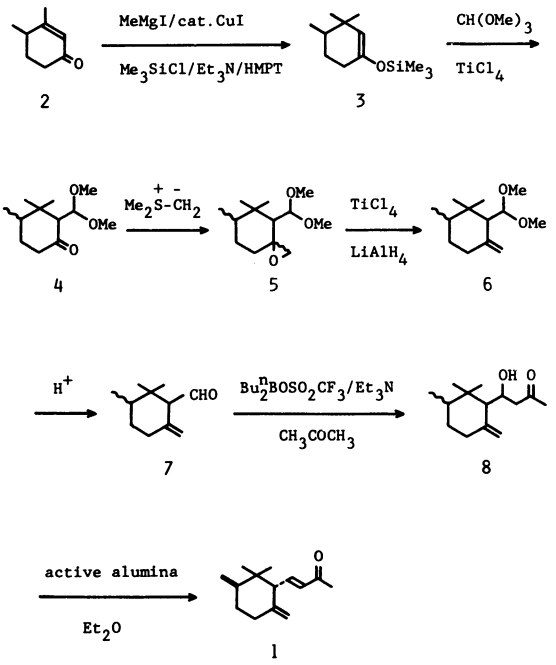
Synopsis. *trans*-γ-Irone was successfully synthesized starting from 3,4-dimethyl-2-cyclohexenone by seven-step reactions including $TiCl_4$-promoted reaction of enol silyl ether and cross-aldol reaction of vinyloxyborane.

Irones have been isolated from Iris oil as very important fragrant constituents.[1] Recently, Ohloff et al. have further identified *trans*-γ-irone (**1**) in Iris oil.[2] Concerning the synthesis of **1**, three methods have been reported.[3] Previously, we reported an efficient method for preparation of γ-ionone.[4] In this paper, we will describe an alternative method for synthesis of **1** starting from an easily accessible 3,4-dimethyl-2-cyclohexenone (**2**) in the similar manner as above. Our synthetic route is outlined in the following scheme.



The reaction of 3,4-dimethyl-2-cyclohexenone (**2**) with methylmagnesium iodide in the presence of a catalytic amount of copper(I) iodide, followed by quenching with trimethylchlorosilane, triethylamine, and hexamethylphosphoric triamide, gave 3,3,4-trimethyl-1-trimethylsiloxy-1-cyclohexene (**3**) in a 70% yield.[5] 2-Dimethoxymethyl-3,3,4-trimethylcyclohexanone (**4**) was obtained in a 72% yield by the reaction of **3** with trimethyl orthoformate in the presence of $TiCl_4$.[6] The conversion of **4** to 4-dimethoxymethyl-5,5,6-trimethyl-1-oxaspiro[2.5]octane (**5**) was carried out in almost the same manner as reported,[7] that is, the reaction of **4** with dimethylsulfonium methylide gave **5** in a 61% yield. The deoxygenation of **5** with low valent titanium compound, prepared from $TiCl_4$ and $LiAlH_4$, afforded 6-methylene-2,2,3-trimethylcyclohexanecarbaldehyde dimethyl acetal (**6**) in an 83% yield, which was further converted to 6-methylene-2,2,3-trimethylcyclohexanecarbaldehyde (**7**)[3a] in a 79% yield by hydrolysis with 2 M HCl (1 M= 1 mol dm^{-3}).

Dibutyl(isopropenyloxy)borane, formed from acetone and dibutylboryl trifluoromethanesulfonate,[8] reacted with **7** to give a mixture of two stereoisomers (**8a** and **8b**) of 4-(6-methylene-2,2,3-trimethylcyclohexyl)-4-hydroxy-2-butanone (**8**) in a 79% yield, which was separated by silica-gel column chromatography. The aldols, **8a** and **8b**, were converted to *trans*-γ-irone (**1**) without accompanying *cis*-isomer on treatment with active alumina in 57% and 36% yields, respectively.

Experimental

Spectra. All bps are uncorrected. ^1H NMR spectra were recorded on a Hitachi R-24A spectrometer. Chemical shifts are reported on the δ scale relative to Me_4Si as an internal standard. IR spectra were taken using a JASCO IRA-2 spectrometer.

3,3,4-Trimethyl-1-trimethylsiloxy-1-cyclohexene (3). To a mixture of 2.8 M methylmagnesium iodide (50 ml, 140 mmol) in ether and copper(I) iodide (400 mg) was added dropwise a solution of 3,4-dimethyl-2-cyclohexenone (**2**) (12.40 g, 100 mmol) in dry ether (40 ml) at 0 °C, and the mixture was stirred for 1 h at 0 °C. Trimethylchlorosilane (30 ml), triethylamine (40 ml), and hexamethylphosphoric triamide (20 ml) were successively added at 0 °C and the mixture was stirred for 24 h at room temperature. The mixture was processed and the product was distilled to give **3** (14.80 g, 70%). Bp 90—93 °C/16 mmHg (1 mmHg=133.322 Pa); IR (neat) 1665 cm^{-1}; NMR (CCl_4) δ=0.15 (s, 9H), 0.82 (s, 3H), 0.88 (d, *J*=6.0 Hz, 3H), 0.98 (s, 3H), 1.2—2.1 (m, 5H), and 4.53 (m, 1H). Found: C, 67.83; H, 11.29%. Calcd for $C_{12}H_{24}SiO$: C, 67.86, H, 11.39%.

2-Dimethoxymethyl-3,3,4-trimethylcyclohexanone (4). To a cold solution (−78 °C) of trimethyl orthoformate (6.89 g, 65 mmol) in dry dichloromethane (100 ml) was added $TiCl_4$ (12.35 g, 65 mmol) under argon atmosphere. A solution of **3** (10.60 g, 50 mmol) in dry dichloromethane (10 ml) was added and the reaction mixture was stirred for 2 h at −78 °C. The mixture was quenched with methanol (20 ml) and poured into a 15% solution of K_2CO_3. After evaporation of the solvent, the residue was distilled to give **4** (7.70 g, 72%). Bp 88—90 °C/1.5 mmHg; IR (neat) 1715, 1125, and 1060 cm^{-1}; NMR (CCl_4) δ=0.75 (s, 3H), 0.90 (d, *J*=6.5 Hz, 3H), 0.97 (s, 3H), 1.2—2.5 (m, 5H), 2.28 (d, *J*=7.0 Hz, 1H), 3.20 (s, 3H), 3.27 (s, 3H), and 4.67 (d, *J*=7.0 Hz, 1H). Found: C, 67.14; H, 10.29%. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35%.

4-Dimethoxymethyl-5,5,6-trimethyl-1-oxaspiro[2.5]octane (5). A mixture of NaH (10 mmol) and dimethyl sulfoxide (5 ml) was stirred for 1 h at 65—70 °C and cooled to room temperature, and then tetrahydrofuran (30 ml) was added. A solution of trimethylsulfonium iodide (2.04 g, 10 mmol) in dimethyl sulfoxide (5 ml) was added dropwise at −20—−15

°C and stirred for 5 min. A solution of **4** (428 mg, 2 mmol) in tetrahydrofuran (5 ml) was added dropwise at the same temperature as above and the mixture was stirred overnight at 0 °C. The mixture was worked up and the product was subjected to silica-gel column chromatography to afford **5** (280 mg, 61%). IR (neat) 3030, 1130, 1075, and 1050 cm^{-1}; NMR (CCl_4) δ=0.80 (d, J=6.5 Hz, 3H), 0.86 (s, 3H), 1.05 (s, 3H), 1.3—2.2 (m, 6H), 2.46 (s, 2H), 3.30 (s, 3H), 3.37 (s, 3H), and 4.47 (d, J=3.0 Hz, 1H). Found: C, 68.23; H, 10.41%. Calcd for $C_{13}H_{24}O_3$: C, 68.38, H, 10.59%.

6-Methylene-2,2,3-trimethylcyclohexanecarbaldehyde Dimethyl Acetal (6). Tetrahydrofuran (16 ml) was added dropwise to $TiCl_4$ (1.29 g, 6.8 mmol) at −78 °C under argon atmosphere and the resulting complex was warmed to room temperature. $LiAlH_4$ (258 mg, 6.8 mmol) was added to the complex, and the mixture was stirred for 1 h, and then triethylamine (5.55 g, 55 mmol) was added. To this was added dropwise a solution of **5** (1.41 g, 6.2 mmol) in tetrahydrofuran (10 ml) on a water bath and the mixture was stirred for 1 h at room temperature. The mixture was worked up and the product was distilled to give **6** (1.09 g, 83%). IR (neat) 1120, 1060, and 890 cm^{-1}; NMR (CCl_4) δ=0.73 (s, 3H), 0.87 (d, J=6.0 Hz, 3H), 0.92 (s, 3H), 1.1—1.8 (m, 3H), 1.9—2.4 (m, 3H), 3.18 (s, 3H), 3.24 (s, 3H), 4.48 (d, J=6.5 Hz, 1H), 4.52 (m, 1H), and 4.70 (m, 1H).

6-Methylene-2,2,3-trimethylcyclohexanecarbaldehyde (7). To a solution of **6** (1.09 g, 5.1 mmol) in ether (30 ml) was added 2 M HCl (30 ml) and the mixture was stirred overnight at room temperature. After separation of the organic layer, it was washed with a saturated solution of $NaHCO_3$ and concentrated. The residue was distilled to give **7** (675 mg, 79%). Bp (bath temperature) 100—110 °C/10 mmHg; IR (neat) 1720, 1640, and 895 cm^{-1}; NMR (CCl_4) δ=0.78 (s, 3H), 0.84 (d, J=6.5 Hz, 3H), 1.05 (s, 3H), 1.2—2.1 (m, 3H), 2.25 (m, 2H), 2.71 (d, J=3.5 Hz, 1H), 4.74 (s, 1H), 4.90 (s, 1H), and 9.73 (d, J=3.5 Hz, 1H). Found: C, 79.36, H, 10.79%. Calcd for $C_{11}H_{18}O$: C, 79.47, H, 10.91%.

4-(6-Methylene-2,2,3-trimethylcyclohexyl)-4-hydroxy-2-butanone (8). To dibutylboryl trifluoromethanesulfonate (303 mg, 1.1 mmol) was added a solution of triethylamine (111 mg, 1.1 mmol) in ether (1.5 ml) at −78 °C under argon atmosphere and the mixture was warmed to room temperature. A solution of acetone (64 mg, 1.1 mmol) in ether (1 ml) was added at −78 °C and the mixture was stirred for 20 min. Then a solution of **7** (158 mg, 0.95 mmol) in ether (2 ml) was added dropwise and the mixture was stirred for 2.5 h at −78 °C. To the reaction mixture was added 1 M buffer solution (pH 7.0) of phosphoric acid (3 ml), methanol (10 ml), and a 30% solution of H_2O_2 (2 ml), successively, and the mixture was stirred for 20 min at room temperature. After addition of water (10 ml), methanol was removed under reduced pressure. The residue was extracted with dichloromethane and the solution was concentrated. Purification by silica-gel column chromatography afforded two stereoisomers (**8a** and **8b**) of **8** (169 mg, 79%). **8a** (117 mg, 55%): IR (neat) 3470, 3070, 1710, 1640, and 890 cm^{-1}: NMR (CCl_4) δ=0.75 (s, 3H), 0.79 (d, J=6.5 Hz, 3H), 1.08 (s, 3H), 1.2—2.3 (m, 6H), 2.15 (s, 3H), 2.52 (m, 2H), 3.22 (s, 1H), 4.50 (m, 2H), and 4.90 (m, 1H). Found: C, 74.86, H, 10.70%. Calcd for $C_{14}H_{24}O_2$: C, 74.95, H, 10.78%; **8b** (52 mg, 24%): IR (neat) 3500, 3070, 1705, 1635, and 885 cm^{-1}; NMR (CCl_4) δ=0.75 (s, 3H), 0.85 (d, J=6.5 Hz, 3H), 1.10 (s, 3H), 1.2—2.3 (m, 6H), 2.10 (s, 3H), 2.42 (d, J=6.0 Hz, 2H), 3.05 (s, 1H), 4.25 (m, 1H), 4.62 (m, 1H), and 4.75 (m, 1H). Found: C, 74.81, H, 10.84%. Calcd for $C_{14}H_{24}O_2$: C, 74.95, H, 10.78%.

trans-*γ-Irone (1).* To a solution of **8a** (55 mg, 0.25 mmol) in ether (5 ml) was added active alumina (0.5 g) and the mixture was stirred overnight at room temperature. Then the mixture was filtered and concentrated. The residue was subjected to silica-gel column chromatography to afford **1** (29 mg, 57%). IR (neat) 1675, 1620, and 890 cm^{-1}; NMR (CCl_4) δ=0.80 (s, 3H), 0.85 (d, J=6.0 Hz, 3H), 0.90 (s, 3H), 1.1—2.4 (m, 5H), 2.15 (s, 3H), 2.60 (d, J=9.0 Hz, 1H), 4.67 (s, 1H), 4.72 (s, 1H), 6.00 (d, J= 16.0z4Hz, 1H), and 6.98 (dd, J=16.0 and 9.0 Hz, 1H). Spectral data of **1** were consistent with those of the authentic sample prepared by the method of Yoshikoshi *et al.*[3b]

In the same manner, **8b** was treated with active alumina to give **1** (36%).

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