Synthesis of (±)-β-Cuparenone Based on a Lewis Acid-Promoted [4⁺+2] Polar Cycloaddition of *m*-Tolylthiomethyl Chloride

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In the presence of $AlCl_3$, *m*-tolylthiomethyl chloride (1) reacted with methyl 3,4-dimethylcyclopent-3-ene-1-carboxylate (4) to give the [4⁺+2] polar cycloaddition product 6, which was transformed into (±)-β-cuparenone (11) in 4 steps.

Keywords (±)-β-cuparenone; α-chlorosulfide; polar cycloaddition; hydroxylation; oxidative glycol cleavage; oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide); desulfurization; sodium metaperiodate; zinc dust

In previous papers,[1] we reported an extremely short synthesis of (±)-cuparene (**7**), an aromatic sesquiterpene, by a reaction sequence involving a Lewis acid-promoted [4⁺+2] polar cycloaddition of *m*-tolylthiomethyl chloride (**1**) with 1,2-dimethylcyclopentene (**2**) followed by desulfurization of the resultant thiochroman derivative **5**. The present paper describes an extended application of this methodology to the synthesis of (±)-β-cuparenone (**11**), another member of the aromatic sesquiterpenes.

Methyl 3,4-dimethylcyclopent-3-ene-1-carboxylate (**4**), the key starting material for this synthesis, was prepared by desulfurization of the corresponding α-(methylthio)ester **3**, synthesized by our method.[2]

The previous study on the cycloaddition of **1** with **2** revealed that ethylaluminum dichloride ($EtAlCl_2$) is the best of several Lewis acids we have examined for this reaction. However, the cycloaddition of **1** with **4** was not effected with $EtAlCl_2$. After much experimentation, we found that the desired cycloadduct **6** could be obtained in 54% yield by using 2 molar eq of aluminum chloride ($AlCl_3$).[3] High performance liquid chromatography (HPLC) showed the adduct **6** to be a mixture of two diastereoisomers in a ratio of 3.4 : 1. Desulfurization of **6** with Raney nickel in boiling ethanol for 24 h afforded, in 79% yield, the cyclopentane **8** as a mixture of two diastereoisomers in a ratio of 1 : 1 [as determined by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy].

Further elaboration of the cyclopentane **8** into (±)-β-cuparenone (**11**) was achieved in a straightforward manner. Thus, the ester **8** was treated with lithium diisopropylamide (LDA) and the resultant ester enolate was quenched with oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) ($MoO_5 \cdot Py \cdot HMPA$)[4] to give, in 75% yield, the α-hydroxy ester **9** as a mixture of two diasteroisomers in a ratio of 1 : 1 (by ^{1}H-NMR). Reduction of **9** with $LiAlH_4$ gave the glycol **10**, which was then subjected to oxidative cleavage with $NaIO_4$ in aqueous tetrahydrofuran (THF) to furnish **11** in 71% yield from **9**. The infrared (IR) and ^{1}H-NMR spectroscopic data of (±)-β-cuparenone thus obtained were identical with those of an authentic sample prepared by the reported procedure.[5a]

Experimental

IR spectra were recorded with a JASCO IRA-1 spectrophotometer. ^{1}H-NMR spectra were determined with a Varian XL-300 (300 MHz) or a JEOL JNM-PMX 60 (60 MHz) spectrometer using tetramethylsilane as an internal standard. High-resolution mass spectra (MS) were obtained with a Hitachi M-80 instrument at 20 eV. Column chromatography was performed on Silica gel 60 PF_{254} (Merck) under pressure.

Methyl 3,4-Dimethylcyclopent-3-ene-1-carboxylate (4) Zinc dust (10 g) was added to a solution of methyl 3,4-dimethyl-1-(methylthio)cyclopent-3-ene-1-carboxylate (**3**)[2] (0.92 g, 4.59 mmol) in acetic acid (10 ml) and the mixture was heated under reflux for 15 h. Dichloromethane (10 ml) was added to the reaction mixture and the precipitated solid was filtered off. The filtrate was washed thoroughly with saturated $NaHCO_3$ solution to remove excess acetic acid and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–ethyl acetate, 19 : 1) to give **4** (0.57 g, 81%)[6] as on oil. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.57 (6H, s), 2.35—2.75 (4H, m), 2.75—3.25 (1H, m), 3.63 (3H, s).

**Methyl *cis*-1,2,3,3a,4,9b-Hexahydro-3a,7,9b-trimethylcyclopenta[*c*][1]-

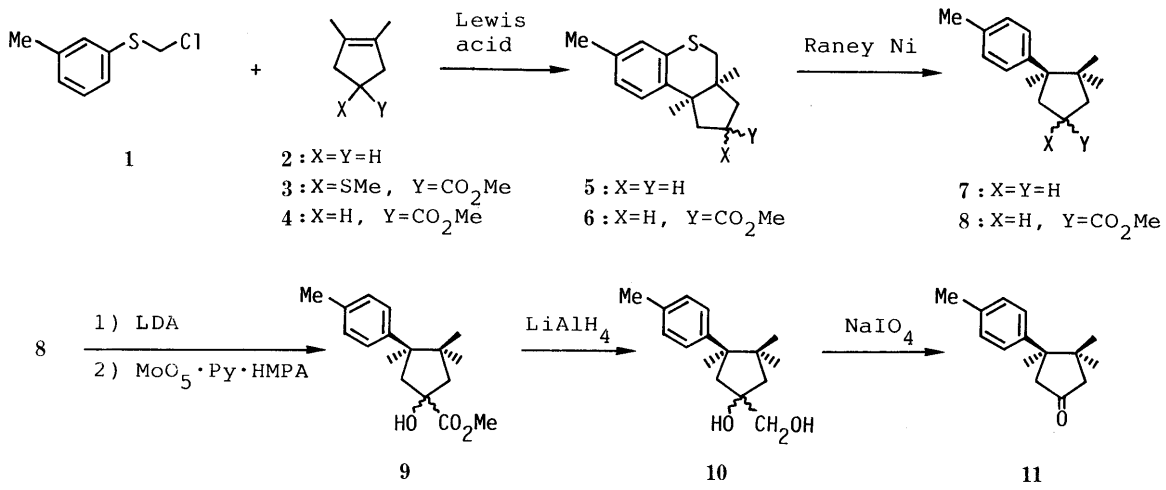

Chart 1

benzothiopyran-2-carboxylate (6) Powdered $AlCl_3$ (0.72 g, 5.42 mmol) was added to a solution of **1**[1] (0.47 g, 2.71 mmol) and **4** (0.42 g, 2.71 mmol) in dichloromethane (20 ml) at 0 °C and the mixture was stirred at the same temperature for 1 h, then at room temperature for 1 h. The reaction was quenched with water (10 ml) and the organic layer was separated. The aqueous layer was further extracted with dichloromethane and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–ethyl acetate, 10 : 1) to give **6** (0.43 g, 54%) as an oil, whose HPLC analysis showed it to be a mixture of two diastereoisomers in a ratio of 3.4 : 1. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.16 (3H, s), 1.29 (3H, s), 1.8—3.1 (7H, m), 2.21 (3H, s), 3.65 (3H, s), 6.7—7.5 (3H, m). Several attempts to obtain an analytically pure sample were unsuccessful, and hence this compound was used immediately in the next stage.

Methyl 3-(4-Methylphenyl)-3,4,4-trimethylcyclopentane-1-carboxylate (8) Raney nickel (W-2) (*ca.* 1.5 g) was added to a solution of **6** (150 mg, 0.52 mmol) in ethanol (5 ml) and the mixture was heated under reflux for 24 h. The Raney nickel was removed by filtration, the filtrate was concentrated *in vacuo*, and the residue was chromatographed on silica gel (hexane–ethyl acetate, 10 : 1) to give **8** (110 mg, 79%) as an oil, whose 300 MHz ^{1}H-NMR spectrum showed it to be a mixture of two diastereoisomers in a ratio of 1 : 1. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.61 (3H, s), 1.095 (3H × 1/2, s), 1.100 (3H × 1/2, s), 1.29 (3H × 1/2, s), 1.31 (3H × 1/2, s), 1.76—1.98 (2H, m), 2.01—2.18 (2H, m), 2.31 (3H, s), 2.78—2.93 (1H × 1/2, m), 2.98—3.14 (1H × 1/2, m), 3.71 (3H × 1/2, s), 3.72 (3H × 1/2, s), 6.98—7.15 (2H, m), 7.2—7.3 (2H, m). Exact MS *m/z*: Calcd for $C_{17}H_{24}O_2$: 260.1775. Found: 260.1776.

Methyl 1-Hydroxy-3-(4-methylphenyl)-3,4,4-trimethylcyclopentane-1-carboxylate (9) A solution of **8** (107 mg, 0.41 mmol) in dry THF (2 ml) was added to a solution of LDA [prepared from diisopropylamine (46 mg, 0.45 mmol) and a 15% solution of butyllithium in hexane (0.29 ml, 0.45 mmol)] in dry THF (5 ml) at −78 °C and the mixture was stirred at the same temperature for 15 min. $MoO_5 \cdot Py \cdot HMPA$[4] (267 mg, 0.62 mmol) was added to the above solution at −78 °C and the mixture was stirred at −20 °C for 2 h. The reaction was quenched with saturated Na_2S solution (2 ml) and the whole was extracted with ethyl ether. The extract was dried over $MgSO_4$, the solvent was evaporated off, and the residue was chromatographed on silica gel (hexane–ethyl acetate, 10 : 1). The first eluate gave the starting material **8** (22 mg, 21%). The second eluate gave **9** (85 mg, 75%) as an oil, whose ^{1}H-NMR spectrum showed it to be a mixture of two diastereoisomers in a ratio of 1 : 1. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3540, 1730. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 0.65 (3H × 1/2, s), 0.81 (3H × 1/2, s), 1.13 (3H × 1/2, s), 1.20 (3H × 1/2, s), 1.38 (3H × 1/2, s), 1.53 (3H × 1/2, s), 2.23 (2H, br s), 2.30 (3H, s), 2.80, 3.22 (2H × 1/2 each, AB q, J = 12 Hz), 3.10—3.65 (1H, m), 3.78 (3H, s), 6.72—7.45 (4H, m). This compound was characterized as the corresponding diol **10**.

1-Hydroxy-3-(4-methylphenyl)-3,4,4-trimethylcyclopentane-1-methanol (10) A solution of **9** (99 mg, 0.36 mmol) in dry ethyl ether was added to a suspension of $LiAlH_4$ (20 mg, 0.54 mmol) in dry ethyl ether (3 ml) at 0 °C and the mixture was stirred at room temperature for 2 h. After usual work-up, the crude products were purified by chromatography on silica gel (hexane–ethyl acetate, 1 : 1) to give **10** (73 mg, 82%) as an oil, whose ^{1}H-NMR spectrum showed it to be a mixture of two diastereoisomers in a ratio of 1 : 1. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3380. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 0.58 (3H × 1/2, s), 0.84 (3H × 1/2, s), 1.12 (3H × 1.2, s), 1.22 (3H × 1/2, s), 1.30 (3H × 1/2, s), 1.57 (3H × 1/2, s), 1.67—2.18 (2H, m), 2.33 (3H, s), 2.5—3.1 (4H, m), 3.60 (2H × 1/2, s), 3.63 (2H × 1/2, s), 6.85—7.45 (4H, m). Exact MS *m/z*: Calcd for $C_{16}H_{24}O_2$: 248.1774. Found: 248.1770.

(±)-β-Cuparenone (11) A solution of $NaIO_4$ (94 mg, 0.44 mmol) in water (1 ml) was added to a solution of **10** (73 mg, 0.29 mmol) in THF (2 ml) and the mixture was stirred at room temperature for 2 h. THF was removed by evaporation, the residue was diluted with water (1 ml), and the whole was extracted with dichloromethane. The extract was dried over $MgSO_4$, the solvent was removed by evaporation, and the residue was chromatographed on silica gel (ethyl acetate) to give **11** (55 mg, 86%) as an oil, which had spectral characteristics identical to those of an authentic sample.[5a] IR ν_{max}^{neat} cm^{-1}: 1740. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 0.72 (3H, s), 1.22 (3H, s), 1.41 (3H, s), 2.16 (2H, s), 2.20 (1H, d, J = 18 Hz), 2.32 (3H, s), 2.97 (1H, d, J = 18 Hz), 7.0—7.06 (4H, br s).

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