Total Synthesis of (*R*)-(-)-Sulcatol, (2*R*)-6-Methyl-5-hepten-2-ol

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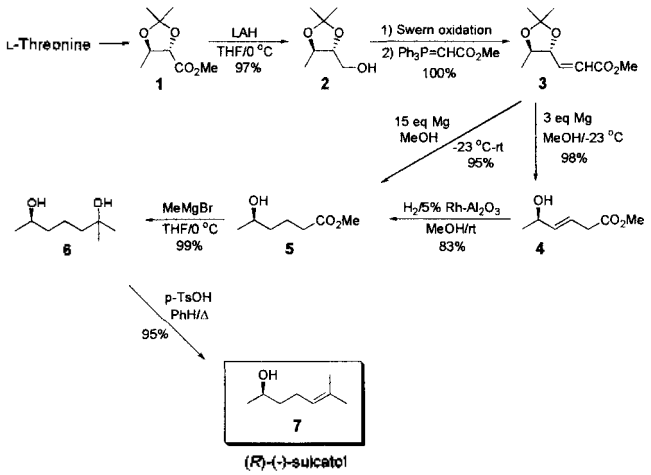
Sulcatol, 6-methyl-5-hepten-2-ol, is the population aggregation pheromone produced by males of *Gnathotrichus sulcatus* and an economically important ambrosia beetle on the Pacific coast of North America.[1] This compound was isolated as a 65/35 mixture of the (*S*)-(+) and (*R*)-(-) enantiomers of 6-methyl-5-hepten-2-ol. In 1975, Mori synthesized for the first time optically pure enantiomers from (*S*)-(+)- and (*R*)-(-)-glutamic acids.[2] Since then many others have synthesized optically pure enantiomers.[3] Here we report total synthesis of (*R*)-(-)-sulcatol via methyl (5*R*)-5-hydroxyhexanoate resulting from reductive *C-O* bond cleavage of methyl 4,5-(isopropylidenedioxy)-2-hexenoate with magnesium metal in absolute methanol. The synthesis of optically pure (*R*)-(-)-sulcatol can be envisaged as shown in Scheme 1.

Optically pure primary alcohol **2**, which is easily prepared from L-threonine in four steps[4] or from the reduction of methyl (4*S*)-*trans*-2,2,5-trimethyl-1,3-dioxolane-4-carboxylate.[4a] Swern oxidation of **2** followed by Wittig in one pot gave **3** in quantitative yield as a mixture 21/71 of *Z* and *E* isomers.[5] Without the separation of isomers, reductive cleavage of **3** with 3 equiv of Mg in absolute MeOH at -23 °C afforded **4** in 98% yield.[5] Catalytic hydrogenation of **4** under atmospheric pressure of hydrogen with 5% Rh/Al_2O_3 gave saturated ester **5** in 83% yield along with methyl 5-oxohexanoate resulting from the migration of hydrogen in 15% yield as a byproduct. When 10% Pd/C was used as the catalyst, the amount of byproduct was increased. In contrast to this result, saturated ester **5** was obtained in 95% yield from **3** without any byproducts with excess Mg (>10 equiv) in MeOH at -23 °C warmed to room temperature.[5,6] Treatment of **5** with 3 equiv of methylmagnesium bromide at 0 °C afforded diol **6** in quantitative yield. In the presence of a catalytic amount of *p*-TsOH, selective dehydration of tertiary alcohol *vs* secondary alcohol of **6** in benzene gave (*R*)-(-)-sulcatol **7** and (2*R*)-6-methyl-6-hepten-2-ol **8** in 95% as an inseparable 13/1 mixture. The ratio was determined by the integration of internal and terminal olefinic protons in NMR spectrum. (*R*)-(-)-sulcatol **7** was synthesized in overall 80% yield from **1** in 6 steps.



Scheme 1

In summary, we have developed a very efficient and facile method for the synthesis of (*R*)-(-)-sulcatol..

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded at 300 MHz, unless otherwise specified, in $CDCl_3$ solution using tetramethylsilane as internal standard. Analytical thin-layer chromatography was performed on precoated silica gel plates (0.25-mm 60 F-254 E. Merck). THF was dried over sodium benzophenone prior to use. MeOH was dried over Mg prior to use. Magnesium, purchased from Aldrich (powder, -50 mesh, 99+%), was used without any special activation.

Methyl *trans*-4,5-(Isopropylidenedioxy)-2-hexanoate (3).[5] This α,β-unsaturated ester was prepared as a mixture of *Z* and *E* (*Z*/*E*; 1/3.4) isomers from the corresponding alcohol via Swern oxidation followed by Wittig reaction in one pot.

Methyl (5*R*)-5-hydroxyhexanoate (5).[7] From **3** with excess Mg: A mixture of **3** (2.0 g, 10 mmol), Mg (3.65 g, 150 mmol), and catalytic amount of $HgCl_2$ in absolute MeOH (100 mL) was stirred at -23 °C for 1.5 h. The reaction mixture was allowed to warm to room temperature and the stirring was continued for 5 h. The reaction mixture was poured into cold 0.5 *N* HCl solution and then extracted with EtOAc (150 mL×2). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and then concentrated *in vacuo* to afford a pale yellow oil. Flash column chromatography (SiO_2, *n*-hexane/EtOAc; 1/1 (v/v)) gave **5** (1.39 g, 95%) as a colorless oil. ^1H NMR (300 MHz) δ 3.79 (m, 1 H), 2.43 (br s, OH, 1 H), 2.33 (t, *J* = 7.2 Hz, 2 H), 1.32-1.83 (m, 4 H), 1.19 (d, *J* = 6.1 Hz, 3 H).

From **4** with $Rh-Al_2O_3$: A mixture of **4** (1.44 g, 10.0 mmol) and catalytic amount of 5% $Rh-AL_2O_3$ on charcoal in MeOH (30 mL) was stirred in 1 atm hydrogen for 2 h. The reaction mixture was filtered through a pad of Celite and the solvent was concentrated *in vacuo* to afford a colorless oil, which was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc; 1/1 (v/v)) to give **5** (1.21 g, 83%) as a colorless oil.

(6*R*)-2,6-Heptanediol (6).[8] To a stirred solution of **5** (1.02 g, 7.0 mmol) in dry THF (50 mL) was added dropwise a solution of methylmagnesium bromide (3.0 M solution in diethyl ether, 10 mL, 30.0 mmol) over 10 min at 0 °C under the nitrogen atmosphere. After 1 h, the reactiom mixture was allowed to warm to room temperature and the stirring was continued for an additional 30 min. The reaction mixture was poured into cold saturated NH_4Cl solution and extracted with EtOAc (100 mL×3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and then concentrated *in vacuo* to afford a pale yellow oil, which was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH; 10/1 (v/v)) to give **6** as a colorless oil. $[a]_D^{25}$ 8.2° (c 1.0 in THF); ^1H NMR (300 MHz) δ 3.82 (m, 1 H), 2.35 (br s, OH, 2 H), 1.35-1.60 (m, 6 H), 1.22 (s, 6 H) 1.19 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75.4 MHz) δ 70.9, 67.6, 43.4, 39.5, 29.3, 29.0, 23.5, 20.3.

(*R*)-(-)-Sulcatol, (2*R*)-(-)-6-methyl-5-hepten-2-ol (7).[2] A stirred solution of **6** (0.88 g, 6.0 mmol) and catalytic amount of *p*-TsOH in benzene (30 mL) was refluxed for 1 h. After cooling the reaction mixture to room temperature, the reaction mixture was poured into cold saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with ether (50 mL×2). The combined organic layer was washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and then concentrated *in vacuo* to afford a pale yellow oil, which was purified by flash column chromatography (SiO_2, *n*-hexane/ether; 1/1 (v/v)) to give a inseparable mixture of **7** and (2*R*)-6-methyl-6-hepten-2-ol **8** (0.74 g, 95%, **7**/**8** = 13/1) as a colorless oil. ^1H NMR (300 MHz) δ 5.15 (m, 1 H, H-5 from **7**), 4.70 (m, 2 H, H-7 from **8**), 3.80 (m, 2 H, H-2 from **7** and H-2 from **8**), 1.90-2.20 (m, 4 H, H-4 from **7** and H-4 from **8**), 1.1-1.85 (other peaks).

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