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A SIMPLE SYNTHESIS OF (S)-(+)-SULCATOL, THE PHEROMONE OF *GNATHOTRICHUS RETUSUS*, EMPLOYING BAKER'S YEAST FOR ASYMMETRIC REDUCTION†

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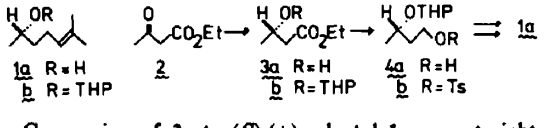
Abstract—Ethyl (*S*)-3-hydroxybutanoate of 87% optical purity was obtained by the yeast reduction of ethyl acetoacetate and was converted into 85–87% optically pure (*S*)-(+)-sulcatol (6-methyl-5-hepten-2-ol) by a 5-step sequence in 73% overall yield.

Sulcatol is the aggregation pheromone first isolated from the boring dust of *Gnathotrichus sulcatus*.[1] Its identification as a 65/35 mixture of the (*R*)-(−)- and (*S*)-(+)-enantiomers of 6-methyl-5-hepten-2-ol evoked interest in its chiral synthesis. Our first synthesis of optically active sulcatol was accomplished by employing glutamic acid as the starting material.[2] The availability of both enantiomers of sulcatol led to the discovery of quite unexpected stereochemistry-pheromone activity relationship: *Gnathotrichus sulcatus* responded to sulcatol only when both enantiomers were present, which meant a synergistic response to enantiomeric mixtures.[3] Since then two other chiral syntheses were reported.[4,5] In the earlier synthesis (*R*)-(−)-sulcatol was prepared from 2-deoxy-D-ribose, while L-fucose was converted to (*S*)-(+)-sulcatol.[4] Ethyl (*S*)-(−)-lactate was the starting material in the later synthesis.[5] (*S*)-(+)-Sulcatol was also prepared by resolution of the phthalic half ester of (±)-sulcatol with brucine.[6] Very recently Borden has found that *Gnathotrichus retusus* responds to (*S*)-(+)-sulcatol in an upwind laboratory bioassay and that the response appears to be inhibited to some extent by the (*R*)-(−)-enantiomer.[7] This prompted us to devise a simple synthesis of (*S*)-(+)-sulcatol for biological use.

Obviously the most direct access to (*S*)-(+)-sulcatol **1a** is the asymmetric reduction of 6-methyl-5-hapten-2-one. Even after recent remarkable progress, chemical asymmetric reduction is still unsatisfactory for this purpose in view of the low optical yield in the case of aliphatic ketones with no unsaturation at the α-carbon.[8] However, microbial reduction of ketones catalyzed by yeast is generally known to give (*S*)-alcohols often in high optical yield.[9] We therefore attempted the reduction of 6-methyl-5-hepten-2-one or 6-methyl-3,5-heptadien-2-one with baker's yeast. But unfortunately in these particular cases the substrates were recovered unchanged after fermentation. So we had to choose another substrate more readily reducible by yeast.

The yeast reduction of ethyl acetoacetate **2** was reported to give ethyl (*S*)-3-hydroxybutanoate **3a**, although no precise determination of the optical yield was described.[10–12] Upon reduction with baker's yeast for a day at 30°, ethyl acetoacetate was converted to ethyl (*S*)-3-hydroxybutanoate **3a** in 67% isolated yield. The reduction could be followed conveniently by disappearance of the positive $FeCl_3$ coloration test for ethyl acetoacetate. The optical purity of the product was determined by the NMR and glc analyses of its (*S*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester[13] to be 86–87%. After the completion of our work, two papars appeared concerning the optical yield of the yeast reduction of ethyl acetoacetate. Fráter reported the optical purity of his reduction product **3a** to be 70% by its NMR analysis in the presence of a chiral shift reagent,[14] while Meyers and Amos found their **3a** to be of 97% optical purity by the similar NMR analysis.[15] The optical yield of this asymmetric reduction thus fluctuates between the range of 70–97% due to the differences in the yeast strain or fermentation condition. The experimental simplicity together with high optical yield makes the yeast reduction particularly acceptable as the starting point in a chiral synthesis of natural products.‡



Conversion of **3a** to (*S*)-(+)-sulcatol **1a** was straightforward. After protection of the OH group as a THP ether, **3b** was reduced with LAH to give an alcohol **4a**. The corresponding tosylate **4b** was treated with a Grignard reagent prepared from 1-bromo-2-methylpropene in the presence of CuI to give the coupling product **1b**. The THP protecting group of **1b** was removed by acid hydrolysis yielding the desired product **1a** in 73% overall yield from **3a**. The optical purity of our gas chromatographically 96% pure sulcatol **1a**, $[\alpha]_D^{22} + 12.6°$ (EtOH), was estimated to be 85 ~ 87% based on the reported $[\alpha]_D$ values (+14.4°[2] and +14.8°[5]) or 89 ± 3% based on the NMR analysis of its (*S*)-(−)-MTPA ester.

In conclusion we added another example of incorporation of a biochemical method into organic synthesis which provided a simple and efficient route to a chiral pheromone, (*S*)-(+)-sulcatol **1a**.

†Pheromone Synthesis—XLI. This work was presented at the Korea–Japan Joint Symposium on Organic Reactions and Syntheses in Seoul, Korea, on 26 April 1980, as a part of K.M.'s lecture. Part XL, C. Hoshino and K. Mori, *Agric. Biol. Chem.* **44**, 3007 (1980).

‡Recently we have obtained 94–97% optically pure ethyl (*S*)-3-hydroxybutanoate **3a** by interrupting the fermentation after 4 hr with 3–4% recovery of ethyl acetoacetate **2** (T. Sugai, unpublished result). Detailed fermentation condition will be reported later with other examples of chiral synthesis starting from **3a**.

EXPERIMENTAL

All b.ps were uncorrected. IR spectra refer to films and were determined on a Jasco IRA-1 spectrometer. NMR spectra were recorded as CCl_4 solns at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer unless otherwise stated. Optical rotations were measured on a Jasco DIP-4 polarimeter.

Ethyl (S)-(+)-3-*hydroxybutanoate* **3a**. Dry yeast (12–15 g, Oriental Yeast Co., Ltd., containing 98.5% yeast and 1.5% sorbitan fatty acid ester) was dispersed to tap water (250 ml) at 30° and sucrose (30 g) was added to it. The flask was shaken at 30° for 10–15 min, when brisk fermentation took place. Ethyl acetoacetate **2** (5.0 g) was added to the fermentation mixture and the shaking culture was continued at 30°. Sucrose (20 g) was added to the mixture after 4–5 hr. Another 20 g of sucrose was again added after 4–5 hr and the fermentation was continued for further 10 hr. The total fermentation period was about 20 hr. Complete consumption of **2** was shown by the disappearance of $FeCl_3$ coloration test. The fermentation broth was mixed with a small amount of ether and filtered through a mixture of Celite and activated charcoal. The filtrate was saturated with NaCl and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated under atm press. The residue resulting from six fermentations (30.0 g of **2**) was distilled to give 20.2 g (67%) of **3a**, b.p. 76–78°/18 mm, n_D^{23} 1.4167; α_D^{23} +16.4° (neat, l = 1 dm); $[\alpha]_D^{23}$ +32.7° (c = 2.50, $CHCl_3$) [lit.[14] $[\alpha]_D^{22}$ +31.3° (c = 1.05, $CHCl_3$); lit.[12] $[\alpha]_D$ +36.5° (c = 1, $CHCl_3$); lit.[11] $[\alpha]_D$ +38.5° ($CHCl_3$); lit.[15] $[\alpha]_D$ +41.7° ($CHCl_3$)]; ν_{max} ~3400 (m), 2960 (m), 2920 (m), 1735 (vs), 1720 (sh), 1380 (m), 1300 (m), 1180 (s), 1090 (m), 1070 (m), 1025 (m) cm^{-1}; δ 1.18 (3 H, d, J = 6 Hz), 1.24 (3 H, t, J = 6 Hz), 2.40 (2 H, d, J = 6 Hz), 3.40 (1 H, s), 4.10 (2 H, q, J = 6 Hz); glc (Column, Thermon 1000, 30 m × 0.3 mm at 70°; Carrier gas, N_2, 40 ml/min): R_t 1687 sec (98.7%). A small amount of **3a** was converted to the corresponding MTPA ester in the conventional manner, which was analyzed by glc and NMR: glc (Yanaco G 180; Column, Thermon 1000, 30 m × 0.3 mm at 170°; Carrier gas, N_2, 40 ml/min): R_t 1510 sec (93.3%), 1550 sec (6.7%). ∴ optical purity = 87%. NMR (60 MHz, MTPA ester (35 mg) and $Eu(fod)_3$ (10 mg) in CCl_4 (0.2 ml)): δ 3.62 (2.8 H, –OMe), 5.00 (0.2 H, –OMe). ∴ optical purity = 86%.

Ethyl (S)-3-*tetrahydropyranyloxybutanoate* **3b**. *p*-TsOH (0.1 g) was added to a soln of **3a** (4.0 g) and dihydropyran (3.0 g) in dry ether (50 ml). The soln was left to stand overnight at room temp, washed with $NaHCO_3$ aq, dried (K_2CO_3) and concentrated *in vacuo* to give 7.0 g (quantitative) of crude **3b**, ν_{max} 2930 (s), 2860 (m), 1735 (vs), 1190 (s), 1130 (s), 1075 (s), 1030 (s), 1020 (s), 995 (s) cm^{-1}. This was employed for the next step without further purification.

(3S)-3-*Tetrahydropyranyloxybutan*-1-*ol* **4a**. A soln of **3b** (7.0 g) in dry ether (20 ml) was added to a stirred and ice-cooled suspension of LAH (1.0 g) in dry ether (80 ml) at 0–5°. The mixture was stirred for 4 hr at room temp. Then excess LAH was destroyed by the addition of H_2O (1 ml), 10% NaOH aq (1 ml) and H_2O (3 ml) to the stirred and ice-cooled mixture. The stirring was continued for 1 hr. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was distilled to give 4.7 g (89% from **3a**) of **4a** b.p. 76–84°/0.8 mm, n_D^{23} 1.4520; $[\alpha]_D^{23}$ +24.7° (c = 1.545, $CHCl_3$); ν_{max} ~3380 (s), 2920 (s), 2860 (s), 1130 (s), 1115 (s), 1070 (s), 1050 (s), 1020 (s), 1000 (s) cm^{-1}; δ ($CDCl_3$) 1.15 (1.5 H, d, J = 6 Hz), 1.25 (1.5 H, d, J = 6 Hz), ~1.4–~2.0 (8 H, m), 2.74 (1 H), ~3.1–~4.2 (4 H, m), ~4.65 (1 H) (Found: C, 61.64; H, 10.28. Calc. for $C_9H_{18}O_3$: C, 62.04; H, 10.41%).

(3S)-3-*Tetrahydropyranyloxybutyl tosylate* **4b**. *p*-TsCl (7.2 g) was added to a soln of **4a** (4.7 g) in dry pyridine (25 ml) with stirring and ice-cooling. The mixture was stirred for 4 hr. Then it was poured into ice-water and extracted with ether. The ether soln was washed with H_2O, $CuSO_4$ soln and $NaHCO_3$ soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 8.4 g (quantitative) of crude **4b**, ν_{max} 2920 (s), 2830 (m), 1590 (m), 1360 (s), 1190 (vs), 1175 (vs), 1120(s), 1070(s), 1030(s), 1020(s), 995(s), 940(s), 885 (s), 810 (s), 765 (s), 665 (s) cm^{-1}. This was employed for the next step without further purification.

(2S)-6-*Methylhept*-5-*en*-2-*ol tetrahydropyranyl ether* **1b**. A Grignard reagent was prepared from 1-bromo-2-methylprop-1-ene (6.75 g) and Mg (1.2 g) in dry THF (25 ml). A soln of **4b** (7.0 g) in dry ether (20 ml) was added to the stirred and cooled Grignard soln at −70° under Ar. Then CuI (0.5 g) was added. After the addition, the reaction temp was gradually raised to 0° during 1 hr and kept there for 3–4 hr. The mixture was left to stand overnight at room temp and then it was stirred and heated under reflux (40°) for 1 hr. After cooling, the mixture was poured into ice-NH_4Cl aq and the organic layer was separated. The aq layer was extracted with ether. The combined organic soln was washed with NH_4Cl aq, $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give *ca* 5 g (quantitative) of crude **1b**, ν_{max} 2900 (s), 2840 (s), 1125 (s), 1070 (s), 1015 (s), 990 (s) cm^{-1}. This was directly used for the final step.

(S)-(+)-*Sulcatol* (6-*methylhept*-5-*en*-2-*ol*) **1a**. Crude **1b** (5 g) was dissolved in THF (8 ml)–AcOH (16 ml)–H_2O (8 ml) and the soln was stirred and heated at 60–80° for 3.5 hr. Then it was diluted with ice-water and extracted with ether. The ether soln was washed with H_2O, $NaHCO_3$ aq and brine, dried (K_2CO_3) and concentrated *in vacuo*. The residual oil (4 g) was chromatographed over neutral alumina (Woelm, Activity Grade II, 120 g, 12.8 × 3.5 cm) in petroleum ether. Elution with petroleum ether removed hydrocarbon impurities. Subsequent elution with petroleum ether–ether (4:1) gave **1a** (2.134 g, 82% from **4b**). This was distilled to give pure **1a**, b.p. 80–82°/35 mm, n_D^{22} 1.4476; $[\alpha]_D^{22}$ +12.6° (c = 1.042, EtOH) [lit.[2] $[\alpha]_D^{23}$ +14.4° (c = 0.998, EtOH). ∴ optical purity of the present material = 87.5%. lit.[5] $[\alpha]_D^{23}$ +14.8° (c = 4.96, EtOH). ∴ optical purity of the present material = 85%]; ν_{max} 3320 (s), 2950 (s), 2900 (s), 2840 (s), 1450 (m), 1375 (m), 1350 (w), 1330 (w), 1305 (w), 1250 (w), 1220 (w), 1170 (w), 1130 (m), 1070 (m), 1020 (w), 985 (w), 950 (w), 930 (w), 900(w), 850(w), 820(w), 740(w) cm^{-1}; δ 1.15 (3 H, d, J = 6 Hz), ~1.2–~1.5 (2 H), 1.62 (3 H, s), 1.68 (3 H, s), ~1.8–~2.3 (2 H), 2.80 (1 H, –OH), 3.72 (1 H, q, J = 6 Hz), 5.12 (1 H, t, J = 6 Hz). These spectral data were identical with those of our previous material.[2] A small amount of **1a** was converted to the corresponding MTPA ester in the conventional manner, which was analyzed by NMR (60 MHz, MTPA ester (41 mg) and $Eu(fod)_3$ (5 mg) in CCl_4 (0.2 ml)): δ 3.83 (~2.8 H, –OMe), 4.50 (~0.2 H, –OMe). ∴ optical purity = 89 ± 3%; glc (Column, Thermon 1000, 30 m × 0.3 mm at 91°; Carrier gas, N_2, 40 ml/min); R_t 490 sec (96%) (Found: C, 74.97; H, 12.72. Calc. for $C_8H_{16}O$: C, 74.94; H, 12.58%).

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