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SYNTHESIS OF OPTICALLY ACTIVE FORMS OF SULCATOL

THE AGGREGATION PHEROMONE IN THE SCOLYTID BEETLE, *GNATHOTRICHUS SULCATUS*†

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Abstract—(*S*)-(+)-Sulcatol (1) and its antipode (1') were synthesized from (*R*)-(−)-glutamic acid (2), and its antipode (2'), respectively. This established the absolute configurations of both enantiomers of sulcatol and afforded key materials to study the relationship between pheromone activity and chirality.

Sulcatol is the population aggregation pheromone produced by males of *Gnathotrichus sulcatus*, an economically important ambrosia beetle on the Pacific coast of North America. About 0·5 mg of the pheromone was isolated from the boring dust of this timber pest and identified as a 65/35 mixture of the (*S*)-(+) and (*R*)-(−) enantiomers of 6-methyl-5-hepten-2-ol (1 and 1', respectively).[1] It is possible that only one enantiomer has biological activity in view of our recent results on (+)- and (−)-*exo*-brevicomin, the pheromone of western pine beetle.[2,3]

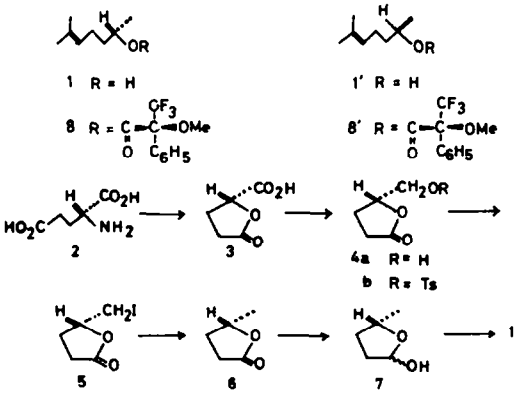
Herein we describe the synthesis of both (*R*)- and (*S*)-forms of optically pure sulcatol. This enabled us to know the sign of the optical rotation of each enantiomer and provided enough materials to compare the biological activity of the enantiomers. It should be emphasized that optically pure enantiomers are required for the bioassay in order to obtain meaningful data.

The synthesis of optically active sulcatol can be envisaged in the following two manners. One is the conventional resolution of (±)-sulcatol. The other is to use an optically active compound of established absolute configuration as the starting material. The latter seemed preferable for the purpose of synthesizing sulcatol with known absolute stereochemistry. Optically active propylene oxide seemed to be a good starting material in combination with an isoprenyl synthon. However, completely optically pure propylene oxide was not easily accessible because all the intermediates and propylene oxide itself is oily and difficult to purify.[4] So we decided to employ readily available (*R*)-(−)- and (*S*)-(+)-glutamic acids (2) as starting materials and converted them to (*S*)-(+)- and (*R*)-(−)-sulcatols as described below.

(*R*)-(−)-γ-Hydroxymethyl-γ-butyrolactone (**4a**) was synthesized from (*R*)-(−)-glutamic acid (2) as described[5] via a crystalline lactonic acid (3). Tosylation of the hydroxy lactone (**4a**) yielded a crystalline tosylate (**4b**). This was repeatedly recrystallized to ensure the highest optical purity. The pure **4b** was heated with LiI in acetone to give an iodide (5). Hydrogenolysis of 5 with Raney nickel W-7 in EtOH in the presence of $CaCO_3$ yielded, after chromatographic purification and distillation, (*S*)-(−)-γ-methylbutyrolactone (6). Both (*R*)- and (*S*)-enantiomers of this lactone (6) are recorded in the literature.[6-9] However, their optical purities are obscure. Our lactone (6) is optically pure, since it has later yielded optically pure sulcatol (1). Reduction of the lactone (6) with i-Bu_2AlH afforded a lactol (7). This was treated with isopropylidene triphenyl phosphorane in DMSO to give (*S*)-(+)-sulcatol (1), which was shown to be dextrorotatory: $[\alpha]_D^{23} + 14{\cdot}4°$ (EtOH). The same sequence of operations starting from (*S*)-(+)-glutamic acid afforded (*R*)-(−)-sulcatol (1'), $[\alpha]_D^{23} - 14{\cdot}5°$ (EtOH). The NMR data of our sulcatol was in good accord with the published data of the natural product.

The optical purity of our products was checked by the MTPA (α-methoxy-α-trifluoromethylphenylacetic acid) ester method developed by Mosher *et al.*[10,11] (*R*)-(−)- and (*S*)-(+)-Sulcatols were esterified with the acyl chloride derived from (*S*)-(−)-MTPA. The NMR spectra of the resulting (*R*, *S*)- and (*S*, *S*)-sulcatol MTPA esters (8' and 8, respectively) were measured at 100 MHz. The resonance for the Me group on the carbinyl carbon of the (*R*, *S*)-ester is centered at lower field position (δ 1·35, d, J = 6 Hz) than the signal of the corresponding Me group in the (*S*, *S*)-ester (δ 1·24, d, J = 6 Hz). This is in accord with the reported correlation of configuration and NMR chemical shift for diastereomeric MTPA esters.[11] No evidence of cross-contamination of the diastereomers was observable in the NMR spectra, which confirmed the high optical purity of our products.

In conclusion the optically active forms of sulcatol were synthesized to study the relationship between



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absolute stereochemistry and pheromone activity. The biological work is in progress by Prof. J. H. Borden and will be published elsewhere in due course.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra refer to films for oils and to nujol mulls for solids and were determined on a Jasco IRA-1 spectrometer. NMR spectra were recorded 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. GLC analyses were performed on a Yanaco G 80 gas chromatograph.

(R)-(−)-γ-*Tosyloxymethyl*-γ-*butyrolactone* (**4b**). Powdered *p*-TsCl (30 g) was added in one portion to an ice-cooled and stirred soln of **4a** (14·2 g) in dry C_5H_5N (80 ml). The mixture was stirred for 2 hr at 0–10°, poured into ice-dil. HCl and extracted with EtOAc. The EtOAc soln was washed with dil. HCl and NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The crystalline residue was recrystallized (four times) from EtOAc–ether to give 16·0 g (48%) of pure **4b**, prisms, m.p. 85–86°; $[\alpha]_D^{23}$ − 46·3° (*c* = 1·33, $CHCl_3$); ν_{max} 1778 (s), 1600 (m), 1375 (s), 1300 (m), 1190 (s), 1180 (s), 1070 (m), 1000 (m), 985 (s), 940 (m), 925 (m), 830 (m), 820 (m), 795 (m), 680 (m) cm^{-1}; δ ($CDCl_3$) ~ 1·8–~2·7 (4 H, m), 2·45 (3 H, s), 4·18 (2 H, d, J = 4 Hz), 4·70 (1 H, m), 7·42 (2 H, d, J = 10 Hz), 7·85 (2 H, d, J = 10 Hz). (Found: C, 53·33; H, 5·14. $C_{12}H_{14}O_5S$ requires: C, 53·32; H, 5·25%.)

(S)-(+)-γ-*Tosyloxymethyl*-γ-*butyrolactone* (**4b'**). In a similar manner, (*S*)-(+)-**4a'** *afforded* (*S*)-(+)-**4b'**, m.p. 84–85°; $[\alpha]_D^{23}$ + 46·2° (*c* = 1·63, $CHCl_3$).

(R)-γ-*Iodomethyl*-γ-*butyrolactone* (**5**). LiI (30 g) was added to a soln of **4b** (16·0 g) in acetone (200 ml) and the mixture was stirred and heated under reflux for 9 hr. Acetone was removed *in vacuo*. The residue was dissolved in water and extracted with EtOAc. The EtOAc soln was washed with $Na_2S_2O_3$ aq and NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give 13·0 g (quantitative) of **5**, ν_{max} 1780 (s), 1340 (m), 1210 (m), 1160 (s), 1010 (m), 980 (m), 905 (m), 870 (w), 805 (w), 790 (w) cm^{-1}. This was employed for the next step without further purification.

(S)-γ-*Iodomethyl*-γ-*butyrolactone* (**5'**). Similarly, (*S*)-(+)-**4b'** (18·6 g) *yielded* **5'** (12·5 g, 82%).

(S)-(−)-γ-*Methyl*-γ-*butyrolactone* (**6**). Raney Ni W-7 (30 g) and powdered $CaCO_3$ (5 g) were added to a soln of **5** (13·0 g) in 99% EtOH (180 ml) and the mixture was stirred for 30 min at room temp. Then the mixture was filtered. The filtrate was concentrated *in vacuo* and the residue was chromatographed over silica gel (Merck Art 7734 Kieselgel 0·05–0·2 mm, 50 g, 16 × 3·5 cm) in light petroleum. Elution with ether-light petroleum (1:2–1:1) gave **6**. This was distilled to give 3·6 g (49·3%) of pure **6**, b.p. 110°/39 mm; n_D^{23} 1·4305; $[\alpha]_D^{23}$ − 29·6° (*c* = 1·29, CH_2Cl_2); ν_{max} 1785 (vs), 1460 (m), 1430 (w), 1395 (m), 1350 (m), 1310 (w), 1290 (w), 1230 (m), 1205 (s), 1180 (vs), 1125 (m), 1100 (m), 1060 (m), 1000 (m), 940 (s), 900 (m), 830 (w), 805, (w)cm^{-1}; δ (CCl_4) 1·37 (3 H, d, J = 7 Hz), ~2·0–~2·6 (4 H), 4·58 (1 H, q, J = 7 Hz). (Found: C, 59·48; H, 8·10: $C_5H_8O_2$ requires: C, 59·98; H, 8·05%).

(R)-(+)-γ-*Methyl*-γ-*butyrolactone* (**6'**). Similarly, (*S*)-**5'** gave (*R*)-(+)-**6'**, b.p. 105°/35 mm; n_D^{23} 1·4299; $[\alpha]_D^{23}$ + 30·1° (*c* = 0·85, CH_2Cl_2).

(S)-γ-*Methyl*-γ-*butyrolactol* (**7**). i-Bu_2AlH (25% in n-hexane, 28 ml) was added dropwise to a stirred and cooled soln of **6** (3·4 g) in dry THF (50 ml) during 15 min at −60 ~ −55° under N_2. The soln was stirred for 40 min at −60°. The reaction was quenched by the addition of sat NH_4Cl aq (10 ml) at −60°. Then the acetone-dry ice bath was removed and the mixture was diluted with ether (150 ml) at room temp. After several min the mixture became gelatinous [$Al(OH)_3$]. The mixture was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 2·5 g (73%) of **7**, ν_{max} 3400 (s), 2900 (s), 1460 (m), 1390 (m), 1360 (w), 1300 (w), 1200 (m), 1125 (m), 1080 (s), 1005 (s), 960 (m), 890 (m), 840 (w), 805 (w) cm^{-1}. This was employed for the next step without further purification.

(R)-γ-*Methyl*-γ-*butyrolactol* (**7'**). Similarly, (*R*)-(+)-**6'** gave (*R*)-**7'**.

(S)-(+)-6-*Methyl*-5-*hepten*-2-*ol* (sulcatol, **1**). To a soln of $NaCH_2SOMe$ (from 3·4 g of 50% NaH) in DMSO (100 ml) was added triphenylisopropylphosphonium bromide (28 g) under N_2 with ice-cooling and stirring. The mixture was stirred for 5 min to yield a deep red soln of the Wittig reagent. A soln of **7** (2·5 g) in dry THF (20 ml) was added dropwise to the stirred soln. The mixture was stirred for 1·5 hr at room temp., poured into ice-water and extracted with *n*-hexane. The extract was washed with 60% MeOH aq (5 ml), water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over neutral alumina (Woelm, activity grade II, 40 g, 8·5 × 2·5 cm) in light petroleum. Elution with light petroleum-ether (4:1) gave **1**. This was distilled to give 0·6 g (20%) of pure **1**, b.p. 91°/34 mm; n_D^{23} 1·4463; $[\alpha]_D^{23}$ + 14·4° (c = 0·998, EtOH); ν_{max} 3350 (s), 3000 (s), 2950 (s), 2880 (s), 1455 (m), 1385 (m), 1360 (w), 1340 (w), 1315 (w), 1260 (w), 1230 (w), 1180 (w), 1135 (m), 1080 (m), 1030 (w), 995 (w), 955 (w), 940 (w), 910 (w), 860 (w), 830 (w), 750 (w) cm^{-1}; δ (100 MHz, CCl_4) 1·14 (3 H, d, J = 6 Hz), ~1·2–~1·5 (2 H, m), 1·61 (3 H, s), 1·68 (3 H, s), ~1·88–~2·25 (2 H), 2·90 (1 H, s, –OH), 3·72 (1 H, q, J = 6 Hz), 5·12 (1 H, t, J = 6 Hz); δ (60 MHz, CCl_4) 1·15 (3 H, d, J = 6 Hz), ~1·3–~1·7 (2 H), 1·62 (3 H, s), 1·69 (3 H, s), ~1·8–~2·3 (2 H), 3·18 (1 H, s, –OH), 3·75 (1 H, q, J = 6 Hz), 5·17 (1 H, t, J = 6 Hz); MS (70 eV): *m/e* 41·0413 (C_3H_5, 59%). 42·0495 (C_3H_6, 50%), 43·0201 (C_2H_3O, 59%), 45·0378 (C_2H_5O, 45%), 53·0401 (C_4H_5, 31%), 55·0565 (C_4H_7, 36%), 56·0632 (C_4H_8, 90%), 59·0514 (C_3H_7O, 63%), 67·0549 (C_5H_7, 45%), 68·0632 (C_5H_8, 36%), 69·0713 (C_5H_9, 31%) 79·0568 (C_6H_7, 22%), 81·0721 (C_6H_9, 36%), 95·0874 (C_7H_{11}, 100%, base peak), 105·0335 (C_7H_5O, 22%), 110·1104 (C_8H_{14}, 31%), 113·0976 ($C_7H_{13}O$, 36%), 128·1232 ($C_8H_{16}O$, 9%, M^+); GLC (Column, 5% LAC-2R-446, 1·5 m × 3 mm i.d. at 100°, Carrier gas, N_2, 1·0 kg/cm²): Rt 3·7 min (96·5% purity). Found: C, 74·73; H, 12·33. $C_8H_{16}O$ requires: C, 74·94; H, 12·58%).

(R)-(−)-6-*Methyl*-5-*hepten*-2-*ol* (sulcatol, **1'**). In the same manner as described above, (*R*)-**7'** gave (*R*)-(−)-sulcatol (**1'**), b.p. 89°/32 mm; n_D^{23} 1·4463; $[\alpha]_D^{23}$ −14·5° (c = 0·74, EtOH); GLC (Column, 5% LAC-2R-446, 1·5 m × 3 mm id. at 100°, Carrier gas, N_2, 1·0 kg/cm²): Rt 3·7 min (97% purity). Both enantiomers of sulcatol were odoriferous to human nose and smelled like geraniol with almost no difference in the odor as tested by the noses of the author and his students, Miss N. Mizumachi, Messers M. Uchida, I. Takemoto and Y. Tachibana.

(S)-(+)-*Sulcatol* (S)-(−)-*MTPA ester* (**8**). This was prepared from (*S*)-(+)-sulcatol (**1**) and (*S*)-(−)-MTPA-Cl by the standard procedure.[10] δ (60 MHz, CCl_4) 1·23 (3 H, d, J = 6 Hz), 1·56 (3 H, s), 1·68 (3 H, s), 3·54 (3 H, s, –OMe); δ (100 MHz, CCl_4) 1·24 (3 H, d, J = 6 Hz), 1·58 (3 H, s), 1·69 (3 H, s), 3·55 (3 H, s, –OMe); GLC (Column, 5% LAC-2R-446, 1·5 m × 3 mm i.d. at 170°, Carrier Gas, N_2, 1·0 kg/cm²): Rt 11·6 min.

(R)-(−)-*Sulcatol* (S)-(−)-*MTPA ester* (**8'**). This showed the following properties: δ (60 MHz, CCl_4) 1·34 (3 H, d, J = 6 Hz), 1·50 (3 H, s), 1·66 (3 H, s), 3·57 (3 H, s, –OMe); δ (100 MHz, CCl_4) 1·35 (3 H, d, J = 6 Hz), 1·51 (3 H, s), 1·66 (3 H, s), 3·58 (3 H, s, –OMe); GLC (Column, 5% LAC-2R-446, 1·5 m × 3 mm i.d. at 170°, Carrier gas, N_2, 1·0 kg/cm²): Rt 11·5 min.

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