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SYNTHESIS OF BOTH THE ENANTIOMERS OF 7-ETHYL-5-METHYL-6,8-DIOXA-BICYCLO[3.2.1]OCT-3-ENE, THE MUS MUSCULUS (HOUSE MOUSE) PHEROMONE†

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Abstract -- Both the enantiomers of the pheromone of the male mouse Mus musculus, exo-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]oct-3-ene, were synthesized from the enantiomers of tartaric acid.

In 1984 Novotny and his coworkers isolated a volatile pheromone from urine of the male mouse of the species Mus musculus.[1,2] When this compound was combined with another uniquely male mouse compound, 2-sec-butyl-4,5-dihydrothiazole, the mixture was an aggregation-promoting principle of the adult male mouse.[1,2] The structure of the pheromone was shown to be exo-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]oct-3-ene **1**, and confirmed by a synthesis of its racemate.[1] Incidentally, (±)-**1** had already been synthesized in 1977 by Chaquin et al. as an intermediate for the synthesis of the racemate of exo-brevicomin **2**, a bark beetle pheromone.[3] Three additional syntheses of (±)-**1** were reported since 1984.[4~6] Herein we report a synthesis of both the enantiomers of the mouse pheromone **1**.[7] The starting materials were the enantiomers of tartaric acid **3** which had been used as early as in 1974 for the first synthesis of the enantiomers of exo-brevicomin **2**.[8]

Our synthesis as shown in the Scheme employed an alkene **5** as an intermediate. The alkene **5** was prepared from a tosylate **4**, and used in our latest synthesis of exo-brevicomin **2**.[9] The tosylate **4**, in turn, was prepared from (2R,3R)-(+)-tartaric acid **3**.[10] The Wacker oxidation[11] of **5** with $PdCl_2$-$CuCl_2$ in DMF in the presence of $NaHCO_3$ gave **6** in 84 % yield. When 1,2-dimethoxyethane was used as the solvent in this reaction in the absence of $NaHCO_3$, exo-brevicomin **2** was the product. So as to ensure the good yield of **6** without formation of **2** as the by-product, the presence of $NaHCO_3$ was necessary even with DMF as the solvent. The ketone **6** was then converted, by treatment with Me_3SiCl and Et_3N in hot DMF,[12] into a mixture of silyl enol ethers **7** and **8**, the former having been the major product. Addition of the mixture of **7** and **8** to PhSeCl and C_5H_5N in CH_2Cl_2[13] yielded a mixture of **9** and **10**. This was purified by SiO_2 chromatography to give pure phenylseleno ketone **9** in 70 % yield from **6**. Treatment of **9** with p-TsOH in wet ether gave **11** in 96 % yield as a stereoisomeric mixture at C-4. Finally oxidation of **11** with m-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 gave (1S,5R,7S)-**1**, $[\alpha]_D^{24}$ +91.5° ($CHCl_3$), in 48 % yield.[4] The

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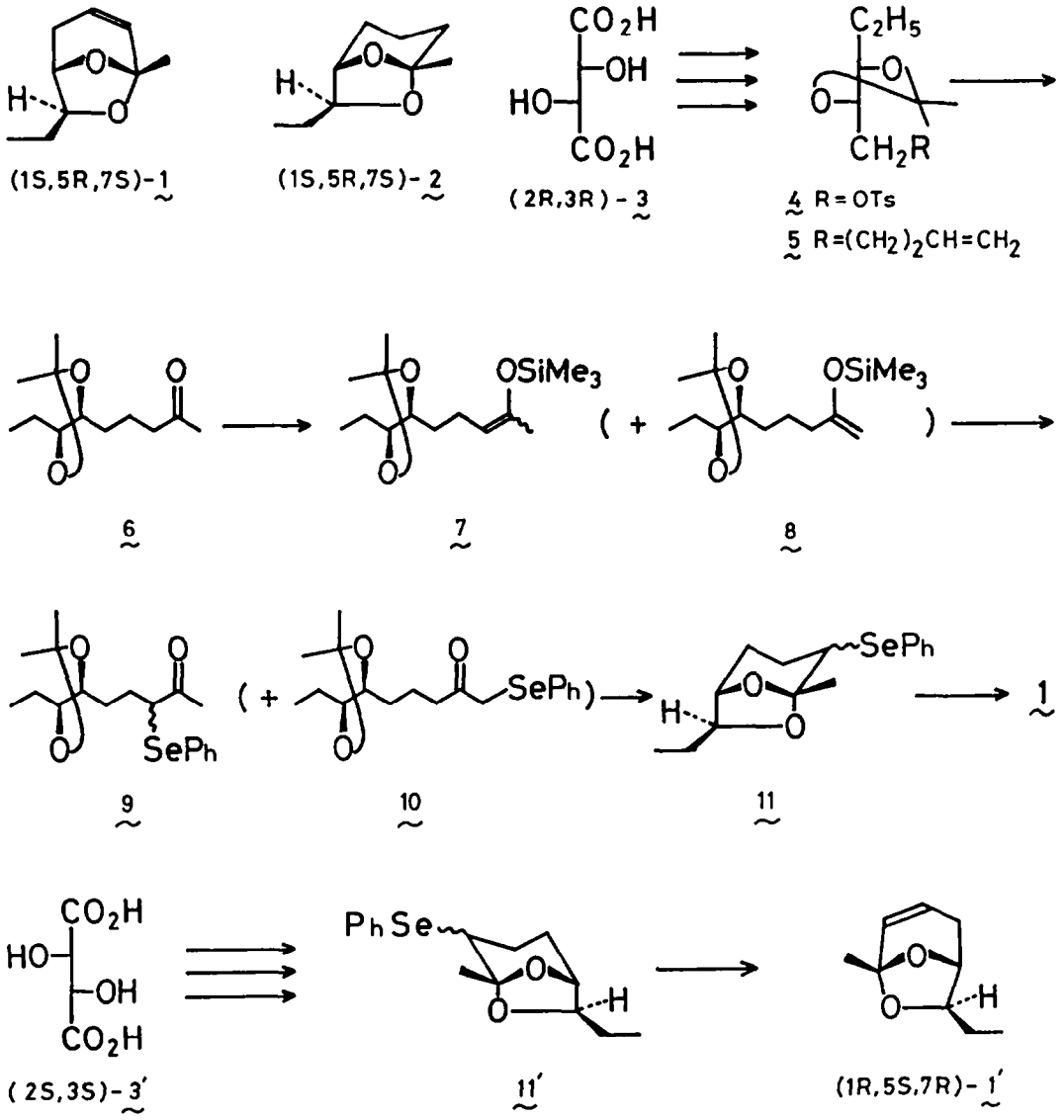

overall yield of (1S,5R,7S)-1 from 5 was 27 % in five steps. Similarly, (1R,5S,7R)-1', $[\alpha]_D^{24}$ -90.5° ($CHCl_3$), was synthesized from (2S,3S)-tartaric acid 2' via 11'. The overall yield of 1' from 5' was 21 % in five steps. The IR, ^1H NMR and mass spectra of 1 and 1' were in accord with the reported data.[1,3,5] In the course of the syntheses (5→1 and 5'→1'), there was no step which might have caused racemization. The enantiomeric purity of 1 and 1' was therefore thought to be ~100 % e.e. Our exo-brevicomin enantiomers, which were also synthesized from 5 and 5', were of 99.8 % e.e.[9]

In summary, both the enantiomers of the mouse pheromone were synthesized. Their biological activity will be studied in due course.

EXPERIMENTAL

All b.ps were uncorrected. IR spectra were measured as films on a Jasco IRA-102 spectrometer. ^{1}H NMR spectra were recorded with TMS as an internal standard at 60 MHz on a Hitachi R-24A spectrometer or at 400 MHz on a JEOL JNM FX-400 spectrometer. ^{13}C NMR spectra were recorded with TMS as an internal standard at 25 MHz on a JEOL JNM FX-100 spectrometer. Optical rotations were measured on a Jasco DIP 140 polarimeter. ORD spectra were measured on a Jasco J-20C spectropolarimeter. Mass spectra were recorded on a JEOL DX-303 spectrometer at 70 eV. Fuji Gel BW-820 MH was used for SiO_2 column chromatography.

4-Ethyl-2,2-dimethyl-5-(4-oxopentyl)-1,3-dioxolane **6**. (a) (4S,5S)-Isomer: $PdCl_2$ (60 % purity, 0.50 g, 1.7 mmol), $CuCl_2$ (1.68 g, 12.5 mmol) and $NaHCO_3$ (0.50 g) were added to a vigorously stirred soln of **4** (1.76 g, 8.9 mmol) in DMF (50 ml) at room temp. After 24 h, 48 h and 72 h (at intervals of 24 h) additional same amounts of $PdCl_2$ (0.50 g), $CuCl_2$ (1.68 g) and $NaHCO_3$ (0.50 g) were added 3 times. The stirring was continued for 20 h at room temp. The mixture was poured into sat NH_4Cl aq and extracted with ether. The ether soln was washed with sat $NaHCO_3$ aq, water and brine, dried ($MgSO_4$) and concentrated in vacuo to give 1.93 g of crude oil. This was purified by SiO_2 chromatography followed by distillation to give 1.60 g (84 %) of **6**, b.p. 89~92°/5 Torr; n_D^{23} 1.4304; $[\alpha]_D^{19}$ -22.9° (c=1.5, $CHCl_3$); νmax 1720 (s), 1370 (s), 1240 (s), 1170 (s), 1105 (s) cm^{-1}; δ (CCl_4) 0.95 (3H, t, J=7 Hz), 1.27 (6H, s), 1.3~1.9 (6H, m), 2.02 (3H, s), 2.15~2.55 (2H, m), 3.2~3.6 (2H, br.s); (Found: C, 66.70; H, 10.06. Calc for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35 %). (b) (4R,5R)-Isomer: In the same manner as discribed above, **5'** (1.94 g, 7.0 mmol) gave 1.71 g (81 %) of **6'**, b.p. 84~86°/3.5 Torr; n_D^{24} 1.4310; $[\alpha]_D^{24}$ +22.5° (c=1.0, $CHCl_3$). The IR and ^{1}H NMR spesctra of **6'** were identical with those of **6**.

4-Ethyl-2,2-dimethyl-5-(4-trimethylsilyloxy-3-pentenyl)-1,3-dioxolane **7** contaminated with a small amount of **8**. (a) (4S,5S)-Isomer: To a soln of Me_3SiCl (1.5ml, 12 mmol) and Et_3N (3.3 ml, 24mmol) in 15 ml of DMF was added 0.87 g (4.0 mmol) of **6** at 45° and the mixture was heated under reflux. After 24 h Me_3SiCl (1.5 ml) and Et_3N (3.3 ml)were added. Then after 48 h same amounts of Me_3SiCl (1.5 ml) and Et_3N (3.3 ml) were added and the refluxing and stirring were continued for 12 h. After cooling, the mixture was diluted with n-pentane and washed with cold sat $NaHCO_3$ aq (x 2). The organic layer was washed rapidly with cold 1N-HCl aq and cold $NaHCO_3$ aq, dried ($MgSO_4$) and concentrated in vacuo to give 1.45 g of crude mixture of silyl ether **7** and terminal olefin silyl ether **8**. This was employed directly in the next step. An analytical sample was obtained by SiO_2 chromatography and distillation. b.p. 98~102°/4 Torr; n_D^{21} 1.4374; $[\alpha]_D^{21}$ -36.1° (c=1.1, Et_2O); νmax 1680 (m), 1265 (m), 1255 (s), 1180 (m), 1105 (m) cm^{-1}; δ (CCl_4) 0.18 (9H, S), 0.97 (3H, t, J=7 Hz), 1.36 (6H, s), 1.73 (3H, s), 1.25~2.4 (6H, m), 3.58 (2H, br.s), 3.9~4.6 (1H, m). (Found: C, 62.44; H, 10.28. Calc for $C_{15}H_{30}O_3Si$: C, 62.88; H, 10.56%). (b) (4R,5R)-Isomer: In the same manner as discribed above, 1.50 g (7.0 mmol) of **6'** gave 2.10 g of crude mixture of silyl ethers **7'** and **8'**. This was employed directly in the next step.

4-Ethyl-2,2-dimethyl-5-(4-oxo-3-phenylselenopentyl)-1,3-dioxolane **9**. (a) (4S,5S)-Isomer: PhSeCl (0.96 g, 5 mmol) was dissolved in 70 ml of CH_2Cl_2 under Ar and cooled to 0°. To that soln was added 0.40 g (5 mmol) of pyridine. After stirring for 30 min, 1.25 g of the crude mixture of **7** and **8** in CH_2Cl_2 (10 ml) was added and the mixture was stirred for 2 h at 5°. Then the mixture was diluted with CH_2Cl_2 and washed with sat $CuSO_4$ aq, water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo to give 1.8 g of crude oil. This was purified by SiO_2 (500 g) chromatography. Elution with benzene-ether gave a small amount (160 mg) of **10** and 1.05 g (70 % from **6**) of pure **9**; n_D^{22} 1.5256; $[\alpha]_D^{22}$ +26.5° (c=1.3, $CHCl_3$); νmax 1705 (s), 1580 (w), 1440 (m), 1380 (m), 1370 (m), 1240 (m), 1170 (m), 1105 (m), 740 (s), 695 (m) cm^{-1}; δ (CCl_4) 0.93 (3H, t, J=7 Hz), 1.28 (6H, s), 1.1~2.1 (6H, m), 2.20 (3H, s), 3.1~3.8 (3H, m), 7.0~7.6 (5H, m). (Found: C, 58.51; H, 7.12. Calc for $C_{18}H_{26}O_3Se$: C, 58.53; H, 7.11 %). (b) (4R,5R)-Isomer: In the same manner as discribed above, 2.10 g of the mixture of silyl ethers, **6'** and **7'**, gave 390 mg of **10'** and 1.59 g (62 % from **6'**) of pure **9'**, $n_D^{23.5}$ 1.5251; $[\alpha]_D^{23.5}$ +15.8° (c=1.3, $CHCl_3$);Although the $[\alpha]_D$ value of **9'** is inconsistent with that of **9**, this was thought to be due to the difference in the isomeric ratio at C-3. (Found: C, 58.51; H, 7.17. Calc for $C_{18}H_{26}O_3Se$: C, 58.53; H, 7.11 %). The IR and ^{1}H NMR spectra of **9'** were almost identical with those of **9**.

exo-7-Ethyl-5-methyl-4-phenylseleno-6,8-dioxabicyclo[3.2.1]octane **11**. (a) (1S,4RS,5R,7S)-Isomer: p-TsOH H_2O (380 mg) and 2~3 drops of water were added to a stirred soln of **9** (790 mg, 2.14 mmol) in ether (8 ml) at room temp. After stirring for 3 h, the mixture was diluted with ether. The ether soln was washed with sat $NaHCO_3$ aq, water and brine, dried ($MgSO_4$) and concentrated in vacuo to give 637 mg (96 %) of **11**. n_D^{23} 1.5540; $[\alpha]_D^{23}$ -86.8° (c=1.6, $CHCl_3$); νmax 1580 (m), 1380 (m), 1235 (m), 1185 (m), 1170 (s), 1025 (s), 995 (m), 965 (s), 870 (m), 855 (s), 740 (s), 690 (m) cm^{-1}; δ (CCl_4) 0.89 (3H, t, J=7 Hz), 1.63 and 1.51 (total 3H, each s), 1.1~2.5 (6H, m), 3.05 (1H, m), 3.6~3.9 (1H, m), 4.0 (1H, br.s), 7.0~7.3 (3H, m), 7.3~7.7 (2H, m). (Found: C, 57.58; H, 6.53. Calc for $C_{15}H_{20}O_2Se$: C, 57.88; H, 6.49 %). (b) (1R,4RS,5S,7R)-Isomer: In the same manner as discribed above, 1.37 g (3.71 mmol) of **9'** gave 1.15 g (99%) of **11'**, n_D^{24} 1.5554; $[\alpha]_D^{24}$ +66.9° (c=1.8, $CHCl_3$). (Found: C, 57.99; H, 6.51. Calc for $C_{15}H_{20}O_2Se$: C, 57.88; H, 6.49 %). The IR and ^{1}H NMR spectra of **11'** were almost identical with those of **11**.

exo-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]oct-3-ene **1**. (a) (1S,5R,7S)-Isomer: To a soln of **11** (610 mg, 1.96 mmol) in 15 ml of dry CH_2Cl_2 was slowly added 445 mg (80 % purity, 2.06 mmol) of MCPBA at 20°. After stirring for 3 h at this temp, the mixture was washed with 10 % Na_2SO_3 aq, sat $NaHCO_3$ aq (x 2) and brine, dried ($MgSO_4$) and concentrated under atm press. The residue was purified by SiO_2 chromatography and distillation to give 145 mg (48 %) of **1**, b.p. 90~92°/52 Torr; n_D^{24} 1.4472; $[\alpha]_D^{24}$ +91.5° (c=1.0, $CHCl_3$); ORD (c=0.02, n-pentane, 25°C) $[\alpha]_{600}$ +250, $[\alpha]_D$ +250, $[\alpha]_{500}$ +275, $[\alpha]_{450}$ +330, $[\alpha]_{400}$ +400, $[\alpha]_{350}$ +520, $[\alpha]_{320}$ +700, $[\alpha]_{300}$ +820, $[\alpha]_{280}$ +1000, $[\alpha]_{260}$ +1260; νmax 3060 (w), 2980 (m), 2950 (m), 1640 (w), 1460 (w), 1425 (m), 1395 (m), 1380 (m), 1345 (w), 1315 (w), 1255 (s), 1200 (s), 1185 (m), 1150 (m), 1130 (m), 1115 (m), 1090 (m), 1065 (m), 1045 (s), 1025 (m), 1019 (s), 1005 (m), 965 (s), 925 (w), 905 (s), 885 (w), 860 (s), 845 (m), 775 (m), 760 (w), 710 (m) cm^{-1}; δ (400 MHz, $CDCl_3$) 0.94 (3H, t, J=7.5 Hz), 1.53 (3H, s), 1.55~1.65 (2H, m), 1.85 (1H, dddd, J=17.9, 4.2, 1.8, 1.1 Hz), 2.65 (1H, dddd, J=17.9, 4.2, 2.3, 2.3 Hz), 3.79 (1H, td, J=6.3, 1.8 Hz), 4.24 (1H, dddd, J=4.2, 1.8, 1.8, 1.1 Hz), 5.71 (1H, dddd, J=9.5, 4.2, 2.3, 1.8 Hz), 5.82 (1H, ddd, J=9.5, 2.3, 1.8 Hz); ^{13}C NMR δ ($CDCl_3$) 9.78, 22.08, 27.49, 32.07, 77.10, 81.97, 102.49, 124.28, 132.03; GLC (Column, 5 % FFAP, 2 m x 4 mm at 100~200°(+2.5°/min); Carrier gas, N_2, 1.0 kg/cm^2): Rt 9.2 min (100 %)); (Found: m/z 154.0915. Calc for $C_9H_{14}O_2$: 154.0994). MS: m/z 155 (M^++1, 2 %), 154 (M^+, 17 %), 125 (40 %), 112 (21 %), 111 (100 %), 97 (25 %), 96 (38 %), 95 (50 %), 94 (19 %), 93 (15 %), 87 (12 %), 85 (34 %), 83 (57 %), 81 (32 %), 79 (12 %), 71 (15 %), 69 (21 %), 68 (23 %), 67 (18 %), 57 (71 %), 55 (19 %), 53 (15 %). (b) (1R,5S,7R)-Isomer: In the same manner as discribed above, 280 mg (0.90 mmol) of **11'** gave 58 mg (42 %) of **1'**, b.p. 75~80°/20 Torr;

n_D^{24} 1.4465; $[\alpha]_D^{24}$ -90.5° (c=0.95, $CHCl_3$); ORD (c=0.02, n-pentane, 25°C) $[\alpha]_{600}$ -380, $[\alpha]_D$ -370, $[\alpha]_{500}$ -400, $[\alpha]_{450}$ -450, $[\alpha]_{400}$ -500, $[\alpha]_{350}$ -675, $[\alpha]_{320}$ -825, $[\alpha]_{300}$ -990, $[\alpha]_{280}$ -1260, $[\alpha]_{260}$ -1755; Although the $[\alpha]_D$ values read from the above ORD measurements were very large (+250, -380), these were thought to be due to the experimental errors caused by the inadequate accuracy of the ORD mechine. GLC (Column, 5 % FFAP, 2 m x 4 mm at 100~200°(+2.5°/min); Carrier gas, N_2, 1.0 kg/cm^2): Rt 9.2 min (100 %); (Found: m/z 154.0954. Calc for $C_9H_{14}O_2$: 154.0994). The IR and ^1H NMR, ^{13}C NMR and mass spectra of 1' were identical with those of **1**.

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