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SYNTHESIS OF ALL OF THE FOUR POSSIBLE STEREOISOMERS OF 5-HYDROXY-4-METHYL-3-HEPTANONE (SITOPHILURE), THE AGGREGATION PHEROMONE OF THE RICE WEEVIL AND THE MAIZE WEEVIL†

KENJI MORI* and **TAKASHI EBATA**

Department of Agricultural Chemistry, The University of Tokyo,
Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

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Abstract--All of the four possible stereoisomers [(4S,5R)-, (4R,5S)-, (4R,5R)- and (4S,5S)-isomers] of 5-hydroxy-4-methyl-3-heptanone (sitophilure) were synthesized from methyl (R)-3-hydroxypentanoate of microbial origin.

Serious economic losses of stored cereal grains are caused by weevils of the genus Sitophilus. To develop pheromone-baited insect traps for the purpose of monitoring the pest populations, Burkholder and his co-workers investigated pheromone of Sitophilus weevils, and were successful in identifying a male-produced aggregation pheromone, common to the rice weevil (Sitophilus oryzae L.) and the maize weevil (S. zeamais Motsch.).[1,2] From the extracts amounting to 2800 insect day equivalents was obtained 7.5 μg of the pheromone named sitophilure, which was identified as (4R*,5S*)-5-hydroxy-4-methyl-3-heptanone **1a** contaminated with < 0.5 % of (4R*,5R*)-**2a** (Fig.1).[2] Due to the scarcity of the natural sitophilure, its absolute configuration remained unknown. Synthesis of all of the four possible stereoisomers of the pheromone [(4R,5S)-**1a**, (4S,5R)-**1a**, (4R,5R)-**2a** and (4S,5S)-**2a**] would provide a clue to clarify the stereochemistry-bioactivity relationship by sub-

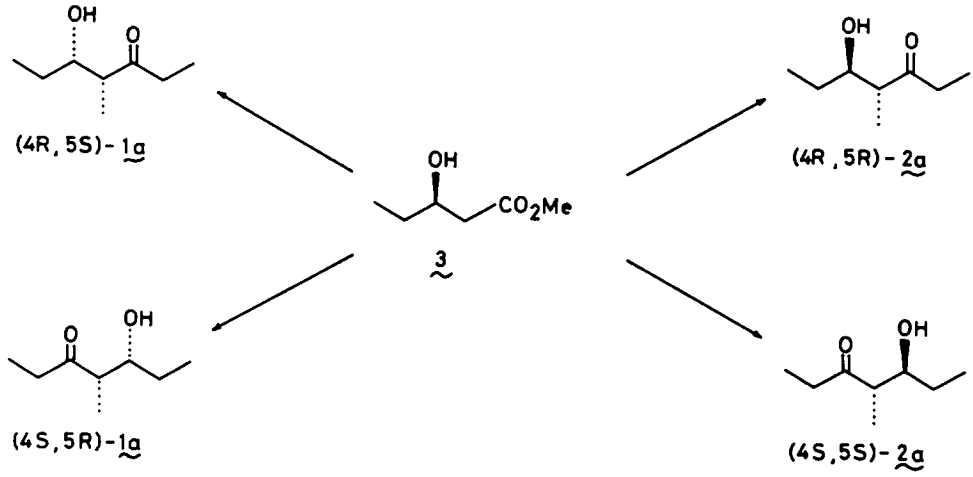

Fig.1. The target molecules and their synthetic plan.

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mitting all of the synthetic samples to careful bioassay. By the request of Prof. Burkholder, we undertook the synthesis of four optically pure stereoisomers of 5-hydroxy-4-methyl-3-heptanone.

Our strategy was to synthesize all of the four stereoisomers starting from a single chiral source, methyl (R)-3-hydroxypentanoate **3**. This hydroxy ester **3** was readily available in quantity by a microbial process,[3] and extensively employed by us for natural products syntheses.[4~7] The key-features of the present synthesis as shown in Fig.2 were : (i) a diastereoselective methylation of **3** to **4** according to Fráter,[8] (ii) non-stereoselective addition of EtMgBr to **6** to give a mixture of **7** and **8** followed by the separation of these two diastereomers, and (iii) oxidation of the unprotected OH group of the diol derivatives **7** and **8** to give the desired ketol enantiomers **2a**. For the synthesis of **1a**, a Mitsunobu inversion of **5b** to **10a** was followed by a sequence of reactions similar to that mentioned above [(ii) and (iii)].

Conversion of the hydroxy ester **3** to **5a** via **4** was reported previously by Mori and Watanabe.[4] After repeated recrystallization, **5a** was saponified with KOH aq to give **5b**. The alcohol **5b** was proved to be both chemically and optically pure (100 %) by analyzing it by GLC or by analyzing the corresponding (R)-α-methoxy-α-trifluoromethylphenylacetate (MTPA ester)[9] **5c** by HPLC. Silylation of **5b** with t-butyldimethylsilyl chloride (TBDMS Cl) gave **5d**, which was hydrogenolyzed over Pd-C to give **5e**. The Swern oxidation[10] of **5e** gave an unstable aldehyde **6**. This aldehyde **6** was immediately treated with EtMgBr to give a diastereomeric mixture of alcohols **7** and **8** (ca 2.4:1 ratio) in 72.9 % yield. These two isomers were readily separable by SiO_2 chromatography, and each of them was fully characterized. The stereostructures **7** and **8** assigned to the alcohols were based on their ^{13}C NMR spectral data. It is well known that ^{13}C NMR spectroscopy is an excellent tool for clarification of such syn- or anti-stereostructures as encountered in **7** or **8**.[11~13] When the relative configuration of the vicinal OH and Me in a compound like **7** or **8** is anti, its methine carbon (CHMe) resonance generally appears downfield of the corresponding resonance of the syn-isomer.[11~13] In the present case, the more polar isomer showed a CHMe signal at 42.5 ppm, while the less polar one exhibited it at 37.1 ppm. We therefore deduced that the less polar isomer must be the syn-isomer **7** and the more polar one should be the anti-isomer **8**. Oxidation of **7** by the Swern method[10] was followed by deprotection of the TBDMS group to give (4R,5R)-**2a**, $[\alpha]_D^{23}$ -37.8° (ether), in 69.1 % yield from **7**. The ^{13}C NMR spectral data of (4R,5R)-**2a** (δ 13.9 for anti-CH_3, δ 51.2 for CHMe and δ 74.9 for CHOH) were in good accord with the data reported for (4R*,5R*)-**2a** (δ 13.9, 50.7, 74.9).[11] We then turned our attention to the conversion of **8** to (4S,5S)-**2a**. The OH group of **8** was protected to give the corresponding THP ether **9a** in 97.7 % yield. The TBDMS group of **9a** was then removed by treatment with $(n\text{-Bu})_4NF$ to furnish **9b** in 88.1 % yield. Finally the Swern oxidation of **9b** was followed by deprotection of the THP protective group to give (4S,5S)-**2a**, $[\alpha]_D^{22}$ +36.8° (ether), in 65.2 % yield. The overall yield of (4R,5R)-**2a** from **3** was 9.1 % in 13 steps, while that of (4S,5S)-**2a** from **3** was 3.1 % in 15 steps.

The next task was the synthesis of both the enantiomers of **1a**. Conversion of **5b** to **10b** was executed as reported previously employing the Mitsunobu inversion (**5b**→**10a**).[4] Both the chemical and optical purities of **10b** were confirmed to be 100 %.[4] The Swern oxidation of **10b** yielded an unstable aldehyde **11**, which was immediately treated with EtMgBr to give a diastereomeric mixture of alcohols **12** and **13** (ca 1:3 ratio) in 76.1 % yield. These two isomers were also readily separable by SiO_2 chromatography and fully characterized by ^{13}C NMR spectroscopy. Namely, the less polar isomer exhibited a CHMe signal at δ 41.6, and the more polar one showed it at δ 38.5. The less polar one was therefore the anti-isomer **12** and the more polar one was the syn-isomer **13**. Hereafter the synthesis followed the route described above for the synthesis of **2a**. Thus the anti-isomer **12** gave (4R,5S)-sitophilure **1a**, $[\alpha]_D^{20}$ -26.7° (ether), in 66.8 % yield. The ^{13}C NMR

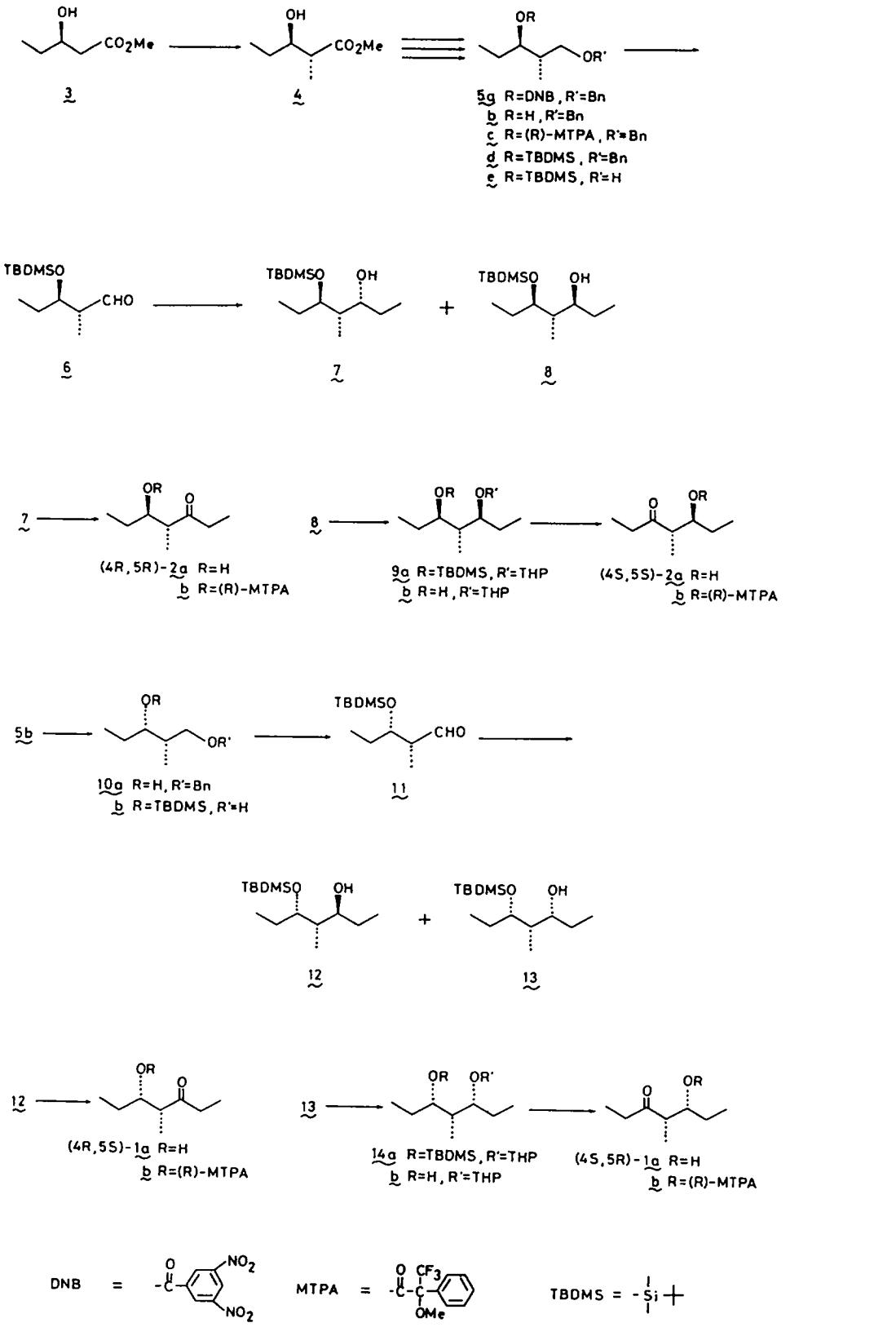

Fig.2. Synthesis of **1a** and **2a**.

spectral data of (4R,5S)-**1a** (δ 10.7 for syn-CH_3, δ 50.9 for CHMe and δ 73.4 for CHOH) were in good accord with the data reported for (4R*,5S*)-**1a** (δ 10.2, 49.7, 72.8).[11] The syn-isomer **13** was converted to (4S,5R)-sitophilure **1a**, $[\alpha]_D^{20}$ +27.0° (ether), in 49.4 % yield via **14a** and **14b**. The mass spectra of the enantiomers of **1a** were entirely identical to those reported for the natural sitophilure[1] and for (4R*,5S*)-**1a**.[2] The overall yield of (4R,5S)-**1a** from **3** was 2.0 % in 13 steps and that of (4S,5R)-**1a** from **3** was 4.3 % in 15 steps.

GLC analyses of synthetic **1a** and **2a** revealed their chemical purities to be > 98 %. Their corresponding (R)-MTPA esters **1b** and **2b** were analyzed by both ^1H and ^{19}F NMR spectroscopy. The results were listed in Table 1. The NMR spectrum of each of the (R)-MTPA esters showed no contamination with any other isomers. The chemical as well as optical purities of each of the isomers were therefore thought to be > 98 %.

Table 1. ^1H and ^{19}F NMR chemical shift values[a] of (R)-MTPA esters of the four isomers of 5-hydroxy-4-methyl-3-heptanone

	500 MHz ^1H NMR (OCH_3)[b]	470 MHz ^{19}F NMR (CF_3)[c]
(4S,5R)-**1b**	3.49 ppm	71.48 ppm
(4R,5S)-**1b**	3.47	71.54
(4S,5S)-**2b**	3.46	71.58
(4R,5R)-**2b**	3.45	71.65

a) measured on a Bruker AM-500 spectrometer in C_6D_6

b) TMS was used as an internal standard.

c) $CFCl_3$ was used as an external standard.

In summary, we synthesized the enantiomers of the pheromone components of the rice weevil and the maize weevil (**1a** and **2a**) employing methyl (R)-3-hydroxypentanoate **3** as a single chiral source. The biological studies on our synthetic stereoisomers of **1a** and **2a** were carried out by Prof. W. E. Burkholder and will be published elsewhere in due course.

EXPERIMENTAL

All b.ps were uncorrected. IR spectra were measured as film on a Jasco IRA-102 spectrometer. ^1H NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer unless otherwise stated. ^1H NMR at 400 MHz spectra were recorded on a Jeolco JNM FX-400 spectrometer and those at 500 MHz were recorded on a Bruker AM-500 spectrometer. ^{13}C NMR spectra were measured on a Jeolco JNM FX-100 spectrometer at 25 MHz. Optical rotations were measured on a Jasco DIP-140 polarimeter. GLC analyses were performed on a Yanaco G-180 gas chromatograph. GLC-MS were measured on a JMS-DX 300 apparatus.

(2S,3R)-2-Methylpentan-1,3-diol 1-benzyl ether **5b**. To a stirred and ice-cooled soln of **5a** (6.43 g, 16.0 mmol) in THF-EtOH (1:1, 50 ml) was added dropwise N KOH aq (21 ml, 21 mmol). The red-violet-coloured reaction mixture was stirred for 2 h at 0° and concentrated in vacuo to remove THF and EtOH. The residue was extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled to give 3.20 g (97.6 %) of pure **5b**, b.p. 115~117°/1.1 Torr; n_D^{25} 1.4947; $[\alpha]_D^{25}$ +21.2° (c=1.05, C_6H_6); νmax 3480 (br), 3090 (w), 3060 (m), 2990 (s), 2960 (s), 2900 (s), 1500 (m), 1455 (m), 1365 (m), 1095 (s), 975 (m), 735 (m), 700 (s) cm^{-1}; δ (CCl_4) 0.86 (3H, d, J=6 Hz), 0.91 (3H, t, J=6 Hz), 1.1~2.0 (3H, m), 2.71 (1H, br.s), 3.1~3.6 (3H, m), 4.41 (2H, s), 7.21 (5H, s). GLC (Column, PEG 20M, 50 m x 0.25 mm at 160°; Carrier gas, N_2, 1.0 kg/cm^2): Rt 33.75 min (single peak), (Found: C, 74.62; H, 9.61. Calc for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68 %).

Determination of the optical purity of **5b**. Both the crude and purified **5b** were converted to the corresponding (R)-MTPA esters **5c** in the usual manner[9] and analysed by HPLC (Column, NUCLEOSIL®50-5, 25 cm x 4.6 mm ; Solvent, n-hexane-THF-MeOH (10000:100:1), 1.1 ml/min; Detected at 254 nm),(before purification) Rt 23.2 min (94.8 %), 25.2 min (5.2 %); (after purification) Rt 25.8 min (single peak). The optical purity of crude **5b** was therefor 89.6 % and that of purified **5b** was 100 %.

(2S,3R)-3-t-Butyldimethylsilyloxy-2-methyl-1-pentanol benzyl ether **5d**. Imidazole (2.28 g, 33.5 mmol) and TBDMSCl (3.27 g, 21.7 mmol) were added to a stirred soln of **5b** (3.11 g, 15.0 mmol) in dry DMF (30 ml). The mixture was stirred overnight at

room temp, poured into ice-water (200 ml) and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled to give 4.58 g (95.2 %) of **5d**, b.p. 118~120°/0.1 Torr; n_D^{25} 1.4709; $[\alpha]_D^{25}$ -6.00° (c=0.87, $CHCl_3$); νmax 3100 (w), 3060 (w), 2990 (s), 2960 (s), 2910 (m), 2880 (s), 1500 (w), 1460 (m), 1100 (s), 1065 (s), 835 (s), 775 (s) cm^{-1}; δ (CCl_4) 0.00 (6H, s), 0.6~1.1 (15H, m, containing 0.88, 9H, s), 1.15~2.15 (3H, m), 3.05~3.90 (3H, m), 4.38 (2H, s), 7.21 (5H, s). (Found: C, 70.74; H, 10.56. Calc for $C_{19}H_{34}O_2Si$: C, 70.75; H, 10.62 %).

(2S,3R)-3-t-Butyldimethylsilyloxy-2-methyl-1-pentanol **5e**. 10 % Pd-C (500 mg) was added to a soln of **5d** (4.50 g, 14.0 mmol) in EtOAc (100 ml) and the suspension was shaken under H_2 at room temp until the H_2 uptake ceased. The mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was distilled to give 3.15 g (97.2 %) of **5e**, b.p. 81~82.5°/2 Torr; n_D^{25} 1.4377; $[\alpha]_D^{25}$ -15.4° (c=0.97, $CHCl_3$); νmax 3390 (br), 2980 (s), 2950 (s), 2900 (m), 2880 (m), 1465 (m), 1070 (m), 1030 (s), 1015 (s), 1005 (s), 835 (s), 770 (s) cm^{-1}; δ (CCl_4) 0.08 (6H, s), 0.7~1.2 (15H, m, containing, 0.90, 9H, s), 1.25~2.10 (3H, m), 2.91 (1H, br.s), 3.20~3.85 (3H, m). (Found: C, 61.88; H, 12.14. Calc for $C_{12}H_{28}O_2Si$: C, 62.01; H, 12.14 %).

(3R,4S,5R)-5-t-Butyldimethylsilyloxy-4-methyl-3-heptanol **7** and its (3S,4S,5R)-isomer **8**. To a cooled (-70°) and stirred soln of oxalyl chloride (2.46 g, 19.4 mmol) in CH_2Cl_2 (35 ml) was added dropwise a soln of DMSO (2.02 g, 25.9 mmol) in CH_2Cl_2 (8 ml) under Ar. The mixture was stirred for 2 min at -70°, and then a soln of **5e** (3.00 g, 12.9 mmol) in CH_2Cl_2 (10 ml) was added dropwise with stirring. After 50 min at -70°, Et_3N (6.53 g, 6.47 mmol) was added dropwise and stirring was continued for 15 min at this temp. The mixture was allowed to warm to 0°, stirred for 20 min at this temp and partitioned between a mixture of C_6H_6-ether (4:1, 50 ml) and water (50 ml). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in ether (50 ml), filtered to remove the insoluble material. The filtrate was concentrated in vacuo to give a crude aldehyde **6**. This product **6** was immediately used for the next step without further purification. A soln of **6** in dry ether (15 ml) was added dropwise to a soln of EtMgBr, which was prepared in the usual manner from EtBr (4.23 g, 38.8 mmol) and Mg (931 mg, 38.8 mg atom) in dry ether (30 ml), with stirring and ice-cooling. The stirring was continued for 15 min. The mixture was then poured into ice and sat NH_4Cl aq and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography over SiO_2 (Fuji Davison BW-820MH, 60 g). Elution with n-hexane-ether (20:1~10:1) gave 1.73 g (51.5 %) of **7** and 720 mg (21.4 %) of **8**. **7**: b.p. 90~91°/3 Torr; n_D^{23} 1.4391; $[\alpha]_D^{23}$ -10.3° (c=0.94, $CHCl_3$); νmax 3550 (br), 2990 (s), 2960 (s), 2900 (m), 2880 (m), 1380 (m), 1040 (s), 1005 (s), 850 (sh), 835 (s), 815 (sh), 790 (sh), 775 (s) cm^{-1}; δ (CCl_4) 0.69 (6H, s), 0.6~1.1 (18H, m, containing 0.90, 9H, s), 1.15~2.10 (5H, m), 2.62 (1H, br.s), 3.42~3.90 (2H, m). ^{13}C-NMR δ (25 MHz, $CDCl_3$) -4.80, -4.31, 9.94, 10.6, 11.2, 18.0, 25.9, 27.5, 27.8, 37.1, 71.7, 80.1. GLC (Column, PEG 20M, 50 m x 0.25 mm at 130°; Carrier gas, N_2, 1.0 kg/cm^2): Rt 7.88 min (single peak). (Found: C, 64.53; H, 12.10. Calc for $C_{14}H_{32}O_2Si$: C, 64.56; H, 12.38 %). **8**: b.p. 86~87°/3 Torr; n_D^{23} 1.4417; $[\alpha]_D^{23}$ -15.0° (c=0.91, $CHCl_3$); νmax 3460 (br), 2980 (s), 2950 (s), 2900 (m), 2880 (m), 1465 (m), 1105 (m), 1095 (m), 1070 (m), 1065 (m), 1035 (m), 1015 (m), 870 (m), 835 (s), 775 (s) cm^{-1}; δ (CCl_4) 0.06 (6H, s), 0.63~1.11 (18H, m, containing 0.89, 9H, s), 1.21~2.22 (6H, m), 3.0~3.9 (2H, m). ^{13}C-NMR δ (25 MHz, $CDCl_3$) -4.61, -4.29, 8.99, 9.60, 12.6, 18.1, 25.9, 26.5, 27.0, 42.5, 75.2, 77.0; GLC (Column, PEG 20M, 50 m x 0.25 mm at 130°; Carrier gas, N_2, 1.0 kg/cm^2): Rt 9.00 min (single peak). (Found: C, 64.14; H, 12.37. Calc for $C_{14}H_{32}O_2Si$: C, 64.56; H, 12.38 %).

(4R,5R)-5-Hydroxy-4-methyl-3-heptanone **2a**. To a cooled (-70°) and stirred soln of oxalyl chloride (1.06 g, 8.31 mmol) in CH_2Cl_2 (15 ml) was added dropwise a soln of DMSO (810 mg, 10.4 mmol) in CH_2Cl_2 (4 ml) under Ar. The mixture was stirred for 5 min at -70°, and then a soln of **7** (1.08 g, 4.15 mmol) in CH_2Cl_2 (5 ml) was added dropwise with stirring. After 50 min at -70°, Et_3N (2.10 g, 20.8 mmol) was added dropwise and the stirring was continued for 15 min at this temp. The mixture was allowed to warm to 0°, stirred for 20 min at this temp and partitioned between a mixture of C_6H_6-ether (4:1, 30 ml) and water (30 ml). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in ether (30 ml) and filtered to remove the insoluble material. The filtrate was concentrated in vacuo to give a crude product. This was immediately used for the next step without further purification. The crude product was mixed with $(n\text{-}Bu)_4NF$ soln in THF (1 M, 12.5 ml, 12.5 mmol) at 0°. After stirring for 3 h at room temp, the mixture was concentrated in vacuo to remove THF. The residue was diluted with water (10 ml) and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Fuji Davison BW-820MH, 60g). Elution with n-hexane-ether (10:1~1:1) gave (4R,5R)-**2a**. This was distilled to give 413 mg (69.1 %) of pure (4R,5R)-**2a**, b.p. 93~95°/17 Torr; n_D^{23} 1.4324; $[\alpha]_D^{23}$ -37.8° (c=1.20, ether); νmax 3480 (br), 3000 (s), 2960 (s), 2900 (m), 1713 (s), 1465 (m), 1415 (m), 1380 (m), 1115 (m), 970 (s) cm^{-1}; δ (400 MHz, C_6D_6) 0.79 (3H, d, J=7 Hz), 0.88 (3H, t, J=7 Hz), 0.92 (3H, t, J=7 Hz), 1.21 (1H, ddq, J=14, 8, 7 Hz), 1.30 (1H, ddq, J=14, 3.5, 7 Hz), 2.02 (1H, dq, J=17.5, 7 Hz), 2.08 (1H, dq, J=17.5, 7 Hz), 2.40 (1H, br.s), 3.41~3.50 (1H, m). ^{13}C-NMR δ (25 MHz, C_6D_6) 7.66, 10.0, 13.9, 27.8, 36.1, 51.2, 74.9, 215.1; GLC (Column, PEG 20M, 50 m x 0.25 mm at 130°; Carrier gas, N_2, 1.0 kg/cm^2): Rt 5.2 min (> 99 %); MS m/z 126 (M^+-18, 12 %), 115 (15 %), 97 (9 %), 86 (27 %), 70 (30 %), 69 (11 %), 59 (14 %), 56 (100 %, base peak), 54 (22 %). HI-MS 126.1068 (M^+-18, calc for $C_8H_{14}O$; 126.1044).

(3S,4S,5R)-4-Methylheptane-3,5-diol 3-THP, 5-t-butyldimethylsilyl ether **9a**. PPTS (50 mg, 0.2 mmol) was added to a soln of **8** (700 mg, 2.69 mmol) and dihydropyran (452 mg, 5.38 mmol). The mixture was stirred overnight at room temp. It was then diluted with ether. The organic layer was washed with sat $NaHCO_3$ aq, water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Fuji Davison BW-820MH, 30 g). Elution with n-hexane-ether (20:1~10:1) gave **9a**. This was distilled to give 905 mg (97.7 %) of pure **9a**, b.p. 110~111°/3 Torr; n_D^{23} 1.4456; $[\alpha]_D^{23}$ 0° (c=0.9, $CHCl_3$); νmax 2970 (sh), 2960 (s), 2900 (m), 2880 (m), 1075 (s), 1065 (s), 1030 (s), 1020 (s), 995 (s), 835 (s), 770 (s) cm^{-1}; δ (CCl_4) 0.02 (6H, s), 0.60~1.05 (18H, m, containing 0.88, 9H, s), 1.18~2.20 (11H, m), 3.11~4.15 (4H, m), 4.35~4.60 (1H, m). (Found: C, 66.25; H, 11.76. Calc for $C_{19}H_{40}O_3Si$: C, 66.22; H, 11.70 %).

(3R,4S,5S)-4-Methylheptane-3,5-diol 5-THP ether **9b**. **9a** (890 mg, 2.59 mmol) was mixed with a THF soln of $(n\text{-}Bu)_4NF$ (1 M, 25.9 ml, 25.9 mmol). This was stirred and heated under reflux overnight. After concentration in vacuo, the residue was diluted with water and extracted with ether. The ether layer was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Fuji Davison BW-820MH, 18 g). Elution with n-hexane-ether (10:1~5:1) gave **9b**. This was distilled to give 524 mg (88.1 %) of pure **9b**, b.p. 107~109°/3 Torr; n_D^{23} 1.4565; $[\alpha]_D^{23}$ +18.5° (c=1.37, $CHCl_3$); νmax 3450 (br), 2980 (s), 2960 (s), 2890 (m), 2860 (sh), 1205 (m), 1170 (m), 1130 (m), 1115 (m), 1075 (m), 1025 (s), 995 (s) cm^{-1}; δ (CCl_4) 0.6~1.15 (9H, m), 1.15~2.10 (11H, m), 2.5~4.1 (5H, m), 4.4~4.8 (1H, m). (Found: C, 67.48; H,

11.34. Calc for $C_{13}H_{26}O_3$: C, 67.78; H, 11.38 %).

(4S,5S)-5-Hydroxy-4-methyl-3-heptanone **2a.** **9b** (505 mg, 2.20 mmol) was oxidized by the same manner as described above for the preparation of (4R,5R)-**2a**. To a soln of oxidized product in MeOH (5ml) was added PPTS (50 mg, 0.2 mmol) at room temp. After stirring for 4 h, this was diluted with ether (30 ml), washed with 50 % sat NaCl aq for three times and dried ($MgSO_4$). After concentration in vacuo, the residue was chromatographed over SiO_2 (Fuji Davison BW-820MH, 7 g). Elution with n-hexane-ether (10:1~5:1) gave (4S,5S)-**2a**. This was distilled to give 206 mg (65.2 %) of pure (4S,5S)-**2a**, b.p. 69~74° (bath temp)/3 Torr; n_D^{22} 1.4329; $[\alpha]_D^{22}$ +36.8° (c=1.25, ether); GLC (Column, PEG 20M, 50 m x 0.25 mm at 130°; Carrier gas, N_2, 0.9 kg/cm^2): Rt 5.9 min (97.9 %), 6.5 min [2.1 %, (4R,5S)-isomer]. HI-MS: m/z 126.1056 (M^+-18, calc for $C_8H_{14}O$; 126.1044).

(3S,4S,5S)-5-t-Butyldimethylsilyloxy-4-methyl-3-heptanol **12** and its (3S,4S,5R)-isomer **13.** In the same manner as described above for the preparation of (3R,4S,5R)-**7** and (3R,4S,5S)-**8**, **10b** (1.80 g, 7.76 mmol) was converted to 396 mg (19.6 %) of **12** and 1.14 g (56.4 %) of **13**. **12**: b.p. 91~92°/4 Torr; n_D^{21} 1.4400; $[\alpha]_D^{21}$ -21.7° (c=0.83, $CHCl_3$); νmax 3510 (br), 2950 (s), 2900 (s), 2870 (s), 1255 (s), 1065 (sh), 1045 (s), 1000 (s), 835 (s), 790 (sh), 775 (s) cm^{-1}; δ (CCl_4) 0.08 (6H, s), 0.64~1.08 (18H, m, containing 0.90, 9H, s), 1.16~1.80 (5H, m), 3.00 (1H, br.s), 3.20~3.85 (2H, m). ^{13}C-NMR δ (25 MHz, $CDCl_3$) -4.51, -4.36, 8.92, 11.3, 13.3, 18.0, 24.5, 25.9, 27.8, 41.6, 74.5, 79.1. GLC (Column, PEG 20M, 50 m x 0.25 mm at 130°; Carrier gas, N_2, 1.0 kg/cm^2): Rt 4.4 min (single peak). (Found: C, 64.22; H, 12.18. Calc for $C_{14}H_{32}O_2Si$: C, 64.56; H, 12.38 %). **13**: b.p. 95~96°/5 Torr; n_D^{21} 1.4426; $[\alpha]_D^{21}$ +32.8° (c=0.81, $CHCl_3$); νmax 3430 (br), 2950 (s), 2900 (s), 2870 (s), 1250 (s), 1160 (sh), 1105 (s), 1070 (s), 1035 (s), 1005 (s), 830 (s), 770 (s) cm^{-1}; δ (CCl_4) 0.08 (6H, s), 0.64~1.05 (18H, m, containing 0.89, 9H, s), 1.12~1.82 (5H, m), 2.05 (1H, br.s), 3.30~3.81 (2H, m). ^{13}C-NMR δ (25 MHz, $CDCl_3$) -4.60, -3.69, 5.52, 9.82, 10.5, 18.0, 25.9, 27.5, 28.0, 38.5, 76.6, 79.0. GLC (Column, PEG 20M, 50 m x 0.25 mm at 130°; Carrier gas, N_2, 1.0 kg/cm^2): Rt 7.0 min (single peak). (Found: C, 64.44; H, 12.08. Calc for $C_{14}H_{32}O_2Si$: C, 64.56; H, 12.38 %).

(4R,5S)-5-Hydroxy-4-methyl-3-heptanone [(4R,5S)-sitophilure] **1a.** In the same manner as described above for the preparation of (4R,5R)-**2a**, **12** (700 mg, 2.69 mmol) was converted to 259 mg (66.8 %) of (4R,5S)-**1a**, b.p. 80~82°/6 Torr; n_D^{20} 1.4379; $[\alpha]_D^{20}$ -26.7° (c=1.52, ether); νmax 3470 (br), 3000 (s), 2960 (s), 2900 (s), 1710 (s), 1465 (s), 1380 (m), 1355 (m), 1105 (m), 1035 (m), 975 (s) cm^{-1}; δ (400 MHz, C_6D_6) 0.85 (3H, t, J=7 Hz), 0.89 (3H, t, J=7 Hz), 0.90 (3H, d, J=7 Hz), 1.13 (1H, ddq, J=4, 14, 7 Hz), 1.37 (1H, ddq, J=8, 14, 7 Hz), 1.92 (1H, dq, J=17.5, 7 Hz), 2.00 (1H, dq, J=17.5, 7 Hz), 2.07 (1H, dq, J=3.5, 7 Hz), 2.40 (1H, br.s), 3.58~3.64 (1H, m). ^{13}C-NMR δ (25 MHz, C_6D_6) 7.78, 10.7, 10.9, 27.8, 35.1, 50.9, 73.4, 214.9; MS m/z 143 (M^+-1, 0.1 %), 129 (2 %), 126 (M^+-18, 23 %), 115 (13 %), 97 (23 %), 86 (59 %), 70 (33 %), 69 (21 %), 59 (29 %), 58 (20 %), 56 (100 %, base peak), 54 (28 %). HI-MS; m/z 126.1043 (M^+-18, calc for $C_8H_{14}O$; 126.1044).

(3R,4S,5S)-4-Methylheptane-3,5-diol 3-THP, 5-t-butyldimethylsilyl ether **14a.** In the same manner as described above for the preparation of (3S,4S,5R)-isomer **9a**, **13** (597 mg, 2.30 mmol) was converted to 769 mg (97.3 %) of pure **14a**, b.p. 138~140°/6 Torr; n_D^{21} 1.4481; $[\alpha]_D^{21}$ -7.11° (c=0.73, $CHCl_3$); νmax 2980 (s), 2960 (s), 2870 (s), 1465 (m), 1150 (m), 1115 (m), 1075 (s), 1035 (s), 1025 (s), 1000 (s), 835 (s), 775 (s) cm^{-1}; δ (CCl_4) 0.02 (6H, s), 0.6~1.05 (18H, m, containing 0.88, 9H, s), 1.15~2.10 (11H, m), 3.1~4.1 (4H, m), 4.38~4.68 (1H, m). (Found: C, 66.04; H, 11.78. Calc for $C_{19}H_{40}O_3Si$: C, 66.22; H, 11.70 %).

(3S,4S,5R)-4-Methylheptane-3,5-diol 5-THP ether **14b.** In the same manner as described above for the preparation of (3R,4S,5S)-isomer **9b**, **14a** (750 mg, 2.18 mmol) was converted to 416 mg (83.0 %) of pure **14b**, b.p. 110~114°/6 Torr; n_D^{22} 1.4564; $[\alpha]_D^{22}$ -13.6° (c=0.82, $CHCl_3$); νmax 3490 (br), 2980 (s), 2955 (s), 2895 (s), 1170 (m), 1115 (m), 1075 (s), 1030 (s), 995 (s), 960 (m) cm^{-1}; δ (CCl_4) 0.82 (3H, d, J=7 Hz), 0.85 (3H, t, J=7 Hz), 0.89 (3H, t, J=7 Hz), 1.1~2.1 (11H, m), 2.80 (1H, br.s), 3.25~4.15 (4H, m), 4.45~4.75 (1H, m). (Found: C, 67.52; H, 11.37. Calc for $C_{13}H_{26}O_3$: C, 67.78; H, 11.38 %).

(4S,5R)-5-Hydroxy-4-methyl-3-heptanone [(4S,5R)-sitophilure] **1a.** In the same manner as described above for the preparation of (4S,5S)-**2a**, **14b** (476 mg, 2.07 mmol) was converted to 182 mg (61.2 %) of pure (4S,5R)-**1a**, b.p. 90~105° (bath temp)/5 Torr; n_D^{20} 1.4372; $[\alpha]_D^{20}$ +27.0° (c=1.24, ether); GLC (Column, PEG 20M, 50 m x 0.25 mm at 130°; Carrier gas, N_2, 1.1 kg/cm^2): Rt 4.7 min [0.6 %, (4R,5R)-isomer] 5.0 min (99.4 %). HI-MS: m/z 126.1050 (M^+-18, calc for $C_8H_{14}O$; 126.1044).

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