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SYNTHESIS OF BOTH THE ENANTIOMERS OF LARDOLURE, THE AGGREGATION PHEROMONE OF THE ACARID MITE, LARDOGLYPHUS KONOI†

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Abstract -- Both the enantiomers of lardolure were synthesized in 100 % optical purity and 99.6 % diastereomeric purity by use of Fráter's diastereoselective alkylation as the key-step. Since (1R,3R,5R,7R)-enantiomer showed the same ORD sign and bioactivity as those shown by the natural pheromone, the structure of lardolure was established unambiguously as (1R,3R,5R,7R)-1,3,5,7-tetramethyldecyl formate.

Our recent synthetic study directed toward the elucidation of the stereochemistry of lardolure,[1] the aggregation pheromone of the acarid mite, Lardoglyphus konoi,[2] enabled us to propose (1R,3R,5R,7R)-stereochemistry for the pheromone, as depicted in **1a**. This proposal was based on our determination of the relative stereochemistry of lardolure as (1R*,3R*,5R*,7R*), and Y. Kuwahara's assignment of the (R)-absolute configuration at C-1 of this pheromone.[1,2] In the present paper, we report the synthesis of both the enantiomers of **1a** in order to confirm the proposed stereochemistry.

Our synthetic plan for lardolure **1a** is shown in Fig. 1. Previously we found that a lactone **6**, having the same relative configuration among the three Me substituents as C-1~C-6 moiety of **1a**, could be prepared quite easily from mesitol in 100 % diastereomeric purity.[1] With this in mind, **1a** was disconnected into C-1~C-6 fragment **4** and C-7~C-10

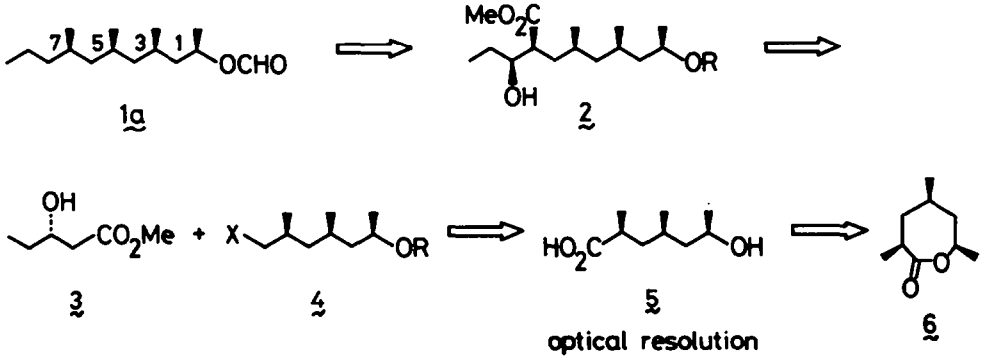

Fig. 1. Retrosynthetic analysis of lardolure.

†Pheromone Synthesis Part 93. Part 92, K. Mori and S. Kuwahara, Tetrahedron the preceding paper. The experimental part of this work was taken from a part of the forthcoming doctoral thesis of S. K. (1986).

fragment 3. Although lardolure **1a** might be prepared in optically active form also by consecutive applications of asymmetric aldol condensation, asymmetric alkylation of enolates and so on,[3] the ready availability of **6** in diastereomerically pure form and also that of **3** in 100 % optical purity (vide infra) made us choose the simpler and more convergent synthetic scheme as shown in Fig. 1. With regard to the diastereoselectivity of Fráter's asymmetric alkylation,[4,5] we had to make a preliminary experiment so as to investigate the reactivity of β-substituted alkylating agents such as **4**, because his experiments had been carried out only with highly reactive alkylating agents such as methyl iodide, allyl bromide and n-propyl bromide. Thus isobutyl iodide was chosen as a model compound. On alkylation with this iodide, racemic **3** gave the corresponding alkylated hydroxy ester in 60 % yield and GLC analysis of the product revealed that the diastereoselectivity of the reaction was 99 %. The higher stereoselectivity of this reaction than that of Fráter's examples (91~97%) might be explained by an increase in the bulkiness of the alkylating agent.

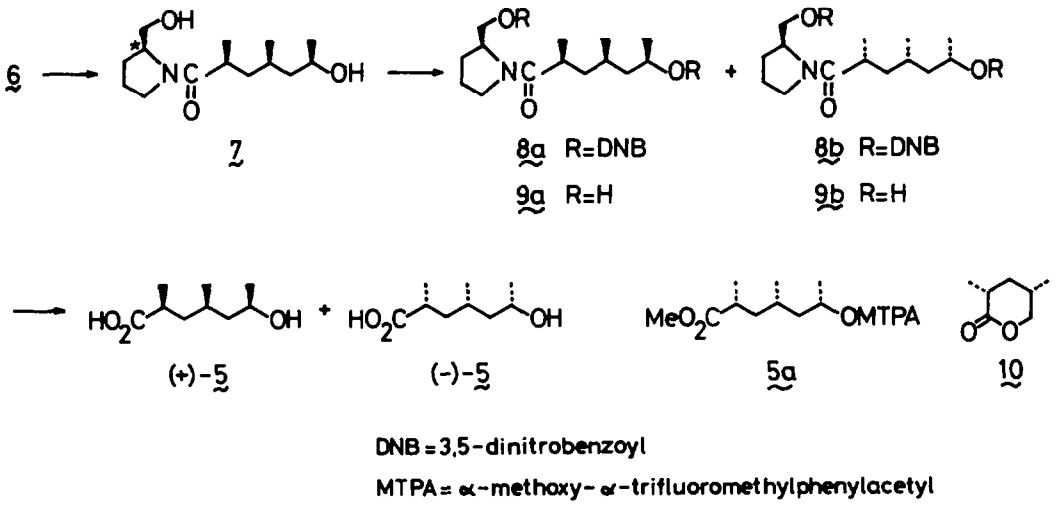

Fig. 2. Optical resolution of the racemic hydroxy acid **5**.

Both (R)- and (S)-**3** are known to be obtainable in 100 % optically pure state either by the microbial β-hydroxylation of pentanoic acid[6] or by the yeast reduction of octyl 3-oxopentanoate[7], respectively, coupled with recrystallization of their corresponding 3,5-dinitrobenzoates.[8,9] The most serious problem in our plan is therefore how to resolve the hydroxy acid **5**, which can be derived from **6**. Several attempts to resolve **5** or its derivatives were made in vain by using either classical or chromatographic methods. Finally, we succeeded in the clean optical resolution of **5** by chromatographic method as shown in Fig. 2. Ring-opening of **6** with (S)-prolinol[10] gave **7** as a diastereomeric mixture in 91 % yield. Although this mixture gave a single spot on TLC, the corresponding bis-3,5-dinitrobenzoates could be separated by SiO_2 chromatography to give more polar **8a** and less polar **8b** in 47% and 50% yield from **7**, respectively. Methanolysis of **8a** gave **9a**, which was readily hydrolyzed with N-HCl[11] to afford a crystalline hydroxy acid (+)-**5** in 59 % yield from **8a**, m.p. 83~85°; $[\alpha]_D^{23}$ +4.3° ($CHCl_3$). In the same manner, **8b** was converted to (-)-**5** in 66 % yield, m.p. 83.5~85°; $[\alpha]_D^{23}$ -4.2° ($CHCl_3$). The optical purity of (-)-**5** was estimated to be 100 % by HPLC analysis of **5a**, and the absolute configurations of (+)-**5** and (-)-**5** were determined as those depicted in Fig. 2, by converting (-)-**5** to the known lactone **10**.[12]

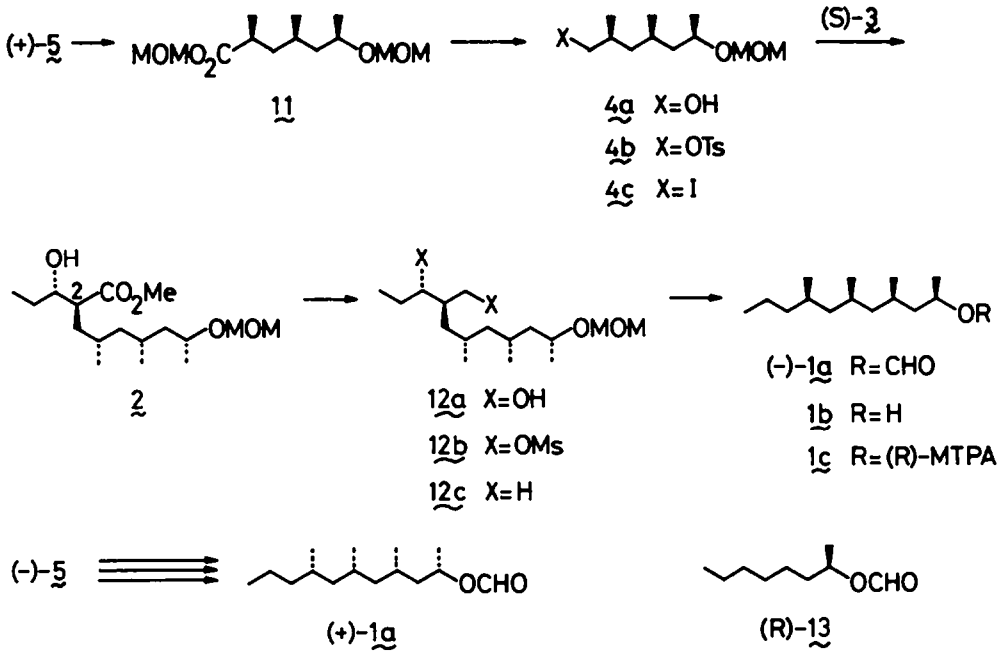

Fig. 3. Synthesis of the enantiomers of lardolure.

Having secured the optically active hydroxy acids (+)-5 and (-)-5, we turned our attention to the conversion of 5 to the alkylating agent **4c** followed by alkylation of 3 with it (Fig. 3). On treatment with MOM-Cl in $(i\text{-Pr})_2NEt$, the hydroxy acid (+)-5 gave **11**, which was reduced with LAH to give **4a**. The alcohol **4a** was treated successively with p-TsCl and NaI to afford (-)-**4c**, $[\alpha]_D^{24}$ -17.9° ($CHCl_3$), in 92 % yield from (+)-5. In the same manner, (+)-**4c**, $[\alpha]_D^{24}$ +18.1° ($CHCl_3$), was obtained in 87 % yield from (-)-5. Alkylation of (S)-3 with (-)-**4c** was carried out according to Fráter's procedure[8,9] to give 2 (R=MOM). In this case, the desired ester 2 and its C-2 epimer were not separable by GLC and the corresponding 3,5-dinitrobenzoates were indistinguishable by HPLC. We therefore could not determine the diastereomeric purity of **2**. However, our preliminary experiment mentioned before allowed us to estimate the diastereoselectivity of this reaction to be about 99 %. LAH reduction of 2 gave a diol **12a** in 79 % yield from (-)-**4c**. Dimesylation of **12a** followed by LAH reduction and acidic treatment afforded **1b** in 62 % yield from **12a**. Finally the alcohol **1b** was formylated with HCO_2H to give (1R,3R,5R,7R)-**1a**, in 91 % yield. Similarly, (1S,3S,5S,7S)-**1a**, was synthesized from (R)-3 and (+)-**4c** in 34 % overall yield. The IR, ^1H NHR, ^{13}C NMR and mass spectra of (+)-**1a** and (-)-**1a** were in good accord with those of the natural pheromone. The optical purities of our synthetic pheromones were determined to be 100 % by HPLC analyses of their corresponding MTPA esters **1c**. GLC analyses of (+)-**1a** and (-)-**1a** revealed their diastereomeric purities to be both 99.6 %. They were contaminated with only 0.4 % of their corresponding C-7 epimers, which resulted from the slightly incomplete diastereoselectivity in the course of the alkylation of 3 with **4c**.

The ORD spectra and bioactivities of our synthetic pheromones were compared with those of the natural pheromone. (1R,3R,5R,7R)-**1a** showed a positive Cotton effect in the range of about 200~240 nm, which was almost the same as that shown by the natural pheromone. On the other hand, (1S,3S,5S,7S)-**1a** showed a negative Cotton effect. Furthermore, only (1R,3R,5R,7R)-**1a** was bioactive. Therefore, we established the structure of lardolure

as (1R,3R,5R,7R)-1,3,5,7-tetramethyldecyl formate.

Finally a comment should be made on the sign of the specific rotation of lardolure enantiomers **1a**. We secured both the enantiomers of **1a** in quantities sufficient for accurate $[\alpha]_D$ measurements. The specific rotation of (1R,3R,5R,7R)-**1a** was shown to be $[\alpha]_D^{23}$ -3.4° (n-hexane), and that of its antipode was $[\alpha]_D^{23}$ +3.6° (n-hexane). According to Y. Kuwahara et al., the natural pheromone was dextrorotatory when measured with an ORD spectrometer, although the exact value at Na D-line could not be read at c=0.1 in n-hexane.[2] Our own ORD measurement at c=6.64 in n-hexane enabled us to read the $[\alpha]_D$ value of (1R,3R,5R,7R)-**1a** as -3.9°. However, at c=0.1 in n-hexane, we were unable to read the exact $[\alpha]_D$ value due to the small S/N ratio under that condition.

Y. Kuwahara et al. deduced the (R)-configuration at C-1 of natural lardolure basing partly on the comparison of the positive sign of rotation at Na D-line of the natural pheromone with the negative rotation of (S)-1-methylheptyl formate **13**.[2] We prepared both the enantiomers of **13**, and measured their rotations: (R)-**13**, $[\alpha]_D^{24}$ +5.6° (n-hexane); (S)-**13**, $[\alpha]_D^{24}$ -5.1° (n-hexane). It thus became clear that (1R,3R,5R,7R)-(-)-**1a** showed the sign of rotation opposite to that of (R)-(+)-**13**. Their ORD spectra, however, exhibited the same positive Cotton effect with a peak at 234 nm. We therefore reached to the well-known conclusion that we should compare not the sign of the rotations but the shape of the ORD spectra of two compounds for the purpose of stereochemical correlation. Reinvestigation was made also on the ^{1}H NMR studies on **1a** and **13** using a chiral shift reagent as reported by Y. Kuwahara et al. (see Experimental).[2] In agreement with their data, (1R,3R,5R,7R)-**1a** and (R)-**13** were shown to belong to the same stereochemical series with (R)-configuration at C-1. Y. Kuwahara's correct stereochemical assignment at C-1 was therefore the result of a combination of the sound interpretation of the ^{1}H NMR data of **1a** and **13** and the incorrect guess concerning the sign of the rotation of natural **1a**. The ORD spectral comparison must have been a better way. The difference in the sign of rotation at Na D-line of (1R,3R,5R,7R)-**1a** and that of (R)-**13** should be due to the effect of the three additional Me groups of **1a** on optical rotation.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films for oils or as nujol mulls for solids on a Jasco IRA-102 spectrometer. ^{1}H NMR spectra were recorded with TMS as an internal standard at 60 MHz in CCl_4 on a Hitachi R-24A spectrometer unless otherwise stated. ^{13}C NMR spectra were recorded at 25 MHz in $CDCl_3$ with TMS as an internal standard on a JEOL JNM FX-100 spectrometer. Optical rotations were measured on a Jasco DIP 140 polarimeter. ORD spectra were recorded on a Jasco J-20C spectropolarimeter. Mass spectra were recorded on a JEOL DX-303 spectrometer, or on a Hitachi RMU-6M spectrometer at 70 eV. GLC analyses were performed on a Yanaco G-180 gas chromatograph. Fuji gel BW 820-MH was used for SiO_2 column chromatography unless otherwise stated. HPLC analyses were performed on Nucleosil® 50-5 column (25 cm x 4.6 mm) by the detection at 254 nm.

N-[(2R*,4S*,6S*)-6-Hydroxy-2,4-dimethylheptanoyl]-(S)-prolinol **7**. A soln of **6** (12.0 g) and (S)-prolinol (8.6 g) in dry toluene (30 ml) was stirred for 32 h at 80~90°. The mixture was concentrated in vacuo. The residue was chromatographed over SiO_2 (Merck Kieselgel 60 Art 7734, 400 g; benzene-EtOAc) to give 17.9 g (91 %) of **7** as a viscous oil, νmax 3400 (s), 3000 (s), 2960 (s), 2900 (s), 1620 (s), 1470 (s), 1440 (s), 1055 (m), 760 (s) cm^{-1}; δ ($CDCl_3$) 0.90 (3H, d, J=6 Hz), 1.0~1.3 (6H, m), 1.3~2.3 (9H, m), 2.35~2.97 (1H, m), 3.1~4.0 (5H, m), 4.03 (2H, s, OH), 4.0~4.4 (1H, m); m/z 258 (M^++1), 257 (M^+), 256 (M^+-1), 242 (M^+-15), 227 (M^+-30), 226 (M^+-31).

N-[(2S,4R,6R)-2,4-Dimethyl-6-(3,5-dinitrobenzoyloxy)heptanoyl]-O-(3,5-dinitrobenzoyl)-(S)-prolinol **8a** and N-[(2R,4S,6S)-2,4-Dimethyl-6-(3,5-dinitrobenzoyloxy)heptanoyl]-O-(3,5-dinitrobenzoyl)-(S)-prolinol **8b**. 3,5-Dinitrobenzoyl chloride (16.0 g) was added portionwise to a stirred and ice-cooled soln of **7** (7.0 g) in dry C_5H_5N (105 ml). The mixture was stirred for 2 h at room temp. It was poured into ice-sat $NaHCO_3$ aq and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with sat $NaHCO_3$, sat $CuSO_4$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Merck Kieselgel 60 Art 7734, 300 g; benzene-EtOAc) to give 18.7 g of a mixture of **8a** and **8b**. TLC analysis of it [Merck Kieselgel 60 F-254, developed with benzene-THF (8:1)]: Rf 0.43 (**8a**), 0.51 (**8b**). This mixture was separated by chromatography over SiO_2 [Merck Kieselgel 60 Art 9385, 800 g; benzene-THF (30:1)] to give 8.28 g (94 %) of **8a** and 9.57 g (quant) of **8b**. **8a** showed the following properties: νmax 3130 (m), 3000 (m), 2950 (m), 2900 (m), 1730 (s), 1635 (s), 1550 (s), 1350 (s), 1280 (s), 1175 (s), 760 (s), 725 (s) cm^{-1}; δ ($CDCl_3$) 0.8~1.25 (6H, m), 1.40 (3H, d, J=6 Hz), 1.25~2.35 (9H, m), 2.35~3.0 (1H, m), 3.4~3.9 (2H, m), 4.2~4.7 (3H, m), 5.0~5.65 (1H, m), 8.94~9.3 (6H, m). HPLC analyses of **8a** and **8b** [n-hexane-THF (4:1), 1.6 ml/min]: Rt 14.5 min (**8b**, single peak), 18.9 min (**8a**, single peak). The IR and NMR spectra of **8b** were almost the same as those of **8a**. These were employed in the next steps without further purifications.

6-Hydroxy-2,4-dimethylheptanoic acid **5**. (a) (2S,4R,6R)-(+)-Isomer: K_2CO_3 (0.26 g) was added to a soln of **8a** (29.2 g) in MeOH (350 ml) and THF (35 ml). The mixture was stirred for 80 min at room temp. After neutralization with p-TsOH H_2O, the

mixture was filtered and the filtrate was concentrated in vacuo. The residue was triturated with ether and the ether soln was concentrated in vacuo. The residue was chromatographed over SiO_2 (120 g, $CHCl_3$-THF) to give 13.6 g of **9a** as a viscous oil. This (13.6 g) was mixed with N-HCl aq and the mixture was stirred for 50 min under reflux. After cooling, the mixture was extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (100 g, benzene-EtOAc) and recrystallized from n-hexane-ether (10:1) to give 4.64 g (59 % from **8a**) of (+)-5 as needles, m.p. 83~85°; $[\alpha]_D^{23}$ +4.3° (c=8.50, $CHCl_3$); νmax 3330 (m), 2970 (s), 2940 (s), 2860 (s), 2600 (m), 1680 (s), 1450 (s), 1380 (m), 1280 (s), 1110 (s), 1090 (s) cm^{-1}; δ ($CDCl_3$) 0.88 (3H, d, J=6 Hz), 1.13 (2x3H, d, J=6 Hz), 1.3~2.0 (5H, m), 2.2~2.8 (1H, m), 3.5~4.1 (1H, m), 6.36 (2H, s, OH and COOH). (Found: C, 62.35; H, 10.34. Calc for $C_9H_{18}O_3$: C, 62.04; H, 10.41 %). (b) (2R,4S,6S)-(-)-Isomer: In the same manner as described above, **8b** (34.6 g) yielded 6.12 g (66 %) of (-)-5, as needles, m.p. 83.5~85°; $[\alpha]_D^{23}$ -4.2° (c=8.69, $CHCl_3$). (Found: C, 62.05; H, 10.25. Calc for $C_9H_{18}O_3$: C, 62.04; H, 10.41 %). Its IR and NMR spectra were identical with those of (+)-5. The corresponding (R)- and (S)-MTPA esters **5a** were prepared from the methyl ester of (-)-5 [obtained by the treatment of (-)-5 with CH_2N_2 in ether] and analyzed by HPLC [n-hexane-THF (40:1) 1.6 ml/min]: Rt 14.6 min [(R)-MTPA ester, single peak], Rt 12.6 min [(S)-MTPA ester, single peak]. Therefore the optical purity of (-)-5 was 100 %.

Conversion of (-)-5 to the known lactone **10**. The Me ester of (-)-5 (0.313 g) was oxidized with PDC (3.2 g) in DMF (6.4 ml) to give a keto ester (0.307 g). Baeyer-Villiger oxidation of the keto ester with excess CF_3CO_3H and Na_2HPO_4 (1.08 g) in CH_2Cl_2 (3.3 ml) gave an acetoxy acid (0.214 g), which was hydrolyzed with 2 N-NaOH aq (1.1 ml) in DMSO (2 ml) to give a δ-hydroxy acid (0.123 g). It was then cyclized as usual (p-TsOH H_2O, 0.02 g; benzene, 2 ml) to give **10** (0.075 g, as needles from n-hexane), m.p. 43~46°; $[\alpha]_D^{21}$ -41° (c=0.39, $CHCl_3$) [lit.[12] $[\alpha]_D^{25}$ -41.1° ($CHCl_3$)]; νmax 1740 (s), 1345 (m), 1210 (m), 1160 (s), 1110 (s), 1050 (m), 1040 (m) cm^{-1}; δ ($CDCl_3$) 0.97 (3H, d, J=6 Hz), 1.24 (3H, d, J=6 Hz), 1.5~2.9 (4H, m), 3.5~4.5 (2H, m).

Methoxymethyl 6-methoxymethoxy-2,4-dimethylheptanoate **11**. (a) (2S,4R,6R)-Isomer. MOM-Cl (5.0 ml) was added to a stirred and ice-cooled soln of (+)-5 (4.41 g) and (i-Pr)$_2$NEt (11.6 ml) in dry CH_2Cl_2 (40 ml). The mixture was stirred for 30 min at 0° and for 40 min at room temp. It was poured into ice-sat $NaHCO_3$ aq and extracted with ether. The ether soln was washed with water and brine, dried (K_2CO_3) and concentrated in vacuo to give 6.62 g of crude (2S,4R,6R)-**11**, νmax 2980 (s), 1740 (s), 1140 (s), 1090 (s), 1040 (s), 920 (s) cm^{-1}. This was employed in the next step without further purification. (b) (2R,4S,6S)-Isomer. In the same manner as described above, (-)-5 (4.0 g) yielded 6.1 g of crude (2R,4S,6S)-**11**. Its IR spectrum was identical with that of (2S,4R,6R)-**11**.

6-Methoxymethoxy-2,4-dimethyl-1-heptanol **4a**. (a) (2S,4R,6R)-Isomer. A soln of crude (2S,4R,6R)-**11** (6.62 g) in dry ether (20 ml) was added to a stirred and ice-cooled suspension of LAH (1.41 g) in dry ether (95 ml). The mixture was stirred for 70 min at room temp. The usual alkaline work-up gave 5.36 g of crude (2S,4R,6R)-**4a**, νmax 3450 (m), 2980 (s), 2950 (s), 1460 (m), 1380 (m), 1140 (m), 1100 (m), 1040 (s), cm^{-1}. This was employed in the next step without further purification. (b) (2R,4S,6S)-Isomer. In the same manner as described above, (2R,4S,6S)-**11** (6.1 g) yielded 5.0 g of crude (2R,4S,6S)-**4a**. Its IR spectrum was identical with that of (2S,4R,6R)-**4a**.

6-Methoxymethoxy-2,4-dimethylheptyl tosylate **4b**. (a) (2S,4R,6R)-Isomer. p-TsCl (8.7 g) was added to a soln of crude (2S,4R,6R)-**4a** (5.2 g) in dry C_5H_5N (40 ml) under ice-cooling. After stirring for 3.5 h at 0~5°, the mixture was poured into ice-water and extracted with ether. The ether soln was washed with sat $CuSO_4$ aq, water and brine, dried ($MgSO_4$) and concentrated in vacuo to give 9.1 g of crude (2S,4R,6R)-**4b**, νmax 2980 (m), 2950 (m), 1600 (w), 1360 (s), 1190 (s), 1180 (s), 1040 (s) cm^{-1}. This was employed in the next step without further purification. (b) (2R,4S,6S)-Isomer. In the same manner as described above, (2R,4S,6S)-**4a** yielded 9.0 g of crude (2R,4S,6S)-**4b**. Its IR spectrum was identical with that of (2S,4R,6R)-**4b**.

1-Iodo-6-methoxymethoxy-2,4-dimethylheptane **4c**. (a) (2S,4R,6R)-(-)-Isomer. $NaHCO_3$ (18 g) and NaI (8.0 g) were added to a soln of (2S,4R,6R)-**4b** (9.1 g) in acetone-DMF (2:1, 120 ml). The mixture was stirred overnight at 70°. It was poured into ice-water and extracted with ether. The ether soln was washed with 10 % $Na_2S_2O_3$ aq and brine, dried (K_2CO_3) and concentrated in vacuo. The residue was chromatographed over SiO_2 (80 g; n-hexane-ether) and distilled to give 7.11 g [92 % from (+)-5] of (2S,4R,6R)-(-)-**4c**, b.p. 78~83°/0.07 Torr; n_D^{24} 1.4766; $[\alpha]_D^{24}$ -17.9° (c=2.48, $CHCl_3$); νmax 2980 (s), 2950 (s), 1460 (m), 1380 (m), 1200 (m), 1140 (m), 1100 (m), 1040 (s), 920 (m), cm^{-1}; δ 0.90 (3H, d, J=5 Hz), 0.98 (3H, d, J=5 Hz), 1.12 (3H, d, J=6 Hz), 1.2~2.0 (6H, m), 2.95~3.3 (2H, m), 3.24 (3H, s), 3.4~3.9 (1H, m), 4.38 (1H, d, J=7 Hz), 4.54 (1H, d, J=7 Hz). (Found: C, 42.26; H, 7.40. Calc for $C_{11}H_{23}O_2I$: C, 42.05; H, 7.38 %). (b) (2R,4S,6S)-(+)-Isomer. In the same manner as described above, (2R,4S,6S)-**4b** (9.0 g) yielded 6.3 g [87 % from (-)-5] of (2R,4S,6S)-(+)-**4c**, b.p. 82~87°/0.08 Torr; n_D^{21} 1.4780; $[\alpha]_D^{22}$ +18.1° (c=2.66, $CHCl_3$). (Found: C, 42.48; H, 7.46. Calc for $C_{11}H_{23}O_2I$: C, 42.05; H, 7.38 %). Its IR and NMR spectra were identical with those of (+)-**4c**.

Methyl 2-(1'-hydroxypropyl)-8-methoxymethoxy-4,6-dimethylnonanoate **2**. (a) (2S,4S,6R,8R,1'S)-Isomer. A soln of LDA was prepared by the addition of a soln of n-BuLi (1.65 N in n-hexane, 56 ml) to a stirred and cooled soln of (i-Pr)$_2$NH (14 ml) in dry THF (82 ml) at 0° under Ar. To this mixture was added a soln of (S)-**3** (6.00 g) in dry THF (30 ml) over a period of 30 min at -78°. After stirring for 50 min at -30~-20°, a soln of (-)-**4c** (3.90 g) in dry THF (15 ml) and dry HMPA (64 ml) was added to the mixture in one portion. It was then stirred for 1.5 h at -10~0°. The mixture was quenched with 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 chromatographed over SiO_2 (Merck Kieselgel 60 Art 9385, 400 g; n-hexane-EtOAc) to give 4.56 g of a mixture of (2S,4S,6R,8R,1'S)-**2** and (S)-**3**, νmax 3500 (m), 2980 (s), 2950 (s), 1740 (s), 1170 (s), 1040 (s) cm^{-1}. The ratio of (2S,4S,6R,8R,1'S)-**12** and (S)-**3** was about 1:1 by NMR analysis. This mixture was employed for the next step without further purification. (b) (2R,4R,6S,8S,1'R)-Isomer. In the same manner as described above, (R)-**3** (2.95 g) and (+)-**4c** (1.91 g) yielded 1.72 g of a mixture of (2R,4R,6S,8S,1'R)-**2** and (R)-**3**. Its IR spectrum was very similar to that of the above mixture.

2-(6'-Methoxymethoxy-2',4'-dimethylheptyl)-1,3-pentanediol **12a**. (a) (2R,3S,2'S,4'R,6'R)-Isomer. A soln of the mixture of (2S,4S,6R,8R,1'S)-**2** and (S)-**3** (4.30 g) in dry ether (20 ml) was added to a stirred and ice-cooled suspension of LAH (1.2 g) in dry ether (60 ml). The mixture was stirred for 80 min at room temp. The usual alkaline work-up gave an oil, which was chromatographed over SiO_2 (70 g; n-hexane-EtOAc) to give 2.70 g [79 % from (-)-**4c**] of (2R,3S,2'S,4'R,6'R)-**12a**. νmax 3400 (m), 2980 (s), 2950 (s), 1460 (m), 1380 (m), 1140 (m), 1100 (m), 1040 (s) cm^{-1}; δ 0.7~1.0 (9H, m), 1.12 (3H, d, J=6 Hz), 1.2~2.0 (11H, m), 3.29 (3H, s), 3.2~4.0 (4H, m), 3.83 (2H, s, OH), 4.45 (1H, d, J=7 Hz); MS: m/z 243 (M^+-18-29), 241 (M^+-18-31), 229 (M^+-61). (b) (2S,3R,2'R,4'S,6'S)-Isomer. In the same manner as described above, the mixture of (2R,4R,6S,8S,1'R)-**2** and (R)-**3** (1.62 g) yielded 1.11 g [67 % from (+)-**4c**] of (2S,3R,2'R,4'S,6'S)-**12a**. Its IR, NMR and MS spectra were identical with those of (2R,3S,2'S,4'R,6'R)-**12a**.

8-Mesyloxy-7-mesyloxymethyl-2-methoxymethoxy-4,6-dimethylundecane **12b**. (a) (2R,4R,6S,7R,8S)-Isomer. MsCl (2.2 ml) was added to a stirred and ice-cooled soln of (2R,3S,2'S,4'R,6'R)-**12a** (2.55 g) and Et_3N (5.2 ml) in dry CH_2Cl_2 (43 ml). The mixture was stirred overnight at 0~5°. It was poured into ice-water and extracted with ether. The ether soln was washed

with sat $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated in vacuo to give 4.20 g of crude (2R,4R,6S,7R,8S)-**12b**, νmax 2980 (s), 2950 (s), 1360 (s), 1180 (s), 1040 (s), 915 (s) cm^{-1}. This was employed in the next step without further purification. (b) (2S,4S,6R,7S,8R)-Isomer. In the same manner as described above, (2S,3R,2'R,4'S,6'S)-**12a** (1.00 g) yielded 1.40 g of crude (2S,4S,6R,7S,8R)-**12b**. Its IR spectrum was identical with that of (2R,4R,6S,7R,8S)-**12b**.

2-Methoxymethoxy-4,6,8-trimethylundecane **12c**. (a) (2R,4R,6R,8R)-Isomer. A soln of (2R,4R,6S,7R,8S)-**12b** (4.20 g) in dry THF (45 ml) was added to a stirred suspension of LAH (1.0 g) in dry THF (40 ml). The mixture was stirred overnight under reflux. The usual alkaline work-up gave an oil, which was chromatographed over SiO_2 (Merck Lobar® column; n-hexane-EtOAc) to give 1.90 g of (2R,4R,6R,8R)-**12c**, νmax 2980 (s), 2940 (s), 2860 (m), 1460 (m), 1380 (m), 1150 (m), 1140 (m), 1100 (m), 1045 (s), 920 (m) cm^{-1}; δ 0.7~1.0 (12H, m), 1.10 (3H, d, J=6 Hz), 1.0~1.9 (13H, m), 3.22 (3H, s), 3.4~3.9 (1H, m), 4.38 (1H, d, J=7 Hz), 4.50 (1H, d, J=7 Hz); MS: m/z 243 (M^+-15), 227 (M^+-31), 213 (M^+-45), 197 (M^+-61). (b) (2S,4S,6S,8S)-Isomer. In the same manner as described above, (2S,4S,6R,7S,8R)-**12b** (1.40 g) yielded 0.52 g of (2S,4S,6S,8S)-**12c**. Its IR and NMR spectra were identical with those of (2R,4R,6R,8R)-**12c**.

4,6,8-Trimethyl-2-undecanol **1b**. (a) (2R,4R,6R,8R)-Isomer. To a soln of (2R,4R,6R,8R)-**12c** (1.75 g) in MeOH (45 ml) was added conc HCl (0.3 ml). The mixture was stirred under reflux for 1.5 h. It was poured into ice-sat $NaHCO_3$ aq and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromtographed over SiO_2 (Merck Kieselgel 60 Art 9385, 60 g; n-hexane-EtOAc) and distilled to give 1.08 g [62 % from (2R,3S,2'S,4'R,6'R)-**12a**] of (2R,4R,6R,8R)-**1b**, b.p. 77~78°/0.25 Torr; n_D^{24} 1.4389; $[\alpha]_D^{23}$ -12.8° (c=5.42, $CHCl_3$); νmax 3360 (m), 2980 (s), 2940 (m), 2860 (m), 1460 (m), 1380 (m), 1155 (m), 1115 (m) cm^{-1}; δ 0.7~1.0 (12H, m), 1.12 (3H, d, J=6 Hz), 1.0~2.0 (13H, m), 1.74 (1H, s, OH), 3.5~4.0 (1H, m). (Found: C, 78.22; H, 13.88. Calc for $C_{14}H_{30}O$: C, 78.43; H, 14.11 %). (b) (2S,4S,6S,8S)-Isomer. In the same manner as described above, (2S,4S,6S,8S)-**12c** (0.515 g) yielded 0.389 g [58 % from (2S,3S,2'R,4'S,6'S)-**12a**] of (2S,4S,6S,8S)-**1b**, b.p. 95~96°/1.2 Torr; n_D^{24} 1.4387; $[\alpha]_D^{23}$ +12.7° (c=5.60, $CHCl_3$). (Found: C, 78.21; H, 14.04. Calc for $C_{14}H_{30}O$: C, 78.43; H, 14.11 %). Its IR and NMR spectra were identical with those of (2R,4R,6R,8R)-**1b**.

1,3,5,7-Tetramethyldecyl formate **1a**. (a) (1R,3R,5R,7R)-(-)-Isomer. A mixture of (2R,4R,6R,8R)-**1b** (0.60 g) and HCO_2H (>98 % purity, 15 ml) was stirred for 1.5 h at 65°. It was poured into ice-sat $NaHCO_3$ aq and extracted with ether. The ether soln was washed with sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Merck Kieselgel 60 Art 9385, 55 g; n-hexane-ether) and distilled to give 0.62 g (91 % of (1R,3R,5R,7R)-**1a**, b.p. 84~87°/1.0 Torr; n_D^{23} 1.4290; $[\alpha]_D^{23}$ -3.4° (c=7.86, n-hexane), $[\alpha]_D^{23}$ -1.7° (c=10.5, $CHCl_3$); ORD (c=0.163, n-hexane) $[\alpha]_{205}^{22}$ -980°, $[\alpha]_{222}^{22}$ 0°, $[\alpha]_{236}^{22}$ +430°; νmax 2980 (s), 2940 (s), 2890 (m), 2860 (m), 1735 (s), 1465 (m), 1380 (m), 1190 (s), 1130 (m) cm^{-1}; δ (100MHz, $CDCl_3$) 0.8~0.95 (12H, m), 1.26 (3H, d, J=6 Hz), 0.95~1.9 (13H, m), 5.0~5.35 (1H, m), 8.05 (1H, s). ^{13}C NMR: δ 14.42, 20.01, 20.30, 20.42, 20.65, 20.94, 26.56, 27.35, 29.75, 39.02, 43.06, 45.37, 45.54, 69.06, 160.85; GLC (Column, OV-101, 50 m x 0.25 mm at 100° + 1°/min; Carrier gas, N_2, 25 ml/min) Rt 82.4min [99.6 %, (1R,3R,5R,7R)-**1a**], 83.5 min [0.4 %, (1R,3R,5R,7S)-epimer] : (Found: m/z 196.2209. Calc for $C_{14}H_{28}$: 196.2191). (Found: C, 74.00; H, 12.35. Calc for $C_{15}H_{30}O_2$: C, 74.32; H, 12.48 %). The ^1H NMR, ^{13}C NMR and mass spectra were identical with those of the natural pheromone. (b) (1S,3S,5S,7S)-(+)-Isomer. In the same manner as described above, (2S,4S,6S,8S)-**1b** (0.30 g) yielded 0.30 g (88 %) of (1S,3S,5S,7S)-**1a**, b.p. 86~87°/1.2 Torr; n_D^{23} 1.4289; $[\alpha]_D^{23}$ +3.6°(c=5.98, n-hexane), $[\alpha]_D^{23}$ +1.8° (c=10.5, $CHCl_3$); ORD (c=0.114, n-hexane) $[\alpha]_{205}^{22}$ +1010°, $[\alpha]_{222}^{22}$ 0°, $[\alpha]_{236}^{22}$ -450°; GLC (Column, OV-101, 50 m x 0.25 mm at 100° + 1°/min; Carrier gas, N_2, 25 ml/min) Rt 82.4 min [99.6 %, (1S,3S,5S,7S)-**1a**], 83.5 min [0.4 %, (1S,3S,5S,7R)-epimer]. (Found: C, 74.03; H, 12.35. Calc for $C_{15}H_{30}O_2$: C, 74.32; H, 12.48 %). The ^1H NMR and ^{13}C NMR spectra were identical with those of (1R,3R,5R,7R)-**1a**.

Determination of the optical purity of (+)-**1a** and (-)-**1a**. Both (+)-**1a** and (-)-**1a** were converted to the corresponding (R)-MTPA ester **1c** and analyzed by HPLC [n-hexane-1,2-dichloroethane (200:1), 1.3 ml/min]: Rt 49.1 min [(1S,3S,5S,7S)-**1c**, single peak], 59.5 min [(1R,3R,5R,7R)-**1c**, single peak]. Therefore both (+)-**1a** and (-)-**1a** were shown to be optically pure.

ORD study of (1R,3R,5R,7R)-**1a** and (R)-1-methylheptyl formate **13**. (i) (1R,3R,5R,7R)-(-)-**1a**. At c=0.102 in n-hexane: $[\alpha]_{210}^{26}$ -706°, $[\alpha]_{220}^{26}$ 0°, $[\alpha]_{234}^{26}$ +427°, $[\alpha]_{250}^{26}$ +196°, $[\alpha]_{589}^{26}$ ~0° (data not legible); at c=6.64 in n-hexane: $[\alpha]_{300}^{23}$ +16°, $[\alpha]_{342}^{23}$ 0°, $[\alpha]_{589}^{23}$ -3.9°; lit.,[2] at c=0.1 in n-hexane: $[\alpha]_{205}^{25}$ -515°, $[\alpha]_{217}^{25}$ 0°, $[\alpha]_{235}^{25}$ +400°, $[\alpha]_{589}^{25}$ + (data not legible). (ii) (R)-1-Methylheptyl formate (R)-**13**: $[\alpha]_D^{23}$ +5.1° (neat, d_4^{24}=0.8551); $[\alpha]_D^{24}$ +5.6° (c=5.02, n-hexane), which was prepared from (R)-2-octanol: $[\alpha]_D^{24}$ -9.1° (neat, d_4^{24}=0.8133, Tokyo Kasei Co., Ltd.). ORD (c=0.177, n-hexane): $[\alpha]_{210}^{26}$ -322°, $[\alpha]_{217}^{26}$ 0°, $[\alpha]_{234}^{26}$ +441°, $[\alpha]_{250}^{26}$ +234°,$[\alpha]_{589}^{26}$ ~0° (data not legible). (S)-1-Methylheptyl formate (S)-**13**: $[\alpha]_D^{23}$ -4.7 ° (neat, d_4^{25}=0.8532); $[\alpha]_D^{24}$ -5.1° (c=5.10, n-hexane), which was prepared from (S)-2-octanol: $[\alpha]_D^{24}$ +8.9° (neat, d_4^{24}=0.8132, Tokyo Kasei Co., Ltd.).

NMR study of **1a** and **13** in the presence of $Eu(TFC)_3$. (i) A mixture of (1R,3R,5R,7R)-**1a** (15.3 mg), (1S,3S,5S,7S)-**1a** (29.0 mg) and $Eu(TFC)_3$ (33 mg, 0.2eq) in CCl_4 (0.3 ml). Chemical shifts of C-1 Me groups: δ 2.06 (3x0.65H, d, J=6 Hz), 2.11 (3x0.35H, d, J=6 Hz). This means that the C-1 Me group of (1R,3R,5R,7R)-**1a** has a larger δ value than that of (1S,3S,5S,7S)-**1a** in the presence of $Eu(TFC)_3$. (ii) A mixture of (R)-**13** (15.4 mg), (S)-**13** (24.4 mg) and $Eu(TFC)_3$ (45 mg, 0.2eq) in CCl_4 (0.3 ml). Chemical shifts of C-1 Me groups: δ 2.09 (3x0.61H, d, J=7 Hz), 2.13 (3x0.39H, d, J=7 Hz). In this case also, a doublet due to the C-1 Me group of the (R)-enantiomer was observed at a lower field.

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REFERENCES

1 K. Mori and S. Kuwahara, Tetrahedron, the preceding paper.
2 Y. Kuwahara, L. T. M. Yen, Y. Tominaga, K. Matsumoto and Y. Wada, Agric. Biol. Chem. **46**, 2283 (1982).
3 For reviews, see Asymmetric Synthesis (Edited by J. D. Morrison), Vol. 3, Academic Press, New York (1984).
4 G. Fráter, Helv. Chim. Acta **62**, 2825 (1979).
5 Idem., ibid. **62**, 2829 (1979).
6 J. Hasegawa, S. Hamaguchi, M. Ogura and K. Watanabe, J. Ferment. Technol. **59**, 257 (1981).
7 K. Mori, H. Mori and T. Sugai, Tetrahedron **41**, 919 (1985).
8 K. Mori and M. Ikunaka, ibid. **40**, 3471 (1984).
9 K. Mori and H. Watanabe, ibid. **41**, 3423 (1985).
10 D. Enders and H. Eichenauer, Chem. Ber. **112**, 2933 (1979).
11 D. A. Evans and J. M. Takacs, Tetrahedron Lett. **21**, 4233 (1980).
12 C. S. Chen, Y. Fujimoto and C. J. Sih, J. Am. Chem. Soc. **103**, 3580 (1981).