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STEREOCHEMISTRY OF LARDOLURE THE AGGREGATION PHEROMONE OF THE ACARID MITE, LARDOGLYPHUS KONOI[†]

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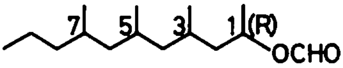
Abstract -- (1R,3R,5R,7R)-Stereochemistry was assigned to lardolure (1,3,5,7-tetramethyldecyl formate) on the basis of GLC comparison of the natural pheromone with the synthetic pheromones prepared in partially stereocontrolled manners.

Lardolure was isolated by Y. Kuwahara et al. as the aggregation pheromone of the acarid mite Lardoglyphus konoi (Sasa et Asanuma) (Acarina: Acaridae), a primary pest for stored products with high protein content such as dried meat and fish meal.[1] Its structure was determined spectroscopically as **1a** and confirmed by synthesizing a diastereomeric mixture of **1a**.[1] In addition, (R)-configuration was assigned to C-1 of **1a** by the comparison of the natural pheromone with (S)-1-methylheptyl formate. Their optical rotations as well as the NMR spectra measured in the presence of a chiral shift reagent were compared.[1] However, the relative stereochemistry of the pheromone **1a** remained unknown. In connection with our synthetic studies on optically active pheromones,[2] we became interested in establishing the stereochemistry of this pheromone.



1a

Because of the presence of four chiral centers in **1a**, eight diastereomers possessing (R)-configuration at C-1 are possible for the structure of lardolure. Therefore we must determine the relative configuration of lardolure. The key to this problem was found in Y. Kuwahara's observations:[1] (1) the synthesized mixture consisting of eight diastereomers of **1a** gave seven peaks when analyzed by capillary GLC; (2) among them, the peak having the shortest retention time coincided with that of the natural pheromone. By using these interesing observations, we planned to determine the stereochemical relationship among the chiral centers.

Our strategy is based on the following consideration: if a mixture consisting of 1,3-syn-diastereomers of **1a** can be prepared stereoselectively and the natural pheromone coincides in GLC retention time with one of them, it is possible to assign 1,3-syn-relationship to the natural pheromone. The same consideration is applicable to both C-3,5-

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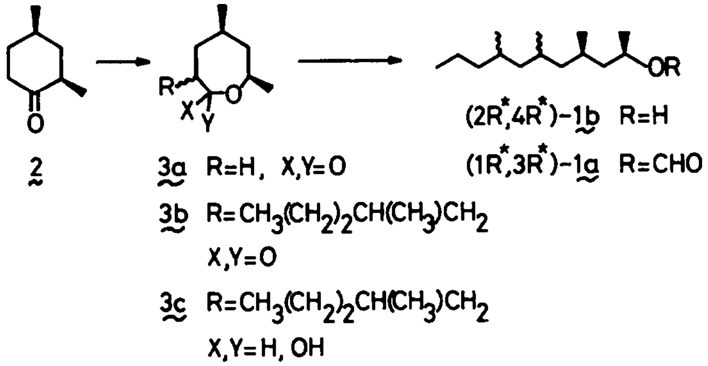
[†] Pheromone Synthesis Part 92. Part 91, K. Mori and T. Ebata, Tetrahedron in press. The experimental part of this work was taken from a part of the forthcoming doctral thesis of S. K. (1986).

relationship and C-5,7-relationship, so that it must be feasible to correlate the configuration of the four Me substituents of **1a**. In order to obtain 1,3-syn-dimethyl building blocks required for the preparation of 1,3-syn-**1a**, 3,5-syn-**1a** and 5,7-syn-**1a**, catalytic hydrogenation of polymethylphenols was chosen by virtue of its cis-selectivity and simplicity.

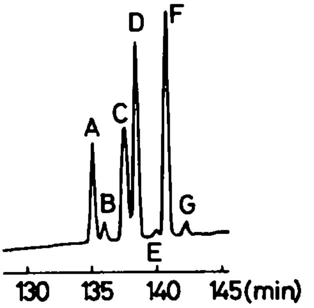
Our synthesis of 1,3-syn-lardolure (1R*,3R*)-**1a** is shown in Scheme 1. Catalytic hydrogenation of 2,4-dimethylphenol was followed by Jones' oxidation to give the known ketone **2** (cis:trans≈85:15).[3] On oxidation with MCPBA, this ketone gave **3a** in 94 % yield. Alkylation of **3a** with 1-iodo-2-methylpentane afforded **3b** in 51 % yield. This was reduced with DIBAL-H to give a mixture of a lactol **3c** and the corresponding hydroxy aldehyde. The Wolff-Kishner reduction of the mixture gave (2R*,4R*)-**1b**, which was esterified with HCO_2H to give 1,3-syn-lardolure (1R*,3R*)-**1a** in 63 % yield from **3b**. The result of its GLC analysis is shown in Fig. 1, where four large peaks and three small peaks can be seen clearly in agreement with Y. Kuwahara's observation. Since this synthesis started from the cis-rich ketone **2** (85:15), the four large peaks **A**, **C**, **D** and **F**, should be ascribed to 1,3-syn-**1a** and the three small peaks, **B**, **E** and **G**, to 1,3-anti-**1a**. Among them, peak **A** showed the same retention time as the peak of the natural pheromone by the coinjection analysis of (1R*,3R*)-**1a** with the natural pheromone. 1,3-syn-Relationship was therefore assigned to the natural pheromone.



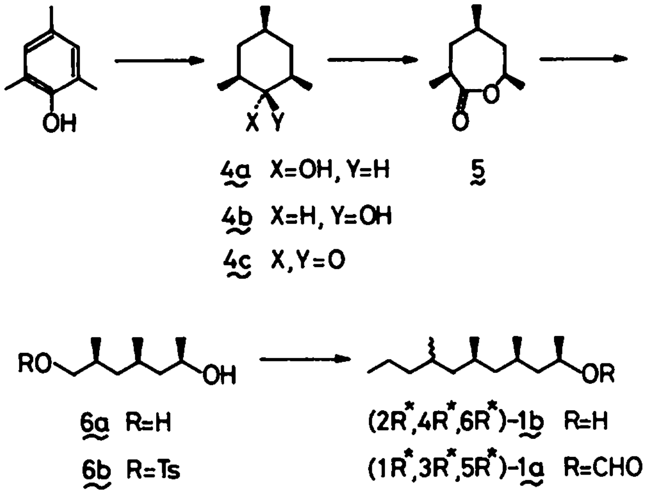
Scheme 1. Synthesis of 1,3-syn-lardolure.

Fig. 1. GLC separation of the isomers of 1,3-syn-lardolure.

(Column, OV-101, 50 m x 0.25 mm at 100° + 0.5°/min; Carrier gas, N_2, 28 ml/min)

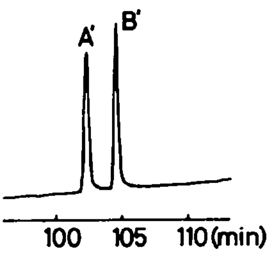


Next we turned our attention to the elucidation of the stereochemical relationship between C-3 and C-5 of **1a**. Since the relative configuration between C-1 and C-3 was already assigned to be syn, we decided to synthesize 1,3,5-syn-lardolure (1R*,3R*,5R*)-**1a** instead of 3,5-syn-lardolure (Scheme 2). Catalytic hydrogenation of mesitol gave a diastereomeric mixture of 2,4,6-trimethyl-1-cyclohexanol[4] containing **4a** (50 %) and **4b** (44 %). The mixture was purified by SiO_2 chromatography to give crystalline **4a** (35 % yield, mp. 68~70°) and oily **4b** (39 % yield). On oxidation with Jones' reagent, both **4a** and **4b** yielded **4c** as a single product in 89 % yield. In the ^{13}C NMR spectra of **4a**, **4b** and **4c**, only six peaks were observed reflecting their symmetrical structures. Baeyer-Villiger oxidation of **4c** gave **5** in 98 % yield. LAH reduction of **5** afforded a diol **6a** and its primary OH group was tosylated selectively to give **6b** in 66 % yield from **5**. Coupling of **6b** with 1-methylbutylmagnesium bromide[5] followed by esterification gave 1,3,5-syn-lardolure (1R*,3R*,5R*)-**1a** as a mixture of epimers at C-7 in 41 % yield from **6b**. As shown in Fig. 2, its gas chromatogram gave only two peaks (**A'** and **B'**) as expected, and peak **A'** was identical in retention time with peak **A** shown in Fig. 1 by the coinjection analysis of

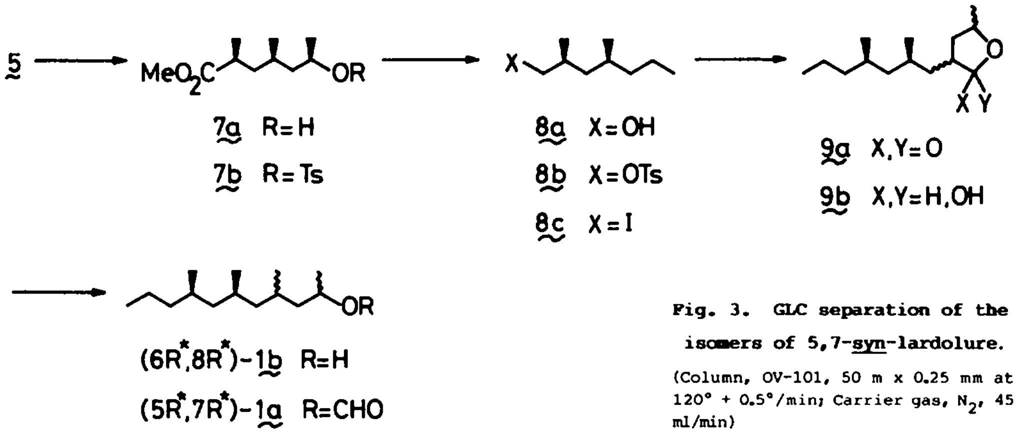


Scheme 2. Synthesis of 1,3,5-*syn*-lardolure.

Fig. 2. GLC separation of the isomers of 1,3,5-*syn*-lardolure.
(Column, OV-101, 50 m x 0.25 mm at 110° + 0.5°/min; Carrier gas, N_2, 27 ml/min)

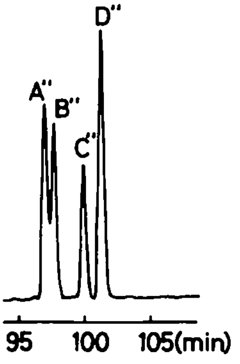


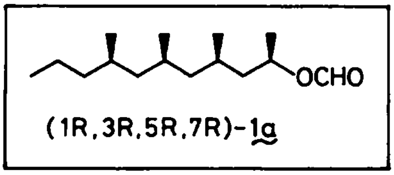
(1*R**,3*R**,5*R**)-1a with (1*R**,3*R**)-1a. Thus peak A' appeared at the same retention time as that of the natural pheromone, because peak A coincided in retention time with the peak of the natural pheromone. Since peak A' was due to one of the C-7 epimers of (1*R**,3*R**,5*R**)-1a, we reasoned that the natural pheromone also had (1*R**,3*R**,5*R**)-stereochemistry, i.e., 1,3,5-*syn*-relationship.



Scheme 3. Synthesis of 5,7-*syn*-lardolure.

Fig. 3. GLC separation of the isomers of 5,7-*syn*-lardolure.
(Column, OV-101, 50 m x 0.25 mm at 120° + 0.5°/min; Carrier gas, N_2, 45 ml/min)





Finally, we prepared 5,7-*syn*-lardolure (5R*,7R*)-**1a** to clarify the relative stereochemistry between C-5 and C-7 of **1a** (Scheme 3). Methanolysis of the lactone **5** gave **7a**. This hydroxy ester **7a** was treated successively with *p*-TsCl, LAH, *p*-TsCl and NaI to give **8c** in 76 % yield from **5** *via* **7b**, **8a** and **8b**. Alkylation of 4-pentanolide with the iodide **8c** gave a mixture of *cis*- and *trans*-**9a** in 50 % yield (*cis*:*trans*≈2:3). Reduction of this mixture with DIBAL-H was followed by the Wolff-Kishner reduction and esterification to give 5,7-*syn*-lardolure (5R*,7R*)-**1a** as a mixture of four diastereomers in 61 % yield from **9a**. As shown in Fig. 3, its gas chromatogram gave four peaks, **A"**, **B"**, **C"** and **D"**. The peak **A"** appeared at the same retention time as the peak **A** shown in Fig. 1. by the coinjection analysis of (5R*,7R*)-**1a** with (1R*,3R*)-**1a**. From the similar consideration as described for (1R*,3R*,5R*)-**1a**, the natural pheromone was proved to have 5,7-*syn*-stereochemical relationship.

On the basis of the three results described above, it was concluded that lardolure had 1,3,5,7-*syn*-relative stereochemistry. Furthermore, if we accept Y. Kuwahara's proposal concerning the (R)-configuration at C-1,[1] lardolure must be (1R,3R,5R,7R)-1,3,5,7-tetramethyldecyl formate (1R,3R,5R,7R)-**1a**.

From a biosynthetic point of view, lardolure is presumed to belong to polyketide-derived natural products. As a similar polyketide-derived natural product, 2,4,6,8-tetramethylundecanoic acid is known as the major component of the preen gland waxes of the greylag goose[6,7]. It is interesting to note that this acid also has (R)-configuration at every chiral center, i.e., (2R,4R,6R,8R)-stereochemistry.[8,9]

In conclusion, we propose (1R,3R,5R,7R)-stereochemistry for lardolure. In the following paper, the synthetic confirmation of this structure assignment for lardolure will be reported.

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. ^{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. GLC analyses were performed on a Yanaco G-180 gas chromatograph. Merck Kieselgel 60 Art 7734 was used for SiO_2 column chromatography unless otherwise stated.

(4R*,6R*)-4-Methyl-6-heptanolide **3a**. To a stirred mixture of 80 % MCPBA (3.9 g) and $NaHCO_3$ (1.9 g) in dry CH_2Cl_2 was added dropwise a soln of **2** (1.80 g) in dry CH_2Cl_2 (4 ml) at room temp. After stirring for 2.5 h, the precipitate was filtered off and the filtrate was washed with 10 % $NaHSO_3$ aq, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 1.90 g (94 %) of **3a**, b.p. 94~96°/4 Torr; n_D^{20} 1.4525; νmax 2960 (s), 2930 (s), 2870 (s), 1730 (vs), 1450 (s), 1190 (s), 1160 (s), 1090 (s) cm^{-1}; δ 0.92 (3H, d, J=6 Hz), 1.26 (3H, d, J=6 Hz), 1.3~2.1 (5H, m) 2.1~2.4 (2H, m), 4.0~4.7 (1H, m); GLC (Column, OV-101, 50 m x 0.25 mm at 110° + 0.5°/min; Carrier gas, N_2, 43 ml/min): Rt 31.8 min (83 %); *trans* isomer at 33.3 min (17 %). (Found: C, 67.15; H, 9.82. Calc for $C_8H_{14}O_2$: C, 67.57; H, 9.93 %).
(2R*S*,4R*,6R*)-4-Methyl-2-[(2R*S*)-2-methylpentyl]-6-heptanolide **3b**. A soln of LDA was prepared by the addition of a soln of *n*-BuLi (1.75 N in *n*-hexane, 27.6 ml) to a stirred and cooled soln of (*i*-Pr)$_2$NH (5.16 g) in dry THF (45 ml) at 0° under Ar. HMPA (48 ml) was added to the soln at -5~-10° and the mixture was cooled to -78°. To the resulting slurry was added dropwise a soln of **3a** (6.00 g) in dry THF (45 ml) over a period of 75 min. After stirring for 25 min, the mixture was warmed to -45°. To the soln was added a soln of 1-iodo-2-methylpentane (11 g) in dry THF (25 ml) at -45~-40°. The soln was allowed to stand for 2 days at -40°. It was then poured into ice-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 (11.01 g) was chromatographed over SiO_2 (500 g; *n*-hexane-EtOAc) and distilled to give 4.88 g (51 %) of **3b**, b.p. 93~95°/0.15 Torr; n_D^{23} 1.4554; νmax 2960 (s), 2930 (s), 2870 (s), 1730 (s), 1460 (m), 1380 (m), 1185 (s), 1115 (s) cm^{-1}; δ 0.89 (3H, t, J=6 Hz), 0.92 (2x3H, d, J=6 Hz), 1.28 (3H, d, J=6 Hz), 1.1~2.1 (12H, m), 2.2~2.8 (1H, m), 4.1~4.7 (1H, m). (Found: C, 74.42; H, 11.56. Calc for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58 %).
(2R*,4R*,6R*S*,8R*S*)-4,6,8-Trimethyl-2-undecanol (2R*,4R*)-**1b**. A soln of DIBAL-H in *n*-hexane [12 ml of 25 (w/v)% soln] was added to a stirred and cooled soln of **3b** (4.50 g) in dry toluene (130 ml) at -70° under Ar. After stirring for 30 min, sat NH_4Cl aq (10 ml) was added at -70°. The mixture was poured into ice-3N HCl and stirred for 30 min at room temp. It was extracted with ether. The ether soln was washed with sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 5.16 g of a mixture of **3c** and a hydroxy aldehyde, νmax 3400 (m), 2960 (s), 2930 (s), 2870 (m), 2700 (w), 1725 (m) cm^{-1}; δ 0.7~1.1 (9H, m), 1.1~2.4 (16H, m), 3.39 (1H, s, OH), 3.5~4.3 (1H, m), 4.47 (0.67H, d, J=7 Hz), 9.43 (0.33H, s, br). This was dissolved in diethylene glycol (24 ml). 80 % $N_2H_4 \cdot H_2O$ (6 g) was added to the soln and the mixture was heated under reflux for 1 h. KOH aq (6.0 g in 6 ml of water) was then added to the soln and the mixture was heated under reflux for 1.5 h. The excess $N_2H_4 \cdot H_2O$ was distilled off and the mixture was stirred and heated for 1.5 h at 200°. After cooling , it was diluted with water and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (3.71 g) was chromatographed over SiO_2 (120 g; *n*-hexane-EtOAc) and distilled to give 3.22 g (76 % from **3b**) of (2R*,4R*)-**1b**, b.p. 108~109°/1.1 Torr; n_D^{23} 1.4390; νmax 3350 (m), 2960 (s), 2930 (s),

2870 (s), 1460 (m), 1380 (m), 1150 (m), 1115 (m), 1055 (m) cm^{-1}; δ 0.7~1.05 (12H, m), 1.12 (3H, d, J=6 Hz), 1.05~2.0 (13H, m), 2.48 (1H, s, OH), 3.35~4.00 (1H, m). (Found: C, 78.26; H, 14.26. Calc for $C_{14}H_{30}O$: C, 78.43; H, 14.11 %).

(1R*,3R*,5R*S*,7R*S*)-1,3,5,7-Tetramethyldecyl formate (1R*,3R*)-**1a**. A mixture of (2R*,4R*)-**1b** (1.50 g) and HCO_2H (>98 % purity, 20 ml) was stirred for 75 min at 65°. It was then poured into ice-sat $NaHCO_3$ aq and extracted with ether. The ether soln was washed with sat $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (Merck Lobar® column; *n*-hexane-Et_2O) and distilled to give 1.40 g (83 %) of (1R*,3R*)-**1a**, b.p. 86~87°/0.9 Torr; n_D^{21} 1.4299; νmax 2970 (s), 2930 (s), 2880 (m), 2850 (m), 1730 (s), 1460 (m), 1380 (m), 1185 (s), 1130 (m) cm^{-1}; δ ($CDCl_3$) 0.7~1.1 (12H, m), 1.25 (3H, d, J=6 Hz), 1.1~2.0 (13H, m), 4.85~5.45 (1H, m), 8.00 (1H, s); GLC (Column, OV-101, 50 m x 0.25 mm at 100° + 0.5°/min; Carrier gas, N_2, 28 ml/min): Rt 135.1 min (14 %), 135.9 min (3 %), 137.5 min (18 %), 138.3 min (30 %), 139.8 min (1 %), 140.7 min (32 %), 142.1 min (2 %). (Found: C, 74.33; H, 12.57. Calc for $C_{15}H_{30}O_2$: C, 74.32; H, 12.48 %). The peak due to the natural pheromone coincided with that of the shortest Rt (135.1 min).

(1r*,2R*,4r*,6S*)-2,4,6-Trimethyl-1-cyclohexanol **4a** and its C-1 epimer **4b**. A mixture of mesitol (10.0 g) and W-7 Raney Ni (2 g) in EtOH (3 ml) was stirred under a hydrogen pressure of 110 atm at 135° for 3 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was diluted with ether. The ether soln was washed with 5 % NaOH aq, water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, Art 9385, 400 g). Elution with *n*-hexane-EtOAc (20:1) gave an oil, which was distilled to give 4.07 g (39 %) of **4b**, b.p. 101~102°/50 Torr; n_D^{22} 1.4531; νmax 3520 (m), 3000 (s), 2950 (s), 2910 (s), 1460 (m), 1380 (m), 1180 (m), 970 (s), 930 (m) cm^{-1}; δ ($CDCl_3$) 0.87 (3H, d, J=5 Hz), 0.91 (2x3H, d, J=6 Hz), 1.1~1.8 (7H, m), 1.61 (1H, s, OH), 3.39 (1H, s, $W_{h/2}$=5 Hz); ^{13}C NMR δ 18.57, 22.42, 32.41, 36.43, 37.26, 74.42. (Found: C, 76.18; H, 12.65. Calc for $C_9H_{18}O$: C, 75.99; H, 12.76 %). Further elution with *n*-hexane-EtOAc (15:1) gave a crystalline solid, which was recrystallized from *n*-hexane to give 3.63 g (35 %) of **4a** as needles, m.p. 68~70°; νmax 3400 (m), 3000 (s), 2960 (s), 1460 (m), 1055 (m), 1045 (m) cm^{-1}; δ ($CDCl_3$) 0.83 (3H, d, J=6 Hz), 0.95 (2x3H, d, J=5 Hz), 1.1~1.8 (7H, m), 2.31 (1H, s, OH), 2.57 (1H, t, J=8 Hz); ^{13}C NMR δ 18.81, 22.05, 31.75, 39.43, 43.03, 82.00. (Found: C, 76.26; H, 12.72. Calc for $C_9H_{18}O$: C, 75.99; H, 12.76 %). GLC analysis of the crude reduction product (Column, OV-101, 50 m x 0.25 mm at 90°; Carrier gas, N_2, 45 ml/min): Rt 31.7 min (50 %, **4a**), 32.4 min (44 %, **4b**), 38.0 min (2 %), 39.2 min (4 %).

(2R*,4r*,6S*)-2,4,6-Trimethylcyclohexanone **4c**. Jones reagent (30 ml) was added to a stirred and cooled soln of **4a** (10.0 g) and **4b** (7.0 g) in acetone (200 ml) at 0~5°. After stirring for 10 min, MeOH was added and the stirring was continued for 10 min. The mixture 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 15.0 g (89 %) of **4c**, b.p. 77~80°/19 Torr; n_D^{19} 1.4423; νmax 2980 (s), 2950 (s), 2890 (s), 1715 (s), 1460 (s), 1380 (m), 1130 (s), 1000 (m) cm^{-1}; δ ($CDCl_3$) 0.94 (3H, d, J=6 Hz), 0.96 (2x3H, d, J=6 Hz), 1.15~2.7 (7H, m); ^{13}C NMR δ 14.51, 21.21, 32.00, 44.20, 45.40, 214.30. (Found: C, 76.98; H, 11.76. Calc for $C_9H_{16}O$: C, 77.09; H, 11.50 %).

(2R*,4S*,6S*)-2,4-Dimethyl-6-heptanolide **5**. To a stirred mixture of 85 % MCPBA (5.8 g) and $NaHCO_3$ (2.9 g) in dry CH_2Cl_2 (40 ml) was added dropwise a soln of **4c** (3.20 g) in dry CH_2Cl_2 (7 ml) at room temp. After stirring for 4 h, the precipitate was filtered off and the filtrate was washed with 10 % $NaHSO_3$ aq, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 3.50 g (98 %) of **5**, b.p. 83~84°/2.5 Torr; n_D^{19} 1.4515; νmax 2990 (jm), 2940 (m), 1730 (s), 1455 (m), 1380 (m), 1200 (s), 1130 (m), 1095 (m), 1035 (m) cm^{-1}; δ 0.92 (3H, d, J=6 Hz), 1.10 (3H, d, J=7 Hz), 1.30 (3H, d, J=7 Hz), 1.3~2.2 (5H, m), 2.3~3.0 (1H, m), 4,2~4.75 (1H, m) (Found: C, 69.17; H, 10.30. Calc for $C_9H_{16}O_2$: C, 69.19; H, 10.32 %).

(2R*,4S*,6S*)-2,4-Dimethyl-1,6-heptanediol **6a**. A soln of **5** (9.00 g) in dry ether (20 ml) was added to a stirred and ice-cooled suspension of LAH (3.0 g) in dry ether (150 ml). The mixture was stirred for 1.5 h at room temp. The usual alkaline work-up gave an oil, which was distilled to give 8.93 g (97 %) of **6a**, b.p. 101~102°/0.95 Torr; n_D^{17} 1.4546; νmax 3350 (s), 2970 (s), 2880 (s), 1460 (m), 1375 (m), 1115 (m), 1055 (s), 1040 (s) cm^{-1}; δ 0.87 (2x3H, d, J=6 Hz), 1.21 (3H, d, J=6 Hz), 1.3~2.0 (6H, m), 3.30 (2H, d, J=5 Hz), 3.65 (2H, s, OH), 3.5~4.0 (1H, m). (Found: C, 67.11; H, 12.42. Calc for $C_9H_{20}O_2$: C, 67.45; H, 12.58 %).

(2R*,4R*,6S*)-4,6-Dimethyl-7-tosyloxy-2-heptanol **6b**. *p*-TsCl (11.3 g) was added to a stirred and ice-cooled soln of **6a** (7.00 g) in dry C_5H_5N (50 ml). After stirring for 3 h at 0~5°, the mixture was poured into ice-3N HCl and extracted with ether. The ether soln was washed with dil HCl, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (500 g, *n*-hexane-EtOAc) to give 9.30 g (68 %) of **6b**, νmax 3600(w), 3450 (w), 3000 (m), 2960 (m), 1610 (w), 1505 (w), 1465 (m), 1360 (s), 1190 (s), 1180 (s), 1100 (m), 965 (s) cm^{-1}. This was employed in the next step without further purification.

(2R*,4R*,6R*,8R*S*)-4,6,8-Trimethyl-2-undecanol (2R*,4R*,6R*)-**1b**. A Grignard reagent was prepared from 2-bromopentane (7.41 g) and Mg (1.40 g) in dry THF (33 ml). This was added dropwise to a soln of **6b** (5.94 g) in dry THF (16 ml) below -50° under Ar. After the addition, a soln of 0.1 M Li_2CuCl_4 in dry THF (0.97 ml) was added. The reaction temp was gradually raised to room temp and the stirring was continued for 60 h. The mixture was poured into ice-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, 270 g; *n*-hexane-EtOAc) and distilled to give 1.91 g (51 %) of (2R*,4R*,6R*)-**1b**, b.p. 85°/0.7 Torr; n_D^{22} 1.4390; νmax 3360 (m), 2970 (s), 2930 (s), 2880 (s), 1460 (m), 1380 (m), 1150 (m), 1115 (m), 1055 (m) cm^{-1}; δ 0.7~1.0 (12H, m), 1.12 (3H, d, J=6 Hz), 1.0~2.0 (13H, m), 2.11 (1H, s, OH), 3.45~4.05 (1H, m). (Found: C, 78.72; H, 14.34. Calc for $C_{14}H_{30}O$: C, 78.43; H, 14.11 %).

(1R*,3R*,5R*,7R*S*)-1,3,5,7-Tetramethyldecyl formate (1R*,3R*,5R*)-**1a**. In the same manner as described for the preparation of (1R*,3R*)-**1a**, (2R*,4R*,6R*)-**1b** (1.00 g) yielded 0.913 g (81 %) of (1R*,3R*,5R*)-**1a**, b.p. 101~102°/1.65 Torr; n_D^{22} 1.4295; νmax 2980 (s), 2940 (s), 2890 (s), 2860 (m), 1730 (s), 1460 (m), 1380 (m), 1185 (s),1130 (m) cm^{-1}; δ ($CDCl_3$) 0.7~1.0 (12H, m), 1.24 (3H, d J=6 Hz), 1.0~2.0 (13H, m), 4.8~5.35 (1H, m), 7.95 (1H, s); GLC (Column, OV-101, 50 m x 0.25 mm at 110° + 0.5°/min; Carrier gas, N_2, 27 ml/min): Rt 102.4 min (45 %), 104.6 min (55 %). The peak of Rt 102.4 min coincided with that of the shortest Rt in (1R*,3R*)-**1a**. (Found: C, 74.03; H, 12.51. Calc for $C_{15}H_{30}O_2$: C, 74.32; H, 12.48 %).

Methyl (2R*,4S*,6S*)-6-hydroxy-2,4-dimethylheptanoate **7a**. To a soln of **5** (11.84 g) in abs MeOH (150 ml) was added conc H_2SO_4 (1.0g). The mixture was stirred for 1 h at room temp. After neutralization with sat $NaHCO_3$ aq, the mixture was concentrated *in vacuo*. The residue was diluted with water and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 15.09 g of crude **7a**, νmax 3450 (m), 2980 (s), 2940 (s), 1730 (s), 1460 (m), 1190 (s), 1170 (s), 1140(s) cm^{-1}. This was employed in the next step without further purification.

Methyl (2R*,4S*,6S*)-2,4-Dimethyl-6-tosyloxyheptanoate **7b**. *p*-TsCl (30 g) was added to a stirred and ice-cooled soln of crude **7a** (15.09 g) in dry C_5H_5N (60 ml). After stirring for 4 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 26.79 g of crude **7b**, νmax 1740 (s), 1360 (s), 1190 (s), 1170 (s), 900 (s) cm^{-1}. This was employed in the next step without further purification.

(2R*,4R*)-2,4-Dimethyl-1-heptanol **8a**. A soln of crude **7b** (26.79 g) in dry ether (50 ml) was added to a stirred and ice-cooled suspension of LAH (8.7 g) in dry ether (400 ml). The mixture was stirred overnight at room temp. The usual alkaline work-up gave an oil, which was chromatographed over SiO_2 (Merck Kieselgel 60 Art 9385, 400 g; n-hexane-EtOAc) and distilled to give 8.94 g (82 % from 5) of **8a**, b.p. 75~76°/6 Torr; n_D^{19} 1.4299; νmax 3380 (m), 2980 (s), 2940 (s), 2890 (s), 1460 (m), 1380 (m), 1030 (m) cm^{-1}; δ 0.7~1.0 (9H, m), 1.0~1.9 (8H, m), 3.05 (1H, s, OH), 3.1~3.6 (2H, m); GLC (Column, PEG 20M, 50 m x 0.25 mm at 85°+ 0.5°/min; Carrier gas, N_2, 50 ml/min): Rt 22.8 min (98 %, single isomer). The absence of C-2 epimer was made sure by the coinjection of **8a** with a mixture of syn- and anti-2,4-dimethyl-1-heptanol (Rt 22.8 min and 23.3 min respectively). (Found: C, 74.64; H, 14.00. Calc for $C_9H_{20}O$: C, 74.93; H, 13.98 %).

(2R*,3R*)-2,4-Dimethylheptyl tosylate **8b**. p-TsCl (21 g) was added to a stirred and ice-cooled soln of **8a** (8.0 g) in dry C_5H_5N (55 ml). After stirring for 3 h at 0~5°, the mixture was poured into ice-3N HCl and extracted with ether. The ether soln was washed with dil HCl, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo to give 19.0 g of crude **8b**, νmax 2960 (s), 2930 (s), 2880 (m), 1595 (m), 1360 (s), 1190 (s), 1170 (s), 960 (s) cm^{-1}. This was employed in the next step without further purification.

(2R*,4R*)-1-Iodo-2,4-dimethylheptane **8c**. NaI (19 g) was added to a soln of crude **8b** (19.0 g) in dry acetone (250 ml). The mixture was stirred for 4 h under reflux and for 3 h at room temp. It was poured into ice-water and extracted with n-hexane. The n-hexane soln was washed with 10 % $Na_2S_2O_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (300 g, n-hexane) to give 13.1 g (93 % from **8a**) of **8c**, νmax 2960 (s), 2920 (s), 2870 (s), 1450 (m), 1375 (m), 1190 (m) cm^{-1}; δ 0.7~1.1 (9H, m), 1.1~1.7 (8H, m), 2.85~3.3 (2H, m). This was employed in the next step without further purification.

(2R*S*,4R*S*)-2-[(2R*,4R*)-2,4-dimethylheptyl]-4-pentanolide **9a**. A soln of LDA was prepared by the addition of a soln of n-BuLi (1.53 N in n-hexane, 30 ml) to a stirred and cooled soln of $(i\text{-}Pr)_2NH$ (4.85 g) in dry THF (60 ml) at 0° under Ar. HMPA (40 ml) was added to the soln at -20° and the mixture was cooled to -69°. To the resulting slurry was added dropwise at -69° a soln of 4-pentanolide (4.0 g) in dry THF (40 ml) over a period of 2.5 h. After stirring for 15 min at -69°, the mixture was warmed to -45°. To the soln was added a soln of **8c** (10.16 g) in dry THF (40 ml) at -40~-45°. The soln was allowed to stand for 33 h at -40°. It was then poured into ice-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, 450 g; n-hexane-EtOAc) and distilled to give 4.52 g (50 %) of **9a**, b.p. 107~109°/0.15 Torr; n_D^{17} 1.4496; νmax 2980 (s), 2940 (s), 2880 (m), 1770 (s), 1460 (m), 1380 (m), 1180 (s), 1120 (m) cm^{-1}; δ 0.7~1.0 (9H, m), 1.0~2.1 (12H, m), 1.30 (1.35H, d, J=6 Hz), 1.34 (1.65H, d, J=6 Hz), 2.1~2.7 (1H, m), 4.0~4.7 (1H, m); GLC (Column, OV-101, 50 m x 0.25 mm at 120° + 0.5°/min; Carrier gas, N_2, 43 ml/min): Rt 90.1 min (45 %), 91.2 min (55 %). (Found: C, 74.12; H, 11.31. Calc for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58 %).

(2R*S*,3R*S*,5R*S*)-2-Hydroxy-5-methyl-3-[(2R*,4R*)-2,4-dimethylheptyl]tetrahydrofuran **9b**. A soln of DIBAL-H in n-hexane [9.7 ml of 25 (w/v) % soln] was added to a stirred and cooled soln of **9a** (3.50 g) in dry toluene (98 ml) below -63° under Ar. After stirring for 35 min at -65~-70°, sat NH_4Cl was added to the mixture. It was poured into ice-3N HCl and stirred for 20 min at room temp. The mixture was extracted with ether. The ether soln was washed with sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo to give 3.61 g of crude **9b**, νmax 3400 (m), 2960 (s), 2920 (s), 1450 (m), 1370 (m), 995 (m) cm^{-1}. This was employed in the next step without further purification.

(2R*S*,4R*S*,6R*,8R*)-4,6,8-Trimethyl-2-undecanol (6R*,8R*)-**1b**. 80 % $N_2H_4 \cdot H_2O$ (4.1 g) was added to a soln of crude **9b** (3.61 g) in diethylene glycol (16.5 ml). The mixture was heated under reflux for 1 h. KOH aq (4.1 g in 4.1 ml of water) was then added to the soln and it was heated under reflux for 1.5 h. The excess $N_2H_4 \cdot H_2O$ was distilled off and the mixture was stirred and heated for 1.5 h at 200°. After cooling, the mixtur was diluted with water 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, 130 g; n-hexane-EtOAc) and distilled to give 2.33 g (70 % from **9a**) of (6R*,8R*)-**1b**, b.p. 105~106°/2.4 Torr; n_D^{21} 1.4390; νmax 3350 (m), 2970 (s), 2930 (s), 1460 (m), 1380 (m), 1150 (m), 1115 (m), 1055 (m) cm^{-1}; δ 0.7~1.0 (12H, m), 1.10 (3H, d, J=6 Hz), 1.0~1.9 (13H, m), 2.30 (1H, s, OH), 3.4~4.0 (1H, m); (Found: C, 78.23; H, 13.63. Calc for $C_{14}H_{30}O$: C, 78.43; H, 14.11 %).

(1R*S*,3R*S*,5R*,7R*)-1,3,5,7-Tetramethyldecyl formate (5R*,7R*)-**1a**. In the same manner as described for the preparation of (1R*,3R*)-**1a**, (6R*,8R*)-**1b** (1.50 g) yielded 1.47 g (87 %) of (5R*,7R*)-**1a**, b.p. 81~82°/0.65 Torr; n_D^{21} 1.4295; νmax 2980 (s), 2940 (s), 2890 (m), 2860 (m), 1730 (s), 1460 (m), 1380 (m), 1185 (s), 1125 (m) cm^{-1}; δ ($CDCl_3$) 0.7~1.0 (12H, m), 1.22 (3H, d, J=6 Hz), 1.0~1.9 (13H, m), 4.75~5.35 (1H, m), 7.93 (1H, s); GLC (Column, OV-101, 50 m x 0.25 mm at 120° + 0.5°/min; Carrier gas, N_2, 45 ml/min): Rt 97.0 min (26 %), 97.7 min (22 %), 100.0 min (17 %), 101.4 min (35 %). The peak of Rt 97.0 min coincided with that of the shortest Rt in (1R*,3R*)-**1a**. (Found: C, 74.56; H, 12.94. Calc for $C_{15}H_{30}O_2$: C, 74.32; H, 12.48 %).

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