Syntheses of the Sex-Attractant of Pine Sawflies

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In order to establish the stereochemistry of the sex attractant of various species of pine sawflies, (2*S*,3*R*,7*R*)-, (2*S*,3*R*,7*S*)- and (2*S*,3*S*,7*S*)-2-acetoxy- and 2-propionyloxy-3,7-dimethylpentadecane were synthesized. The alcohol moiety of each pheromone was prepared by the coupling of Grignard reagent of C_{12} block with tosylate of C_5 block. The C_{12} blocks, (*R*)- and (*S*)-1-bromo-2-methylundecane, were prepared from (*R*)-(+)-pulegone. The C_5 blocks, (2*R*,3*S*)- or (2*S*,3*S*)-2-methyl-3-tetrahydropyranyloxy-1-(tosyloxy)butane, were derived from (2*S*,3*S*)- or (2*R*,3*S*)-2-methyl-3-hydroxybutyric acid prepared by the enantio-differentiating hydrogenation of methyl 2-methyl-3-oxobutyrate over the asymmetrically modified nickel catalyst.

Virgin females of pine sawflies (*Hymenoptera, Diprionidae*) utilize a powerful sex pheromone to attract males. In 1967, Jewett *et al.*[1] reported that the chemical structure of *N. lecontei* (red headed pine sawfly) was an acetate of (2*R**,3*R**)-3,7-dimethyl-2-pentadecanol (*erythro*-**1**). At the same time, it was proposed that the pheromones of various sawflies were either acetates or propionates of **1**.

The acetate or propionate of the synthesized racemic **1**[2] (a mixture of all possible isomers) was, however, much less active than the natural pheromone and could not discriminate a difference among species. These data suggested that not only a sort of ester moiety but also stereochemistry of **1** were essential factors to distinguish the many sympatric species of sawflies.

In order to clarify the stereochemistry of the pheromones, we have synthesized optically active *erythro*-isomers, (2*S*,3*S*,7*R*/*S*)- and (2*R*,3*R*,7*R*/*S*)-**1**, and *threo*-isomers, (2*S**,3*R**,7*R*/*S*)-, (2*S*,3*R*,7*R*/*S*)- and (2*R*,3*S*,7*R*/*S*)-**1**.[3,4] The field assay of these compounds against *N. lecontei* clearly showed that the natural pheromone must be erythro (2*S*,3*S*)-configuration.[5,6] Later, K. Mori *et al.*[7] synthesized the four *erythro*-isomers: (2*R*,3*R*,7*R*)-, (2*R*,3*R*,7*S*)-, (2*S*,3*S*,7*R*)- and (2*S*,3*S*,7*S*)-**1**. The field assay carried out by Kraemer *et al.*[8] showed that only the acetate of (2*S*,3*S*,7*S*)-1 was highly active against *N. lecontei*. Thus the pheromone of *N. lecontei* was expected to be a single component and its structure was established to be (2*S*,3*S*,7*S*)-**1**. Although (2*S*,3*S*)- or (2*S*,3*S*,7*S*)-**1** attracted many other *Neodiprion* families in the field, its potency for attraction was very weak compared to that of the natural pheromone of each species.

In the course of the field assay by using *erythro*-and *threo*-isomers, we have found that the pheromone of various species other than *N. lecontei* was not a single component but a mixture of *threo*-and *erythro*-isomers. For example, a mixture of (2*S*,3*S*,7*S*)- and (2*S*,3*R*,7*R*/*S*)-**1** in a different ratio functioned for the discrimination of two closely related species, *N. sertifer* and *N. banksianae*.[9] On carrying out the stereochemical studies of this pheromone in detail, the syntheses of optically pure *threo*-isomer as well as *erythro*-isomer were absolutely necessary. Although the synthetic methods of four possible *erythro*-isomers have been reported,[7,10,11] the methods were not applicable for the synthesis of the optically pure *threo*-isomers. This report describes the method for the syntheses of optically pure three essential stereoisomers for the biological study of the pheromone of sawfly: (2*S*,3*R*,7*R*)-, (2*S*,3*R*,7*S*)- and (2*S*,3*S*,7*S*)-**1**.

Results and Discussion

The most reliable procedure to prepare an optically pure stereoisomer is to assemble optically pure building blocks by a method which does not involve the bond breaking and bond forming process at the chiral center of each block. Our synthetic procedure was designed in line with the above mentioned policy. The procedure consists of the preparation of optically pure C_{12} blocks and C_5 blocks and their couplings,as shown in Fig. 1.

Optically pure C_{12} blocks, (*R*)- and (*S*)-1-bromo-3-methylundecane (**9**), were prepared from (*R*)-(+)-citronellic acid (**3**) ($[\alpha]_D^{20}$+8.89° (neat), lit,[12] $[\alpha]_D^{25}$+8.48° (neat)) derived from (*R*)-(+)-pulegone (**2**) ($[\alpha]_D^{20}$+21.97° (neat)) supplied by courtesy of Takasago Perfume Industry Co. The resulting (*R*)-3 was determined to be essentially optically pure by the GLC method developed in this study. A diastereomeric mixture of amides

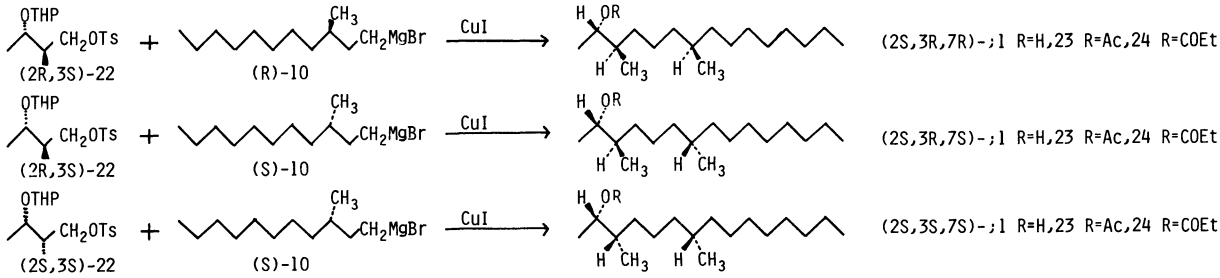

Fig. 1. Preparation of 3,7-dimethyl-2-pentadecanol (**1**) and its derivatives, (**23**) and (**24**).

from citronellic acid and α-methylbenzylamine was found to be completely resolved by capillary GLC (OV-101, 50 m (L)×0.25 mm (I.D)). When the **3** used for this study was converted to its amide with (*S*)-α-methylbenzylamline ($[\alpha]_D^{20}$−39° (neat), Aldrich Co.), the diastereomeric excess (d.e.) of the resulting amide was 98%. However, the (*S*)-α-methylbenzylamine[13] was found to be not optically pure. The GLC analysis with a chiral capillary column (OA-500, 40 m (L)×0.25 mm (I.D)) indicated that the enantiomeric excess (e.e.) of this amine was 98%. If our citronellic acid had been contaminated with some antipode, the d.e. value of amide would have been less than 98%.

From the fact that the d.e. value of amide and the e.e. value of amine were identical, and that the optical rotation of our citronellic acid was slightly higher than the reported value[12], it was concluded that the (*R*)-citronellic acid must be optically pure.

The procedure for the preparation of (*R*)-**9** is shown in Fig. 2. (*R*)-Ethyl citronellate (**4**) prepared by the esterification of (*R*)-**3** was ozonized in methanol.[14] The hydrogenolysis of the ozonide over Pd/C gave ethyl (*R*)-3-methyl-6-oxohexanoate (**5**). The reaction of (*R*)-**5** with Wittig reagent[15] prepared from pentyltriphenylphosphonium bromide and butyllithium gave ethyl (*R*)-3-methyl-6-undecenoate (**6**). Hydrogenation of (*R*)-**6** over Pt(Adam's) gave ethyl (*R*)-3-methylundecanoate (**7**), which was reduced with lithium aluminum hydride to give (*R*)-3-methyl-1-undecanol (**8**). The bromination[16] of (*R*)-**8** gave (*R*)-**9**: $[\alpha]_D^{20}$ −4.07° (*c* 4.9, hexane). The (*R*)-**9** was converted to Grignard reagent ((*R*)-**10**) ((*R*)-C_{12} block) in ether right before the use for the coupling reaction.

The procedure for the preparation of (*S*)-**9** is shown in Fig. 3. The reduction of (*R*)-**4** with lithium aluminum hydride gave the corresponding alcohol(**11**), which was then converted to a tosylate ((*R*)-**12**). The coupling of (*R*)-**12** with hexylmagnesium chloride in the presence of copper(I) iodide[17] gave (*R*)-2,6-dimethyl-2-tetradecene (**13**). The ozonolysis of (*R*)-**13** in dichloromethane and oxidative cleavage of the ozonide with hydrogen peroxide in formic acid[14] gave (*S*)-4-methyldodecanoic acid (**14**). The Hunsdiecker reaction[18] of (*S*)-**14** gave (*S*)-**9**: $[\alpha]_D^{20}$ +4.04° (*c* 4.5, hexane). The (*S*)-**9** was converted to Grignard reagent ((*S*)-**10**) ((*S*)-C_{12} block) in ether right before the use for the coupling reaction.

As the optical rotations of (*R*)-and of (*S*)-**9** were the same value within experimental error, it was concluded that no racemization took places in each step of the reaction process. Therefore, these bromides (**9**) must be optically pure.

The preparation of C_5 blocks is shown in Fig. 4.

The hydrogenation of methyl 2-methyl-3-oxobutyrate (**15**) over the nickel catalyst modified with (*S,S*)-tartaric acid, ((*S,S*)-TA-MHNi) gave a mixture of methyl *threo*-and *erythro*-3-hydroxy-2-methylbutyrate (**16**) in a ratio of 25 to 75[19,20]. The effective isolation of *threo*-and *erythro*-isomer on a practical scale was successfully achieved by the crystallization method. The procedure shown in Fig. 4 enabled us to isolate *threo*-isomer with 55% recovery and *erythro*-isomer with 54% recovery. The advantage of this method is that *threo*-and *erythro*-isomers were obtained at once; furthermore the optical purity of each diastereomer was approximately 60%.

The mixture of *threo*-and *erythro*-**16** was saponified to sodium 3-hydroxy-2-methylbutyrate (**17**). The sodium salt thus obtained was dissolved in a minimum amount of methanol. By the slow addition of acetone to the solution, sodium salt of *threo*-isomer was preferentially precipitated as crystals. The recrystallization of the sodium salt from methanol–acetone gave pure *threo*-**17** (optical purity 60%, (2*S*,3*S*) in excess). *Erythro*-isomer enriched in the mother liquid of the first crystallization converted to cyclohexylammonium salt (**19**). Three succesive recrystallizations from EtOH gave pure *erythro*-**19** (optical purity 60%, (2*R*,3*S*) in excess).

Enrichments of optical purity of *threo*-and *erythro*-2-

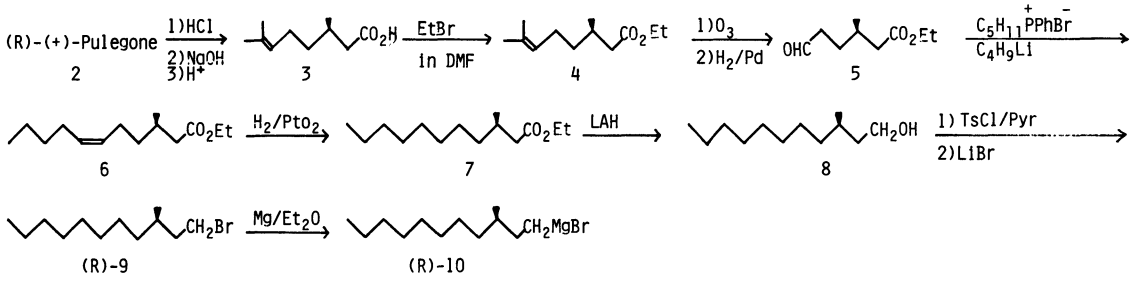

Fig. 2. Preparation of (R)-C_{12} building block.

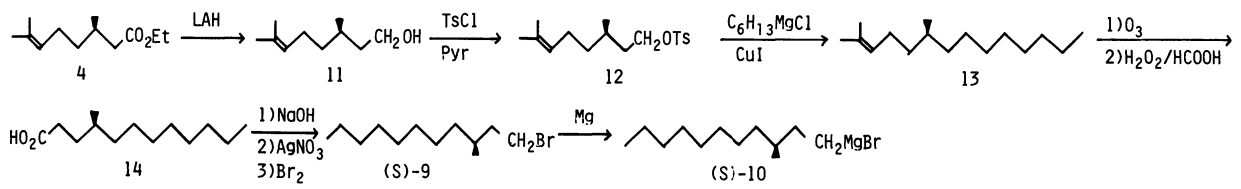

Fig. 3. Preparation of (*S*)-C_{12} building block.

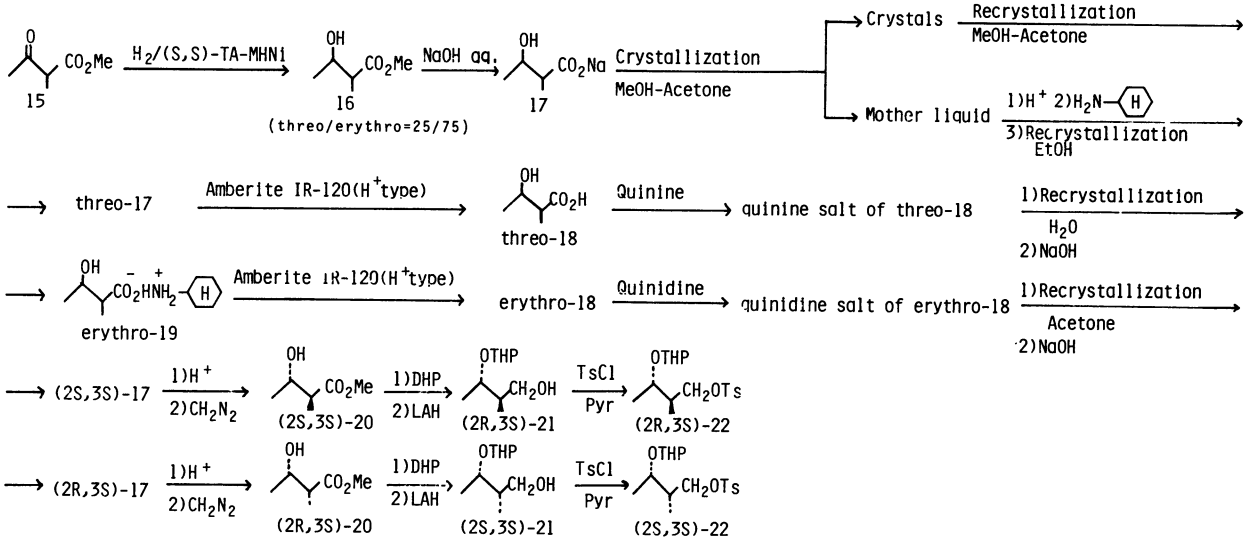

Fig. 4. Preparation of C_5 building blocks.

hydroxy-3-methylbutyric acid (**18**) were carried out by the recrystallization of quinine (*threo*-) and quinidine (*erythro*-) salt respectively. Removal of base by sodium hydroxide gave pure (2*S*,3*S*)-and (2*R*,3*S*)-**17**. The **17** was esterified to the corresponding methyl ester (**20**). After the protection of hydroxyl group of **20** by the treatment of dihydropyran, the resulting compounds were reduced with lithium aluminum hydride to give 2-methyl-3-tetrahydropyranyloxy-1-butanol (**21**). Tosylation of **21** by the conventional procedure gave 2-methyl-3-tetrahydropyranyloxy-1-(tosyloxy)butane (**22**), as shown in Fig. 4.

The coupling reaction of **22** with **10** was carried out by the reported method[17] to give the corresponding alcohol, as shown in Fig. 1. The stereochemical purity at the 2 and 3 position of the resulting (2*S*,3*S*, 7*S*)-, (2*S*,3*R*,7*S*)- and (2*S*,3*R*,7*R*)-**1** were determined by the analytical GLC (Capillary column PEG 20M, 50 m (L)×0.25 mm (I.D)) which can detect at least 0.2% of contaminated epimer. The optical purity of these compounds were also proved by the ^{1}H-NMR.

Each alcohol was converted to the acetate and propionate by the conventional procedure and the resulting esters were employed for the field assays. The synergistic effect of the acetate of (2*S*,3*R*,7*R*)-**1** on the acetate of (2*S*,3*S*,7*S*)-**1** in *N. sertifer* was clearly demonstrated.[21] For other species, the highly biological activity of the mixture of the acetate of (2*S*,3*R*,7*R*)- or (2*S*,3*R*,7*S*)-**1** and acetate of (2*S*,3*S*,7*S*)-**1** has been observed.[9] Details of the biological studies will be published elsewhere.

Experimental

All melting and boiling points are uncorrected. IR spectra were recorded on a Shimadzu IR-420 spectrometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ solution at 200 MHz with TMS as an internal standard on a JOEL FX-200 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The analytical GLC and preparative GLC were carried out on a Shimadzu GC-6A gas chromatograph.

(R)-(+)- *Citronellic Acid (3).* This was prepared from (*R*)-(+)-pulegone (**2**), $[\alpha]_D^{20}$ +21.97° (neat), supplied by Takasago Perfume Industry Co., in 80% yield by the reported method[12]: bp 98.5 °C/1.5 mmHg†; $[\alpha]_D^{20}$ +8.89° (neat), lit,[12] $[\alpha]_D^{20}$ +8.48° (neat); GLC (3% OV-17 on Chromosorb W, 2 m×3 mm, at 150—220°, temperature gradient, 8 °C/min, carrier gas N_2, 1.4 kg/cm^{-2}), Rt 11 min (a single peak).

Determination of the Optical Purity of (R)-(+)-citronellic Acid. To the (*R*)-**3** (0.1 ml) in a test tube was added dicyclohexylcarbodiimide (DCC) (0.2 g) in ethyl acetate (0.5 ml) and then (*S*)-α-methylbenzylamine (0.2 ml) (Aldrich Co. $[\alpha]_D^{20}$−39° (neat), the e.e. was 98%, which was determined by the method described in the following section). After the mixture was allowed to stand for 1 h, acetic acid was added to this to decompose excess DCC. The white crystals which precipitated were removed by using a centrifuge. The supernatant was subjected to GLC analysis (capillary column OV-101, 50 m (L)×0.25 mm (I.D), at 160 °C, carrier gas N_2, 1.4 kg/cm^2). Under these conditions, (*R**,*S**)- and (*R**,*R**)-amide were completely resolved at the retention times of 69.4 min and 71.4 min respectively at 160 °C. The d.e. of the (*R*,*S*)-amide obtained above was calculated to be 98% from the ratio of the two peaks. The d.e. value was identical with the e.e. value of the (*S*)-α-methylbenzylamine employed. When the same **3** as above was allowed to react with (*R*)-α-methylbenzylamine (Aldrich Co. $[\alpha]_D^{20}$+38° (neat), the e.e. was determined to be 97%), the d.e. of (*R*,*R*)-amide was calculated to be 97% from the ratio of the two peaks. Since the d.e. values of these amides corresponded to the e.e. values of the α-methylbenzylamine employed for analyses, (*R*)-**3** was expected to be optically pure.

Determination of Optical Purity of (R)- and (S)-α-Methylbenzylamine. To (*R*)- or (*S*)-amine (0.1 ml) dissolved in ether (2 ml), trifluoroacetic anhydride (2 ml) was added. After removing the water soluble matter by washing with water, the ether solution was dried over $MgSO_4$. The resulting ethereal solution of *N*-trifluoroacetyl-α-methylbenzylamine was subjected to GLC analysis on OA-500 (Sumitomo Chemical Co. Ltd; capillary column coated with chiral compound, 40 m (L)×0.25 mm (I.D), at 150 °C, carrier gas N_2, 1.4 kg/cm^2). The (*R*)- and (*S*)-*N*-trifluoroacetamide were completely resolved at the retention time of 17.9 and 19.3 min at 150 °C respectively.

† 1 mmHg≈133.322 Pa.

Ethyl Citronellate (4). This was prepared from sodium salt of (*R*)-**3** and ethyl bromide in DMF. From 150 g of 3, 166 g (94.4%) of **4** was obtained: bp 66—68°C/1.5 mmHg; $[\alpha]_D^{20}$+2.6° (*c* 4.5, hexane); GLC(3% OV-17 on Chromosorb W, 2 m×3 mm, at 140 °C, carrier gas N_2, 1.4 kg/cm²), Rt 7 min (a single peak).

Ethyl (R)-3-Methyl-6-oxohexanoate (5). Ozone (4% in carrier gas) was introduced into 25 g of **4** dissolved in methanol (20 ml) in a carrier gas (O_2) (flow rate 0.2 l/min) at −70 °C. After the excess ozone in the reaction mixture was blown off by N_2 gas, the residue was transferred into a flask which contained a suspension of the preactivated Pd/C (100 mg) in methanol (20 ml). The reaction was continued until the theoretical amount of hydrogen was absorbed under atmospheric pressure at room temperature. After removal of Pd/C by filtration, and evaporation of methanol from the filtrate, the residue was distilled *in vacuo* to give 14.5 g (67%) of **5**: bp 124 °C/20 mmHg; $[\alpha]_D^{20}$ +4.0° (*c* 5.1, hexane); GLC (2.5% PEG 20M+3% $AgNO_3$ on Uniport B, 2 m×3 mm, at 150 °C, carrier gas N_2, 1.4 kg/cm²), Rt 5 min (a single peak); NMR ($CDCl_3$, TMS), δ=9.79 (1H for −CHO, s); IR (neat), 1720 and 1740 cm⁻¹ for aldehyde and ester groups. Found: C, 61.31; H, 9.48%. Calcd for $C_9H_{16}O_3$: C,62.76; H, 9.36%.

Ethyl (R)-3-Methyl-6-undecenoate (6). Pentyltriphenylphosphonium bromide was prepared from triphenylphosphine and 1-bromopentane in dry benzene.[15]

Butyllithium (4.28 g in 40 ml of hexane) was added dropwise into a suspension of the above pentyltriphenylphosphonium bromide (27.6 g) in anhydrous ether (200 ml) under nitrogen at room temperature. Into the solution of the ylide thus obtained, a solution of (*R*)-**5** (11.5 g) in ether (20 ml) was added dropwise at room temperature. The mixture was refluxed for 2 h and allowed to stand overnight at room temperature. After removal of insoluble matter by filtration, the ether in the filtrate was evaporated under reduced pressure. The residue was eluted with a 1 to 1 mixture of hexane and ether on a silica gel column (Wakogel C-100). The eluate was concentrated *in vacuo* and the residue was distilled to give 9.6 g (63.6%) of **6**: bp 91—92 °C/1.5 mmHg; $[\alpha]_D^{20}$+0.24° (*c* 5.4, hexane). Found: C, 72.34; H, 11.34%. Calcd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58%.

Ethyl (R)-3-Methylundecanoate (7). The **6** (9.6 g) was hydrogenated over Pt-black (60 mg) in methanol (20 ml). The distillation of the reaction product gave 9.3 g of (*R*)-**7**: bp 107—109 °C/5 mmHg; $[\alpha]_D^{20}$ +1.83° (*c* 5, hexane); GLC (2.5% PEG-20M+3% $AgNO_3$ on Uniport B, 2 m×3 mm, at 180 °C, carrier gas N_2, 1.4 kg/cm²), Rt 3.8 min (a single peak); IR (neat), 1738 cm⁻¹ for ester group.

(R)-3-Methyl-1-undecanol (8). The **7** (9.3 g) in dry ether (20 ml) was reduced with lithium aluminum hydride (2.3 g) in dry ether (100 ml). The reaction mixture was worked up by conventional procedures to give 7.6 g (>99%) of (*R*)-**8**: bp 137—140 °C/15 mmHg; $[\alpha]_D^{20}$ +4.8° (*c* 5.1, hexane); GLC (3% OV-17 on Chromosorb W, 2 m×3 mm, at 160 °C, carrier gas N_2, 1.4 kg/cm²), Rt 8 min (a single peak); IR (neat), 3300, 2900, 2840, 1450, 1380, 1050 cm⁻¹; NMR ($CDCl_3$, TMS), δ=0.92 (6H, overlapped t and d, 2×C<u>H</u>₃-), 1.26 (17H, br s, -(C<u>H</u>₂)₈- and -C<u>H</u>-), 3.69 (2H, t, -C<u>H</u>₂OH). Fond: C, 77.26; H, 14.15%. Calcd for $C_{12}H_{26}O$: C, 77.35; H, 14.07%.

(R)-1-Bromo-3-methylundecane (9). *p*-Toluenesulfonyl chloride (11.7 g) was added to (*R*)-**8** (7.6 g) in dry pyridine (40 ml) under stirring and ice-cooling. The mixture was stirred for 2 h and allowed to stand overnight in a refrigerator. Then it was poured onto ice-water and extracted with ether. The extract was washed with water, aqueous $CuSO_4$, $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the tosylate of **8** as viscous oil: IR (neat), 2900, 1600, 1450, 1360, 1180, 1100, 940 cm⁻¹. Anhydrous lithium bromide (3.6 g) was added to a stirred solution of the tosylate (7 g) in acetone (20 ml) at once. The reaction mixture was kept at around 40 °C for 1 h. The resulting insoluble matter was separated by filtration and washed with ether. The filtrate and washing were combined and concentrated *in vacuo*. The residue was chromatographed over silica gel (Wacogel C-100). Elution with hexane gave 7.2 g (70.6%) of (*R*)-**9**: bp 99—105 °C/5 mmHg; GLC (3% OV-17 on Chromosorb W, 2 m×3 mm, at 170 °C, carrier gas N_2, 1.4 kg/cm²), Rt 9 min (96% purity with 4% unidentified impurity, Rt 7 min). The analytical sample is purified by a preparative GLC (10% OV-17 on Chromosorb W , 5 m×4 mm, at 210 °C), $[\alpha]_D^{20}$ −4.07° (*c* 4.9,hexane); IR (neat), 2900, 2850, 1450, 1370, 1255, 720, 645 cm⁻¹; NMR ($CDCl_3$, TMS), δ=0.89 (6H, overlapped t and d, 2×C<u>H</u>₃-), 1.27 (14H, s, -(C<u>H</u>₂)₇-), 1.5—1.93 (3H, m, BrCH₂C<u>H</u>₂C<u>H</u>(CH₃)-), 3.41 (2H, t, BrC<u>H</u>₂-). Found: C, 57.95; H, 10.21%. Calcd for $C_{12}H_{25}Br$: C, 57.83; H, 10.11%.

(R)-Citronellol (11). The reduction of (*R*)-**4** with lithium aluminum hydride gave (*R*)-**11** in 96% yield: bp 117 °C/18 mmHg; $[\alpha]_D^{20}$ +6.16° (*c* 4.9, hexane); GLC (3% OV-17 on Chromosorb W, 2 m×3 mm, at 150 °C, carrier gas N_2, 1.4 kg/cm²), Rt 2.5 min (a single peak).

(R)-Citronellyl Tosylate (12). This was prepared by the reaction between **11** and *p*-toluenesulfonyl chloride in dry pridine. From 31.5 g of (*R*)-**11**, 55 g (87.8%) of crude (*R*)-**12** was obtained as a viscous oil. The product was used for the next step without further purification.

(R)-2,6-Dimethyl-2-tetradecene (13). Grignard reagent was prepared from Mg (10.7 g) and 1-chlorohexane (53 g) in dry ether (200 ml). To this reagent, cooled at −70 °C, a solution of (*R*)-**12** (55 g) in ether (100 ml) was added gradually. Then well pulverized CuI (4.2 g) was added to the mixture at once. The temperature of the reaction mixture was kept at −70 °C for 1 h, then gradually raised to room temperature. The mixture was allowed to stand over night, refluxed for 1 h and then poured into aqueous NH_4Cl, and extracted three times with ether. The combined extract was washed with aqueous NH_4Cl, $NaHCO_3$ and brine and dried over $MgSO_4$. After removal of the ether *in vacuo*, the residue was chromatographed over silica gel (Wakogel C-100). The fraction eluted with 1% ether in hexane (150 ml) was concentrated *in vacuo* and distilled to give 35 g (80.1% from **12**) of the pure **13**: bp 134—140 °C/13 mmHg; $[\alpha]_D^{20}$−1.67° (*c* 5.5, hexane); GLC (3% OV-17 on Chromosorb W, 2 m×3 mm, at 160 °C, carrier gas N_2, 1.4 kg/cm²), Rt 9 min (a single peak); IR (neat), 2900, 2840, 1450, 1370, 820 720 cm⁻¹; NMR ($CDCl_3$, TMS), δ=0.87 (6H, overlapped t and d, 2×C<u>H</u>₃-), 1.26 (17H, br s, -(C<u>H</u>₂)₈- and -C<u>H</u>-), 1.64 (6H, d, =C(C<u>H</u>₃)₂), 1.9 (2H, m, -C<u>H</u>₂-CH=C-), 5.11 (1H, t, -C<u>H</u>=C-).

(S)-4-Methyldodecanoic Acid (14). The ozonolysis of **13** (35 g) in CH_2Cl_2 (50 ml) at −70 °C and the oxidative cleavage of the resulting ozonide with 35% H_2O_2/HCOOH by the reported procedur[14] gave 25 g (89.5%) of **14**: bp 130—140 °C/1.5 mmHg; $[\alpha]_D^{20}$−0.6° (*c* 5.3, hexane); IR (neat), 3000, 2890, 2840, 2600, 1710, 1700, 1450, 1420, 1280, 1210, 915 cm⁻¹. Found: C, 72.00; H, 12.58%. Calcd for $C_{13}H_{26}O_2$: C, 72.84; H, 12.23%. A small portion of the product was converted to methyl ester. NMR ($CDCl_3$, TMS) of the ester showed signals as follows: δ=0.88 (6H, overlapped t and d, 2×C<u>H</u>₃-), 1.26 (17H, br s, -(C<u>H</u>₂)₈ -and -C<u>H</u>-), 2.38 (2H, m, -C<u>H</u>₂CO₂-), 3,66 (3H, s, -COOC<u>H</u>₃).

(S)-Bromo-3-methylundecane (9). To a solution of potassium hydroxide (6.6 g) in water (300 ml) was added (*S*)-**14** (25 g) with stirring. The solution of potassium salt of **14** thus obtained and the solution of $AgNO_3$ (19.9 g) were added simultaneously into 100 ml of hot water (60 °C) at about the same rate. The resulting white precipitate was filtered, washed with water and acetone, and dried over P_2O_5 to give 33.6 g of silver salt of **14**. To a suspension of silver salt of **14**

(33.6 g) in CCl_4 (200 ml, dried over molecular sieves) was slowly added dried bromine (16.75 g) in CCl_4 (50 ml) with stirring and cooling. The mixture was kept under ice-cooling for 1 h and allowed to stand for 2 h at room temperature. After that, the temperature of the mixture was gradually increased to refluxing temperature. The reaction was continued until no more generation of carbon dioxide was observed. The insoluble matter in the reaction mixture was filtered off and washed with hexane (200 ml). The combined filtrate and washing were concentrated *in vacuo*. The residue was distilled to give 22 g (84.6%) of (*S*)-**9**: bp 90—93 °C/3 mmHg; GLC (3% OV-17 on Chromosorb W, 2 m×3 mm, at 165 °C, carrier gas N_2, 1.4 kg/cm^2), Rt 13 min (95% purity with unidentified impurity, Rt 8 min). The analytical sample is purified by a preparative GLC (10% OV-17 on Chromosorb W, 5 m×4 mm, at 210 °C: $[\alpha]_D^{20}$ +4.04° (*c* 4.5, hexane); Found: C, 57.45; H, 10.01%. Calcd for $C_{12}H_{25}Br$: C, 57.83; H, 10.11%. The IR and NMR spectra were identical with those of (*R*)-**9**.

Methyl threo-*and* erythro-*3-Hydroxy-2-methylbutyrate (16).* Methyl 2-methyl-3-oxobutyrate (**15**) (120 g) dissolved in THF (300 ml) was hydrogenated over reduced nickel (7.6 g) modified with (*S,S*)-tartaric acid (MHNi) in an autoclave (1000 ml capacity) by the procedure reported before[19,20] to give 116 g (95%) of crude methyl 3-hydroxy-2-methylbutyrate (**16**): bp 79—81 °C/18 mmHg. GLC (5% NPGS on Chromosorb W, 2 m×3 mm, at 90 °C, carrier gas N_2, 1.4 kg/cm^2) indicated that the products consisted of 25% of *threo*-**16** (retention time 12.8 min) and 75% of *erythro*-**16** (retention time 14.1 min). Seven repeated runs gave 833 g of crude **16**.

The Separation of threo-*and erythro-3-Hydroxy-2-methylbutyric Acid (18).* The **16** obtained above was saponified with 30% aqueous sodium hydroxide at 0 °C to give sodium 3-hydroxy-2-methylbutyrate (**17**). The aqueous solution of **17** was concentrated *in vacuo* at 40 °C to give 800 g of white crystalline **17**. A 200 g part of the crystals was dissolved in hot methanol (*ca.* 800 ml), and acetone (*ca.* 600 ml) was gradually added to the solution at room temperature until crystals of the sodium salt appeared. The crystals thus obtained were filtered to give 56.4 g of crude *threo*-**17**. Four repeated runs of this procedure gave 216 g of the salt. Three recrystallizations from methanol–acetone gave 108.8 g (13.6% from **16**) of pure *threo*-**17**. A small portion of the salt was acidified and the resulting acid was converted to methyl ester by the treatment of diazomethane. The GLC (5% NPGS on Chromosorb W, 2 m×3 mm, at 90 °C, carrier gas N_2, 1.4 kg/cm^2) of the methyl ester showed a single peak of the *threo*-isomer; Rt 12.8 min: $[\alpha]_D^{20}$ +22.4° (*c* 5, MeOH). The optical purity of the ester was calculated to be 61% based on the reported value ($[\alpha]_D^{20}$ +36.80° (*c* 5, MeOH)) for optically pure (2*S*,3*S*)-**20**.[22]

The mother liquids obtained from the original crystallization and the first recrystallization, as mentioned before, were combined and concentrated to dryness. The residue (534 g) was acidified with hydrochloric acid and was extracted with three 150 ml portions of ether. The evaporation of the extracts under reduced pressure gave 448.4 g (95% recovery from **17**) of 3-hydroxy-2-methylbutyric acid (**18**) enriched with *erythro*-isomer. The resulting **18** was dissolved in ethanol (650 ml) and then the solution was mixed with cyclohexylamine (380 g) under nitrogen. The mixture was allowed to stand overnight in a refrigerator. The crystals which precipitated were collected and recrystallized twice from ethanol to give 494.4 g (40% from **16**) of pure cyclohexylammonium salt (*erythro*-**19**). A small portion of the salt was acidified, and the free acid was converted to methyl ester with diazomethane. The GLC (5% NPGS on Chromosorb W, 2 m×3 mm, at 90 °C, carrier gas N_2, 1.4 kg/cm^2) of the ester showed a single peak corresponding to the *erythro*-isomer; Rt 14.1 min: $[\alpha]_D^{20}$ −8.5° (*c* 5, MeOH). The optical purity of the ester was calculated to be 60% based on the reported value ($[\alpha]_D^{20}$ +14.32° (*c* 5, MeOH)) for optically pure (2*S*, 3*R*)-**20**.[22]

Enrichment of Optical Purity of threo-*18.* *Threo*-**17** (90 g) dissolved in water (1000 ml) was passed through the column of Amberlite IR-120 (H^+ type) and the resulting solution of acid was converted to quinine salt with quinine (210 g) by the procedure reported before.[22] The quinine salt was recrystallized from water three times to give 144 g (51% from *threo*-**17**) of pure crystals of quinine salt: mp 154 °C; $[\alpha]_D^{20}$ −163° (*c* 2, 50% aq EtOH). The crystals were dissolved in water (200 ml) and the solution was mixed with 5% aqueous solution of NaOH until the pH of the mixture became 10. After removal of quinine precipitated by filteration, the filtrate was concentrated to dryness. Crystallization of the residue from ethanol–acetone gave 45 g (98% from quinine salt) of (2*S*,3*S*)-**17**: $[\alpha]_D^{20}$ +10.6° (*c* 10, H_2O).

Enrichment of Optical Purity of erythro-*18.* *Erythro*-**19** (100 g) in water (1000 ml) was passed through the column packed with Amberlite IR-120 (H^+ type) and the eluted acid was treated with 149 g of quinidine. The resulting quinidine salt was recrystallized three times from acetone.[22]

The purified quinidine salt thus obtained amounted to 101.8 g (58% from *erythro*-**19**): mp 100 °C; $[\alpha]_D^{20}$ +172° (*c* 1, H_2O). The quinidine salt dissolved in water was treated with 5% aqueous solution of NaOH while stirring. After removal of the quinidine which precipitated, the filtrate was concentrated to dryness. Crystallization of the residue from ethanol–acetone gave 30.0 g (93.2% from quinidine salt) of (2*R*,3*S*)-**17** as crystals: $[\alpha]_D^{20}$ +7.5° (*c* 10, H_2O).

Methyl (2S,3S)-3-Hydroxy-2-methylbutyrate ((2S,3S)-20). The **18** liberated from (2*S*,3*S*)-**17** (20 g) by the treatment with 12M[††] HCl (48 ml) was extracted with three 40 ml portions of ether. After the extract was concentrated to *ca.* 80 ml, an excess amount of ethereal diazomethane was added to the solution. After removal of the ether, the residue was distilled *in vacuo* to give 17.6 g (95.2%) of (2*S*,3*S*)-**20**: bp 75 °C/13 mmHg; $[\alpha]_D^{20}$ +36.80° (*c* 5, MeOH); GLC (5% NPGS on Chromosorb W, 2 m×3 mm, at 90 °C, carrier gas N_2, 1.4 kg/cm^2), Rt 12.8 min. (a single peak); NMR ($CDCl_3$, TMS), δ=1.17 (3H, d, J=7.1 Hz, $C\underline{H}_3$- at C-2), 1.24 (3H, d, J=6.4 Hz, $C\underline{H}_3$- at C_3), 2.47 (1H, quintet, -C$\underline{H}$(CH_3)-CO_2CH_3), 2.64—2.72 (1H, br, -O$\underline{H}$), 3.72 (3H, s, -$CO_2C\underline{H}_3$), 3.85 (1H, quintet, $CH_3C\underline{H}$(OH)-). Found: C, 54.45; H, 9.16%. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15%. In the NMR, methyl protons of ester group of (2*S*,3*S*)-**20** and that of (2*R*,3*R*)-**20** showed different chemical shift in the presence of chiral shift reagent. As for the sample of (2*S*,3*S*)-**20**, no detectable signals of antipode was observed when the spectra was measured with 17.5 mg of the sample and 45 mg of Eu(hfc)$_3$ in $CDCl_3$ (0.4 ml).

Methyl (2R,3S)-3-Hydroxy-2-methylbutyrate ((2R,3S)-20). By the procedure mentioned above, 20 g of (2*R*,3*S*)-**17** was converted into 17 g (92%) of (2*R*,3*S*)-**20**: bp 75 °C/15 mmHg; $[\alpha]_D^{20}$ −14.3° (*c* 5, MeOH); GLC (5% NPGS on Chromosorb W, 2 m×3 mm, at 90 °C, carrier gas N_2, 1.4 kg/cm^2), Rt 14.0 min. (a single peak); NMR ($CDCl_3$, TMS), δ=1.18 (3H, d, J=6.4 Hz, $C\underline{H}_3$- at C_3), 1.19 (3H, d, J=7.6 Hz, $C\underline{H}_3$- at C_2), 2.3—2.7 (2H, m, -C$\underline{H}$(CH_3)CO_2CH_3 and -O$\underline{H}$), 3.71 (3H, s, $-CO_2C\underline{H}_3$), 3.2—4.2 (1H, m, $CH_3C\underline{H}$(OH)-). Found: C, 54.60; H, 9.46%. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15%. In the NMR, methyl protons of ester group of (2*R*,3*S*)-**20** and that of (2*S*,3*R*)-**20** showed different chemical shifts in the presence of chiral shift reagent. As for the present sample, no detectable signals of antipode was observed when the spectra were measured with the sample (19.2 mg) and Eu(hfc)$_3$(100 mg) in $CDCl_3$ (0.4 ml).

(2R,3S)-2-Methyl-3-tetrahydropyranyloxy-1-butanol ((2R,3S)-21). To the solution (2*S*,3*S*)-**20** (13.5 g) and dihydro-

†† 1M=1 mol dm^{-3}.

pyran (7.8 g) in dry ether (20 ml) was added *p*-toluenesulfonic acid (0.1 g) with stirring at room temperature. The reaction mixture was allowed to stand overnight at room temperature and washed with aqueous $NaHCO_3$, and dried over K_2CO_3. This material was employed for the next step without further purification. To a stirred and ice-cooled suspension of lithium aluminum hydride (5.7 g) in dry ether (200 ml) was added dropwise the above ester in dry ether (30 ml). The mixture was refluxed for 3 h, cooled down to room temperature and hydrolyzed with the theoretical amount of water (10.8 g). The white precipitate was filtered on Celite and washed with ether. The combined filtrate was concentrated *in vacuo*. The distillation of the residue gave 12.2 g (83.7%) of (2*R*,3*S*)-**21**: bp 86.6 °C/2 mmHg; IR (neat), 3600—3800, 2800, 2700, 1430—1450, 1370, 1110—1120, 1010, 970, 930, 900, 870, 800 cm^{-1}. Found: C, 64.00; H, 10.91%. Calcd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71%.

(2S,3S)-2-Methyl-3-tetrahydropyranyloxy-1-butanol ((2*S*,3*S*)-**21**). By the same method as discribed above, (2*R*,3*S*)-**20** (20 g) was converted to 15.1 g (68%) of (2*S*,3*S*)-**21**: bp 93 °C/3 mmHg. Found: C, 63.60; H, 10.82%. Calcd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71%.

(2R,3S)-2-Methyl-3-tetrahydropyranyloxy-1-(tosyloxy)butane ((2R,3*S*)-**22**). The (2*R*,3*S*)-**21** (12.2 g) was added dropwise to the solution of *p*-toluenesulfonyl chloride (14.9 g) in dry pyridine (50 ml) cooled on an ice bath. After the reaction mixture was allowed to stand in a refrigerator overnight, it was poured into ice-water (100 ml), and extracted with three 20 ml portions of ether. The combined extract was washed with water, aqueous $CuSO_4$, $NaHCO_3$, and then brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 21 g (95.4%) of crude (2*R*,3*S*)-**22**.

(2S,3S)-2-Methyl-3-tetrahydropyranyloxy-1-(tosyloxy)butane ((2*S*,3*S*)-**22**). The (2*S*,3*S*)-**21** (12.2 g) was treated with 14.9 g of *p*-toluenesulfonyl chloride. The reaction product was worked up by the same procedure as before to give 18.3 g (83%) of crude (2*R*,3*S*)-**22**.

(2S,3R,7R)-3,7-Dimethyl-2-pentadecanol ((2*S*,3R,7R)-**1**). Grignard reagent, (*R*)-**10** was prepared from magnesium (0.43 g) and (*R*)-**9** (4.4 g) in well dried ether (30 ml). After the solution of (*R*)-**10** was cooled down to −70 °C in a Dry Ice-acetone bath, (2*R*,3*S*)-**21** (3 g) dissolved in ether (10 ml) and CuI (0.2 g) were added to the solution with stirring. The temperature of the reaction mixture was gradually raised to 5 °C and kept at 5 °C for 3 h and then overnight at room temperature. After the reaction mixture was refluxed and cooled down, the resulting ether solution was poured into ice-cooled NH_4Cl and the ethereal layer separated out. The aqueous layer was extracted with three 10 ml portions of ether. The combined ethereal solution was washed with aqueous NH_4Cl, $NaHCO_3$ and brine and then evaporated *in vacuo*. The remaining material was treated with *p*-toluenesulfonic acid (0.2 g) in methanol (20 ml) to give crude (2*S*,3*R*,7*R*)-**1**. The crude **1** was purified on a column (Wacogel C-100) with hexane (120 ml) and then 50% ether in hexane (100 ml). The (2*S*,3*R*,7*R*)-**1** was eluted in the second fraction. After removal of the solvent *in vacuo*, the distillation of the residue gave 1.9 g (84.4% from (2*R*,3*S*)-**22**) of (2*S*,3*R*,7*R*)-**1**: bp 116 °C/0.5 mmHg; $[\alpha]_D^{20}$ +16.03° (*c* 5.2, hexane); GLC (capillary column PEG 20M, 50 m (L)×0.25 mm (I.D), at 140 °C, carrier gas N_2, 1.2 kg/cm^2), Rt 15.5 min (a single peak); IR (neat) 3300, 2900, 2850, 1465, 1377, 1095 cm^{-1}; NMR ($CDCl_3$, TMS), δ=0.85 (9H, overlapped t and d, CH_3- at C-3, C-7 and terminal), 1.12 (3H, d, *J*=6.4 Hz, CH_3- at C-2), 1.26 (22H, br s, -(CH_2)$_{10}$-and 2×-C<u>H</u>-), 3.6 (1H, m, -C<u>H</u>(OH)-). Found: C, 79.04; H, 14.30%. Calcd for $C_{17}H_{36}O$: C, 79.61; ,H, 14.15%. (2*S*,3*R*)-**1** and (2*S*,3*S*)-**1** can be distinguished in the capillary GLC and ^{1}H-NMR. The capillary GLC (PEG 20M) results showed that the retention times of the former and the later were 15.5 min and 15.2 min, respectively. The present sample showed a single peak (Rt 15.5) and no peak of (2*S*,3*S*)-**1** (Rt. 15.2 min) was observed. By NMR, only doublet splitting of C-1 methyl signals was observed. Those analyses indicated that the sample was completely free from (2*S*,3*S*)-**1**.

(2S,3R,7S)-3,7-Dimethyl-2-pentadecanol ((2*S*,3R,7*S*)-**1**). This was obtained from (*S*)-**10** and (2*R*,3*S*)-**22** in 80% yield by the procedure mentioned before: bp 106.5—108 °C/0.4 mmHg; $[\alpha]_D^{20}$ +16.36° (*c* 3.5, hexane), GLC (capillary column PEG 20M, 50 m (L)×0.25 mm (I.D), at 130 °C, carrier gas N_2, 1.2 kg/cm^2), Rt 15.5 min (a single peak); IR (neat), 3300, 2900, 2850, 1465, 1377, 1095 cm^{-1}; NMR ($CDCl_3$, TMS), δ=0.85 (9H, overlapped t and d, CH_3-at C-3, C-7 and terminal), 1.16 (3H, d, *J*=6.4 Hz, CH_3- at C-2), 1.26 (22H, br s, -(CH_2)$_{10}$- and 2×-C<u>H</u>-), 3.6 (1H, m, -C<u>H</u>(OH)-). Found: C, 78.76; H, 14.29%. Calcd for $C_{17}H_{36}O$: C, 79.61; H, 14.15%. It was shown that the product was completely free from (2*S*,3*S*)-**1** in the capillary GLC and NMR analyses of this sample under the same conditions as mentioned before.

(2S,3S,7S)-3,7-Dimethyl-2-pentadecanol ((2*S*,3*S*,7*S*)-**1**). This was obtained from (*S*)-**10** and (2*S*,3*S*)-**22** in 52% yield by the method mentioned before: bp 110—117 °C/0.5 mmHg; $[\alpha]_D^{20}$ −10.4° (*c* 3.7, hexane); GLC (capillary column PEG 20M, 50 m (L)×0.25 mm (I.D), at 130 °C, carrier gas N_2, 1.2 kg/cm^2), Rt 15.2 min (a single peak); IR (neat) 3300, 2900, 2850, 1450, 1370, 1400, 920, 715 cm^{-1}; NMR ($CDCl_3$, TMS), δ=0.86 (9H, overlapped t and d, CH_3- at C-3, C-7 and terminal), 1.15 (3H, d, *J*=6.4 Hz, CH_3- at C-2), 1.26 (22H, br s, -(CH_2)$_{10}$- and 2×-C<u>H</u>-), 3.6 (1H, m, -C<u>H</u>(OH)-). Found: C, 78.95; H, 14.32%. Calcd for $C_{17}H_{36}O$: C, 79.61; H, 14.15%.

It was shown that the sample was completely free from (2*R*,3*S*)-isomer in the capillary GLC and NMR analyses

Table 1. Analytical date of (2*S*,3*R*,7*R*)-, (2*S*,3*R*,7*S*)-, or (2*S*,3*S*,7*S*)-2-acetoxy- and 2-propionyloxy-3,7-dimethylpentadecane

Compounds	r.t. of GLC[a)]	$[\alpha]_D^{20}$ in hexane	Elemental analysis	
			Calcd for $C_{19}H_{28}O_2$	Found
(2*S*,3*R*,7*R*)-**23**	16.1 min	+6.97±0.06 (*c* 1.4)	C, 76.45; H, 12.83	C, 76.03; H, 13.52
(2*S*,3*R*,7*S*)-**23**	16.1 min	+6.39±0.04 (*c* 4.9)		C, 76.39; H, 13.13
(2*S*,3*S*,7*S*)-**23**	15.8 min	−6.05±0.04 (*c* 4.3)		C, 75.98; H, 13.44
			Calcd for $C_{20}H_{40}O_2$	Found
(2*S*,3*R*,7*R*)-**24**	18.6 min	+7.03±0.03 (*c* 7.2)	C, 76.86; H, 12.90	C, 76.09; H, 13.00
(2*S*,3*R*,7*S*)-**24**	18.6 min	+6.67±0.04 (*c* 4.5)		C, 76.28; H, 12.92
(2*S*,3*S*,7*S*)-**24**	18.1 min	−6.16±0.03 (*c* 6.6)		C, 76.75; H, 13.07

a) Retention times at 130 °C on capillary column (PEG 20 M, 50 m(L) × 0.25 mm(I.D), carrier gas N_2, 1.4 kg/cm^2).

as mentioned before.

The Preparation of Pheromone. (2*S*,3*R*,7*R*)-, (2*S*,3*R*,7*S*)- and (2*S*,3*S*,7*S*)-3,7-dimethyl-2-pentadecanol were converted to the corresponding acetates and propionates by the conventional method respectively. The analytical data of the products are summarized in Table 1.

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