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Pheromone synthesis. Part 256: Synthesis of the four stereoisomers of 5,11-dimethylpentacosane, a new sex pheromone component of the male *Galleria mellonella* (L.), with high stereochemical purities as determined by the derivatization-HPLC analysis of the eight stereoisomers of 5,11-dimethyl-8-pentacosanol☆

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ABSTRACT

All the four stereoisomers of 5,11-dimethylpentacosane (>96.8% purity) were synthesized via the stereoisomers of 5,11-dimethyl-8-pentacosanol, whose stereoisomeric compositions could be determined precisely by their low temperature HPLC analysis after derivatization. 5,11-Dimethyl-8-pentacosanol was prepared by a Grignard reaction between 3-methylheptylmagnesium bromide and 4-methyloctadecanal, both of which were prepared from the commercially available enantiomers of citronellal (97–98% ee). Alternatively, (*R*)-3-methyl-1-heptanol could be prepared from methyl (*R*)-3-hydroxybutanoate (100% ee). Pd/C-catalyzed hydrogenation of a 5-methyl-1-alkene caused partial racemaization at C-5.

1. Introduction

The greater wax moth, *Galleria mellonella* (L.) (Lepidoptera: Pyralidae: Galleriinae), is a serious pest of the honeybee, *Apies mellifera* (L.). Its male-produced pheromone was identified in 1973 as a mixture of undecanal and nonanal by Leyrer and Monroe.[2] More detailed analyses of pheromone gland extracts and volatiles released by male *G. mellonella* (L.) resulted in the identification of the aldehydes, primary alcohols and fatty acids with nonane and undecane skeletons.[3] However, tests executed in an apiary showed that a 7:3 ratio of the undecanal/nonanal mixture could not attract the female moths.[4]

In 2014 Svensson et al. identified 5,11-dimethylpentacosane (**1**, Fig. 1) as a new pheromone component of the male greater wax moth, and synthesized it as a mixture of four stereoisomers, which acted as a behavioral synergist to the aldehydes.[5] Unfortunately, the level of attraction to the three-component mixture was still lower than that to the male extract.[5]

In order to establish the stereochemistry of the naturally occurring 5,11-dimethylpentacosane (**1**), it is necessary to synthesize all the four stereoisomers of **1**, and bioassay them separately after mixing with the aldehydes. This paper reports the synthesis of the four stereoisomers of **1** starting from the enantiomers of citronellal (**2**).[†]

2. Results and discussion

2.1. Retrosynthetic analysis of 5,11-dimethylpentacosane

Fig. 1 shows the retrosynthetic analysis of (5*R*,11*R*)-5,11-dimethylpentacosane (**1**). Since it is difficult to directly determine the stereochemical purity of (5*R*,11*R*)-**1**, (5*R*,8*RS*,11*R*)-5,11-dimethyl-8-pentacosanol (**A**) is chosen as the key intermediate. Our experience teaches us that the stereochemical analysis of **A**

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† Syntheses were carried out by K.M., while K.A. executed the HPLC analyses.

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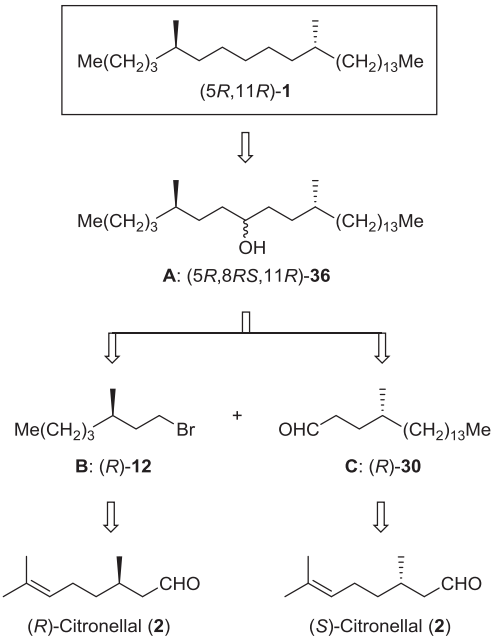


Fig. 1. Structure of (5*R*,11*R*)-5,11-dimethylpentacosane (**1**) and its retrosynthetic analysis to identify the enantiomers of citronellal (**2**) as its starting materials.

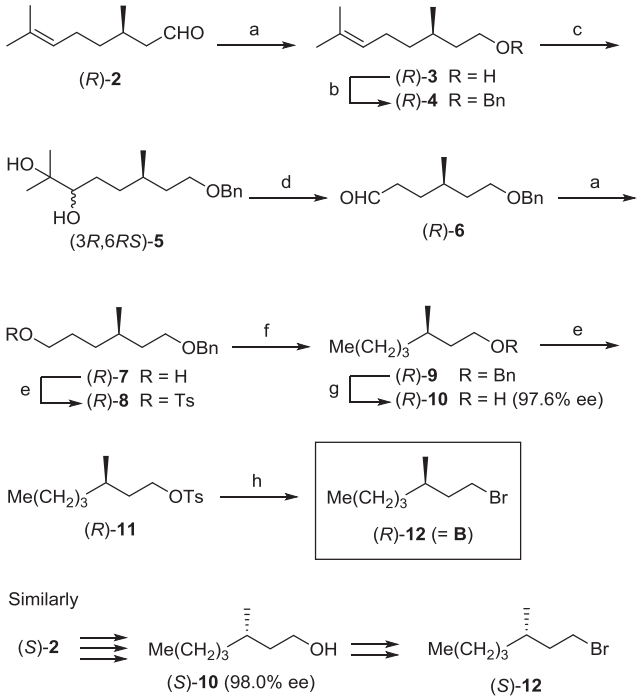
must be possible by HPLC after derivatization,[6–10] and the reductive removal of the hydroxy group at C-8 is feasible via its mesylate.[10] The alcohol **A** can be prepared from (*R*)-3-methylheptyl bromide (**B**) and (*R*)-4-methyloctadecanal (**C**) by means of a Grignard reaction. Synthesis of (*R*)-**B** is possible employing (*R*)-citronellal (**2**) as the starting material, while that of (*R*)-**C** is also possible by starting from (*S*)-citronellal (**2**). Both the enantiomers of citronellal (**2**, 97–98% ee) are commercially available and frequently employed in synthesis.[11]

2.2. Synthesis of the enantiomers of 3-methylheptyl bromide from the enantiomers of citronellal

2.2.1. Successful route. As to the synthesis of the enantiomers of 3-methylheptyl bromide (**B**), we examined various different routes. The most straightforward and successful one was that summarized in Scheme 1. This route converted citronellal enantiomers (97–98% ee) to the enantiomers of **B** in 32% overall yield (10 steps). The key-step of the route is one-carbon elongation of tosylate **8** under the Schlosser conditions[12] to give **9**.

The first step of the route leading to **B**: (*R*)-**12** was reduction of (*R*)-citronellal (**2**) with $LiAlH_4$ to give (*R*)-citronellol (**3**), which was converted to the corresponding benzyl (Bn) ether (*R*)-**4** by treatment with *t*-BuOK and BnCl in DMSO. Dihydroxylation of (*R*)-**4** to (3*R*,6*RS*)-**5** was executed with a catalytic amount of OsO_4 in the presence of *N*-methylmorpholine *N*-oxide (NMO) in aqueous acetone and *t*-BuOH.[13] Cleavage of glycol **5** with periodic acid gave aldehyde (*R*)-**6**, which was reduced with $LiAlH_4$ to give diol monobenzyl ether (*R*)-**7**. The corresponding tosylate (*R*)-**8** was treated with MeMgBr in the presence of Li_2CuCl_4 in THF[12] to give (*R*)-**9** in 75% yield.

Hydrogenolytic removal of the benzyl group of **9** was best carried out with hydrogen and $Pd(OH)_2/C$ (Pearlman catalyst) in EtOH to give (*R*)-**10**, whose enantiomeric purity was 97.6% ee as determined by its enantioselective GC analysis on a Chiramix® column.[14] The corresponding tosylate (*R*)-**11** was treated with LiBr in DMF to furnish (*R*)-3-methylheptyl bromide [**B**: (*R*)-**12**], $[\alpha]_D^{24}$ −6.94 (*c* 4.27, pentane). We secured 7.0 g of (*R*)-**12**, which was sufficient for the preparation of the required amounts of (5*R*,11*R*)- and (5*R*,11*S*)-**1**. Similarly, 4.7 g of (*S*)-**12**, $[\alpha]_D^{23}$ +7.25 (*c* 4.24, pentane), was prepared from (*S*)-citronellal (**2**) via (*S*)-**10** (98.0% ee). The present method will serve as a useful general procedure to prepare the enantiomers of 3-methyl-1-alkanols from the enantiomers of citronellal (**2**).



Scheme 1. Synthesis of the enantiomers of 3-methylheptyl bromide (**12**). Reagents; (a) $LiAlH_4$, THF (quant.); (b) *t*-BuOK, BnCl, DMSO (92%); (c) OsO_4, NMO, *t*-BuOH, acetone, H_2O (85%); (d) $HIO_4 \cdot 2H_2O$, THF (87%); (e) TsCl, DMAP, C_5H_5N (91% for **8**; 99% for **11**); (f) MeMgBr, Li_2CuCl_4, THF (75%); (g) H_2, $Pd(OH)_2/C$, EtOH (85%); (h) LiBr, DMF (82%).

2.2.2. Less successful routes: the enantiomers of 3-methyl-6-heptenyl pivalate partially racemized upon hydrogenation over Pd/C. Several years ago the enantiomers of 3-methyl-6-hepten-1-ol[15] and their acetates (**13**, Scheme 2)[16] were prepared from the enantiomers of citronellal, and employed in pheromone synthesis as building blocks for olefin cross metathesis reactions. Hydrogenation of **13** will give 3-methylheptyl acetate, which can be utilized in the present synthesis. Since the acetyl group of **13** was not stable enough as a protective group, a route starting from citronellyl pivalate (**14**) was examined as summarized in Scheme 2. The bulky pivalate group would tolerate the conditions required for the Wittig olefination (**16**→**17**).

Accordingly, (*R*)-citronellol (**3**) was acylated with pivaloyl chloride to give (*R*)-**14**. Epoxidation of (*R*)-**14** with *m*-chloroperbenzoic acid (MCPBA) furnished (3*R*,6*RS*)-**15**, which was treated with periodic acid dihydrate to afford aldehyde (*R*)-**16**. Treatment of (*R*)-**16** with methylene triphenylphosphorane gave (*R*)-**17** in 65% yield. Hydrogenation of (*R*)-**17** over 10% Pd/C (Kojima Chemical Co.) in EtOH provided (*R*)-3-methylheptyl pivalate (**18**). The pivaloyl group of **18** was removed by alkaline hydrolysis to furnish (*R*)-**10** (5.4 g). The overall yield of (*R*)-**10** was 32% based on (*R*)-**2** (7 steps). Enantioselective GC analysis of the present (*R*)-**10** on a Chiramix® column, however, revealed it to be of as low as 86% ee. Its (*S*)-isomer (**10**), similarly prepared from (*S*)-**2**, was only of 80% ee. The employed Pd/C catalyst caused partial racemization of **17** in the course of its hydrogenation to **18**. Apparently, migration of the terminal double bond to the inner position(s) took place prior to hydrogenation, which caused the observed partial racemization at C-3.

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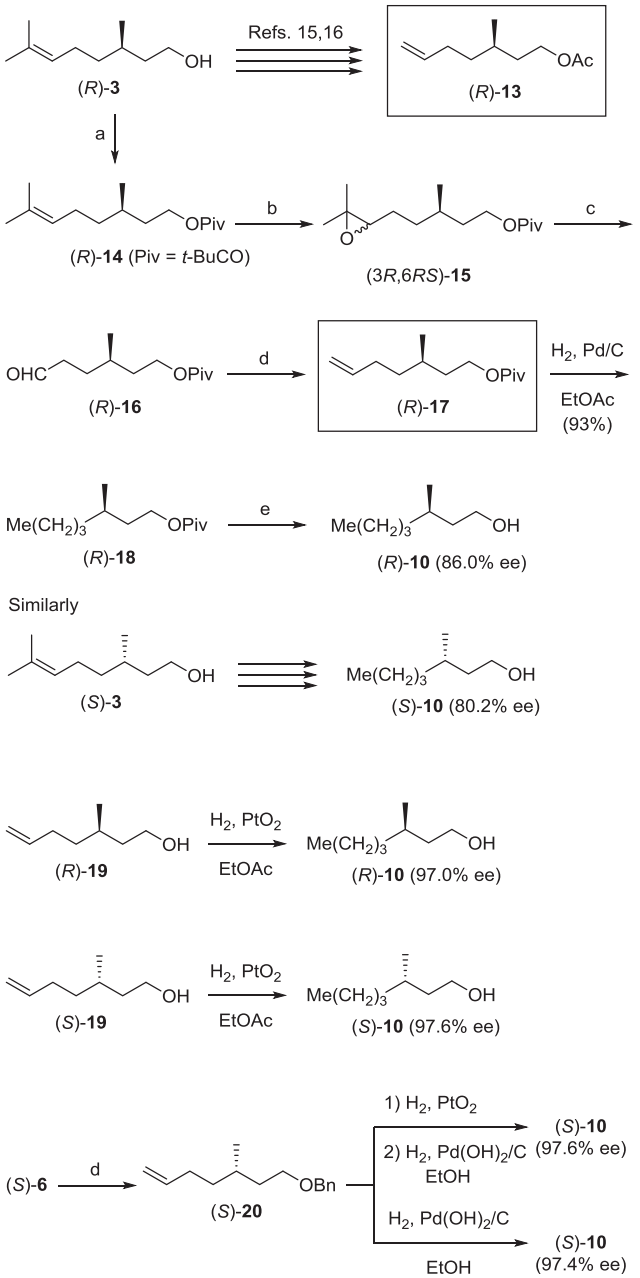


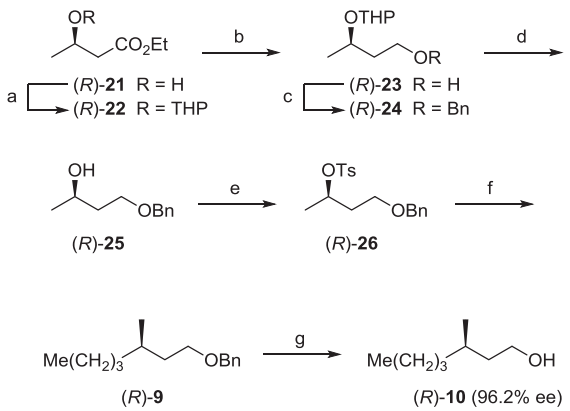
Scheme 2. Synthesis of the enantiomers of 3-methyl-1-heptanol (**10**) via the pivalate (**17**) and benzyl ether (**20**) of the enantiomers of 3-methyl-6-hepten-1-ol (**19**). Reagents: (a) PivCl, DMAP, C_5H_5N, C_6H_6 (96%); (b) MCPBA, CH_2Cl_2 (quant.); (c) $HIO_4 \cdot 2H_2O$, THF (63%); (d) $Ph_3P(Me)Br$, *n*-BuLi, THF [65% for (*R*)-**17**; 70% for (*S*)-**20**]; (e) KOH, MeOH (88%).

Since the partial racemization at a methyl branching position far separated from a double bond is quite problematic in enantioselective synthesis,[17,18] several additional hydrogenation experiments were carried out. Hydrogenation of the enantiomers of 3-methyl-6-hepten-1-ol (**19**; prepared from citronellal of 97–98% ee) over Adams's PtO_2 (Kojima Chemical Co.), in EtOAc caused no racemization at all, giving (*R*)-**10** of 97.0% ee and (*S*)-**10** of 97.6% ee. When hydrogenation of (*S*)-3-methyl-6-heptenyl benzyl ether (**20**) was executed successively with PtO_2 followed by $Pd(OH)_2/C$ (TCI), the product was (*S*)-**10** of 97.6% ee. Hydrogenation of (*S*)-**20** over $Pd(OH)_2/C$ in EtOH directly gave (*S*)-**10** of 97.4% ee. A lesson learned through the hydrogenation experiments is that the enantiomeric purity of the product should always be checked precisely by enantioselective GC. Accordingly, the method described in 2.2.1 is the preferable one for the preparation of the enantiomers of 3-methyl-1-heptanol (**10**), because it does not involve the hydrogenation of a double bond. Another option is to use diimide reduction instead of catalytic hydrogenation.[17,18]

2.3. Synthesis of (*R*)-3-methyl-1-heptanol from ethyl (*R*)-3-hydroxybutanoate

Over thirty years ago, Mori and Sugai converted ethyl (*S*)-3-hydroxybutanoate (**21**; 88% ee) into (*S*)-3-methyl-1-heptanol {**10**; 88% ee, $[\alpha]_D^{22.4}$ −2.19(*c* 6.45, $CHCl_3$)}.[19] At that time it was difficult to secure the pure enantiomers of ethyl 3-hydroxybutanoate. Now they are commercially available. We therefore planned to prepare (*R*)-**10** starting from commercially available PHB (poly-β-hydroxybutyrate) produced by a microorganism, which is a polymer of pure (*R*)-3-hydroxybutanoic acid. Ethanolysis of PHB readily provided enantiomerically pure ethyl (*R*)-3-hydroxybutanoate (**21**; 100% ee) in 72% yield.[20,21]

Scheme 3 shows the synthesis of (*R*)-3-methyl-1-heptanol (**10**) starting from (*R*)-**21**. The hydroxy ester (*R*)-**21** was converted to (*R*)-3-tosyloxybutyl benzyl ether (**26**) via (*R*)-**22**–**25** as reported previously.[22] In our 1982 synthesis (*S*)-**26** was treated with $(n\text{-Bu})_2CuLi$, giving (*S*)-**9** with inversion of configuration at C-3. In the present case, (*R*)-**26** was treated with *n*-BuMgBr in the presence of Li_2CuCl_4 under the Schlosser conditions[12] to give (*R*)-**9** in 77% yield. Hydrogenolytic removal of the benzyl group of (*R*)-**9** was executed over $Pd(OH)_2/C$ in EtOH to give (*R*)-**10** (96.2% ee). Thus, erosion of the enantiomeric purity in the course of the conversion of (*R*)-**21** to (*R*)-**10** was only 3.8%. The step, which contributed most for the decline of the enantiomeric purity could not be identified, because we did not determine the enantiomeric purity of each of the intermediates. It is generally accepted that tosylates give products of S_N2-type inversion.[23] The overall yield of (*R*)-**10** was 25% based on PHB (8 steps), which was slightly lower than that (39%) of (*R*)-**10** based on (*R*)-citronellal (**2**, 8 steps).



Scheme 3. Synthesis of (*R*)-3-methyl-1-heptanol (**10**) by starting from ethyl (*R*)-3-hydroxybutanoate (**21**). Reagents: (a) DHP, TsOH, Et_2O (quant.); (b) $LiAlH_4$, THF (85%); (c) NaH, BnCl, THF (91%); (d) dil. HCl, MeOH (99%); (e) TsCl, C_5H_5N (85%); (f) *n*-BuMgBr, Li_2CuCl_4, THF (77%); (g) H_2, $Pd(OH)_2/C$, EtOH (70%). Poly-β-hydroxybutyrate (PHB) gave (*R*)-**21** in 72% yield.

The present PHB-based synthesis is a general one, and can be widely applied to the synthesis of optically active 3-methyl-1-alkanols. Use of the Schlosser conditions for the alkylative inversion at C-3 of (*R*)-**26** was shown to be a remarkable improvement for the scalable preparation of 3-methyl-1-alkanols, because it avoids the use of a stoichiometric or excess amount of the Gilman-type R_2CuLi. The yield in the present work (77%) by applying *n*-BuMgBr and Li_2CuCl_4 was higher than that (55%) with $(n\text{-Bu})_2CuLi$.

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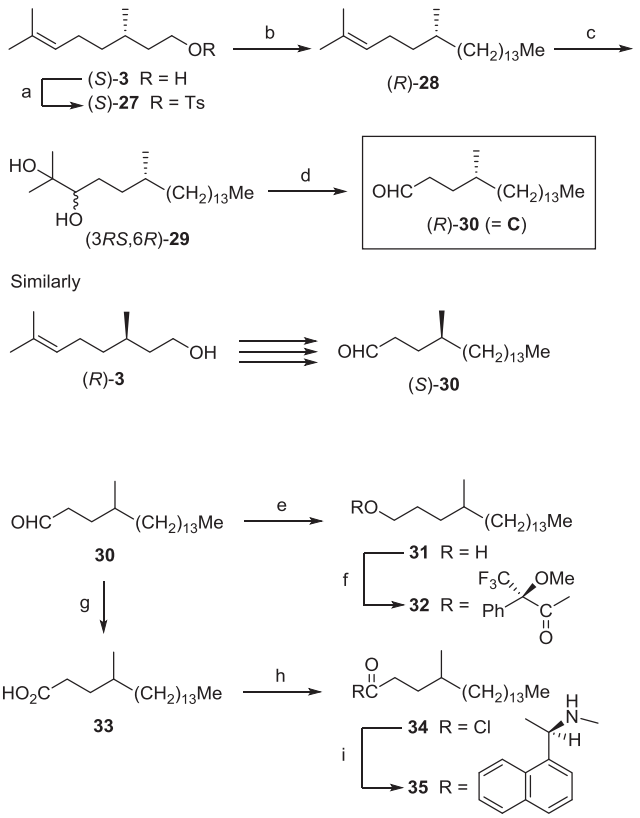
2.4. Synthesis of the enantiomers of 4-methyloctadecanal

The enantiomers of 4-methyloctadecanal (**30**) were prepared from the enantiomers of citronellol (**3**) by the known method[24] as shown in Scheme 4. Tosylation of (*S*)-citronellol (**3**) gave the corresponding tosylate (*S*)-**27**. Chain-elongation of (*S*)-**27** was executed with *n*-$C_{12}H_{25}MgBr$ and Li_2CuCl_4 under the Schlosser conditions[12] to give (*R*)-**28**. Dihydroxylation of (*R*)-**28** with OsO_4 and NMO gave a diastereomeric mixture of diols (3*RS*,6*R*)-**29**, whose cleavage with $HIO_4 \cdot 2H_2O$ afforded (*R*)-4-methyloctadecanal (**30**). The overall yield of (*R*)-**30** was 87% based on (*S*)-**3** (4 steps). Similarly, (*R*)-citronellol (**3**) was converted to (*S*)-**30**.

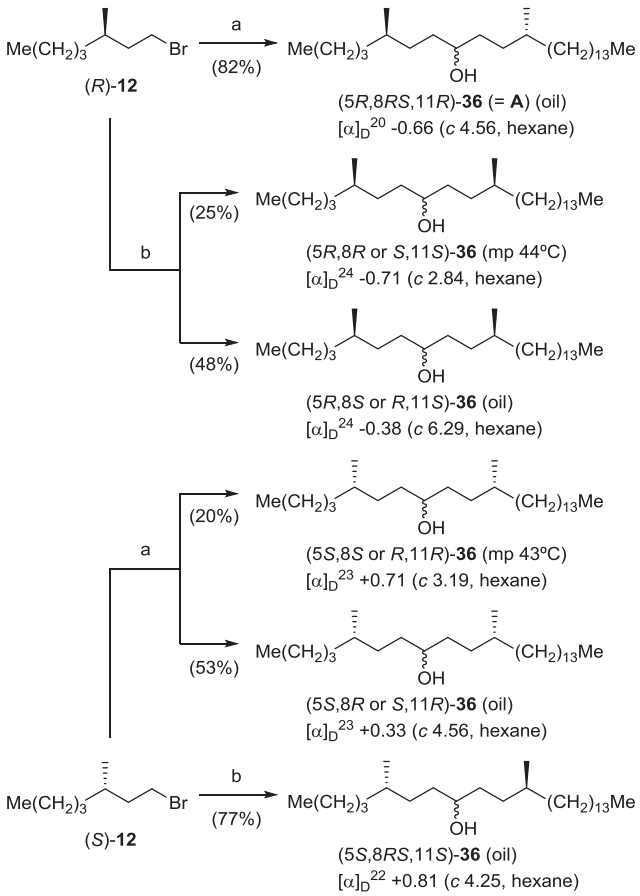


Scheme 4. Synthesis of the enantiomers of 4-methyloctadecanal (**30**). Reagents: (a) TsCl, C_5H_5N (quant.); (b) $Me(CH_2)_{11}Br$, Mg, Li_2CuCl_4, THF; (c) OsO_4, NMO, *t*-BuOH, acetone, H_2O [50% of crystalline **29** and 45% of oily **29** (2 steps)]; (d) $HIO_4 \cdot 2H_2O$, THF (92%); (e) $LiAlH_4$, THF (quant.); (f) (*S*)-MTPACl, DMAP, C_5H_5N, CH_2Cl_2; (g) Jones CrO_3, acetone; (h) $(COCl)_2$, C_6H_6; (i) (*R*)-1-(1-naphthyl)ethylamine, Et_3N, C_6H_6.

Attempts were made to determine the enantiomeric purity of **30**. First, separation of the corresponding alcohols (*R*)- and (*S*)-**31** was examined by enantioselective GC on a Chiramix® column, and they were found to be inseparable. Secondly, the alcohols (*R*)- and (*S*)-**31** were esterified with (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPACl),[25] and the resulting MTPA esters (*R*)- and (*S*)-**32** were analyzed by ^1H NMR and GC–MS. Unfortunately, the two diastereomers (*R*)- and (*S*)-**32** could not be distinguished from each other. Finally, the enantiomers of acid **33** were prepared from **30** by oxidation, and the corresponding acyl chloride **34** was treated with (*R*)-1-(1-naphthyl)ethylamine to give the diastereomers of amide **35**. They could not be distinguished from each other by ^1H NMR and GC–MS analyses. Accordingly, we assumed the enantiomeric purity of the enantiomers of **30** to be 97–98% ee, reflecting the ee of the starting enantiomers of citronellal (**2**). This assumption was later verified by analyzing the stereoisomeric composition of **36** (see 2.6).

2.5. Synthesis of all the stereoisomers of 5,11-dimethyl-8-pentacosanol and their conversion to all the four stereoisomers of the pheromone component, 5,11-dimethylpentacosane

Since the stereoisomeric pairs of both bromide **12** and aldehyde **30** were provided, the next stage was the coupling of these two building blocks by a Grignard reaction to give all the stereoisomers of 5,11-dimethyl-8-pentacosanol (**36**) as shown in Scheme 5. The Grignard reaction between (*R*)-3-methylheptylmagnesium bromide and (*R*)-4-methyloctadecanal (**30**) yielded a mixture of two diastereomeric alcohols (5*R*,8*R*,11*R*)-**36** and (5*R*,8*S*,11*R*)-**36** as an oil.

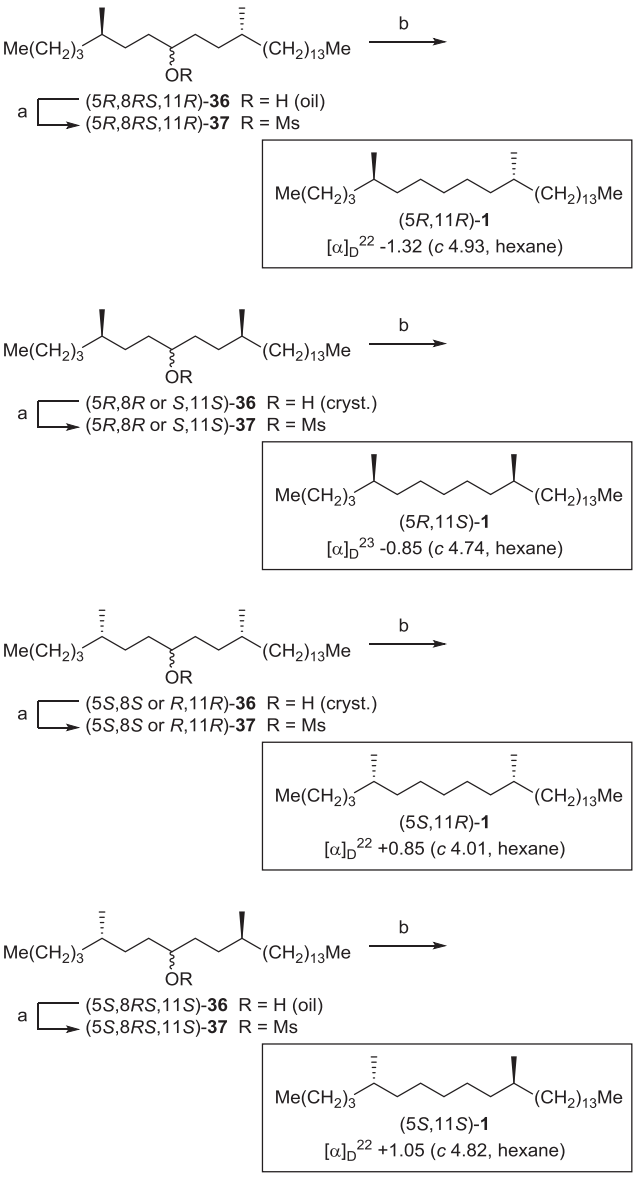


Scheme 5. Synthesis of all the stereoisomers of 5,11-dimethyl-8-pentacosanol (**36**). Reagents: (a) (i) Mg, THF; (ii) (*R*)-4-methyloctadecanal (**30**); (b) (i) Mg, THF; (ii) (*S*)-**30**.

In the same manner, (*R*)-3-methylheptylmagnesium bromide and (*S*)-**30** gave a diastereomeric mixture of two alcohols (5*R*,8*R*,11*S*)-**36** and (5*R*,8*S*,11*S*)-**36**, one of which was obtained as crystals with low mp. Since the hydroxy group at C-8 was to be removed later, no attempt was made to assign the absolute configuration at C-8 of the crystalline material, whose crystal shape and size (small needles) made its X-ray analysis difficult. The crystalline (5*R*,8*R* or *S*, 11*S*)-**36** was employed for the final deoxygenation reaction. Similarly, as shown in Scheme 5, crystalline (5*S*,8*S* or *R*,11*R*)-**36** and oily (5*S*,8*R* or *S*,11*R*)-**36** were obtained by treating aldehyde (*R*)-**30** with the Grignard reagent derived from

(*S*)-**12**. Finally, addition of the Grignard reagent derived from (*S*)-**12** to aldehyde (*S*)-**30** yielded a diastereomeric mixture (5*S*,8*RS*,11*S*)-**36** as an oil.

Scheme 6 shows the conversion of the stereoisomers of 5,11-dimethyl-8-pentacosanol (**36**) to all the four stereoisomers of 5,11-dimethylpentacosane (**1**). Removal of the hydroxy group at C-8 of **36** was executed in two steps by (i) mesylation of alcohol **36** to give the corresponding mesylate **37** and (ii) reduction of **37** with $LiAlH_4$ in THF to give **1**. When fresh $LiAlH_4$ was employed for the reduction, no formation of alkenes was observed, and pure **1** could be secured. In a previous work, a small amount (1.4%) of alkenes was generated in the course of the reduction of 12-methanesulfonyloxy-15-methylheptacosane, when it was reduced with aged $LiAlH_4$.[26] It might have been due to the presence of a small amount of LiOH and $Al(OH)_3$ on the surface of aged $LiAlH_4$.



Scheme 6. Synthesis of the four stereoisomers of 5,11-dimethylpentacosane (**1**). Reagents: (a) MsCl, DMAP, C_5H_5N, CH_2Cl_2 (quant.); (b) $LiAlH_4$, THF [50% for (5*R*,11*R*)-**1**; 52% for (5*R*,11*S*)-**1**; 74% for (5*S*,11*R*)-**1**; 49% for (5*S*,11*S*)-**1**].

All the four stereoisomers of 5,11-dimethylpentacosane (**1**) were obtained as colorless oils, and they were of >96.8% purity as evidenced by the analytical works detailed in the next section (2.6). They showed IR, ^1H NMR and MS spectra virtually identical to those of the natural product.[5] Their ^{13}C NMR spectra were consistent with that reported for the racemic and diastereomeric mixture of synthetic **1**.[5]

2.6. Separation of the eight stereoisomers of 5,11-dimethyl-8-pentacosanol by Ohrui-Akasaka's derivatization-reversed phase HPLC method, and estimation of the stereoisomeric composition of the four synthetic stereoisomers of 5,11-dimethylpentacosane

Although systematic comparison of ^{13}C NMR spectra is useful in determining the stereostructures of methyl-branched alkanes,[27] we believe derivatization-reversed phase HPLC method developed by Ohrui and Akasaka is more convenient in natural products chemistry in general and pheromone chemistry in particular, especially when they possess a hydroxy group.

Ohrui designed chiral and fluorescent derivatizing agents such as (1*R*,2*R*)- and (1*S*,2*S*)-2-(anthracene-2,3-dicarboximido)cyclohexanecarboxylic acid (**38**, Fig. 2; commercially available from Tokyo Chemical Industry Co., TCI-A1657 and A1658).[28–31] Due to the fluorescent nature of the anthracene moiety of the reagent, detection of the derivatives is possible at 10^{-15} mol levels. Ohrui-Akasaka's method was employed by us to determine the absolute configuration and stereoisomeric composition of the New World screwworm fly pheromone,[32] tribolure (the pheromone of the red flour beetle),[8,33] and CH503 (*Drosophila melanogaster* pheromone).[9] At present, this HPLC method is the most powerful one in determining the absolute configuration of a stereogenic center separated from a hydroxy or carboxy group.

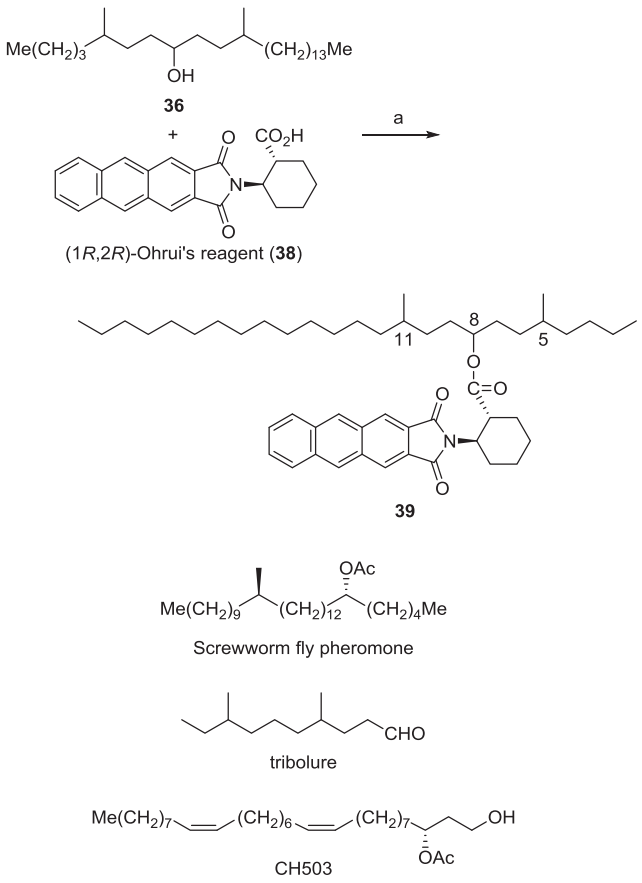


Fig. 2. Derivatization of **36** to **39** for HPLC analysis. Reagents: (a) EtN=C=N$(CH_2)_3NMe_2$·HCl (EDC), DMAP, toluene, MeCN.

Derivatization of the six crystalline or oily samples of 5,11-dimethyl-8-pentacosanol (**36**) with (1*R*,2*R*)-**38** in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) and 4-dimethylaminopyridine (DMAP) afforded ester **39**, whose eight stereoisomers could be separated on a Develosil C30-UG-3 column at −55 °C by elution with a mixture of MeOH/MeCN/THF/2,3,3-trimethylpentane (2:8:22:10, *v*/*v*/*v*/*v*) at a flow rate of 0.2 mL/min. Each of the eight peaks in the chromatogram (Fig. 3a) could be assigned to a specific stereoisomer by separately analyzing the six samples of the stereoisomers of **36** after derivatization to **39**. Note that the absolute configuration at C-8 remains unknown.

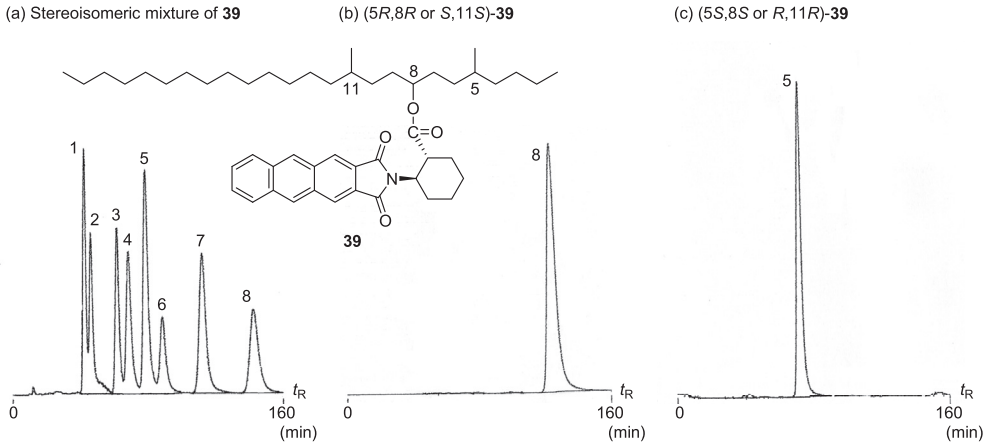
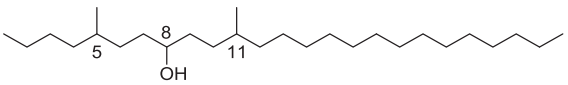


Fig. 3. HPLC separation of the stereoisomers of **36** after derivatization to **39**. Column: Develosil C30-UG3, 4.6 mm i.d.×150 mm; mobile phase: MeOH/MeCN/THF/2,3,3-trimethylpentane=2:8:22:10 (*v*/*v*/*v*/*v*); column temperature; −55 °C; flow rate: 0.2 mL/min; peaks (1) t_R 42.4 min, (5*R*,8*R* or *S*,11*R*)-**39**; (2) 46.3 min, (5*S*,8*R* or *S*,11*S*)-**39**; (3) 61.5 min, (5*R*,8*S* or *R*,11*R*)-**39**; (4) 68.4 min, (5*R*,8*S* or *R*,11*S*)-**39**; (5) 78.3 min, (5*S*,8*S* or *R*,11*R*)-**39**; (6) 88.7 min, (5*S*,8*S* or *R*,11*S*)-**39**; (7) 112.0 min (5*S*,8*R* or *S*,11*R*)-**39**; (8) 142.5 min, (5*R*,8*R* or *S*,11*S*)-**39**.

Table 1 shows the stereoisomeric composition of the synthetic stereoisomers of 5,11-dimethyl-8-pentacosanol (**36**) as determined by the HPLC analysis of **39**. All the samples possess satisfactory stereochemical purity at C-11 (96–99% ee), verifying the high ee of the enantiomers of 4-methyloctadecanal (**30**). The crystalline alcohols (5*R*,8*R* or *S*,11*S*)-**36** and (5*S*,8*S* or *R*,11*R*)-**36** were relatively pure (94.08% and 92.76%, respectively) after single recrystallization. These single-recrystallized alcohols **36** were converted to the final products **1**. Other oily samples of **36** were shown to be a mixture of major two diastereomers at C-8 and other minor stereoisomers. The crystalline alcohols (5*R*,8*R* or *S*,11*S*)- and (5*S*,8*S* or *R*,11*R*)-**36** could be purified further by an additional recrystallization. As shown in Fig. 3b and c and Table 2, they were of 99.05% and 98.22% stereochemical purities.

Although it was impossible to determine the absolute configuration at C-8 of the crystalline **36**, we were able to determine the stereoisomeric composition of the each sample of **39** (hence **36**) with regard to the absolute configuration at C-5 and C-11 as shown in Table 3. Because mesylation of **36** and reduction of the resulting mesylate **37** does not affect the enantiomeric purities at C-5 and C-11, the stereoisomeric compositions of the stereoisomers of **1** must be same as those listed in Table 3. Accordingly, the populations (%) of the desired isomer in our synthetic 5,11-dimethylpentacosane are 98.8% for (5*R*,11*R*)-**1**, 98.7% for (5*R*,11*S*)-**1**, 97.2% for (5*S*,11*R*)-**1** and 96.8% for (5*S*,11*S*)-**1**. Fig. 3 and Tables 1–3 clearly demonstrate the high purities of our samples. It should be noted that a single recrystallization of the 8-hydroxylated precursors [(5*R*-,8*R* or *S*,11*S*)- and (5*S*,8*S* or *R*,11*R*)-**36**] of (5*R*,11*S*)- and (5*S*,11*R*)-**1** did not increase the purities of the final products remarkably. The purities of (5*R*,11*S*)- and (5*S*,11*R*)-**1** (98.7 and 97.2%, respectively) were almost the same as those of (5*R*,11*R*)- and (5*S*,11*S*)-**1** (98.8 and 96.8%, respectively), whose precursors were oily and could not be purified by recrystallization. The enantiomeric purities of the final products

Table 1
Stereoisomeric composition of the synthetic stereoisomers of 5,11-dimethyl-8-pentacosanol (**36**) as determined by the HPLC analysis of **39** derived from **36**



36

HPLC peak no.	Stereochemical assignment	Synthetic samples and their stereoisomeric composition (% ratio of the peak areas)					
		(5*R*,8*RS*,11*R*)-**36**	(5*R*,8*R* or *S*,11*S*)-**36**		(5*S*,8*S* or *R*,11*R*)-**36**		(5*S*,8*RS*,11*S*)-**36**
			Crystals	Oil	Crystals	Oil	
1	5*R*,8*R* or *S*,11*R*	52.00	0.00	0.37	0.59	1.00	1.25
2	5*S*,8*R* or *S*,11*S*	0.00	0.21	1.38	0.92	1.19	52.64
3	5*R*,8*S* or *R*,11*R*	46.83	0.12	0.13	0.00	1.12	0.56
4	5*R*,8*S* or *R*,11*S*	0.00	4.59	81.75	1.02	0.00	0.58
5	5*S*,8*S* or *R*,11*R*	0.12	0.00	0.00	92.76	26.48	0.00
6	5*S*,8*S* or *R*,11*S*	0.04	0.62	0.87	0.00	1.37	44.13
7	5*S*,8*R* or *S*,11*R*	0.94	0.37	0.00	4.44	68.73	0.21
8	5*R*,8*R* or *S*,11*S*	0.06	94.08	15.50	0.26	0.00	0.64

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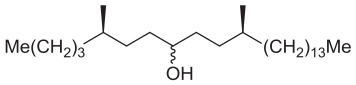
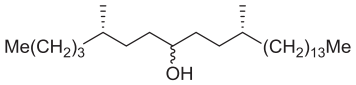
Table 2
Stereoisomeric composition of the two crystalline stereoisomers of 5,11-dimethyl-8-pentacosanol (**36**) after two recrystallizations as determined by the HPLC analysis of **39** derived from them



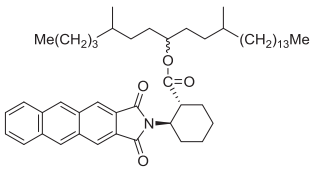
(5*R*,8*R* or *S*,11*S*)-**36** (mp 44°C)



(5*S*,8*S* or *R*,11*R*)-**36** (mp 43°C)

HPLC peak no.	Stereochemical assignment	Synthetic samples and their stereoisomeric composition (% ratio of the peak areas)	
		(5*R*,8*R* or *S*,11*S*)-**36**	(5*S*,8*S* or *R*,11*R*)-**36**
1	5*R*,8*R* or *S*,11*R*	0.00	0.40
2	5*S*,8*R* or *S*,11*S*	0.00	0.88
3	5*R*,8*S* or *R*,11*R*	0.07	0.00
4	5*R*,8*S* or *R*,11*S*	0.12	0.00
5	5*S*,8*S* or *R*,11*R*	0.20	98.22
6	5*S*,8*S* or *R*,11*S*	0.20	0.00
7	5*S*,8*R* or *S*,11*R*	0.37	0.50
8	5*R*,8*R* or *S*,11*S*	99.05	0.00

Table 3
Stereoisomeric composition of the samples of **39** with regard to the absolute configurations at C-5 and C-11



39

Peaks 1 and 3 represent (5*R*,11*R*)-**39**.
Peaks 2 and 6 represent (5*S*,11*S*)-**39**.
Peaks 4 and 8 represent (5*R*,11*S*)-**39**.
Peaks 5 and 7 represent (5*S*,11*R*)-**39**.

HPLC peaks due to	Synthetic samples and their stereoisomeric composition (% ratio of the peak areas)			
	(5*R*,11*R*)-**39**	(5*R*,11*S*)-**39** from crystalline **36**	(5*S*,11*R*)-**39** from crystalline **36**	(5*S*,11*S*)-**39**
(5*R*,11*R*)-**39**	98.84	0.12	0.59	1.80
(5*R*,11*S*)-**39**	0.06	98.68	1.28	1.22
(5*S*,11*R*)-**39**	1.06	0.37	97.20	0.21
(5*S*,11*S*)-**39**	0.04	0.83	0.93	96.77

could be determined from the figures in Table 3, and were 98.8% ee for (5*R*,11*R*)-**1**, 98.3% ee for (5*R*,8*S*)-**1**, 95.9% ee for (5*S*,8*R*)-**1** and 95.0% ee for (5*S*,11*S*)-**1**. Further biological studies require the four stereoisomers of **1** in highest purities, because it has been shown that the biological activity of the stereoisomers of similar dimethylalkanes may be different.[34]

3. Conclusion

All the four stereoisomers of 5,11-dimethylpentacosane (**1**), a new pheromone component of *Galleria mellonella* (L.), were synthesized in satisfactory purities (96.8–98.8%) by starting from the enantiomers of citronellal (**2**), which as well as those of ethyl 3-hydroxybutanoate (**21**) were shown to be useful starting materials for the synthesis of the enantiomers of 3-methyl-1-alkanols. The enantiomers of citronellal (**2**) serve as the starting materials for the synthesis of the enantiomers of 4-methylalkanals. Ohrui-Akasaka's derivatization-HPLC method was again proved to be a versatile method for the determination of the stereochemical composition of methyl-branched alkanols. Bioassay of the four stereoisomers of **1** against *G. mellonella* females will be carried out in due course by Svensson et al. in Sweden. The future result will further enrich our knowledge about stereochemistry-bioactivity relationships among pheromones.[35,36]

4. Experimental

4.1. General

Melting points are uncorrected values. Refractive indices were measured on an Atago DMT-1 refractometer. Optical rotations were measured on a Jasco P-1020 polarimeter. IR spectra were measured on a Jasco FT/IR-410 spectrometer. ^{1}H NMR spectra (400 MHz, TMS at δ=0.00 as internal standard) and ^{13}C NMR spectra (100 MHz, $CDCl_3$ at δ=77.0 as internal standard) were recorded on a Jeol JNM-AL 400 spectrometer. GC–MS were measured on Agilent Technologies 5975 inert XL. HRMS were recorded on Jeol JMS-SX102A, Waters Synapt G2 HDMS, or Varian 901-MS Ion Spec QFT-7. Column chromatography was carried out on Merck Kieselgel 60 Art 1.07734.

4.2. Citronellyl benzyl ether (4)

4.2.1. (R)-Isomer. Powdered *t*-BuOK (14.6 g, 130 mmol) was added portionwise to a stirred solution of (*R*)-**3** (17.8 g, 114 mmol) in dry DMSO (120 mL). Stirring was continued for 10 min to generate a homogeneous solution. A solution of BnCl (19.0 g, 150 mmol) in dry C_6H_6 (10 mL) was added over 15 min to the stirred solution. The reaction was exothermic, and the temperature of the mixture rose

up to about 50 °C. Stirring was continued for an additional 1 h, when the mixture became heterogeneous with separated KCl crystals. It was then diluted with ice and water, and extracted with hexane. The hexane solution was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give 25.7 g (92%) of (*R*)-**4** as a colorless oil, bp 125–128 °C/2 Torr; n_D^{24}=1.4956; $[\alpha]_D^{23}$ +3.02 (*c* 4.55, hexane); ν_{max} (film): 3087 (w), 3064 (w), 3030 (w), 2962 (s), 2925 (s), 2855 (s), 1496 (m), 1454 (s), 1377 (m), 1364 (m), 1100 (s), 1028 (w), 734 (s), 697 (s); δ_H ($CDCl_3$): 0.88 (3H, d, *J* 6.4), 1.10–1.20 (1H, m), 1.30–1.40 (1H, m), 1.40–1.48 (1H, m), 1.59 (3H, s), 1.68 (3H, s), 1.55–1.71 (2H, m), 1.90–2.05 (2H, m), 3.45–3.52 (2H, m), 4.50 (2H, s), 5.09 (1H, *t*, *J* 7.6), 7.24–7.30 (1H, m), 7.33–7.37 (4H, m; peaks at 7.33 and 7.34); GC–MS [column: HP-5MS, 5% phenylmethylsiloxane, 0.25 mm i.d.×30 m; carrier gas, He; press: 60.7 kPa; temp: 70–230 °C (+10 °C/min)]: t_R 15.66 min (93.0%). MS (70eV, EI): *m*/*z*: 155 (6), 138 (14), 137 (20), 95 (26), 91 (100), 81 (53), 69 (55), 55 (13), 41 (20). HRMS calcd for $C_{17}H_{26}O$: 246.1984, found: 246.2011.

4.2.2. (S)-Isomer. Similarly, (*S*)-**3** (17.8 g, 114 mmol) gave 24.7 g (88%) of (*S*)-**4**, bp 125–127 °C/2 Torr, as a colorless oil; n_D^{27}=1.4956; $[\alpha]_D^{26}$ −3.06 (*c* 5.13, hexane). Its IR, ^{1}H NMR and MS spectra were identical to those of (*R*)-**4**. GC–MS [same conditions as those for (*R*)-**4**]: t_R 15.67 min (92.7%). HRMS calcd for $C_{17}H_{26}O$: 246.1984, found: 246.2012.

4.3. 8-Benzyloxy-2,6-dimethyloctane-2,3-diol (5)

4.3.1. (3RS,6R)-Isomer. A solution of OsO_4 (150 mg, 0.6 mmol) in *t*-BuOH (15 mL) and a 50% aqueous solution of NMO (30.0 g, ca. 140 mmol) were added to a solution of (*R*)-**4** (25.8 g, 105 mmol) in acetone (240 mL), *t*-BuOH (150 mL) and water (60 mL). The dark-colored mixture was stirred for 4 d at room temperature. The resulting clear and yellowish solution was stirred for 15 min after the addition of powdered Na_2SO_3 (25 g, ca. 200 mmol) to reduce OsO_4 and NMO. The mixture was then concentrated in vacuo. The residue was diluted with water, and the resultant biphasic mixture of a yellowish oil and a dark aqueous solution was extracted with EtOAc. The EtOAc solution was washed successively with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residual oil (39.5 g) was chromatographed over SiO_2 (150 g). Elution with hexane/EtOAc (20:1) gave some impure materials (1.11 g). Further elution with hexane/EtOAc (2:1) gave 25.0 g (85%) of (3*RS*,6*R*)-**5** as a viscous oil, n_D^{25}=1.5038; $[\alpha]_D^{25}$ +3.92 (*c* 4.29, hexane); ν_{max} (film): 3420 (br s), 3088 (w), 3064 (w), 3030 (w), 2953 (s), 2926 (s), 2868 (s), 1496 (w), 1455 (m), 1378 (m), 1099 (s), 1075 (s), 736 (m), 698 (s); δ_H ($CDCl_3$): 0.885 (1.5H, d, *J* 6.4), 0.898 (1.5H, d, *J* 6.4), 1.12 (3H, s), 1.20 (3H, s), 1.15–1.40 (2H, m), 1.40–1.55 (2.5H, m), 1.55–1.72 (2.5H, m), 2.30–2.80 (2H, br), 3.28 (1H, br s), 3.51 (2H, dt-like, *J* 6.8, 16), 4.49 (2H, s), 7.26 (1H, m), 7.32, 7.33 (total 4H, both s). HRMS calcd for $C_{17}H_{28}O_3$: 280.2038, found: 280.2062.

4.3.2. (3RS,6S)-Isomer. Similarly, (*S*)-**4** (22.2 g, 90 mmol) gave 23.5 g (93%) of (3*RS*,6*S*)-**5** as a viscous oil, n_D^{25}=1.5036; $[\alpha]_D^{25}$ −4.82 (*c* 4.07 hexane); Its IR and ^{1}H NMR spectra were identical with those of (3*RS*,6*R*)-**5**. HRMS calcd for $C_{17}H_{28}O_3$: 280.2038, found: 280.2072.

4.4. 6-Benzyloxy-4-methylhexanal (6)

4.4.1. (R)-Isomer. $HIO_4 \cdot 2H_2O$ (22.3 g, 98 mmol) was added portionwise to a vigorously stirred and ice-cooled solution of (3*RS*,6*R*)-**5** (25.0 g, 89 mmol). in THF (180 mL) at 5–10 °C. The ice-cooled mixture was stirred for 30 min. The homogeneous solution soon turned turbid, and then HIO_3 precipitated out. The mixture was diluted with water, and extracted with hexane. The hexane solution was washed successively with water, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residual oil (28.4 g) was chromatographed over SiO_2 (130 g). Elution with hexane/EtOAc (15:1) gave 17.1 g (87%) of (*R*)-**6** as a colorless oil, n_D^{22}=1.4980; $[\alpha]_D^{24}$ +2.26 (*c* 5.03, hexane); ν_{max} (film): 3087 (w), 3063 (w), 3031 (w), 2956 (m), 2927 (s), 2862 (s), 2719 (w), 1724 (s), 1454 (m), 1365 (m), 1100 (s), 1028 (m), 738 (s), 698 (s); δ_H ($CDCl_3$): 0.89 (3H, d, *J* 6.8), 1.40–1.51 (2H, m), 1.60–1.72 (3H, m), 2.35–2.50 (2H, m), 3.45–3.53 (2H, m), 4.49 (2H, s), 7.22–7.30 (1H, m), 7.30–7.38 [4H, m (7.32, s)], 9.74 (1H, t, *J* 1.6); GC–MS (same conditions as those for **4**): t_R 14.79 min (99.5%). MS (70eV, EI): *m*/*z*: 220 (<1) [M^+], 107 (28), 91 (100), 79 (7), 77 (6), 65 (11), 41 (5), HRMS calcd for $C_{14}H_{20}O_2$: 220.1463, found: 220.1485.

4.4.2. (S)-Isomer. Similarly, (3*RS*,6*S*)-**5** (19.5 g 70 mmol) gave 11.7 g (76%) of (*S*)-**6** as a colorless oil, n_D^{24}=1.4962; $[\alpha]_D^{24}$ −2.34 (*c* 4.86, hexane); GC–MS (same conditions as those for **4**): t_R 14.79 min (94.1%). Its IR, ^{1}H NMR and MS spectra were identical with those of (*R*)-**6**. HRMS calcd for $C_{14}H_{20}O_2$: 220.1463, found: 220.1481.

4.5. 6-Benzyloxy-4-methyl-1-hexanol (7)

4.5.1. (R)-Isomer. A solution of (*R*)-**6** (17.0 g, 77 mmol) in dry THF (30 mL) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (1.5 g, 39 mmol) in dry THF (120 mL). The mixture was stirred for 30 min at 0–5 °C, and then treated with water (5 mL; dropwise addition with ice-cooling) to destroy excess $LiAlH_4$. The mixture was acidified with dil HCl and ice, and extracted with Et_2O. The Et_2O solution was successively washed with water, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo to give 17.4 g (quant.) of (*R*)-**7** as a colorless oil, n_D^{24}=1.5018; $[\alpha]_D^{26}$ +1.24 (*c* 4.39, hexane); ν_{max} (film): 3388 (br s), 3087 (w), 3063 (w), 3031 (w), 2930 (s), 2867 (s), 1454 (m), 1365 (m), 1098 (s), 1074 (s), 1058 (s), 1027 (m), 737 (s), 698 (s); δ_H ($CDCl_3$): 0.89 (3H, d, *J* 6.4), 1.10–1.20 (1H, m), 1.32–1.50 (3H, m), 1.50–1.70 (4H, m), 3.45–3.53 (2H, m), 3.58–3.74 (2H, m), 4.49 (2H, s), 7.22–7.30 (1H, m), 7.32–7.34 [4H, m (7.33, s)]; GC–MS (same conditions as those for **4**): t_R 15.48 min (99.2%). MS (70 eV, EI): *m*/*z*: 222 (4) [M^+], 107 (51), 91 (100), 79 (6), 65 (11), 41 (6). HRMS calcd for $C_{14}H_{22}O_2$: 222.1620, found: 222.1643.

4.5.2. (S)-Isomer. Similarly, (*S*)-**6** (9.50 g, 43 mmol) gave 9.20 g (96%) of (*S*)-**7** as a colorless oil, n_D^{25}=1.5012; $[\alpha]_D^{26}$ −1.66 (*c* 4.20, hexane). Its IR, ^{1}H NMR and MS spectra were identical with those of (*R*)-**7**. GC–MS (same conditions as those for **4**): t_R 15.50 min (95.2%). HRMS calcd for $C_{14}H_{22}O_2$: 222.1620, found: 222.1637.

4.6. 6-Benzyloxy-4-methylhexyl tosylate (8)

4.6.1. (R)-Isomer. TsCl (16.4 g, 86 mmol) was added portionwise to a stirred and ice-cooled solution of (*R*)-**7** (17.3 g, 77 mmol) and DMAP (50 mg) in dry C_5H_5N (70 mL). The mixture was stirred for 1.5 h at 0–5 °C. It was then diluted with ice and water, and extracted with Et_2O. The Et_2O solution was washed successively with dil. HCl, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo to give 26.5 g (91%) of (*R*)-**8** as a viscous oil, ν_{max} (film): 3088 (w), 3064 (w), 3033 (w), 2955 (m), 2926 (m), 2867 (m), 1598 (m), 1496 (m), 1454 (m), 1361 (s), 1189 (s), 1176 (s), 1098 (s), 964 (s), 917 (s), 815 (s), 737 (s), 664 (s), 555 (s). This oil was employed in the next step without further purification.

4.6.2. (S)-Isomer. Similarly, (*S*)-**7** (9.1 g) gave 16.1 g (quant.) of (*S*)-**8** as an oil. Its IR spectrum was identical with that of (*R*)-**8**. This was employed in the next step without further purification.

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4.7. 3-Methylheptyl benzyl ether (9)

4.7.1. (R)-Isomer. A solution of MeMgBr in Et_2O (3 M, 50 mL, 150 mmol) was added to stirred and cooled (dry ice/acetone) dry THF (50 mL) at −40 °C under argon. A solution of (*R*)-**8** (26.5 g, 70.6 mmol) in dry THF (50 mL) was added dropwise to the stirred and cooled Grignard reagent to make it homogeneous. Then Li_2CuCl_4 in THF (0.1 M, 3.0 mL, 0.3 mmol) was added through a syringe to the mixture at −78 °C. Stirring was continued overnight with gradual rise of the temperature to room temperature. The mixture was treated with ice and dil. HCl, and extracted with Et_2O. The Et_2O solution was washed successively with water, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give 11.7 g (75%) of (*R*)-**9** as a colorless oil, bp 135–138 °C/6 Torr; n_D^{23}=1.4834; $[\alpha]_D^{24}$ +1.79 (*c* 4.26, hexane); ν_{max} (film): 3087 (w), 3064 (w), 3031 (w), 2956 (s), 2926 (s), 2858 (s), 2793 (w), 1455 (m), 1364 (m), 1101 (s), 1028 (m), 734 (s), 697 (s); δ_H ($CDCl_3$): 0.87 (3H, d, *J* 6.8), 0.88 (3H, t, *J* 6.8), 1.08–1.18 (1H, m), 1.20–1.25 (4H, m), 1.39–1.46 (1H, m), 1.50–1.60 (1H, m), 1.60–1.70 (2H, m), 3.47–3.52 (2H, m), 4.50 (2H, s), 7.24–7.30 (1H, m), 7.30–7.40 [4H, m(7.33, s)]; GC–MS (same conditions as those for **4**): t_R 13.42 min (95.4%). MS (70 eV, EI): *m*/*z*: 220 (<1) [M^+], 129 (3), 111 (8), 108 (9), 92 (49), 91 (100), 69 (24), 55 (6), 41 (8). HRMS calcd for $C_{15}H_{24}O$: 220.1827, found: 220.1854.

4.7.2. (S)-Isomer. Similarly, (*S*)-**8** (16.1 g, 41 mmol) gave 7.26 g (80%) of (*S*)-**9** as a colorless oil, bp 125–128 °C/5 Torr; n_D^{23}=1.4816; $[\alpha]_D^{24}$ −1.95 (*c* 4.33, hexane). Its IR, ^{1}H NMR and MS spectra were identical with those of (*R*)-**9**. GC–MS (same conditions as those for **4**): t_R 13.43 min (97.2%). HRMS calcd for $C_{15}H_{24}O$: 220.1827, found: 220.1859.

4.8. 3-Methyl-1-heptanol (10)

4.8.1. (R)-Isomer. Pearlman's $Pd(OH)_2$/C (TCI P1528, 20% Pd on C wet with ca. 50% water, 950 mg) was added to a solution of (*R*)-**9** (11.6 g), 53 mmol) in 99% EtOH (40 mL). The mixture was stirred vigorously under H_2 (balloon) for 2.5 h at room temperature. Exothermic reduction was observed. The mixture was then filtered through Celite to remove the catalyst, the Celite layer was washed with Et_2O, and the filtrate was concentrated in vacuo. The residue was distilled to give 5.84 g (85%) of (*R*)-**10** as a colorless oil, bp 113–116 °C/52 Torr; n_D^{24}=1.4282; $[\alpha]_D^{26}$ +3.19 (*c* 5.35, hexane); ν_{max} (film): 3329 (br m), 2957 (s), 2927 (s), 2872 (s), 1460 (m), 1378 (m), 1056 (s), 958 (w), 845 (w), 728 (w); δ_H ($CDCl_3$): 0.891 (3H, d, *J* 6.6), 0.891 (3H, t, *J* 6.4), 1.10–1.20 (1H, m), 1.20–1.40 (6H, m), 1.50–1.65 (3H, m), 3.62–3.72 (2H, m); GC–MS [column: HP-5MS, 5% phenylmethylsiloxane, 0.25 mm i.d.×30 m; carrier gas, He; Press; 48.7 kPa; temp; 40–230 °C (+5 °C/min)]: t_R 11.46 min (100.0%). MS (70 eV, EI): *m*/*z*: 112 (5) [$(M-H_2O)^+$], 97 (7), 84 (95), 83 (46), 70 (94), 69 (52), 57 (36), 56 (59), 55 (100), 43 (65), 41 (77), 39 (32), 31 (31). HRMS calcd for $C_8H_{18}O$: 130.1358, found: 130.1360.

4.8.2. (S)-Isomer. Similarly, (*S*)-**9** (7.2 g, 33 mmol) gave 3.88 g (91%) of (*S*)-**10** as a colorless oil, bp 115–118 °C/63 Torr; n_D^{25}=1.4284; $[\alpha]_D^{26}$ −3.22 (*c* 3.86, hexane); Its IR, ^{1}H NMR and MS spectra were identical with those of (*R*)-**10**. GC–MS [same conditions as described for (*R*)-**10**]: t_R 11.45 min (99.3%). HRMS calcd for $C_8H_{18}O$: 130.1358, found: 130.1359.

*4.8.3. Determination of the enantiomeric purity of (R)- and (S)-**10** by enantioselective GC (courtesy of T. Hasegawa Co.).* Instruments: Agilent HP 6890 and HP 5975C gas chromatographs; column: 50% octakis(2,3-di-*O*-methoxymethyl-6-*O*-*t*-butyldimethylsilyl)-γ-cyclodextrin (0.25 mm i.d.×30 m); column temp: 40–180 °C (+0.7 °C/min); carrier gas, He; flow rate, 0.7 mL/min: t_R 65.5 min for (*R*)-**10**, 69.1 min for (*S*)-**10** (baseline separation). (*R*)-**10**, 97.6% ee; (*S*)-**10**, 98.0% ee.

4.9. 3-Methylheptyl tosylate (11)

4.9.1. (R)-Isomer. TsCl (10.0 g, 53 mmol) was added portionwise to a stirred and ice-cooled solution of (*R*)-**10** (5.8 g, 45 mmol) and DMAP (20 mg) in dry C_5H_5N (20 mL) at 0–5 °C. The mixture was stirred for 2 h at 0–5 °C, diluted with ice and water, and extracted with Et_2O. The Et_2O solution was washed successively with dil. HCl, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo to give 12.6 g (99%) of (*R*)-**11** as a colorless oil, ν_{max} (film): 2957 (s), 2928 (s), 2871 (m), 1599 (m), 1464 (m), 1302 (s), 1189 (s), 1177 (s), 945 (s), 664 (s), 555 (s). This was employed in the next step without further purification.

4.9.2. (S)-Isomer. Similarly, (*S*)-**10** (3.8 g, 29 mmol) gave 8.3 g (quant.) of (*S*)-**11** as a colorless oil. Its IR spectrum was identical with that of (*R*)-**11**. This was employed in the next step without further purification.

4.10. 3-Methylheptyl bromide (12)

4.10.1. (R)-Isomer. LiBr (7.0 g, 80 mmol) was added to a solution of (*R*)-**11** (12.6 g, 45 mmol) in DMF (40 mL). The mixture was swirled to dissolve LiBr (exothermic). It was then stirred and heated at 70 °C for 45 min. After cooling, it was diluted with ice and water, and extracted with pentane. The pentane solution was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give 7.0 g (82%) of (*R*)-**12** as a colorless oil, bp 100–102 °C/48 Torr; n_D^{24}=1.4506; $[\alpha]_D^{24}$ −6.94 (*c* 4.27, pentane); ν_{max} (film): 2958 (s), 2927 (s), 2871 (m), 1465 (m), 1379 (m), 648 (m), 568 (w); δ_H ($CDCl_3$): 0.888 (3H, d, *J* 6.4), 0.896 (3H, t, *J* 6.4), 1.10–1.20 (1H, m), 1.20–1.35 (5H, m), 1.58–1.70 (2H, m), 1.84–1.92 (1H, m), 3.38–3.50 (2H, m); GC–MS (same conditions as described for **10**): t_R 13.21 min (94.7%). MS (70 eV, EI): *m*/*z*: 194 (1) [M^+], 192 (1) [M^+], 166 (7), 164 (5), 151 (40), 149 (41), 85 (100), 71 (16), 70 (20), 69 (16), 57 (30), 56 (16), 55 (62), 43 (46), 41 (54), 39 (24). HRMS calcd for $C_8H_{17}Br$: 192.0514, found: 192.0513.

4.10.2. (S)-Isomer. Similarly, (*S*)-**11** (8.3 g, 29 mmol) gave 4.69 g (83%) of (*S*)-**12** as a colorless oil, bp 98–100 °C/47 Torr; n_D^{23}=1.4510; $[\alpha]_D^{23}$ +7.25 (*c* 4.24, pentane). Its IR, ^{1}H NMR and MS spectra were identical with those of (*R*)-**12**. GC–MS (same conditions as described for **10**): t_R 13.21 min (92.0%). HRMS calcd for $C_8H_{17}Br$: 192.0514, found: 192.0528.

4.11. Citronellyl pivalate (14)

4.11.1. (R)-Isomer. A solution of *t*-BuCOCl (PivCl, 14.5 g, 120 mmol) in dry C_6H_6 (10 mL) was added dropwise to a stirred and ice-cooled solution of (*R*)-**3** (17.2 g, 110 mmol) and DMAP (20 mg) in dry C_5H_5N (60 mL). After the addition, the mixture was stirred for 1 h at 10 °C-room temperature. The mixture containing precipitated $C_5H_5N{\cdot}HCl$ was diluted with ice and water, and extracted with Et_2O. The Et_2O solution was washed successively with dil. HCl, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give 25.8 g (96%) of (*R*)-**14** as a colorless oil, bp 95–98 °C/3 Torr; n_D^{27}=1.4380; $[\alpha]_D^{26}$ +0.46 (*c* 4.82, hexane); ν_{max} (film): 2966 (s), 2927 (s), 2873 (m), 1731 (s), 1480 (m), 1459 (m), 1284 (s), 1159 (s); δ_H ($CDCl_3$): 0.92 (3H, d, *J* 6.8), 1.19 (9H, s), 1.16–1.65 (5H, m), 1.60 (3H, s), 1.68 (3H, s), 1.95–2.01 (2H, m), 4.07–4.11 (2H, m), 5.09 (1H, t, *J* 6.8); GC–MS (same conditions as described for **4**): t_R 12.24 min (97.3%). MS (70 eV, EI): *m*/*z*: 138 (56)

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[(M-PivOH)$^+$], 123 (99), 105 (42), 95 (100), 81 (99), 69 (71), 57 (89), 41 (58). HRMS calcd for $C_{15}H_{28}O_2$: 240.2089, found: 240.2121.

4.11.2. (S)-Isomer. Similarly, (*S*)-**3** (22.6 g, 143 mmol) gave 31.5 g (92%) of (*S*)-**14** as a colorless oil, bp 105–108 °C/4 Torr; n_D^{28}=1.4380; $[\alpha]_D^{26}$ −0.45 (*c* 4.70, hexane); Its IR, ^{1}H NMR and MS spectra were identical with those of (*R*)-**14**. GC–MS (same conditions as described for **4**): t_R 12.24 min (97.5%). HRMS calcd for $C_{15}H_{28}O_2$: 240.2089, found: 240.2113.

4.12. 6,7-Epoxycitronellyl pivalate (15)

4.12.1. (R)-Isomer. MCPBA (wet, 70% purity, 26.0 g, 115 mmol) was added portionwise to a vigorously stirred and ice-cooled solution of (*R*)-**14** (25.8 g, 108 mmol) in CH_2Cl_2 (150 mL) at 5–20 °C. After the addition, the mixture was stirred for 40 min at 5–10 °C. It was then diluted with hexane, and filtered to remove MCBA. The filtrate was washed with Na_2CO_3 solution containing a small amount (1–2 g) of $Na_2S_2O_4$ and brine, dried ($MgSO_4$), and concentrated in vacuo to give 28.0 g (quant.) of (3*R*,6*RS*)-**15** as a colorless oil, ν_{max} (film): 2961 (s), 2929 (s), 2873 (m), 1729 (s), 1480 (m), 1461 (m), 1379 (m), 1285 (m), 1161 (s); δ_H ($CDCl_3$): 0.94 (3H, d, *J* 6.4), 1.19 (9H, s), 1.27 (3H, s), 1.38 (3H, s), 1.39–1.72 (7H, m), 2.69 (1H, t, *J* 7.5), 4.08–4.13 (2H, m); GC–MS (same conditions as described for **4**): t_R 13.51 min (97.1%); MS (70 eV, EI): 257 (<1) [(M+H)$^+$], 154 (16), 129 (24), 103 (41), 85 (32), 83 (33), 69 (60), 57 (100), 55 (35), 41 (35). This was employed in the next step without further purification.

4.12.2. (S)-Isomer. Similarly, (*S*)-**14** (31.5 g, 131 mmol) gave 33.95 g (quant.) of (3*S*,6*RS*)-**15** as a colorless oil, whose IR, ^{1}H NMR and MS spectra were identical to those of (3*R*,6*RS*)-**15**. GC–MS (same conditions as described for **4**): t_R 13.51 min (97.5%). This was employed in the next step without further purification.

4.13. 4-Methyl-6-pivaloyloxyhexanal (16)

4.13.1. (R)-Isomer. $HIO_4 \cdot 2H_2O$ (26.2 g, 115 mmol) was added portionwise to a vigorously stirred and ice-cooled solution of (3*R*,6*RS*)-**15** (28.0 g, 108 mmol) in THF (150 mL) and Et_2O (80 mL) over 10 min at 0–15 °C. The mixture was stirred for another 10 min at 0–5 °C. The solution became turbid, and HIO_3 precipitated. Then the mixture was diluted with Et_2O and iced water. The Et_2O solution was washed successively with water, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give 14.6 g (63%) of (*R*)-**16**, bp 115–120 °C/3 Torr. An unidentified by-product (4.9 g), bp 76–95 °C/3 Torr, was also obtained. Aldehyde (*R*)-**16** was a colorless oil, n_D^{27}=1.4352; $[\alpha]_D^{26}$ −0.42 (*c* 4.20, hexane); ν_{max} (film): 2962 (s), 2933 (s), 2874 (m), 2720 (w), 1726 (s), 1480 (m), 1461 (m), 1285 (m), 1163 (s), 1036 (w), 771 (w); δ_H ($CDCl_3$): 0.94 (3H, d, *J* 6.8), 1.19 (9H, m), 1.44–1.75 (5H, m), 2.46 (2H, m), 4.08–4.15 (2H, m), 9.78 (1H, s); GC–MS (same conditions as described for **4**): t_R 11.31 min (86.3%); MS (70 eV, EI): *m*/*z*: 112 (14) [(M-PivOH)$^+$], 103 (24), 95 (19), 85 (14), 69 (28), 57 (100), 41 (31). HRMS calcd for $C_{12}H_{22}O_3$: 214.1569, found: 214.1584.

4.13.2. (S)-Isomer. Similarly, (3*S*,6*RS*)-**15** (33.9 g) gave 14.9 g (53%) of (*S*)-**16**, bp 115–125 °C/3 Torr; n_D^{27}=1.4348; $[\alpha]_D^{25}$ +0.43 (*c* 4.43, hexane). Its IR, ^{1}H NMR and MS spectra were identical with those of (*R*)-**16**. GC–MS (same conditions as described for **4**): t_R 11.30 min (70%, impurities at t_R 7.13 and 13.81 min). HRMS calcd for $C_{12}H_{22}O_3$: 214.1569, found: 214.1566.

4.14. 3-Methyl-6-heptenyl pivalate (17)

4.14.1. (R)-Isomer. A solution of $Ph_3P{=}CH_2$ was prepared by dropwise addition of *n*-BuLi in hexane (1.6 M, 65 mL, 104 mmol) to a stirred and cooled (dry ice/acetone) suspension of $Ph_3P(Me)Br$ (35.7 g, 100 mmol) in dry THF (140 mL) under argon at −40–30 °C. The stirred and orange-colored mixture was warmed up to 0 °C, and then cooled again at −78 °C. To the stirred and cooled Wittig reagent was added a solution of (*R*)-**16** (16.5 g, 78 mmol) in dry THF (20 mL) at −70–60 °C. The stirred mixture was left to stand overnight at −60 °C to room temperature. It was then partitioned between hexane and MeOH/H_2O (2:1, 90 mL). The hexane layer was separated, washed successively with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (30 g) was chromatographed over SiO_2 (80 g). The fractions eluted with hexane/EtOAc (50:1–30:1) were combined (11.9 g), and distilled to give 10.7 g (65%) of (*R*)-**17** as a colorless oil, bp 83–86 °C/3 Torr; n_D^{26}=1.4302; $[\alpha]_D^{26}$ −1.51 (*c* 4.19, hexane); ν_{max} (film): 3078 (w), 2961 (s), 2930 (s), 1731 (s), 1641 (w), 1480 (m), 1460 (m), 1284 (s), 1159 (s), 909 (m); δ_H ($CDCl_3$): 0.92 (3H, d, *J* 6.8), 1.19 (9H, s), 1.20–1.30 (1H, m), 1.39–1.50 (2H, m), 1.55–1.72 (2H, m), 2.00–2.18 (2H, m), 4.05–4.15 (2H, m), 4.94 (1H, dt, *J* 10.4, 2), 5.01 (1H, dt, *J* 17.2, 2), 5.76–5.85 (1H, m); GC–MS (same conditions as described for **4**): t_R 9.69 min (91.1%). MS (70 eV, EI): *m*/*z*: 110 (21) [(M-PivOH)$^+$], 103 (22), 95 (46), 81 (63), 69 (41), 68 (45), 57 (100), 41 (39). HRMS calcd for $C_{13}H_{24}O_2$: 212.1776, found: 212.1801.

4.14.2. (S)-Isomer. Similarly, (*S*)-**16** (14.8 g) gave 7.90 g (54%) of (*S*)-**17**, bp 84–86 °C/4 Torr; $n_D^{26.5}$=1.4285; $[\alpha]_D^{20}$ +2.81 (*c* 4.30, hexane). Its IR, ^{1}H NMR and MS spectra were identical with those of (*R*)-**17**. GC–MS (same conditions as described for **4**): t_R 9.68 min (86.4%, impurity at t_R=7.13 min). HRMS calcd for $C_{13}H_{24}O_2$: 212.1776, found: 212.1808.

4.15. 3-Methylheptyl pivalate (18)

4.15.1. (R)-Isomer. 10% Pd/C (Kojima Chemical Co, Lot No. 801077; 500 mg) was added to a solution of (*R*)-**17** (10.6 g, 51 mmol) in EtOAc (15 mL). The mixture was vigorously stirred under H_2 (balloon) for 3.5 h. The reaction was exothermic. Then the mixture was filtered through Celite, and the Celite layer was washed with EtOAc. The combined EtOAc solution was concentrated in vacuo. The residue was distilled to give 10.0 g (93%) of (*R*)-**18** as a colorless oil, bp 80–82 °C/3 Torr; n_D^{27}=1.4210; $[\alpha]_D^{26}$ −0.4 (*c* 4.09, hexane); ν_{max} (film): 2959 (s), 2929 (s), 2873 (m), 1731 (s), 1480 (m), 1461 (m), 1284 (s), 1158 (s), 1135 (w), 770 (w); δ_H ($CDCl_3$): 0.89 (3H, t, *J* 7), 0.90 (3H, d, *J* 6.4), 1.19 (9H, s), 1.13–1.25 (1H, m), 1.25–1.35 (5H, m), 1.37–1.47 (1H, m), 1.48–1.67 (1H, m), 1.61–1.69 (1H, m), 4.09 (2H, m); GC–MS (same conditions as described for **4**): t_R 9.77 min (90.6%). MS (70 eV, EI): *m*/*z*: 157 (5) [(M-*t*-Bu)$^+$], 129 (4), 112 (24) [(M-PivOH)$^+$], 103 (27), 85 (17), 71 (22), 70 (50), 57 (100), 41 (39). HRMS calcd for $C_{13}H_{27}O_2$ [($C_{13}H_{26}O_2$+H)$^+$]: 215.2011, found: 215.2020.

4.15.2. (S)-Isomer. Similarly, (*S*)-**17** (7.80 g) was hydrogenated and the product was fractionally distilled to give a forerun (696 mg), bp 50–60 °C/5 Torr and then (*S*)-**18** (6.06 g, 77%), bp 83–87 °C/5 Torr; $n_D^{26.5}$=1.4190; $[\alpha]_D^{26}$ +1.97 (*c* 4.27, hexane). Its IR, ^{1}H NMR and MS spectra were identical with those of (*R*)-**18**. GC–MS (same conditions as described for **4**): t_R 9.77 min (85.3%, impurity at t_R=7.13 min). HRMS calcd for $C_{13}H_{27}O_2$ [($C_{13}H_{26}O_2$ +H)$^+$]: 215.2011, found: 215.1999.

4.16. 3-Methyl-1-heptanol (10) from 18

*4.16.1. (R)-**10** from (R)-**18**.* A mixture of (*R*)-**18** (10.0 g, 47 mmol) and KOH (5.6 g, 100 mmol) in MeOH (80 mL) was stirred and heated under reflux for 6 h. MeOH was then removed in vacuo. The residue was diluted with water, and extracted with Et_2O. The Et_2O solution was washed successively with water and brine, dried ($MgSO_4$), and

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concentrated in vacuo. The residue was distilled to give 5.4 g (88%) of (*R*)-**10** as a colorless oil, bp 108–111 °C/50 Torr; n_D^{27}=1.4270; $[\alpha]_D^{26}$ +2.45 (*c* 4.98, hexane). Its IR, ^{1}H NMR and MS spectra were identical with those of (*R*)-**10** prepared from (*R*)-**9**. GC–MS (same conditions as described in 4.8.1): t_R 11.57 min (93.5%). HRMS calcd for $C_8H_{18}O$: 130.1358, found: 130.1359. Enantioselective GC analysis of the present sample was executed as described in 4.8.3. The present (*R*)-**10** was a mixture of 93.9% of (*R*)-**10** and 7.0% of (*S*)-**10**. It was of 86.0% ee.

*4.16.2. (S)-**10** from (S)-**18**.* Similarly, (*S*)-**18** (6.0 g, 28 mmol) gave 3.05 g (84%) of (*S*)-**10** as a colorless oil, bp 110–115 °C/53 Torr; n_D^{25}=1.4274; $[\alpha]_D^{25}$ −1.19 (*c* 4.61, hexane). Its IR, ^{1}H NMR and MS spectra were identical with those of (*R*)-**10.** GC–MS (same conditions as described in 4.8.1): t_R 11.53 min (89.4%). HRMS calcd for $C_8H_{18}O$: 130.1358, found: 130.1359. Enantioselective GC analysis of the present sample was executed as described in 4.8.3. The present (*S*)-**10** was a mixture of 9.9% of (*R*)-**10** and 90.1% of (*S*)-**10**. It was of 80.2% ee.

4.17. Preparation of 10 by hydrogenation of 19 or 20 over PtO_2 and/or $Pd(OH)_2/C$

*4.17.1. Enantiomeric purities of (R)- and (S)-**10** prepared by hydrogenation (H_2/PtO_2) of (R)- and (S)-**19**.* GC analysis was carried out as described in 4.8.3. (*R*)-**10** was a mixture of 98.5% of (*R*)-**10** and 1.5% of (*S*)-**10**: 97.0% ee. (*S*)-**10** was a mixture of 1.2% of (*R*)-**10** and 98.8% of (*S*)-**10**: 97.6% ee.

*4.17.2. Enantiomeric purity of (S)-**10** prepared by hydrogenation of (S)-**20** with H_2/PtO_2 followed by $H_2/Pd(OH)_2/C$.* GC analysis was carried out as described in 4.8.3. (*S*)-**10** was a mixture of 1.2% of (*R*)-**10** and 98.8% of (*S*)-**10**: 97.6% ee.

*4.17.3. Enantiomeric purity of (S)-**10** prepared by hydrogenation of (S)-**20** with $H_2/Pd(OH)_2/C$ only.* GC analysis was carried out as described in 4.8.3. (*S*)-**10** was a mixture of 1.3% of (*R*)-**10** and 98.7% of (*S*)-**10**: 97.4% ee.

4.18. (*R*)-3-Methylheptyl benzyl ether (9) from (*R*)-butane-1,3-diol 1-benzyl ether (25)

(*R*)-Butane-1,3-diol 1-benzyl ether {**25**, 3.04 g, n_D^{21}=1.5060; $[\alpha]_D^{23}$ +0.96 (*c* 4.42, $CHCl_3$)} was prepared from ethyl (*R*)-3-hydroxybutanoate {**21**, 100% ee; n_D^{19}=1.4224; $[\alpha]_D^{19}$ −43.4 (*c* 4.10, $CHCl_3$)} according to refs.[21,22] The corresponding tosylate[22] (**26**, 4.80 g, 14.5 mmol) in dry THF (10 mL) was added dropwise to a stirred and cooled solution of *n*-BuMgBr [prepared from *n*-BuBr (3.60 g, 26 mmol) and Mg (720 mg, 30 mmol) in dry THF (20 mL)] at −78 °C under argon. Subsequently, a solution of Li_2CuCl_4 (0.1 M, 1.0 mL, 0.1 mmol) was added to the stirred mixture at −78 °C. Stirring was continued for 2 h at −78 °C, and the mixture was left to stand overnight with gradual raise of the temperature. The mixture was acidified with ice and dil. HCl, and extracted with Et_2O. The Et_2O extract was washed successively with water, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give 1.44 g (77%) of (*R*)-**9** as a colorless oil, bp 97–102 °C/2 Torr; n_D^{19}=1.4844; $[\alpha]_D^{21}$ +3.08 (*c* 4.29, hexane). The larger specific rotation of the present sample in comparison to the previous one (+1.79, see 4.7.1) must be due to the presence of impurities. Its IR, ^{1}H NMR and MS spectra were virtually identical with those of (*R*)-**9** described in 4.7.1. GC–MS (same conditions as described as those for **4**): t_R 13.63 min (86.5%). Hydrogenolytic removal of the benzyl group of (*R*)-**9** over $Pd(OH)_2/C$ gave (*R*)-**10**. The present (*R*)-**10** was a mixture of 98.1% of (*R*)-**10** and 1.9% of (*S*)-**10**: 96.2% ee as determined by GC analysis (see 4.8.3). Erosion of the enantiomeric purity in the course of the conversion of PHB to (*R*)-**10** was 3.8% ee or 1.9% of the (*S*)-isomer was generated.

4.19. 4-Methyloctadecanal (30)

This was synthesized from the enantiomers of citronellol (**3**) via **27**, **28** and **29** according to ref. 24.

4.19.1. (R)-Isomer. Labile and easily air-oxidized colorless oil, n_D^{26}=1.4470; $[\alpha]_D^{25}$ +1.25 (*c* 4.06, hexane). Its IR and ^{1}H NMR spectra were identical to those reported previously.[24] GC–MS (same conditions as described for **4**): t_R 18.64 min (97.6%). MS (70 eV, EI): *m*/*z*: 282 (<1) [M^+], 264 (3), 238 (12), 223 (4), 210 (10), 182 (8), 125 (8), 111 (21), 97 (32), 95 (41), 85 (58), 82 (55), 71 (39), 69 (48), 57 (100), 56 (73), 43 (55), 41 (43). HRMS calcd for $C_{19}H_{38}O$: 282.2923, found: 282.2921.

4.19.2. (S)-Isomer. Labile and easily air-oxidized colorless oil, n_D^{26}=1.4470; $[\alpha]_D^{25}$ −1.41 (*c* 4.18, hexane). Its IR, ^{1}H NMR and MS spectra were identical with those of (*R*)-**30.** GC–MS (same conditions as those described for **4**): t_R 18.68 min (98.0%). HRMS calcd for $C_{19}H_{38}O$:282.2923, found: 282.2921.

*4.19.3. Attempted GC separation of the enantiomers of **30** and **31**.* A Chiramix® column (0.25 mm i.d.×30 m) was employed; column temperature 40–180 °C (+0.7 °C/min); carrier gas: He; flow rate: 0.7 mL/min; injection temperature: 230 °C. *Analysis of **30**.* t_R of (*R*)-**30**: 230.6 min; t_R of (*S*)-**30**: 230.4 min. No basepeak separation was observed. *Analysis of **31**.* t_R of (*R*)-**31**: 259.1 min; t_R of (*S*)-**31**: 259.1 min. No separation at all. The enantiomeric purities of the enantiomers of **30** and **31** could not be determined by enantioselective GC analysis.

4.20. Attempted determination of the enantiomeric purity of the enantiomers of 4-methyloctadecanal (30)

*4.20.1. Preparation and analysis of (R)-MTPA ester (**32**) of the enantiomers of 4-methyl-1-octadecanol (**31**).* Reduction of (*R*)-**30** (705 mg) with $LiAlH_4$ (70 mg) in dry THF (5 mL) gave 700 mg (99%) of (*R*)-**31**, ν_{max} (film): 3342 (m), 2925 (s), 2853 (s), 1466 (m), 1039 (m), 721 (w). (*S*)-MTPACl (25 mg) was added to a solution of (*R*)-**31** (10 mg) and DMAP (2 mg) in CH_2Cl_2 (2 drops) and C_5H_5N (2 drops), and the mixture was left to stand for 3 d at room temperature. It was then diluted with Et_2O and water. The Et_2O solution was washed successively with dil. HCl, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo to give 29 mg of (*R*)-MTPA ester (**32**) of (*R*)-**31**. Similarly, (*R*)-MTPA ester (**32**) of (*S*)-**31** was also prepared. In the ^{1}H NMR spectra of the (*R*)-MTPA esters (**32**) of (*R*)- and (*S*)-**31**, no significant difference could be observed with regard to the δ-values of CH_3(0.83) at C-4, OMe (3.56) and CH_2O (4.27–4.34). Both diastereomers **32** showed the same t_R (17.52 min) in its GC–MS (same conditions as those for **4**). Accordingly, the enantiomeric purities of the enantiomers of **31** could not be determined.

*4.20.2. Preparation and analysis of (R)-1-(1-naphthyl)ethylamide (**35**) of the enantiomers of 4-methyloctadecanoic acid (**33**).* Oxidation of (*R*)-**30** (705 mg) in acetone (6 mL) with Jones CrO_3 (1 mL) gave 690 mg (93%) of (*R*)-**33**, ν_{max} (film): 2954 (s), 2920 (s), 2850 (s), 1698 (s), 1470 (s), 944 (m), 719 (m). Oxalyl chloride (0.5 mL) was added to a solution of (*R*)-**33** (150 mg) in C_6H_6 (5 mL), and the mixture was stirred and heated under reflux for 10 min. It was then concentrated in vacuo to give (*R*)-**34** as an oil, which was dissolved again in dry C_6H_6 (5 mL). The solution of (*R*)-**34** was added dropwise to a stirred and ice-cooled solution of (*R*)-1-(1-naphthyl)ethylamine (200 mg) and Et_3N (500 mg) in dry C_6H_6 (5 mL), and the mixture was left to

stand overnight at room temperature. After conventional work-up, 200 mg (89%) of (*R*,*R*)-amide (**35**) was obtained as an oil, ν_{max} (film): 3301 (m), 2953 (s), 2923 (s), 2852 (s), 1653 (s), 1632 (s), 1600 (m), 1536 (s), 1465 (m), 1377 (m), 799 (w), 779 (m); δ_H ($CDCl_3$): 0.83 (3H, d, *J* 6.4), 0.88 (3H, t, *J* 6.8), 1.00–1.10 (1H, m), 1.15–1.30 (26H, br s), 1.67 (3H, d, *J* 6.8), 2.10–2.20 (2H, m), 5.64 (1H, d, *J* 7.2), 5.93 (1H, m), 7.43–7.47 (1H, m), 7.50–7.54 (3H, m), 7.80 (1H, d, *J* 8.8), 7.86 (1H, d, *J* 7.6), 8.09 (1H, d, *J* 8.0); GC–MS (same conditions as those for **4**): t_R 28.28 min. Similarly, (*S*,*R*)-amide (**35**) was prepared from (*S*)-**30**. Its ^{1}H NMR spectrum was identical with that of (*R*,*R*)-**35**. (*S*,*R*)-**35** showed t_R 28.22 min in its GC–MS. Due to the no difference in ^{1}H NMR and GC–MS properties between (*R*,*R*)- and (*S*,*R*)-**35**, the enantiomeric purities of the enantiomers of **33** could not be determined.

4.21. 5,11-Dimethyl-8-pentacosanol (36)

4.21.1. (5R,8RS,11R)-Isomer. A 3 mL-portion of a solution of (*R*)-**12** (3.5 g, 18 mmol) in dry THF (15 mL) was added to Mg turnings (528 mg, 22 mmol) and I_2 (20 mg). The stirred mixture was heated with a heat gun to initiate the reaction. The dark mixture soon became colorless with brisk boiling. The rest of the bromide solution was added dropwise to the stirred mixture so as to maintain the refluxing due to the exothermic reaction. After the addition, the mixture was stirred and heated under reflux for 15 min. The stirred mixture was then cooled in an ice-bath, and a solution of (*R*)-**30** (4.0 g, 14 mmol) in dry THF (10 mL) was added dropwise to it. When the exothermic reaction ceased, the mixture was stirred and heated at 50 °C for 30 min, then cooled, acidified with ice and dil. HCl, and extracted with Et_2O. The Et_2O solution was washed successively with water, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (6.70 g) was chromatographed over SiO_2 (70 g). Elution with hexane/EtOAc (30:1) gave 4.58 g [82% based on (*R*)-**30**] of (5*R*,8*RS*,11*R*)-**36** as a colorless oil, which solidified in a deep freezer, n_D^{20}=1.4572; $[\alpha]_D^{20}$ −0.66 (*c* 4.56, hexane); ν_{max} (film): 3346 (m), 2955 (s), 2925 (s), 2854 (s), 1465 (m), 1377 (m), 1040 (m), 721 (m); δ_H ($CDCl_3$): 0.80–0.90 (12H, m), 1.07–1.15 (2H, m), 1.15–1.50 (43H, m), 3.50–3.60 (1H, m); GC–MS [column: HP-5MS, 5% phenylmethylsiloxane, 0.25 mm i.d.×30 m; carrier gas, He; press:52.8 kPa; temp: 50 °C (2 min) −300 °C (+15 °C/min)]: t_R 19.15 min (88.6%); MS (EI, 70 eV): *m*/*z*: 378 (10) [$(M-H_2O)^+$], 297 (8), 283 (69), 238 (39), 223 (22), 210 (14), 197 (6), 181 (13), 157 (12), 143 (60), 125 (56), 111 (50), 97 (76), 83 (92), 69 (100), 57 (88), 55 (54), 43 (50), 41 (32). HRMS calcd for $C_{27}H_{55}O$ [$(M-H)^+$]: 395.4253, found: 395.4242.

4.21.2. (5R,8R or S, 11S)-Isomer (crystals) and (5R,8S or R, 11S)-isomer (oil). Similarly, (*R*)-**12** (3.50 g, 18 mmol) and (*S*)-**30** (4.01 g, 14 mmol) gave 4.86 g [87% based on (*S*)-**30**] of (5*R*,8*RS*,11*S*)-**36** as a colorless oil, which solidified partially. Recrystallization of the solid from acetone gave (5*R*,8*R* or *S*, 11*S*)-**36** (1.4g, 25%) as rhombs, mp 41.5–42.0 °C. An analytical sample was obtained by further recrystallization from acetone, mp 43.5–44.0 °C; $[\alpha]_D^{24}$ −0.71 (*c* 2.84, hexane); ν_{max} (Nujol): 3310 (m), 3219 (m), 1295 (w), 1233 (w), 1154 (w), 1130 (w), 1085 (w), 1056 (m), 976 (w), 939 (w), 918 (w), 881 (m), 846 (w), 763 (w), 719 (m); δ_C ($CDCl_3$): 14.09, 14.13, 14.15, 19.62, 19.75, 22.69, 23.01, 27.02, 29.25, 29.36, 29.65, 29.69, 30.00, 31.92, 32.85, 32.88, 34.85, 36.57, 36.88, 72.89. Its ^{1}H NMR and MS spectra were virtually identical with those of (5*R*,8*RS*,11*R*)-**36**. GC–MS [same conditions as those for (5*R*,8*RS*,11*R*)-**36**]: t_R 19.14 min (100%). HRMS calcd for $C_{27}H_{55}O$ [$(M-H)^+$]: 395.4253, found; 395.4247. Its mother liquor (2.70 g, 48%) was obtained as a colorless oil of (5*R*,8*S* or *R*, 11*S*)-**36**, n_D^{20}=1.4573; $[\alpha]_D^{24}$ −0.38 (*c* 6.29, hexane). Its IR, ^{1}H NMR and MS spectra were indistinguishable from those of (5*R*,8*RS*,11*R*)-**36**. GC–MS (same conditions as those for (5*R*,8*RS*,11*R*)-**36**]: t_R 19.15 min (86.6%). HRMS calcd for $C_{27}H_{55}O$ [$(M-H)^+$]: 395.4253, found: 395.4253.

4.21.3. (5S,8S or R,11R)-Isomer (crystals) and (5S,8R or S,11R)-isomer (oil). Similarly, (*S*)-**12** (2.40 g, 12.4 mmol) and (*R*)-**30** (2.75 g, 9.8 mmol) gave 3.41 g [89% based on (*R*)-**30**] of (5*S*,8*RS*,11*R*)-**36** as a colorless oil, which solidified partially. Recrystallization from acetone gave 775 mg (20%) of (5*S*,8*S* or, *R*,11*R*)-**36** as fine rhombs, mp 39–40 °C. An analytical sample was obtained by further recrystallization from acetone, mp 42.5–43.0 °C; $[\alpha]_D^{23}$ +0.71 (*c* 3.19, hexane). Its IR, ^{1}H NMR and MS spectra were identical with those of the crystalline (5*R*,8*R* or *S*,11*S*)-**36**. GC–MS (same conditions as those for (5*R*,8*RS*,11*R*)-**36**]: t_R 19.13 min (100%). HRMS calcd for $C_{27}H_{55}O$ [$(M-H)^+$]: 395.4253, found: 395.4242. Its mother liquor (2.03 g, 53%) was obtained as a colorless oil of (5*S*,8*R* or *S*,11*R*)-**36**, n_D^{21}=1.4568; $[\alpha]_D^{23}$ +0.33 (*c* 4.56, hexane). Its IR, ^{1}H NMR and MS spectra were consistent with those of (5*R*,8*RS*,11*R*)-**36**. GC–MS (same conditions as those for (5*R*,8*RS*,11*R*)-**36**]: t_R 19.15 min (79.7%). HRMS calcd for $C_{27}H_{55}O$ [$(M-H)^+$]: 395.4253, found: 395.4253.

4.21.4. (5S,8RS,11S)-Isomer. Similarly, (*S*)-**12** (2.40 g, 12.4 mmol) and (*S*)-**30** (2.75 g, 9.8 mmol) gave 2.98 g [77% based on (*S*)-**30**] of (5*S*,8*RS*,11*S*)-**36** as a colorless oil, n_D^{21}=1.4572; $[\alpha]_D^{22}$ +0.81 (*c* 4.25, hexane). Its IR, ^{1}H NMR and MS spectra were identical with those of (5*R*,8*RS*,11*R*)-**36**. GC–MS (same conditions as those for (5*R*,8*RS*,11*R*)-**36**]: t_R 19.15 min (81.5%). HRMS calcd for $C_{27}H_{55}O$ [$(M-H)^+$]: 395.4253, found: 395.4251.

4.22. 8-Methanesulfonyloxy-5,11-dimethylpentacosane (37)

4.22.1. (5R,8RS,11R)-Isomer. A solution of MsCl (1.50 g, 13 mmol) in dry CH_2Cl_2 (3 mL) was added to a stirred and ice-cooled solution of (5*R*,8*RS*,11*R*)-**36** (1.50 g, 3.8 mmol) and DMAP (20 mg) in dry C_5H_5N (6 mL). The mixture was stirred for 1 h at 0–5 °C, and left to stand overnight in a refrigerator. It was then diluted with ice-water, and extracted with Et_2O. The Et_2O solution was washed successively with dil. HCl, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo to give 1.85 g (quant.) of (5*R*,8*RS*,11*R*)-**37** as a colorless oil, ν_{max} (film): 2955 (s), 2925 (s), 2854 (s), 1465 (m), 1377 (m), 1359 (m), 1176 (s), 903 (s), 532 (m). This was employed in the next step without further purification.

4.22.2. (5R,8RS,11S)-Isomer. Similarly, 1.08 g (2.7 mmol) of crystalline (5*R*,8*R* or *S*,11*S*)-**36** gave 1.19 g (92%) of (5*R*,8*R* or *S*,11*S*)-**37** as an oil, and 1.50 g (3.8 mmol) of oily (5*R*,8*S* or *R*,11*S*)-**36** gave 1.81 g (quant.) of (5*R*,8*S* or *R*,11*R*)-**37** as a slightly yellowish oil. Their IR spectra were consistent with that of (5*R*,8*RS*,11*R*)-**37.**

4.22.3. (5S,8RS,11R)-Isomer. Similarly, 710 mg (1.8 mmol) of crystalline (5*S*,8*S* or *R*,11*R*)-**36** gave 770 mg (90%) of (5*S*,8*S* or *R*,11*R*)-**37** as an oil, and 1.50 g (3.8 mmol) of oily (5*S*,8*R* or *S*,11*R*)-**36** gave 1.80 g (quant.) of (5*S*,8*R* or *S*,11*R*)-**37** as a slightly yellowish oil. Their IR spectra were consistent with that of (5*R*,8*RS*,11*R*)-**37**.

4.22.4. (5S,8RS,11S)-Isomer. Similarly, 1.50 g (3.8 mmol) of (5*S*,8*RS*,11*S*)-**36** gave 1.81 g (quant.) of (*5S*,*8RS*,*11S*)-**37** as a slightly yellowish oil. Its IR spectrum was identical with that of (*5R*,*8RS*,*11R*)-**37**.

4.23. 5,11-Dimethylpentacosane (1)

4.23.1. (5R,11R)-Isomer. A solution of (5*R*,8*RS*,11*R*)-**37** (1.85 g, 3.8 mmol) in dry THF (5 mL) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (350 mg, 9 mmol) in dry THF (15 mL). After the addition, the mixture was stirred and heated under reflux for 1 h. After cooling, the excess $LiAlH_4$ was destroyed

by dropwise addition of water to the stirred mixture under ice-cooling. The mixture was then acidified with dil. HCl and ice, and extracted with Et_2O. The Et_2O solution was washed successively with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography (twice) over SiO_2 (each 20 g). Elution with hexane gave 715 mg (50%) of (5*R*,11*R*)-**1**. Single chromatographic purification was not enough to remove an impurity eluted with hexane in later fractions. Properties of (5*R*,11*R*)-**1**: a colorless oil, which solidified in a deep freezer, n_D^{22}=1.4510; $[\alpha]_D^{22}$ −1.32 (*c* 4.93, hexane); ν_{max} (film): 2956 (s), 2925 (s), 2853 (s), 1465 (m), 1377 (m), 1302 (w), 1154 (w), 722 (m); δ_H ($CDCl_3$): 0.837 (3H, d, *J* 6.4), 0.840 (3H, d, *J* 6.4), 0.863–0.905 (6H, m), 1.05–1.15 (4H, m), 1.20–1.42 (40H, br s); δ_C ($CDCl_3$): 14.13, 14.18, 19.76, 22.73, 23.09, 27.14, 27.17, 29.39, 29.42, 29.71, 29.75, 29.79, 30.09, 30.43, 31.98, 32.79, 32.81, 36.83, 37.16; GC–MS (same conditions as those for **4**): t_R 28.54 min (96.6%); MS (70 eV, EI): *m*/*z*: 380 (<1) [M^+], 365 (12) [$(M-CH_3)^+$], 323 (30), 295 (12), 225 (25), 224 (36), 183 (41), 169 (12), 155 (21), 141 (26), 127 (31), 113 (34), 99 (40), 85 (100), 71 (68), 57 (83), 43 (68). HRMS calcd for $C_{27}H_{56}$: 380.4382, found: 380.4391.

4.23.2. (5R,11S)-Isomer. Similarly, 1.19 g (2.5 mmol) of (5*R*,8*R* or *S*,11*S*)-**37** (prepared from crystalline **36**) gave 494 mg (52%) of (5*R*,11*S*)-**1** as a colorless oil, which solidified in a deep freezer, n_D^{21}=1.4520; $[\alpha]_D^{23}$ −0.85 (*c* 4.74, hexane); ν_{max} (film): 2956 (s), 2925 (s), 1465 (m), 1377 (m), 1303 (w), 1153 (w), 722 (m); δ_H($CDCl_3$): 0.836 (3H, d, *J* 6.4), 0.840 (3H, d, *J* 6.4), 0.863–0.905 (6H, m), 1.05–1.15 (4H, m), 1.20–1.42 (40H, br s); δ_C($CDCl_3$): 14.13, 14.18, 19.73, 22.71, 23.07, 27.11, 27.14, 29.36, 29.39, 29.68, 29.73, 29.76, 30.06, 30.39, 31.95, 32.75, 32.77, 36.80, 37.12; MS (70 eV, EI): *m*/*z*: 380 (<1) [M^+], 365 (10) [$(M-CH_3)^+$], 323 (27), 295 (12), 225 (24), 224 (32), 183 (36), 169 (9), 155 (19), 141 (20), 127 (25), 113 (31), 99 (36), 85 (100), 71 (76), 57 (92), 43 (78). GC–MS (same conditions as those for **4**): t_R 28.52 min (98.3%); Its IR, ^1H and ^{13}C NMR, and MS spectra were indistinguishable from those of (5*R*,11*R*)-**1**. HRMS calcd for $C_{27}H_{56}$: 380.4382, found: 380.4388.

4.23.3. (5S,11R)-Isomer. Similarly, 770 mg (1.6 mmol) of (5*S*,8*S* or *R*,11*R*)-**37** (prepared from crystalline **36**) gave 456 mg (74%) of (5*S*,11*R*)-**1** as a colorless oil, which solidified in a deep freezer, n_D^{21}=1.4512; $[\alpha]_D^{22}$ +0.85 (*c* 4.01, hexane); GC–MS (same conditions as those for **4**): t_R 28.53 min (98.7%); Its IR, ^1H and ^{13}C NMR and MS spectra were identical with those of (5*R*,11*S*)-**1**. HRMS calcd for $C_{27}H_{56}$: 380.4382, found: 380.4375.

4.23.4. (5S,11S)-Isomer. Similarly, 1.81 g (3.8 mmol) of (5*S*,8*RS*,11*S*)-**37** gave 709 mg (49%) of (5*S*,11*S*)-**1** as a colorless oil, which solidified in a deep freezer, n_D^{21}=1.4510; $[\alpha]_D^{22}$ +1.05 (*c* 4.82, hexane); GC–MS (same conditions as those for **4**): t_R 28.51 min (98.2%); Its IR, ^1H and ^{13}C NMR and MS spectra were identical with those of (5*R*,11*R*)-**1**. HRMS calcd for $C_{27}H_{56}$: 380.4382, found: 380.4388.

4.24. HPLC analysis of 39

4.24.1. Analytical HPLC instruments. The HPLC pump used was Tosoh DP-8020 equipped with Rhodyne 7125 sample injector with a 5 μL sample loop. The fluorescene detector was Jasco FP-920 with a 16 μL flow cell. The integrator was Chromatocorder 21 (System Instrument, Tokyo, Japan). Cryocool CC100-II was used to control the column temperature.

4.24.2. Sample preparation. Alcohol **36** (ca.2 mg) was dissolved in about 1 mL of toluene/acetonitrile (1:1). Excess amounts of (1*R*,2*R*)-**38**, DMAP and EDC were added to the sample solution (about 0.3 mL). The solution was stood for more than 1 h at room temperature. An aliquot was then loaded onto a silica gel TLC plate (80 mm length, silica gel 60 F254, Art-5554, Merck), and the plate was developed with hexane/EtOAc (10:1, *v*/*v*). The target spot (Rf=0.54) detected by fluorescence was collected, packed in a Pasteur pipette, and eluted with EtOAc/MeOH (4:1, *v*/*v*). The eluate was used for an HPLC analysis.

4.24.3. HPLC separation. The derivative **39** was separated on a reversed phase column (Develosil C-30-UG3, 3 μm, 4.6 mm i.d.×150 mm) by elution with a mixture of MeOH/MeCN/THF/2,3,3-trimethylpentane (2:8:22:10, *v*/*v*/*v*/*v*) at a rate of 0.2 mL/min at −55 °C. The detection was executed by monitoring the fluorescence intensity at 462 nm (excitation at 298 nm).

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