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Pheromone synthesis. Part 245: Synthesis and chromatographic analysis of the four stereoisomers of 4,8-dimethyldecanal, the male aggregation pheromone of the red flour beetle, *Tribolium castaneum*☆

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ABSTRACT

All four stereoisomers of 4,8-dimethyldecanal (**1**) were synthesized from the enantiomers of 2-methyl-1-butanol and citronellal. Enantioselective GC analysis enabled separation of (4*R*,8*R*)-**1** and (4*R*,8*S*)-**1** from a mixture of (4*S*,8*R*)-**1** and (4*S*,8*S*)-**1**, when octakis-(2,3-di-*O*-methoxymethyl-6-*O*-*tert*-butyldimethylsilyl)-γ-cyclodextrin was employed as a chiral stationary phase. Complete separation of the four stereoisomers of **1** on reversed-phase HPLC at −54 °C was achieved after oxidation of **1** to the corresponding carboxylic acid **12** followed by its derivatization with (1*R*,2*R*)-2-(2,3-anthracenedicarboximido) cyclohexanol, and the natural **1** was found to be a mixture of all the four stereoisomers.

1. Introduction

Does an organism produce a single enantiomer of a chiral semiochemical or a mixture of stereoisomers? It is an interesting but difficult question to answer, because powerful separation technologies are required to analyze the stereoisomeric composition of a scarce natural product. We recently made the unexpected discovery that the male aggregation pheromone of the red flour beetle [*Tribolium castaneum* (Herbst). COLEOPTERA: Tenebrionidae] is a mixture of all four stereoisomers of 4,8-dimethyldecanal (**1**, Fig. 1). The present paper describes our chemical works underlying that discovery, that is, the synthesis and chromatographic analysis of the four stereoisomers of **1** to establish the conditions for their separation.

In 1980, Suzuki identified 4,8-dimethyldecanal (**1**) as the male-produced aggregation pheromone of the red flour beetle, *T. castaneum* (Herbst), and the confused flour beetle, *Tribolium confusum* (Jacquelin duVal).[2,3] He then synthesized a mixture of all four stereoisomers of **1**, and found it to be less active than the natural pheromone.[4] Later, in 1987, the trivial name 'tribolure' was given to **1**, when it was found also to be the aggregation pheromone of *Tribolium freemani* (Hinton).[5]

Enantioselective synthesis of all four stereoisomers of **1** was first achieved in 1983 by Mori et al.[6] Since then many different syntheses of the enantiomers or stereoisomeric mixtures of **1** have been reported.[7–9] Based on bioassay of the four stereoisomers of **1** on *T. castaneum*, Suzuki and Mori concluded that the natural tribolure was (4*R*,8*R*)-**1**, because it was as active as the natural pheromone.[10] Subsequently, a 4:1 mixture of (4*R*,8*R*)-**1** and (4*R*,8*S*)-**1** was found to be ten times more active than (4*R*,8*R*)-**1** alone, although (4*R*,8*S*)-**1** itself was inactive at lower doses.[11] That result

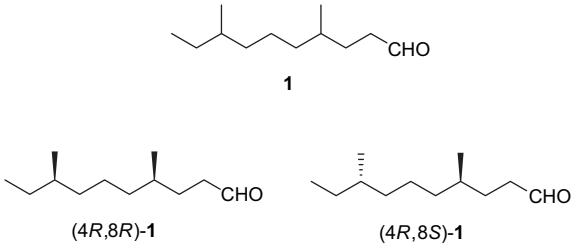

Fig. 1. 4,8-Dimethyldecanal (**1**), the male aggregation pheromone of *T. castaneum*.

☆ For Part 244, see Ref. 1.

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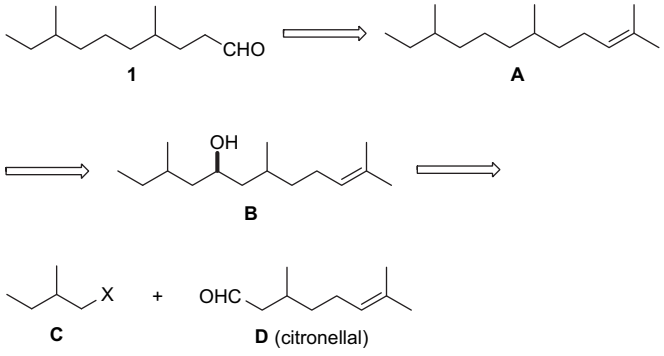
puzzled us, and in 1987 Suzuki et al. speculated that the aggregation pheromone of the three species (*T. castaneum*, *T. confusum* and *T. freemani*) might be a mixture of (4*R*,8*R*)-**1** (main active component) and some other stereoisomers.[5] Unfortunately it was impossible to verify that hypothesis in 1980s, because there was no good method available at that time to analyze precisely the stereoisomeric composition of the natural tribolure.

The scientific situation concerning optically active compounds has changed dramatically since then. Both synthetic and analytical techniques to prepare and evaluate enantiopure compounds have made remarkable progress. Thus, enantioselective synthesis of the stereoisomers of **1** (by K.M.) was a relatively easy task, and their separation was feasible by chromatographic means such as enantioselective GC (by S.T.) or reversed-phase HPLC after derivatization (by K.A.). On the basis of these chemical studies described below, biological experiments (by Y. Lu et al.) on these important pest insects of stored products were conducted subsequently.

2. Results and discussion

2.1. Synthesis of the four stereoisomers of 1 and their derivatization to provide analytical samples 12, 13, and 14

Scheme 1 shows our retrosynthetic analysis of **1**. 4,8-Dimethyldecanal (**1**) can be prepared by cleaving the double bond of



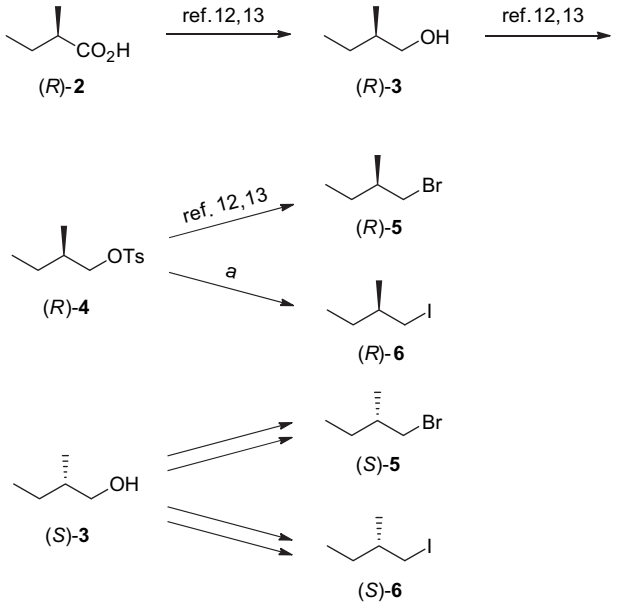
Scheme 1. Retrosynthetic analysis of 4,8-dimethyldecanal (**1**).

alkene **A**, which is obtained by deoxygenation of alcohol **B**. Coupling of **C** with **D** (citronellal) gives **B**. In the 1980s only (*S*)-**C** and (*R*)-**D** were commercially available, and therefore the present strategy could be used only for the preparation of (4*S*,8*S*)-**1** or a mixture of stereoisomers.[4] At present, both the enantiomers of **C** as well as **D** are available. Accordingly, the strategy is applicable to the synthesis of all four stereoisomers of **1**.

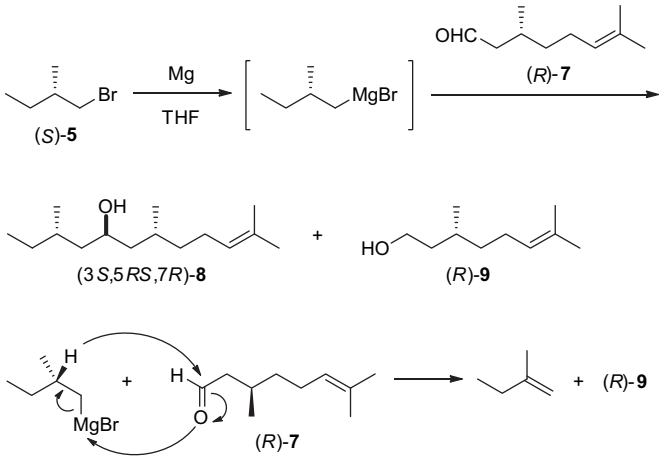
Scheme 2 summarizes the synthesis of the enantiomers of 2-methylbutyl bromide (**5**) and iodide (**6**). The starting acid (*R*)-**2** was supplied by T. Hasegawa Co.,[12,13] while alcohol (*S*)-**3** was commercially available. These starting materials were converted to the enantiomers of **5** and **6** by standard methods.[12,13]

The next step was the addition of a Grignard reagent prepared from (*S*)-**5** and magnesium in THF to (*R*)-citronellal (**7**). This reaction turned out to be problematic. After chromatographic purification of the product, the more polar fractions were combined and distilled, which was expected to yield (3*S*,5*RS*,7*R*)-**8** (Scheme 3). However, the product obtained in 40–50% yield based on (*S*)-**5** was an almost 1:1 mixture of the desired **8** and (*R*)-citronellol (**9**), which was generated by reduction of (*R*)-**7** with the Grignard reagent as shown in Scheme 3.

To circumvent the problem, we turned our attention to the use of 2-methylbutyllithium instead of the Grignard reagent. Alkyllithium is known to give the desired product without yielding the



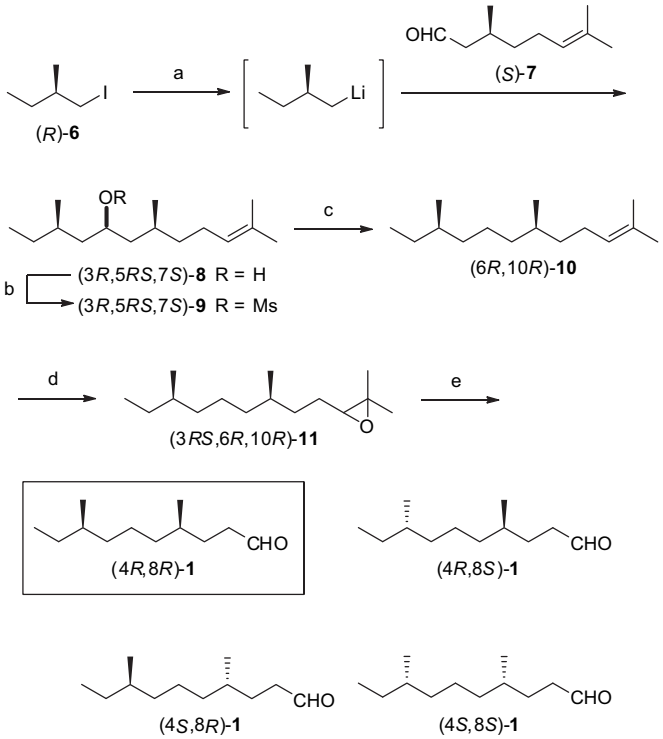
Scheme 2. Synthesis of the enantiomers of **5** and **6**. Reagents: (a) NaI, DMF [70% for (*R*)-**6**; 80% for (*S*)-**6**].



Scheme 3. Synthesis of (3*S*,5*RS*,7*R*)-**8** by Grignard reaction.

unwanted reduction product.[14–16] Accordingly, 2-methylbutyl iodide (**6**) in diethyl ether was treated with 2 equiv of *tert*-butyllithium in pentane at −78 °C to effect transmetallation (Scheme 4). Addition of the resulting organolithium reagent to (*S*)-citronellal (**7**) took place without event to give the desired (3*R*,5*RS*,7*S*)-**8** in 75% yield after chromatographic purification and distillation.

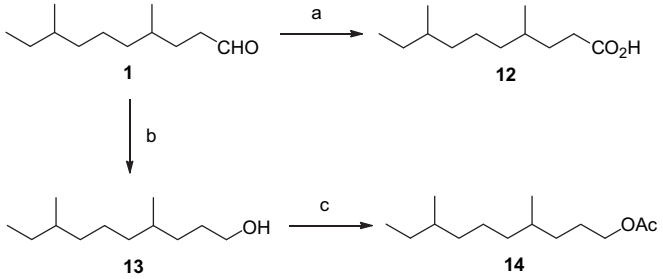
In order to remove the hydroxyl group of **8**, it was first mesylated to give mesylate (3*R*,5*RS*,7*S*)-**9**. Subsequent reduction of **9** with lithium aluminum hydride gave crude (6*R*,10*R*)-**10** (84% purity) in 70% yield after distillation. Epoxidation of (6*R*,10*R*)-**10** with *m*-chloroperbenzoic acid (MCPBA) afforded epoxide (3*RS*,6*R*,10*R*)-**11** (M^+=226) as a stereoisomeric mixture at C-3 contaminated with two unidentified impurities (2.1% and 2.2%, respectively, both with M^+=240). Finally, treatment of **11** with periodic acid dihydrate in THF and diethyl ether gave (4*R*,8*R*)-4,8-dimethyldecanal (**1**, 92% purity), $[\alpha]_D^{27}$ −7.34 (*c* 4.11, $CHCl_3$), in 50% yield after chromatographic purification and distillation. Its IR, ^1H and ^{13}C NMR, and MS data were identical with those reported previously.[2,6–8] The overall yield of (4*R*,8*R*)-**1** was 25% based on (*R*)-**6** (five steps). Its enantiomeric purity was considered as 97% ee at C-4 and >99% ee at C-8, respectively, reflecting the purity of (*R*)-**2** (>99% ee) and that of (*S*)-**7** (97% ee). Similarly, (4*R*,8*S*)-**1**, $[\alpha]_D^{25}$ +10.1



Scheme 4. Synthesis of (4*R*,8*R*)-**1**. Reagents; (a) *t*-BuLi, pentane, Et_2O; then (*S*)-**7** (75%); (b) MsCl, C_5H_5N, CH_2Cl_2 (quant.); (c) $LiAlH_4$, THF (70%); (d) MCPBA, CH_2Cl_2 (96%); (e) $HIO_4{\cdot}2H_2O$, THF, Et_2O (50%).

(*c* 4.11, $CHCl_3$), (4*S*,8*R*)-**1**, $[\alpha]_D^{25}$ −9.06 (*c* 4.12, $CHCl_3$), and (4*S*,8*S*)-**1**, $[\alpha]_D^{25}$ +7.20 (*c* 4.17, $CHCl_3$) were synthesized. All the stereoisomers of **1** could thus be secured in >1 g quantities sufficient for bioassay.

In order to determine the best conditions for chromatographic separation of the four stereoisomers of **1** or its derivatives, several derivatives of **1** were prepared by sacrificing a small portion of **1**. As shown in Scheme 5, Jones oxidation of **1** gave 4,8-dimethyldecanoic acid (**12**). Reduction of **1** with lithium aluminum hydride afforded 4,8-dimethyl-1-decanol (**13**), and acetylation of **13** yielded 4,8-dimethyldecyl acetate (**14**). These were used in the analytical studies as described below.



Scheme 5. Conversion of **1** to **12**, **13**, and **14**. Reagents: (a) Jones CrO_3, Me_2CO (75%–quant.); (b) $LiAlH_4$, Et_2O (85–90%); (c) Ac_2O, C_5H_5N (88–93%).

2.2. Partial separation of the four stereoisomers of 1 and 13 by enantioselective GC

GC[17] and LC[18] are known to be powerful analytical tools in pheromone science. Their application to enantiomer separation of pheromones was reviewed recently.[19]

Separation of the four stereoisomers of **1**, **13**, and **14** was examined on eight different chiral stationary phases including Chiramix®[20] based on cyclodextrins as shown in Fig. 2. All of them failed to separate the stereoisomers of the acetate **14**.

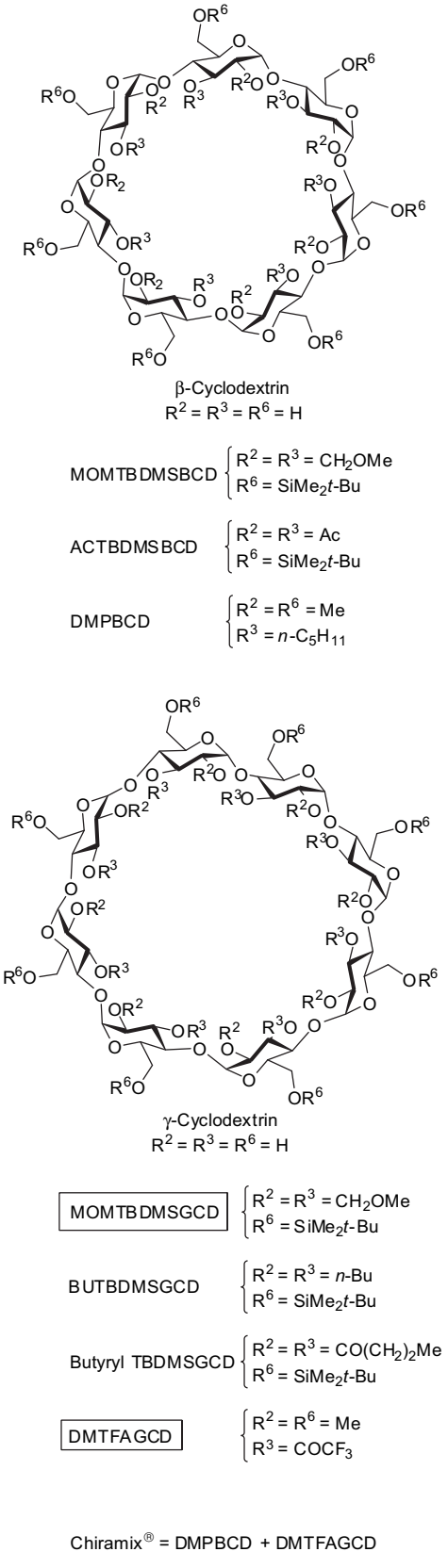


Fig. 2. Structures of cyclodextrin-based chiral stationary phases used in the present work. Partial separation of **1** was observed with MOMTBDMSGCD and DMTFAGCD.

Fortunately, two γ-cyclodextrin-based stationary phases were effective in partially separating the stereoisomers of **1** and **13**. A mixture of (4*R*,8*R*)- and (4*R*,8*S*)-4,8-dimethyl-1-decanol (**13**) could

be separated from a mixture of (4*S*,8*R*)- and (4*S*,8*S*)-**13**, employing octakis-(2,3-di-*O*-methoxymethyl-6-*O*-*tert*-butyldimethylsilyl)-γ-cyclodextrin[21] or octakis-(2,6-di-*O*-methyl-3-*O*-trifluoroacetyl)-γ-cyclodextrin.[22]

A mixture of the stereoisomers of tribolure (**1**) showed three peaks when it was analyzed over octakis-(2,3-di-*O*-methoxymethyl-6-*O*-*tert*-butyldimethylsilyl)-γ-cyclodextrin. The three peaks were identified as (4*R*,8*R*)-**1**, (4*R*,8*S*)-**1**, and a mixture of (4*S*,8*R*)-**1** and (4*S*,8*S*)-**1**. When octakis-(2,6-di-*O*-methyl-3-*O*-trifluoroacetyl)-γ-cyclodextrin was used as the stationary phase, a mixture of (4*R*,8*R*)- and (4*R*,8*S*)-**1** could be separated from a mixture of (4*S*,8*R*)- and (4*S*,8*S*)-**1**. Gas chromatograms showing the partial separation of the four stereoisomers of **1** are illustrated in Fig. 3.

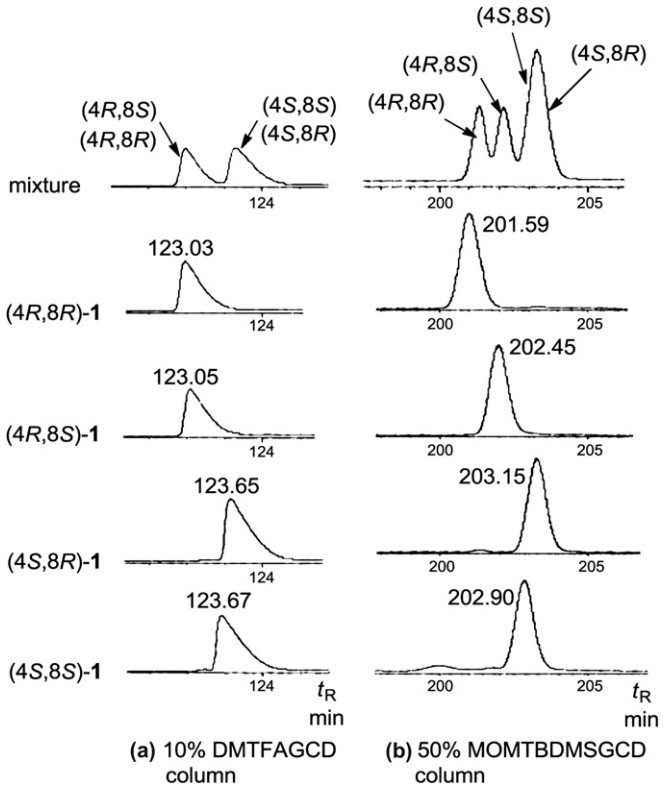


Fig. 3. GC separation of the stereoisomers of 4,8-dimethyldecanal (**1**) on (a) 10% DMTFAGCD (two peaks) and (b) 50% MOMTBDMSGCD (three peaks). For conditions, see Experimental.

It was concluded that complete GC separation of the four stereoisomers of **1** could not be realized by the stationary phases so far examined. Nevertheless, GC proved to be a simple method for the preliminary analysis of the natural pheromone without any derivatization.

2.3. Complete separation of the four stereoisomers of 12 by Ohrui–Akasaka's derivatization-reversed phase HPLC method

Ohrui and Akasaka recently developed a powerful method for the determination of enantiomeric purity at a remote stereogenic center far separated from functional groups.[23–25] They designed optically active and fluorescent derivatizing reagents including (1*R*,2*R*)- and (1*S*,2*S*)-2-(anthracene-2,3-dicarboximido)cyclohexanecarboxylic acid (**15**, Fig. 4; commercially available from Tokyo Kasei: TCI-A1657) and (1*R*,2*R*)- and (1*S*,2*S*)-2-(anthracene-2,3-dicarboximido)cyclohexanol (**17**).[25,26] Due to the fluorescent nature of the reagents, detection of the derivatives is possible at 10^{-15} mol levels. The

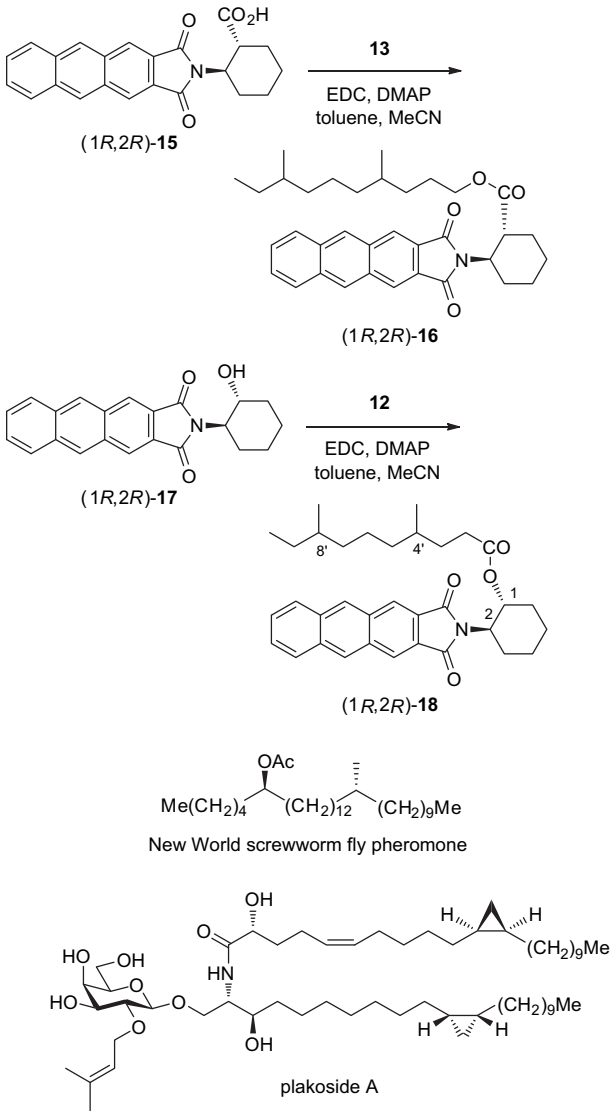


Fig. 4. Structures of chiral and fluorescent derivatizing reagents, (1*R*,2*R*)-2-(anthracene-2,3-dicarboximido)cyclohexanecarboxylic acid (**15**) and (1*R*,2*R*)-2-(anthracene-2,3-dicarboximido)cyclohexanol (**17**). Their applications in determination of stereochemistry are also illustrated.

reagent **15** was employed to determine the enantiomeric purity of the New World screwworm fly pheromone,[27] while **17** was used in the determination of the absolute configuration of a marine natural product, plakoside A.[28]

Derivatization of alcohol **13** with the fluorescent reagent (1*R*,2*R*)-**15** in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC), and 4-dimethylaminopyridine (DMAP) in toluene and acetonitrile afforded **16**, whose four stereoisomers were eluted as three broad peaks upon HPLC analysis, indicating that complete separation could not be achieved.

Fortunately, derivatization of acid **12** with the reagent (1*R*,2*R*)-**17** gave satisfactory results. The four stereoisomers of the resulting derivative (1*R*,2*R*)-**18** could not be separated by the C-30 column at 40 °C, but they were completely separable by the ODS second column kept at −54 °C as shown in Fig. 5. Assignment of the each peak was made possible by comparing its retention time (t_R) with that of the authentic stereoisomer of (1*R*,2*R*)-**18**. The LC–LC system using these two columns was very effective to remove interfering substances and also to reduce the time for analysis of the natural samples. Accordingly, the Ohrui–Akasaka method of analysis was

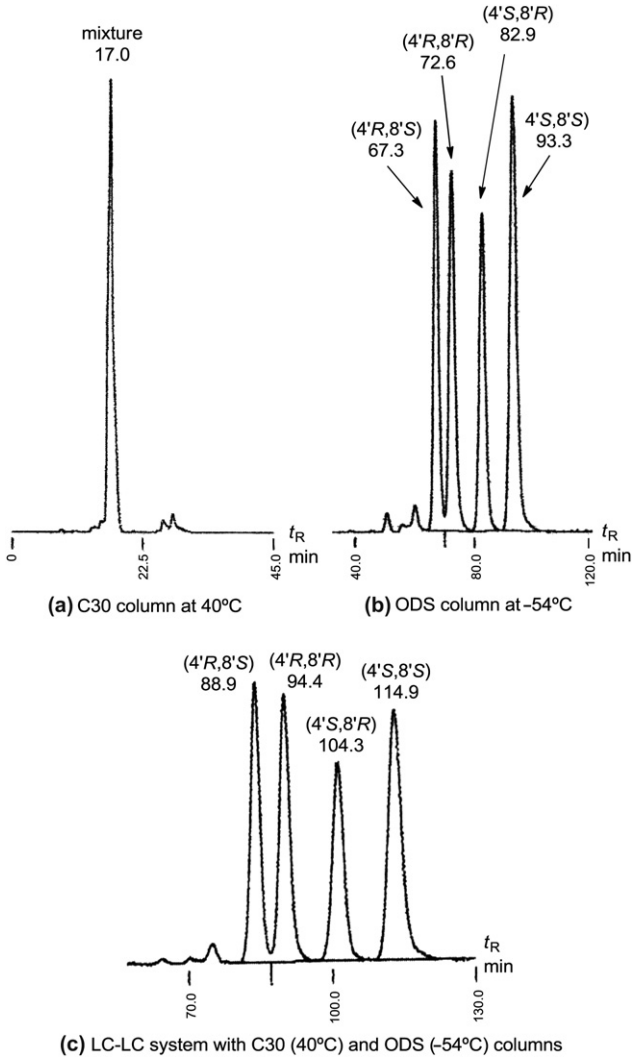


Fig. 5. HPLC separation of the stereoisomers of (1*R*,2*R*)-**18**. (a) Elution from the C30 column. Eluent: MeOH; Flow rate: 0.3 mL/min; Column temp: 40 °C. (b) Separation on the ODS column. Eluent: MeOH/MeCN/THF/hexane=220:200:80:4; Flow rate: 0.4 mL/min; Column temp: −54 °C. (c) Separation by LC–LC system with the C30 and the ODS columns.

used to determine the stereoisomeric composition of the naturally occurring **1** of *T. castaneum*.

3. Conclusion

The four stereoisomers of 4,8-dimethyldecanal (tribolure, **1**) were synthesized. They could be separated partially by enantioselective GC, and completely by reversed-phase HPLC after derivatization to (1*R*,2*R*)-**18** employing Ohrui–Akasaka's reagent (1*R*,2*R*)-**17**. Established separation methods were used to determine the stereoisomeric composition of naturally occurring tribolure. The most important result of the analysis was the fact that the natural tribolure of *T. castaneum* was a mixture of (4*R*,8*R*)-, (4*R*,8*S*)-, (4*S*,8*R*)-, and (4*S*,8*S*)-**1** in a ratio of about 4:4:1:1 (Y. Lu et al. manuscript in preparation). In the course of the biosynthesis of tribolure by *T. castaneum*, the configuration at C-8 is not at all controlled, while that at C-4 is controlled partially to give a 4:1 ratio of (4*R*)- and (4*S*)-isomers. Details of the above analytical results as well as the stereochemistry–pheromone activity relationships will be the subject of another paper.

4. Experimental

4.1. General

Boiling points are uncorrected values. Refractive indices (n_D) 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-SX 102 A. Column chromatography was carried out on Merck Kieselgel 60 Art 1.07734.

4.2. 2-Methylbutyl iodide (6)

4.2.1. (R)-Isomer. A solution of (*R*)-2-methylbutyl tosylate (**4**, 41.0 g, 169 mmol) in DMF (200 mL) was stirred and heated with NaI (60 g, 400 mmol) at 60 °C for 1 h. The mixture was diluted with water, and the heavy iodide layer was separated. The aqueous layer was extracted with pentane. The iodide and the extract were combined, washed with water and brine, dried ($MgSO_4$), and concentrated through a Vigreux column at atmospheric pressure. The residue was distilled to give 24.8 g (70%) of (*R*)-**6**. Bp 144–146 °C; n_D^{22}=1.4942; $[\alpha]_D^{26}$ −5.32 (*c* 4.87, pentane); ν_{max} (film): 2960 (s), 1456 (m), 1379 (m), 1194 (s); δ_H ($CDCl_3$): 0.89 (3H, t, *J* 7.2, CH_2CH_3), 0.98 (3H, d, *J* 7.2, $CHCH_3$), 1.20–1.32 (1H, m), 1.35–1.45 (2H, m), 3.15–3.25 (2H, m); GC–MS [column: HP-5MS, 5% phenylmethylsiloxane, 30 m×0.25 mm i.d.; press: 48.7 kPa; temp: 40–230 °C (+5 °C/min)]: t_R 3.47 (2.3%, 2-methylbutyl chloride), 7.35 min [97.3%, (*R*)-**6**]. MS of (*R*)-**6** (70 eV, EI): *m*/*z* 198 (21) [M^+, $C_5H_{11}I$], 169 (4), 127 (5), 71 (100), 55 (17), 43 (71), 39 (32). HRMS calcd for $C_5H_{11}I$: 197.9905, found: 197.9907.

4.2.2. (S)-Isomer. In the same manner, (*S*)-**4** (57.3 g, 237 mmol) yielded 37.8 g (89%) of (*S*)-**6**, Bp 145–146 °C; n_D^{21}=1.4962; $[\alpha]_D^{27}$ +5.30 (*c* 4.88, pentane); GC [under the same conditions for (*R*)-**6**]: t_R 7.36 min [98.3%, (*S*)-**6**]. Its IR, ^{1}H NMR, and mass spectra were identical to those of (*R*)-**6**. HRMS calcd for $C_5H_{11}I$: 197.9905, found: 197.9910.

4.3. 3,7,11-Trimethyl-10-dodecen-5-ol (8)

4.3.1. (3R,5RS,7S)-Isomer. A solution of *t*-BuLi in pentane (1.6 M, 35 mL, 56 mmol) was added dropwise to a stirred and cooled solution of (*R*)-**6** (5.54 g, 28 mmol) in dry Et_2O (50 mL) at −78 °C under argon. The mixture was stirred for 10 min at −78 °C, and then for 10 min at room temperature. The solution was cooled again at −78 °C, and a solution of (*S*)-**7** (3.85 g, 25 mmol) in dry Et_2O (10 mL) was added dropwise to the stirred mixture at −78 °C. The dry ice-acetone bath was removed, and the mixture was stirred for 1.5 h. It was then quenched with ice, dil HCl and NH_4Cl solution. The mixture was extracted with Et_2O. The Et_2O solution was washed with $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (5.50 g) was chromatographed over SiO_2 (50 g). Elution with hexane/EtOAc (9:1) gave 5.29 g of crude **8**, which was distilled to give 4.22 g (75%) of pure (3*R*,5*RS*,7*S*)-**8**. Bp 110–116 °C/3 Torr; n_D^{21}=1.4585; $[\alpha]_D^{24}$ −6.89 (*c* 4.11, hexane); ν_{max} (film): 3327 (m, O–H), 2962 (s), 2924 (s), 1460 (m), 1377 (m), 1059 (m); δ_H ($CDCl_3$): 0.86–0.93 (9H, m, CH_3), 1.08–1.22 (3H, m), 1.22–1.32 (2H, m), 1.32–1.50 (3H, m), 1.50–1.70 (3H, m), 1.61 (3H, s, $C{=}CCH_3$), 1.68 (3H, s, $C{=}CCH_3$), 1.90–2.10 (2H, m), 3.79 (1H, m, C*H*OH), 5.10 (1H, t-like C=CH); GC–MS [column: HP-5S, 5% phenylmethylsiloxane, 30 m×0.25 mm i.d.; press: 60.7 kPa; temp: 70–230 °C (+10 °C/min)]: t_R 13.09 [51.0%, (3*R*,5*R* or *S*,7*S*)-**8**],

13.23 min [45.8%, (3*R*,5*S* or *R*,7*S*)-**8**]. These two isomers showed the same MS (70 eV, EI): *m*/*z* 226 (0.7) [M^+, $C_{15}H_{30}O$], 208 (1), 197 (4), 152 (7), 141 (40), 123 (23), 109 (61), 95 (48), 82 (100), 81 (57), 69 (61), 55 (34), 41 (44). HRMS calcd for $C_{15}H_{30}O$: 226.2297, found: 226.2301.

4.3.2. (3S,5RS,7S)-Isomer. In the same manner, 5.54 g (28 mmol) of (*S*)-**6** and 3.80 g (24.7 mmol) of (*S*)-**7** afforded 4.73 g (84%) of (3*S*,5*RS*,7*S*)-**8**. Bp 129–132 °C/6 Torr; n_D^{24}=1.4580; $[\alpha]_D^{25}$ +12.1 (*c* 4.39, hexane). Its IR, ^{1}H NMR, and mass spectra were virtually identical to those of (3*R*,5*RS*,7*S*)-**8**. GC [under the same conditions as for (3*R*,5*RS*,7*S*)-**8**]: t_R 13.12 [44.3%, (3*S*,5*R* or *S*,7*S*)-**8**], 13.22 min [52,4%, (3*S*,5*S* or *R*,7*S*)-**8**]. HRMS calcd for $C_{15}H_{30}O$: 226.2297, found: 226.2299.

4.3.3. (3R,5RS,7R)-Isomer. In the same manner, 5.54 g (28 mmol) of (*R*)-**6** and 3.85 g (25 mmol) of (*R*)-**7** yielded 4.32 g (77%) of (3*R*,5*RS*,7*R*)-**8**. Bp 123–126 °C/5 Torr; n_D^{22}=1.4582; $[\alpha]_D^{25}$ −11.4 (*c* 4.10, hexane). Its IR, ^{1}H NMR, and mass spectra were identical with those of (3*S*,5*RS*,7*S*)-**8**. GC [under the same conditions as for (3*R*,5*RS*,7*S*)-**8**]: t_R 13.12 [46.4%, (3*R*,5*R* or *S*,7*R*)-**8**], 13.22 min [50.7%, (3*R*,5*S* or *R*,7*R*)-**8**]. HRMS calcd for $C_{15}H_{30}O$: 226.2297, found: 226.2308.

4.3.4. (3S,5RS,7R)-Isomer. In the same manner, 5.54 g (28 mmol) of (*S*)-**6** and 3.80 g (24.7 mmol) of (*R*)-**7** afforded 4.84 g (86%) of (3*S*,5*RS*,7*R*)-**8**. Bp 121–123 °C/5 Torr; n_D^{22}=1.4582; $[\alpha]_D^{26}$ +6.60 (*c* 4.31, hexane). Its IR, ^{1}H NMR, and mass spectra were identical with those of (3*R*,5*RS*,7*S*)-**8**. GC [under the same conditions as for (3*R*,5*RS*,7*S*)-**8**]: t_R 13.09 [51.1%, (3*R*,5*R* or *S*,7*S*)-**8**], 13.23 min [48.9%, (3*R*,5*S* or *R*,7*S*)-**8**]. HRMS calcd for $C_{15}H_{30}O$: 226.2297, found: 226.2293.

4.4. Methanesulfonate (9) of 3,7,11-trimethyl-10-dodecen-5-ol

4.4.1. (3R,5RS,7S)-Isomer. A solution of MsCl (2.30 g, 20 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a stirred and ice-cooled solution of (3*R*,5*RS*,7*S*)-**8** (3.87 g, 17 mmol) in dry pyridine (15 mL). The mixture was stirred for 5 h at 0–5 °C. It was then quenched by pouring into ice-water. The mixture was extracted with Et_2O. The extract was washed with dil HCl, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo to give 4.87 g (quant.) of (3*R*,5*RS*,7*S*)-**9**, ν_{max} (film): 2962 (s), 2927 (s), 1462 (m), 1336 (s), 899 (s); δ_H($CDCl_3$): 0.87–0.97 (9H, m, CH_3), 1.10–1.25 (2H, m), 1.25–1.55 (4H, m), 1.55–1.65 (4H, m), 1.61 (3H, s, C=CCH_3), 1.68 (3H, s, C=CCH_3), 1.71–1.81 (1H, m), 1.90–2.10 (2H, m), 2.99 (3H, s, CH_3SO_2), 4.82–4.95 (1H, m), 5.05–5.15 (1H, m). This was employed in the next step without further characterization.

4.4.2. (3S,5RS,7S)-Isomer. In the same manner, 4.80 g (21 mmol) of (3*S*,5*RS*,7*S*)-**8** afforded 6.65 g (quant.) of (3*S*,5*RS*,7*S*)-**9**. Its IR and ^{1}H NMR spectra were virtually identical to those of (3*R*,5*RS*,7*S*)-**9**.

4.4.3. (3R,5RS,7R)-Isomer. In the same manner, 4.30 g (19 mmol) of (3*R*,5*RS*,7*R*)-**8** afforded 5.80 g (quant.) of (3*R*,5*RS*,7*R*)-**9**. Its IR and ^{1}H NMR spectra were identical with those of (3*S*,5*RS*,7*S*)-**9**.

4.4.4. (3S,5RS,7R)-Isomer. In the same manner, 4.80 g (21 mmol) of (3*S*,5*RS*,7*R*)-**8** yielded 6.38 g (quant.) of (3*S*,5*RS*,7*R*)-**9**. Its IR and ^{1}H NMR spectra were identical with those of (3*R*,5*RS*,7*S*)-**9**.

4.5. 2,6,10-Trimethyl-2-dodecene (10)

4.5.1. (6R,10R)-Isomer. A solution of the mesylate (3*R*,5*RS*,7*S*)-**9** (4.85 g, ca. 17 mmol) in dry THF (10 mL) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (0.80 g, 21 mmol) in dry THF (40 mL). The mixture was stirred at 60 °C for 2 h, and at room temperature for 1 h. It was then treated with ice and dil HCl. The mixture was extracted with hexane. The hexane solution was washed with water, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give 2.53 g (70%) of (6*R*,10*R*)-**10**. Bp 93–96 °C/3 Torr; n_D^{21}=1.4462; $[\alpha]_D^{27}$ −5.20 (*c* 4.16, hexane); ν_{max} (film): 2962 (s), 2925 (s), 2873 (s), 2729 (w), 1462 (m), 1377 (m), 825 (w); δ_H ($CDCl_3$): 0.80–0.90 (9H, m, CH_3), 1.00–1.20 (4H, m), 1.20–1.50 (7H, m), 1.57 (1H), 1.61 (3H, s, C=CCH_3), 1.68 (3H, s, C=CCH_3), 1.86–2.05 (2H, m), 5.10 (1H, t-like, C=CH); GC–MS [under the same conditions as for (3*R*,5*RS*,7*S*)-**8**]: t_R 10.84 (8.7%, unidentified, M^+ 208), 10.87 (7.3%, unidentified, M^+ 208), 11.17 min [84.0%, (6*R*,10*R*)-**10**]. MS of (6*R*,10*R*)-**10** (70 eV, EI): *m*/*z* 210 (33) [M^+, $C_{15}H_{30}$], 140 (7), 126 (17), 125 (15), 111 (28), 97 (19), 83 (32), 70 (71), 69 (100), 57 (48), 56 (40), 55 (37), 41(47). HRMS calcd for $C_{15}H_{30}$: 210.2348, found: 210.2344.

4.5.2. (6R,10S)-Isomer. In the same manner, 6.60 g (ca. 21 mmol) of (3*S*,5*RS*,7*S*)-**9** gave 3.44 g (72%) of (6*R*,10*S*)-**10**. Bp 102–106 °C/5 Torr; n_D^{24}=1.4462; $[\alpha]_D^{25}$ +11.9 (*c* 4.56, hexane). Its IR, ^{1}H NMR, and mass spectra were virtually identical to those of (6*R*,10*R*)-**10**. GC [under the same conditions as for (6*R*,10*R*)-**10**]: t_R 10.85 (6.7%), 10.88 (7.4%), 11.17 min [85.9%, (6*R*,10*S*)-**10**]. HRMS calcd for $C_{15}H_{30}$: 210.2348, found: 210.2345.

4.5.3. (6S,10R)-Isomer. In the same manner, 4.25 g (ca. 19 mmol) of (3*R*,5*RS*,7*R*)-**9** furnished 2.98 g (75%) of (6*S*,10*R*)-**10**. Bp 100–103 °C/4 Torr; n_D^{21}=1.4468; $[\alpha]_D^{25}$ −12.0 (*c* 4.39, hexane). Its IR, ^{1}H NMR, and mass spectra were identical with those of (6*R*,10*S*)-**10**. GC [under the same conditions as for (6*R*,10*R*)-**10**]: t_R 10.85 (7.8%), 10.88 (8.2%), 11.17 min [84.0%, (6*S*,10*R*)-**10**]. HRMS calcd for $C_{15}H_{30}$: 210.2348, found: 210.2345.

4.5.4. (6S,10S)-Isomer. In the same manner, 4.75 g (ca. 21 mmol) of (3*S*,5*RS*,7*R*)-**9** afforded 3.89 g (82%) of (6*S*,10*S*)-**10**. Bp 105–108 °C/6 Torr; n_D^{24}=1.4456; $[\alpha]_D^{28}$ +5.29 (*c* 4.38, hexane). Its IR, ^{1}H NMR, and mass spectra were identical with those of (6*R*,10*R*)-**10**. GC [under the same conditions as for (6*R*,10*R*)-**10**]: t_R 10.84 (6.2%), 10.87 (5.4%), 11.17 min [88.4%, (6*S*,10*S*)-**10**]. HRMS calcd for $C_{15}H_{30}$: 210.2348, found: 210.2352.

4.6. 2,3-Epoxy-2,6,10-trimethyldodecane (11)

4.6.1. (3RS,6R,10R)-Isomer. MCPBA (65% purity, 4.0 g, 15 mmol) was added portionwise to a stirred and ice-cooled solution of (6*R*,10*R*)-**10** (2.50 g, 12 mmol) in dry CH_2Cl_2 (50 mL) at 5–10 °C. The mixture was stirred for 1 h at 0–5 °C, and then diluted with Et_2O. The solution was successively washed with Na_2CO_3 solution containing a small amount of $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo to give 2.58 g (96%) of (3*RS*,6*R*,10*R*)-**11**, ν_{max} (film): 2960 (s), 2925 (s), 2873 (s), 1462 (m), 1377 (m), 1327 (w), 1250 (w), 1122 (m), 897 (w), 872 (w); δ_H ($CDCl_3$): 0.80–0.90 (9H, m, CH_3), 0.86–1.10 (2H, m), 1.10–1.20 (2H, m), 1.23–1.40 (5H, m), 1.28 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.40–1.50 (2H, m), 1.50–1.60 (2H, m), 1.60–1.68 (1H, br. s), 2.70 (1H, t-like, *J* 6.0, epoxide H); GC–MS [under the same conditions as for (3*R*,5*RS*,7*S*)-**8**]: t_R 13.13 [46.1%, (3*R* or *S*,6*R*,10*R*)-**11**], 13.23 [49.4%, (3*S* or *R*, 6*R*,10*R*)-**11**], 13.78 (2.1%, unidentified, M^+ 240), 13.89 min (2.2%, unidentified, M^+ 240). MS of the two isomers of (3*R*,10*R*)-**11** was identical with each other (70 eV, EI): *m*/*z* 226 (1) [M^+, $C_{15}H_{30}O$], 197 (6), 152 (9), 141 (44), 123 (24), 109 (64), 95 (50), 82 (100), 81 (58), 69 (58), 55 (33), 41 (42). This was employed in the next step without further characterization.

4.6.2. (3RS,6R,10S)-Isomer. In the same manner, 2.57 g (11.9 mmol) of (6*R*,10*S*)-**10** afforded 2.70 g (quant.) of (6*RS*,6*R*,10*S*)-**11**. Its IR, ^{1}H

NMR, and mass spectra were virtually identical to those of (3*RS*,6*R*,10*R*)-**11**.

4.6.3. (3RS,6S,10R)-Isomer. In the same manner, 3.31 g (15.8 mmol) of (6*S*,10*R*)-**10** furnished 3.25 g (91%) of (3*RS*,6*S*,10*R*)-**11**. Its IR, ^{1}H NMR, and mass spectra were identical with those of (3*RS*,6*R*,10*S*)-**11**.

4.6.4. (3RS,6S,10S)-Isomer. In the same manner, 3.80 g (18.1 mmol) of (6*S*,10*S*)-**10** gave 4.14 g (quant.) of (3*RS*,6*S*,10*S*)-**11**. Its spectral data were identical with other stereoisomers.

4.7. 4,8-Dimethyldecanal (1)

4.7.1. (4R,8R)-Isomer. A solution of (3*RS*,6*R*,10*R*)-**11** (2.50 g, 11.1 mmol) in Et_2O (10 mL) was added dropwise to a stirred and ice-cooled solution of $HIO_4{\cdot}2H_2O$ (3.42 g, 15 mmol) in THF (40 mL) at 0–5 °C. The mixture was stirred for 20 min at 0–5 °C, diluted with water, and extracted with Et_2O. The Et_2O solution was successively washed with water, $NaHCO_3$ solution containing a small amount of $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (20 g). Elution with hexane and hexane/EtOAc (10:1) gave 1.43 g of crude (4*R*,8*R*)-**1**, which was distilled to give 1.12 g (50%), of (4*R*,8*R*)-**1**. Bp 93–96 °C/4 Torr; n_D^{24}=1.4370; $[\alpha]_D^{27}$ −7.34 (*c* 4.11, $CHCl_3$); ν_{max} (film): 2958 (s), 2927 (s), 2873 (s), 2713 (w, O=C-H), 1728 (s, C=O), 1462 (m), 1379 (m), 1136 (w), 1014 (w); δ_H($CDCl_3$): 0.80–0.93 (9H, m, CH_3), 1.00–1.18 (3H, m), 1.18–1.38 (6H, m), 1.38–1.50 (2H, m), 1.62–1.72 (1H, m), 2.35–2.50 (2H, m), 9.77 (1H, t-like, CHO); δ_C($CDCl_3$): 11.4, 19.3, 19.4, 24.4, 28.9, 29.5, 32.4, 34.4, 36.9, 37.1, 41.7, 202.8 (C=O); GC–MS [under the same conditions as for (3*R*,6*RS*,7*S*)-**8**]. t_R 10.17 [92.2%, (4*R*,8*R*)-**1**], 12.91 min (7.8%, unidentified, M^+ 226). MS of (4*R*,8*R*)-**1** (70 eV, EI): *m*/*z* 183 (<1)[M^+−1], 140 (22), 137 (13), 125 (11), 111 (36), 95 (53), 85 (60), 81 (51), 71 (62), 70 (93), 69 (73), 57 (100), 56 (62), 55 (71), 43 (56), 41 (69). HRMS calcd for $C_{12}H_{24}O$: 184.1827, found: 184.1824.

4.7.2. (4R,8S)-Isomer. In the same manner, 2.65 g (11.7 mmol) of (3*RS*,6*R*,10*S*)-**11** gave 1.49 g (68%) of (4*R*,8*S*)-**1**. Bp 100–106 °C/6 Torr; n_D^{21}=1.4380; $[\alpha]_D^{25}$ +10.1 (*c* 4.22, $CHCl_3$). Its IR, ^{1}H and ^{13}C NMR, and mass spectra were virtually identical to those of (4*R*,8*R*)-**1**. GC [under the same conditions as for (4*R*,8*R*)-**1**]: t_R 10.16 [95.3%, (4*R*,8*S*)-**1**], 12.91 min (4.7%, unidentified, M^+ 226). HRMS calcd for $C_{12}H_{24}O$: 184.1827, found: 184.1817.

4.7.3. (4S,8R)-Isomer. In the same manner, 3.20 g (14.1 mmol) of (3*RS*,6*S*,10*R*)-**11** afforded 1.57 g (63%) of (4*S*,8*R*)-**1**. Bp 90–92 °C/3 Torr; n_D^{25}=1.4376; $[\alpha]_D^{25}$ −9.06 (*c* 4.12, $CHCl_3$). Its IR, ^{1}H and ^{13}C NMR, and mass spectra were identical with those of (4*R*,8*S*)-**1**. GC [under the same conditions as for (4*R*,8*R*)-**1**]: t_R 10.17 [91.7%, (4*S*,8*R*)-**1**], 12.91 min (8.3%, unidentified, M^+ 226). HRMS calcd for $C_{12}H_{24}O$: 184.1827, found: 184.1848.

4.7.4. (4S,8S)-Isomer. In the same manner, 4.10 g (18.1 mmol) of (3*RS*,6*S*,10*S*)-**11** furnished 1.80 g (54%) of (4*S*,8*S*)-**1**. Bp 106–109°C/6 Torr; n_D^{24}=1.4368; $[\alpha]_D^{25}$ +7.20 (*c* 4.17, $CHCl_3$). Its IR, ^{1}H and ^{13}C NMR, and mass spectra were identical with those of (4*R*,8*R*)-**1**. GC [under the same conditions as for (4*R*,8*R*)-**1**]: t_R 10.17 [94.4%, (4*S*,8*S*)-**1**], 12.91 min (5.6%, unidentified, M^+ 226). HRMS calcd for $C_{12}H_{24}O$: 184.1827, found: 184.1824.

4.8. 4,8-Dimethyldecanoic acid (12)

4.8.1. (4R,8R)-Isomer. Jones chromic acid (0.5 mL, 2.4 mmol) was added to a stirred and ice-cooled solution of (4*R*,8*R*)-**1** (170 mg, 0.9 mmol) in acetone (3 mL). After 30 min, MeOH was added to destroy excess CrO_3. The mixture was diluted with water, and extracted with Et_2O. The Et_2O solution was extracted with 5% NaOH solution (10 mL×3). The alkaline solution was acidified with dil HCl, and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give 138 mg (75%) of (4*R*,8*R*)-**12**, ν_{max} (film): 3500–3000 (m, br), 2927 (s), 2675 (m, br), 1711 (s, C=O), 1462 (m), 1414 (m), 1379 (m), 1284 (m), 941 (m, br); δ_H ($CDCl_3$): 0.80–0.92 (9H, m, CH_3), 1.00–1.16 (3H, m), 1.16–1.40 (6H, m), 1.40–1.50 (2H, m), 1.62–1.74 (1H, m), 2.28–2.42 (2H, m); GC–MS [under the same conditions as for (3*R*,5*RS*,7*S*)-**8**]: t_R 12.37 [96.0%, (4*R*,8*R*)-**12**], 12.75 min (2.1%, unidentified, M^+226). MS of (4*R*,8*R*)-**12** (70 eV, EI): *m*/*z* 200 (1) [M^+, $C_{12}H_{24}O_2$], 171 (6), 153 (11), 143 (48), 141 (26), 111 (15), 101 (19), 99 (16), 97 (15), 85 (57), 83 (32), 73 (100), 72 (60), 70 (42), 57 (63), 55 (55), 43 (36), 41 (42).

4.8.2. (4R,8S)-Isomer. In the same manner, (4*R*,8*S*)-**1** (156 mg, 0.8 mmol) gave 170 mg (quant.) of (4*R*,8*S*)-**12**. Its IR, ^{1}H NMR, and mass spectra were virtually identical to those of (4*R*,8*R*)-**12**. GC [under the same conditions as for (4*R*,8*R*)-**12**]: t_R 12.32 [90.4%, (4*R*,8*S*)-**12**].

4.8.3. (4S,8R)-Isomer. In the same manner (4*S*,8*R*)-**1** (227 mg, 1.2 mmol) afforded 218 mg (88%) of (4*S*,8*R*)-**12**. Its IR, ^{1}H NMR, and mass spectra were identical with those of (4*R*,8*S*)-**12**. GC [under the same conditions as for (4*R*,8*R*)-**12**]: t_R 12.33 [92.5%, (4*S*,8*R*)-**12**].

4.8.4. (4S,8S)-Isomer. In the same manner, (4*S*,8*S*)-**1** (263 mg, 1.4 mmol) furnished 275 mg (96%) of (4*S*,8*S*)-**12**. Its IR, ^{1}H NMR, and mass spectra were identical with those of (4*R*,8*R*)-**12**. GC [under the same conditions as for (4*R*,8*R*)-**12**]: t_R 12.34 [97.1%, (4*S*,8*S*)-**12**].

4.9. 4,8-Dimethyl-1-decanol (13)

4.9.1. (4R,8R)-Isomer. A solution of (4*R*,8*R*)-**1** (395 mg, 2.1 mmol) in dry Et_2O (5 mL) was added to a stirred and ice-cooled suspension of $LiAlH_4$ (76 mg, 2 mmol) in dry Et_2O (5 mL). After stirring for 30 min, the mixture was worked up by acidification and Et_2O extraction to give 339 mg (85%) of (4*R*,8*R*)-**13**, ν_{max} (film): 3332 (m, O–H), 2927 (s), 1462 (m), 1377 (m), 1059 (m), 899 (w); δ_H ($CDCl_3$): 0.80–0.93 (9H, m, CH_3), 1.02–1.20 (4H, m), 1.20–1.45 (8H, m), 1.45–1.65 (3H, m), 3.63 (2H, t, *J* 6.8); GC–MS [under the same conditions as for (3*R*,5*RS*,7*S*)-**8**]: t_R 11.02 [85.5%, (4*R*,8*R*)-**13**], 13.19 min (8.43%, unidentified, M^+ 226). MS of (4*R*,8*R*)-**13** (70 eV, EI): *m*/*z* 185 (<1) [M^+−1], 140 (26), 125 (17), 111 (26), 97 (29), 84 (42), 83 (41), 70 (74), 69 (100), 57 (47), 56 (38), 55 (57), 43 (30), 41 (51).

4.9.2. (4R,8S)-Isomer. In the same manner, (4*R*,8*S*)-**1** (604 mg, 3.3 mmol) furnished 546 mg (90%) of (4*R*,8*S*)-**13**. Its IR, ^{1}H NMR, and mass spectra were virtually identical to those of (4*R*,8*R*)-**13**. GC [under the same conditions as for (4*R*,8*R*)-**13**]: t_R 11.01 [84.9%, (4*R*,8*S*)-**13**]. 13.19 min (5.71%, unidentified, M^+ 226).

4.9.3. (4S,8R)-Isomer. In the same manner, (4*S*,8*R*)-**1** (611 mg, 3.3 mmol) gave 556 mg (90%) of (4*S*,8*R*)-**13**. Its IR, ^{1}H NMR, and mass spectra were identical with those of (4*R*,5*S*)-**13**. GC [under the same conditions as for (4*R*,8*R*)-**13**]: t_R 11.01 [83.2%, (4*S*,8*R*)-**13**], 13.19 min (8.59%, unidentified, M^+ 226).

4.9.4. (4S,8S)-Isomer. In the same manner, (4*S*,8*S*)-**1** (618 mg, 3.4 mmol) afforded 541 mg (87%) of (4*S*,8*S*)-**13**. Its IR, ^{1}H NMR, and mass spectra were identical with those of (4*R*,8*R*)-**13**. GC [under the same conditions as for (4*R*,8*R*)-**13**]: t_R 11.02 [88.45%, (4*S*,8*S*)-**13**], 13.19 min (6.70%, unidentified, M^+ 226).

4.10. 4,8-Dimethyldecyl acetate (14)

4.10.1. (4R,8R)-Isomer. Acetic anhydride (1 mL, 10.6 mmol) was added to an ice-cooled solution of (4*R*,8*R*)-**13** (161 mg, 0.9 mmol) in

dry pyridine (2 mL). The mixture was left to stand overnight at room temperature. Subsequent work-up gave 173 mg (88%) of (4*R*,8*R*)-**14**, ν_{max} (film): 2297 (s), 1743 (s, C=O), 1462 (m), 1365 (m), 1240 (s), 1038 (m); δ_H ($CDCl_3$): 0.81–0.92 (9H, m, CH_3), 1.02–1.20 (4H, m), 1.20–1.45 (8H, m), 1.52–1.70 (2H, m), 2.05 (3H, s), 4.04 (2H, t, *J* 6.8); GC–MS [under the same conditions as for (3*R*,5*RS*,7*S*)-**8**]: t_R 12.60 [86.2%, (4*R*,8*R*)-**14**], 14.20 min (7.2%, unidentified). MS of (4*R*,8*R*)-**14** [70 eV, EI]: *m*/*z* 229 (<1) [M^++1], 185 (3), 168 (7), 140 (53), 125 (25), 111 (42), 97 (53), 84 (58), 83 (67), 71 (53), 70 (90), 69 (100), 57 (58), 56 (43), 55 (63), 43 (100), 41 (50).

4.10.2. (4R,8S)-Isomer. In the same manner, (4*R*,8*S*)-**13** (360 mg, 1.9 mmol) gave 386 mg (87%) of (4*R*,8*S*)-**14**. Its IR, ^{1}H NMR, and mass spectra were virtually identical to those of (4*R*,8*R*)-**14**. GC [under the same conditions as for (4*R*,8*R*)-**14**]: t_R 12.62 [78.9%, (4*R*,8*S*)-**14**], 14.20 min (5.9%, unidentified).

4.10.3. (4S,8R)-Isomer. In the same manner, (4*S*,8*R*)-**13** (327 mg, 1.8 mmol) gave 373 mg (93%) of (4*S*,8*R*)-**14**. Its IR, ^{1}H NMR, and mass spectra were identical with those of (4*R*,8*S*)-**14**. GC [under the same conditions as for (4*R*,8*R*)-**14**]: t_R 12.62 [79.1%, (4*S*,8*R*)-**14**], 14.20 min (8.2%, unidentified).

4.10.4. (4S,8S)-Isomer. In the same manner, (4*S*,8*S*)-**13** (326 mg, 1.8 mmol) gave 361 mg (90%) of (4*S*,8*S*)-**14**. GC [under the same conditions as for (4*R*,8*R*)-**14**]: t_R 12.62 [86.6%, (4*S*,8*S*)-**14**], 14.20 min (6.6%, unidentified).

4.11. Stability of 4.8-dimethyldecanal (1) upon storage

*4.11.1. Storage of neat (4R,8S)-**1** at room temperature in the presence of air.* Neat (4*R*,8*S*)-**1** was left to stand for a week in an open flask at room temperature. The major part of the content was (4*R*,8*S*)-**12** by IR and MS comparisons. GC–MS [under the same conditions as for (4*R*,8*S*)-**12**]: t_R 10.16 [6.5%, (4*R*,8*S*)-**1**], 12.19 [89.1%, (4*R*,8*S*)-**12**], 12.91 min (4.4% unidentified, M^+ 226). The major component showed a mass spectrum identical to that of **12**.

*4.11.2. Storage of neat (4R,8S)-**1** in a refrigerator.* Neat (4*R*,8*S*)-**1** was left to stand for a week in a refrigerator at 5 °C. There was no observable change as checked by GC–MS.

*4.11.3. Storage of a hexane solution of (4R,8S)-**1** at room temperature.* A solution of (4*R*,8*S*)-**1** in hexane was filled up into a small vial, and left to stand for a week at room temperature. There was no observable change as checked by GC–MS.

4.12. Partial separation of the four stereoisomers of 1 and 13 by enantioselective GC

4.12.1. Instrument and conditions for enantioselective GC. Instrument: Agilent 7890 gas chromatograph; column: eight cyclodextrin-based stationary phases were examined (see Fig. 2), 30 m×0.25 mm i.d.; thickness of the stationary phase: 0.25 μm; column temperature: 40–180 °C (+0.7 °C/min); carrier gas: He, 0.7 mL/min; detector: FID; injection port temperature: 230 °C; detector temperature: 250 °C.

4.12.2. Separation by enantioselective GC. (a) t_R of the stereoisomers of **1** (on 10% DMTFAGCD): 123.03 (4*R*,8*R*), 123.05 (4*R*,8*S*), 123.65 (4*S*,8*R*), 123.67 (4*S*,8*S*) min. (b) t_R of the stereoisomers of **1** (on 50% MOMTBDMSGCD): 201.59 (4*R*,8*R*), 202.45 (4*R*,8*S*), 202.90 (4*S*,8*S*), 203.15 (4*S*,8*R*) min (see Fig. 3). (c) t_R of the stereoisomers of **13** (on 10% DMTFAGCD): two peaks at 122.96 [(4*R*)-isomers] and 123.64 min [(4*S*)-isomers] (d) t_R of the stereoisomers of **13** (on 50% MOMTBDMSGCD): two peaks at 129.26 [(4*R*)-isomers] and 129.64 [(4*S*)-isomers] min.

4.13. Complete separation of the four stereoisomers of (1*R*,2*R*)-18 by reversed-phase HPLC

4.13.1. Instruments for analytical HPLC. The HPLC pumps used were Tosoh DP-8020 equipped with Rheodyne 7125 sample injector with a 100 μL sample loop for the first separation and Jasco PU-980 for the second separation, respectively. Tosoh PT-8000 was used for column switching. The fluorescence 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 second column temperature.

*4.13.2. Preparation of (1R,2R)-**18**.* Excess amounts of the (1*R*,2*R*)-reagent (**17**), DMAP, and EDC were added to a solution of acid **12** in toluene/acetonitrile (1:1, v/v). The solution was stood for more than 1 h at room temperature. An aliquot was then loaded onto a silica gel TLC (7 cm length, Silica gel 60 F_{254}, Art-5554, Merck) and developed with hexane/ethyl acetate (4:1, v/v). The target spot detected by fluorescence was collected, packed in a Pasteur pipette, and eluted with ethyl acetate/methanol (4:1, v/v). After evaporation of the solvent with a nitrogen gas stream, the residual (1*R*,2*R*)-**18** was dissolved in methanol and used for HPLC analysis.

4.13.3. Separation by HPLC. The acid derivative (1*R*,2*R*)-**18** was separated at first on a Develosil C30-UG-3 column (3 μm,, 15 cm×4.6 mm i.d., Nomura Chemical Co., Aichi, Japan) eluted with methanol at the rate of 0.3 mL/min and at 40 °C. The eluate from the first column between 15.6 min and 19.9 min was introduced onto the second column (Develosil ODS-HG-3, 3 μm,15 cm×4.6 mm i.d.) by valve device switching to remove interfering peaks and reduce the time for analysis. The separation of the stereoisomers of (1*R*,2*R*)-**18** was performed by elution with a mixture of methanol/acetonitrile/THF/hexane (220/200/80/4, v/v/v/v) at a rate of 0.4 mL/min at −54 °C. The detection was carried out by monitoring the fluorescence intensity at 462 nm (excitation at 298 nm). Since the mixture of all authentic derivatives was eluted from the first column between 16.0 min and 19.2 min as a broad single peak, the eluate was introduced onto the second column with a slightly wide range. t_R of (1*R*,2*R*)-**18**: 67.3 (4′*R*,8′*S*), 72.6 (4′*R*,8′*R*), 82.9 (4′*S*,8′*R*), 93.3 (4′*S*,8′*S*) on the ODS column [see Fig. 5(b)] and 88.9 (4*R*′,8′*S*), 94.4 (4′*R*,8′*R*), 104.3 (4′*S*,8′*R*), 114.9 (4′*S*,8′*S*) on the LC–LC system [see Fig. 5(c)], respectively.

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