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ABSTRACT

The enantiomers of (*anti*-1,2-dimethyl-3-methylenecyclopentyl)acetaldehyde, one of which is the female sex pheromone of the pineapple mealybug (*Dysmicoccus brevipes*), were synthesized. Chirality was introduced by means of lipase-catalyzed asymmetric acetylation of (±)-2,3-dimethyl-2-cyclopenten-l-ol. X-ray analysis of (-)-camphanate ester of (1*S*,2*S*)-(-)-2-(1,2-dimethyl-3-methylenecyclopentyl)ethanol confirmed its (1*S*,2*S*)-absolute configuration. The natural pheromone was identified with the (1*S*,2*S*)-aldehyde by comparing the specific rotation, enantioselective GC retention time and pheromone activity.

☆ For Part 261, see Ref.1. This work was orally reported by K.M. as his lecture at International Chemical Ecology Conference 2017 (August 24, 2017) in Kyoto, Japan.

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1. Introduction

The pineapple mealybug [*Dysmicoccus brevipes* (Cockerell), Homoptera: Pseudococcidae] is a pest infesting pineapples in Okinawa.[2] Tabata et al. isolated 2.1 mg of its female sex pheromone from 672,000 virgin females, and identified it as (1,2-dimethyl-3-methylenecyclopentyl)acetaldehyde (**1**, Fig.1).[3] Synthesis of the racemates of *anti*-**1** with two methyl groups in *anti*-configuration and its *syn*-isomer enabled the assignment of the *anti*-stereochemistry to the natural pheromone, because *anti*-**1** showed no NOE between the two methyl groups while *syn*-**1** clearly showed NOE.[4] As to the absolute configuration of the natural pheromone, it remained unknown to date.

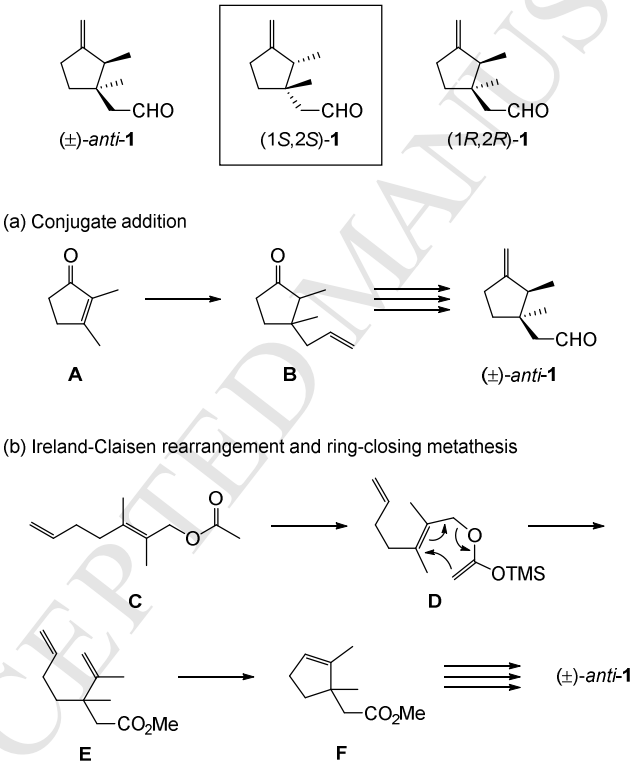


Fig.1. Structure [(1*S*,2*S*)-**1**] of the pineapple mealybug pheromone and the previous syntheses of its racemate.

The obvious way to solve the problem was to synthesize both (1*S*,2*S*)- and (1*R*,2*R*)-**1** and compare their physical and biological properties with those of the natural pheromone. Our two syntheses of (±)-**1** were based on either conjugate addition [**A**→**B,** Fig.1 (a)] or Ireland-Claisen rearrangement (**C** →**D** →**E**) and ring-closing metathesis [**E** →**F**, Fig.1 (b)].[4] Unfortunately, these two routes were difficult to be

modified to give pure enantiomers of *anti*-**1**. We therefore explored a different route, which allowed us to assign (1*S*,2*S*)-absolute configuration to the natural pheromone. The X-ray crystallographic analysis of a derivative of one of the synthetic intermediates confirmed the configuration assigned to the natural pheromone. The present paper describes in detail the synthesis of (1*S*,2*S*)-**1** and its identification as the natural pheromone.

2. Results and discussion

2.1. Retrosynthetic analysis of (1*S*,2*S*)-1

Fig.2 shows the retrosynthetic analysis of (1*S*,2*S*)-**1**. Since the stereoisomers at C-2 were separable by SiO_2 chromatography,[4] introduction of chirality at C-1 was planned by means of Ireland's ester-enolate Claisen rearrangement [(*S*)-**H** → (*S*)-**G**].[4,5]

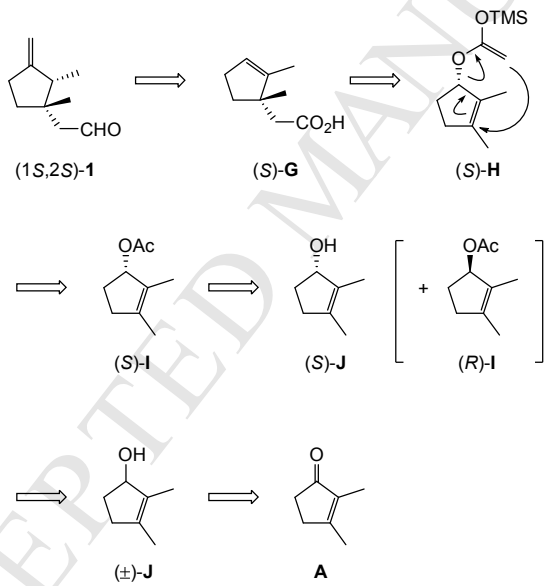
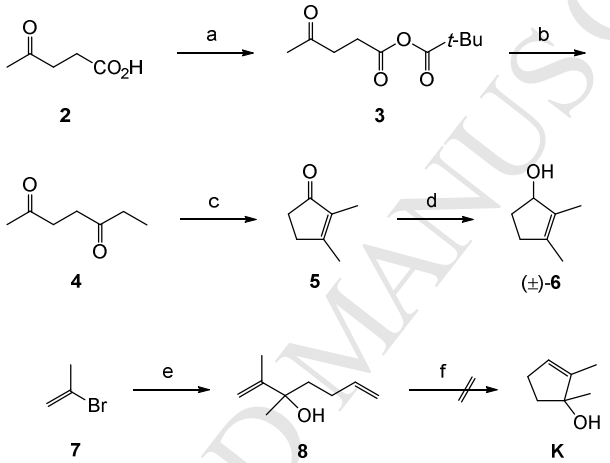


Fig.2. Retrosynthetic analysis of (1*S*,2*S*)-**1** basing on lipase-catalyzed asymmetric acetylation of (±)-**J**.

The substrate (*S*)-**I** for the rearrangement would be prepared by acetylation of (*S*)-**J**, whose preparation would be executed by lipase-catalyzed asymmetric acetylation of (±)-**J**. Reduction of the known 2,3-dimethyl-2-cyclopenten-1-one (**A**)[4] would afford the racemic alcohol (±)-**J**. Another product (*R*)-**I** of the enzymatic acetylation would eventually give (1*R*,2*R*)-**1**. The above plan enabled us the synthesis of (1*S*,2*S*)-**1** in an amount sufficient for its physical as well as biological identification with the natural pheromone.

2.2. Synthesis of (±)-2,3-dimethyl-2-cyclopenten-1-ol (6)

For the successful synthesis of (1*S*,2*S*)-**1**, it was necessary to secure at least over 20 g of (±)-**6** (Scheme 1). Accordingly, a scalable synthesis of the parent ketone **5** was explored at first. Although there exists a number of different syntheses of **5**, none of them is scalable, due to its multi-step nature or its use of expensive reagents.[4] Gratifyingly, Prof. S. Kobayashi, a former student of Prof. Mukaiyama, suggested K.M. to adopt Mukaiyama's procedure for the conversion of levulinic acid (**2**) to 2,5-heptanedione (**4**) via mixed anhydride **3**.[6] Base-catalyzed aldol cyclization of **4** is known to give the desired ketone **5**.[7]



Scheme 1. Synthesis of (±)-**6**, the substrate for enzymatic acetylation. Reagents: (a) *t*-BuCOCl, Et_3N, Et_2O (99%); (b) EtMgBr, THF, -60°C (54%); (c) NaOH, EtOH, H_2O, reflux (67%); (d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 10-15°C (81%); (e) Mg, THF; 5-hexen-2-one (56%); (f) Grubbs II, CH_2Cl_2 (N.R.).

Some modifications and scale-up of the Mukaiyama procedure afforded 10 g of **5** in a single batch as follows (Scheme 1). Levulinic acie (**2**) was treated with pivaloyl chloride in the presence of Et_3N in Et_2O to give mixed anhydride **3** in a quantitative yield. Addition of 1 eq of EtMgBr in THF to **3** was executed at -60°C to keep the ketone carbonyl of **3** intact, giving **4** in 54% yield after distillation. Cyclization of **4** with NaOH in aqueous EtOH according to Welch[7] furnished **5** in 67% yield, whose GC and spectral properties were identical with those of an authentic sample.[4] Reduction of **5** with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ in MeOH according to Luche[8] afforded (±)-2,3-dimethyl-2-cyclopenten-1-ol (**6**) in 81% yield. Nearly 40 g of (±)-**6** could be prepared from levulinic acid (**2**) through the present four-step synthesis in 29% overall yield. The above route to **5** is superior to any other route examined previously.[4]

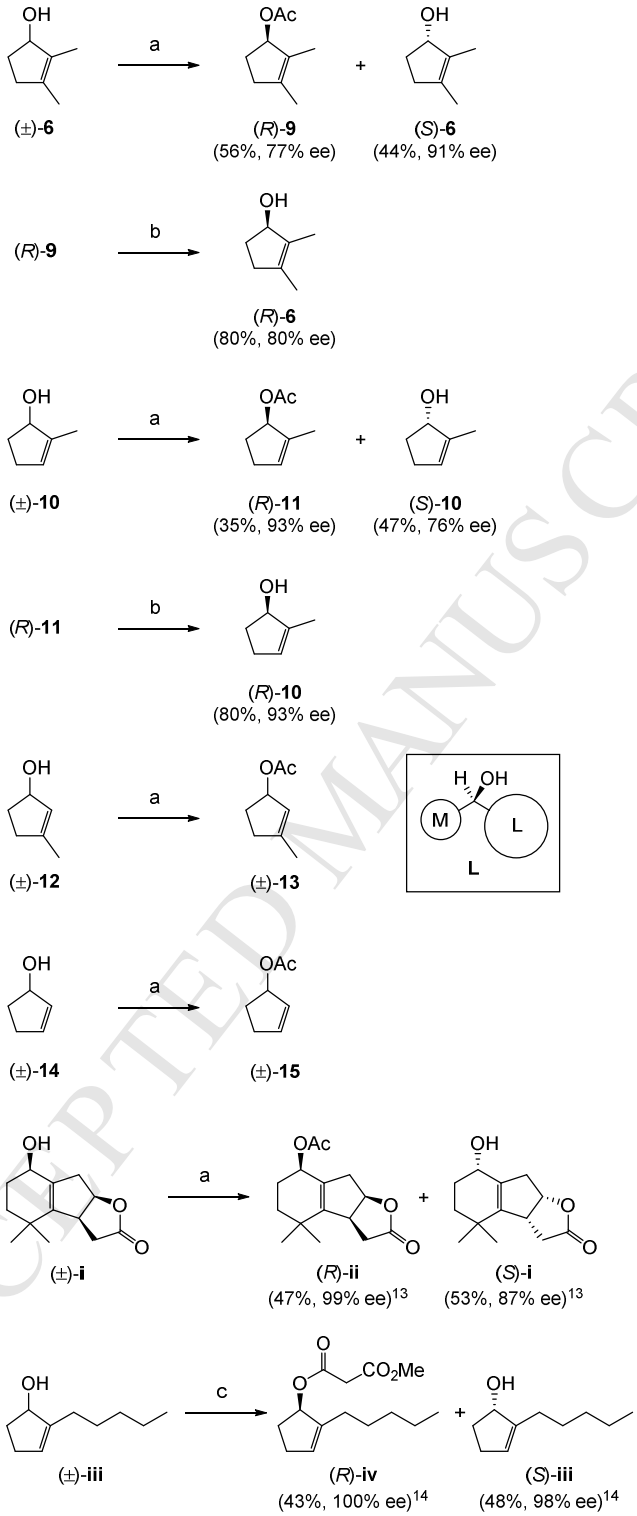
An unsuccessful attempt was made to prepare **5** in a different manner. 1,2-Dimethyl-2-cyclopenten-1-ol (**K**) will give **5** by chromic acid oxidation accompanied with allylic rearrangement. Synthesis of **K** seemed possible by ring-closing metathesis of **8**, which was synthesized from 5-hexen-2-one by treatment with a Grignard reagent prepared from **7** and Mg in THF. Ring-closing metathesis of **8**, however, was unsuccessful with second-generation Grubbs catalyst. No **K** could be observed, and the starting **8** was recovered.

2.3. Lipase-catalyzed asymmetric acetylation of (±)-6 and (±)-10

Lipases and esterases are user-friendly biocatalysts in natural product synthesis to secure enantiopure alcohols and esters.[9,10] In 1991 Kazlauskas et al. proposed an empirical rule to predict which enantiomer of a secondary alcohol reacts faster in reactions catalyzed by lipase.[11] For esters of secondary alcohols, the enantiomer shown in **L** (Scheme 2) reacts faster than the other enantiomer. Crystallographic and molecular-modeling studies of lipase B from *Candida antarctica* revealed a stereospecificity pocket for secondary alcohols **L**.[12] Accordingly, lipase-catalyzed asymmetric acetylation of (±)-**6** is expected to give (*R*)-acetate **9** and (*S*)-alcohol **6**. Earlier and published results supported the above assumption, because lipase-catalyzed acetylation of (±)-**i** and (±)-**iii** yielded (*R*)-**ii**[13] and (*R*)-**iv**.[14]

Prior to the large scale enzymatic acetylation of (±)-**6**, four 2-cyclopenten-1-ols (±)-**6**, **10**, **12** and **14** were subjected to asymmetric acetylation with lipase and vinyl acetate so as to know the general feature of the reaction. Lipase AK (Amano) was selected as the enzyme of choice, basing on our previous experience.[13] The racemic alcohol (±)-**6** and vinyl acetate in (i-Pr)$_2$O was stirred with lipase AK for 7 h at room temperature. The resulting products were chromatographed over alumina (pH 9-11) to give (*R*)-(+)-**9** and (*S*)-(-)-**6**. The present relationship between absolute configuration and sign of rotation was in accord with Hill's result that (*R*)-2-cyclopenten-1-ol is dextrorotatory.[15]

It must be emphasized that the separation of (*R*)-**9** from (*S*)-**6** was possible only over slightly basic alumina. Chromatography over silica gel or neutral alumina resulted in exothermic decomposition of the products giving dienes. The allylic system in **6** and **9** was very unstable due to the facile elimination under acidic conditions. The instability of **6** and **9** under slightly acidic conditions also became apparent when (±)-**6** was subjected to Akai's oxovanadium catalyst (VMPS)-catalyzed dynamic kinetic resolution.[16] Instead of dynamic kinetic resolution of (±)-**6**, its decomposition took place to give a dark-colored suspension, affording useless dienes.



Scheme 2. Asymmetric acetylation of (±)-**6** and (±)-**10**. Reagents: (a) vinyl acetate, lipase AK, $(i\text{-Pr})_2O$, room temp; (b) K_2CO_3,MeOH, room temp; (c) $CH_2(CO_2Me)_2$, Novozyme 435, $KHCO_3$.

After the separation, the enantiomeric purities of (*R*)-**9** and (*S*)-**6** were determined by enantioselective GC, and found to be 77% ee for (*R*)-**9** (56% yield) and 91% ee for (*S*)-**6** (44% yield). The result showed that nearly enantiopure (*R*)-**9** and (*S*)-**6** would be obtained by repeating the enzymatic acetylation once more against (*R*)-**6** derived from (*R*)-**9** of 77% ee and also against (*S*)-**6** of 91% ee.

Asymmetric acetylation with lipase AK of (±)-2-methyl-2-cyclopenten-1-ol (**10**) furnished (*R*)-**11** (35% yield, 93% ee) and (*S*)-**10** (47% yield, 76% ee). However, when (±)-**12** and (±)-**14**, both lacking the methyl group at C-2, were subjected to asymmetric acetylation, the products were racemic acetates (±)-**13** and (±)-**15**. It is therefore concluded that the presence of a methyl group at C-2 of (±)-**6** and (±)-**10** is crucial for the successful lipase-catalyzed asymmetric acetylation.

2.4. Preparative scale asymmetric acetylation of (±)-6 and chirality transfer by Claisen rearrangement to give the enantiomers of 17 after methylation

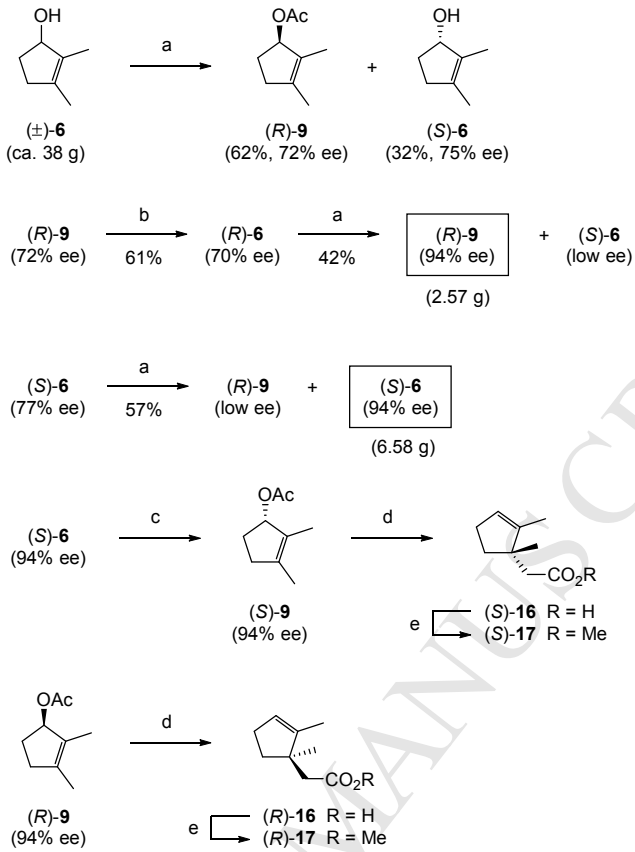
The next stage of the synthesis was preparation of nearly enantiopure (*R*)- and (*S*)-**9**, and their conversion to (*R*)- and (*S*)-**16** by Ireland-Claisen rearrangement.

As shown in Scheme 3, lipase-catalyzed asymmetric acetylation of (±)-**6** was repeated twice to further increase the enantiomeric purities of the products. Eventually it was possible to obtain 2.57 g of (*R*)-**9** (94% ee) and 6.58 g of (*S*)-**6** (94% ee) starting from about 38 g of (±)-**6**. Chemical acetylation with Ac_2O and pyridine of (*S*)-**6** gave 5.50 g of (*S*)-**9** (94% ee). It must be added that in the course of methanolysis of (*R*)-**9** to give (*R*)-**6** as well as in the course of chemical acetylation of (*S*)-**6**, partial elimination of AcOH took place, decreasing the yields of (*R*)-**6** and (*S*)-**9**. This also indicates the ease of elimination of the acetoxy group at C-1 of **9**.

Ireland-Claisen rearrangement of **9** to give (1,2-dimethyl-3-cyclopentenyl)acetic acid (**16**) was the key step of the present synthesis, effecting the chirality transfer from C-O to C-C bonds.[5,17] As already noticed by Jäger,[17] the rearrangement was accompanied by elimination of AcOH, and the best yield of (*S*)-**16** was 56%, while (*R*)-**16** was obtained in 30% yield. Methylation of **16** was executed with K_2CO_3 and MeI in acetone/DMF to give 2.08 g of (*S*)-(-)-**17** from 5.38 g of (*S*)-**9**. The amount secured was sufficient for its conversion to (1*S*,2*S*)-**1**. Similarly, (*R*)-(+)-**17** (988 mg) was prepared from 2.30 g of (*R*)-**9**.

2.5. Improved synthesis of (±)-*anti*-1 starting from (±)-17

Considering the limited amount (2.08 g) of the secured (*S*)-**17**, it seemed appropriate to modify and improve the existing synthetic steps[4] necessary for the conversion of **17** to *anti*-**1**. Scheme 4 summarizes the result of such endeavor executed with more accessible racemates.

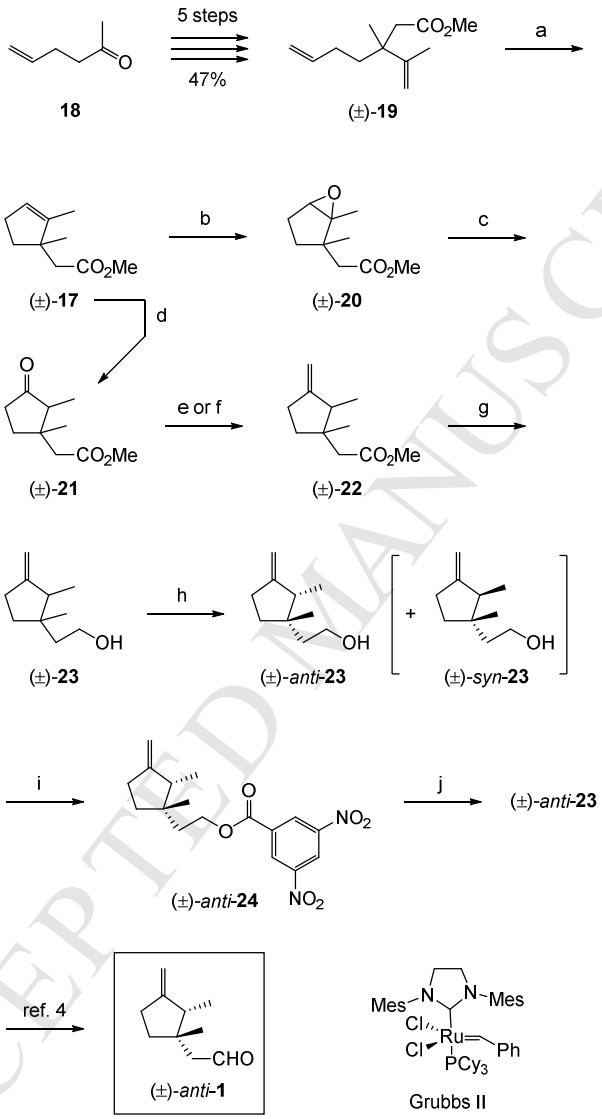


Scheme 3. Preparative scale asymmetric acetylation of (±)-**6** and subsequent synthesis of the enantiomers of **17**. Reagents: (a) vinyl acetate, lipase AK, $(i\text{-Pr})_2O$, room temp; (b) K_2CO_3,MeOH; (c) Ac_2O, C_5H_5N (62%); (d) TMSCl, $LiN(i\text{-Pr})_2$, THF; then heat at 60°C [56% of (*S*)-**16** and 30% of (*R*)-**16**]; (e) K_2CO_3,MeI, acetone, DMF [64% of (*S*)-**17** and 68% of (*R*)-**17**].

The acyclic ester (±)-**19** was prepared in 47% yield (5 steps) starting from **18** as reported previously.[4] Ring-closing metathesis of (±)-**19** was conducted with 0.5 mol% of Grubbs II catalyst to give (±)-**17** in 84% yield. Conversion of (±)-**17** to keto ester (±)-**21** was achieved by hydroboration-oxidation in 57% yield.[4] However, an alternative two-step process via epoxy ester (±)-**20** was found to be experimentally less demanding. Epoxidation of (±)-**17** with *m*-chloroperbenzoic acid (MCPBA) gave (±)-**20**, which was treated with $BF_3 \cdot OEt_2$ in CH_2Cl_2 to give (±)-**21**.[14] The epoxidation was non-stereoselective, and (±)-**21** was obtained as a ca. 1:1 mixture of its two diastereoisomers.

The next methylenation step was previously carried out with Tebbe, Petasis or Ando reagents.[4] Considering the compatibility with the ester group of (±)-**21**, methylenation

in the present work was executed with Lombardo reagent[18] or Yan reagent.[19] When Lombardo reagent (CH_2Br_2, Zn, $TiCl_4$) was employed, (±)-**21** furnished (±)-**22** in 86% yield, while the yield was 33% by using Yan reagent (CH_2Cl_2, Mg, $TiCl_4$).



Scheme 4. Optimization of the synthetic steps employing racemic intermediates. Reagents: (a) Grubbs II (0.5 mol%), CH_2Cl_2, reflux (84%); (b) MCPBA, CH_2Cl_2 (69%); (c) $BF_3 \cdot OEt_2$, CH_2Cl_2 (83%); (d) $BH_3 \cdot SMe_2$, Et_2O; then Jones CrO_3, acetone (57%) (e) CH_2Br_2, Zn, $TiCl_4$, THF (86%); (f) CH_2Cl_2, Mg, $TiCl_4$ (33%); (g) $LiAlH_4$, Et_2O (82%-quant.); (h) SiO_2 chromatog. (45% for *anti*-**23**); (i) DNBCl, DMAP, C_5H_5N (74%); (j) NaOH, MeOH, H_2O (77%).

Reduction of (±)-**22** with $LiAlH_4$ gave (±)-**23** in 82% yield. The diastereoisomers of (±)-**23** could be separated by silica gel chromatography, and (±)-*anti*-**23** (*anti*/*syn*= 93:7-90:10) was secured in 27% yield (1.41 g) as the earlier eluting isomer. Owing to the tailing of the earlier eluting (±)-*anti*-**23**, the later eluting (±)-*syn*-**23** could not be obtained pure in an amount sufficient for its further conversion to (±)-*syn*-**1**. This causes no problem, because (±)-*syn*-**1** is known to be biologically inactive.[3,4] Oxidation of (±)-*anti*-**23** will give (±)-*anti*-**1** in good yield.[4]

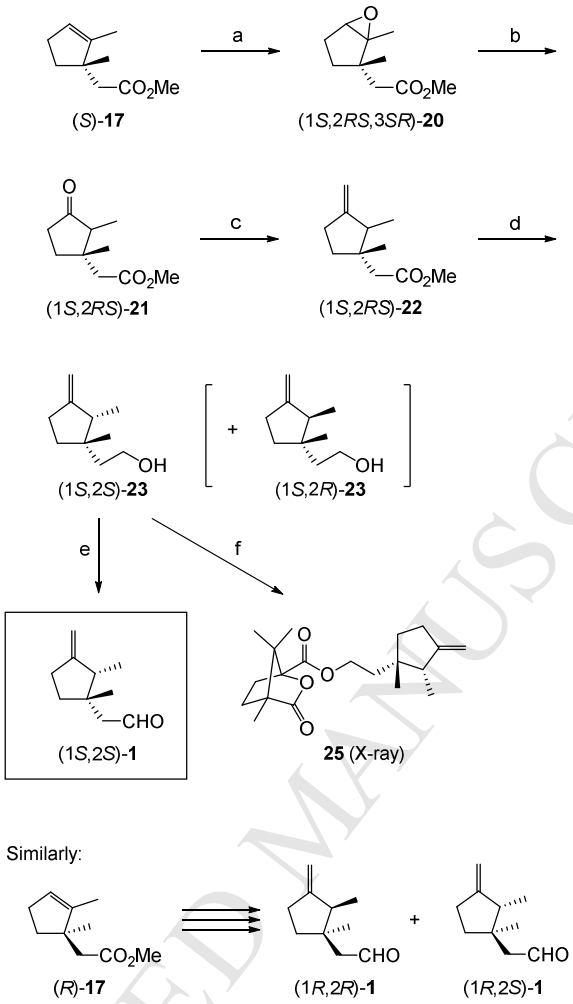
An attempt was made to further purify (±)-*anti*-**23** by converting it to crystalline 3,5-dinitrobenzoate (±)-*anti*-**24**. Treatment of (±)-*anti*-**23** with 3,5-dinitrobenzoyl chloride (DNBCl) and DMAP in pyridine gave (±)-*anti*-**24**, mp 62-64°C, in 74% yield after recrystallization from EtOAc/hexane. It gave back (±)-**23** upon alkaline hydrolysis. The purity of the recovered alcohol was *anti*/*syn* = 100:7. Unfortunately pure (±)-*anti*-**23** could not be obtained via (±)-*anti*-**24**.

The above described efforts to improve the synthetic steps provided 1.15 g of (±)-*anti*-**23** and 7.15 g of a diastereomeric mixture of (±)-**23** for further biological studies.

2.6. Synthesis of (1*S*,2*S*)-1 and its identification with the natural pheromone

Basing on the experience obtained in the course of improving the synthetic steps leading to (±)-**23**, (*S*)-**17** was converted to the optically active pheromone (1*S*,2*S*)-**1** as shown in Scheme 5.

Epoxidation of (*S*)-**17** with MCPBA gave **20** in 93% yield, which was treated with $BF_3 \cdot OEt_2$ to furnish quantitatively (-)-keto ester (1*S*,2*RS*)-**21**. Lombardo reagent converted **21** into (1*S*,2*RS*)-**22** in 72% yield. Reduction of the ester **22** with $LiAlH_4$ was followed by chromatographic separation to give 284 mg (30%) of (1*S*,2*S*)-(-)**23**, $[\alpha]_D^{26}$ -26.7 (*c* 0.52, hexane). Finally, oxidation of **23** with azadol[20] and diacetoxyiodobenzene (DAIB) in CH_2Cl_2, afforded (1*S*,2*S*)-**1**, $[\alpha]_D^{25}$ -47.6 (*c* 0.50, hexane), in 69% yield (87 mg). Since the specific rotation of the natural pheromone was reported as $[\alpha]_D^{26.3}$-39.45 (*c* 0.075, hexane), the absolution configuration of the natural pheromone was determined as 1*S*,2*S*. Comparison of the enantioselective GC retention time (t_R) of the natural pheromone with that of (1*S*,2*S*)-**1** also confirmed the identity (see 4.26.3). The natural pheromone was enantiomerically pure (1*S*,2*S*)-**1**. In the same manner, 1.00 g of (*R*)-**17** yielded 90 mg of a mixture of (1*R*,2*R*)- and (1*R*,2*S*)-**1**, $[\alpha]_D^{24}$ +15.5 (*c* 0.61, hexane). This was used for the enantioselective GC comparison with the natural pheromone, and a portion of it was further purified by $SiO_2/AgNO_3$ chromatography to give (1*R*,2*R*)-**1** in an amount sufficient for the field bioassay.



Scheme 5. Synthesis of the natural pheromone (1*S*,2*S*)-**1** and preparation of a crystalline derivative **25** for X-ray analysis. Reagents: (a) MCPBA,CH_2Cl_2 (93%); (b) $BF_3 \cdot OEt_2$, CH_2Cl_2 (quant.); (c) CH_2Br_2, Zn, $TiCl_4$, THF (72%); (d) $LiAlH_4$, Et_2O (95%); then SiO_2 chromatog. (30%); (e) DAIB, azadol, CH_2Cl_2 (69%); (f) (-)-camphanic chloride, DMAP, $CHCl_3$, C_5H_5N (98%).

2.7 Confirmation of the absolute configuration of (1*S*,2*S*)-(-)-1 by X-ray crystallographic analysis of 25

The (1*S*,2*S*)-absolute configuration assigned to the naturally occurring (-)-**1** was based on the *S*-configuration of (-)-**6**, which was deduced on the basis of the empirical rule on the stereochemical outcome of lipase-catalyzed asymmetric acetylation.[11,12] In order to confirm the stereochemical assignment, a crystalline ester **25** (Scheme 5) was prepared by treatment of (1*S*,2*S*)-**23** with (-)-camphanic chloride. The absolute configuration of (1*S*)-(-)-camphanic chloride is known.[21] Accordingly, solving the

structure of **25** by X-ray analysis allows us to confirm the absolute configuration of (1*S*,2*S*)-**23**. Fortunately, recrystallization of **25** from EtOAc furnished plates suitable for X-ray analysis. Fig.3 shows the X-ray structure of **25**.

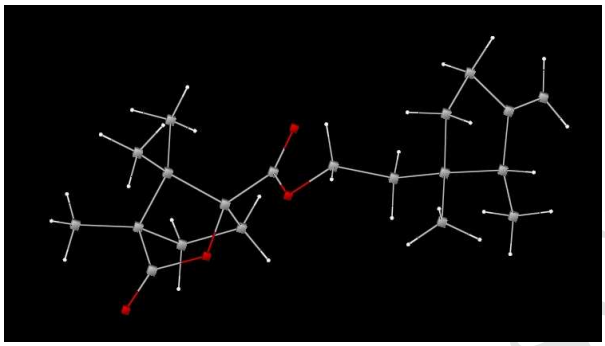


Fig.3. X-ray structure of (-)-2-(*anti*-1,2-dimethyl-3-methylelnecyclopentyl)ethyl camphanate (**25**). For details see CCDC 1516035.

As can be seen from Fig.3, (-)-**23** possesses (1*S*,2*S*)-stereochemistry. The present X-ray analysis, whose details are deposited as CDCC1560305, confirmed the absolute configuration of (-)-**23**, and hence that of (-)-**1** as (1*S*,2*S*).

2.8. Bioassay of the synthetic enantiomers (1*S*,2*S*)- and (1*R*,2*R*)-1

The attractiveness of each the enantiomer of *anti*-**1** was tested by a trap bioassay at a pineapple field in Okinawa. As shown in Fig.4, the naturally occurring (1*S*,2*S*)-**1** attracted significantly greater number of males than its opposite enantiomer.

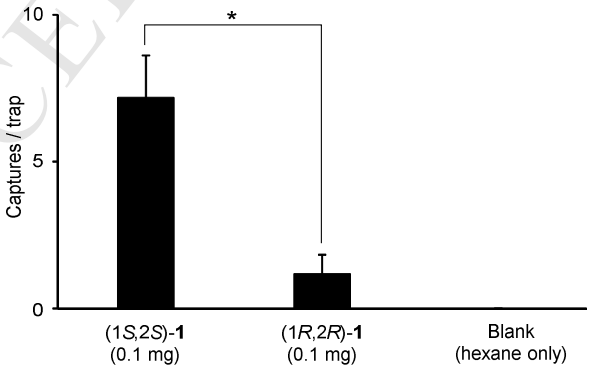


Fig.4. Numbers (mean + SEM; *N*=6) of *Dysmicoccus brevipes* males captured by field traps baited with (1*S*,2*S*)- and (1*R*,2*R*)-**1**. An asterisk indicates a significant difference according to ANOVA ($P < 0.005$).

3. Conclusion

The stereostructure of the female-produced sex pheromone of the pineapple mealybug, *Dysmicoccus brevipes* (Cockerell), was established as (1*S*,2*S*)-(-)-(1,2-dimethyl-3-methylenecyclopentyl)acetaldehyde (**1**) by chemo-enzymatic synthesis employing lipase AK (Amano). The overall yield of (1*S*,2*S*)-**1** was 0.44% (13 steps) based on levulinic acid (**2**). X-ray analysis of **25** confirmed (1*S*,2*S*)-stereochemistry of the intermediate (1*S*,2*S*)-(-)-**23**. The natural pheromone was seven times more bioactive than its opposite enantiomer.

4. Experimental

4.1. General

All bps and mp are uncorrected values. Refractive indices were measured on an Atago DMT-1 refractometer. IR spectra were measured on a Jasco FT/IR-410 spectrometer. ^{1}H NMR spectra (400 MHz, TMS at δ=0.00 as the internal standard) and ^{13}C NMR spectra (100 MHz, $CDCl_3$ at δ=77.0 as the internal standard) were recorded on a Jeol JNM-ECZ 400S/L1 spectrometer. GC-MS were measured on Agilent Technologies 5975 inert XL. HRMS were recorded on Jeol JMS-T100GCV. Silica gel column chromatography was carried out on Merck Kieselgel 60 Art 1.00734.

4.2. Levulinoyl pivaloyl anhydride (3)

A solution of pivaloyl chloride (6.00 g, 50 mmol) in dry Et_2O (5 mL) was added dropwise to a stirred and ice-cooled solution of levulinic acid (**2**, 5.80 g, 50 mmol) and Et_3N(5.0 g, 50 mmol) in dry Et_2O (65 mL) at 5-10^{o}C. The solution was stirred for 1.5 h at 5-10^{o}C, and the precipitated $Et_3N\cdot HCl$ was filtered off. The solid salt was washed with Et_2O. The combined filtrate and washings were dried ($MgSO_4$), and concentrated in vacuo to give 9.91 g (99%) of **3** as a colorless oil, νmax (film): 2979 (m), 2938 (w), 2876 (w), 1814 (s), 1744 (m), 1720 (s), 1366 (m), 1046 (s), 1015 (s), 684 (m). This oil was used immediately in the next step.

4.3. 2,5-Heptanedione (4)

A solution of EtMgBr in THF (1M, 50 mL, 50 mmol) was added dropwise over 30 min to a stirred and cooled solution of **3** (9.91 g, 50 mmol) in dry THF (30 mL) at -60^{o}C under argon. After the addition, the mixture was stirred for further 30 min at -60^{o}C. Subsequently the cooling bath was removed, and the mixture was left to stand for 1 h with stirring. The reaction was quenched by the addition of ice and NH_4Cl solution, and the mixture was extracted with Et_2O. The Et_2O solution was washed successively with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residues

obtained from two runs were combined and distilled in vacuo to give 6.40 g (54% based on 11.6 g of **3**) of **4** as a colorless oil, bp 116-123°C/0.6 kPa; n_D^{22}=1.4264; νmax (film): 2978 (m), 2940 (m), 2909 (m), 1714 (s), 1414 (M), 1362 (m), 1166 (m), 1117 (m); δ_H ($CDCl_3$): 1.06 (3H, t, *J*=7.2 Hz), 2.18 (3H, s), 2.46-2.50 (2H, m), 2.65-2.74 (4H, m); GC-MS [column: HP-5ms, 5% phenylmethylsiloxane, 0.25 mm x 30 m; carrier gas, He; press. 61 kPa; temp: 70-230°C (+10°C/min)]: t_R 5.13 min (88.1%); MS (70 eV, EI): *m*/*z*: 99 (100) [$(M-C_2H_5)^+$] 85 (4), 71 (34), 57 (47), 43 (53). HRMS calc for $C_7H_{12}O_2$: 128.0837, found: 128.0839.

4.4. 2,3-Dimethyl-2-cyclopenten-1-one (5)

A solution of **4** (9.52 g, 85 mmol) in 99% EtOH (30 mL) was added to a solution of NaOH (2.0 g, 50 mmol) in water (100 mL). The mixture was stirred and heated under reflux for 4.5 h. After cooling, the mixture was saturated with NaCl and extracted with Et_2O. The Et_2O extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give 5.46 g (67%) of **5** as a colorless oil, bp 118-124°C/8.2 kPa (ref.[4] bp 105-107°C/56 Torr); n_D^{25}=1.4844; νmax (film): 2919 (m), 2864 (w), 1698 (s), 1651 (m), 1442 (m), 1388 (m), 1330 (m), 1065 (m); δ_H ($CDCl_3$): 1.66 (3H, s), 2.02 (3H, s), 2.34 (2H, m), 2.46 (2H, m); δ_C ($CDCl_3$): 7.96, 17.27, 31.59, 34.26, 136.35, 170.02, 210.01; GC-MS (same conditions as those used for **4**): t_R 5.37 min (97.6%); MS (70 eV, EI): *m*/*z*: 110 (97) [M^+], 95 (30), 81 (12), 67 (100), 54 (14), 53 (12), 39 (17). These spectral data were identical with those reported previously.[4]

4.5. (±)-2,3-Dimethyl-2-cyclopenten-1-ol (6)

Sodium borohydride (11.9 g, 314 mmol) was added portionwise over 15 min to a stirred and ice-cooled solution of **5** (23.67 g, 215 mmol) and $CeCl_3 \cdot 7H_2O$ (120.0 g, 314 mmol) in MeOH (500 mL) at 10-15°C. After the addition, the mixture was stirred for 30 min at 5-10°C. It was then diluted with ice and brine and extracted with Et_2O. The Et_2O extract was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give 19.53 g (81%) of (±)-**6** as a colorless oil, bp 58-59°C/0.2 kPa; n_D^{25}=1.4731; νmax (film): 3326 (s), 2964 (s), 2914 (s), 2848 (s), 2737 (w), 1684 (w), 1442 (s), 1380 (m), 1330 (m), 1182 (m), 1063 (m), 1029 (m), 993 (m); δ_H ($CDCl_3$): 1.46-1.80 (2H, m), 1.65 (6H, s), 2.10-2.30 (2H, m), 2.32-2.45 (1H, m), 4.57 (1H, br. s); GC-MS (same conditions as those used for **4**): t_R 4.09 min (95.1%); MS (70 eV, EI): *m*/*z*: 112 (19) [M^+], 111 (14), 97 (100), 79 (33), 77 (20), 55 (12), 43 (11), 41 (11). HRMS calc for $C_7H_{12}O$: 112.0888, found: 112.0880.

4.6. (±)-2,3-Dimethyl-1,6-heptadien-3-ol (8)

A solution of 2-bromopropene (**7**, 20 g, 165 mmol) in dry THF (50 mL) was added dropwise to a stirred suspension of Mg turnings (4.1 g, 171 mmol) in dry THF (10 mL)

containing a trace amount of I_2 (10 mg). After adding 3 mL of the solution of **7**, the mixture was heated with a heat gun to initiate the reaction. Subsequently, the rest of the solution was added slowly to maintain the refluxing of the mixture. The Grignard reagent was then cooled with an ice-bath, and a solution of 5-hexen-2-one (15.0 g, 153 mmol) was added dropwise to the stirred and ice-cooled mixture. After the addition, the mixture was stirred and heated at 40°C for 30 min. It was then cooled, poured onto ice and dil HCl/NH_4Cl solution, 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 12.0 g (56%) of **8** as a colorless oil, bp 57-59°C/0.4 kPa; n_D^{26}=1.4570; νmax (film): 3422 (br. s), 3079 (m), 2976 (s), 2944 (m), 1641 (m), 1446 (m), 1374 (m), 1110 (m), 997 (m), 905 (s); ($CDCl_3$): 1.32 (3H, s), 1.62 (1H, s), 1.64-1.70 (2H, m), 1.75 (3H, s), 1.90-2.15 (2H, m), 4.82-5.10 (4H, m), 5.80-5.90 (1H, m); GC-MS (same conditions as those used for **4**): t_R 4.65 min (92.8%); MS (70 eV, EI): *m/z*: 125 (3) [$(M-CH_3)^+$], 107 (9), 97 (9), 86 (19), 85 (100), 69 (19), 57 (34), 43 (41). HRMS calc for $C_9H_{16}O$: 140.1201, found: 140.1205.

4.7. Lipase AK-catalyzed asymmetric acetylation of (±)-6 to give (*R*)-9 and (*S*)-6

Lipase AK Amano (400 mg) was added to a solution of (±)-**6** (2.20 g, 20 mmol) and vinyl acetate (4 mL, 3.7 g, 43 mmol) in (*i*-Pr)$_2$O (40 mL). The mixture was stirred for 7 h at room temperature (22°C), and filtered to remove the enzyme, which was washed thoroughly with Et_2O. The combined filtrate and washings were concentrated in vacuo. The residue (3.24 g) was chromatographed over Al_2O_3 (Wako Chemical 010-01525, 300 mesh, pH 9.0-11.0; 80 g). [CAUTION: Both (*R*)-**9** and (*S*)-**6** are very unstable against acid. Use of silica gel or neutral alumina causes total decomposition of the products.] Elution with pentane/EtOAc (100:1) gave (*R*)-**9** (1.82 g, 56%). Further elution with pentane/EtOAc (10:1) gave (*S*)-**6** (1.05 g, 44%). These were purified by distillation to give (*R*)-**9** (482 mg) and (*S*)-**6** (667 mg) both as colorless oils. They showed the following properties. *(R)-2,3-Dimethyl-2-cyclopentenyl acetate (**9**)*: bp 44°C/0.8 kPa; n_D^{22}=1.4556; $[\alpha]_D^{23}$ +53.4 (*c* 1.71, hexane); Chiral GC [Column: Chiramix®, 0.25 mm x 60 m; column temp: 40-180°C(+0.7°C/min); carrier gas, He; flow rate, 0.7 mL/min]: t_R 98.3 min [11.4%, (*S*)-**9**], 98.7 min [88.6%, (*R*)-**9**], 77% ee; νmax (film): 2971 (m), 2917 (m), 2852 (m), 1734 (s), 1440 (m), 1371 (m), 1243 (s), 1015 (m), 990 (m), 968 (m), 876 (m); δ_H ($CDCl_3$): 1.60 (3H, s), 1.68 (3H, s), 1.62-1.72 (1H, m), 2.04 (3H, s), 2.15-2.34 (2H, m), 2.38-2.48 (1H, m), 4.58 (1H, d-like, *J*=5.6 Hz); GC-MS (same conditions as those used for **4**): t_R 6.42 min (86%); MS (70 eV, EI): *m/z*: 154 (<1) [M^+], 97 (17), 95 (47), 94 (96), 93 (17), 91 (18), 79 (100), 77 (34), 67 (13), 43 (21), 39 (9). HRMS calc

for $C_9H_{14}O_2$: 154.0994, found: 154.1012. *(S)-2,3-Dimethyl-2-cyclopenten-1-ol* (***6***): bp 63-64°C/0.8 kPa; n_D^{23}=1.4742; $[\alpha]_D^{23}$ -55.6 (*c* 1.61, hexane); Chiral GC (same conditions as those used for **9** except that the column temp was increased at the rate of +0.5°C/min): t_R 118.0 min [95.5%, (*S*)-**6**], 119.90 min [4.5%, (*R*)-**6**], 91% ee; νmax (film): 3230 (s), 2965 (s), 2914 (s), 2849 (s), 1684 (w), 1442 (m), 1063 (s), 1029 (m), 933 (s); δ_H ($CDCl_3$): 1.640 (3H, s), 1.642 (3H, s), 1.52-1.70 (2H, m), 2.10-2.28 (2H, m), 2.38 (1H, m), 4.56 (1H, br s); GC-MS (same conditions as those used for **4**): t_R 4.09 min (88.9%); MS (70 eV, EI): *m*/*z*: 112 (19) [M^+], 111 (14), 97 (100), 94 (14), 91 (10), 79 (35), 77 (21), 55 (13), 43 (13), 41 (12). HRMS calc for $C_7H_{12}O$: 112.0888, found: 112.0879.

4.8. (±)-2-Methyl-2-cyclopenten-1-ol (10)

Sodium borohydride (1.80 g, 47 mmol) was added over 15 min to a stirred and ice-cooled solution of commercially available 2-methyl-2-cyclopenten-1-one (TCI, 3.08 g, 32 mmol) and $CeCl_3 \cdot 7H_2O$ (17.5 g, 47 mmol) in MeOH (42 mL) at 5-10°C. The mixture was stirred for 30 min at 5-10°C, and worked up as described for (±)-**6** to give (±)-**10** (2.29 g, 73%) as a colorless oil, bp 60-61°C/1.6 kPa; n_D^{23}=1.4720; νmax (film): 3327 (s), 3039 (m), 2963 (s), 2939 (s), 2915 (s), 2855 (s), 1659 (w), 1449 (m), 1055 (s), 1031 (s), 973 (m), 823 (m); δ_H ($CDCl_3$): 1.60-1.70 (2H, m), 1.76 (3H, s), 2.10-2.20 (1H, m), 2.25-2.32 (1H, m), 2.32-2.46 (1H, m), 4.56 (1H, br. s), 5.50 (1H, s-like); GC-MS [same conditions as those used for **4** except temp: 40-230°C (+6°C/min)]: t_R 5.71 min (99.0%); MS (70 eV, EI): *m*/*z*: 98 (53) [M^+], 97 (46) [$(M-H)^+$], 83 (100), 79 (29), 77 (12), 69 (16), 55 (30), 43 (18), 41 (22), 39 (20). HRMS calc for $C_6H_{10}O$: 98.0732, found: 98.0722.

4.9. Lipase AK-catalyzed asymmetric acetylation of (±)-10 to give (*R*)-11 and (*S*)-10

Lipase AK Amano (350 mg) was added to a solution of (±)-**10** (2.29 g, 23 mmol) and vinyl acetate (2 mL, 1.85 g, 21.5 mmol) in $(i\text{-Pr})_2O$ (35 mL). The mixture was stirred for 3 h at room temperature (22°C), and filtered to remove the enzyme, which was washed thoroughly with Et_2O. The combined organic solution was concentrated in vacuo. The residue (2.72 g) was chromatographed over Al_2O_3 (Wako 010-01525, 40 g). Elution with pentane/EtOAc (100:1) gave (*R*)-**11** (1.13 g, 35%). Further elution with pentane/EtOAc (10:1) gave (*S*)-**10** (1.07 g, 47%), both as colorless oils. They showed the following properties. *(R)-2-Methyl-2-cyclopentenyl acetate (**11**)*: bp 65-66°C/2.3 kPa; n_D^{23}=1.4490; $[\alpha]_D^{21}$ +67.1 (*c* 4.77, hexane); Chiral GC [same conditions as those used for (*R*)-**9**]: t_R 81.4 min [96.4%, (*R*)-**11**], 89.6 min [3.6%, (*S*)-**11**], 93% ee; νmax (film): 3045 (w), 2970 (m), 2942 (m), 2920 (m), 2859 (m), 1735 (s),

1438 (m), 1372 (m), 1243 (s), 1047 (m), 1027 (s), 974 (m), 833 (m), δ_H ($CDCl_3$): 1.71 (3H, s), 1.70-1.79 (1H, m), 2.05 (3H, s), 2.20-2.30 (1H, m), 2.31-2.50 (2H, m), 5.58 (1H, t, *J*=5.2 Hz), 5.65 (1H, s); GC [same conditions as those used for (±)-**10**]: t_R 10.14 min (99.0%); MS (70 eV, EI): *m*/*z*: 140 (<1) [M^+], 97 (15), 83 (20), 81 (41), 80 (100), 79 (82), 77 (13), 53 (9), 43 (34), 41 (11), 39 (9). HRMS calc for $C_8H_{12}O_2$: 140.0837, found: 140.0853. *(S)-2-Methyl-2-cyclopenten-1-ol (**10**)*: bp 67-68°C/2.7 kPa: n_D^{23}=1.4710; $[\alpha]_D^{22}$ -58.2 (*c* 3.02, hexane); Chiral GC [column: heptakis-(2,3-di-*O*-acetyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin, 0.25 mm x 30 m; column temp: 40-180°C (+0.5°C/min); carrier gas, He; flow rate, 0.7 mL/min]: 61.2 min [12.2%, (*R*)-**10**], 65.4 min [87.7%, (*S*)-**10**], 76% ee; νmax (film): 3327 (br. s), 3039 (m), 2963 (s), 2939 (s), 2915 (s), 2855 (s), 1659 (w), 1449 (m), 1055 (s), 1031 (s), 973 (m), 824 (s); δ_H ($CDCl_3$): 1.60-1.70 (2H, m), 1.76 (3H, s), 2.10-2.20 (1H, m), 2.22-2.42 (2H, m), 4.56 (1H, s), 5.50 (1H, s-like); GC-MS [same conditions as used for (*S*)-**6]**: t_R 5.68 min (96.9%); MS (70 eV, EI): *m*/*z*: 98 (52) [M^+], 97 (46), 83 (100), 79 (30), 77 (13), 69 (15), 55 (30), 43 (18), 41 (22), 39 (21). HRMS calc for $C_6H_{10}O$: 98.0732, found: 98.0725.

4.10. (*R*)-2,3-Dimethyl-2-cyclopenten-1-ol (6) via methanolysis of (*R*)-9

Potassium carbonate (700 mg, 4 mmol) was added to a solution of (*R*)-**9** (92.8% ee, 348 mg, 2.3 mmol) in MeOH (5 mL). The mixture was stirred for 3 h at room temperature (22°C). It was then concentrated in vacuo, diluted with water, and extracted with Et_2O. The extract was washed successively with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give 202 mg (80%) of (*R*)-**6** as a colorless oil, $[\alpha]_D^{22}$ +43.1 (*c* 1.98, hexane); Chiral GC [same conditions as those used for (*S*)-**6**]: t_R 118.3 min [10.0%, (*S*)-**6**], 119.6 min [90.0%, (*R*)-**6**], 80% ee. Its spectral data were identical to those of (*S*)-**6**. The reason was unclear why the unexpected partial racemization took place in the present step.

4.11. (*R*)-2-Methyl-2-cyclopenten-l-ol (10) via methanolysis of (*R*)-11

In the same manner as described above for (*R*)-**6**, a mixture of (*R*)-**11** (770 mg, 5 mmol) and K_2CO_3 (1.40 g, 9 mmol) in MeOH (10 mL) was stirred for 3 h at room temperature (22°C). Subsequent work-up yielded 430 mg (80%) of (*R*)-**11** as a colorless oil, $[\alpha]_D^{21}$ +68.9 (*c* 3.65, hexane); Chiral GC [same conditions as those used for (*S*)-**10**]: t_R 60.8 min [96.7%, (*R*)-**11**], 66.0 min [3.3%, (*S*)-**11**], 93% ee. Its spectral data were identical to those of (*S*)-**11**.

4.12. Lipase AK-catalyzed asymmetric acetylation of (±)-6 in a preparative scale to give (*R*)-9 and (*S*)-6

*4.12.1. Asymmetric acetylation of (±)-**6**.* Lipase AK Amano (3.0 g) was added to a

solution of (±)-**6** (19.5 g, 174 mmol) and vinyl acetate (30.0 g, 349 mmol) in (*i*-Pr)$_2$O (300 mL). The mixture was stirred for 4.5 h at room temperature (22^{o}C), and filtered to remove the enzyme, which was washed with Et$_2$O. The combined filtrate and washings were concentrated in vacuo. The residue was chromatographed over Al_2O_3 (Wako Chemial, 010-01525, 300 mesh, pH 9.0-11.0; 200 g). Elution with pentane/EtOAc (100:1) gave 15.9 g (62%) of (*R*)-**9** (ca. 75% ee) as a colorless oil. Further elution with pentane/EtOAc (4:1) gave 6.24 g (32%) of (*S*)-**6** (77% ee) as an oil.

*4.12.2. Methanolysis of (R)-**9** to give (R)-**6**.* Potassium carbonate (50.0 g, 362 mmol) was added to a solution of (*R*)-**9** (ca. 75% ee, 15.9 g, 103 mmol) in MeOH (150 mL) and H_2O (10 mL). The mixture was stirred for 2 h at 35-40^{o}C. Subsequent work-up in the same manner as described in 4.10 gave 16.95 g of an oil. This was chromatographed over Al_2O_3 (Wako Chemical, 010-01525, 170 g). Elution with pentane gave hydrocarbon byproducts (7.09 g) obtained by elimination of AcOH from (*R)*-**9**. Further elution with pentane/EtOAc (4:1) gave 7.12 g (61%) of (*R*)-**6** (ca. 70% ee).

*4.12.3. Lipase AK-catalyzed asymmetric acetylation of (R)-**6** of ca. 70% ee to give (R)-**9** of 94% ee.* Lipase AK Amano (1.0 g) was added to a solution of (*R*)-**6** (ca. 70% ee, 6.34 g, 57 mmol) and vinyl acetate (6.0 g, 70 mmol) in (*i*-Pr)$_2$O (100 mL). The mixture was stirred for 3 h at room temperature (22^{o}C). Further work-up in the same manner as described in 4.9 gave 7.35 g of an oil. This was chromatographed over Al_2O_3 (Wako Chemical, 010-01525, 150 g). Elution with pentane/EtOAc (100:1) gave 4.00 g (46%) of (*R*)-**9**, and further elution with pentane/EtOAc (3:1) gave 2.94 g of the recovered impure **6**. The acetate (*R*)-**9** was distilled to give 2.57 g {42% recovery based on the starting **6** or 9.6% based on (±)-**6** [19% recovery of the existing (*R*)-**6**]} of (*R*)-**9**, bp 63-65^{o}C/0.8 kPa; n_D^{23}=1.4560; $[\alpha]_D^{23}$ +68.4 (*c* 1.42, hexane); Chiral GC [same conditions as used for (*R*)-**9** in 4.7]: t_R 102.2 [3.1%, (*S*)-**9**], 102.6 min [96.9%, (*R*)-**9**], 94% ee; Chemical purity by GC [same conditions as used for (*R*)-**9** in 4.7]: t_R 6.37 min (88.1%). Its IR, ^{1}H NMR and MS data were identical with those reported in 4.7. δ_C ($CDCl_3$): 11.26, 14.27, 21.38, 29.43, 35.77, 84.25, 129.33, 138.94, 171.36. HRMS calc for $C_9H_{14}O_2$: 154.0994, found: 154.1007.

*4.12.4. Lipase AK-catalyzed asymmetric acetylation of (S)-**6** of ca. 77% ee to give (S)-**6** of 94% ee.* Lipase AK Amano (2.0 g) was added to a solution of (*S*)-**6** (ca. 77% ee, 11.6 g, 103 mmol) and vinyl acetate (8.90 g, 103 mmol) in (*i*-Pr)$_2$O (200 mL). The mixture was stirred for 4 h at room temperature (22^{o}C). Further work-up in the same manner as described in 4.9 gave 12.7 g of an oil. This was chromatographed over Al_2O_3 (Wako Chemical, 010-01525, 200 g). Elution with pentane/EtOAc (100:1) gave

4.10 g of (*S*)-**9** of low ee. Further elution with pentane/EtOAc (3:1) gave 6.58 g [57% recovery based on the starting alcohol or 33.7% based on (±)-**6** or 67% recovery of (*S*)-**6** in the starting (±)-**6**] of (*S*)-**6** of ca. 94% ee, $[\alpha]_D^{24}$ -58.8 (*c* 1.87, hexane); Chemical purity by GC [same conditions as those described for (*S*)-**6** in 4.7]: t_R 4.03 min (99.5%). This was employed for the next step without distillation.

4.13. (*S*)-2,3-Dimethyl-2-cyclopentenyl acetate (9) by chemical acetylation of (*S*)-6

Acetic anhydride (15 mL) was added to a solution of the above described (*S*)-**6** (6.49 g, 57.9 mmol) in dry C_5H_5N (40 mL). After the exothermic reaction, the mixture was stirred for 2 h at 40°C. It was then cooled, poured into ice and water, and extracted with Et_2O. The Et_2O solution was washed successively with water, $CuSO_4$ solution, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give 5.50 g (62%) of (*S*)-**9**, bp 61-63°C/0.8 kPa; n_D^{22}=1.4572; $[\alpha]_D^{22}$ -59.1 (*c* 1.36, hexane); Chiral GC [same conditions as those used for (*R*)-**9**]: t_R 102.1 [96.9%, (*S*)-**9**], 102.8 min [3.1%, (*R*)-**9**], 94% ee; δ_C ($CDCl_3$): 11.26, 14.27, 21.39, 29.43, 35.77, 84.26, 129.32, 138.97, 171.38. Its IR, ^{1}H NMR and MS data were identical with those of (*R*)-**9**. Chemical purity by GC [same conditions as those used for (*R*)-**9**]: t_R 2.90 (11%), 4.03 (21%), 6.39 min [68%, (*S*)-**9**]. HRMS calc for $C_9H_{14}O_2$: 154.0994, found: 154.1003.

4.14. 2-(1,2-Dimethyl-2-cyclopentenyl)acetic acid (16)

4.14.1. (S)-Isomer. A solution of LiN(*i*-Pr)$_2$ (TCI, 1.5 M in THF, PhEt and heptane, 36 mL, 54 mmol) was added dropwise over 15 min to a stirred and cooled solution of (*S*)-**9** (5.38 g, 34.9 mmol) and TMSCl (18.3 mL=15.7 g, 145 mmol) in dry THF (25 mL) at -78 to -60°C under argon. The mixture was stirred for 15 min at -78°C, and allowed to reach room temperature. It was then stirred and heated at 60°C (bath temperature) for 3 h. After cooling, MeOH (22 mL) was added dropwise, keeping the inner temperature below 40°C. The mixture was placed in a separatory funnel, and the acid **16** was extracted with 5% NaOH solution (35 mL x 3). The alkaline solution was washed with Et_2O, and the aqueous layer was acidified with dil HCl (containing 25 mL of conc HCl) and ice. The separated acid was extracted with Et_2O. The extract was washed successively with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give 3.00 g (56%) of crude (*S*)-**16** as a slightly yellowish oil, $[\alpha]_D^{21}$ -16.4 (*c* 1.79, Et_2O); νmax (film): 3040-2690 (br m), 1705 (s), 1439 (m), 1409 (m), 1287 (m), 1253 (m), 920 (m). This was used in the next step without further purification.

4.14.2. (R)-Isomer. In the same manner as described above (*R*)-**9** (2.30 g, 14.9 mmol), 1.5 M LiN(*i*-Pr)$_2$ (13.3 mL, 19.9 mmol) and TMSCl (7.6 mL, 60 mmol) in THF (10 mL) gave 0.68 g (30%) of crude (*R*)-**16**, $[\alpha]_D^{21}$ +16.9 (*c* 1.65, Et_2O). Its IR

spectrum was identical with those of (*S*)-**16**. This was used in the next step without further purification.

4.15. Enantiomers of methyl 2-(1,2-dimethyl-2-cyclopentenyl)acetate (17)

4.15.1. (S)-Isomer. Potassium carbonate (7.0 g, 51 mmol) and MeI (12.0 g, 84.5 mmol) were added to a solution of crude (*S*)-**16** (3.00 g, 19.5 mmol) in DMF (10 mL) and acetone (30 mL). The mixture was stirred for 2 d at room temperature. After removing acetone in vacuo, the mixture was diluted with water, and extracted with Et_2O. The Et_2O solution was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give 2.08 g [64% or 35% based on (*S*)-**9**] of (*S*)-**17** as a colorless oil, bp 74-77^oC/0.7 kPa: n_D^{23}=1.4552; $[\alpha]_D^{23}$ -17.8 (*c* 1.36, hexane); νmax (film): 3038 (w), 2954 (s), 2851 (m), 1739 (vs), 1437 (m), 1218 (s), 1165 (m), 1131 (m), 1018 (m), 846 (m); δ_H ($CDCl_3$): 1.09 (3H, s), 1.62 (3H, s), 1.64-1.74 (1H, m), 2.06-2.14 (1H, m), 2.16-2.22 (2H, m), 2.27 (1H, d, *J*=13 Hz), 2.35 (1H, d, *J*=13 Hz), 3.64 (3H, s), 5.30 (1H, br s); δ_C ($CDCl_3$): 12.41, 24.95, 29.23, 37.13, 43.28, 48.46, 51.33, 124.71, 145.44, 172.93; GC-MS (same conditions as those used for **4**): t_R 6.89 min (87.1%); MS (70eV, EI): *m*/*z*: 168 (21) [M^+], 96 (8), 95 (97), 94 (100), 93 (28), 91 (13), 79 (32), 77 (13), 67 (16), 55 (7). HRMS calc for $C_{10}H_{16}O_2$: 168.1150, found: 168.1149.

4.15.2. (R)-Isomer. In the same manner as described above, (*R*)-**16** (1.34 g, 8.7 mmol), K_2CO_3 (3.4 g, 25 mmol) and MeI (6.8 g, 48 mmol) gave 988 mg (68%) of (*R*)-**17** as a colorless oil, bp 70-72^oC/0.7 kPa; n_D^{22}=1.4562; $[\alpha]_D^{21}$ +16.7 (*c* 1.33, hexane): Its IR, ^1H NMR and MS data were identical with those of (*S*)-**17**. δ_C ($CDCl_3$): 12.42, 24.95, 29.23, 37.13, 43.28, 48.47, 51.33, 124.71, 145.44, 172.93; GC-MS (same conditions as those used for **4**): t_R 6.88 min (81%). HRMS calc for $C_{10}H_{16}O_2$: 168.1150, found: 168.1149.

4.15.3. Racemate. Ring closing metatheses of (±)-**19** gave (±)-**17** as a colorless oil, bp 78-80^oC/1 kPa; δ_C ($CDCl_3$): 12.41, 24.94, 29.22, 37.12, 43.27, 48.46, 51.31, 124.70, 145.42, 172.91. HRMS calc for $C_{10}H_{16}O_2$: 168.1150, found: 168.1168.

4.16. (±)-Methyl (1,2-dimethyl-2,3-epoxycyclopentyl)acetate (20)

m-Chloroperbenzoic acid (MCPBA, 70% pure, 18.8 g, 76 mmol) was added portionwise over 15 min to a stirred and cooled (ice-salt bath) solution of (±)-**17** (10.6 g, 63.1 mmol) in CH_2Cl_2 (150 mL) at <15^oC. The mixture was stirred for 45 min at -10^oC, and filtered. The filter cake was thoroughly washed with pentane. The combined filtrate and washings were successively washed with $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (70 g). Elution with pentane/EtOAc (20:1) gave 8.01 g (69%) of (±)-**20** as a colorless oil, n_D^{23}=1.4532; νmax (film): 2955 (s), 2876 (m), 1738 (s), 1439 (s), 1199 (s),

1097 (m), 1014 (m), 837 (m); δ_H ($CDCl_3$): 1.03 (1.8H, s), 1.12 (1.2H, s), 1.31 (1.8H, s), 1.32 (1.2H, s), 1.20-1.42 (1H, m), 1.50-1.72 and 1.82-1.92 (total 2H, m), 2.24 (1H, s), 2.38-2.48 (2H, m), 3.26 (1H, s, *J*=14 Hz), 3.65 (3H, s); δ_C ($CDCl_3$): 12.96, 13.04, 20.86, 21.87, 25.42, 25.82, 31.89, 32.78, 40.64, 41.49, 42.56, 42.86, 51.48, 51.62, 63.82, 64.63, 68.23, 68.37, 172.27, 172.86; GC-MS (same conditions as those used for **4**): t_R 8.60 (41.2%), 8.88 min (55.3%); MS of (±)-**20** with t_R=8.60 min (70 eV, EI): *m*/*z*: 184 (<1) [M^+], 169 (4), 153 (15), 125 (91), 111 (83), 110 (100), 109 (75), 95 (52), 81 (19), 67 (21), 55 (38), 43 (59), 41 (28); MS of (±)-**20** with t_R=8.88 min (70 eV, EI); *m*/*z*: 184 (<1) [M^+], 169 (6), 153 (6), 125 (92), 111 (41), 110 (100), 109 (77), 95 (51), 81 (19), 67 (19), 55 (36), 43 (53), 41 (26). HRMS calc for $C_{10}H_{16}O_3$: 184.1099, found: 184.1114 (short t_R), 184.1115 (long t_R).

4.17. (±)-Methyl (1,2-dimethyl-3-oxocylopentyl)acetate (21)

*4.17.1. Rearrangement of (±)-**20**.* A solution of (±)-**20** (8.01 g, 43.5 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise over 15 min to a stirred and ice-cooled solution of $BF_3 \cdot OEt_2$ (1.8 mL, 2.0 g, 14 mmol) in dry CH_2Cl_2 (120 mL) at 8-11°C under argon. After the addition, the pale orange-colored solution was stirred for 5 min at 7°C, and then quenched with sat. $NaHCO_3$ solution (50 mL). The mixture was stirred for 1 h at room temperature. The CH_2Cl_2 layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic solution was washed with brine, dried ($MgSO_4$), and concentrated under atmospheric pressure with a Vigreux column. The residue was distilled to give 6.62 g (83%) of (±)-**21** as a colorless oil, bp 90-93°C/0.3 kPa; n_D^{23}=1.4610. Its IR, ^{1}H NMR and MS spectra were identical with those reported previously.[4] δ_C ($CDCl_3$): 7.89, 8.29, 19.76, 25.86, 32.14, 33.08, 34.84, 34.98, 38.68, 44.86, 51.56, 55.97, 171.97, 172.32, 219.44, 219.93; GC-MS (same conditions as those used for **4**): t_R 9.88 (51.1%), 10.09 min (48.9%). HRMS calc for $C_{10}H_{16}O_3$: 184.1099, found: 184.1083 (short t_R), 184.1087 (long t_R).

*4.17.2. Hydroboration-oxidation of (±)-**17**.* A solution of $BH_3 \cdot THF$ (0.9 M, 50 mL, 45 mmol) was added dropwise over 15 min to a stirred and ice-cooled solution of (±)-**17** (12.9 g, 76.8 mmol) in dry Et_2O (50 mL) at 5-10°C under argon. The mixture was stirred for 3 h at room temperature (22°C). Water (15 mL) was added dropwise over 5 min to a stirred and ice-cooled mixture, which was further stirred for 5 min to destroy excess BH_3. The mixture was then concentrated in vacuo to remove Et_2O and THF. The residue was diluted with Et_2O (100 mL), acetone (50 mL), and water (50 mL). The mixture was stirred and cooled in an ice-bath. Jones CrO_3 (45 mL, 360 mequiv) was added dropwise over 20 min to the stirred and ice-cooled solution until red color persisted. The mixture was further stirred for 10 min, and MeOH (20 mL) was added

to destroy the excess CrO_3. Then the mixture was diluted with water 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 8.0 g (57%) of (±)-**21** as a colorless oil, bp 78-85°C/0.2 kPa. Its spectral data coincided with those reported previously.[4] GC purity: 82.7% (t_R 9.90 min/ t_R 10.08 min =100:82). HRMS calc for $C_{10}H_{16}O_3$: 184.1099, found: 184.1112 (short t_R), 184.1107 (long t_R).

4.18. (±)-Methyl (1,2-dimethyl-3-methylenecyclopentyl)acetate (±)-22

4.18.1. With Lombardo's $CH_2Br_2/Zn/TiCl_4$ reagent. (a) Activation of Zn. Zinc powder (Wako Chemical, 25 g) was stirred with 2% HCl (60 mL) for 1 min, and collected on a filter by vacuum filtration. The zinc powder was placed into a beaker, and washed successively with 2% HCl (60 mL), pure water (60 mL), 99% EtOH (40 mL) and Et_2O (40 mL). After removing Et_2O by decantation, the remaining zinc powder was dried in vacuo (0.13 kPa) for 2 d over blue silica. *(b) Preparation of the reagent.* The activated and dried zinc powder (20.2 g, 310 mmol), CH_2Br_2 (7.1 mL, 100 mmol) and dry THF (175 mL) were placed in a 500 mL flask under argon. The mixture was stirred and cooled at -40°C. Titanium tetrachloride (8.0 mL, 82 mmol) was added dropwise to the stirred mixture at -40°C to give a dark slurry. The mixture was stirred at -5°C for 3 d. It was then diluted with dry CH_2Cl_2 (35 mL) with cooling in an ice-bath. *(c) Reaction with (±)-**21**.* A solution of (±)-**21** (6.60 g, 35.9 mmol) in dry CH_2Cl_2 (25 mL) was added to the stirred and ice-cooled slurry of the above reagent over 10 min. The dark mixture was stirred for 1.5 h at room temperature (22°C), and diluted with Et_2O (200 mL). The mixture was added slowly to a stirred slurry of $NaHCO_3$ (75 g, 890 mmol) in water (40 mL) in a beaker. (CAUTION: Foaming !), and the mixture was stirred for 1 h. Then the mixture was filtered through Celite, and the Celite layer was washed with Et_2O. The combined filtrate and washings were washed with water and brine, dried ($MgSO_4$), and concentrated under atmospheric pressure with a Vigreux column. The residue was chromatographed over SiO_2 (60 g). Elution with pentane/EtOAc (20:1) gave 5.61 g (86%) of (±)-**22** as a colorless oil. Its spectral properties were identical with those reported previously. GC-MS (same conditions as used for **4**): t_R 8.38 (52.1%), 8.50 min (31.4%). HRMS calc for $C_{11}H_{18}O_2$: 182.1307, found: 182.1322 (short t_R), 182.1323 (long t_R).

4.18.2. With Yan's $CH_2Cl_2/Mg/TiCl_4$ reagent. A solution of (±)-**21** (4.27 g, 23.2 mmol) in dry CH_2Cl_2 (30 mL) and dry THF (20 mL) was added dropwise over 20 min to a stirred and ice-cooled mixture of magnesium powder (Aldrich, 4.45 g, 186 mmol), $TiCl_4$ (4.9 mL, 46 mmol) and dry CH_2Cl_2 (50 mL) at 0-5°C under argon. The mixture

was stirred for 30 min at 0-5°C and for another 30 min at room temperature to give a dark green solution. The reaction was quenched by addition of a slurry of $NaHCO_3$ (22 g, 297 mmol) and water (20 mL) under ice-cooling (CAUTION: Foaming !), and diluted with Et_2O (100 mL). The mixture was filtered through Celite, which was washed with Et_2O, and the filtrate was extracted with Et_2O. The organic solution was washed with water and brine, dried ($MgSO_4$), and concentrated. The residue (ca. 5.82 g) was chromatographed over SiO_2 (70 g). Elution with pentane/EtOAc (30:1) gave 1.41 g (33%) of (±)-**22** as a colorless oil. Its spectral data were identical with those of (±)-**22**.[4]

4.19. (±)-2-(1,2-Dimethyl-3-methylenecyclopentyl)ethanol (23).

A solution of (±)-**22** (7.52 g, 41.3 mmol) in dry Et_2O (50 mL) was added dropwise over 15 min to a stirred and ice-cooled suspension of $LiAlH_4$ (1.20 g, 31.6 mmol) in dry Et_2O (50 mL) at 5-15°C. The mixture was stirred for 10 min at 0-5°C and for 1 h at room temperature (21°C). It was then ice-cooled, and the excess $LiAlH_4$ was destroyed by dropwise addition of water (20 mL). The mixture was acidified with dil HCl and ice, and extracted with Et_2O. The Et_2O solution was washed successively with water, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated under atmospheric pressure with a Vigreux column. The residue was distilled to give 5.21 g (82%) of (±)-**23** as a colorless oil, bp 105-110°C/1.2 kPa. Its spectral data were identical with those reported previously.[4] Its GC purity was ca. 100% [(±)-*anti*-**23**/(±)-*syn*-**23**=1.2:1]. A sample (7.15 g) of (±)-**23** was stored for further biological use.

The oily (±)-**23** (5.21 g) prepared similarly was chromatographed over SiO_2 (70 g). Elution with pentane/EtOAc (20:1) gave 0.95 g (18%) of (±)-*anti*-**23** rich fraction (*anti*/*syn*= 93:7-90:10 as judged by GC). The later eluting *anti*/*syn* mixture was rechromatographed over SiO_2 (60 g). Elution with pentane/EtOAc (20:1) gave 1.41 g (27%) of *anti* rich fraction (*anti*/*syn*= 93:7). The (±)-*anti*-**23**-rich fractions were combined (45%) and used for the next step.

4.20. (±)-2-(*anti*-1,2-Dimethyl-3-methylenecyclopentyl)ethyl 3,5-dinitrobenzoate (24)

3,5-Dinitrobenzoyl chloride (4.60 g, 20 mmol) and DMAP (50 mg, 0.41 mmol) were added to a stirred and ice-cooled solution of (±)-*anti*-**23** (93% pure, 2.10 g, 13.6 mmol) in dry C_5H_5N (25 mL). The mixture was stirred for 3 h at 0-5°C, diluted with ice and water, and extracted with Et_2O. The Et_2O extract was washed successively with water, dil HCl, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo to give 5.35 g (quant.) of a solid, which was recrystallized from EtOAc/hexane to give 1.61 g of

the first crop of **24** as leaflets, 1.68 g of the second crop of **24** as fine leaflets, and 0.24 g of the third crop of **24** as fine crystals. The yield of **24** was 3.53 g (74%). The first crop melted at 62-64°C, and its IR, ^{1}H and ^{13}C NMR spectra were identical with those reported previously.[4]

4.21. (±)-2-(*anti*-1,2-Dimethyl-3-methylenecyclopentyl)ethanol (23)

Crystalline (±)-*anti*-**24** (3.35 g, 9.63 mmol) was added to a solution of NaOH (1.60 g, 40 mmol) in MeOH/H_2O [1:1 (v/v), 15 mL]. The mixture was stirred and heated under reflux for 30 min to give a dark red solution. This was diluted with water, and extracted with Et_2O. The Et_2O solution was washed with water and brine, dried ($MgSO_4$), and concentrated under atmospheric pressure with a Vigreux column. The residue was distilled in vacuo to give 1.15 g (77%) of (±)-*anti*-**23** (*anti*/*syn*=100:7 by GC analysis) as a colorless oil, bp 108-110°C/1.6 kPa; n_D^{24}=1.4782; νmax (film): 3328 (br s), 3072 (w), 2956 (s), 2871 (s), 1655 (m), 1454 (s), 1379 (m), 1054 (s), 1037 (s), 1000 (m), 878 (s); δ_H ($CDCl_3$): 0.94 (3H, d, *J*= 7.2 Hz), 1.00 (3H, s), 1.20-1.39 (4H, m), 1.66-1.74 (1H, m), 1.96-2.06 (1H, br), 2.22-2.43 (2H, m), 3.63-3.80 (2H, t-like), 4.74 (1H, s), 4.82 (1H, s); δ_C ($CDCl_3$): 12.16, 25.12, 29.24, 35.17, 36.13, 42.76, 50.66, 60.32, 104.82, 157.15; GC-MS (same conditions as those used for **4**): t_R 8.31 min (91.8%); MS (70 eV, EI): *m*/*z*: 154 (<1) [M^+], 121 (25), 110 (48), 109 (100), 108 (28), 107 (25), 95 (24), 93 (37), 79 (26), 67 (43), 41 (25). HRMS calc for $C_{10}H_{18}O$: 154.1358, found: 154.1344. A sample (1.09 g) of (±)-*anti*-**23** was stored for further biological use.

4.22. Enantiomers of methyl (1,2-dimethyl-2,3-epoxycyclopentyl)acetate (20)

4.22.1. (1S,2RS,3SR)-Isomer. In the same manner as described in 4.16 for (±)-**20**, (*S*)-**17** (2.00 g, 11.9 mmol) in CH_2Cl_2 (30 mL) was epoxidized with MCPBA (3.20 g, 15 mmol) to give 2.04 g (93%) of (1*S*,2*RS*,3*SR*)-**20** as a colorless oil. Its IR and MS data were identical with those of (±)-**20**. GC-MS (same conditions as those used for **4**): t_R 8.56 (33.7%), 8.84 min (59.6%). HRMS calc for $C_{10}H_{16}O_3$: 184.1099, found: 184.1103 (short t_R), 184.1096 (long t_R).

4.22.2. (1R,2SR,3RS)-Isomer. In the same manner as described in 4.16 for (±)-**20**, (*R*)-**17** (1.00 g, 0.59 mmol) in CH_2Cl_2 (15 mL) was epoxidized with MCPBA (1.60 g, 7.5 mmol) to give 0.99 g (90%) of (1*R*,2*SR*,3*RS*)-**20** as a colorless oil. Its IR and MS data were identical with those of (±)-**20**. GC-MS (same conditions as those used for **4**): t_R 8.56 (37.6%), 8.83 min (50.0%). HRMS calc for $C_{10}H_{16}O_3$: 184.1099, found: 184.1100 (short t_R), 184.1098 (long t_R).

4.23. Enantiomers of methyl (1,2-dimethyl-3-oxocyclopentyl)acetate (21)

4.23.1. (1S,2RS)-Isomer. In the same manner as described in 4.17.1, (1*S*,2*RS*,3*SR*)-**20** (1.85 g, 10.1 mmol) in CH_2Cl_2 (10 mL) was treated with $BF_3 \cdot OEt_3$

(0.6 mL, 0.67 g, 4.7 mmol) in CH_2Cl_2 (30 mL) to give 1.85 g (quant.) of (1*S*,2*RS*)-**21** as a colorless oil, $[\alpha]_D^{24}$ -2.35 (*c* 1.67, hexane). Its IR and MS data were identical with those of (±)-**21**. GC-MS (same conditions as those used for **4**): t_R 9.86 (47.9%), 10.07 min (46.0%). HRMS calc for $C_{10}H_{16}O_3$: 184.1099, found: 184.1098 (short t_R), 184.1096 (long t_R).

4.23.2. (1R,2SR)-Isomer. In the same manner as described in 4.17.1, (1*R*,2*SR*,3*RS*)-**20** (0.99 g, 5.38 mmol) in CH_2Cl_2 (5 mL) was treated with $BF_3{\cdot}OEt_2$ (0.3 mL, 0.33 g, 2.4 mmol) in CH_2Cl_2 (15 mL) to give 0.92 g (93%) of (1*R*,2*SR*)-**21** as a colorless oil, $[\alpha]_D^{24}$ +1.30 (*c* 1.46, hexane). Its IR and MS data were identical with those of (±)-**21**. GC-MS (same conditions as those used for **4**): t_R 9.82 (43.2%), 10.03 min (49.8%). HRMS calc for $C_{10}H_{16}O_3$: 184.1099, found: 184.1097 (short t_R), 184.1093 (long t_R).

4.24. Enantiomers of methyl (1,2-dimethyl-3-methylenecyclopentyl)acetate (22)

4.24.1. (1S,2RS)-Isomer. In the same manner as described in 4.18.1, (1*S*,2*RS*)-**21** (1.84 g, 10 mmol) in CH_2Cl_2 (10 mL) was added to the stirred and ice-cooled Lombardo reagent (70 mL) under argon to give 1.33 g (72%) of (1*S*,2*RS*)-**22** as a colorless oil, $[\alpha]_D^{23}$ -20.1 (*c* 1.50, hexane). Its IR and MS data were identical with those of (±)-**22**. GC-MS (same conditions as those used for **4**): t_R 8.34 (49.8%), 8.51 min (41.8%). HRMS calc for $C_{11}H_{18}O_2$: 182.1307, found: 182.1305 (short t_R), 182.1309 (long t_R).

4.24.2. (1R,2SR)-Isomer. In the same manner as described in 4.18.1, (1*R*,2*SR*)-**22** (0.91 g, 4.9 mmol) in CH_2Cl_2 (5 mL) was added to the stirred and ice-cooled Lombardo reagent (35 mL) under argon to give 0.41 g (46%) of (1*R*,2*SR*)-**22** as a colorless oil, $[\alpha]_D^{24}$ +17.6 (*c* 0.64, hexane). Its IR and MS data were identical with those of (±)-**22**. GC-MS (same conditions as those used for **4**): t_R 8.34 (45.6%), 8.51 min (40.9%). HRMS calc for $C_{11}H_{18}O_2$: 182.1307, found: 182.1306 (short t_R), 182.1308 (long t_R).

4.25. Enantiomers of 2-(1,2-dimethyl-3-methylenecyclopentyl)ethanol (23)

*4.25.1. (1S,2RS)-**23** and its purification to give (1S,2S)-**23**.* In the same manner as described in 4.19, (1*S*,2*RS*)-**22** (1.16 g, 6.37 mmol) in dry Et_2O (10 mL) was added to a stirred and ice-cooled suspension of $LiAlH_4$ (250 mg, 6.6 mmol) in dry Et_2O (10 mL) to give 0.93 g (95%) of (*1S*,2*RS*)-**23**, $[\alpha]_D^{22}$ +5.4 (*c* 1.40, hexane), as a colorless oil. This was chromatographed over SiO_2 (25 g). Elution with pentane/EtOAc (20:1) gave (1*S*,2*S*)-**23** (82 mg), a mixture of (1*S*,2*S*)- and (1*S*,2*R*)-**23** (646 mg) and (1*S*,2*R*)-**23** (93 mg). The mixture (646 mg) was rechromatographed over SiO_2 (25 g). Elution with pentane/EtOAc (20:1) gave (1*S*,2*S*)-**23** (79 mg), a mixture of (1*S*,2*S*)- and (1*S*,2*R*)-**23** (277 mg), and (1*S*,2*R*)-**23** (215 mg). The mixture (277 mg) was further rechromatographed over SiO_2 (10 g). Elution with pentane/EtOAc (20:1) gave

(1*S*,2*S*)-**23** (123 mg). All the (1*S*,2*S*)-**23** fractions were combined to give 284 mg (30%) of (1*S*,2*S*)-**23**, n_D^{24}=1.4762; $[\alpha]_D^{26}$ -26.7 (*c* 0.52, hexane); νmax (film): 3346 (br m), 3072 (w), 2960 (s), 2871 (s), 1655 (m), 1455 (m), 1379 (m), 1125 (m), 1054 (m), 1036 (m), 877 (s); δ_C ($CDCl_3$): 12.17, 25.13, 29.25, 35.18, 36.16, 42.78, 50.67, 60.36, 104.83, 157.16. Its ^{1}H NMR and MS spectra were identical with those of (±)-*anti*-**23**. GC-MS (same conditions as those used for **4**): t_R 8.28 min (91.6%). HRMS calc for $C_{10}H_{18}O_2$: 154.1358, found: 154.1365. (1*S*,2*R*)-**23** was not purified further. Its specific rotation was $[\alpha]_D^{26}$ +45.4 (*c* 0.65, hexane) in one case and $[\alpha]_D^{26}$ +37.8 (*c* 0.53, hexane) in another case. νmax (film): 3853 (br m), 3073 (w), 2960 (s), 2937 (s), 2872 (m), 1655 (m), 1454 (m), 1379 (m), 1054 (m), 1037 (s), 1008 (m), 876 (s).

*4.25.2. (1R,2SR)-**23**.* In the same manner as described in 4.19, (1*R*,2*SR*)-**21** (0.31 g, 1.7 mmol) in dry Et_2O (5 mL) was added to a stirred and ice-cooled suspension of $LiAlH_4$ (100 mg, 2.6 mmol) in dry Et_2O (5 mL) to give 0.23 g (88%) of (1*R*,2*SR*)-**23**, $[\alpha]_D^{23}$ -6.67 (*c* 0.58, hexane). Its spectral data were identical with those of (1*S*,2*RS*)-**23**. Due to the scarcity of the material, (1*R*,2*SR*)-**23** was not purified by SiO_2 chromatography. GC-MS (same conditions as those used for **4**): t_R 8.27 (50.9%), 8.43 min (48.0%). HRMS calc for $C_{10}H_{18}O$: 154.1358, found: 154.1365 (short t_R), 154.1364 (long t_R).

4.26. Enantiomers of 2-(1,2-dimethyl-3-methylenecyclopentyl)acetaldehyde (1).

4.26.1. (1S,2S)-Isomer. Diacetoxyiodobenzene (DAIB, 354 mg, 1.10 mmol) was added to a stirred solution of (1*S*,2*S*)-**23** (128 mg, 0.83 mmol) and azadol (15 mg, 0.1 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 15 min at room temperature (22^{o}C), and diluted with Et_2O. It was then washed successively with $NaHCO_3$ solution containing a small amount of $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo to give an oil (420 mg). This was chromatographed over SiO_2 (5 g). Elution with pentane/EtOAc (50:1) gave 87 mg (69%) of (1*S*,2*S*)-**1** as a colorless oil, n_D^{24}=1.4710; $[\alpha]_D^{25}$ -47.6 (*c* 0.50, hexane) {natural pheromone: $[\alpha]_D^{26.3}$ -39.45 (*c* 0.0752, hexane)}; Chiral GC [column: Chiramix, 0.25 mm i.d. x 60 m; column temp: 40-180^o (+0.7^{o}C/min); carrier gas, He: flow rate 1.2 mL/min]: t_R120.2 [97.3%, (1*S*,2*S*)-**1**], 121.3 min [2.7%, (1*R*,2*R*)-**1**], 94.6% ee; νmax (film): 3074 (w), 2959 (s), 2872 (m), 2731 (w), 1721 (s), 1655 (w), 1455 (m), 1388 (m), 881 (m); δ_H ($CDCl_3$): 0.95 (3H, d, *J*= 7.2 Hz), 1.18 (3H, s), 1.45-1.52 (1H, m), 1.80-1.90 (1H, m), 2.10 (2H, s), 2.09-2.16 (1H, m), 2.25-2.40 (1H, m), 2.40-2.55 (1H, m), 4.79 (1H, s-like), 4.88 (1H, s-like), 9.83 (1H, t, *J*=2.8 Hz); δ_C ($CDCl_3$): 12.06, 25.15, 28.95, 35.63, 43.64, 47.41, 50.42, 105.81, 155.67, 203.98; GC-MS (same conditions as those used for **4**): t_R 6.96 min (91.0%); MS (70 eV, EI): *m*/*z*: 152 (<1) [M^+], 110 (10), 109 (100), 108 (50), 93 (19),

91 (15), 81 (8), 79 (7), 77 (11), 67 (28), 41 (10). HRMS calc for $C_{10}H_{16}O$: 152.1201, found: 152.1205.

4.26.2. (1R,2RS)-Isomer. In the same manner as described above, (1*R*,2*RS*)-**23** (137 mg, 0.89 mmol) was oxidized with DAIB (354 mg, 1.10 mmol) and azadol (15 mg, 0.1 mmol) in CH_2Cl_2 (4 mL) to give 90 mg (67%) of a mixture of (1*R*,2*R*)- and (1*R*,2*S*)-**1** (10:9 as analyzed by GC) as a colorless oil. Due to the scarcity, it was not further separated by SiO_2 chromatography. It showed the following properties: $[\alpha]_D^{24}$ +15.5 (*c* 0.61, hexane)}; Chiral GC [same conditions as those used for (1*S*,2*S*)-**1**]: t_R 120.4 [1.3%, (1*S*,2*S*)-**1**], 121.1 [51.6%, (1*R*,2*R*)-**1**], 92.5% ee; 123.2 [45.1%, (1*R*,2*S*)-**1**], 123.7 min [2.0%, (1*S*,2*R*)-**1**], 95.8% ee: νmax (film): 3074 (w), 2961 (s), 2872 (m), 2731 (w), 1721 (vs), 1655 (w), 1455 (w), 1382 (w), 879 (m); GC-MS (same conditions as those used for **4**): t_R 6.95 (50.2%), 7.08 min (45.0%); MS of the mixture [(1*S*,2*R*)- and (1*R*,2*S*)-**1**] was almost the same as that of (1*S*,2*S*)-**1**. HRMS calc for $C_{10}H_{16}O$: 152.1201, found: 152.1218 (short t_R), 152.1211 (long t_R).

*4.26.3. Identification of the natural pheromone as (1S,2S)-**1** by chiral GC.* Chiral GC analysis: [column, Supelco 24304, beta dex 120, 0.25 mm i.d. x 30 m; column temp, 100-180°C (+5°C/min); carrier gas, N_2, flow rate 20 mL/min]: t_R (1*S*,2*S*)-**1**=13.957; natural **1**=13.949; (1*R*,2*R*)-**1**=14.118, (1R,2S)-**1**=14.555 min. The natural **1** was therefore (1*S*,2*S*)-**1**.

4.27. (-)-2-(1,2-Dimethyl-3-methylenecyclopentyl)ethyl camphanate (25)

(-)-Camphanic chloride (TCI, 100 mg, 0.46 mmol) was added to a solution of (1*S*,2*S*)-**23** (40 mg, 0.26 mmol) and DMAP (5 mg, 0.04 mmol) in $CHCl_3$ (0.4 mL) and dry C_5H_5N (1 mL). The mixture was left to stand overnight at room temperature. It was then poured into iced water, and extracted with Et_2O. The Et_2O extract was washed successively with dil HCl, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo to give 85 mg (98%) of **25** as a solid. This was recrystallized from EtOAc/hexane to give leaflets, mp 119-120°C (sinter at 85-86°C) (A sample for X-ray crystallographic analysis was recrystallized from EtOAc to give plates). $[\alpha]_D^{25}$ -16.6 (*c* 0.07, Et_2O); νmax (nujol): 3066 (w), 1784 (s), 1759 (w), 1720 (s), 1653 (w), 1402 (m), 1377 (m), 1346 (m), 1320 (m), 1271 (s), 1170 (m), 1099 (s), 1060 (m), 1022 (m), 931 (m), 919 (m), 882 (m); δ_H ($CDCl_3$): 0.93 (3H, d, *J*=7.0 Hz), 0.95 (3H, s), 1.03 (3H, s), 1.05 (3H, s), 1.11 (3H, s), 1.46 (2H, t, *J*=7.2 Hz), 1.64-1.76 (2H, m), 1.86-2.12 (4H, m), 2.24-2.34 (1H, m), 2.35-2.52 (2H, m), 4.28 (2H, t, *J*=7.6 Hz), 4.78 (1H, s), 4.85 (1H, s); δ_C ($CDCl_3$): 9.85, 12.18, 16.93, 24.86, 29.07, 29.12, 30.76, 31.66, 35.04, 42.76, 50.59, 54.30, 54.92, 63.68, 77.36, 91.24, 105.26, 156.53, 178.33. HRMS calc for $C_{20}H_{30}O_4$: 334.2144, found; 334.2133.

4.28. X-ray crystal structure determination of 25

4.28.1. Instrument and softwares. The intensity data were collected on a Rigaku R-Axis Rapid diffratometer. Rapid auto ver. 2.30 Rigaku and CrystalStructure Ver 4.2 Rigaku were used for control and analysis, respectively. GBX 100 was used as a digital microscope.

4.28.2. Experimental conditions. X-ray source: Cu. Cu-Kα irradiation (λ=1.54187 Å) was used.

4.28.3. Crystal data. Empirical formula: $C_{20}H_{30}O_4$, formula weight: 334.45; Crystal color and habit: colorless, block; Crystal dimensions: 0.100 x 0.100 x 0.050 mm; Crystal system: orthorhombic; Lattice type: primitive; Lattice parameters: a=6.26573 (17) Å, b=6.8852 (2) Å, c=44.5126 (13) Å, V=1920.70 (9) $Å^3$; Space group: $P2_12_12_1$ (#19); Z value:4; D calc: 1.157 g/cm^3, F_{000}: 728.000, $\mu(CuK_\alpha)$: 6.332 cm^{-1}

4.28.4. Intensity measurements. No. of reflections measured: total: 22392; Unique: 3725 (R_{int}=0.0527); Friedel pairs: 1488; Corrections: Lorenz polarization absorption (trans. factors: 0.639-0.969).

4.28.5. Structure solution and refinement. Solution: Direct methods (S1R 97); Refinement: Full-matrix least-square on F; Function minimized: $\Sigma w(|Fo|-|Fc|)^2$; Least squares weights: $1/[0.0010F_0^2 +1.0000\sigma (F_0^2)]$; $2\Theta_{max}$ cutoff: 143.7°; Anomalous dispersion: All non-hydrogen atoms; No. of observations (all reflections): 3725; No. of variables: 248; Reflection/Parameter ratio: 15.02; Residuals: R[I>2.00σ (I)]: 0.0916; Residuals R (all reflections): 0.1301; Residuals: wR (all reflections) 0.1233; Goodness of fit indicator: 1.755; Flack parameter (Friedel pairs=1488): 0.3 (6); Max shift/Error in final cycle: 0.009; Maximum peak in final diff. map: 0.52 $e^-/Å^3$; Minimum peak in final diff. map: -4.8$e^-/Å^3$. Crystallographic data for the structure **25** (Fig.8) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1560305. Copies of the data may be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 44(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.UK].

4.29. Bioassay of (1*S*,2*S*)- and (1*R*,2*R*)-1

Both the synthetic (1*S*,2*S*)-**1** and a mixture of (1*R*,2*R*)- and (1*R*,2*S*)-**1** were further purified by $SiO_2/AgNO_3$ chromatography to give >99% pure (1*S*,2*S*)- and (1*R*,2*R*)-**1**. Their enantiomeric purities were 94.6% ee for (1*S*,2*S*)-**1** and 92.5% ee for (1*R*,2*R*)-**1** (see 4.26.1 and 4.26.2). The attractiveness of each the enantiomer of *anti*-**1** was tested by a trap bioassay at a pineapple field (ca. 1200 m^2) of the Okinawa Prefectural Agricultural Research Center (26.6°N, 127.9°E; Nago-shi, Okinawa, Japan) from June 17 to July 3, 2017. Attractants (0.1 mg) dissolved in hexane (100 μL) were

impregnated into red rubber septa (8 mm outside diameter 19 mm height; Wheaton; Millville, NJ, USA) and incubated overnight at room temperature, while the solvent evaporated. White delta-traps with 11 cm x 22 cm sticky boards (Sankei Chemical Co., Kagoshima, Japan) baited with the septa were placed 0.5 m above the ground at 5-m intervals. Three blocks of traps with two sets of three attractant treatments including a control (solvent only), in total six traps for each treatment, were prepared. Data were log-transformed and analyzed by using analysis of variance, which was performed by using the *aov* function of the R software v. 3. 2. 5. Both of the synthetic enantiomers of *anti*-**1** showed attractiveness to mealybug males in the field trap bioassay, while no males were captured by the blank trap. The males showed significantly more responses to (1*S*,2*S*)-**1** than to the opposite enantiomer (1*R*,2*R*)-**1** (ANOVA, $F_{1,6}$=27.8, P=0.00188; see Fig.4)

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Captions of Figures and Schemes

Fig.1. Structure [(1*S*,2*S*)-**1**] of the pineapple mealybug pheromone and the previous syntheses of its racemate.

Fig.2. Retrosynthetic analysis of (1*S*,2*S*)-**1** basing on lipase-catalyzed asymmetric acetylation of (±)-**J**.

Fig.3. X-ray structure of (-)-2-(*anti*-1,2-dimethyl-3-methylelnecyclopentyl)ethyl camphanate (**25**). For details see CCDC 1516035.

Fig.4. Numbers (mean + SEM; *N*=6) of *Dysmicoccus brevipes* males captured by field traps baited with (1*S*,2*S*)- and (1*R*,2*R*)-**1**. An asterisk indicates a significant difference

according to ANOVA ($P < 0.005$).

Scheme 1. Synthesis of (±)-**6**, the substrate for enzymatic acetylation. Reagents: (a) *t*-BuCOCl, Et_3N, Et_2O (99%); (b) EtMgBr, THF, -60°C (54%); (c) NaOH, EtOH, H_2O, reflux (67%); (d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 10-15°C (81%); (e) Mg, THF; 5-hexen-2-one (56%); (f) Grubbs II, CH_2Cl_2 (N.R.).

Scheme 2. Asymmetric acetylation of (±)-**6** and (±)-**10**. Reagents: (a) vinyl acetate, lipase AK, $(i\text{-Pr})_2O$, room temp; (b) K_2CO_3,MeOH, room temp; (c) $CH_2(CO_2Me)_2$, Novozyme 435, $KHCO_3$.

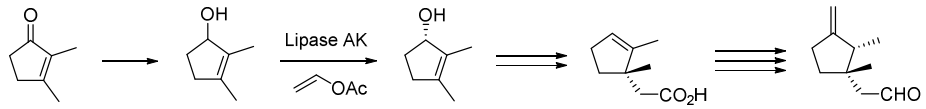
Scheme 3. Preparative scale asymmetric acetylation of (±)-**6** and subsequent synthesis of the enantiomers of **17**. Reagents: (a) vinyl acetate, lipase AK, $(i\text{-Pr})_2O$, room temp; (b) K_2CO_3,MeOH; (c) Ac_2O, C_5H_5N (62%); (d) TMSCl, $LiN(i\text{-Pr})_2$, THF; then heat at 60°C [56% of (*S*)-**16** and 30% of (*R*)-**16**]; (e) K_2CO_3,MeI, acetone, DMF [64% of (*S*)-**17** and 68% of (*R*)-**17**].

Scheme 4. Optimization of the synthetic steps employing racemic intermediates. Reagents: (a) Grubbs II (0.5 mol%), CH_2Cl_2, reflux (84%); (b) MCPBA, CH_2Cl_2 (69%); (c) $BF_3 \cdot OEt_2$, CH_2Cl_2 (83%); (d) $BH_3 \cdot SMe_2$, Et_2O; then Jones CrO_3, acetone (57%) (e) CH_2Br_2, Zn, $TiCl_4$, THF (86%); (f) CH_2Cl_2, Mg, $TiCl_4$ (33%); (g) $LiAlH_4$, Et_2O (82%-quant.); (h) SiO_2 chromatog. (45% for *anti*-**23**); (i) DNBCl, DMAP, C_5H_5N (74%); (j) NaOH, MeOH, H_2O (77%).

Scheme 5. Synthesis of the natural pheromone (1*S*,2*S*)-**1** and preparation of a crystalline derivative **25** for X-ray analysis. Reagents: (a) MCPBA,CH_2Cl_2 (93%); (b) $BF_3 \cdot OEt_2$, CH_2Cl_2 (quant.); (c) CH_2Br_2, Zn, $TiCl_4$, THF (72%); (d) $LiAlH_4$, Et_2O (95%); then SiO_2 chromatog. (30%); (e) DAIB, azadol, CH_2Cl_2 (69%); (f) (-)-camphanic chloride, DMAP, $CHCl_3$, C_5H_5N (98%).

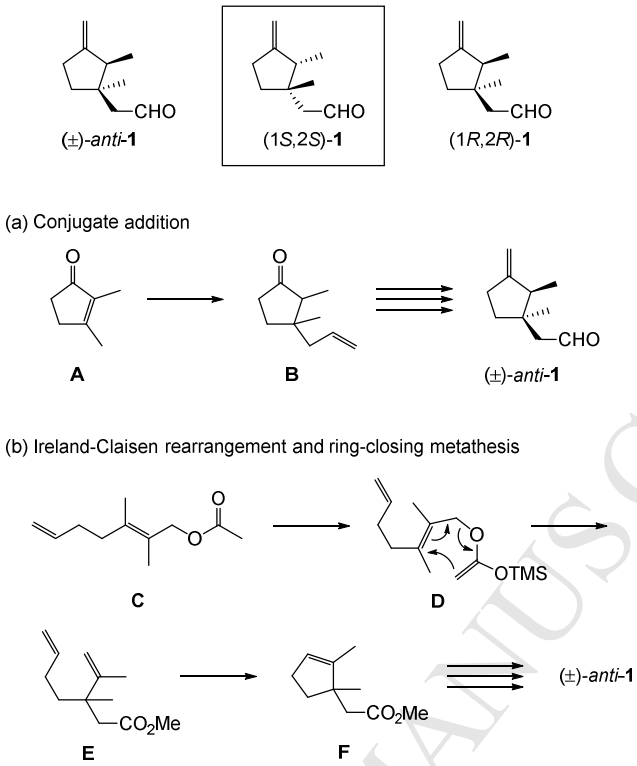
Pheromone synthesis. Part 262: Determination of the absolute configuration of the female sex pheromone [(1*S*,2*S*)-(–)-(1,2-dimethyl-3-methylenecyclopentyl)acetaldehyde] of the pineapple mealybug (*Dysmicoccus brevipes*) by synthesis coupled with X-ray analysis

Kenji Mori*, Jun Tabata



(1*S*,2*S*)-(–)-**1**

K. Mori
Graphical abstract.



K. Mori
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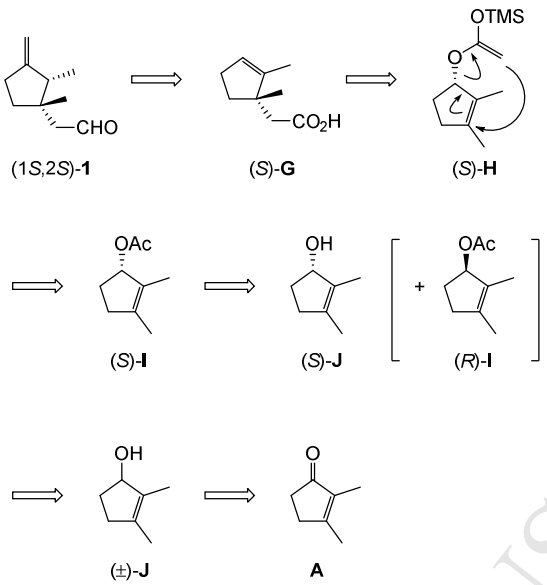

K. Mori
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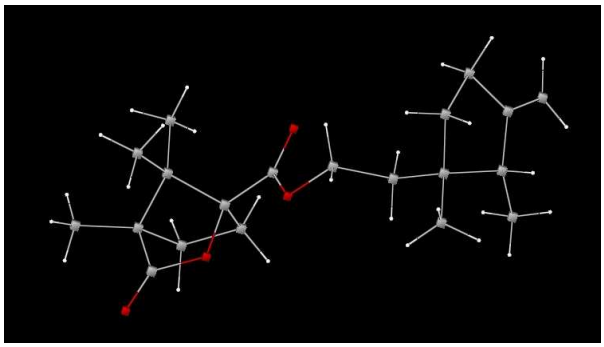

K. Mori
Fig. 3.

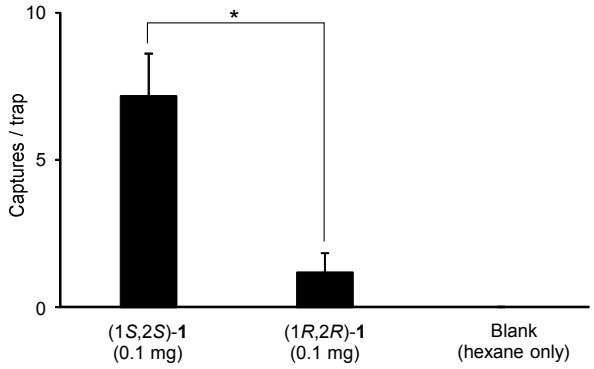

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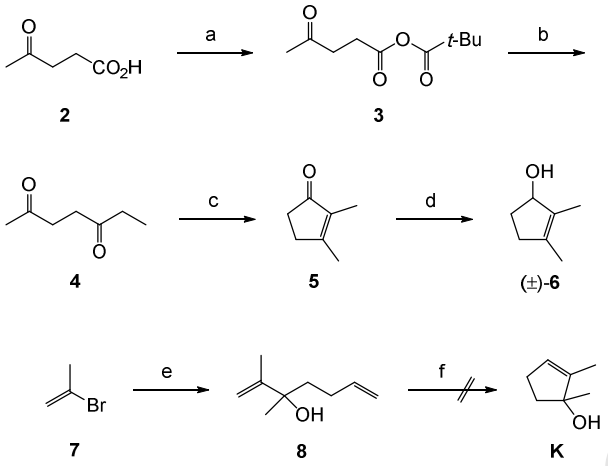
Fig. 4.



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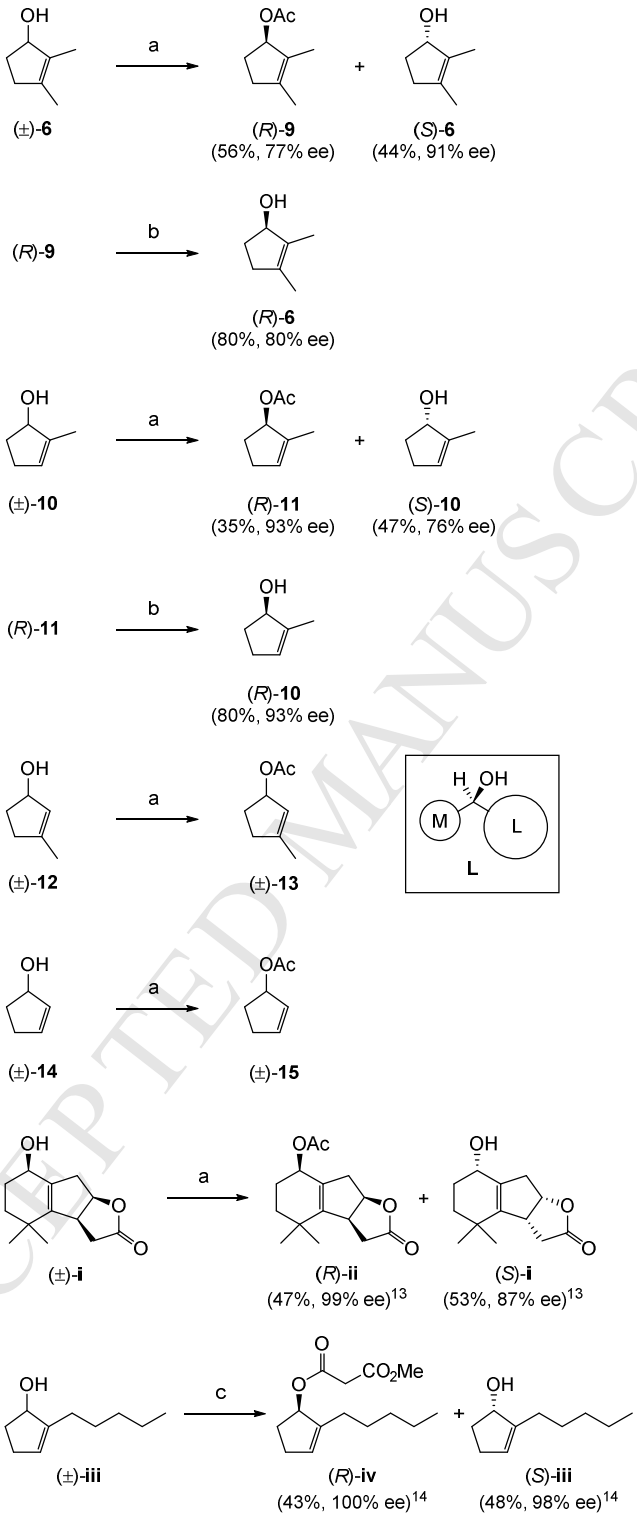

K. Mori
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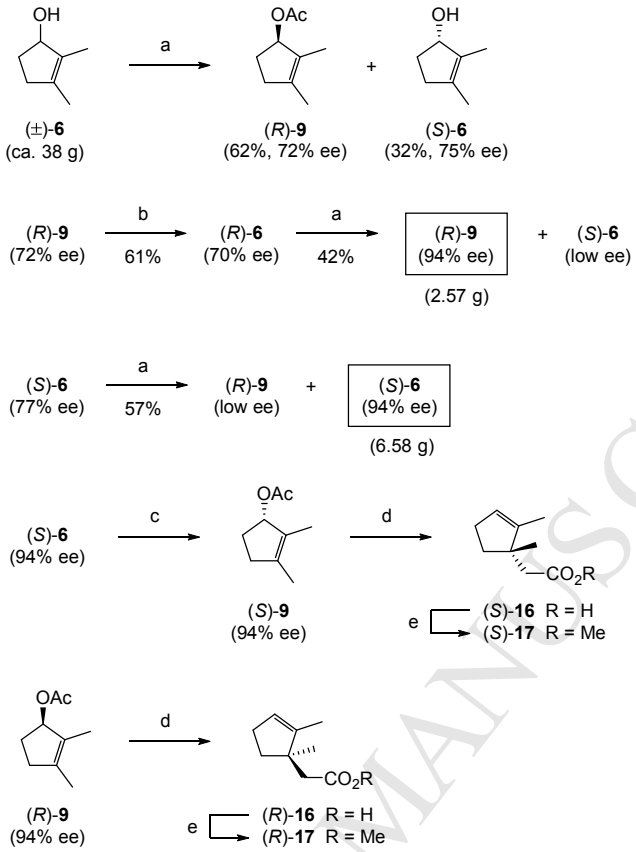

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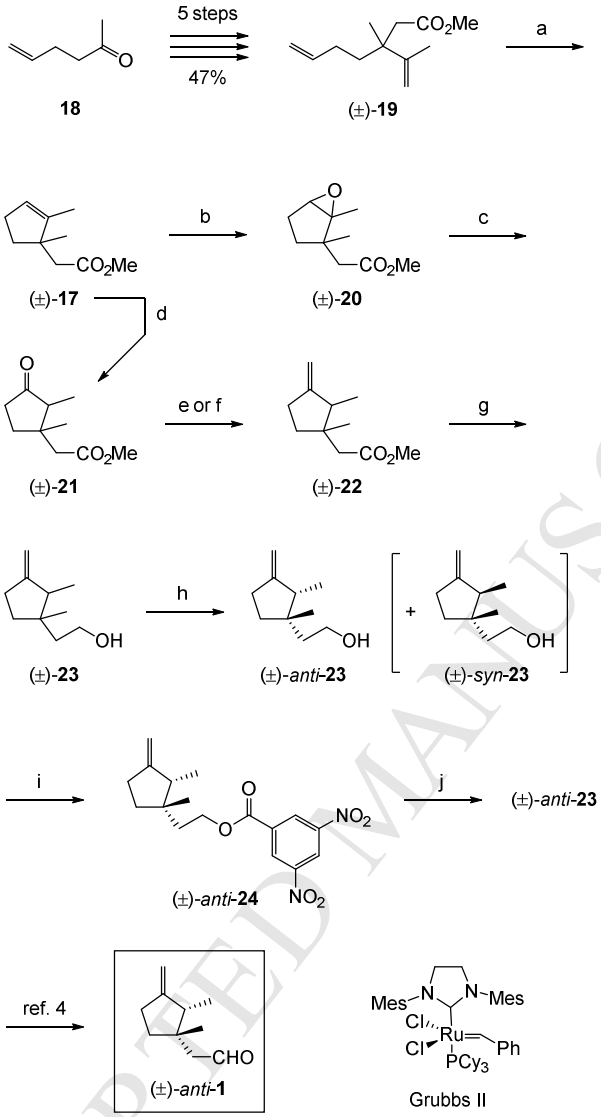

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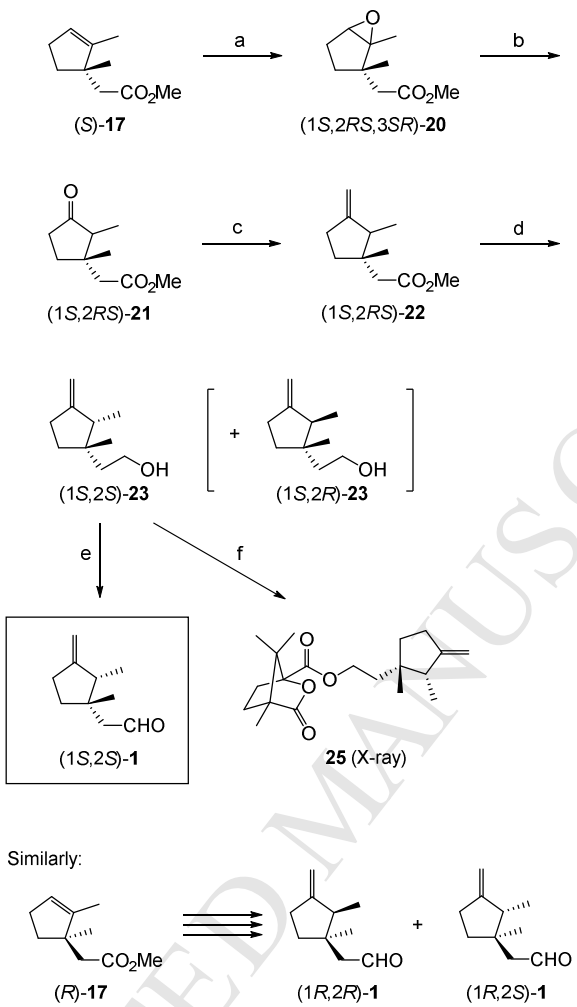

K. Mori
Scheme 5.