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Enantiomers of *Cis*- and *Trans*-3-(4-propyl-cyclopent-2-enyl) Propyl Acetate. A Study on the Bioactive Conformation and Chiral Recognition of a Moth Sex Pheromone Component

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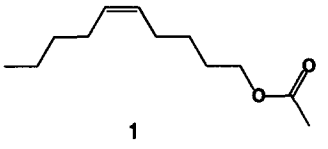
Abstract—The enantiomers of *cis*- and *trans*-3-(4-propyl-cyclopent-2-enyl) propyl acetate, which are conformationally constrained analogues of (*Z*)-5-decenyl acetate (**1**), a sex pheromone component of the turnip moth, *Agrotis segetum*, have been synthesized and tested using the electrophysiological single-sensillum technique. The analogues mimic a *cisoid* and *transoid* conformation of **1**, respectively. In addition, the enantiomers of each of the *cis*- and *trans*-isomers are conformationally constrained analogues of enantiomeric *cisoid* and *transoid* conformations of **1**. Thus, the compounds prepared and tested are well suited to investigate the nature of the bioactive conformation of the natural pheromone component **1** and the chiral sense of its interaction with the receptor. Electrophysiological single-sensillum recordings show that the activity of the most active *cis*-isomer, which has a (1*S*,4*R*)-configuration, is more than two orders of magnitude higher than that of the most active *trans*-isomer. Furthermore, the (1*S*,4*R*)-isomer is at least 100 times more active than its enantiomer. These results strongly support a previously proposed *cisoid* bioactive conformation of **1**. Furthermore, the (1*S*,4*R*)-configuration of most active stereoisomer identifies the chiral sense of the interaction between the natural pheromone component **1** and its receptor. © 1997 Elsevier Science Ltd.

Introduction

On the basis of an analysis of single-cell electrophysiological data and molecular mechanics calculated conformational energies for dienic analogues of (*Z*)-5-decenyl acetate (**1**), a sex pheromone component of the turnip moth, *Agrotis segetum*, a bioactive conformation for **1** has previously been proposed.[1] This conformation has the *cisoid*-arrangement of the two chains attached to the (*Z*)-double bond (Fig. 1). An alternative *transoid*-conformation (Fig. 1) was shown to be incompatible with the experimental data. The *cisoid*-conformation has, in a number of studies, been employed as a model for the bioactive conformation of **1** and used to rationalize experimental single-cell data.[1–11]



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To test the proposal about a *cisoid* bioactive conformation for **1**, two conformationally constrained analogues, the *cis*- and *trans*-cyclohexene analogues shown in Figure 2, were synthesized by Bengtsson[12] and tested in a single-cell bioassay. Only the *cis*-analogue displayed any activity, the *trans*-analogue was virtually inactive. Although these results support the proposed *cisoid* bioactive conformation of **1**, the *cis*-cyclohexene analogue unfortunately displayed only a low activity, ca. 1000 times lower than that of **1**. The low activity was suggested to be due to repulsive steric interactions between a particular hydrogen atom in the cyclohexene ring and the receptor as shown in Figure 3.

In the present work we have synthesized the enantiomers of *trans*- and *cis*-3-(4-propyl-cyclopent-2-enyl) propyl acetate, **2** and **3**, respectively (Fig. 4) and tested the compounds by single-cell electrophysiology using the antennal sensillum of male *A. segetum* containing the olfactory receptor cell specifically tuned to the natural pheromone component **1**. Compounds **2** and **3** are conformationally constrained analogues of **1** that

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Key words: Structure–activity, single-cell recordings, pheromone analogues, chiral recognition, *Agrotis segetum*.

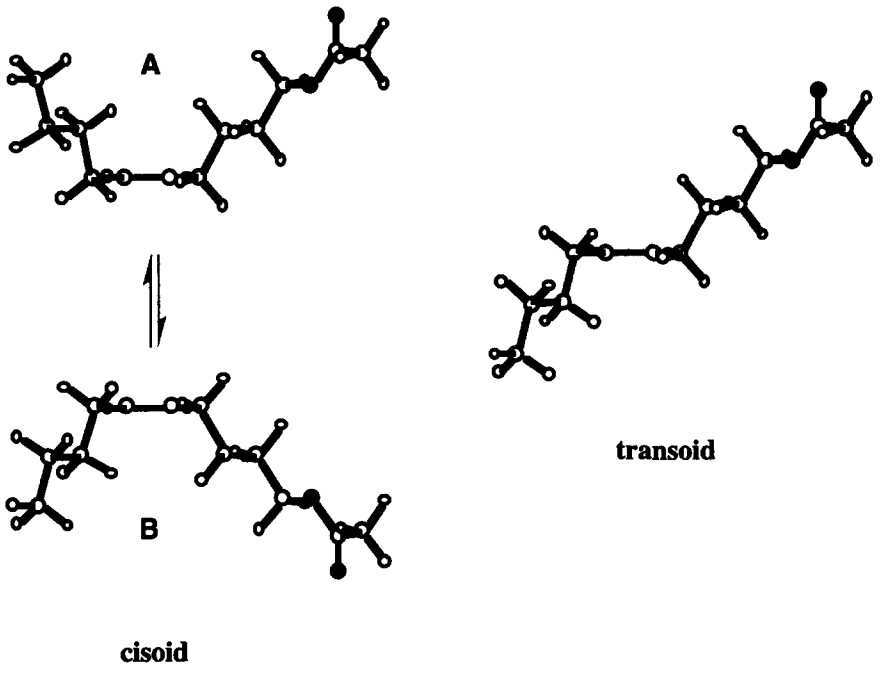

Figure 1. The *cisoid* and the *transoid* conformations of **1**. The two 'enantiomeric' conformations **A** and **B** for the *cisoid* conformation are shown.

display conformations similar to the *transoid* and *cisoid* conformations of **1** (Fig. 1), but which can not interconvert. Furthermore, these analogues do not have a hydrogen atom in a position that in the corresponding *cis*- and *trans*-cyclohexene analogues was suggested to cause a steric repulsive interaction with the receptor. Analogues **2** and **3** may be used to probe not only the *transoid* and *cisoid* alternatives to the bioactive conformation of **1**, but also give information on the enantioselectivity of the receptor and, thus, provide information on the chirality of the recognition of the achiral natural pheromone component **1** by its receptor.

Chiral recognition by pheromone receptors has been reported in a number of studies. In a study of methyl substituted analogues of **1**, Jönsson et al.[9] showed that a receptor tuned to **1** is able to differentiate between the enantiomers of 4- and 7-monomethyl substituted analogues. Furthermore, assuming a *cisoid* bioactive conformation of **1**, the single-cell activities of the stereoisomers of the 4,7-dimethyl substituted analogue indicate that the bioactive conformation of the achiral pheromone component **1** has a chiral sense corresponding to conformation A in Figure 1. However, the electrophysiological activities of the 4,7-dimethyl substituted analogues are very low precluding an unambiguous conclusion.

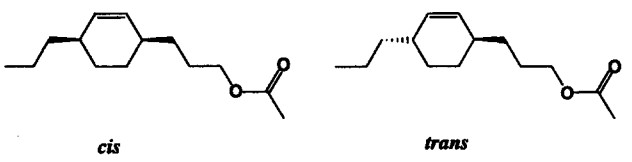

Figure 2. *Cis*- and *trans*-cyclohexene analogues of **1**.

Chapman et al.[13,14] have suggested that 9-(2-cyclopentene-1-yl)-nonyl acetate is able to mimic (*Z*)-11-tetradecenyl acetate, a pheromone component of *Ostrinia nubilalis* and *Argyrotaenia velutinana*. The *S*-enantiomer of the analogue was found to be more active than the *R*-form when tested in a sex stimulation assay for *O. nubilalis*. However, for *A. velutinana* both enantiomers were found to be less active than the racemic mixture. From these results it was suggested that the ligand–receptor interaction is stereoselective for both species, that *O. nubilalis* has one receptor which recognizes the *S*-form and that *A. velutinana* has two stereoselective receptors, one which recognizes the *S*- and one the *R*-enantiomer. Bestman et al.[15] have tested the same analogue by electroantennography (EAG) and found that both *O. nubilalis* and *A. velutinana* displayed higher activity for the *S*-form than for the *R*-form, by a factor of 30 and 10, respectively.

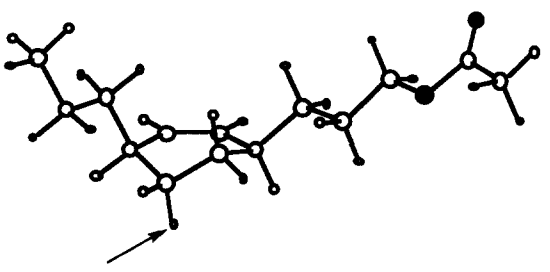

Figure 3. The *cis*-cyclohexene analogue with the hydrogen proposed to cause repulsive steric interactions with the receptor indicated.

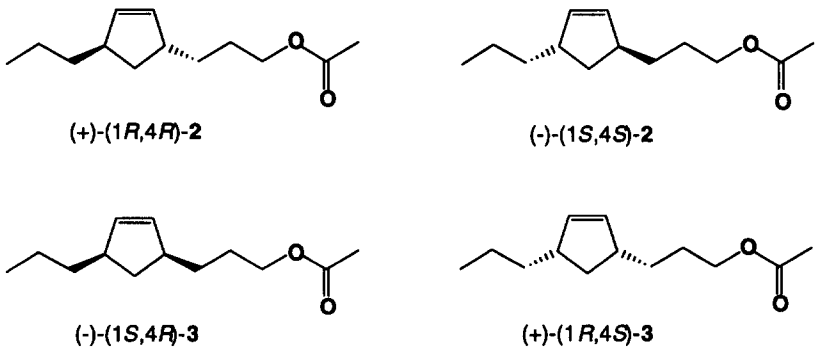

Figure 4. The *cis*-and *trans*-cyclopentene analogues of **1**.

Schwarz et al.[16] tested the analogue in a flight tunnel assay and found the enantiomers and the racemic mixture to be inactive. Using the EAG technique, Bestman et al.[15] have tested other chiral analogues of (*Z*)-11-tetradecenyl acetate. For instance, the *R*-form of the 13-methyl analogue was found to be more active than the *S*-form by a factor of about 100 for *O. nubilalis* as well as for *A. velutinana*. Schwarz[16] found these enantiomers to be inactive in flight tunnel experiments with *O. nubilalis*. However, the *R*-form was found to be be the most active enantiomer in a sex stimulation assay.

With the exception of the study by Jönsson et al.,[9] the results of the chiral recognition of pheromone component analogues, discussed above, were all obtained by EAG (or by behavioral bioassays). To be able to unambiguously interpret electrophysiological results in terms of interactions between a pheromone component and its receptor, single-cell recordings have to be employed. However, such recordings involving chiral analogues of an achiral natural pheromone component are very scarce. Bestman et al.[17] have tested 14-methyl analogues of bombykol and bombykal and found the *R*-form to be the most active enantiomer by a factor of about three, for the alcohol as well as for the aldehyde analogue, when tested on *Bombyx mori*. For *Manduca sexta*, the *S*-enantiomer of the aldehyde was found to be 100 times more active than the *R*-form. Chiral analogues of (6*E*,11*Z*)-hexadecadienyl acetate together with the corresponding aldehyde pheromone components of *Antheraea pernyi* and *Antheraea polyphemus*, including a methyl group in position 13, were also tested in a single-cell assay by Bestman et al.[17] The *S*-enantiomer of the acetate analogue was found to be more active than the *R*-form by a factor of three for both species. The *S*-enantiomer was the most active enantiomer of the aldehyde analogue by a factor of 10 and 50, respectively.

Results

Synthesis of the enantiomers of compounds 2 and 3

The preparation of compounds **2** and **3** is outlined in Figures 5 and 6. The chiral key intermediate, lactone **6**, was prepared in four steps from the *racemic* mixture of endo-bicyclo[2.2.1]hept-5-en-2-yl acetate (**4**) (Fig. 5). According to Eichberger et al.[18] and Oberhauser et al.,[19] (+)-(1*R*,2*R*,4*R*)-**5** may be obtained in about 90% ee and (1*S*,2*S*,4*S*)-endo-bicyclo[2.2.1]hept-5-en-2-yl acetate in about 96 % ee by enzymatic ester hydrolysis with a lipase from *Candida cylindracea*. The alcohol (+)-(1*R*,2*R*,4*R*)-**5** is commercially available from Chiroscience Ltd. We obtained (−)-(1*S*,2*S*,4*S*)-**5** in 95% ee and used the commercially available (+)-(1*R*,2*R*,4*R*)-**5**, which was determined to have 98% ee. The enantiomeric excess was determined by GLC on a chiral β-cyclodextrin column employing the trifluoroacetate derivative of the alcohol (see Experimental section).

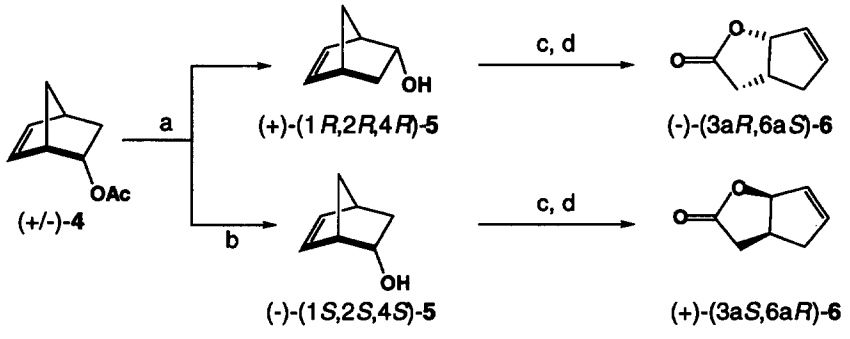

Figure 5. The synthesis of the enantiomers of lactone **6**. (a) Lipase from *C. cylindracea*. (b) $LiAlH_4$ reduction. (c) Swern oxidation. (d) Acidic Baeyer–Villiger oxidation.

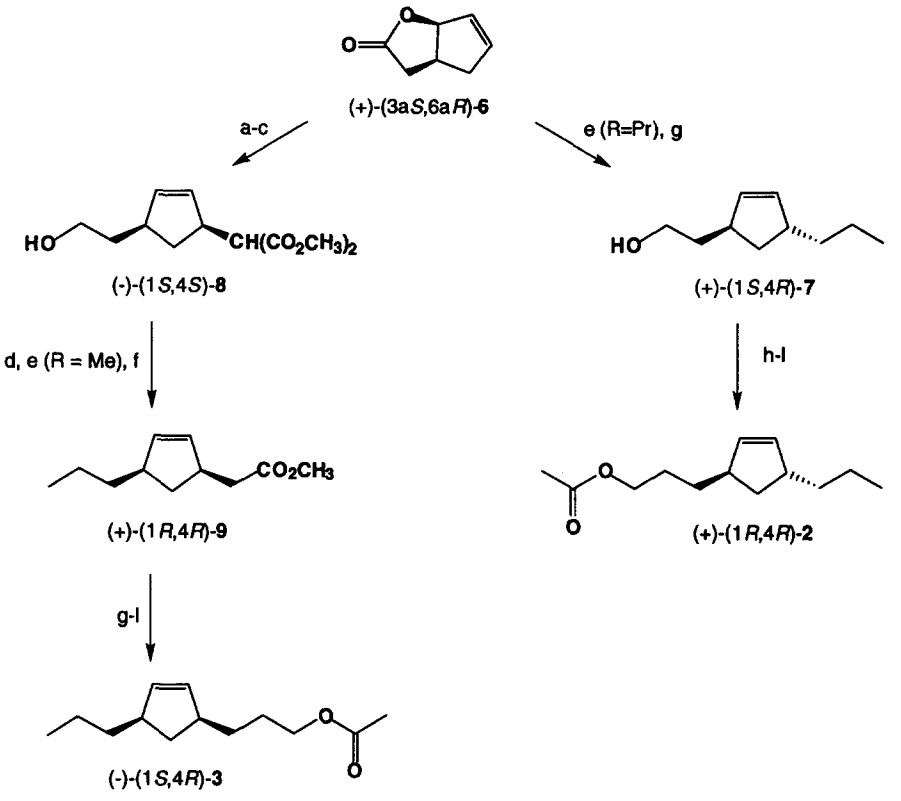

Figure 6. The synthesis of the *cis*-(−)-(1*S*,4*R*)-**3** and *trans*-(+)-(1*R*,4*R*)-**2**-cyclopentene analogues from (+)-(3a*S*,6a*R*)-**6**. (a) $Pd(PPh_3)_4$,NaCH(-$CO_2CH_3)_2$.(b) $(COCl)_2$. (c)$LiAl(tBuO)_3H$. (d) TsCl. (e) RMgl, CuBr-MeS_2. (f) DMSO, LiCl. (g) $LiAlH_4$. (h) TsCl. (i) NaCN. (j)NaOH, 60% EtOH. (k) $LiAlH_4$. (l) $(CH_3CO)_2O$, DMAP, Pyridine.

The alcohol **5** was oxidized under Swern conditions[20] to bicyclo[2.2.1]hept-5-en-2-one (Fig. 5). This ketone was further oxidized under acidic Bayer–Villiger conditions[21,22] and the lactone **6** was obtained in about 70% yield from the alcohol **5**. The absolute configuration at the stereogenic carbon at position 4 in bicyclo[2.2.1]-hept-5-en-2-ol and bicyclo[2.2.1]hept-5-en-2-one is untouched throughout the reactions and, therefore, controls the configuration of the *cis*-lactone **6**.

Each of the enantiomers of **6** were then subjected to palladium-catalysed alkylation with sodium malonate[23] or alkylation with a suitable magnesium cuprate reagent[24] as shown in Figure 6 for (+)-(3a*S*,6a*R*)-**6**. In this manner we obtained a *cis*- and a *trans*-product with known absolute configurations, (−)-(1*S*,4*S*)-**8** and (+)-(1*S*,4*R*)-**7**, respectively.

The stereochemistry is directed by the choice of the starting material, (+)-(3a*S*,6a*R*)-**6** or (−)-(3a*R*,6a*S*)-**6**, and the reaction sequence used. The *cis*-product is generated as a single isomer by the previously described regio- and stereo-controlled palladium-catalysed alkylation reaction.[23] The *trans*-product was also obtained from a previously described regio- and stereo-controlled reaction with stoichiometric amounts of CuBr-Me_2S and a Grignard reagent.[25] In each of these reactions only the desired isomer was obtained according to GLC and NMR. The chain could then be elaborated in a straightforward manner to give the analogues of (*Z*)-5-decenyl acetate. From (+)-(3a*S*,6a*R*)-**6** the *cis*-enantiomer (−)-(1*S*,4*R*)-**3** and the *trans*-enantiomer (+)-(1*R*,4*R*)-**2** were obtained. The other lactone enantiomer ((−)-(3a*R*,6a*S*)-**6**) provided the *cis*-enantiomer (+)-(1*R*,4*S*)-**3** and the *trans*-enantiomer (−)-(1*S*,4*S*)-**2**. Thus, from the *racemic* endo-bicyclo[2.2.1]hept-5-en-2-yl acetate all four stereoisomers of the cyclopentene analogues **2** and **3** could be obtained with control of the absolute configurations.

Electrophysiological single-cell recordings

The results of the electrophysiological single-cell recordings, including corrections for differences in volatility (see Experimental section), for the stereoisomers of **2** and **3** are shown in Figure 7 which also includes the corresponding data for the racemates. The results display significant differences in the activities of the *cis*- and *trans*-isomers **2** and **3**, with the *cis*-isomers being more active than the *trans*-isomers. For the *cis*- as well as the *trans*-isomers, the enantiomer displaying a 1*S* configuration is clearly the most active. The most active *cis*-isomer ((1*S*,4*R*)-**3**) displays more than two orders of magnitude higher activity than the most active *trans*-isomer ((1*S*,4*S*)-**2**). Furthermore, the *cis*-isomer (1*S*,4*R*)-**3** is ca. 100 times more active than its enantiomer ((1R,4*S*)-**3**). As part of the activity of

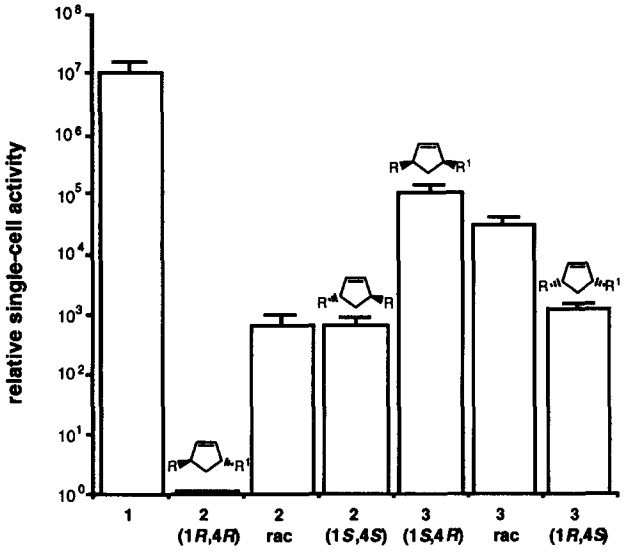

Figure 7. Relative electrophysiological single-cell activities (+SEM) for compounds **1–3**. The data are corrected for differences in volatility.

(1*R*,4*S*)-**3** may be due to the presence of small amounts of the more active enantiomer (1*S*,4*R*)-**3**, this factor is a lower limit of the enantioselectivity displayed by the receptor.

The most active of the four stereoisomers, (1*S*,4*R*)-**3**, is found to be 95 times less active than **1**, whereas the other stereoisomers are more than 8000 times less active than **1**.

Discussion

For the interpretation of the electrophysiological single-cell results, the chemical and enantiomeric purity of the compounds is of high importance. The purity of the compounds was determined by capillary GLC and NMR. No trace of the *cis*-isomer could be found in the *trans* compound and no *trans*-isomer could be detected in the *cis* compound. The enantiomeric excess (ee) of the stereoisomers was estimated from the enantiomeric purities of (1*R*,2*R*,4*R*)-**5** and (1*S*,2*S*,4*S*)-**5**, considering that the reactions chosen for the alkylations are regio- and stereocontrolled. (−)-(1*S*,4*R*)-**3** was then found to have 95% ee, its enantiomer (+)-(1*R*,4*S*)-**3** had 98% ee, the *trans*-isomers (−)-(1*R*,4*R*)-**2** had 95% ee, and (+)-(1*S*,4*S*)-**2** had 98% ee.

The results of the present study of conformationally constrained analogues of **1** strongly support a *cisoid* bioactive conformation of **1** (Fig. 1) as was previously proposed by Bengtsson et al.[1] The *cis*-cyclopentene analogue (1*S*,4*R*)-**3** displays a high activity, whereas both enantiomers of the *trans*-analogue are more than 100 times less active than (1*S*,4*R*)-**3** (Fig. 7). (1*S*,4*R*)-**3** is a factor of about 95 times less active than the natural pheromone component **1** (Fig. 7). As shown in Figure 8, *cis*-1,4-disubstituted cyclopentenes may adopt two types of conformations, diequatorial and diaxial. According to molecular mechanics calculations using the MM3(92) program developed by Allinger and co-workers,[26–28] the diequatorial form is the most stable one. The calculated energy difference between the two conformations of **3** shown in Figure 8 is 0.9 kcal/mol. However, as is clearly seen in Figure 8, only the diaxial conformation is compatible with the proposed bioactive conformation of **1**. In order to optimally mimic the structure of the proposed bioactive conformation of **1**, with respect to the relative positions in space of the terminal methyl group, the double bond and the acetate group, additional conformational changes of the alkyl chains in diaxial conformer are required. In total the calculated energy cost for the *cis* compound **3** to adopt a bioactive conformation corresponding to that of **1** in Figure 8, is

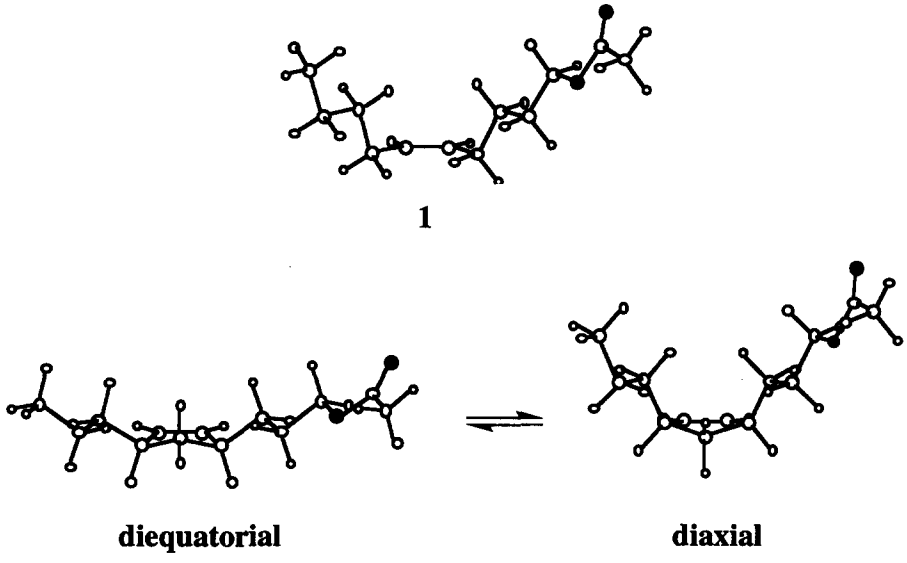

Figure 8. The proposed bioactive conformation of **1** and the diequatorial and diaxial conformations of **3**.

1.7 kcal/mol. This is 1.1 kcal/mol higher than the corresponding energy penalty calculated for **1**.[3] However, the calculated energy penalties correspond to conformational enthalpy differences. The cyclopentene derivative (1*S*,4*R*)-**3** (and its isomers) is less flexible than **1** and consequently less entropy is lost in the binding of the cyclopentenes to the receptor. Searle and Williams[29] have estimated the entropic cost (TΔS) of restricting a rotor in a hydrocarbon chain to be 0.4–0.9 kcal/mol. Applying this estimate to (1*S*,4*R*)-**3** and **1** it follows that the conformational energy penalties in terms of free energies may be similar for (1*S*,4*R*)-**3** and **1**. Thus, the lower activity of (1*S*,4*R*)-**3** compared to **1** is most probably not due to a larger conformational free energy penalty for the bioactive conformation of (1*S*,4*R*)-**3**.

A reason for the difference in activity between (1*S*,4*R*)-**3** and **1** may be found at the level of the pheromone binding proteins (PBP). It has been demonstrated that the PBP may have different affinities for the natural pheromone component and for analogues.[30,31] Thus, observed differences in electrophysiological activity may be due to differences in affinities to the PBP as well as to the receptor. The possibility of a recognition of the pheromone-PBP complex by the receptor has also been discussed.[30,31] A more detailed interpretation of electrophysiological activities of pheromone components awaits further progress in the knowledge of ligand binding to PBPs.

The substantial difference in the activity of the enantiomers of the *cis*-analogue **3** clearly shows that the receptor is able to differentiate between the enantiomeric *cisoid* conformations A and B of **1**, shown in Figure 1. Considering the significantly higher activity of (1*S*,4*R*)-**3** compared to that of its enantiomer, we conclude that the natural pheromone component **1** interacts with its receptor, with the chiral sense of its alkyl-chains corresponding to that of conformation A in Figure 1. This is in accordance with the (less unambiguous) conclusion drawn by Jönsson et al.[9] on the basis of structure–activity studies on chiral dimethyl substituted analogues of **1**.

The properties of the compounds studied in the present work suggest that these type of compounds may be useful tools in the elucidation of the bioactive conformation and chiral recognition of pheromone components of monoene acetate type in other moth species. The synthetic schemes developed for compounds **2** and **3** (Figs 5 and 6) can easily be modified to allow for the preparation of conformationally constrained chiral analogues of pheromone components of monoene acetate type with other chain lengths and/or double bond positions.

Conclusions

The electrophysiological single-cell results obtained in the present study show that the activity of the most active *cis*-isomer, (1*S*,4*R*)-**3**, is more than two orders of magnitude higher than that of the most active *trans*-isomer. Thus, the previously proposed *cisoid* bioactive conformation of the natural pheromone component **1** is strongly supported. Furthermore, as the (1*S*,4*R*)-isomer is at least 100 times more active than its enantiomer, the (1*S*,4*R*)-configuration defines the chiral sense of the interaction between the natural pheromone component **1** and its receptor. This corresponds to the enantiomeric conformation displayed by conformation A in Figure 1.

Experimental

Synthesis

All air and water sensitive reactions were performed under a nitrogen or argon atmosphere in oven dried glassware. Anhydrous diethyl ether (ether) and tetrahydrofuran (THF) were distilled from dark blue solutions of the sodium benzophenone radical anion. The dimethyl sulfide complex of cuprous bromide was prepared according to House et al.[32] Pyridine was stored over molecular sieves 4 Å and KOH pellets prior to distillation over CaH_2. Dimethyl sulfoxide (DMSO) and dichloromethane (DCM) were dried with CaH_2 and molecular sieves 4 Å, respectively, prior to distillation. *p*-Toluenesulfonyl chloride (TsCl) was purified by dissolution in a minimum amount of chloroform, was filtered and diluted with pentane, five times the volume of chloroform, and finally treated with charcoal, filtered, and evaporated. Flash chromatography was performed on TLC silica gel 60H with the eluting solvents indicated in the text. Thin-layer chromatography (TLC), silica gel 60 F254, was used to monitor the reactions. Anisaldehyde-mixture (ethanol, 550 mL; sulfuric acid, 20.7 mL; acetic acid, 6.3 mL; and 4-methoxy benzaldehyde, 15.3 mL) or UV-light (254 nm) was used for detection. Analytical GLC was performed with a Varian 3400 capillary GLC fitted with a DB-Wax (J&W Scientific) 30 m column. Preparative GLC was performed on a 6 m × 4 mm OV-351 column. The purity of the isolated final products were ≥99%. No sample contained any detectable amount of the natural pheromone component. Specific rotation was determined on a Perkin–Elmer polarimeter 141. ^1H and ^{13}C NMR spectra were recorded on a Varian XL-300 or a Bruker DRX 400 spectrometer. High-resolution mass spectra were recorded on a Jeol JMS-SX 102 spectrometer. The enantiomeric excess was determined from the trifluoroacetic ester derivative of **5**. A GLC sample of alcohol **5** (1–2 mg) in DCM (0.5–1 mL) was treated with trifluoroacetic acid anhydride (0.3–0.5 mL), after 0.5 h the sample was evaporated, DCM was added and the mixture was injected on a Perkin–Elmer Autosystem GLC fitted with a β-DEX 120 (Supelco), permethylated β-cyclodextrin fused silica capillary column.

(±)Acetic acid endo-bicyclo[2.2.1]hept-5-en-2-yl ester (4). To achieve the title compound, racemic endo/exo bicyclo[2.2.1]hept-5-en-2-ol was first subjected to a Swern oxidation.[20] Oxalyl chloride (24

mL, 0.28 mol) in DCM (450 mL) was cooled to −50 °C and DMSO (39 mL, 0.55 mol) in DCM (150 mL) was added dropwise. The reaction mixture was stirred for 15 min. The alcohol (20 g, 0.18 mol) dissolved in DCM (160 mL) was added. Stirring was continued and the temperature was allowed to reach −10 °C. After cooling to −30 °C, triethylamine (128 mL, 0.92 mol) was added. The mixture was permitted to reach room temperature and water was added. The aqueous layer was separated and extracted with DCM. The combined organic layers were washed with 2.5 M HCl, water, saturated Na_2CO_3 solution, water and brine, dried ($MgSO_4$) and then evaporated. The crude ketone was reduced according to Oberhauser et al.[19] to obtain the endo-bicyclo[2.2.1]hept-5-en-2-ol. To a cooled (−10 °C) solution of bicyclo[2.2.1]hept-5-en-2-one in methanol (140 mL) $NaBH_4$ (1.43 g, 0.038 mol) was added in small portions keeping the temperature at −10 °C. The reaction was monitored by TLC and when all starting material was consumed, the reaction mixture was quenched with 5 M HCl, saturated with NaCl and extracted with DCM. The combined organic layers were washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated to give the crude endo-alcohol. A mixture of the crude endo-alcohol, DCM (150 mL), 4-dimethylamino pyridine (DMAP) (1.6 g, 0.013 mol) and pyridine (33 mL, 0.41 mol) was cooled on an ice bath and acetic anhydride (32 mL, 0.34 mol) was added. The mixture was allowed to reach room temperature and stirred over night. When no alcohol could be detected on TLC, the reaction was quenched on ice–water and extracted with ether. The combined organic extracts were washed with 2.5 M HCl, water, saturated Na_2CO_3 solution and brine, dried over Na_2SO_4 and evaporated. The crude material was purified by flash chromatography (petroleum ether:ethyl acetate (9:1)) and the title compound (13.8 g, 0.091 mol) was obtained in 50% yield from *endo/exo*-bicyclo[2.2.1]-hept-5-en-2-ol (three steps). δ_H (400 MHz) 0.92 (dt, 1H, J = 12.6, 3.3 Hz, CH_2), 1.31 (broad d, 1H, J = 8.9 Hz, CH_2), 1.46 (ddt, 1H, J = 8.9, 3.8, 2.0 Hz, CH_2), 1.97 (s, 3H, CH_3CO), 2.14 (ddd, 1H, J = 12.8, 8.1, 4.1 Hz, CH_2), 2.81–2.85 (m, 1H, C*H*–C=), 3.11–3.15 (m, 1H, C*H*–C=), 5.27 (dt, 1H, J = 8.3, 3.3 Hz, C*H*(OCO)), 5.96 (dd, 1H, J = 5.7, 2.9 Hz, C*H*=), 6.34 (dd, 1H, J = 5.7; 3.1 Hz, C*H*=).

(1*S*,2*S*,4*S*)acetic acid endo-bicyclo[2.2.1]hept-5-en-2-yl ester ((1*S*,2*S*,4*S*)-4). The resolution was performed according to Eichberger et al.[18] and Oberhauser et al.[19] The pH in a buffer of $NaH_2PO_4 \cdot H_2O$ (1.48 g) and water (500 mL) was adjusted to 7.2 by addition of 1 M NaOH solution. Lipase from *C. cylindracea* (4.4 g) was added and the mixture was equilibrated for 15 min while the pH was kept at 7.2. The enzyme/buffer mixture was poured into a round bottom flask with the *racemic* ester **4** (9.8 g, 0.064 mol). The reaction was vigorously stirred over night. The pH was then adjusted to 7.2 with 40 mL of 1 M NaOH, indicating a conversion of about 62%. The hydrolysis was stopped by adding DCM. The mixture was filtered with Hyflo supergel and separated. The aqueous layer was extracted with DCM. The organic layers were dried over $MgSO_4$ and evaporated. The crude material was purified by flash chromatography (petroleum ether:ethyl acetate (9:1)) and the title compound (2.95 g, 0.02 mol) was afforded in 60% yield.

(−)-(1*S*,2*S*,4*S*)-*endo*-bicyclo[2.2.1]hept-5-en-2-ol ((1*S*,2*S*,4*S*)-5). $LiAlH_4$ (2.9 g, 0.076 mol) in ether (150 mL) was cooled to −10 °C and the (1*S*,2*S*,4*S*)-acetic acid *endo*-bicyclo[2.2.1]hept-5-en-2-yl ester (3.6 g, 0.024 mol) in ether (100 mL) was added dropwise. Stirring was continued for 2 h at −5 °C and 1 h at 0 °C, then TLC indicated a complete reduction and the mixture was cooled to −10 °C, quenched by slowly adding water (6 mL), 15% aqueous NaOH (6 mL) and water (17 mL) again, and kept stirring for about 3 h. The white precipitate was filtered off with celite and thoroughly rinsed with ether and ethyl acetate. The filtrate was dried ($MgSO_4$) and evaporated to give the alcohol (2.26 g, 0.020 mol, 88% yield). The enantiomeric excess was determined to be 95%. δ_H (300 MHz) 0.75 (dt, 1H, J = 12.0, 3.0 Hz, CH_2), 1.28 (broad d, 1H, J = 8.2 Hz, CH_2), 1.43–1.50 (m, 1H, CH_2), 2.09 (ddd, 1H, J = 12.0, 8.0, 3.7 Hz, CH_2), 2.77–2.84 (broad s, 1H, C*H*-C=), 2.95–3.02 (broad s, 1H, C*H*-C=), 4.42–4.52 (m, 1H, C*H*OH), 6.05 (dd, 1H, J = 5.9, 2.9 Hz, C*H*=) 6.45 (dd, 1H, J = 5.9, 2.9 Hz C*H*=). $[\alpha]^{25}_D$ −138° (*c* 2; $CHCl_3$).

(+)-(1*R*,2*R*,4*R*)-*endo*-bicyclo[2.2.1]hept-5-en-2-ol ((1*R*,2*R*,4*R*)-5). This compound was purchased from Chiroscience Ltd. The enantiomeric excess was found to be 98%. $[\alpha]^{25}_D$ +155° (*c* 2; $CHCl_3$).

(1*S*,4*S*)-*Endo*-bicyclo[2.2.1]hept-5-en-2-one. The alcohol (−)-(1*S*,2*S*,4*S*)-**5** (2.26 g, 20.0 mmol) was oxidized as described above with oxalyl chloride (2.9 mL) and DMSO (4.7 mL) in DCM to give the ketone. δ_H (400 MHz) 1.86 (dd, 1H, J = 16.5, 4.3 Hz, CH_2), 1.96 (dd, 1H, J = 16.5, 3.3 Hz, CH_2), 1.97–2.10 (m, 1H, CH_2), 2.18–2.23 (m, 1H, CH_2), 3.01–3.03 (m, 1H, C*H*-C=), 3.18–3.21 (m, 1H, C*H*-C=), 6.10–6.13 (m, 1H, C*H*=), 6.57 (dd, 1H, J = 5.6, 2.8 Hz, C*H*=). δ_C (100 MHz) 37.7, 40.5, 51.3, 56.3, 131.0, 143.5, 216.0. High-resolution MS (CI, CH_4) (MH+), found 109.0654; calcd. 109.0653.

(+)-(3a*S*,6a*R*)-3,3a,4,6a-tetrahydro-cyclopenta[*b*]-furan-2-one ((3a*S*,6a*R*)-6). The lactone was obtained by a Baeyer–Villiger oxidation under acidic conditions.[21,22] The crude (1*S*,4*S*)-*endo*-bicyclo[2.2.1]-hept-5-ene-2-one was dissolved in ether (35 mL) and H_2SO_4 (0.3 mL) was added. With cooling on an ice bath, 30 % H_2O_2 (3.2 mL) was added dropwise. The reaction mixture was allowed to reach room temperature and when the oxidation was completed, as judged by TLC, the cooling bath was put back and the reaction mixture was treated with sodium sulfite until no peroxides could be indicated by the iodine test. The layers were separated and the aqueous layer was extracted with ether. The combined organic

extracts were dried ($MgSO_4$) and evaporated. The crude material was purified by flash chromatography (ether) and (3a*S*,6a*R*)-**6** was afforded (1.46 g, 11.7 mmol) in 60% yield from the alcohol, (−)-(1*S*,2*S*,4*S*)-**5** (two steps). δ_H (400 MHz) 2.28–2.35 (m, 1H, C*H*$_2$), 2.32 (dd, 1H, J = 18.4, 5.8 Hz, C*H*$_2$), 2.77 (ddtd, 1H, J = 17.5, 8.2, 2.3, 1.2 Hz, C*H*$_2$), 2.84 (dd, 1H, J = 18.4, 10.5 Hz, C*H*$_2$), 3.10–3.19 (m, 1H, C*H*), 5.52 (broad d, 1H, J = 7.6 Hz, C*H*OCO), 5.87 (dq, 1H, J = 5.7, 2.2 Hz, C*H*=), 6.08 (dtd, 1H, J = 5.7, 2.4, 1.0 Hz, C*H*=). δ_C (100 MHz) 35.5, 36.5, 40.0, 90.0, 129.4, 137.6, 177.7. High-resolution MS (CI-CH_4) (MH+) found 125.0603; calcd. 125.0603. $[\alpha]^{25}_D$ +130° (*c* 2; $CHCl_3$).

(−)-(3a*R*,6a*S*)-3,3a,4,6a-tetrahydro-cyclopenta[*b*]-furan-2-one ((3a*R*,6a*S*)-6). This compound was obtained from the alcohol (−)-(1*R*,2*R*,4*R*)-**5** as described above for its enantiomer. $[\alpha]^{25}_D$ −133° (*c* 2; $CHCl_3$).

(+)-2-(*Trans*-4*R*-propyl-cyclopent-2-en-1*S*-yl) ethanol ((1*S*,4*R*)-7). The lactone was reacted with an organocopper-magnesium reagent according to Curran et al.[24] but with reversed order of addition, i.e. the organocopper reagent was first generated and then added to the lactone to achieve the *trans*-cyclopentene compound. To a cooled (−20 °C) suspension of CuBr–Me_2S (1.32 g, 6.4 mmol), dimethyl sulfide (8 mL), THF (16 mL), and 0.8 M propylgrignard reagent (8.3 mL, 6.6 mmol) was added. The reaction mixture was stirred for 15 min and then transferred into a cooled (−50 °C) solution of (+)-(3a*S*,6a*R*)-**6** (0.4 g, 3.2 mmol) and THF (8 mL). The reaction was monitored by TLC and the starting material was consumed after 0.5 h. The reaction was quenched with 3 M HCl and extracted with ether. The organic extracts were washed with brine and water, dried ($MgSO_4$) and concentrated. The crude acid was reduced with $LiAlH_4$ (0.34 g, 9.0 mmol) as described above. The received material was purified with flash chromatography (petroleum ether:ethyl acetate (3:2)) to give (1*S*,4*R*)-**7** (0.35 g, 2.8 mmol) in 70% yield from (+)-(3a*S*,6a*R*)-**6**. δ_H (400 MHz) 0.91 (t, 3H, J = 7 Hz, C*H*$_3$), 1.21–1.38 (m, 5H, C*H*$_2$, O*H*), 1.53–1.71 (m, 4H, C*H*$_2$), 2.65–2.74 (m, 1H, C*H*-C=), 2.76–2.85 (m, 1H, C*H*-C=), 3.65–3.75 (m, 2H, C*H*$_2$OH) 5.68 (dt, 1H, J = 5.7, 1.9 Hz, C*H*=), 5.71 (dt, 1H, J = 5.7, 1.9 Hz, C*H*=). δ_C (100 MHz) 14.7, 21.5, 37.0, 38.7, 39.3, 41.7, 44.9, 62.3, 134.3, 135.8. High-resolution MS, (CI-CH_4) MH+; found 155.1436; calcd. 155.1436. $[\alpha]^{25}_D$ +195° (*c* 2; $CHCl_3$).

(−)-2-(*Trans*-4*S*-propyl-cyclopent-2-en-1*R*-yl) ethanol ((1*R*,4*S*)-7). This compound was obtained as described above for its enantiomer. $[\alpha]^{25}_D$ −180° (*c* 2; $CHCl_3$).

Toluene-4-sulfonic acid 2-(*trans*-4*R*-propyl-cyclopent-2-en-1*S*-yl) ethyl ester. Alcohol **7** (0.34 g, 2.2 mmol), pyridine (5 mL), and DMAP (40 mg, 0.3 mmol) in DCM (10 mL) was cooled on an ice bath and treated with TsCl (0.84 g, 4.4 mmol). The mixture was allowed to reach room temperature and stirred over night. After quenching with ice–water the mixture was extracted with ether. The organic extracts were washed with 2.5 M HCl, aqueous $CuSO_4$ solution, $NaHCO_3$ solution, and dried ($MgSO_4$). Then the solvents were removed and the crude product was analysed by NMR. δ_H (300 MHz) 0.87 (t, 3H, C*H*$_3$), 1.15–1.34 (m, 4H, C*H*$_2$), 1.50–1.78 (m, 4H, C*H*$_2$), 2.45 (s, 3H, C*H*$_3$Ar), 2.56–2.78 (m, 2H, C*H*-C=), 4.05 (dt (AB part of an ABXY), 2H, J = 6.6 Hz, C*H*$_2$O), 5.51 (dt, 1H, J = 5.7, 2.0 Hz, C*H*=), 5.66 (dt, 1H, J = 5.6, 2.1 Hz, C*H*=), 7.33–7.37 (broad d, 2H, J = 8.3 Hz, Ar*H*), 7.77–7.82 (broad d, 2H, J = 8.3 Hz, Ar*H*).

3-(*Trans*-4*R*-propyl-cyclopent-2-en-1*R*-yl) propionitrile. The crude product from above in DMSO (12 mL) was treated with NaCN (1 g) and heated to 60 °C over night. The reaction mixture was poured into ice–water and extracted with ether, and the organic layer was washed with water and brine, dried ($MgSO_4$), then concentrated and analysed by NMR. δ_H (300 MHz) 0.90 (t, 3H, CH_3), 1.18–1.36 (m, 4H, C*H*$_2$), 1.58–1.80 (m, 4H, C*H*$_2$), 2.32 (t, 2H, C*H*$_2$CN), 2.62–2.74 (m, 2H, C*H*-C=), 2.76–2.88 (m, 1H, C*H*-C=), 5.60 (dt, 1H, J = 5.7, 2.1 Hz, C*H*=), 5.74 (dt, 1H, J = 5.7, 2.0 Hz, C*H*=).

3-(*Trans*-4*R*-propyl-cyclopent-2-en-1R-yl) propionic acid. The crude nitrile (0.30 g) was refluxed with NaOH (2 g) in 60% ethanol for 3 h. The mixture was treated with ice, acidified with 5 M HCl, extracted with ether, washed with brine and water, and dried with ($MgSO_4$). The acid (0.27 g) was analysed by NMR. δ_H (300 MHz) 0.90 (t, 3H, C*H*$_3$), 1.18–1.38 (m, 4H, C*H*$_2$), 1.56–1.76 (m, 4H, C*H*$_2$), 2.35 (t, 2H, C*H*$_2$CO), 2.60–2.75 (m, 2H, C*H*-C=), 5.60 (dt, 1H, J = 5.8, 1.7 Hz, *H*C=), 5.74 (dt, 1H, J = 5.6, 1.9 Hz, C*H*=).

3-(*Trans*-4*R*-propyl-cyclopent-2-en-1*R*-yl) propan-1-ol. The crude acid was reduced to the alcohol by $LiAlH_4$ (0.17 g) in the same manner as described above for compound **4**. The alcohol was analysed by NMR. δ_H (300 MHz) 0.90 (t, 3H, C*H*$_3$), 1.20–1.66 (m, 10 H, C*H*$_2$), 2.62–2.72 (m, 2H, C*H*-C=), 3.65 (t, 2H, C*H*$_2$OH), 5.64–5.72 (m, 2H, *H*C=).

(+)-3-(*Trans*-4*R*-propyl-cyclopent-2-en-1*R*-yl) propyl acetate ((1*R*,4*R*)-2). The crude alcohol (0.20 g) was treated with pyridine (6 mL) and DMAP (10 mg) and cooled on an ice bath. Acetic anhydride (6 mL) was added. When no alcohol could be detected by TLC the mixture was poured into ice, extracted with ether, washed with 5 M HCl, $CuSO_4$ aqueous solution, water, and dried ($MgSO_4$). The crude product was purified by flash chromatography (petroleum ether:ethyl acetate (9:1)). 0.182 g (0.87 mmol) of the final product was isolated in a total yield of 40% from (+)-(1*S*,4*R*)-**7** or 27% from the lactone (+)-(3a*S*,6a*R*)-**6**. δ_H (400 MHz) 0.90 (t, 3H, J = 7.1 Hz, C*H*$_3$), 1.21–1.47 (m, 6H, C*H*$_2$), 1.61–1.70 (m, 4H, C*H*$_2$), 2.06 (s, 3H, C*H*$_3$), 2.64–2.74 (m, 2H, CH-C=),

4.07 (t, 2H, J = 6.8 Hz, CH_2O), 5.65 (dt, 1H, J = 5.7, 1.7 Hz, *H*C=), 5.70 (dt, 1H, J = 5.6, 1.6 Hz, C*H*=). δ_C (100 MHz) 14.8, 21.4, 21.5, 27.4, 32.6, 36.9, 38.8, 44.7, 45.0, 65.2, 134.3, 135.7, 171.6. High resolution MS (CI-NH_3) MNH_4+: found 228.1957; calcd 228.1964. $[\alpha]^{25}_D$ +178 ° (*c* 1; $CHCl_3$).

(−)-3-(*Trans*-4*S*-propyl-cyclopent-2-en-1*S*-yl) propyl acetate ((1*S*,4*S*)-2). This compound was prepared as described above for its enantiomer. $[\alpha]^{25}_D$ −110 ° (*c* 1; $CHCl_3$).

2-(*Cis*-4*S*-carboxymethyl-cyclopent-2-en-1*S*-yl) malonic acid dimethyl ester. The *cis*-cyclopentene analogue was synthesized from a palladium-catalysed alkylation reaction of (+)-(3a*S*,6a*R*)-**6** according to Trost et al.[23] To a solution of (+)-(3a*S*,6a*R*)-**6** (1.0 g, 8.1 mmol) and tetrakis(triphenylphosphine)palladium (0.17 g, 0.4 mmol) in THF (16 mL) sodium malonate was added (generated from NaH 60% (1.2 g, 30 mmol) in THF (100 mL) and dimethyl malonate (2.9 mL, 25 mmol) after stirring for 15 min at room temperature). The mixture was refluxed for 1 h when the starting material was consumed as indicated by TLC. The reaction was quenched with 3 M HCl and extracted with ether. The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude material was purified by flash chromatography using a gradient solvent (petroleum ether:ethyl acetate (3:2), and ethyl acetate), the pure acid was isolated (1.8 g, 7.0 mmol) in 87% yield. δ_H (400 MHz) 1.22 (dt, 1H, J = 13.2, 7.7 Hz, CH_2), 2.37 (dd, 1H, J = 15.9, 8.0 Hz, CH_2), 2.45–2.53 (m, 1H, CH_2), 2.49 (dd, 1H, J = 15.9, 6.9 Hz, CH_2), 3.08–3.17 (m, 1H, C*H*-C=), 3.32 (d, 1H, J = 9.3 Hz, C*H*(COOCH_3)$_2$), 3.37–3.44 (m, 1H, C*H*-C=), 3.75 (s, 3H, CH_3O), 3.76 (s, 3H, CH_3O), 5.72 (dt, 1H, J = 5.7, 2.2 Hz, *H*C=), 5.78 (dt, 1H, J = 5.7, 2.0 Hz, *H*C=). δ_C (100 MHz) 35.2, 40.8, 42.0, 45.8, 53.0, 57.5, 133.0, 136.0, 169.2, 178.0.

2-(*Cis*-4*S*-chlorocarbonylmethyl-cyclopent-2-en-1*S*-yl) malonic acid dimethyl ester. The acid (1.8 g, 7.0 mmol) was diluted in ether (30 mL) and cooled on an ice bath. Oxalyl chloride (4.1 mL) and DMF (80 μL) were added and the mixture was stirred 0.5 h at 0 °C and 3 h at room temperature. Then the reaction mixture was evaporated and treated with CCl_4 and evaporated again. This was repeated three times, giving the pure acid chloride in quantitative yield. δ_H (300 MHz) 1.23 (dt, 1H, J = 13.3, 7.5 Hz, CH_2), 2.49 (dt, 1H, J = 13.3, 8.0 Hz, CH_2), 2.91 (dd, 1H, J = 17.1, 7.9 Hz, CH_2), 3.03 (dd, 1H, J = 17.1, 6.6 Hz, CH_2), 3.15–3.25 (m, 1H, C*H*-C=), 3.32 (d, 1H, J = 9.0 Hz, C*H*(COOCH_3)$_2$), 3.35–3.45 (m, 1H, C*H*-C=), 3.74 (s, 3H, CH_3O), 3.75 (s, 3H, CH_3O) 5.71 (dt, 1H, J = 5.3, 1.8 Hz, *H*C=), 5.76 (dt, 1H, J = 5.3, 1.9 Hz, *H*C=).

(−)-2-[*Cis*-4*S*-(2-hydroxyethyl)-cyclopent-2-en-1*S*-yl] malonic acid dimethyl ester ((1*S*,4*S*)-8). The acid chloride (2 g, 7.3 mmol) in THF (16 mL) was reduced, according to Brown et al.,[33] with Li$Al(t$BuO$)_3$H (6.5 g, 25.7 mmol) and THF (16 mL) at 0 °C. The reaction was stirred for 4 h and was then quenched with H_2O (2 mL) and allowed to stir overnight. The mixture was filtered with celite which was thoroughly rinsed with ether and ethyl acetate, the filtrate was dried ($MgSO_4$) and evaporated to give the crude product which was purified by flash chromatography (petroleum ether:ethyl acetate (3:2)). The product (0.8 g, 3.3 mmol) was isolated in 45% yield. δ_H (300 MHz) 1.14 (dt, 1H, J = 13.0, 7.8 Hz, CH_2), 1.50–1.78 (m, 2H, CH_2), 2.35 (dt, 1H, J = 13.0, 7.8 Hz, CH_2), 2.72–2.84 (m, 1H, C*H*-C=), 3.27 (d, 1H, J = 9.5 Hz, C*H*(COOCH_3)$_2$), 3.22–3.40 (m, 1H, C*H*-C=), 3.62–3.78 (m, 2H, CH_2OH), 3.72 (broad s, 6H, CH_3O) 5.64 (dt, 1H, J = 5.7, 2.0 Hz, *H*C=), 5.76 (dt, 1H, J = 5.7, 2.0 Hz, *H*C=). High-resolution MS (CI-NH_3) MH+: found 243.1227; calcd 243.1232. $[\alpha]^{25}_D$ −10° (*c* 2; $CHCl_3$).

(+)-2-[*Cis*-4*R*-(2-hydroxyethyl)-cyclopent-2-en-1*R*-yl] malonic acid ester ((1*R*,4*R*)-8). The compound was obtained as described above for its enantiomer. $[\alpha]^{25}_D$ +11° (*c* 2; $CHCl_3$).

2-(*Cis*-4*S*-[2-(toluene-4-sulfonyloxy)-ethyl]-cyclopent-2-en-1*S*-yl] malonic acid dimethyl ester. The alcohol (0.80 g, 3.3 mmol) was dissolved in DCM (10 mL) and pyridine (2 mL), DMAP (40 mg) and TsCl were added (1.0 g, 5.2 mmol) to give the title compound as described above. The crude product was purified by flash chromatography (petroleum ether:ethyl acetate (3:2)) to give the pure material (0.79 g, 2.0 mmol) in 60% yield. δ_H (300 MHz) 1.06 (dt, 1H, J = 13.0, 7.8 Hz, CH_2), 1.55–1.68 (m, 1H, CH_2), 1.74–1.80 (m, 1H, CH_2), 2.27 (dt, 1H, J = 13.0, 7.8 Hz, CH_2), 2.45 (s, 3H, ArCH_3) 2.68–2.80 (m, 1H, C*H*-C=), 3.24 (d, 1H, J = 9.3 Hz, C*H*(COOCH_3)$_2$), 3.22–3.38 (m, 1H, C*H*-C=), 3.73 (s, 3H, CH_3O), 3.74 (s, 3H, CH_3O), 4.00–4.14 (m, 2H, CH_2O) 5.62–5.68 (m, 2H, *H*C=) 7.33–7.39 (broad d, 2H, J = 8.6 Hz, Ar*H*) 7.76–7.82 (broad d, 2H, J = 8.4 Hz, Ar*H*).

2-(*Cis*-4*R*-propyl-cyclopent-2-en-1*S*-yl) malonic acid dimethyl ester. The tosylated product (0.77 g, 1.95 mmol) was added to a suspension of CuBr–Me_2S (110 mg, 0.5 mmol) and THF (20 mL). The mixture was cooled to −20 °C and 4 equiv of MeMgI/ether solution (1.0 M) was added. The reaction mixture was allowed to reach room temperature and stirred for 3 h when TLC indicated a complete reaction. The mixture was poured into ice–water and extracted with ether. The combined organic extracts were washed with NH_4Cl and brine, dried ($MgSO_4$) and concentrated. The crude material was purified using flash chromatography (petroleum ether:ethyl acetate (3:2)) to give the pure product (0.38 g, 1.6 mmol) in 81% yield. δ_H (300 MHz) 0.90 (t, 3H, J = 6.8 Hz, CH_3), 1.07 (dt, 1H, J = 12.9, 7.7 Hz, CH_2), 1.21–1.40 (m, 4H, CH_2), 2.30 (dt, 1H, J = 12.9, 7.8 Hz, CH_2), 2.58–2.70 (m, 1H, C*H*-C=), 3.22 (d, 1H, J = 9.8 Hz, C*H*(COOCH_3)$_2$), 3.20–3.36 (m, 1H, C*H*-C=), 3.73 (broad s, 6H, CH_3O), 5.59 (dt, 1H, J = 5.6, 2.2 Hz, *H*C=), 5.74 (dt, 1H, J = 5.6, 2.0 Hz, *H*C=).

(+)-(*Cis*-4*R*-propyl-cyclopent-2-en-1*R*-yl) acetic acid methyl ester ((1*R*,4*R*)-9). The malonate was decarboxylated under conditions described by Krapcho.[34] The starting material (0.36 g, 1.5 mmol) was dissolved in DMSO (5 mL), and LiCl (71 mg, 1.7 mmol) and H_2O (27 μL, 1.5 mmol) was added. The mixture was heated to about 150 °C during 4 h when the decarboxylation was complete according to TLC. The reaction was allowed to cool and poured into ice–water and extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude material was purified by flash chromatography (petroleum ether:ethyl acetate (10:1)) to give **9** in 97% yield (0.26 g, 1.45 mmol). δ_H (300 MHz) 0.89 (t, 3H, J = 7.1 Hz, CH_3), 0.95 (dt, 1H, J = 12.8, 7.6 Hz, CH_2), 1.20–1.45 (m, 4H, CH_2), 2.28 (dd, 1H, J = 15.2, 8.1 Hz, CH_2), 2.32 (dt, 1H, J = 12.8, 8.0 Hz, CH_2), 2.42 (dd, 1H, J = 15.2, 6.9 Hz, CH_2), 2.58–2.70 (m, 1H, C*H*-C=), 2.98–3.08 (m, 1H, C*H*-C=), 3.65 (s, 3H, CH_3O), 5.60 (dt, 1H, J = 5.6, 2.0 Hz, *H*C=), 5.69 (dt, 1H, J = 5.6, 2.0 Hz, *H*C=). $[\alpha]^{25}_D$ +11° (*c* 2; $CHCl_3$)

(−)-(*Cis*-4*S*-propyl-cyclopent-2-en-1*S*-yl) acetic acid methyl ester (1*S*,4*S*)-9). The compound was prepared as described above for its enantiomer. $[\alpha]^{25}_D$ −11° (*c* 2; $CHCl_3$).

2-(*Cis*-4*R*-propyl-cyclopent-2-en-1*R*-yl) ethanol. The ester (0.21 g, 1.15 mmol) was reduced with $LiAlH_4$ (0.12 g, 3.2 mmol) as described above to give the alcohol (0.14 mg, 0.94 mmol) in 81% yield. δ_H (300 MHz) 0.88–1.00 (m, 4H, CH_3, CH_2), 1.20–1.80 (m, 6H, CH_2), 2.27 (dt, 1H, J = 12.5, 8.0 Hz, CH_2), 2.55–2.80 (m, 2H, C*H*-C=), 3.66–3.75 (m, 2H, CH_2OH), 5.64 (dt, 1H, J = 5.8, 1.9 Hz, *H*C=), 5.67 (dt, 1H, J = 5.8, 1.9 Hz, *H*C=).

The following steps were performed in the same manner as for the corresponding *trans*-isomer **7**.

Toluene 4-sulfonic acid 2-(*cis*-4*R*-propyl-cyclopent-2-en-1*R*-yl) ethyl ester. δ_H (300 MHz) 0.81(dt, 1H, J = 12.6, 7.9 Hz, CH_2), 0.88 (t, 3H, J = 7.0 Hz, CH_3), 1.15–1.40 (m, 4H, CH_2), 1.52–1.64 (m, 1H, CH_2), 1.74–1.86 (m, 1H, CH_2), 2.14 (dt, 1H, J = 12.5, 8.0 Hz, CH_2), 2.45 (s, 3H, $ArCH_3$), 2.50–2.70 (m, 2H, C*H*-C=), 4.06 (dt (AB part of an ABXY), 2H, J = 6.6 Hz, CH_2), 5.48 (dt, 1H, J = 5.6, 2.2 Hz, *H*C=), 5.63 (dt, 1H, J = 5.6, 2.2 Hz, *H*C=), 7.31–7.35 (broad d, 2H, J = 8.5 Hz, Ar*H*), 7.77–7.81 (broad d, 2H, J = 8.3 Hz, Ar*H*).

3-(*Cis*-4*R*-propyl-cyclopent-2-en-1*S*-yl) propionitrile. δ_H (300 MHz) 0.84–0.96 (m, 4H, CH_3, CH_2), 1.20–1.45 (m, 4H, CH_2), 1.56–1.70 (m, 1H, CH_2), 1.76–1.88 (m, 1H, CH_2), 2.29 (dt, 1H, J = 12.6, 8.0 Hz, CH_2), 2.35 (t, 2H, J = 8.1 Hz, CH_2CN), 2.58–2.82 (m, 2H, C*H*-C=), 5.57 (dt, 1H, J = 5.6, 2.1 Hz, *H*C=), 5.72 (dt, 1H, J = 5.6, 2.1 Hz, *H*C=).

3-(*Cis*-4*R*-propyl-cyclopent-2-en-1*S*-yl) propionic acid. δ_H (300 MHz) 0.84–0.94 (m, 4H, CH_3, CH_2), 1.20–1.44 (m, 4H, CH_2), 1.56–1.68 (m, 1H, CH_2), 1.72–1.85 (m, 1H, CH_2), 2.25 (dt, 1H, J = 12.5, 8.0 Hz, CH_2), 2.36 (t, 2H, J = 8.0 Hz, CH_2CO) 2.56–2.70 (m, 2H, C*H*-C=), 5.59 (dt, 1H, J = 5.6, 1.8 Hz, *H*C=), 5.67 (dt, 1H, J = 5.6, 2.0 Hz, *H*C=).

3-(*Cis*-4*R*-propyl-cyclopent-2-en-1*S*-yl) propan-1-ol. δ_H (300 MHz) 0.84–0.94 (m, 4H,CH_3, CH_2), 1.16–1.65 (m, 8H, CH_2), 2.24 (dt, 1H, J = 12.5, 7.8 Hz, CH_2), 2.52–2.65 (m, 2H, C*H*-C=), 3.64 (t, 2H, J = 6.5 Hz, CH_2OH), 5.59–5.67 (m, 2H, *H*C=).

(−)-3-(*Cis*-4*R*-propyl-cyclopent-2-en-1*S*-yl) propyl acetate ((1*S*,4*R*)-3). The acylation step was performed as described above, to give the title compound (0.86 g, 0.40 mmol), after purification by flash chromatography, in 80% yield (35% from (+)-(1*R*,4*R*)-**9** and 9% from (+)-(3a*S*,6a*R*)-**6**). δ_H (400 MHz) 0.87–0.94 (m, 4H, CH_3, CH_2), 1.23–1.54 (m, 6H, CH_2), 1.64–1.70 (m, 2H, CH_2), 2.06 (s, 3H, CH_3CO), 2.26 (dt, 1H, J = 12.6, 8.0 Hz, CH_2), 2.58–2.67 (m, 2H, C*H*-C=), 4.07 (t, 2H, J = 6.8 Hz, CH_2O), 5.63 (dt, 1H, J = 5.6, 1.6 Hz, C*H*=), 5.67 (dt, 1H, J = 5.6, 1.7 Hz, C*H*=). δ_C (100 MHz) 14.7, 21.4, 21.6, 27.5, 33.4, 37.8, 39.6, 45.7, 45.9, 65.2, 134.4, 135.8; 171.7. High-resolution MS (CI-NH_3) MNH_4+: found 228.1961, calcd 228.1964. $[\alpha]^{25}_D$ −6 ° (*c* 2; $CHCl_3$).

(+)-3-(*Cis*-4*S*-propyl-cyclopent-2-en-1*R*-yl) propyl acetate ((1*R*,4*S*)-3). This compound was prepared as described above for its enantiomer. $[\alpha]^{25}_D$ +7 ° (*c* 2; $CHCl_3$).

Electrophysiology

The biological activities were determined by single-cell electrophysiology.[35] The sensillum type SW1 of *A. segetum*, housing the olfactory receptor cell specifically tuned to (*Z*)-5-decenyl acetate, was used.[36–38] The method was modified according to van der Pers and den Otter[39] and has previously been described.[2,4] The stimulus amounts used for the pheromone component **1** were 10^{-4}–10^{-1} μg, in decadic steps. For the racemic *cis*-compound (±)-**3** and for *cis*-(−)-(1*S*,4*R*)-**3** the amounts used were 10^{-2}–10^{1} μg and for the *cis*-(+)-(1*R*,4*S*)-**3**, the racemic *trans*-compound (±)-**2** and the enantiomers, (+)-(1*R*,4*R*)-**2** and (−)-(1*S*,4*S*)-**2**, the amounts used were 10^{-1}–10^{2} μg, all in decadic steps. For each stimulus loading, ten replicates were recorded and the mean value of the number of action potentials generated during one second from the onset of stimulation was used in the construction of the dose–response curves. The errors were expressed as standard errors of the mean (SEM). The electrophysiological activity of each compound in relation to that of **1** is expressed as the reciprocal of the relative quantities required to elicit the same response from the receptor as the natural pheromone component **1**. Differences in volatility between compounds **2**, **3** and **1** were taken into account by correcting the activities by using relative vapor pressures as has previously been described.[3,4,40] The

correction is based on vapor pressure data[41] for *cis*-2-butene and cyclopentene, *cis*-2-pentene and 3-methyl-cyclopentene, and *cis*-2-hexene and 3-ethyl cyclopentene. The logarithm of the quotient of the vapor pressure for the olefin and the vapor pressure for its cyclic analogue gives the correction. The mean value of the quotient was used. The correction was added to the logarithm of the relative activities. The correction used is +0.52, where a positive correction value indicates a lower vapor pressure for the cyclopentene analogues than for the natural component **1** and, therefore, the real activities for the analogues are somewhat higher than the measured activities.

Molecular mechanics calculations

Molecular geometries and conformational energies were calculated by using the molecular mechanics program MM3(92), developed by Allinger and co-workers[26–28] as implemented in the molecular modeling package MacMimic/MM3(92).[42]

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