Review

Stereochernical studies on pheromone communications

By Kenji MORI*1,†

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Abstract: Pheromonal communications are heavily dependent on the stereochemistry of pheromones. Their enantioselective syntheses could establish the absolute configuration of the naturally occurring pheromones, and clarified the unique relationships between absolute configuration and bioactivity. For example, neither the (R)- nor (S)-enantiomer of sulcatol, the aggregation pheromone of an ambrosia beetle, is behaviorally active, while their mixture is bioactive. Recent results as summarized in the present review further illustrate the unique and diverse relationships between stereochemistry and bioactivity of pheromones.

Keywords: absolute configuration, chemical communications, chemical synthesis, chirality, pheromones, stereochemistry

1. Introduction and early studies

Butenandt’s discovery in 1959 of bombykol (1, Fig. 1) as the sex attractant of female silkworm moth (Bombyx mori L.)1) was the beginning of the now prospering field of chemical ecology. In the same year, Karlson and Lüscher proposed a new term “pheromone”, which is derived from the Greek words pherein (to transfer) and hormon (to excite).2) Pheromones are substances that are secreted by an individual and received by a second individual of the same species, in which they induce a specific reaction such as special behavior or a developmental process.

Achiral bombykol (1) poses no stereochemical problem except the olefin geometry. Later in 1969 Silverstein and co-workers isolated a chiral and levorotatory alcohol (2) as the sex pheromone of the dermestid beetle (Trogoderma inclusum LeConte).3) In order to study the significance of chirality in pheromonal communications, the first thing to do was to determine the absolute configuration of the naturally occurring pheromone. Subsequently, by bioassaying the synthetic stereoisomers of the pheromone, we can gain knowledge about stereochemistry-bioactivity relationships.

In 1973 when I began the synthesis of (S)-2, almost nothing was known about the absolute configuration of chiral and non-racemic pheromones, and it was not even clear whether enantiomeric composition would play a role at all in pheromonal communications. Difficulties are often encountered in stereochernical studies of pheromones, because they are usually obtained in small quantities (several ng to pg) as volatile oils. Stereochernical studies of pheromones are therefore beyond the scope of conventional methods of stereochernical assignment, such as degradation to a simple compound of known absolute configuration or X-ray crystallographic analysis.

My way since 1973 to circumvent these difficulties has been through enantioselective synthesis of the target pheromone itself by starting from a compound of known absolute configuration. If chiroptical properties or enantioselective gas chromatographic (GC) behavior of the natural pheromone is recorded, then these data can be compared with the corresponding data of the synthetic material. The absolute configuration of the natural pheromone can thus be clarified and established.

My 1973 synthesis of the (S)-enantiomer of (Z)-14-methyl-8-hexadecen-1-ol (2, Fig. 1), the dermestid beetle pheromone artefact, from (S)-2-methyl-1-butanol showed (S)-2 to be dextrorotatory.4,5) Because 2 isolated from the insect was levorotatory, its absolute configuration was unambiguously assigned as R. Subsequently in 1980, the genuine pheromone of the dermestid beetle was shown to be
aldehyde (R)-2′ (trogodermal). Its (S)-isomer was biologically inactive, and only (R)-2′ was pheromonally active.

2. Chirality determines the bioactivity of pheromones

In 1974 it was of interest to me whether the enantiomers of highly dissymmetric compounds might evoke totally different olfactory reactions or not, and therefore I undertook the synthesis of the enantiomers of exo-brevicomin (3, Fig. 2) and frontalin (4). These two bicyclic acetals were known to be the components of the aggregation pheromone of the western pine beetle (Dendroctonus brevicomis LeConte).

As shown in Fig. 2, (1R,5S,7R)-(+)-exo-brevicomin (3) was synthesized from unnatural (2S,3S)-(--)-tartaric acid, while its natural (2R,3R)-(+)-isomer yielded (1S,5R,7S)(--)-3. The enantiomers of frontalin (4) were synthesized from the enantiomers of 4-carboxy-4-pentanolide. When these synthetic enantiomers of 3 and 4 (together with myrcene, a terpene of the host pine tree) were bioassayed in the U.S.A. against the western pine beetle, only (1R,5S,7R)-(+)-3 and (1S,5R)(--)-4 were bioactive. It is interesting to note that the skeletal framework of (+)3 possesses (1R,5S)-configuration, while that of (--)4 possesses the opposite (1S,5R)-stereochemistry.

In the cases of trogodermal (2′), exo-brevicomin (3) and frontalin (4), only a single enantiomer of the pheromone was highly bioactive. It thus became clear that bioactivity depends on the chirality of the pheromones. This result was in accord with the conventional wisdom that a single enantiomer is important.

3. Insects’ diversity in recognizing the stereochemistry of pheromones

3.1. Sulcatol—synergistic response based on enantiomerism. Sulcatol (5, Fig. 3) is the male-produced aggregation pheromone of Gnaathothrichus sulcatus LeConte, an economically destructive ambrosia beetle in the Pacific coast of North America. The naturally occurring 5 was shown to be a 35 : 65 mixture of (R)-5 and (S)-5 by 1H-NMR analysis of its Mosher ester (α-methoxy-α-trifluoromethylphenylacetate). The reason why the beetle produces an enantiomeric mixture was unclear at the time of its discovery.
3.2. Disparlure—the unnatural enantiomer is an antagonist. Disparlure (6) is the sex pheromone of the female gypsy moth (Lymantria dispar L.), which is a forest pest in the U.S.A. and Eurasian continent. In 1976 we synthesized both \((7R,8S)-(+)\)-6 and \((7S,8R)-(+)\)-6 by starting from the naturally occurring and cheap (+)-tartaric acid.\(^{(14,15)}\) Our samples were bioassayed by Vité et al. in Germany and Roelofs et al. in the U.S.A. Vité found that the unnatural \((-)\)-6 drastically reduced the response of the moths to the naturally occurring \((+)\)-6,\(^{(16)}\) while Roelofs suggested the existence of two receptors for the enantiomers of 6, one with the greatest affinity to the natural \((+)\)-6, the other with greater affinity for \((-)\)-6.\(^{(17)}\)

3.3. Olean—one enantiomer is active against males whereas the opposite enantiomer affects females. An unusual stereochemistry-bioactivity relationship was observed in the case of olean (7), the female-produced sex pheromone of the olive fruit fly (Bactrocera oleae Gmelin). Both \((R)\)- and \((S)\)-7 were synthesized by us from abundant \((S)\)-malic acid\(^{(18,19)}\) and bioassayed in Greece by Haniotakis.\(^{(20)}\) Male flies were activated by \((R)\)-7, whereas \((S)\)-7 was active against females. Enantioselective GC analysis of natural olean (7) by Schurig revealed it to be \((\pm)\)-7.\(^{(20)}\) Accordingly, the female-produced pheromone activates male olive fruit flies and also the female herself.

4. Recent examples of pheromone synthesis:

(1) A single stereoisomer of the insect pheromone shows bioactivity

4.1. Aggregation pheromone of the Colorado potato beetle. In 2002 Oliver et al. identified \((S)\)-1,3-dihydroxy-3,7-dimethyl-6-octen-2-one \((8, 8,\text{Fig. } 4)\) as the male-produced aggregation pheromone of the Colorado potato beetle (Leptinotarsa decemlineata Say), which is a major pest of potatoes, tomatoes and eggplants.\(^{(21)}\)

We carried out an enzyme-assisted synthesis of \((S)\)-8 and its enantiomer to obtain them in gram-quantities.\(^{(22)}\) The field trial to catch adult beetles was conducted in the U.S.A. In this case of 8, \((S)\)-8 was attractive for both male and female L. decemlineata while \((R)\)-8 was inactive, and the presence of \((R)\)-8 in \((\pm)\)-8 abolished the response to \((S)\)-8.\(^{(21,22)}\)

4.2. Aggregation pheromone of the stink bug Eysarcoris lewisi Distant. Pecky rice (rice grain damaged by insects) is a serious problem in Japanese rice production. A stink bug (Eysarcoris lewisi Distant) is known as one of the major species of rice

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In 1975 I synthesized both \((R)\)- and \((S)\)-5 by starting from the enantiomers of glutamic acid.\(^{(12)}\) Their bioassay was executed in Canada, and Borden et al. found neither \((R)\)-5 nor \((S)\)-5 to be bioactive.\(^{(13)}\) The maximum response of the beetle was to a 1:1 racemic mixture of the enantiomers, and the response to \((\pm)\)-5 was significantly greater than that to the naturally occurring 35:65 mixture.\(^{(13)}\) It therefore became clear that the beetles must produce a mixture of the enantiomers of 5, if they are to communicate with each other. This discovery in 1976 was the first example of a synergistic response based on enantiomerism.

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![Fig. 3. Synthesis of sulcatol (5), disparlure (6) and olean (7).](image-url)
bugs that cause pecky rice in northern Japan. Its male-produced aggregation pheromone was identified as (2Z,6R,1'S,5'S,)-9 (Fig. 5).²³–²⁵

In 2007 to 2008, synthesis of 9 and its isomers was executed by us in two different ways employing either chemical or enzymatic asymmetric reactions.²³,²⁴ Figure 5 summarizes the chemical asymmetric synthesis of (2Z,6R,1'S,5'S,)-9.²⁴ The natural isomer (2Z,6R,1'S,5'S,)-9 was of course as bioactive as the natural product, while (2Z,6S,)-isomers and (2Z,6R,1'R,5'R,)-9 were inactive. No antagonistic activity was observed with the (2Z,6S,)-isomers.²⁵

### 4.3. Sex pheromone of Paulownia bagworm.

Paulownia bagworm (*Paulownia variegata* Snell) is an economically important forest defoliator in China. Its female-produced sex pheromone was identified in 2006 by Gries et al. as 1'-ethyl-2'-methylpropyl 3,13-dimethylpentadecanoate (10, Fig. 6).²⁶ They synthesized (±)-, (R)- and (S)-2-methyl-3-pentanol, and

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### References

1. Gries, et al. (2006). 3,13-dimethylpentadecanoate.
2. Grubbs I catalyst.
3. PCy₃.
4. RuCl₂.
5. Cl₂R. 1'R,5'R,}-9 were inactive. No antagonistic activity was observed with the (2Z,6S,)-isomers.²⁵

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**Fig. 4.** Synthesis of (S)-(+)–8, the Colorado potato beetle pheromone.

**Fig. 5.** Synthesis of (2Z,6R,1'S,5'S,)-9, the pheromone of *Eysarcoris lewisi* Distant.

**Fig. 6.** Synthesis of (3R,13R,1’S,5’S)-10, the Paulownia bagworm pheromone.
prepared their esters with a stereoisomeric mixture of 3,13-dimethylpentadecanoic acid. Bioassay of the esters showed (1’S)- and (1’RS)-1’-ethyl-2’-methylproplyl 3,13-dimethylpentadecanoate (10) to be pheromonally active. Accordingly, the absolute configuration of the alcohol moiety of the natural pheromone must be S. The (1’R)-isomer was inactive but not an antagonist.26)

In order to determine the absolute configuration at C-3 and also at C-13 of (1’S)-10, we synthesized all of the four stereoisomers of 10 employing the olefin cross metathesis reaction between the enantiomers of A and those of B.25) Bioassay of the four stereoisomers of (1’S)-10 in China revealed the natural pheromone to be (3R,13R,1’S)-10, although (3R,13S,1’S)-10 was about 5% as active as the natural pheromone. This means that the configuration at C-13 is not so important for the bioactivity of 10 as that at C-3.27)

4.4. Aggregation pheromone of the flea beetles Aphthona flav a and Phyllotreta cruci fer a e. In 2001 Bartelt et al. identified four himachalene-type sesquiterpenes including 11 (Fig. 7) as the male-produced pheromone candidates of Phyllotreta and Aphthona flea beetles.28) They assigned the absolute configuration depicted as (−)-11 (Fig. 7) to the natural product and synthesized (±)-11.29)

In 2004 we synthesized both the enantiomers of the four sesquiterpenes,30) and found (−)-11 to be biologically inactive.31) The absolute configuration of our (−)-11, which was prepared from (S)-citronellal, was confirmed by the X-ray analysis of the (−)-ketone shown in Fig. 7.30 Bioassays of our synthetic enantiomers in Hungary clearly showed the enantiomers belonging to the stereoisomeric series as depicted in (+)-11 were the natural pheromone components.

The reason for this stereochemical discrepancy was later solved by my unambiguous synthesis of (R)-ar-himachalene.32) Bartelt et al. measured the specific rotation of their ar-himachalene of insect origin as a hexane solution, and compared their observed value \[ [\alpha]_D > +10 (\epsilon = 0.001, \text{hexane}) \] with that \[ [\alpha]_D > +5.9 (\epsilon = 1.35, \text{CHCl}_3) \] of (S)-ar-himachalene as measured by Pandey and Dev as a chloroform solution.33) Then Bartelt concluded that their ar-himachalene with dextrorotation must be with S-configuration. My own work, however, revealed that (R)-ar-himachalene is dextrorotatory (+3.8) in hexane but levorotatory (−2.4) in chloroform.32 Bartelt’s comparison should have been done as a chloroform solution. When one compares the sign of the optical rotation of one’s sample with previous data by others, it is most important to use exactly the same solvent as employed by others.

4.5. 1,2-Ditigloyl-3-oleoylglycerol, the pheromone of the Drosophila fruit fly. In 2011 Yew et al. demonstrated the presence of triacylglycerols in cuticles of two species of Drosophila fruit flies, Drosophila arizonae and Drosophila mojavensis.34) The structures of some of the triacylglycerols were subsequently proposed including that of 12 (Fig. 8).35) The structures were new and unusual to be comprised of zero or one acetic acid, two or one tiglic acid(s) and a fatty acid. These triacylglycerols are secreted by male flies from the ejaculatory bulb, transferred to females during mating, and inhibit courtship from other males. Accordingly, Drosophila triacylglycerols are novel class of pheromones.35)

Mori’s synthetic triacylglycerols30 including (R)-1,2-ditigloyl-3-oleoylglycerol (12) and its (S)-isomer were bioassayed against Drosophila fruit flies, and (R)-(+) 12 was found to suppress copulation of
the flies at a dosage of 75 ng per female, while (S)-
(-)-12 was inactive. Other triacylglycerols were also
synthesized, and will be bioassayed soon.37)

5. Recent examples of pheromone synthesis:
(2) Pheromones with more complicated
stereochemistry-bioactivity relationships

5.1. Supellapyrone, the female sex phero-
monoe of the brownbanded cockroach. Supella-
pyrone (13, Fig. 9) was identified by Roelofs and
coworkers as the female-produced sex pheromone
of the brownbanded cockroach (Supella longipalpa
Fabricius).38) Leal et al. proposed its absolute con-
figuration as 2'R,4'R.39) We synthesized (2'R,4'R)-
13 in 1994,40) and then prepared in 2001 all the four
stereoisomers of 13 as summarized in Fig. 9.41)
Asymmetric acetylation of meso-A with vinyl acetate
and lipase AK yielded (2'R,4'S)-B, which gave the
natural pheromone (2'R,4'R)-(++)-13 and its enan-
tiomer (2'S,4'S)-(++)-13. On the other hand, enzym-
ic resolution of (+)-A gave (2'S,4'S)-D and
(2'R,4'R)-E, which furnished (2'S,4'R)-(++)-13 and
(2'R,4'S)-(++)-13, respectively.41)

Behavioral bioassay of these four stereoisomers
of 13 revealed (2'R,4'R)-13 to be the most bioactive
isomer with only 0.3 pg delivered on a filter paper
being sufficient to elicit 50% male response.42) The
(2'S,4'R)- and (2'S,4'S)-isomers showed weak ac-
activity (only 1% of the natural isomer), while (2'R,4'S)-
13 was totally inactive.

5.2. Quercivorol, the male aggregation pher-
omone of an ambrosia beetle. Massive mortality of
oak trees has occurred in Japan since the late 1980s.
An ambrosia beetle, Platypus quercivorus Maruyama,
is a vector of a fungus Raffaelea quercivora, which
is the causative agent of the massive mortality.
The male aggregation pheromone of the beetle was
identified by Nakashima,43) Tokoro44) and their
coworkers as (1S,4R)-4-isopropyl-1-methyl-2-cyclo-
hexen-1-ol (14, Fig. 10), and given the name quercivorol.44)
Synthesis of (1S,4R)-(−)-quercivorol (14) was
achieved via (R)-cryptone by starting from (S)-
perillyl alcohol.53) Their stereoisomers (1R,4R)-,
(1S,4S)- and (1R,4S)-14 were also synthesized and bioassayed.44–46 The naturally occurring (1S,4R)-14 was quite bioactive, but (1R,4S)-14 was moderately active (25–50%), too. It must be added that (±)-14 was also moderately active, and could be used for population monitoring of Platypus quercivorus. No pheromone activity was shown by (1R,4R)- and (1S,4S)-14.

5.3. 3,11-Dimethyl-2-nonacosanone, the female sex pheromone of the German cockroach. In 1974 Nishida et al. identified 3,11-dimethyl-2-nonacosanone (15, Fig. 11) as the major component of the courtship stimulating sex pheromone of the female German cockroach (Blattella germanica L.).47 Our synthesis in 1978 of all the four stereoisomers of 15 enabled us to assign (3S,11S)-absolute configuration to the natural 15.48 In 1990 we published our second synthesis of 15,49 which made us to secure extremely pure four stereoisomers of 15 by recrystallizing both the intermediates and the final products themselves. Bioassay of the pure stereoisomers of 15 by Eliyahu et al. revealed an interesting fact that all four stereoisomers of 15 elicited responses from all of the males, and the natural (3S,11S)-15 was the least effective of the four stereoisomers at eliciting courtship responses in males.50 This is the first example of a natural pheromone having less bioactivity than its stereoisomers that do not occur naturally. Synthesis of all the six components of the female Blattella germanica pheromone was also achieved recently.51

5.4. 4,8-Dimethyldecanal, the male aggregation pheromone of the red flour beetle. The red flour beetle (Tribolium castaneum Herbst) is a major cosmopolitan pest of stored cereal grains and other agricultural products. The feeding adult male produces an aggregation pheromone (tribolure), which is attractive to both sexes. In 1980 Suzuki identified it as 4,8-dimethyldecanal (16, Fig. 12).52 Our synthesis of the four stereoisomers of 16 in 198353 was immediately followed by their bioassay.54,55 Both Suzuki and Levinson arrived at the same conclusion that (4R,8R)-16 must be the natural pheromone, because the pheromone activity of (4R,8R)-16 was as strong as that of the natural product. In 1984,
biosynthesis of 16 active than (4)

(4)

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cheekly synthesized again the four stereoisomers of

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Fig. 12. Synthesis of 4,8-dimethyldecanal (16, tribolure).

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however, Suzuki et al. found that a 4 : 1 mixture of

(4R,8R)-16 and (4R,8S)-16 was ten times more active

than (4R,8S)-16 alone, although (4R,8S)-16

itself was inactive at lower doses.56) This fact puzzled

us, but in 1980s there was no good method available

to analyze precisely the stereoisomeric composition

of the natural 16.

Fortunately, Ohrui and his co-workers recently

developed a new analytical method to estimate the

stereoisomeric composition of this type of chiral

compounds by low temperature HPLC separation of

their derivatives (see Fig. 12).57) We therefore

synthesized again the four stereoisomers of 16.58)

The result of analysis was surprising: the natural

pheromone was a mixture of all four stereoisomers at

a ratio of about 4 : 1 of (4R,8R)/(4R,8S)/(4S,8R)/(4S,8S)-16.59) This finding means that the

biosynthesis of 16 in Tribolium castanum is not

stereoselective. The configuration at C-8 of 16 is not

at all controlled, while that at C-4 is controlled

partially to give a 4 : 1 ratio of (4R)- and (4S)-

isomers. The reason for this stereochemical hetero-

geneity must be solved in future by biologists.

5.5. CH503, the male sex pheromone of the

fruit fly Drosophila melanogaster. In 2009, Yew

et al. isolated a new pheromone named CH503 from

the male fruit fly, Drosophila melanogaster, and

identified it as 3-acetoxy-11,19-octacosadien-1-ol (17,

Fig. 13).60) The CH503 pheromone is transferred

from males to females during mating, remains on the

surface of females for at least ten days and inhibits

courtship as an anti-aphrodisiac.60) The geometries of

the two double bonds and absolute configuration at

C-3 of CH503 remained unknown. This stereoche-

mical problem was solved by our synthesis as shown

in Fig. 13.61),62)

We first synthesized in 2010 the enantiomers of

(11Z,19Z)-17, and found (3S,11Z,19Z)-(+)-17 to be bioactive, while (3R,11Z,19Z)-(−)-17 was only slightly bioactive at the equivalent dose of 50 ng.

We therefore thought that (3S,11Z,19Z)-17 might be the naturally occurring CH503.61) The remaining six stereoisomers of 17 were subsequently synthesized in 2012.62) Complete separation of the eight stereoisomers of 17 by HPLC at −20 °C was achieved after their esterification with (1R,2R)-2-(2,3-anthracene-

dicarboximido)cyclohexanecarboxylic acid,57) and natural CH503 was identified as (3R,11Z,19Z)-17 with only weak bioactivity.62) Curiously, regardless of the geometry of the two double bonds, all of the (S)-
stereoisomers of 17 were highly bioactive. It was therefore impossible to determine the stereorecognition of CH503 on the basis of bioassay data alone, because the natural 17 was only slightly bioactive.

Synthesis and bioassay of the analogues of

CH503 such as 3-acetoxy-11,19-octacosadien-1-ol (D), 3-acetoxyoctacosan-1-ol (E), (Z)-3-acetoxy-11-

octacosen-1-ol (F) and (Z)-3-acetoxy-19-octacosen-

1-ol (G) revealed none of them to be bioactive.63) Accordingly, the two double bonds at C-11 and C-19 are necessary for bioactivity of CH503. Biology of CH503 was recently discussed by Yew and co-

workers.64)

6. Summary of the stereochemistry-bioactivity

relationships among pheromones

The stereochemistry-bioactivity relationships

among pheromones were reviewed in depth in 2007

by dealing with about 140 chiral pheromones.65) The

diverse relationships as summarized in Fig. 14
were clarified only through experiments in chemical synthesis and bioassay.\(^{66}\)

The most prevailing category is A. Only one enantiomer is bioactive, and the opposite enantiomer does not inhibit the action of the pheromone. About 60% of the chiral pheromones belong to this category. Pheromones (2\(Z\),6\(R\),1\(′\),5\(S\),5\(′\))-9, (+)-11 and (\(R\))-\(\pm\)-12 in this review belong to this category A. In the next category B, only one enantiomer is bioactive, while its opposite enantiomer inhibits the action of the pheromone. Pure enantiomers must be manufactured for the practical use of disparlure.
(6, the gypsy moth pheromone) and japonilure (the Japanese beetle pheromone) in pest management. The pheromone \((S)-(+)\)-8 in this review belongs to category B.

In category C, only one enantiomer is bioactive, and its diastereomer inhibits the action of the pheromone. Diastereoselective synthesis of the active stereoisomer or removal of the antagonistic diastereomer is necessary to provide an active pheromone for pest control. Practical use of the pheromone of the cigarette beetle will be discussed in the next section.

The natural pheromone is a single enantiomer, and all the stereoisomers are bioactive. The natural pheromone of the German cockroach is a mixture of the four stereoisomers: \((4R,8R)/(4R,8S)/(4S,8R)/(4S,8S)\) = 4:4:1:1. (\(4R,8R\))-Isomer is the only one with high activity, although it is less active than the mixture.

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One enantiomer is active on male insects, while the other is active on females.

Only the meso-isomer is active.

Only one enantiomer is bioactive, and the antipode does not inhibit the action of the pheromone.

Only one enantiomer is bioactive, but its diastereomer inhibits the action of the pheromone.

The natural pheromone is a single stereoisomer, and all the stereoisomers are bioactive.

The natural pheromone is a single enantiomer, and its diastereomer inhibits the action of the pheromone.

The natural pheromone is a single stereoisomer, and all the stereoisomers are bioactive.

Both the enantiomers are required for bioactivity.

The natural pheromone is a single enantiomer, the antipode does not inhibit the action of the pheromone.

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The natural pheromone is a single enantiomer, and its enantiomer or some of its diastereomers are also bioactive. This is category D. In the case of the sex pheromone of the maritime pine scale, the chirality at the stereogenic center remote from the carbonyl group is not so important. Pheromones \((2'R,4'R)-(+)\)-13, \((1S,4R)-(+)\)-14 and \((3R,11Z,19Z)-(+)\)-17 belong to category D.
In category E, the natural pheromone is a single stereoisomer, but all the stereoisomers are also bioactive. The German cockroach pheromone (3S,11S)-(+)-15 belongs to this category. The cockroach uses the least effective of the four stereoisomers of 15 as the pheromone, because of the stereochemical restriction in the course of its biosynthesis. The biosynthesis allows only (3S,11S)-(+)-15 to be produced.

In category F, even in the same genus, different species use different enantiomers. Accordingly, chirality is used to segregate the species.

In category G, both enantiomers are required for bioactivity as already mentioned in the case of sulcatol (5).

We already discussed category H in the case of 4,8-dimethyldecanal (16). Category I was also treated in the case of olean (7).

In category J, only the optically inactive meso-isomers are employed as the pheromones. Indeed, the diversity is the keyword of pheromone response. The origin of the observed diversity must be clarified in future by biologists. Structural biology of the complex between a pheromone and its receptor protein will teach us something about the origin of diversity in pheromone response.

7. Future prospects and practical application of pheromone research

7.1. Future prospects. The traditional method for evaluating a pheromone sample was to observe the behavior of the organism caused by the sample. A modern method called electroantennographic detection very much assisted to find out minor but indispensable components of a pheromone. Schneider in Germany was the first to use electroantennogram (EAG) to study pheromone perception by male silkworm moth. His study in 1957 revealed that slow olfactory receptor potentials could be recorded from an isolated insect antenna placed between two glass capillary microelectrodes connected to an amplifier and recording instrument. When gas chromatographic (GC) separation of a crude pheromone extract is coupled with EAG detection, one can find out any pheromonally active minor components in a complex mixture. Investigation over forty years of the male-produced sex pheromone of the dried bean beetle (Acanthoscelides obtectus Say) illustrates the importance of GC-EAG detection.

In 1970 Horler isolated an optically active allene (−)-18 (Fig. 15) as the male-produced sex pheromone of the dried bean beetle, which is a destructive pest of stored beans. The unique structure of 18 as a chiral allene evoked interest of chemists, and its absolute configuration was determined as R by Pirkle’s synthesis of enantiomerically enriched (R)-(−)-18. We also synthesized the enantiomers of 18 in 1981 basing on the chemical optical resolution of intermediate A. A better synthetic method using enzymatic resolution of A was later developed in 2012. The synthetic (−)-18, however, could not attract the dried bean beetle as efficiently as the natural pheromone.

Vuts et al. identified two new and minor components [(2E,4Z)-19 and (2E,4Z,7Z)-20] of the dried bean beetle pheromone by using GC-EAG method. These two unsaturated esters 19 and 20 were synthesized. A three-component mixture of (2E,4R)-(−)-18, (2E,4Z)-19 and (2E,4Z,7Z)-20 indeed attracted as many dried bean beetles as the natural pheromone could do. As long as a period of forty-five years was necessary to finally identify...
all of the pheromone components so as to make a practical lure.

Search of missing minor components of a pheromone bouquet will continuously increase the number of pheromones which can be used practically in pest control.

7.2. Practical application. There are many insect pheromones commercially available for pest management. An example will be given here, which illustrates the successful efforts in Japan to commercialize an insect pheromone.

The cigarette beetle (*Lasioderma serricorne* Fabricius) is a serious cosmopolitan pest of cured tobacco leaves and dried food-stuffs. Pheromone biology of the cigarette beetle was precisely recorded by Levinson. Difficulty in detecting the infestation of this tiny beetle (2–3 mm in length) made Chuman et al. at Japan Tobacco Corporation to study its female-produced sex pheromone. In 1979 they identified it as 4,6-dimethyl-7-hydroxy-3-nonanone (21, Fig. 16). They then synthesized it as a racemic and diastereomeric mixture confirming the pheromone activity of the synthetic sample, and named it serricornin.75) Ono at Fuji Flavor Co. (a subsidiary of Japan Tobacco) soon developed a simple synthesis of (4S,6S,7S)-21 as a stereoisomeric mixture, and the synthesis served as a practical and commercial method for manufacturing 21.76)

The absolute configuration of serricornin (21) was established by joint efforts of Chuman and Mori. Both Mori et al. and Chuman et al. prepared the naturally occurring (4S,6S,7S)-serricornin (21) in 1982.77,78) Minor components of the pheromone bouquet were carefully investigated by Chuman et al. to find out anhydroserricornin, serricorone and serricorole as depicted in Fig. 16.79) Meanwhile, a more convenient synthesis of (4S,6S,7S)-21 was achieved by Mori and Watanabe in 1985.80) By using the synthetic materials, Chuman’s group found that (4S,6S,7R)-21, a diastereomer of serricornin, could work as an antagonist of the pheromone action,81) while anhydroserricornin was not a strong attractant.82)

Basing on all of the above results, Fuji Flavor Co. developed an efficient “serrico” trap baited with the pheromone for the detection and mass trapping of the cigarette beetles in food and cigarette factories. Figure 17 shows (a) a cigarette beetle, (b) “new serrico”, the pheromone-baited trap to catch the cigarette beetles, and (c) mass trapping of the cigarette beetles by “new serrico”. This pheromone-based pest management is widely used in food industries all over the world to prevent the contamination of cigarette beetles in food products.

8. Conclusions

Stereochemical studies on pheromonal communications firmly established the importance of chirality in pheromone perception, and the following three conclusions must be remembered. (1) Chirality of pheromones is very important for the expression of their bioactivity. (2) Natural pheromones are not always enantiomerically pure. Sometimes only such “impure” pheromones can express bioactivity. (3) The existing dogma “only one enantiomer is bioactive” must be modified. Progress in pheromone science will eventually allow us to utilize pheromone technology as one of the environmentally benign methods for pest control.83)
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Profile

Kenji Mori was born in 1935. After obtaining his Ph.D. in organic chemistry in 1962, he was appointed as assistant professor in the Department of Agricultural Chemistry at the University of Tokyo (1962), and was promoted to associate professor (1968) and professor (1978). In all, he spent 42 years at the University of Tokyo. Currently, he is Professor Emeritus. Dr. Mori worked for 7 years (1995–2001) as a professor at Science University of Tokyo. At present, he is a consultant at Toyo Gosei Co., Ltd., and a Senior Visiting Scientist at RIKEN Research Cluster for Innovation. He was awarded Japan Academy Prize (1981), the Silver Medal of the International Society of Chemical Ecology (1996), Fujihara Prize (1998), the American Chemical Society’s Ernest Guenther Award in the Chemistry of Natural Products (1999), the Special Prize of the Society of Synthetic Organic Chemistry, Japan (2003), the Frantisek Form Memorial Medal of the Academy of Sciences of the Czech Republic (2003), the Chirality Medal of the Italian Chemical Society (2010), and the Lifetime Achievement Award in Chemical Ecology of the Asia-Pacific Association of Chemical Ecologists (2013).