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Review

Significance of chirality in pheromone science

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Abstract—Pheromones play important roles in chemical communication among organisms. Various chiral and non-racemic pheromones have been identified since the late 1960s. Their enantioselective syntheses could establish the absolute configuration of the naturally occurring pheromones and clarified the relationships between absolute configuration and bioactivity. For example, neither the (*R*)- nor (*S*)-enantiomer of sulcatol, the aggregation pheromone of an ambrosia beetle *Gnathotrichus sulcatus*, is behaviorally active, while their mixture is bioactive. In the case of olean, the olive fruit fly pheromone, its (*R*)-isomer is active for the males, and the (*S*)-isomer is active for the females. About 140 chiral pheromones are reviewed with regard to their stereochemistry–bioactivity relationships. Problems encountered in studying chirality of pheromones were examined and analyzed to think about possible future directions in pheromone science.

Contents

Keywords: Absolute configuration; Chemical communications; Chirality; Pheromones; Stereochemistry.
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1. Introduction

Pheromone science began in 1959 when Butenandt clarified the structure **1** (Fig. 1) of bombykol, the sex pheromone of the female silkworm moth, *Bombyx mori*.[1] The term 'pheromone' was coined in the same year by Karlson and Lüscher.[2] The name is derived from the Greek *pherein*, to transfer, and *hormon*, to excite. 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.

Because it is achiral, bombykol (**1**) poses no stereochemical problem except the olefin geometry. Subsequently in the late 1960s a number of chiral pheromones were identified such as *exo*-brevicomin (**2**), the aggregation pheromone of the western pine beetle, *Dendroctonus brevicomis*.[3] An understanding of the relationship between stereostructure and biological effect requires that the absolute configuration of naturally occurring chiral pheromones must be determined.

In 1973, when I began my studies on pheromone synthesis, almost nothing was known about the absolute configuration of chiral pheromones, and it was not even clear whether enantiomeric composition would play a role at all. Difficulties are often encountered in stereochemical studies of pheromones, because they are usually obtained in small quantities (several μg) as volatile oils. Stereochemical studies of pheromones are therefore beyond the scope of conventional methods of stereochemical assignment, such as degradation to a simple compound of known absolute configuration or X-ray crystallographic analysis. The best way to circumvent these difficulties is by enantioselective synthesis of the target pheromone starting from a compound of known absolute configuration. If chiroptical properties or gas chromatographic behavior on optically active stationary phases of the natural pheromone are recorded, then these data can be compared with the corresponding data of the synthetic material. The absolute configuration of the natural pheromone will thus be clarified and established.

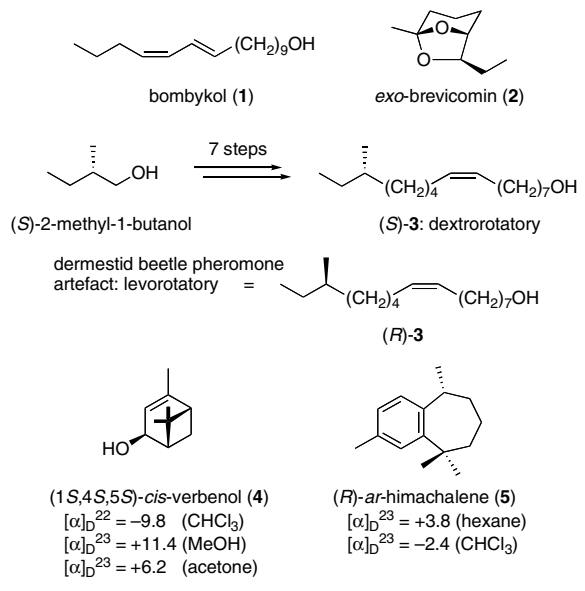


Figure 1. Structures and chiroptical properties of some insect pheromones.

The usefulness of this approach was first demonstrated in 1973 (Fig. 1).[4,5] The synthesis of the (*S*)-enantiomer of (*Z*)-14-methyl-8-hexadecen-1-ol (**3**), the dermestid beetle pheromone artefact,[6] from (*S*)-2-methylbutan-1-ol showed (*S*)-**3** to be dextrorotatory.[4,5] Because **3** isolated from the insect was levorotatory, its absolute configuration was unambiguously assigned as (*R*)-**3**. There is a practical and important notice. When comparing the specific rotations of the natural and synthetic pheromones, the same solvent must be employed. Otherwise, the sign of the rotation can just be reversed in a different solvent, as shown in the cases of **4** (a pheromone component of *Ips* bark beetles)[7] and **5** (a pheromone component of the flea beetle, *Aphthona flava*).[8]

Of course bioassays using synthetic pheromone candidates of known absolute configuration can establish the absolute configuration of the bioactive stereoisomer. Usually the absolute configuration of the bioactive isomer represents that of the natural pheromone. Care should be, however, paid in this approach, because even the unnatural stereoisomer(s) may show bioactivity. Two review chapters are available concerning the determination of the absolute configuration of pheromones.[9,10]

Since 1973 synthesis starting from a compound of known absolute configuration has become the standard method for determining the absolute configuration of pheromones. Aspects of enantioselective synthesis of pheromones are reviewed thoroughly.[11–13] If determination of the absolute configuration of pheromones were the only task for chemists working in the area of chemical communications, it could be just a part of traditional natural products chemistry. However, investigations in this area have led to the interesting and exciting discoveries that the relationships between absolute configuration and pheromone activity are diverse and complicated.[14]

Henceforth in the present review, general aspects of the subject will be treated in Sections 2, 3 and 5, while Section 4, 'Survey of stereochemistry–bioactivity relationships among pheromones' treats individual pheromones of about 140 organisms. Readers who are interested only in general aspects may skip Section 4. It is also true, however, that the important things are revealed only through a detailed treatise.

2. Bioactivity of pheromones depends on their chirality

In 1974, three groups synthesized enantiomerically pure pheromones independently, and their bioassay definitely proved that the bioactivity depends on the absolute configuration of pheromones (Fig. 2). Silverstein and co-workers converted the enantiomers of 2-methyl-4-pentenoic acid to the enantiomers of 4-methyl-3-heptanone (**6**) the principal alarm pheromone of the leaf-cutting ant, *Atta texana*.[15] The (*S*)-isomer, (+)-**6**, was ca. 400 times more active than (*R*)-(−)-**6** against the worker ants, and (*R*)-**6** did not inhibit response to (*S*)-**6**. Accordingly, (±)-**6** was also active.

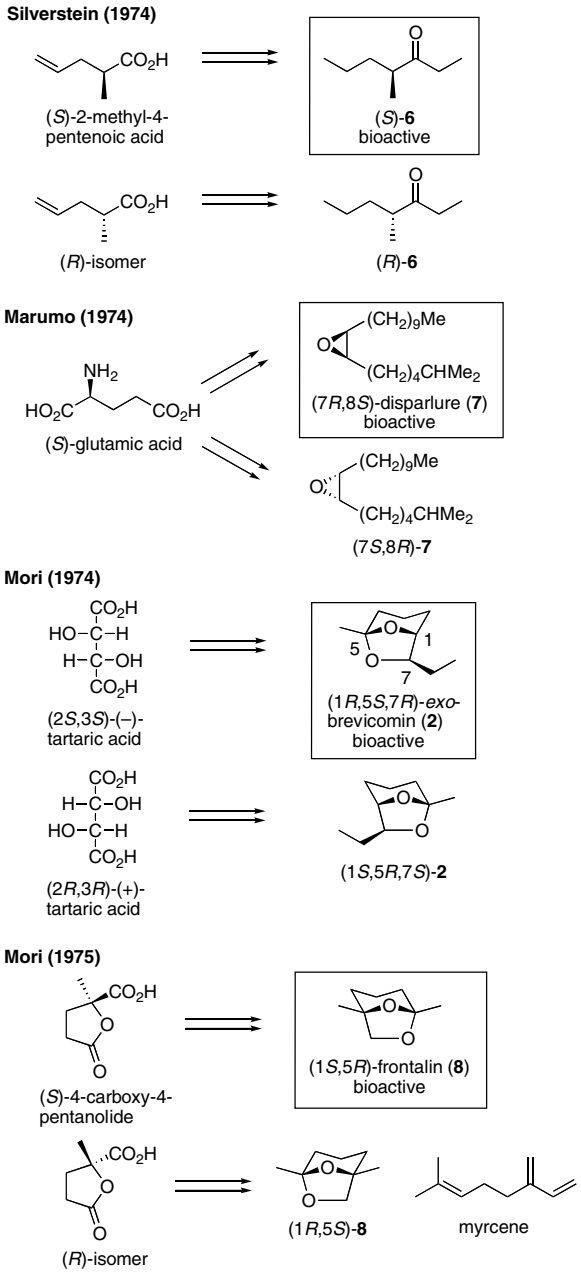


Figure 2. Early syntheses of the enantiomers of pheromones (1).

Marumo and co-workers synthesized the enantiomers of disparlure (**7**), the sex pheromone of the female gypsy moth, *Lymantria dispar*.[16] They prepared both (7*R*,8*S*)-**7** and (7*S*,8*R*)-**7** from (*S*)-glutamic acid. Behavioral response of the male gypsy moth to the enantiomers of **7** in the laboratory showed (7*R*,8*S*)-**7** (active at 10^{-10} g/mL) to be more active than (±)-**7** (active at 10^{-7} g/mL), whereas (7*S*,8*R*)-**7** was active at 10^{-4} g/mL only. (7*R*,8*S*)-**7** was 10^6 times more active than (7*S*,8*R*)-**7**.

At that time it was of interest to me whether the enantiomers of highly dissymmetric compounds might evoke totally different olfactory reactions or not, and thus I undertook the synthesis of the enantiomers of *exo*-brevicomin (**2**).[17] Two intramolecular bicyclic acetals, *exo*-brevicomin (**2**) and frontalin (**8**), were known to be the components of the aggregation pheromone of the western pine beetle, *D. brevicomis*, although their absolute configuration had not been clarified. (+)-*exo*-Brevicomin (1*R*,5*S*,7*R*)-**2** was synthesized from unnatural (2*S*,3*S*)-(−)-tartaric acid, while its natural (2*R*,3*R*)-(+)-isomer yielded (1*S*,5*R*,7*S*)-(−)-**2**. Pure enantiomers of *exo*-brevicomin were sent to David L. Wood in the USA in early 1974. Only (1*R*,5*S*,7*R*)-(+)-**2** was bioactive against *D. brevicomis*, when mixed with (±)-frontalin (**8**) and the achiral monoterpene myrcene of the host pine tree. The antipodal (1*S*,5*R*,7*S*)-(−)-**2** had no activity at all. Because frontalin (**8**) was also a pheromone component, its enantiomers were also synthesized by starting from the enantiomers of 4-carboxy-4-pentanolide.[18] Only (1*S*,5*R*)-(−)-frontalin (**8**) was bioactive against *D. brevicomis*. It is interesting to note that the skeletal framework of **2** possesses (1*R*, 5*S*)-configuration, while that of **8** possesses the opposite stereochemistry. Biological details of this work were published later.[19]

In all the studies discussed above, only a single enantiomer of the pheromone was found to be highly bioactive. It thus became clear that bioactivity depends on the chirality of the pheromones. This result is in accord with the generally accepted belief that a single enantiomer is important. But the reader will later see many cases that differ.

3. Diversity in recognition of chirality by organisms

3.1. Synergistic response based on enantiomers—sulcatol

Sulcatol (**9**, Fig. 3) is the aggregation pheromone produced by males of *Gnathotrichus sulcatus*, an economically important ambrosia beetle in the Pacific coast of North America.[20] Silverstein and co-workers showed the natural pheromone to be a 35:65 mixture of (*R*)-**9** and (*S*)-**9** by ^{1}H NMR analysis of its Mosher ester

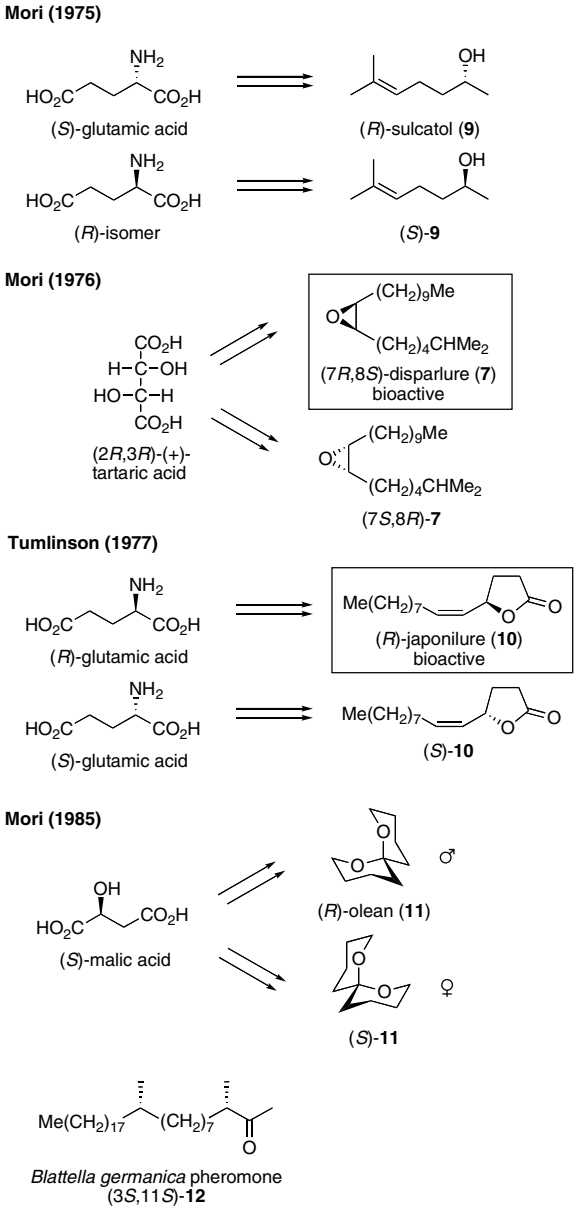


Figure 3. Early syntheses of the enantiomers of pheromones (2), and the structure (3*S*,11*S*)-**12** of the sex pheromone of the German cockroach.

(α-methoxy-α-trifluoromethylphenylacetate).[20] The reason why the beetle produces a mixture of enantiomers was unclear at the time of its discovery. The enantiomers of sulcatol were synthesized by myself by starting from the enantiomers of glutamic acid.[21] When they were bioassayed in Canada, Borden et al. found neither (*R*)-**9** nor (*S*)-**9** to be bioactive.[22] The maximum response of the beetle was to a racemic mixture (50:50) of the enantiomers, and the response to (±)-**9** was significantly greater than that to a 35:65 mixture. It thus became clear that the beetles must produce a mixture of enantiomers of **9** if they are to communicate with each other. This discovery in 1976 was the first example of a synergistic response based on enantiomers.

It must be added that in a closely related species, *Gnathotrichus retusus*, the insect produces and goes to (*S*)-sulcatol.[217] Therefore, in the case of sulcatol, both enantiomers are necessary in one species (*G. sulcatus*), but one enantiomer is active in a closely related species (*G. retusus*).

3.2. Inhibition by the wrong enantiomer—disparlure and japonilure

As already described in Section 2, (±)-displarlure (**7**) is not as active as (7*R*,8*S*)-(+)-**7**, and (7*S*,8*R*)- (−)-**7** is almost inactive.[16] Dosage-response effects of the inactive (7*S*,8*R*)-(−)-**7′** were therefore evaluated by Vité et al. on the gypsy moth[23] by employing the enantiomers of disparlure synthesized by us from (+)-tartaric acid.[24,25] Although the response to low concentrations (10^{-3}–10^{-5} dilution) of (7*R*,8*S*)-(+)-**7** was not affected substantially by addition of equal or lower concentrations of (7*S*,8*R*)-(−)-**7**, concentrations of (7*S*,8*R*)-(−)-**7** higher than those of the antipode drastically reduced the response of the moths. Electroantennographic studies on the gypsy moth by Miller et al. by use of the differential receptor saturation technique suggest the existence of one receptor type with the greatest affinity for (7*R*,8*S*)-**7**, and another type with greater affinity for (7*S*,8*R*)-**7**.[26]

Japonilure (*R*)-**10** is the sex pheromone produced by the female Japanese beetle, *Popillia japonica*.[27] Because (±)-**10** was biologically inactive, Tumlinson et al. carefully studied in 1977 the relationship between the enantiomeric purity of **10** and its pheromone activity.[27] They synthesized the enantiomers of japonilure, starting from the enantiomers of glutamic acid. The bioactive enantiomer is (*R*)-(−)-**10**, and (*S*)-(+)-**10** severely inhibits the action of (*R*)-**10**. Accordingly, (*R*)-**10** of 99% ee is only two-thirds as active as pure (*R*)-**10**; that of 90% ee is one-third as active, that of 80% ee is one-fifth as active as pure (*R*)-**10**. Both (*R*)-**10** of 60% ee and (±)-**10** were inactive. These results illustrate dramatically the importance of enantiomeric composition in chemical communication. Later in 1996, Leal found that the sex pheromone of the female scarab beetle, *Anomala osakana*, is (*S*)-**10**, while (*R*)-**10** interrupts the attraction caused by (*S*)-**10**.[28] Here again, chirality accounts for species discrmination.

3.3. One enantiomer is active against males whereas the opposite enantiomer affects females—olean

An unusual example of the relationship between stereochemistry and pheromone activity is that of olean (**11**), the sex pheromone produced by the female olive fruit fly, *Bactrocera oleae*. Both enantiomers of **11** were synthesized by us from (*S*)-malic acid,[29,30] and bioassayed in Greece by Haniotakis et al.[31] Surprisingly, (*R*)-**11** was active against males, whereas (S)-**11** was active against females.[31] GC analysis on a chiral stationary phase of natural olean by Schurig revealed it to be (±)-**11**.[31] Thus, the female-produced pheromone activates male olive fruit flies and the female herself.

3.4. All the stereoisomers are bioactive, and the natural pheromone is the least active among them—the German cockroach pheromone

Females of the German cockroach, *Blattella germanica*, produce (3*S*,11*S*)-**12** as their contact sex pheromone. We synthesized all of the four stereoisomers of **12** in 1981.[32] Nishida et al. identified (3*S*,11*S*)-**12** as the natural pheromone, and found all the isomers to be bioactive.[33] Our second synthesis of (3*S*,11*S*)-**12** and its three stereoisomers in 1990 afforded highly pure isomers of **12**.[34] Bioassay of the four isomers of **12** by Schal and co-workers revealed that the natural pheromone (3*S*,11*S*)-**12** was the least effective of the four isomers at eliciting courtship responses in males.[35] The cockroach produces the least active (3*S*,11*S*)-**12** due to the stereochemical restriction in the course of its biosynthesis. In the laboratory, however, all the stereoisomers of **12** with more potent pheromone activity can be synthesized.

3.5. Role of chirality in the communication among Asian elephants

According to Rasmussen's recent study, male Asian elephants (*Elephas maximus*) release frontalin (**8**) from the temporal-gland on the face during musth, which is an annual period of sexual activity and aggression.[36] The ratio of frontalin enantiomers enables other elephants to distinguish both the maturity of male elephants in musth and the phase of musth. In young males, significantly more (1*R*,5*S*)-(+)- than (1*S*,5*R*)-(−)-frontalin is released. As the elephant matured, the ratio becomes almost equal to emit (±)-frontalin. Musth periods get longer as males age. Secretions containing high concentrations of frontalin at racemic ratios attracted follicular phase females, whereas the secretions repulsed males as well as luteal-phase and pregnant females. The importance of the enantiomeric composition of frontalin (**8**) in the behavior of Asian elephants could be noticed only after the advent of enantioselective GC. It must be added that bark beetles employ (1*S*,5*R*)-(−)-frontalin (**8**) as their pheromone components.

3.6. Chirality plays a role even with an achiral pheromone

The European corn borer, *Ostrinia nubilalis*, and the redbanded leaf roller, *Argyrotaenia velutinana*, use (*Z*)-11-tetradecenyl acetate (**13**, Fig. 4) both as a sex attractant and as a precopulatory behavior pheromone. The two pheromone receptor systems are different. The sex attractant system requires specific ratios of (*Z*)- to (*E*)-11-tetradecenyl acetate for each insect, and the precopulatory behavior pheromone system is relatively insensitive to the presence or absence of (*E*)-11-tetradecenyl acetate. Chapman et al. demonstrated that within the precopulatory behavior pheromone system, there are at least two different receptors for **13**, that the receptors for achiral **13** are chiral, and that **13** is coiled differently (**13A** and **13B**) in the two receptors.[37] Chapman's unique strategy for clarifying the situation was to synthesize the pure enantiomers of **14**, which were regarded as conformationally fixed mimics of the two conformers of **13**.

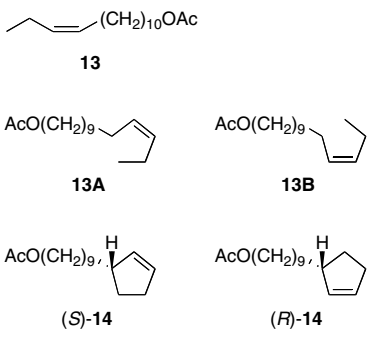


Figure 4. The two conformers **13A** and **13B** of (*Z*)-11-tetradecenyl acetate (**13**), which correspond to the chiral pheromone mimics (*S*)- and (*R*)-**14**.

Although the European corn borer responds to (*S*)-**14** (which mimics conformer **13A**) as strongly as it does to the natural pheromone **13**, it responds only weakly to (*R*)-**14** (which mimics conformer **13B**). The response to (±)-**14** is intermediate between the responses to the pure enantiomers. These data are consistent with the presence of a single stereoselective pheromone receptor. The redbanded leaf roller, on the other hand, responds equally to (*R*)- and (*S*)-**14**, but responds much more strongly to (±)-**14** than to either enantiomer. The greater activity of (±)-**14** in the redbanded leaf roller requires two stereospecific receptors, one sensitive to (*R*)-**14** and the other sensitive to (*S*)-**14**. The redbanded leaf roller has thus evolved two receptors, which sense different conformations (**13A** and **13B**) of the achiral (but prochiral) pheromone **13**.

It has become clear from the work of Chapman et al.[37] that the detection system for this particular precopulatory behavior pheromone makes very clever use of the prochiral character of the achiral olefinic pheromone. Chirality is important even among achiral olefinic pheromones, because the receptor is chiral.

4. Survey of stereochemistry–bioactivity relationships among pheromones

The relationships between stereochemistry and bioactivity are far from straightforward as already described in Section 3. In this Section, a more extensive survey of stereochemistry–bioactivity relationships among pheromones will be presented, referring to many structures of pheromones as shown in Figures 5–11.[38–192] Organisms utilize chirality to enrich and diversify their communication systems.[182] The stereochemistry–bioactivity relationships are classified into 10 categories as explained below.[183] It must be emphasized that these 10 categories were found only through experiments by using pure pheromone enantiomers of synthetic origin.

4.1. Only a single enantiomer is bioactive, and its opposite enantiomer does not inhibit the response to the active stereoisomer

Figures 5–7 show the structures of pheromones belonging to this category. Since 1974 this category

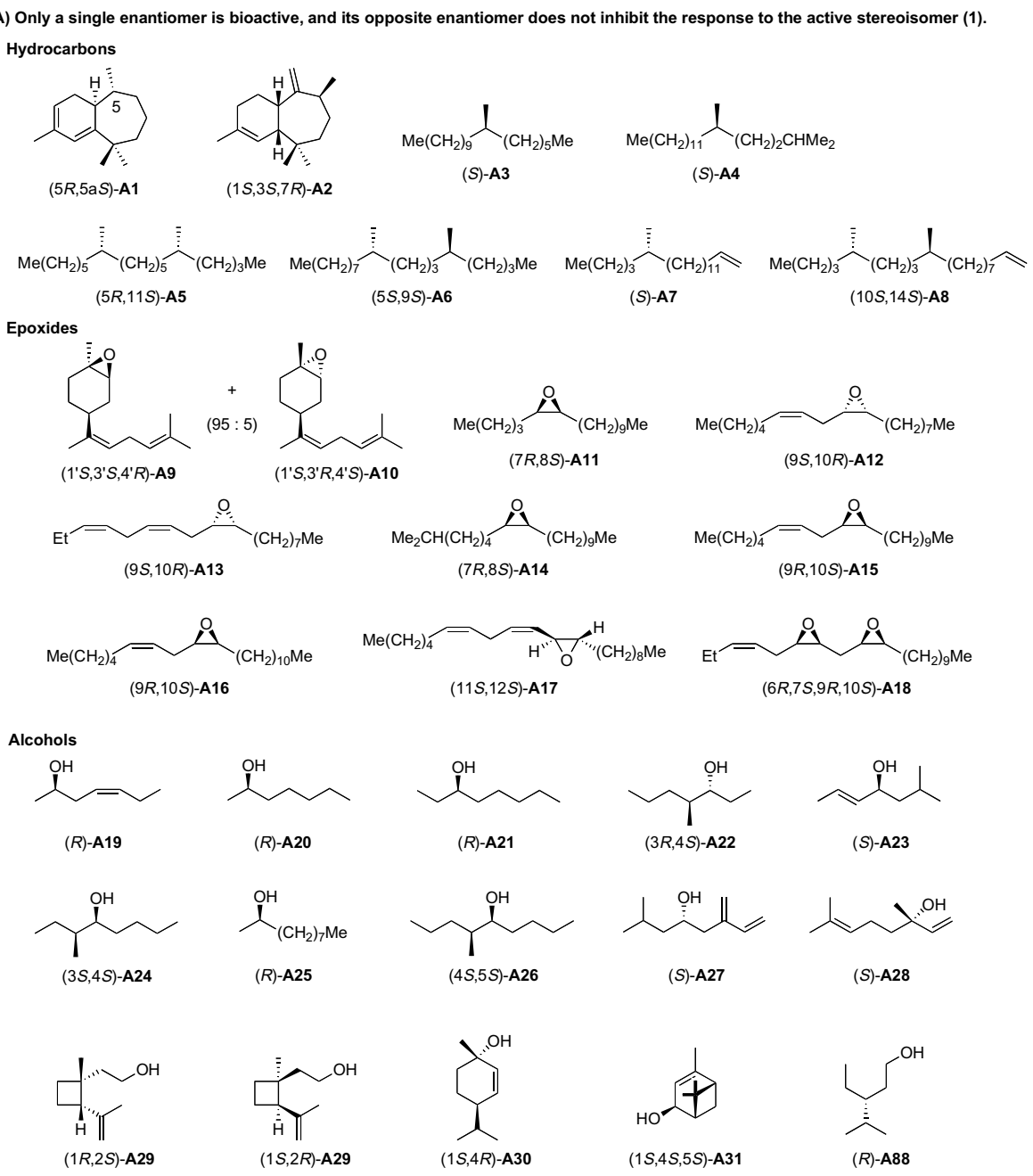


Figure 5. Stereochemistry–bioactivity relationships (1). Names of the organisms which release the pheromones **A1**–**A31** are listed below together with the references for their bioassays; **A1**, flea beetle, *Phyllotreta cruciferae*[38]; **A2**, sandfly, *Lutzomyia longipalpis* from Jacobina, Brazil[39]; **A3**, *Lambdina fiscellaria lugubrosa*,[40,41] *Lambdina athasaria*,[42] *Lambdina pellucidaria*[42]; **A4**, *Lambdina fiscellaria lugubrosa*[40,41]; **A5**, *Lambdina fiscellaria*[43]; **A6**, mountain-ash bentwing, *Leucoptera scitella*[44]; **A7**, peach leafminer, *Lyonetia clarkella*[187]; **A8**, apple leafminer, *Lyonetia prunifoliella* in Korea[45]; **A9** and **A10**, green stink bug, *Acrosternum hilare*[46]; **A11** (monachalure), nun moth, *Lymantria monacha*[47]; **A12** and **A13**, mulberry looper, *Hemerophila atrilineata*[48]; **A14**, *Lymantria fumida*[47]; **A15** and **A16**, painted apple moth, *Teia anartoides*[49]; **A17** (posticlure), tussock moth, *Orgyia postica*[50]; **A18** (leucomalure), satin moth, *Leucoma salicis*[51]; **A19** and **A20**, moth, *Eriocrania cicatricella*[52]; **A21**, ant, *Myrmica rubra*[53]; **A22**, ponerine ant, *Leptogenys diminuta*[54]; **A23** (rhynchophorol), American palm weevil, *Rhynchophorus palmarum*[55]; **A24** (phoenicol), African palm weevil, *Rhynchophorus phoenicis*[56,57]; **A25**, ant, *Crematogaster castanea*[58]; **A26**, palm weevils, *Rhynchophorus bilineatus*, *R. ferrugineus*, and *R. vulneratus*[59]; Indian sugarcane weevil, *Metamasius hemipterus sericeus*[60]; palm weevil, *Dynamis borassi*[61]; **A27** (ipsenol), fivespined engraver, *Ips grandicollis*,[188] and European fir engraver, *Pityokteines curvidens*[189]; **A28** (linalool), bee, *Colletes cunicularius*[62]; (1*R*,2*S*)-**A29** (grandisol), cotton boll weevil, *Anthonomus grandis*,[63] (1*S*,2*R*)-**A29**, *Pisodes nemorensis* and *P. strobi*[64]; both enantiomers of grandisol, Pecan weevil, *Curculio caryae*[65]; **A30** (quercivorol), ambrosia beetle, *Platypus quercivorus*[66]; **A31** (*cis*-verbenol), *Ips typographus*.[190] **A88**, queen sex pheromone of the slave-making ant, *Polyergus breviceps*.[216]

has been found to be the most common relationship, and the majority (about 60%) of the chiral pheromones belong to this group. Pheromones in this category can be used as their racemates in practical applications.

In the case of nepetalactone (**A69**), only the (4a*S*,7*S*,7a*R*)-isomer is active as the sex pheromone of the vetch aphid, *Megoura viciae*,[100] but to cats both enantiomers of **A69** are powerful attractants.[184] The bark beetle pheromone *exo*-brevicomin (**A79**)[19] shares the same

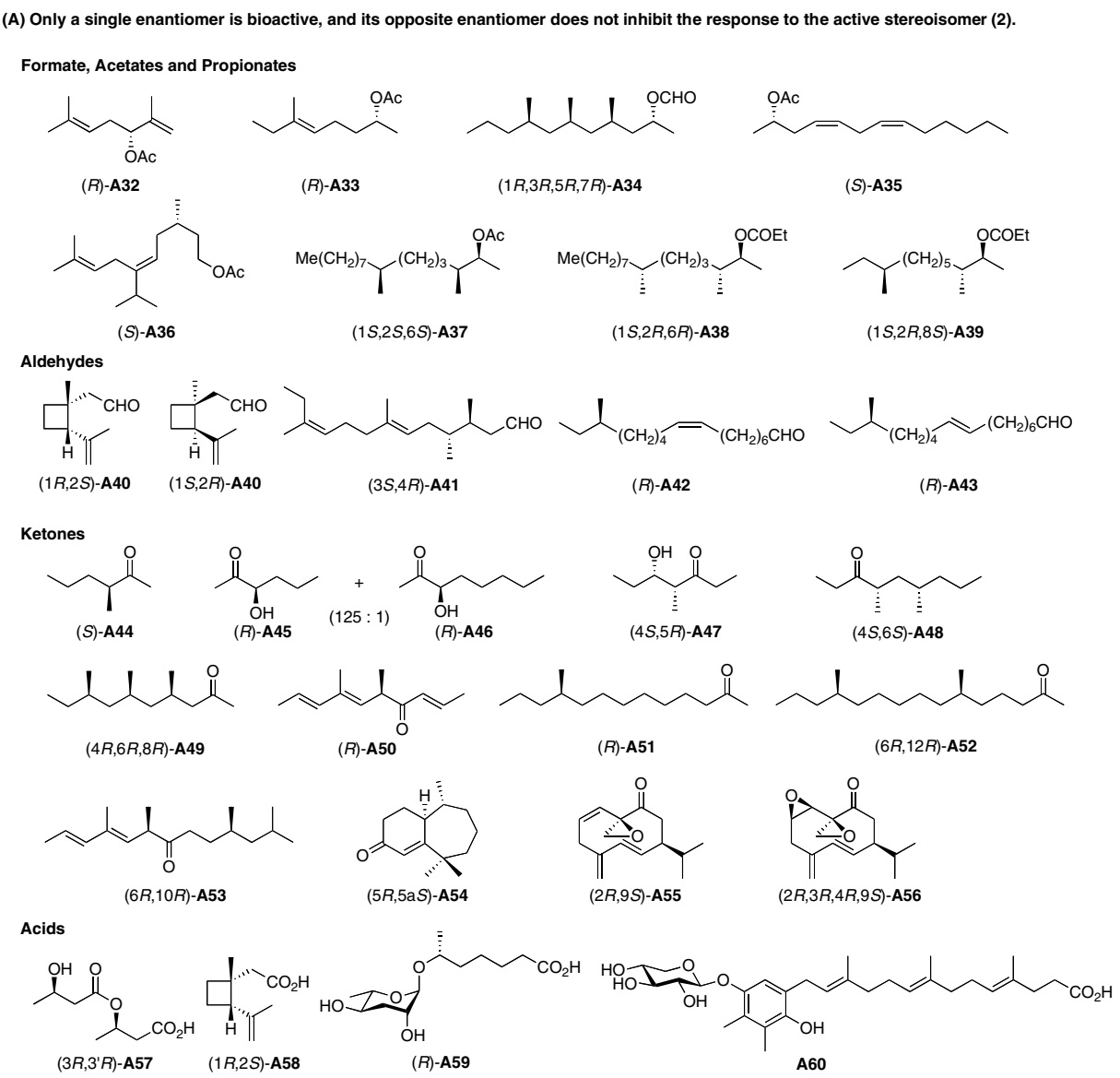


Figure 6. Stereochemistry–bioactivity relationship (2). Names of the organisms which release the pheromones **A32**–**A60** are listed below together with the references for their bioassays: **A32**, comstock mealy bug, *Pseudococcus comstockii*[67]; **A33** (quadrilure), square-necked grain beetle, *Cathartus quadricollis*[68]; **A34** (lardolure), mite, *Carpoglyphus lactis*[69]; **A35**, Douglas-fir cone gall midge, *Contarinia oregonensis*[70]; **A36**, yellow scale, *Aonidiella citrina*[71]; **A37**, white pine sawfly, *Neodiprion pinetum*.[72,73] Methyl-branched and long-chain aliphatic alcohols as their acetates or propionates are employed as sex pheromones of pine sawflies.[74] **A38**, pine sawfly, *Diprion similis*[73]; pine sawfly, *Gilpinia pallida*[75]; **A39**, pine sawfly, *Diprion nipponica*[76]; (1*R*,2*S*)-**A40** (grandisal), *Pissodes strobi* (60% ee)[64]; (1*S*,2*R*)-**A40**, *Pissodes nemorensis* (100% ee)[64]; *P. strobi* antennae detect both enantiomers of **A29** and **A40**. The antennae of *P. nemorensis* respond significantly more to (1*R*,2*S*)-**A40** than to its enantiomer, despite the fact that the insect produces only (1*S*,2*R*)-**A40**. **A41** (faranal), pharaoh's ant, *Monomorium pharaonis*[77]; **A42** [(*Z*)-trogodermal] and **A43** [(*E*)-trogodermal], dermestid beetle, *Trogoderma inclusum*[78]; khapra beetle, *T. granarium*[79]; **A44**, leaf-cutting ant, *Atta texana*[15]; **A45** and **A46**, long horn beetle, *Anaglyptus subfasciatus*[80]; **A47** (sitophilure), rice weevil, *Sitophilus oryzae*, and maize weevil, *Sitophilus zeamais*[175,191]; **A48**, Limnephilid caddis flies, *Patanophylax latipennis*, *P. cingulatus* and *Glyphotaelius pellacidus*,[81] **A49** (chortolure), storage mite, *Chortoglyphus arcuatus*[82]; **A50**, Israeli pine bast scale, *Matsucoccus josephi*[83]; **A51**, southern corn rootworm, *Diabrotica undecimpunctata howardi*[84]; **A52**, banded cucumber beetle, *Diabrotica balteata*[192]; **A53** (matsuone), Japanese pine scale, *Matsucoccus thunbergianae*[85,86]; **A54**, flea beetle, *Phyllotreta cruciferae*[38]; **A55** (periplanone-A), American cockroach, *Periplaneta americana*[87]; **A56** (periplanone-B), American cockroach, *Periplaneta americana*[88]; **A57**, spider, *Linyphia triangularis*. This acid induces web reduction by males[89]; **A58** (grandisoic acid), plum curculio, *Conotrachelus nenuphar*[90]; **A59** (daumone), worm, *Caenorhabditis elegans*.[91] This acid induces the morphological changes that accompany worm hibernation and postpones aging. **A60** (lurlenic acid), green flagellate, *Chlamydomonas allensworthii*.[92] Only the natural D-xyloside is bioactive.

skeletal structure as that of dehydro-*exo*-brevicomin (**A78**), which is the pheromone of the male house mouse, *Mus musculus*, that induces his aggressive behavior.[113] It is interesting to note that animals as different as the mouse and the bark beetle biosynthesize these bicyclic acetals with the same absolute configuration.

4.2. Only one enantiomer is bioactive, and its opposite enantiomer inhibits the response to the pheromone

The structures of pheromones belonging to this group are shown in Figure 8. In practical application of these pheromones, pure enantiomers of the pheromones have

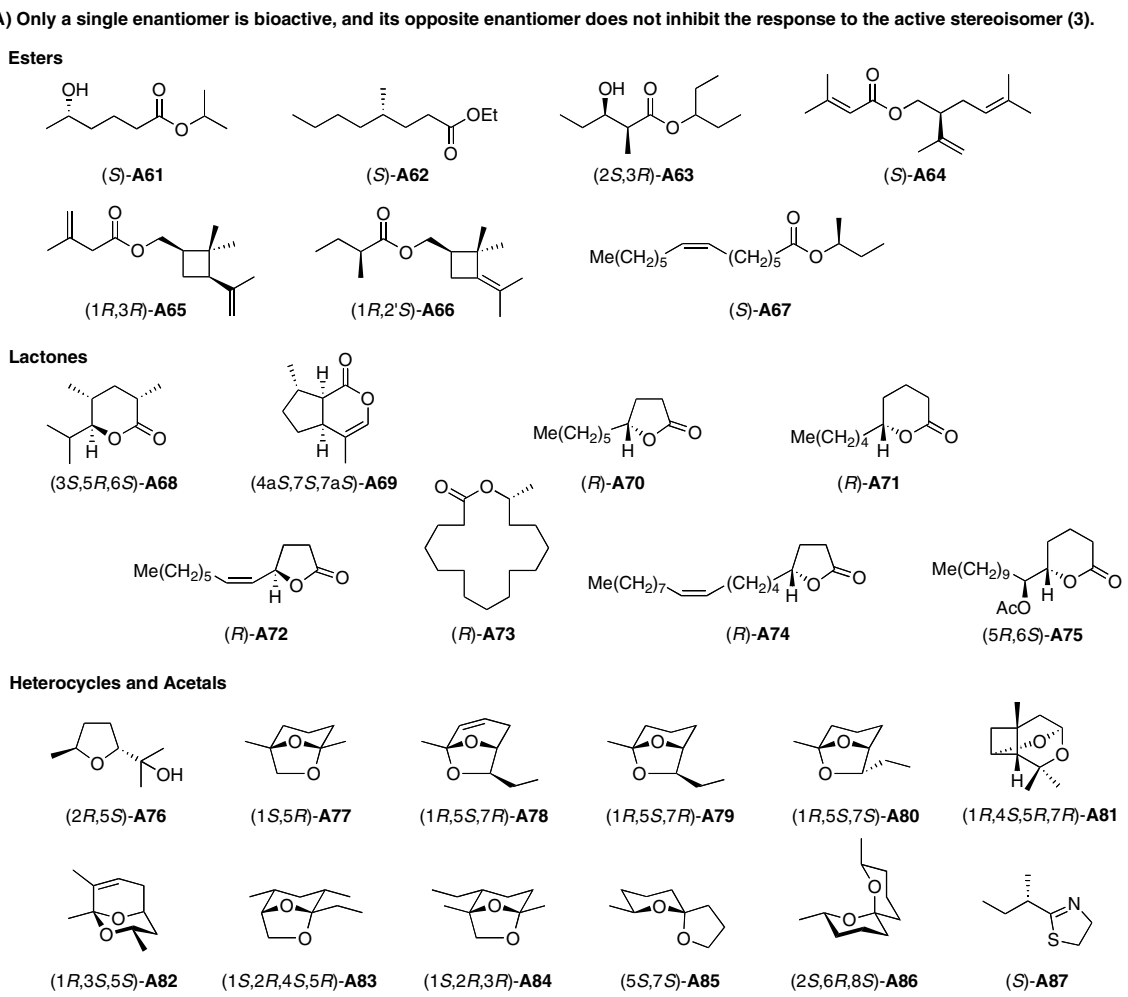


Figure 7. Stereochemistry–bioactivity relationships (3). Names of the organisms which release the pheromones **A61**–**A87** are listed below together with the references for their bioassays: **A61**, asparagus fly, *Plioreocepta poeciloptera*[93]; **A62**, coconut rhinoceros beetle, *Oryctes rhinoceros*[94]; **A63** (sitophilate), granary weevil, *Sitophilus granarius*[79,191]; **A64**, vine mealybug, *Planococcus ficus*[95]; **A65**, citrus mealybug, *Pseudococcus cryptus*[96,181]; **A66**, pink hibiscus mealybug, *Maconellicoccus hirsutus*[97]; **A67**, vine bud moth, *Theresimima ampellophaga*[98]; **A68**, wasp, *Macrocentrus grandii*[99]; **A69** (nepetalactone), aphid, *Megoura viciae*[100]; **A70**, *Osmoderma eremita*[101]; **A71**, North American porcupine, *Erethizon dorsatum* (warning odor)[102]; **A72** (buibuilactone), scarab beetle, *Anomala cuprea*,[103] and *Anomala octiescostata*[104,105]; **A73**, stink bug, *Piezodarus hybneri*[106]; **A74**, currant stem girdler, *Janus integer*[107]; **A75**, southern house mosquito, *Culex pipiens fatigans*[108]; **A76** (pityol), bark beetle, *Pityophthorus pityographus*,[109] white pine cone beetle, *Conophthorus coniperda*,[110] and red pine cone beetle, *Conophthorus resinosae*,[111] **A77** (frontalin), western pine beetle, *Dendroctonus brevicomis*,[19] and southern pine beetle, *Dendroctonus frontalis*[112]; **A78** (dehydro-*exo*-brevicomin), house mouse, *Mus musculus*[113]; **A79** (*exo*-brevicomin), western pine beetle, *Dendroctonus brevicomis*[19]; **A80** (*endo*-brevicomin), southern pine beetle, *Dendroctonus frontalis*[112]; **A81** (lineatin), striped ambrosia beetle, *Trypodendron lineatum*[114,115]; **A82**, hepialid moth, *Endoclita excrescens*[116]; **A83** (α-multistriatin), smaller European elm bark beetle, *Scolytus multistriatus*[117]; **A84** (bicolorin), *Taphrorychus bicolor*,[118] **A85** (conophthorin), white pine cone beetle, *Conophthorus coniperda*,[110] and red pine cone beetle, *Conophthorus resinosae* (repellent)[111,119]; **A86**, palaearctic bee, *Andrena wilkella*,[120] and fruit fly, *Bactrocera latifrons*[121]; **A87**, house mouse, *Mus musculus*.[122]

to be synthesized. Indeed, pure (7*R*,8*S*)-disparlure (**B1**, the gypsy moth pheromone) as well as pure (*R*)-japonilure (**B13**, the Japanese beetle pheromone) are manufactured and used practically in pest control.

4.3. Only one enantiomer is bioactive, and its diastereomer inhibits the response to the pheromone

Figure 8 also shows structures of pheromones belonging to this category. Serricornin (**C1**) is commercially important for the population monitoring and mass trapping of the cigarette beetle, *Lasioderma serricorne*. Bioactivity of the stereoisomers of **C1** was studied carefully by Chuman and co-workers in the course of developing practical pheromone traps.[133,134] Only (4*S*,6*S*,7*S*)-**C1** was bioactive. Its (4*S*,6*S*,7*R*)-isomer was inhibitory against the action of (4*S*,6*S*,7*S*)-**C1**. Accordingly, the commercial pheromone lure must be manufactured without contamination of the (4*S*,6*S*,7*R*)-isomer.

Stegobinone (**C2**) is the sex pheromone component of the female drugstore beetle, *Stegobium paniceum*. Very low bioactivity of the racemic and diastereomeric mixture of synthetic stegobinone indicated the presence of inhibitor(s) in the synthetic product. It was later shown that the addition of (2*S*,3*R*,1′*S*)-epistegobinone to stegobinone (**C2**) significantly reduces the response of male drugstore beetle.[135] Stegobinone (**C2**) is so readily epimerizable at C-1′ that even enantiomerically pure **C2** cannot be used as a practical attractant.

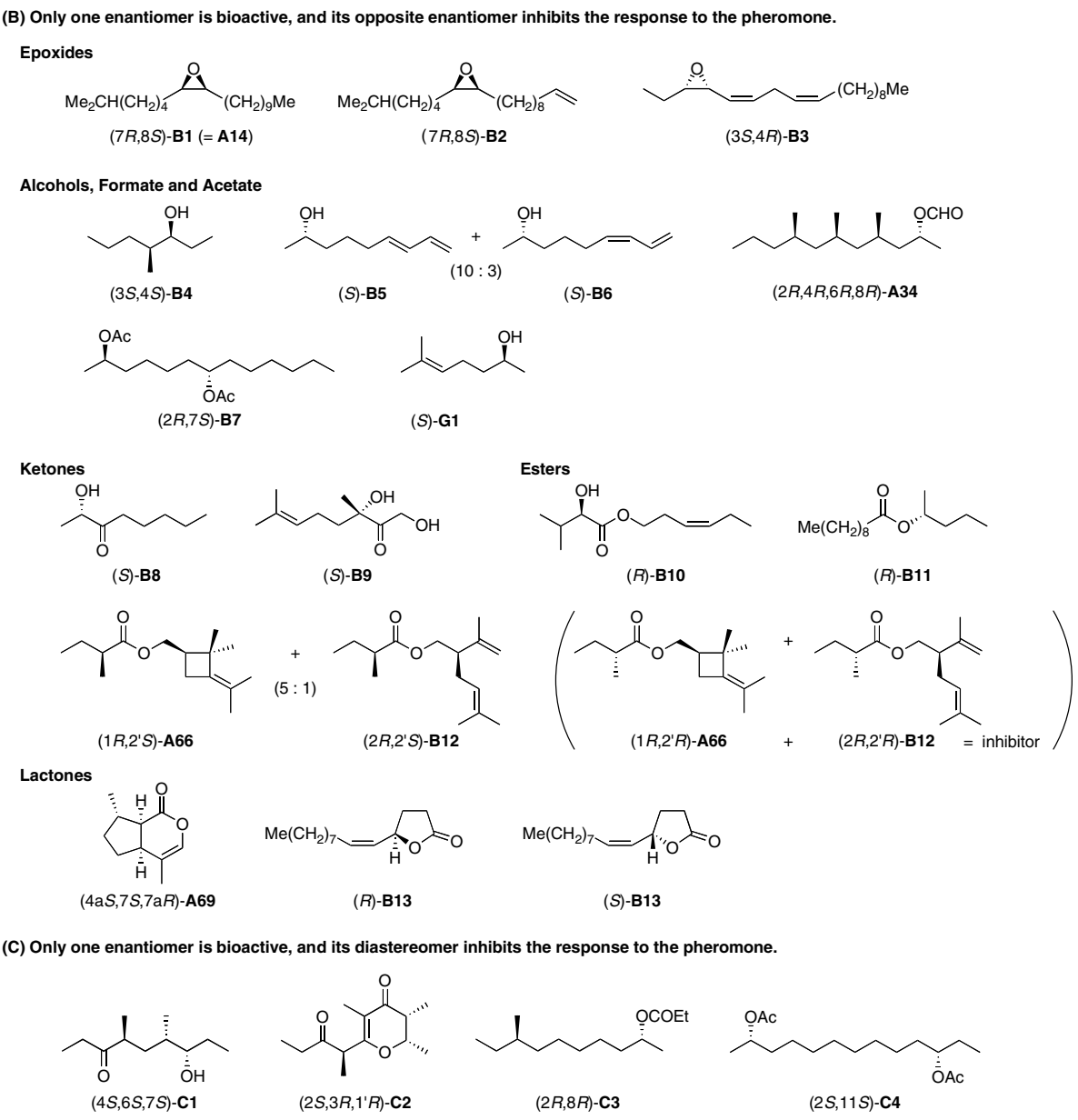


Figure 8. Stereochemistry–bioactivity relationships (4). Names of the organisms which release the pheromones **B1**–**B13** and **C1**–**C4** are listed below together with the references for their bioassays: **B1** (disparlure), gypsy moth, *Lymantria dispar*[16,23,26]; **B2**, gypsy moth, *Lymantria dispar* (trace component)[123]; **B3**, geometrid moth, *Milionia basalis pryeri*[124] **B4**, *Scolytus amygdali*[125]; **B5** and **B6**, banded apple pigmy, *Stigmella malella*,[126] **A34** (lardolure), acarid mite, *Lardoglyphus konoi*[69]; **B7**, aphidophagous gall midge, *Aphidoletes aphidimyza*[127]; Not only the (2*S*,7*R*)-isomer but also the (2*R*,7*R*)-diastereomer inhibits the action of (2*R*,7*S*)-**B7**.[127] (*S*)-**G1**, ambrosia beetle, *Gnathotrichus retusus*.[217] **B8**, grape borer, *Xylotrechus pyrrhoderus*[128]; **B9**, Colorado potato beetle, *Leptinotarsa decemlineata*[129]; **B10**, assassin bug, *Pristhesancus plagipennis*[130]; Contamination of (*S*)- as well as (*E*)-isomers causes inhibition of the activity of **B10**[130] **B11**, bagworm, *Oiketicus kirbyi*[131]; **A66** and **B12**, hibiscus mealybug, *Macronellicoccus hirsutus*[97,181]; A mixture of (1*R*,2′*S*)-**A66** and (2*R*,2′*S*)-**B12** (5:1) is the pheromone, and a mixture of (1*R*,2′*R*)-**A66** and (2*R*,2′*R*)-**B12** are inhibitory.[97] **A69** (nepetalactone), blackberry-cereal aphid, *Sitobion fragariae*[132]; (*R*)-**B13** (japonilure), Japanese beetle, *Popillia japonica*[27]; (*S*)-**B13**, scarab beetle, *Anomala osakana*[28]; **C1** (serricornin), cigarette beetle, *Lasioderma serricorne*[133,134]; **C2** (stegobinone), drugstore beetle, *Stegobium paniceum*[135]; **C3**, northern corn rootworm, *Diabrotica barberi*[136]; **C4**, pea midge, *Contarinia pisi*[137]; The (2*S*,11*S*)-isomer is the pheromone. The (2*S*,11*R*)- and (2*R*,11*S*)-isomers are strong inhibitors. The (2*R*,11*R*)-isomer does not inhibit.[137]

4.4. The natural pheromone is a single enantiomer, and its opposite enantiomer or diastereomer is also active

The structures of pheromones belonging to this group are shown in Figure 9. The most potent component of the female sex pheromone of the New World screwworm fly, *Cochliomyia hominivorax*, is (6*R*,19*R*)-6-acetoxy-19-methylnonacosane (**D3**).[140] However, all of the four stereoisomers of **D3** showed similar and strong pheromone activity at 0.5 μg level.[162]

Females of the maritime pine scale, *Matsucoccus feytaudi*, use (3*S*,7*R*)-**D5** as the sex pheromone. Its (3*R*,7*R*)-isomer also showed bioactivity similar to the natural pheromone, while *M. feytaudi* males responded

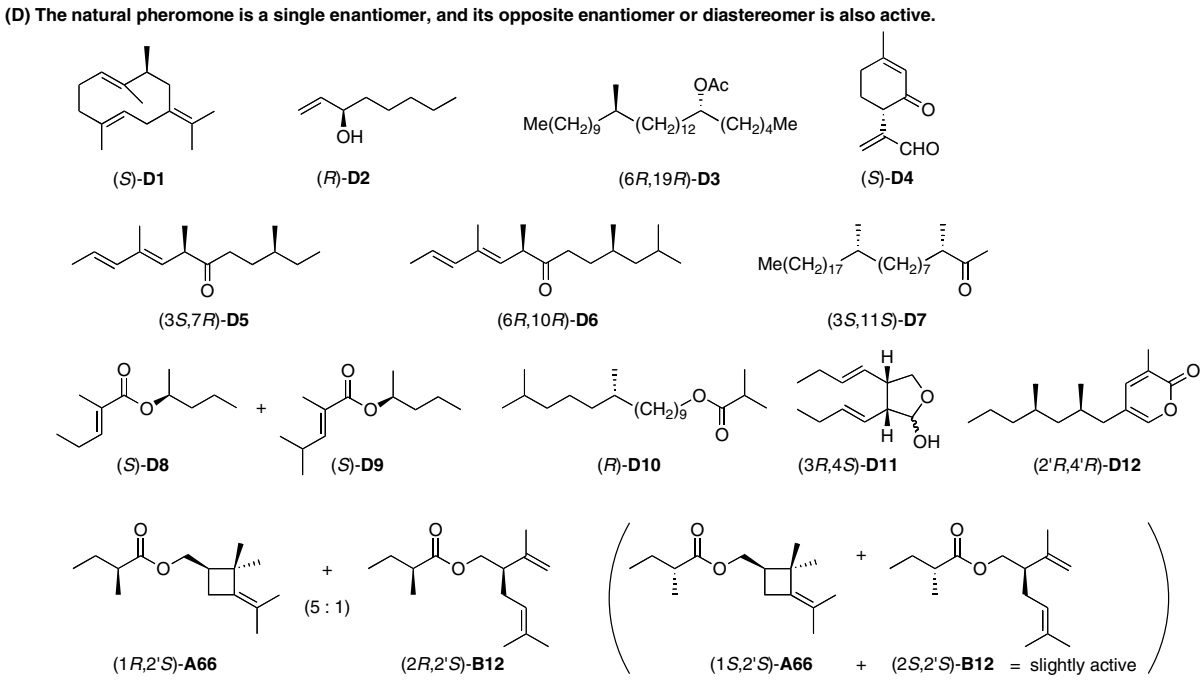


Figure 9. Stereochemistry–bioactivity relationships (5). Names of the organisms which release the pheromone **D1**–**D12** are listed below together with the references for their bioassays: **D1** (9-methylgermacrene-B), sandfly from Lapinha, Brazil, *Lutzomyia longipalpis*[138]; The unnatural (*R*)-isomer is weakly active, and the racemate is also active.[138] **D2**, foreign grain beetle, *Ahasverus advena*[139]; **D3**, New World screwworm fly, *Cochliomyia hominivorax*[140]; **D4** (vesperal), longhorn beetle, *Vesperus xatarti*[141,142]; **D5**, maritime pine scale, *Matsucoccus feytaudi*; Its (3*R*,7*R*)-isomer is also active.[143] **D6** (matsuone), *Matsucoccus resinosae*; Its (6*R*,10*S*)-isomer is as half as active as the natural pheromone.[144] **D7**, German cockroach, *Blattella germanica*[33,35]; **D8** (dominicalure1) and **D9** (dominicalure 2), lesser grain borer, *Rhyzopertha dominica*[145]; **D10**, tea tussock moth, *Euproctis pseudoconspersa*[146–149]; EAG responses of male antennae exposed to either the natural pheromone or (*R*)-**D10** were indistinguishable.[148] **D11**, spined citrus bug, *Biprorulus bibax*[150]; **D12** (supellapyrone), brownbanded cockroach, *Supella longipalpa*[151,152]; **A66** and **B12**, hibiscus mealybug, *Macronellicoccus hirsutus*[97]; A mixture of (1*R*,2′*S*)-**A66** and (2*R*,2′*S*)-**B12** (5:1) is the pheromone, while a mixture of (1*S*,2′*S*)-**A66** and (2*S*,2′*S*)-**B12** is slightly active.[97,181]

very weakly to the two other stereoisomers.[143] It therefore seems that only the stereochemistry at C-7 is important for the expression of bioactivity.

Dominicalure 1 [(*S*)-**D8**] and dominicalure 2 [(*S*)-**D9**] are the male-produced aggregation pheromone components of the lesser grain borer, *Rhyzopertha dominica*. They are attractive to both sexes of that insect. The natural (*S*)-**D8** and (*S*)-**D9** were about twice as active as their unnatural enantiomers (*R*)-**D8** and (*R*)-**D9** as assayed by field tests.[145]

The female sex pheromone of the brownbanded cockroach, *Supella longipalpa*, is (2′*R*,4′*R*)-supellapyrone (**D12**). The natural (2′*R*,4′*R*)-pheromone and its (2′*S*,4′*R*)-isomer give almost equivalent electroantennographic (EAG) responses. The (2′*S*,4′*S*)-isomer is only 10% as active as the (2′*R*,4′*R*)-pheromone, and (2′*R*,4′*S*)-isomer gives no EAG responses. Behaviorally, (2′*R*,4′*R*)-**D12** is the most active, (2′*S*,4′*R*)- and (2′*S*,4′*S*)-isomers are marginally active (1%), while (2′*R*,4′*S*)-isomer is totally inactive. In the field test, (2′*R*,4′*R*)-**D12** was active, the (2′*S*,4′*R*)-isomer was far less active, and both (2′*S*,4′*S*)- and (2′*R*,4′*S*)-isomers were inactive.[152]

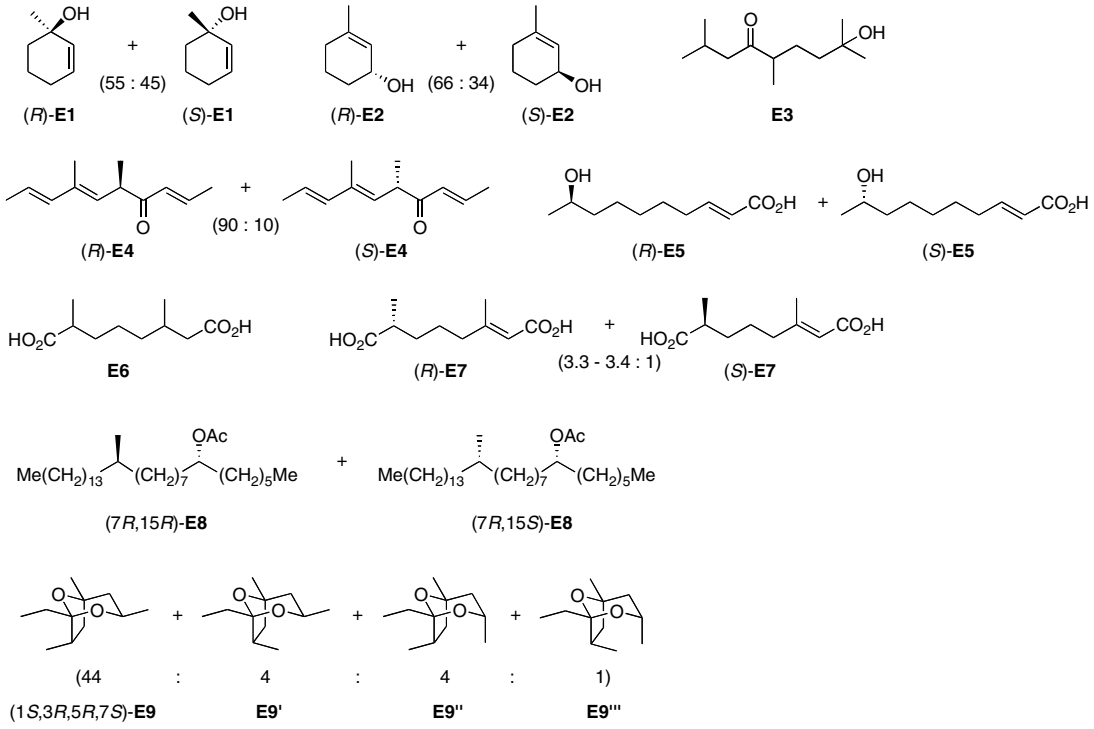
4.5. The natural pheromone is a mixture of enantiomers or diastereomers, and both enantiomers or all the diastereomers are separately active

Figure 10 shows the structures of the pheromones belonging to this group. Females of the Douglas-fir beetles, *Dendroctonus pseudotsugae*, produce an average of a 55:45 mixture of (*R*)-**E1** and (*S*)-**E1**.[153] The combined effect of the enantiomers was additive rather than synergistic, and both enantiomers are required for maximum response.

Both enantiomers of the hydroxy acid **E5**, a component of the mandibular gland secretion of the queen honey bee *Apis mellifera*, are required for optimal formation and maintenance of the retinue response.[155] The ratio of (*R*)-**E5** to (*S*)-**E5** increases with the age of the queen honeybee.[155]

The azuki bean beetle, *Callosobruchus chinensis*, uses callosobruchusic acid **E7** as its pheromone. Although (*R*)-**E7** is the major component of the natural pheromone (*R*:*S* = 3.3–3.4:1), (*R*)-**E7** is only a half as active as (*S*)-**E7**.[159,160]

(E) The natural pheromone is a mixture of enantiomers or diastereomers, and both the enantiomers or all the diastereomers are separately active.



(F) Different enantiomers or diastereomers are employed by different species.

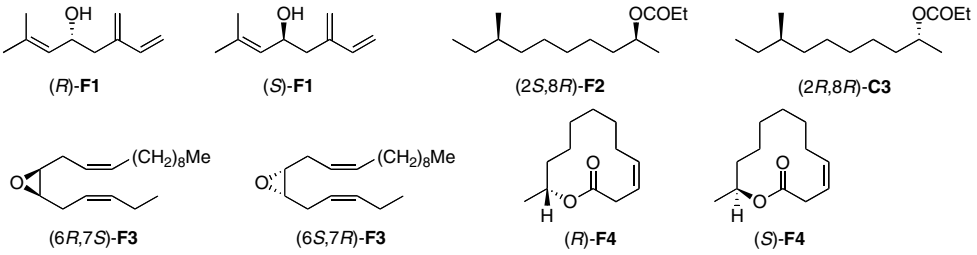


Figure 10. Stereochemistry–bioactivity relationships (6). Names of the organisms which release the pheromones **E1**–**E9** and **F1**–**F4** are listed below together with the references for their bioassays; **E1** and **E2** (seudenol), Douglas-fir beetle, *Dendroctonus pseudotsugae*[153]; **E3** (stigmolone), myxobacterium, *Stigmatella aurantiaca*[154]; The natural pheromone is a ca. 1:1 mixture of the enantiomers. Both the enantiomers are separately active.[154] **E4**, Israeli pine bast scale, *Matsucoccus josephi*.[83] The natural pheromone is a 9:1 mixture of enantiomers. In a field test, (*R*)-**E4** was ten times more active than (*S*)-**E4**.[83] **E5**, honey bee, *Apis mellifera*[155]; There is a report that (*R*)-**E5** is ten times more active than (*S*)-**E5**.[156] **E6**, cowpea weevil, *Callosobruchus maculatus*[157,158]; The natural pheromone is a mixture of all the four isomers, all of which induce copulation behavior in males at similar doses. **E7** (callosobruchusic acid), azuki bean beetle, *Callosobruchus chinensis*[159,160]; (7*R*,15*R*)-**E8** and (7*R*,15*S*)-**E8**, New World screwworm fly, *Cochliomyia hominivorax*[140]; All the four diastereomers are active.[161,162] **E9** (sordidin), **E9′**, **E9″**, **E9‴**, banana weevil, *Cosmopolites sordidus*,[163–165] The major pheromone is **E9**. All the isomers are electrophysiologically active. **F1** (ipsdienol), (*R*)-**F1**; bark beetles *Ips calligraphus* and *Ips avulsus*,[167] (*S*)-**F1**: bark beetle, California fivespined ips, *Ips paraconfusus*[166]; *Ips pini* uses a mixture of enantiomers.[167,168] (2*S*,8*R*)-**F2**, corn rootworm, *Diabrotica porracea*,[169] (2*R*,8*R*)-**F2** (=**C3**), western corn rootworm, *Diabrotica virgifera virgifera*,[170] (6*R*,7*S*)-**F3**, geometrid moth, *Colotois pennaria*,[171] (6*S*,7*R*)-**F3**, geometrid moth, *Erannis defoliaria*[171] (*R*)-**F4**, merchant grain beetle, *Oryzaephilus mercator*[172]; (*S*)-**F4**, rusty grain beetle, *Cryptolestes ferrugineus*.[172].

4.6. Different enantiomers or diastereomers are employed by different species

Ipsdienol (**F1**) plays a decisive role in the communication systems of bark beetles belonging to the genus *Ips* (Fig. 10). (*R*)-Ipsdienol (**F1**) is the aggregation pheromone of the bark beetles *Ips calligraphus* and *Ips avulsus*,[166] and (*S*)-ipsdienol (**F1**) is the pheromone component of the California fivespined ips, *Ips paraconfusus*.[185] *Ips pini* in New York employs a mixture of (*R*)-**F1**:(*S*)-**F1** = 32–56:68–44, while that in California uses a mixture of (B)-**F1**:(S)-**F1** = 89–98:2–11.[167,168]

The female-produced diastereomeric sex pheromones **F2** and **C3** of corn rootworms were extensively studied by Tumlinson. Males of the western corn rootworm, *Diabrotica virgifera virgifera*, responded strongly to (2*R*,8*R*)-**C3**,[170] while males of *Diabrotica porracea* responded to its diastereomer (2*S*,8*R*)-**F2**.[169]

Chirality of pheromones is important to discriminate between two species of the winter-flying geometrid moths in Middle Europe. Thus (6*R*,7*S*)-**F3** is the pheromone of *Colotois pennaria*, while *Erannis defoliaria* uses (6*S*,7*R*)-**F3** as its pheromone.[171]

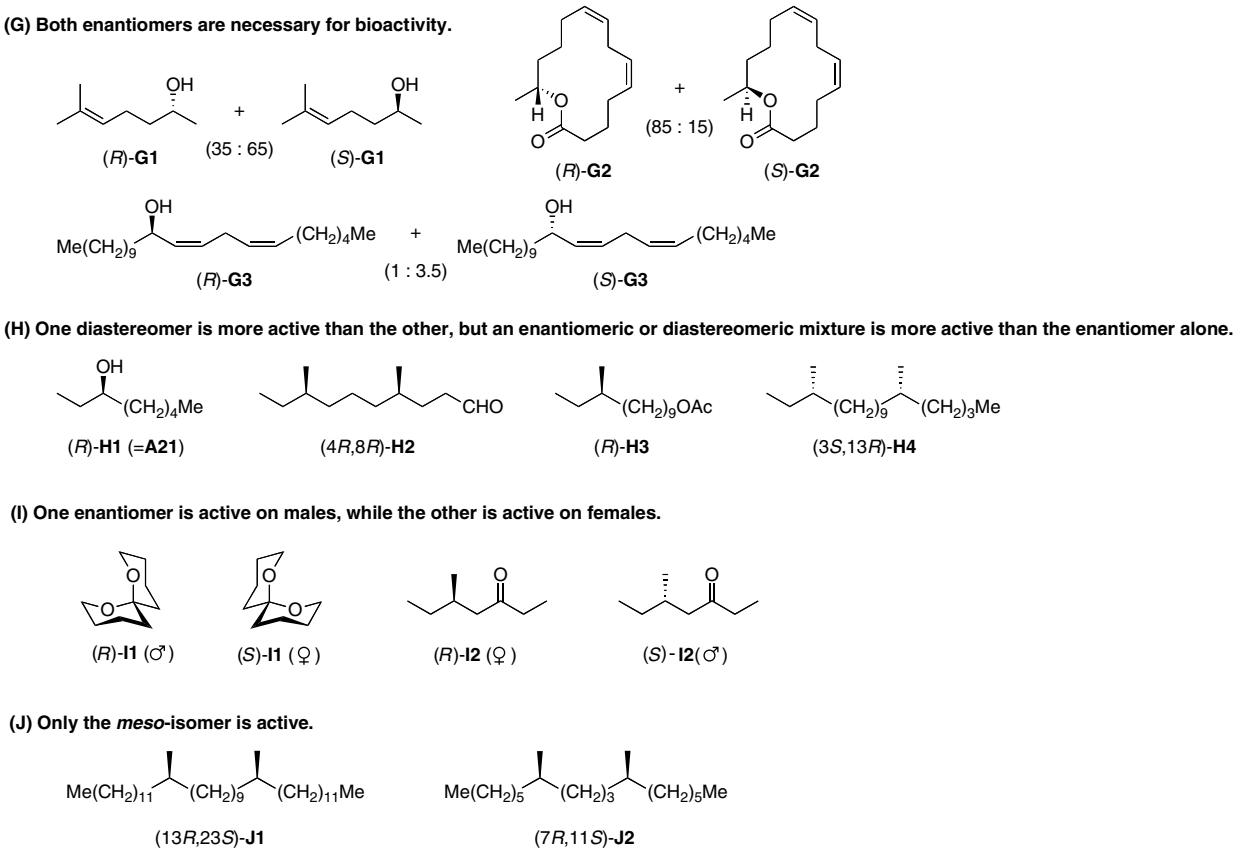


Figure 11. Stereochemistry–bioactivity relationships (7). Names of the organisms which release the pheromones **G1**–**G3**, **H1**–**H4**, **I1**, **I2**, **J1**, and **J2** are listed below together with the references for their bioassays: (*R*)-**G1** and (*S*)-**G1** (sulcatol), ambrosia beetle, *Gnathotrichus sulcatus*[22]; (*R*)-**G2** and (*S*)-**G2**, grain beetle, *Cryptolestes turcicus*[172,173]; (*R*)-**G3** and (*S*)-**G3**, tussock moth, *Orgyia detrita*[174]; **H1**, ant, *Myrmica scabrinodis*[53]; **H2** (tribolure), red-flour beetle, *Tribolium castaneum*[176]; **H3**, smaller tea tortrix moth, *Adoxophyes* sp.[177]; **H4**, western false hemlock looper, *Nepytia freemani*[178]; **I1** (olean), olive fruit fly, *Bactrocera oleae*[31]; **I2**, Nereid marine polychaete, *Platynereis dumerilii*[179,186]; **J1**, tsetse fly, *Glossina pallidipes*[180]; **J2**, spring hemlock looper, *Lambdina athasaria*.[42]

Species discrimination between the two species of grain beetles is also done by the use of the enantiomers of the lactone **F4**. The merchant grain beetle, *Oryzaephilus mercator*, uses (*R*)-**F4** as its pheromone, while (*S*)-**F4** is the aggregation pheromone of the rusty grain beetle, *Cryptolestes ferrugineus*.[172]

4.7. Both enantiomers are necessary for bioactivity

Sulcatol (**G1**, Fig. 11) was already discussed in Section 3.1. There are two additional pheromones belonging to this category. In the case of the grain beetle *Cryptolestes turcicus*, neither (*R*)-**G2** nor (*S*)-**G2** was bioactive as the aggregation pheromone. However, their mixture [(*R*)-**G2**:(*S*)-**G2** = 85:15] was bioactive.[172,173] The tussock moth *Orgyia detrita* uses a 1:3.5 mixture of (*R*)-**G3** and (*S*)-**G3** as its pheromone. It is also known that (±)-**G3** is more bioactive than the naturally occurring 1:3.5 mixture.[174]

4.8. One enantiomer is more active than the other, but an enantiomeric or diastereomeric mixture is more active than the enantiomer alone

In the case of the ant *Myrmica scabrinodis*, the naturally occurring mixture of (*R*)-**H1** and (*S*)-**H1** [(*R*)-**H1**:(*S*)-**H1** = 9:1] was more attractive than the pure (*R*)-**H1** or (±)-**H1**, while (*S*)-**H1** was inactive.[53]

Tribolure [(4*R*,8*R*)-**H2**] is the male-produced aggregation pheromone of the red-flour beetle, *Tribolium castaneum*. Suzuki found that (4*R*,8*R*)-**H2** to be as active as the natural pheromone, while a mixture of (4*R*,8*R*)-**H2** and its (4*R*,8*S*)-isomer in a ratio of 4:1 was about 10 times more active than (4*R*,8*R*)-**H2** alone.[176]

The smaller tea tortrix moth, *Adoxophyes* sp., uses (*R*)-**H3** as a minor component of its pheromone bouquet, and (*R*)-**H3** was found to be slightly more active than (*S*)-**H3**. Further field tests suggested that there is an optimum *R*:*S* ratio of 95:5 for trapping of males.[177]

In the case of the pheromone of the western false hemlock looper, *Nepytia freemani*, (3*S*,13*R*)-**H4** is electroantennographically most active, but other isomers are also EAG active. In field tests, (3*S*,13*R*)-**H4** was the only stereoisomer to attract males, but the four stereoisomer blend was 3.6 times more attractive than (3*S*,13*R*)-**H4** alone.[178]

4.9. One enantiomer is active on males, while the other is active on females

Olean (*R*)-**I1** is active against the male olive fruit fly, *B. oleae*, while (*S*)-**I1** activates the female, as has been discussed in Section 3.3. Another example is 5-methyl-3-heptanone (**I2**), which has been isolated as

a pheromone in the coelomic fluid of gravid specimens of Nereid marine polychaetes. It is responsible for the induction of the nuptial dance behavior prior to the release of gametes in *Platynereis dumerilii*, and the female-produced (*S*)-**I2** attracts the males, while the male-produced (*R*)-**I2** is active on females.[179,186]

4.10. Only the *meso*-isomer is active

There are some alkane pheromones with methyl branchings, whose *meso*-isomers are bioactive. Thus (13*R*,23*S*)-**J1** is active as the sex stimulant pheromone of the female tsetse fly, *Glossina pallidipes*.[180] Neither its (13*R*,23*R*)- nor the (13*S*,23*S*)-isomer is bioactive.

Female-produced sex pheromone components of the spring hemlock looper moth, *Lambdina athasaria*, are 7-methylheptadecane and 7,11-dimethylheptadecane. After our synthesis of all of their stereoisomers, a mixture of (*S*)-7-methylheptadecane and (7*R*,11*S*)-**J2** (*meso*-isomer) was found to be bioactive.[42]

5. Prospects in stereochemical studies of pheromones

Our knowledge in this area of pheromone science increased enormously after three decades of research by many research groups. Nevertheless, there are many remaining things to be clarified. We need new methodologies to solve the problems. In this Section, new methods and trends will be summarized.

5.1. Advances in analytical methods

Precise determination of the enantiomeric purity of an optically active compound is of fundamental importance in the study of chiral pheromones. GC and HPLC analysis on various optically active stationary phases became the standard method for that purpose.[9,10]

Ohrui and Akasaka recently developed a promising method for the determination of enantiomeric purity at a remote stereogenic center far separated from functional groups.[193–195] They designed optically active and fluorescent derivatizing reagents like (1*R*,2*R*)- and (1*S*,2*S*)-2-(2,3-anthracenedicarboximido)cyclohexanol (**15**, Fig. 12). Due to the fluorescent nature of the reagent, detection of the derivatives is possible at 10^{-15} M level. The reagent **15** was used by us to determine the absolute configuration of plakoside A (**16**), a marine galactosphingolipid.[196] Oxidative degradation of **16** gave chiral and cyclopropane-containing carboxylic acid **17**. Authentic samples of both enantiomers of **17** were prepared and condensed with **15** to give ester **18** and its diastereomer. The mixture of **18** and its diastereomer could be separated cleanly, when it was subjected to HPLC analysis at a low temperature (−50 °C). The ester **18** derived from the natural plakoside A (**16**) was identified as (6*S*,7*R*)-**18**. Similarly, the stereochemistry of the sphingosine part was also determined to establish the absolute configuration of plakoside A as depicted in **16**.

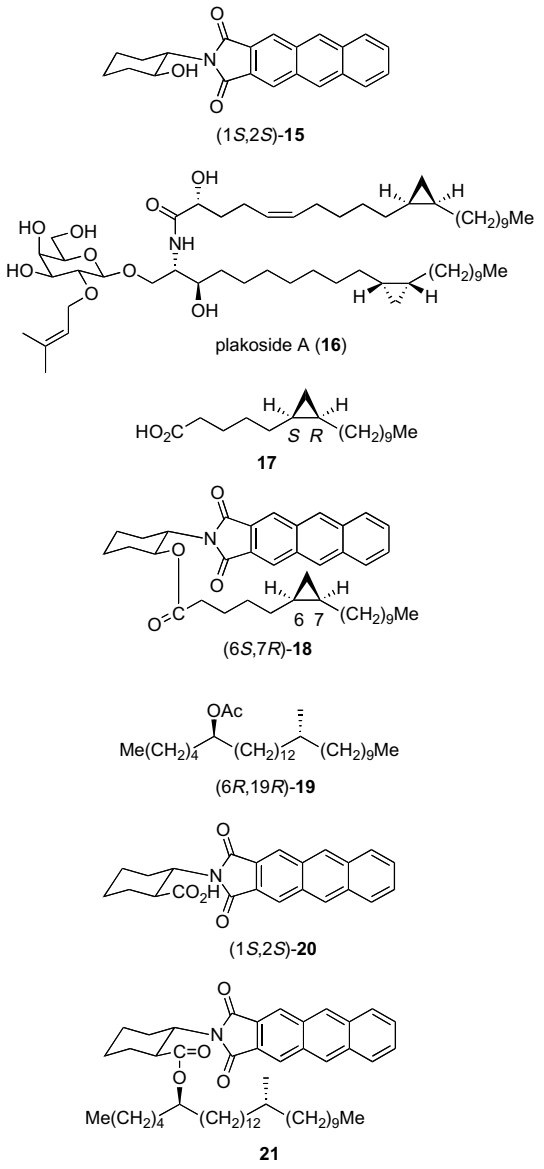


Figure 12. Structures of compounds related to the HPLC analysis of **18** and **21**.

This technique was then applied for the determination of the enantiomeric purity of the synthetic pheromone of the New World screwworm fly, *C. hominivorax*.[161,162] The most bioactive component of the New World screwworm fly pheromone is the acetate **19**. To estimate the enantiomeric purity of the parent alcohol prior to acetylation to give **19**, the alcohol was esterified with (1*S*,2*S*)-2-(2,3-anthracenedicarboximido)cyclohexanecarboxylic acid (**20**). The ester **21** derived from the four diastereomers of **19** could be separated by HPLC at a low temperature (−30 or −40 °C), and the natural pheromone was shown to be (6*R*,19*R*)-**19** by employing 10–20 femtomoles of the samples.[140] This method will be used widely to determine the absolute configuration of a stereogenic center far remote from alcoholic or carboxylic functionalities.[157,159,197] Of course authentic samples with known absolute configuration must be prepared so as to be employed as reference samples.

5.2. Advances in synthetic methods

In order to study the relationships between stereochemistry and pheromone activity, we must have useful synthetic methods to prepare all of the possible stereoisomers. A review is available, which summarizes the advances in this field between 1990 and early 2003.[198] More recent examples will be given below to illustrate the trends in modern pheromone synthesis.

The cane beetle *Antitrogus parvulus* is a pest on sugarcane crops in Australia. From its cuticular hydrocarbons Kitching and his co-workers isolated and identified 4,6,8,10,16,18-hexamethyldocosane (**22**, Fig. 13),[199,200] whose absolute configuration and biological roles remained unknown. The presence of six methyl groups on a docosane straight chain made it difficult to synthesize various stereoisomers of **22** under good stereocontrol. In 2005 Herber and Breit synthesized the hydrocarbon **22**, and determined the absolute configuration of the natural product as (4*S*, 6*R*,8*R*,10*S*,16*R*,18*S*)-**22**.[201] Subsequently in 2007 Burgess and co-workers reported another synthesis of (4*S*,6*R*,8*R*,10*S*,16*R*,18*S*)-**22**.[202] It is now possible to determine the absolute configuration of a pheromone with numerous stereogenic centers by employing powerful enantioselective synthetic methods, provided the stereoisomers can be separated so that analytical data of the natural product can be unambiguously compared with those of synthetic samples.

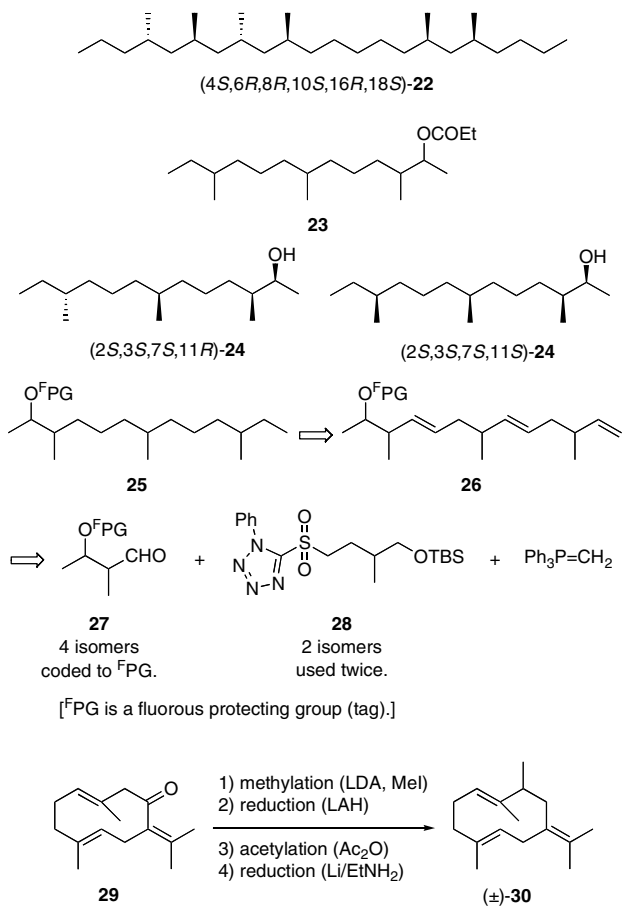


Figure 13. Structures of compounds related to new trends in pheromone synthesis.

Some pine sawflies are severe pests on pines in northern hemisphere. Their pheromones were studied extensively in the USA,[72,73] Sweden[74,75] and Japan,[76] and shown to be acetates or propionates of methyl-branched and long-chain secondary alcohols such as **A37**, **A38**, and **A39** (Fig. 6). There are some pheromones with four stereogenic centers such as the propionate **23** (Fig. 13) of 3,7,11-trimethyltridecan-2-ol (sex pheromone of *Macrodiprion pallipes*),[203] and the acetate of 3,7,9-trimethyltridecan-2-ol (sex pheromone of *Macrodiprion nemoralis*).[204] Hedenström and his co-workers synthesized all of their 16 possible stereoisomers.[203,204] Although the synthesis of their stereoisomeric mixtures was not so difficult,[205] the enantioselective synthesis of all the 16 stereoisomers of these pheromones was indeed a result of tremendous effort and patience.[203,204] After preparing all the 16 isomers of **24**, it was confirmed that (2*S*,3*S*,7*S*,11*R*)-**24** and (2*S*,3*S*,7*S*,11*S*)-**24** were used as pheromone precursors in female *Microdiprion pallipes*.[203]

In 2005 Curran and his co-workers published much more efficient syntheses of the 16 stereoisomers of **23** on 10–20 mg scale based on his own method of fluorous mixture synthesis.[206] As shown in Figure 13, the isomers were synthesized via **25** and **26** by connecting three building blocks, **27**, **28** and methylenetriphenylphosphorane. The inherent efficiency in mixture synthesis was illustrated by the tactic of using **28** twice. This allowed for an iterative approach where a sequence of deprotection, oxidation and olefination was repeated three times. In Curran's synthesis only 32 synthetic reactions were necessary to achieve the synthesis of the 16 stereoisomers of **23**. Curran recommends fluorous tag encoding method for the efficient synthesis of multiple stereoisomers of pheromones.

Another direction to facilitate the practical use of pheromones is to synthesize a pheromone by a short-step-transformation of a readily available natural product. This approach is useful especially when even a racemate can work as a pheromone. Thus Hooper et al. converted germacrone (**29**) into (±)-**30**, the racemate of the sex pheromone (**D1**) of the sand fly, *Lutzomyia longipalpis*.[207] Germacrone (**29**) is produced in a high concentration (59%) in the essential oil of the cranesbill, *Geranium macrorrhizum*.[207]

Application of enantioselective reactions by means of enzymes has been actively pursued in pheromone synthesis, and three review articles are available concerning this subject.[218–220]

5.3. Advances in biological methods and others

The monumental works of Axel and Buck unraveled the biological mechanism of the sense of smell.[208,209] Advances in pheromone biology was also remarkable. In 2000, the three-dimension structure of the pheromone-binding protein of the silkworm moth, *B. mori*, with bound bombykol was determined by X-ray diffrac-

tion.[210] Plettner et al. showed that the two pheromone-binding protein (PBP1 and PBP2) from the gypsy moth. *L. dispar*, bind differently to both enantiomers of displarlure. PBP1 has a higher affinity for the unnatural (−)-isomer, while PBP2 has a higher affinity for (+)-disparlure.[211]

Electrophysiological response of pheromone receptor cells in antennae of insects can be detected by the method called electroantennographic detection (EAD) as pioneered by Schneider in 1957.[221] Detection of pheromone components separated by gas chromatography (GC) with EAD offers an extremely sensitive method of pheromone detection. Coupled GC–EAD analysis is the most powerful technique to detect pheromonally active compounds. Its tremendous advantages in detecting achiral as well as chiral odorants are summarized in reviews.[222–224]

Several other reviews are available in pheromone science. Pickett reviewed chemistry and biology of volatile isoprenoids that control insects.[212] Millar's review on polyene hydrocarbons and epoxides as lepidopteran sex pheromones is a good source of further examples of synergism and antagonism between enantiomers.[213] Kitching summarized his studies on the chiral pheromones of Australian insects, in which several new analytical and synthetic methods were illustrated.[214] Francke and Schulz contributed a concise review chapter dealing with pheromone chemistry.[215]

6. Conclusion

Recent progress in organic analysis and synthesis is most evident in the fact that pure enantiomers can be synthesized with higher enantiomeric purity than that ever possible in the past. It is thus doubtful whether (*R*)-**6** or (7*S*,8*R*)-**7** has been active at all or not. Judging from the primitive level of asymmetric synthesis in 1970s, it might be just the very small amounts of (*S*)-**6** or (7*R*, 8*S*)-**7** in the 'less active' sample which contributed to its very low activity. Nevertheless, enantioselective synthesis is still an expensive way of manufacturing pheromones. Accordingly, prior to the practical application of pheromones, their stereochemistry–pheromone activity relationships must be studied carefully. If possible, it is convenient to use stereoisomeric mixtures of pheromones. In case there is a need for enantioselective synthesis, the least expensive way of manufacturing the pheromone must be found out and put to the practice.

The extensive works over three decades by us and others revealed unprecedented and diverse stereochemistry–pheromone activity relationships. Diversity is indeed the keyword of pheromone response. However, we still do not know much about the exact mechanism of such enantioselective recognitions in biological systems. This fact brings me to the conclusion leading to my future prospect: 'What we see now is like the dim image in a mirror; then we shall see face to face. What I know now is only partial; then it will be complete (I Corinthians 13:12).'

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