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FEATURE ARTICLE

Pheromones: synthesis and bioactivity†

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Pheromones play an important role in chemical communication among organisms. Various chiral and non-racemic pheromones have been identified since the late 1960s. Their enantioselective syntheses were achieved so as to establish the absolute configuration of the naturally occurring pheromones and also to clarify the relationship between absolute configuration and the bioactivity of the chiral pheromones.

Four recent examples of pheromone synthesis are given. The enantiomers of sordidin 14, the banana weevil pheromone, have been synthesized starting from (*S*)-propylene oxide. (−)-*exo*-Isobrevicomin 17 and its (−)-*endo*-isomer 21, the components of the volatiles of the mountain pine beetle, have been synthesized by employing the Sharpless asymmetric dihydroxylation and lipase-catalysed acetylation as the key reactions. The enantiomers of (*Z*)-hexadeca-7,15-dien-4-olide 24, the sex pheromone of the yellowish elongate chafer, have been synthesized *via* lipase-catalysed resolution. Lurlene 27, the pheromone of the green flagellate *Chlamydomonas allensworthii*, has been synthesized by employing a phenyl sulfone coupling reaction as the key reaction.

The relationships between absolute configuration and bioactivity are diverse. For example, neither the (*R*)- nor the (*S*)-enantiomer of sulcatol 10, the aggregation pheromone of the ambrosia beetle *Gnathotrichus sulcatus*, is bioactive, but when combined to give an enantiomeric mixture they become active. In the case of olean 46, the olive fruit fly pheromone, (*R*)-46 is active for the males, while (*S*)-46 is active for the females.

Introduction

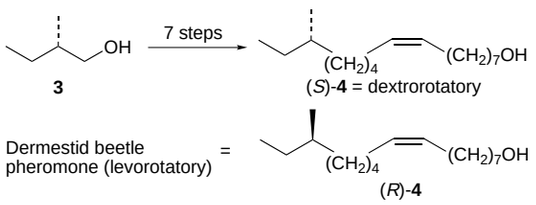
Pheromone chemistry began in 1959 when Butenandt established the structure **1** of bombykol, the sex pheromone of the silkworm moth (*Bombyx mori*). Subsequently in late 1960s a number of chiral pheromones were identified, as exemplified by *exo*-brevicomin **2**, the aggregation pheromone of the western pine beetle (*Dendroctonus brevicomis*). The absolute configuration of a chiral and non-racemic pheromone must be studied to elucidate the stereostructure of the naturally occurring material and also to clarify the relationship between stereochemistry and pheromone activity.

Mori demonstrated in 1973 that the naturally occurring and levorotatory dermestid beetle pheromone was (*R*)-**4** by converting the commercially available (*S*)-**3** to the dextrorotatory (*S*)-**4** (Scheme 1).[1,2] This work was the first successful identification of the absolute configuration of an insect pheromone by its enantioselective synthesis.

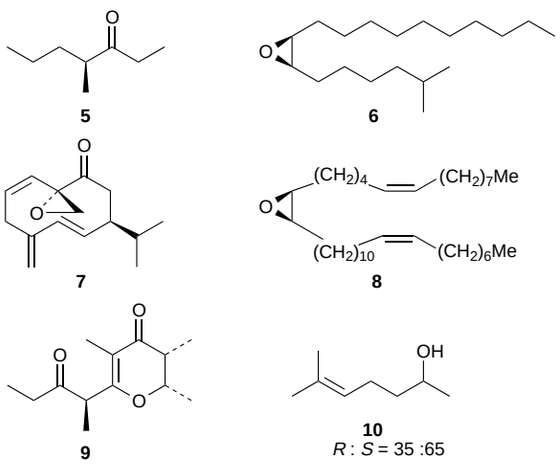
In 1974 three independent groups synthesized both the enantiomers of three different insect pheromones. Riley *et al*. synthesized the enantiomers of the alarm pheromone of the leaf-cutting ant (*Atta texana*), and found the (*S*)-isomer **5** to be about 400 times more active than the (*R*)-isomer.[3] The enantiomers of disparlure, the gypsy moth (*Lymantria dispar*) pheromone, were synthesized by Marumo's group, and they examined the electroantennographical (EAG) and behavioural responses of the male gypsy moth to the enantiomers.[4] (7*R*,8*S*)-(+)-Disparlure **6** was the most effective, (±)-**6** came second, while the (7*S*,8*R*)-(−)-isomer inhibited the activity of (+)-**6**.[4] Mori synthesized both the enantiomers of *exo*-brevicomin by starting from the enantiomers of tartaric acid.[5] Only (+)-*exo*-brevicomin **2** was bioactive against the western pine beetle.[6] The discovery that the absolute configuration of pheromones was of the utmost importance to the expression of their bioactivities accelerated stereochemical studies on insect pheromones.

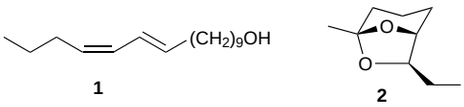
Synthesis of pheromone enantiomers can solve the stereochemical problems in pheromone chemistry, if proper methods are available for the discrimination of the enantiomers. Limited availability of the naturally occurring chiral pheromones makes it difficult to determine their absolute configuration by conventional means, especially because most of the pheromones are volatile liquids. A synthetic sample of a pheromone with known absolute configuration is useful as a reference material to assign the absolute configuration of the naturally occurring one. Accordingly, one must compare the synthetic sample with the natural pheromone by physical and/or biological methods.

The classical and accepted method for the assignment of absolute configuration is the comparison of the specific rotation of an unknown sample with that of the reference. The magnitude of the specific rotation, however, varies very much according to



Scheme 1





the structure of the pheromone. The largest $[\alpha]_D$ value observed among insect pheromones was $[\alpha]_D^{24}$ −547 (hexane) in the case of periplanone A **7**, the American cockroach pheromone,[7] and the smallest was $[\alpha]_D$ 0 in the case of the nymph recognition pheromone **8** of the cockroach, *Nauphoeta cinerea*.[8] Therefore, in the case of the latter, an attempt to measure the specific rotation of the natural product does not provide useful information as to its absolute configuration. If a chiral pheromone has carbonyl chromophores such as in the case of stegobinone **9**, the drugstore beetle pheromone, its CD spectrum provides useful information.[9]

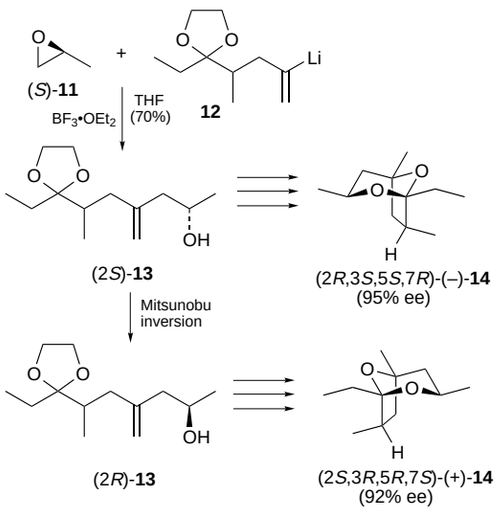
Determination of the absolute configuration and estimation of the enantiomeric composition of a chiral pheromone are possible by NMR spectroscopic methods, if a sufficient amount of the sample is available to measure the spectrum in the presence of a chiral shift reagent and/or after derivatization with a chiral derivatizing reagent. The enantiomeric purity of sulcatol **10**, the male-produced aggregation pheromone of the ambrosia beetle *Gnathotrichus sulcatus*, was determined as 30% ee [(*S*)-(+) > (*R*)-(−)] by the NMR method.[10]

HPLC with cellulose-based chiral stationary phases or GC with cyclodextrin-based chiral stationary phases are two popular methods for determination of the absolute configuration of pheromones.[11] Even with achiral stationary phases, HPLC and GC are useful for analysing chiral pheromones after derivatization with a chiral derivatizing reagent. Cyclodextrin-based GC columns are particularly useful, and almost all of the recent results on stereochemical studies of pheromones have been obtained using them.[11,12]

Synthesis of the enantiomers of sordidin

Aspects of pheromone synthesis have been reviewed.[13–16] In particular two of them deal with enantioselective synthesis of pheromones.[15,16] Enantioselective synthesis of a chiral and non-racemic pheromone can be executed by one of the following three methods: (i) derivation from a known chiral and non-racemic building block, (ii) use of chemical or enzymatic asymmetric reactions, and (iii) use of chemical or enzymatic enantiomer separation (*i.e.* resolution) at a certain stage of the synthesis. Four recent examples from our group will be given here.

The enantiomers of sordidin **14**, the male-produced aggregation pheromone of the banana weevil (*Cosmopolites sordidus*),[17] were synthesized as summarized in Scheme 2.[18] (*S*)-Propylene oxide **11** was employed as the chiral building block. Cleavage of **11** with the alkenyllithium **12** in the presence of boron trifluoride–diethyl ether yielded the homoallylic alcohol (2*S*)-**13**. This was converted to (−)-sordidin **14**. Mitsunobu inversion of (2*S*)-**13** afforded (2*R*)-**13**, which furnished (+)-sordidin **14**. The enantiomers of **14** were compared with the natural pheromone by GC analysis (Cyclodex B® column), and (+)-**14** coincided with the natural product. The absolute configuration of natural sordidin was therefore determined as 1*S*,3*R*,5*R*,7*S*.[18]

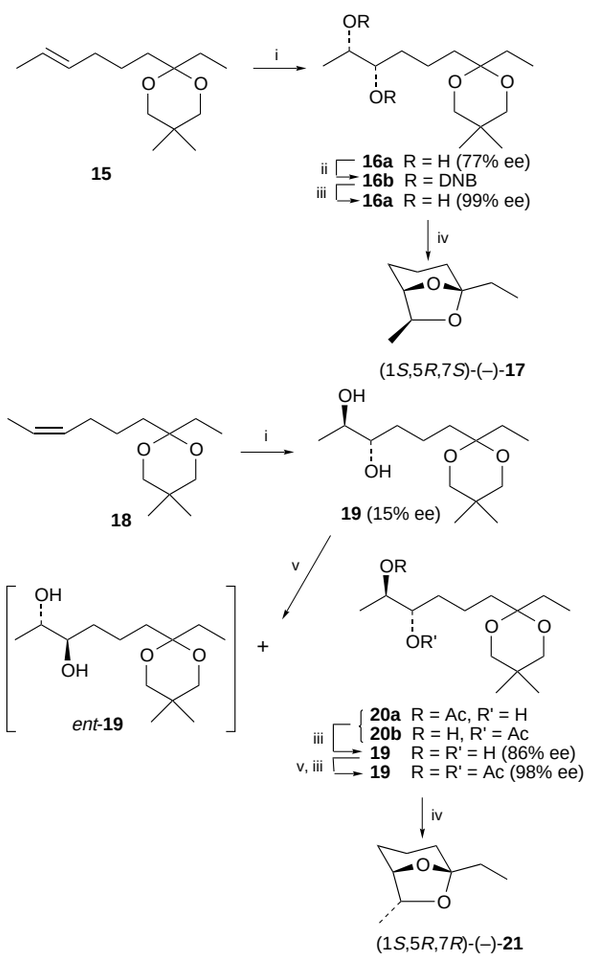


Scheme 2

Synthesis of (−)-*exo*- and (−)-*endo*-isobrevicomins

Both the *exo*- and *endo*-isomers of isobrevicomin **17** and **21** were isolated in 1996 by Francke *et al*. as the components of the volatiles obtained from male mountain pine beetles (*Dendroctonus ponderosae*).[19] They synthesized (1*S*,5*R*,7*S*)-(−)-**17** by starting from (+)-tartaric acid, and the natural **17** was found to be (1*S*,5*R*,7*S*)-**17** of at least 90% ee by GC analysis.[19]

The naturally occurring *endo*-isobrevicomin may share the same (1*S*,5*R*)-6,8-dioxabicyclo[3.2.1]octane skeleton as depicted for **21**, but it needed to be proved. We therefore synthesized both (1*S*,5*R*,7*S*)-**17** and (1*S*,5*R*,7*R*)-**21** as summarized in Scheme 3.[20] Sharpless asymmetric dihydroxylation of **15** with AD-mix-α® gave the diol **16a** (77% ee). This was purified *via* the crystalline *bis*- 3,5-dinitrobenzoate **16b** to give pure **16a** (99% ee), which furnished (1*S*,5*R*,7*S*)-**17** by acid treatment. Similar dihydroxylation of **18** with AD-mix-α® afforded the diol **19** of 15% ee. The diol **19** was then purified by lipase-catalysed asymmetric acetylation. Treatment of **19** (15%



Scheme 3 *Reagents*: i, AD-mix-α®, $MeSO_2NH_2$, Bu^tOH, H_2O (94% for both **16a** and **19**); ii, 3,5-dinitrobenzoyl chloride (DNBCl), C_5H_5N, CH_2Cl_2, then recrystallization (59%); iii, K_2CO_3, MeOH [92% for **16a** (99% ee); 53% for **19** (86% ee) based on **19** (15% ee); 77% for **19** (98% ee) based on **19** (86% ee); iv, dil. HCl (64%); v, CH_2=CHOAc, immobilized lipase PS (Amano), Bu^tOMe, then chromatographic separation of *ent*-**19** and **20a**,**b**

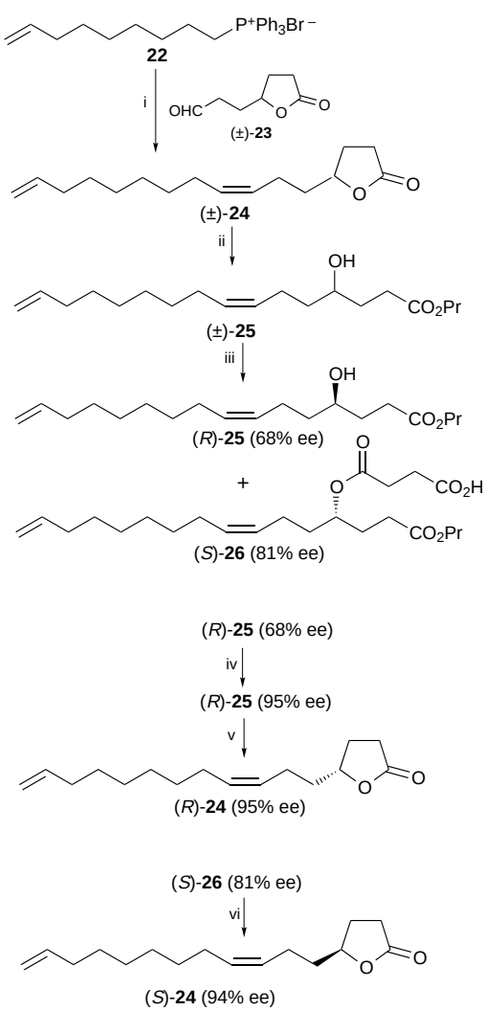
ee) with vinyl acetate and immobilized lipase PS (Amano) gave a mixture of *ent*-**19** and **20a**,**b** which could be separated by chromatography. Deacetylation of **20a**,**b** to give **19** (86% ee) was followed by the second enzymatic enrichment of the enantiomeric purity to give **19** of 98% ee. Acid treatment of **19** (98% ee) furnished (−)-*endo*-isobrevicomin **21**. Gas chromatographic comparison of (−)-**21** with the naturally occurring *endo*-isobrevicomin established its absolute configuration.

Synthesis of the enantiomers of (*Z*)-hexadeca-7,15-dien-4-olide

(*R*,*Z*)-Hexadeca-7,15-dien-4-olide **24** is the female-produced sex pheromone of the yellowish elongate chafer (*Heptophylla picea*).[21] The absolute configuration of the natural pheromone was assigned as *R* by the conversion of (*S*)-malic acid to (*R*)-**24**, which was identical with the natural product.[21]

We became interested in synthesizing both the enantiomers and the racemate of **24** so as to clarify the stereochemistry–bioactivity relationship. Because (±)-**24** had to be prepared for its biological evaluation, its optical resolution was considered to be the most convenient way to prepare both the enantiomers of **24**. The synthesis is summarized in Scheme 4.[22] The Wittig reagent prepared from **22** reacted with the aldehyde (±)-**23** under the Bestmann conditions to give (±)-lactone **24**, ($Z:E$ = 96.5 : 3.5). Enzymatic methods were employed for the optical resolution of (±)-**24**. The lactone (±)-**24** was first converted to the hydroxy ester (±)-**25**, which was treated with succinic anhydride in the presence of lipase PS (Amano) to give (*R*)-**25** (68% ee) and (*S*)-**26** (81% ee). The mixture was readily separable by chromatography. Treatment of (*R*)-**25** (68% ee) with pig pancreatic lipase (PPL) in diethyl ether converted (*R*)-**25** (68% ee) to a mixture of (*R*)-**25** (95% ee) and (*S*)-**24** (30% ee), which was separated by chromatography. Subsequent treatment of the hydroxy ester (*R*)-**25** (95% ee) with Amberlyst-15 yielded the (*R*)-lactone **24**, (95% ee). For the preparation of the non-natural (*S*)-lactone (**24**), the (*S*)-succinoyl ester **26**, (81% ee) was submitted to enzymatic lactonization catalysed by lipase OF-360 (Meito) to give the enantiomerically enriched (*S*)-**24** (94% ee). In the present case, asymmetric catalysis of lipases was useful for the preparation of both the enantiomers of **24**. Biotransformations catalysed by enzymes and microorganisms are frequently employed in pheromone synthesis.[15,23]

Bioassay of our synthetic samples revealed both (*R*)-**24** and (±)-**24** to be bioactive. This means that (*S*)-**24** is not inhibitory.



Scheme 4 *Reagents*: i, $NaN(SiMe_3)_2$, THF (66%); ii, KOH, H_2O, then PrBr, DMF(91%); iii, succinic anhydride, lipase PS (Amano), $Pr^i{}_2O$ [56% of (*R*)-**25** and 41% of (*S*)-**26**]; iv, PPL, Et_2O (74%); v, Amberlyst-15, hexane (89%); vi, lipase OF-360 (Meito), 0.3 M phosphate buffer (pH = 7) (52%)

Synthesis of lurlene

The sex pheromone produced by the female gametes of *Chlamydomonas allensworthii* was isolated, named as lurlene, and identified as **27** by Starr, Jaenicke and Marner in 1995.[24,25] Lurlene **27** attracts the male gametes at a concentration as low as 10^{-12} M.[24] Our first synthesis of **27** was achieved by employing the palladium-catalysed Stille coupling between the stannane **28** and the allylic acetate **29** as the key step (Scheme 5).[26] The coupling reaction, however, brought about the partial isomerization of the (*E*) double bond at C-12 to give a mixture of **30** and its (12*Z*)-isomer in a ratio of 2 : 1.[26] This mixture could not be separated, and therefore was processed to give the final product as a bioactive mixture of lurlene **27** and its (12*Z*)-isomer.

Our second synthesis of lurlene **27** utilized the sulfone coupling reaction, and afforded the final product as pure (12*E*)-lurlene **27**.[27] The crucial steps of the second synthesis are also shown in Scheme 5. The isoprenoidal side-chain part **31** was synthesized from (*E*,*E*)-farnesol, converted to the corresponding dianion, and alkylated with the aromatic part **32** to give the phenyl sulfone **33**. Palladium-catalysed reductive desulfonylation[28] of **33** gave the pure aglycone part **34**, which was converted to lurlene **27** *via* **30**.

The pheromones of organisms other than insects are now under active investigation.

Stereochemistry–bioactivity relationships among insect pheromones

The most notable advance in pheromone science in the last two decades is the recognition of the importance of chirality in pheromone perception. Fig. 1 summarizes the stereochemistry–pheromone activity relationships. The relationships are divided into ten categories as detailed below.

(*a*) *Only a single enantiomer is bioactive, and its opposite enantiomer does not inhibit the action of the pheromone*

This is the most common relationship, and the majority (about 60%) of the chiral pheromones belong to this category. Other bioregulators such as hormones generally belong to this category. Many people therefore believed that this relationship must be the only reasonable one. As we shall see later, there are many other cases.

Only the (1*R*,5*S*,7*R*)-isomer of *exo*-brevicomin (**2**) is bioactive.[6] (3*S*,4*R*)-Faranal **35** is the bioactive enantiomer of the trail following pheromone of the pharaoh's ant.[29]

(*b*) *Only one enantiomer is bioactive, and its opposite enantiomer inhibits the action of the pheromone*

Disparlure (7*R*,8*S*)-**6** is the first studied pheromone which belongs to this group.[4] Under field conditions, males of the gypsy moth (*Lymantria dispar*) and males of the nun moth (*Lymantria monacha*) responded to (7*R*,8*S*)-**6**. However, the addition of (7*S*,8*R*)-**6** significantly suppressed response by *L. dispar*, while (7*S*,8*R*)-**6** did not show such an effect on the response of *L. monacha*.[30]

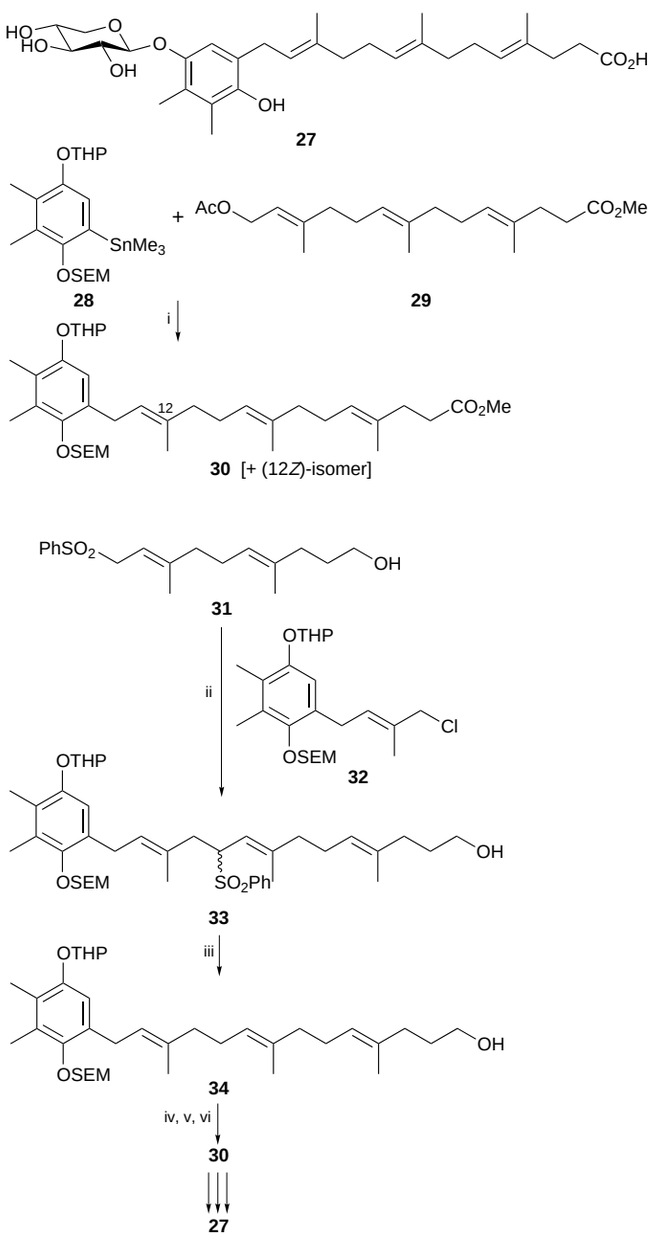
Japonilure (*R*)-**36** is the female-produced sex pheromone of the Japanese beetle.[31] The bioactive enantiomer is (*R*)-(+)-**36**, while (*S*)-**36** strongly inhibits the action of (*R*)-**36**. Accordingly, (+)-**36** of 99% ee was about 2/3 as active as the pure (*R*)-**36**, that of 90% ee was about 1/3 as active as (*R*)-**36**, that of 80% ee was about 1/5 as active as (*R*)-**36**, and both (+)-**36** of 60% ee and (±)-**36** were inactive.[31]

For the practical use of pheromones belonging to this category, one must synthesize highly pure enantiomers in order to ensure trap capture of the insects. Enantiomerically pure commercial products are now available in the cases of disparlure **6** and japonilure **36**.

(*c*) *Only one enantiomer is bioactive, and its diastereomer inhibits the action of the pheromone*

Sericornin (4*S*,6*S*,7*S*)-**37** is the female-produced sex pheromone of the cigarette beetle. Bioactivity of the stereoisomers of **37** was studied by Mori *et al.* in the course of developing practical pheromone traps.[32] Only (4*S*,6*S*,7*S*)-**37** was bioactive, and its (4*S*,6*S*,7*R*)-isomer was inhibitory against the action of (4*S*,6*S*,7*S*)-**37**. Accordingly, the commercial pheromone lure must be manufactured without contamination with the (4*S*,6*S*,7*R*)-isomer.

Stegobinone (2*S*,3*R*,1′*R*)-**9** is one of the two components of the female-produced sex pheromone of the drugstore beetle. It has been shown that the addition of (2*S*,3*R*,1′*S*)-epistegobinone



Scheme 5 *Reagents*: i, 0.05 equiv. bis(dibenzylideneacetone)palladium(0) [$Pd(dba)_2$], 3 equiv. LiCl, DMF (98%, $E : Z = 2 : 1$); ii, 2 equiv. BuLi, THF, HMPA (62%); iii, 0.1 equiv. $PdCl_2$[1,3-bis(diphenylphosphino)propane] [$PdCl_2(dppp)$], 3 equiv. $LiBEt_3H$, THF (93%); iv, Dess–Martin periodinane; v, $NaClO_2$, NaH_2PO_4, DMSO, MeCN, H_2O; vi, CH_2N_2, Et_2O (73% based on **34**)

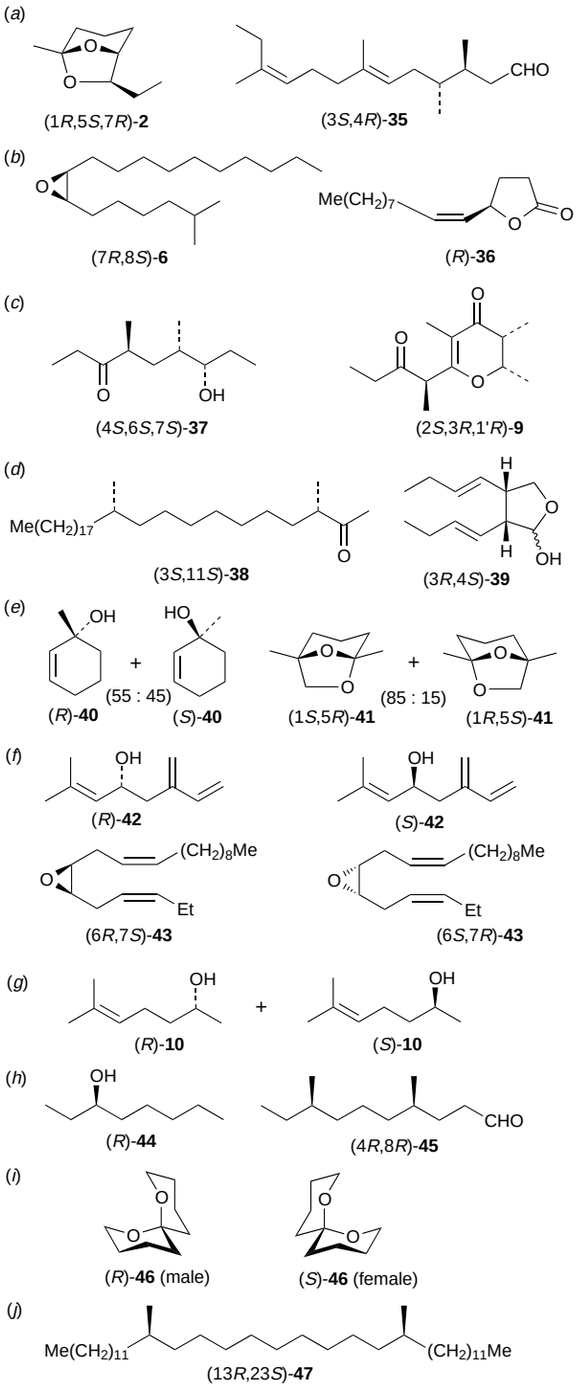


Fig. 1 Relationships between stereochemistry and bioactivity of insect pheromones. The names of the insects which release the pheromones **2**, **6**, **9** and **35**–**47** are listed below: (*a*) **2** (*exo*-brevicomin), western pine beetle *Dendroctonus brevicomis*; **35** (faranal), pharaoh's ant *Monomorium pharaonis*; (*b*) **6** (disparlure), gypsy moth *Lymantria dispar*; **36** (japonilure), Japanese beetle *Popillia japonica*; (*c*) **37** (serricornin), cigarette beetle *Lasioderma serricorne*; **9** (stegobinone), drugstore beetle *Stegobium paniceum*; (*d*) **38**, German cockroach *Blattella germanica*; **39**, spined citrus bug *Biprorulus bibax*; (*e*) **40**, Douglas-fir beetle *Dendroctonus pseudotsugae*; **41** (frontalin), southern pine beetle *Dendroctonus frontalis*; (*f*) **42** (ipsdienol), (*R*)-isomer: bark beetles *Ips calligraphus* and *I. avulsus*; (*S*)-isomer: California five spined ips *I. paraconfusus*; (*R*) and (*S*)-isomers: pine engraver *Ips pini*; **43**, (6*R*,7*S*)-isomer; geometrid moth *Colotois pennaria*; (6*S*,7*R*)-isomer: geometrid moth *Erannis defoliaria*; (*g*) **10** (sulcatol), ambrosia beetle *Gnathotrichus sulcatus*; (*h*) **44**, ant *Myrmica scabrinodis*; **45** (tribolure), red-flour beetle *Tribolium castaneum*; (*i*) **46** (olean), olive fruit fly *Bactrocera oleae*; (*j*) **47**, tsetse fly *Glossina pallidipes*.

to **9** significantly reduces the response of the male drugstore beetles to the pheromone.[33]

(d) The natural pheromone is a single enantiomer, while its antipode or diastereomer is also active

Male German cockroaches do not discriminate among the four stereoisomers of the female-produced sex pheromone, although the natural product is (3*S*,11*S*)-**38**.[34]

The male spined citrus bug produces (3*R*,4*S*)-**39** as an aggregation pheromone. The opposite (3*S*,4*R*)-enantiomer of the pheromone is also bioactive, indicating that the insect does not discriminate between the enantiomers.[35]

(e) The natural pheromone is an enantiomeric mixture, and both the enantiomers are separately active

Female Douglas-fir beetles produce a 55 : 45 mixture of (*R*)- and (*S*)-**40** as a component of their aggregation pheromone. The combined effect of the enantiomers of **40** was additive, rather than synergistic, and both the enantiomers are required for maximum response.[36]

Male southern pine beetles produce an 85 : 15 mixture of (1*S*,5*R*)-frontalin **41** and its (1*R*,5*S*)-isomer.[37] In laboratory and field bioassays, the response of the beetles was significantly greater to the mixture of (1*S*,5*R*)-**41** and α-pinene than to (1*R*,5*S*)-**41** and α-pinene, although both were active. Both the enantiomers of **41** stimulated the same olfactory cells, suggesting that each cell has at least two types of enantioselective receptors.[37]

(f) The different enantiomers or diastereomers are used by different species

(*S*)-Ipsdienol **42** is the pheromone component of the California five spined ips (*Ips paraconfusus*), while other bark beetles *I. calligraphus* and *I. avulsus* respond to (*R*)-**42**.[38] Further detailed study was reported on variation of the enantiomeric purity of **42** in the bark beetle *I. pini*.[39]

Chirality of pheromones is important for discrimination between two species of the winter-flying geometrid moths in Middle Europe. Thus (6*R*,7*S*)-**43** is the pheromone of *Colotois pennaria*, while *Erannis defoliaria* uses (6*S*,7*R*)-**43** as its pheromone.[40]

(g) Both the enantiomers are required for bioactivity

Sulcatol **10** is the male-produced aggregation pheromone of the ambrosia beetle *Gnathotrichus sulcatus*. Neither (*R*)-**10** nor (*S*)-**10** was bioactive. But when combined to give a racemic mixture, the synthetic **10** was more active than the natural pheromone, which was a mixture of (*R*)-**10** and (*S*)-**10** in a ratio of 35 : 65.[41]

(h) One enantiomer is more active than the other stereoisomer(s), but an enantiomeric or a diastereomeric mixture is more active than the most active enantiomer alone

In the case of the trail following pheromone **44** of the ant *Myrmica scabrinodis*, the naturally occurring mixture of (*R*)-**44** and (*S*)-**44** (*R* : *S* = 9 : 1) was more attractive than pure (*R*)-**44** or (±)-**44**, while (*S*)-**44** was inactive.[42]

Tribolure (4*R*,8*R*)-**45** is the male-produced aggregation pheromone of the red-flour beetle *Tribolium castaneum*. Suzuki *et al*. found (4*R*,8*R*)-**45** to be as active as the natural pheromone, while a mixture of (4*R*,8*R*)-**45** and its (4*R*,8*S*)-isomer in a ratio of 8 : 2 was about ten times more active than (4*R*,8*R*)-**45** alone.[43]

(i) One enantiomer is active on male insects, while the other is active on females

Olean **46** is the female-produced sex pheromone of the olive fruit fly. Its (*R*)-isomer was active on the males, while the

(*S*)-isomer was active on the females.[44] The natural olean was racemic.[44]

(*j*) *Only the* meso-*isomer is active*

In the case of the tsetse fly sex pheromones, *meso*-alkanes seem to be bioactive. Thus (13*R*,23*S*)-**47** was active as the sex-stimulant pheromone of the female tsetse fly, *Glossina pallidipes*, while neither (13*R*,23*R*)-**47** nor (13*S*,23*S*)-**47** was bioactive.[45]

Conclusion

The progress of synthetic organic chemistry in this last quarter of the 20th century is manifested by the fact that we can now synthesize the pure enantiomers of a pheromone with even higher enantiomeric purity than that of the naturally occurring one. This has been made possible by the development of various methods of both asymmetric synthesis and stereochemical analysis. We can now determine the absolute configuration of a natural pheromone and investigate the stereochemistry–bio-activity relationships on the basis of highly enantioselective synthesis of the pheromones.

Chemists and biologists are able to unveil the remarkable biodiversity in the stereochemical aspects of pheromone perception. Insects use chirality to enrich their communication systems. The next task for biochemists and molecular biologists is to clarify the biochemical mechanisms which make the diversity possible.

Finally, from the standpoint of practical applications, one must not forget that the stereoisomers of pheromones can be inhibitors of the pheromone action.

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Footnote

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