Semiochemicals – Synthesis, Stereochemistry, and Bioactivity

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Received March 6, 1998

Keywords: Chirality / Ecology / Pheromones / Semiochemicals / Structure-activity relationship

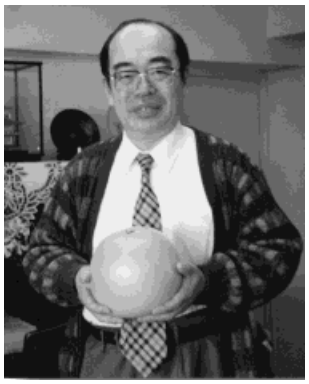
The syntheses of some new pheromones and other semiochemicals is reported. The target molecules are the pheromone (**20**) of a myxobacterium, a plant germination stimulant [sorgolactone (**22a**)], a plant leaf-closing factor [phyllanthurinolactone (**24a**)], the pheromone [stegobiol (**25**) and stegobinone (**26**)] of the drugstore beetle, and the pheromone [frontalin (**27**)] of the southern pine beetle. Like other natural products, semiochemicals are not always enantiomerically pure, and their enantiomeric heterogeneity is taken advantage of by organisms to increase the diversity in chemical communications. Relationships between absolute configuration and bioactivity of pheromones, rather than being simple, are extremely complicated and unpredictable.

1. Introduction

The aim of this *Microreview* is to summarize the present state of our understanding with regard to the following two simple questions: "Are semiochemicals always enantiomerically pure?" and "Is a single enantiomer of a semiochemical always responsible for bioactivity?". Our enantioselective syntheses of semiochemicals have enabled us to answer both of these questions in the negative.

"Semiochemicals" are biofunctional molecules that spread information between individuals. The word is derived from "semio" (Greek = sign), and is synonymous with "signal substances". They are divided into two groups; pheromones and allelochemicals. Pheromones are biofunctional molecules that are used for communication between individuals within the same species. The term "pheromone" was coined by Karlson and Lüscher, and is derived from the Greek "pherein" (= to transfer) and "hormon" (= to excite)[1]. On the other hand, allelochemicals are biofunctional molecules that are used for communication between individuals belonging to different species. The word was derived from "allelon" (Greek = of each other). After the publication of a book named *Chemical Ecology* in 1970[2] and also after the launch of a periodical named *Journal of Chemical Ecology* in 1974, the term "Chemical Ecology" has become widely accepted as a new discipline to study the chemistry and biology of semiochemicals.

The endeavor of our group over two decades in this area of chemical ecology has been focused on the enantioselective syntheses of semiochemicals. Why have we concentrated our efforts not in the isolation of such compounds, but in their synthesis? Of course without the efforts of those who isolate and identify the semiochemicals in order to propose



Kenji Mori was born in Seoul, Korea, in 1935 and is the son of a Japanese Christian Pastor. He obtained his B.Sc. (1957, agricultural chemistry), M.Sc. (1959, biochemistry) and Ph.D. (1962, organic chemistry) degrees from the University of Tokyo. He remained there until March 1995 (1962–1968, assistant; 1968–1978, associate professor; 1978–1995, professor), and then moved to Science University of Tokyo. His research interests include the enantioselective synthesis of pheromones and other biofunctional molecules, biotransformations and chemical ecology. He has been honored by awards from the Japan Academy (in 1981 in the presence of the late Emperor Hirohito) and the International Society of Chemical Ecology (Silver Medal in 1996 in Prague).

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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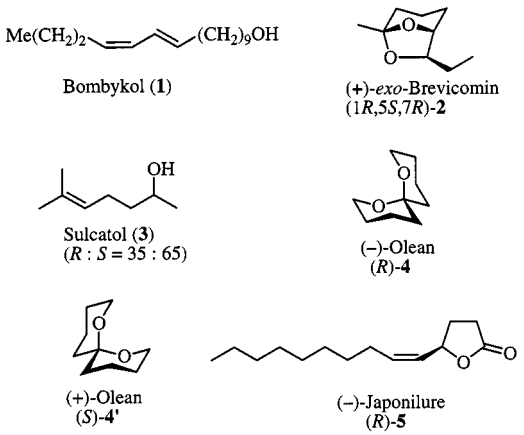
their overall structures, no one can synthesize them. Semiochemicals, however, are usually obtained in mg to μg quantities. It is therefore difficult to determine their absolute configuration by conventional methods unless they are nicely crystalline and can be analyzed by X-ray diffraction. Accordingly, the enantioselective synthesis of a semiochemical is often a prerequisite for the establishment of its structure. For example, in an attempt to determine the absolute configuration of a sub-nanogram quantity of a semiochemical by GC analysis using chiral stationary phases, one must secure a reference sample with known absolute configuration. Moreover, synthesis is frequently the only way to obtain a substantial amount of semiochemicals to be evaluated biologically. Thirdly, through enantioselective syntheses, we can prepare the enantiomers and also the diastereomers of a semiochemical, and thus can compare their biological activities to clarify the structure-activity relationships. Pheromone synthesis along this line enabled us, and others, to elucidate the biodiversity in the chirality recognition of pheromones[3].

The first insect pheromone bombykol (**1**, Scheme 1) was identified by Butenandt in 1959, and was shown to be achiral. It therefore posed no stereochemical problem except the olefin geometry, although *cis*/*trans* isomerism was quite important for the bioactivity of olefinic pheromones. Subsequently, in the 1960′s a number of chiral pheromones such as *exo*-brevicomin (**2**), the pheromone of the western pine beetle, were isolated, which started stereochemical studies in semiochemicals. In 1974 both enantiomers of *exo*-brevicomin (**2**) were synthesized[4], and only its (+) isomer was found to be bioactive[5]. This was in accord with the generally accepted view that a single enantiomer of bioregulators is responsible for the bioactivity.

Scheme 1. Structures of some insect pheromones

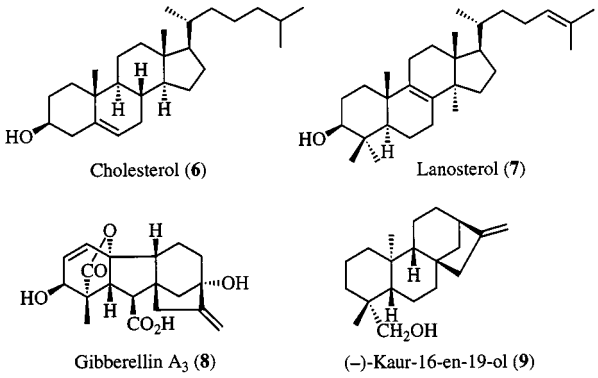


In 1975, however, both enantiomers of sulcatol (**3**), the pheromone of the ambrosia beetle *Gnathotrichus sulcatus*[6], were synthesized and in this case a surprising bioassay result was observed[7]. The pheromone activity of sulcatol (**3**) was observed only in the presence of both enantiomers. Neither of these isomers was active in isolation, and the natural product was an enantiomeric mixture[8]. Another unusual case is that of olean (**4** and **4′**), the olive fruit fly (*Bactrocera oleae*) pheromone. Our synthetic enantiomers of olean[9] were bioassayed in Greece[10]. (*R*)-Olean (**4**) was active against the male of the species, while (*S*)-**4′** was active against the female. (±)-Olean is produced by the female olive fruit fly. Japonilure [(*R*)-(−)-**5**] is the sex pheromone of the Japanese beetle (*Popillia japonica*). Since (±)-**5** was inactive, Tumlinson et al. carefully studied the relationship between the enantiomeric purity of **5** and its bioactivity[11]. The bioactive enantiomer is (*R*)-**5**, while (*S*)-**5′** strongly inhibits the action of (*R*)-**5**. As a result, (−)-**5** of 99% *e.e.* was about two thirds as active as pure (*R*)-**5**, that of 90% *e.e.* was about one third as active as (*R*)-**5**, that of 80% *e.e.* was about one fifth as active as (*R*)-**5**, and both (−)-**5** of 60% *e.e.* and (±)-**5** were inactive[11]. The diversity of the pheromone stereochemistry-activity relationships is indeed beyond our imagination.

2. Semiochemicals and Stereochemistry − Are They Pure Enantiomers?

In the case of sulcatol (**3**), the natural semiochemical is not at all enantiomerically pure, as mentioned previously. Is this an extremely rare occurrence? Many of the primary metabolites are found as pure enantiomers such as D-glucose in starch and L-amino acids in proteins. A steroid like cholesterol (**6**, Scheme 2) and a triterpene such as lanosterol (**7**) are believed to occur naturally as single enantiomers. It is a remarkable feat of nature to produce single enantiomers of these isoprenoid compounds despite their structural complexity. It is also well established that the phytohormone gibberellin A_3 (**8**) and the related diterpenoid (−)-kaur-16-en-19-ol (**9**) occur as single enantiomers. When (±)-**9** was synthesized over 30 years ago, it was impressing by the fact that it was exactly 50% as active as (−)-**9** as a plant growth promoter[12].

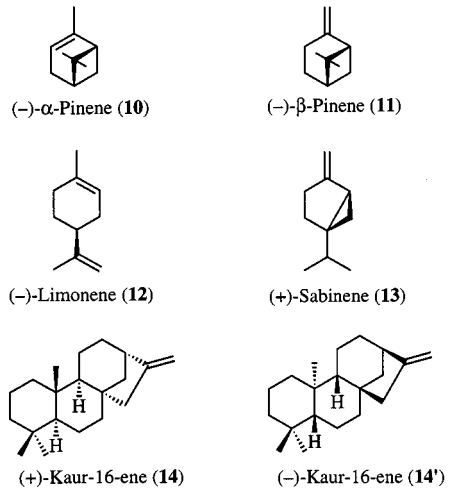
Scheme 2. Structures of higher isoprenoids that are enantiomerically pure



There are some mono- and diterpenoids, both enantiomers of which are naturally occurring (Scheme 3). Norin recently studied the enantiomeric composition of monoterpenoids including *α*-pinene (**10**) in common spruce (*Picea abies*)[13]. He and his coworkers found a variation in the enantiomeric ratio of *α*-pinene from 90% of the (−) isomer to almost 80% of the (+) isomer. The variation was observed among the different parts (wood, bark, root and needles) of the tree, and also among individual trees. They

also showed large individual variations in enantiomeric composition of β-pinene (**11**), limonene (**12**) and sabinene (**13**) in the xylem of *Picea abies*.

Scheme 3. Structures of mono- and diterpenoids, both enantiomers of which are naturally occurring

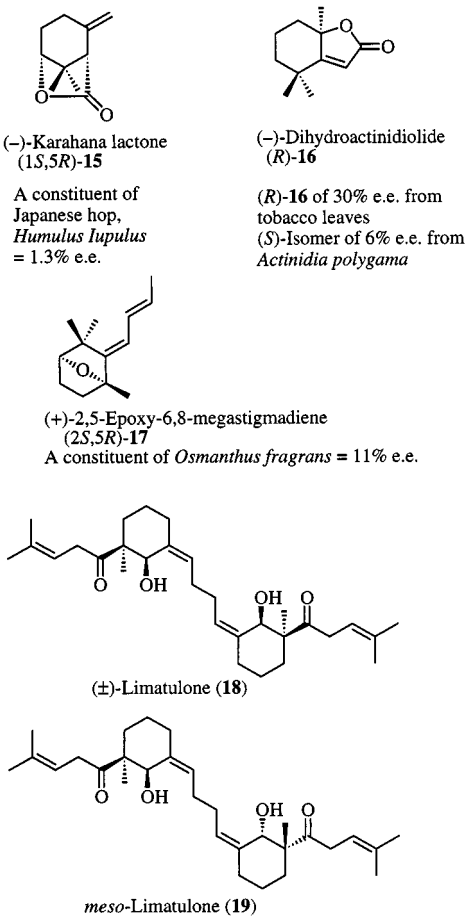


Another group of workers also estimated the enantiomeric composition of α-pinene (**10**) in the conifer resins from *Agathis* and *Araucaria* genera, and found that the enantiomeric ratios for **10** vary tremendously between trees of different age but of the same species[14]. (−)-Kaur-16-ene (**14′**), a diterpenoid, is the precursor of the plant hormone gibberellins, and is ubiquitous among higher plants. It was also found as a metabolite of *Gibberella fujikuroi*, which is the fungal producer of the gibberellins. Its opposite enantiomer, (+)-kaur-16-ene (**14**), is also known as a constituent of a plant *Podocarpus ferrugineus*[15].

Scheme 4 shows some other examples of natural products that are enantiomerically impure. Through the synthesis of enantiomerically pure karahana lactone (**15**)[16], dihydroactinidiolide (**16**)[17] and 2,5-epoxy-6,8-megastigmadiene (**17**)[18], and by comparing their specific rotations with those of their corresponding natural sources, it was revealed that the natural products were of low enantiomeric purity. These compounds might have been generated by degradation of carotenoids through a non-enzymatic photosensitized oxygenation process that is devoid of enantioselectivity.

Limatulone (Scheme 4) is an unusual triterpene that occurs as its racemate (**18**) and also as the *meso* isomer (**19**)[19][20]. In 1985, Faulkner and his coworkers reported the isolation of an allelochemical limatulone as a defensive metabolite of the limpet *Achmeia* (*Collisella*) *limatula*[21]. This triterpene is a potent feeding inhibitor against fish and crab, and even at the level of 0.05% dry weight of food pellets induces regurgitation in the intertidal fish *Gibbonsia elegans*, a known limpet predator. The natural product was reported to be optically inactive[21], inferring that it must be either (±)-**18** or *meso*-**19**. We synthesized both of these examples[19]. The ^{1}H- and ^{13}C-NMR spectra of the natural product were identical with those of (±)-**18**. Moreover, the

Scheme 4. Examples of natural products that are enantiomerically impure



Both **18** and **19** are produced by *Achmeia limatula*.

^{1}H-NMR spectrum of a less bioactive fraction from the HPLC separation of *Achmeia limatula* metabolite[20] coincided with that of the synthetic *meso*-**19**. It is clear that the limpet *Achmeia limatula* produces both (±)-**18** and *meso*-**19**. It must be added that under chemical conditions so far examined, no retroaldol-aldol process took place to convert **18** into **19** or vice versa. The mechanism by which the limpet biosynthesizes the three stereoisomers of limatulone [(+)-**18**, (−)-**18** and *meso*-**19**] simultaneously must await further investigation. It is now clear that nature does not always produce enantiomerically pure compounds.

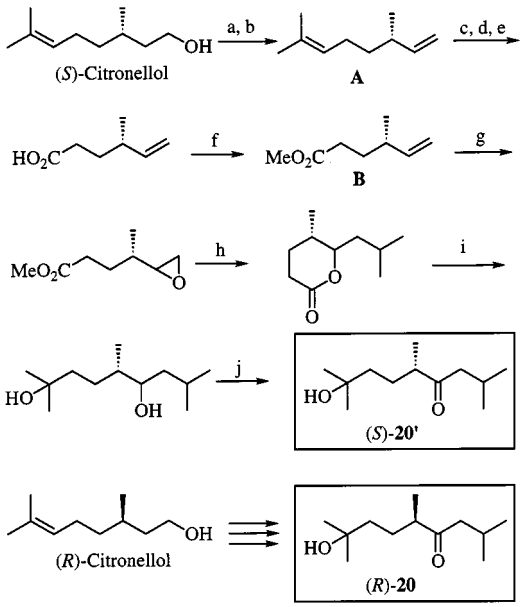
3. Some Recent Examples of the Synthesis of Enantiomerically Pure Semiochemicals

Aspects of pheromone synthesis have been reviewed[22][23][24][25]. Enantioselective synthesis of chiral and non-racemic semiochemicals is performed by one of the following three methods: (i) derivation from a known chiral and non-racemic building block, (ii) use of chemical or enzymatic separation of the enantiomers (resolution) at a certain stage of the synthesis, and (iii) use of chemical or enzymatic asymmetric reactions. Five of our recent examples will be discussed here.

Synthesis of a Myxobacterium Pheromone

Myxobacteria are unique procaryotes that undergo multicellular development including swarming and aggregation of their cells and formation of fruiting bodies. Very recently it became clear that the myxobacterium *Stigmatella aurantica* secretes a pheromone to aggregate the starving cells at the beginning of the developmental part of their life cycle. The pheromone thus induces the formation of the fruiting body of *S. aurantica*[26]. Plaga and his coworkers proposed **20** (or **20′**) as the structure of the pheromone on the basis of its spectral analysis[26]. In order to clarify the absolute configuration of the natural pheromone, we carried out a synthesis of both (*R*)-**20** and (*S*)-**20′** (Scheme 5)[27]. Because the pheromone **20** possesses only one stereogenic center as a methyl branching at C-5, citronellol was chosen as the ideal starting material. Our synthesis was straightforward and is shown in Scheme 5[27]. Bioassay of **20** and **20′** on *S. aurantica* proved both of them to be bioactive at a concentration of 1 nM. It is still an open question as to whether the natural pheromone is a single enantiomer or not.

Scheme 5. Synthesis of the enantiomers of the aggregation pheromone (**20**) of the myxobacterium *Stigmatella aurantica*[a]

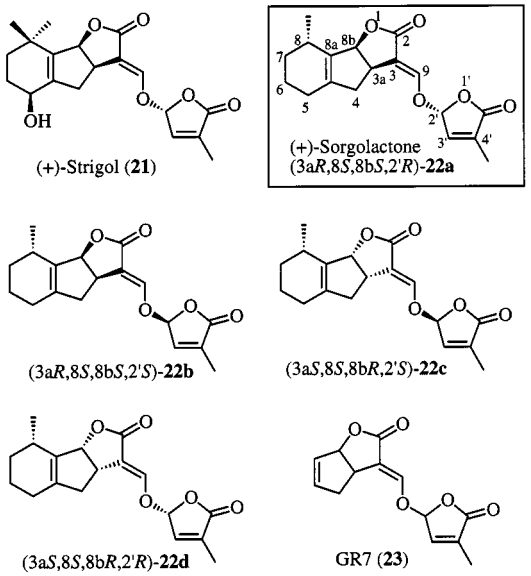


[a] Reagents: (a) NaH, CS_2 then MeI. – (b) Heat (45%). – (c) MCPBA, CH_2Cl_2. – (d) $HIO_4{\cdot}2H_2O$, THF/Et_2O. – (e) Jones CrO_3, Me_2CO (45% based on **A**). – (f) K_2CO_3, MeI, Me_2CO (89%). – (g) MCPBA, $NaHCO_3$, CH_2Cl_2. – (h) *i*PrMgCl, CuBr·Me_2S, THF (32% based on **B**). – (i) MeMgBr, THF (55%). – (j) Dess–Martin periodinane, C_5H_5N, CH_2Cl_2 (65%).

Synthesis of Sorgolactone

Parasitic weeds of the genera *Orobanche* and *Striga* are known to cause severe yield losses in grains and legumes, especially in Africa. The seeds of such weeds remain dormant in soil until exudates from their host plant induce germination. (+)-Strigol (**21**, Scheme 6) was isolated from cotton root exudates as a strong stimulant for the germination of such weeds. A number of syntheses of **21** have been reported since the first synthesis by Sih and his coworkers[28]. Another germination stimulant, sorgolactone (**22a**), was isolated from *Sorghum bicolor*, a genuine host plant, in 1992 by Hauck et al.[29]. Independently in 1997 we, as well as Zwanenburg and his coworkers, synthesized sorgolactone (**22a**) and its stereoisomers (**22b**–**22d**)[30][31][32]. Biological evaluation of our products **22a**–**22d**, employing clover broomrape (*Orobanche minor*) seeds, revealed that all of these compounds are strong germination stimulants[31][32]. In the particular case of sorgolactone, the stereochemistry seems to be unimportant for the expression of its bioactivity. Indeed, a compound as simple as GR 7 (**23**) is known to be an active stimulant of weed germination[33]. Scheme 7 summarizes our synthesis of **22a**–**22d**[32]. Methyl (*R*)-citronellate was employed as the chiral and non-racemic building block, and the key-step was the radical cyclization to give **A**.

Scheme 6. Structures of the germination stimulants for parasitic weeds

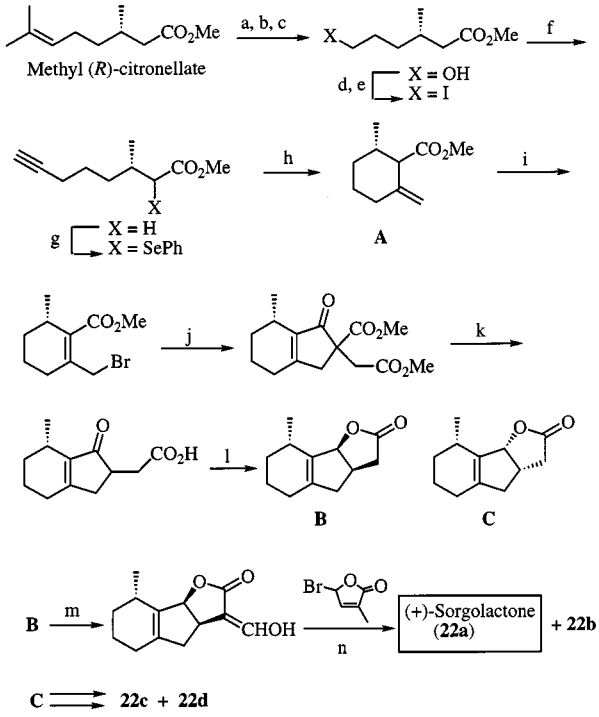


Synthesis of Phyllanthurinolactone

The phenomenon of nyctinasty or "plant sleep" has been known for many years. For example, the pinnate leaves of a large tamarind tree (*Tamarindus indica* L.) fold together at night as if the tree sleeps. In 1995 Yamamura and his coworkers isolated phyllanthurinolactone (**24a**, Scheme 8) as the leaf-closing factor of *Phyllanthus urinaria*[34]. It was bioactive only for that plant in the daytime at a concentration of 100 nM. They proposed the structure **24a**, although the absolute configuration of the aglycone part remained unknown[34].

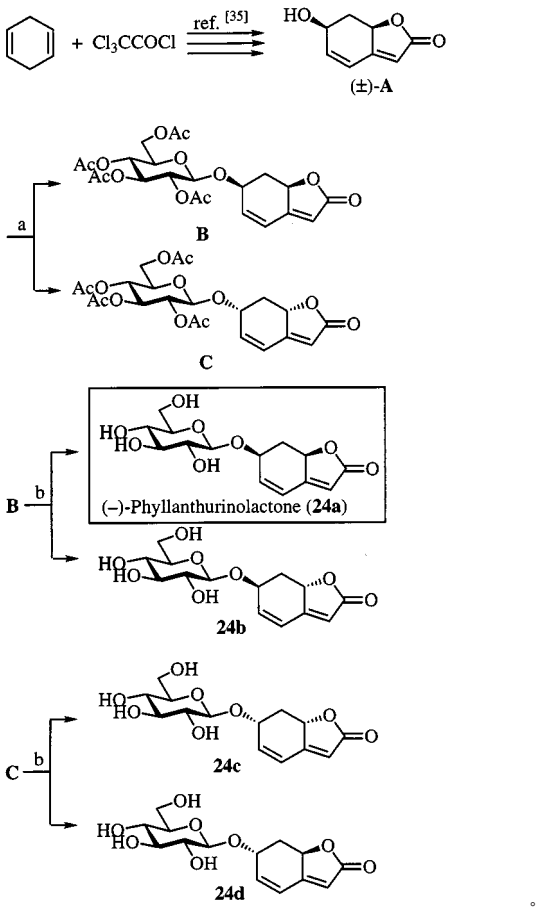
We synthesized phyllanthurinolactone (**24a**) and its stereoisomers (**24b**–**24d**) as shown in Scheme 8[35]. Our strategy was to prepare the racemic aglycone (±)-**A**, and resolve it by employing D-glucose as the resolving agent. The resolution of (±)-**A** successfully furnished **B** and **C**. The structure of **C** was solved by its X-ray analysis. Deacetylation of **B** or **C** was problematic due to the instability of the resulting glucosides. By employing potassium cyanide in

Scheme 7. Synthesis of (+)-sorgolactone and its stereoisomers[a]



[a] Reagents: (a) MCPBA, CH_2Cl_2. − (b) $HIO_4{\cdot}2H_2O$, THF/Et_2O. − (c) $NaBH_4$, MeOH (91%, 3 steps). − (d) TsCl, C_5H_5N. − (e) NaI, Me_2CO (82%, 2 steps). − (f) LiC≡CH·EDA, THF/DMSO (37%). − (g) (1) LDA (2 equiv.), THF; (2) PhSeBr; (3) dil. HCl (69%). − (h) Bu_3SnH, AIBN, C_6H_6 (55%). − (i) (1) $C_5H_5N{\cdot}HBr{\cdot}Br_2$, $CHCl_3$; (2) C_5H_5N, (52%). − (j) (1) NaH, $CH_2(CO_2Me)_2$, THF; (2) $BrCH_2CO_2Me$ (81%). − (k) 6 N HCl, AcOH (96%). − (l) (1) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, then dil. HCl; (2) MPLC separation (21% of **B** and 30% of **C**). − (m) NaH, HCO_2Et, Et_2O (quant.). − (n) (1) K_2CO_3, *N*-methylpyrrolidone; (2) SiO_2 chromatography (42% of **22a** and 41% of **22b**).

Scheme 8. Synthesis of (−)-phyllanthurinolactone and its stereoisomers[a]



[a] Reagents: (a) Acetobromo-D-glucose, Ag_2CO_3, AgOTf, MS 4 A, CH_2Cl_2 (15.6% of **B** and 15.6% of **C**). − (b) KCN (0.1 equiv.), MeOH (52% of **24a** and 22% of **24b**; 52% of **24c** and 22% of **24d**).

methanol as the base, **B** yielded the desired product **24a** and its stereoisomer **24b**. Likewise, **C** gave **24c** and **24d**. The leaf-closing activity of **24a**−**24d** was bioassayed employing the leaves of *Phyllanthus urinaria*. Only the naturally occurring **24a** was bioactive at concentrations of 10^{-3}, 10^{-4} and 10^{-5} g/l, while the unnatural stereoisomers **24b**, **24c** and **24d** were totally inactive. The bioactivity thus strongly depends on the stereochemistry of the bioregulator.

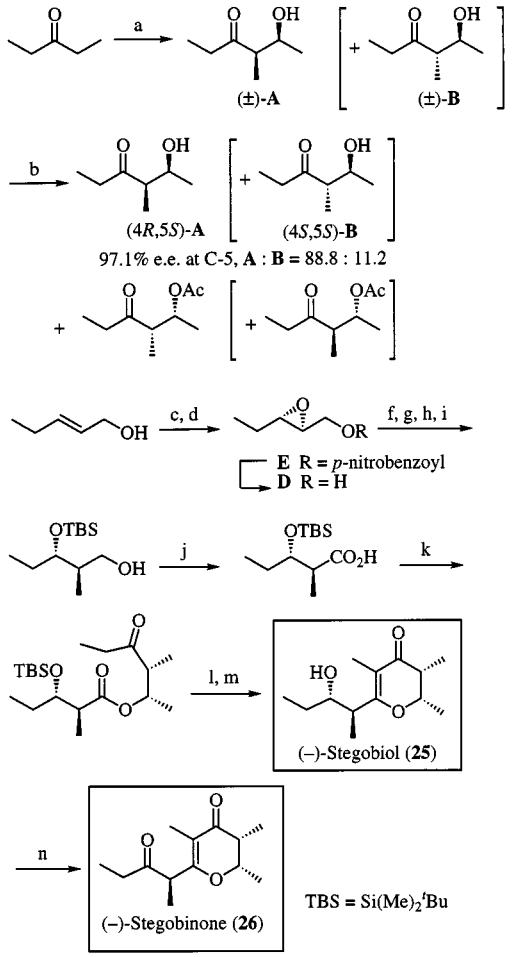
Synthesis of Stegobiol and Stegobinone

Stegobinone (**26**, Scheme 9)[36] and stegobiol (**25**)[37] are the components of the female-produced sex pheromone of the drugstore beetle (*Stegobium paniceum*). (2*S*,3*R*,1′*S*)-Epistegobinone, the stereoisomer of **26** at C-1′, is known to strongly inhibit the action of **26**[38]. Scheme 9 summarizes our synthesis of stegobiol (**25**) and its oxidation to stegobinone (**26**)[39]. We used enzymatic separation of the enantiomers (step b) and the Sharpless asymmetric epoxidation (step c) for the introduction of asymmetry. Repeated enzymatic acetylation of (±)-**A** furnished (4*R*,5*S*)-**A** as the non-acetylated material, while recrystallization of **E** could enhance the enantiomeric purity of the epoxy alcohol **D**. Both enzymatic and chemical asymmetric reactions were employed to achieve the goal. Another important point in this synthesis was the usefulness of the Dess−Martin oxidation for the preparation of such a readily epimerizable (at C-1′) compound as **26**. When **25** was oxidized under Swern conditions, impure and oily **26** was obtained, while the Dess−Martin oxidation yielded pure and crystalline stegobinone (**26**).

Synthesis of Frontalin

Frontalin (**27**, Scheme 10) is the component of the aggregation pheromone of the southern pine beetle (*Dendroctonus frontalis*), the western pine beetle (*Dendroctonus brevicomis*) and the Douglas-fir beetle (*Dendroctonus pseudotsugae*). The 1975 synthesis of **27** and its opposite enantiomer[40] was followed by bioassay to reveal the pheromone activity of only (−)-**27**[5]. There was a need to supply 10 g of (−)-**27** of over 76% *e.e.* for the field test against the Jeffrey pine beetle, an aggressive pest of Jeffrey pine in the U.S.A. The route summarized in Scheme 10 was efficient enough to fullfil this need[41]. Asymmetric reduction of **A** with baker′s yeast gave (1*R*,2*S*)-**B** in 52% yield with 97.7% *e.e.* and 99.0% *d.e.* Methylation of the dianion derived from **B** gave (1*R*,2*S*)-**C** (90.4% *d.e.* after fractional distillation).

Scheme 9. Synthesis of (−)-stegobiol and (−)-stegobinone[a]



[a] Reagents: (a) Bu_2BOTf, iPr_2NEt, Et_2O then MeCHO, −78°C (51%). − (b) Novozyme 435, CH_2=CHOAc, MS 4 A, hexane (twice) (33%). − (c) $Ti(OiPr)_4$, $tBuOOH$, (+)-diethyl tartrate, MS 3 A, CH_2Cl_2. − (d) p-$O_2NC_6H_4COCl$, C_5H_5N, CH_2Cl_2 (2 steps, 63%). − (e) NaOH, MeOH/H_2O (87%). − (f) (1) Me_2CuLi, Et_2O; (2) $NaIO_4$, H_2O (41%). − (g) $tBuCOCl$, C_5H_5N, CH_2Cl_2 (91%). − (h) TBSCl, imidazole, DMF (quant.). − (i) KOH, MeOH (80%). − (j) $RuCl_3$, $NaIO_4$, CCl_4, MeCN, pH = 7 buffer (84%). − (k) (1) 2,6-$Cl_2C_6H_3COCl$, Et_3N, THF; (2) (4R,5S)-**A**, DMAP, C_6H_6 (90%). − (l) $TiCl_4$ (5 equiv.), iPr_2NEt (8 equiv.), CH_2Cl_2, −78°C, 3 h then ca. −10 to −20°C, 2 d (66%). − (m) HF, MeCN/H_2O (47%). − (n) Dess−Martin periodinane, C_5H_5N, CH_2Cl_2 (quant.).

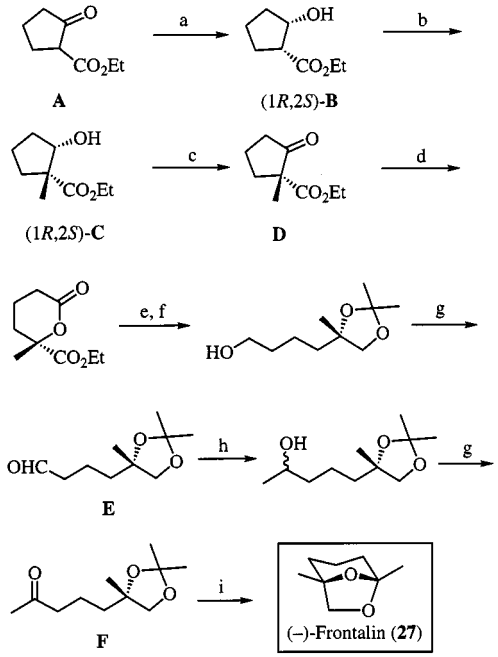
This was converted to frontalin (**27**, 89.1% *e.e.*) as shown in the Scheme. Biotransformations such as the use of Lipases or baker′s yeast often simplify the problems in enantioselective synthesis[42].

4. Stereochemistry-Bioactivity Relationships Among Pheromones and Other Bioregulators

Is a Single Enantiomer Always Responsible for Bioactivity?

As mentioned in the Introduction, it has generally been believed that only one enantiomer is bioactive and its opposite enantiomer is inactive in the case of a chiral and bioactive natural product. (*S*)-Glutamic acid (**28**, Scheme 11) has taste, while its opposite enantiomer is completely devoid of taste. Only the naturally occurring (6*S*,1′*S*)-hernandulcin (**29**) is a sweetener[43]. We synthesized the pure

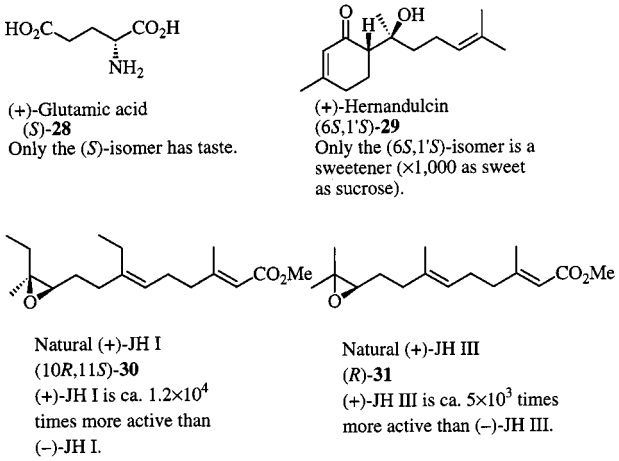
Scheme 10. Synthesis of (−)-frontalin[a]



[a] Reagents: (a) Baker′s yeast, sucrose, H_2O (52%). − (b) LDA (2.25 equiv.), MeI (1.45 equiv.), THF (87%). − (c) Jones CrO_3, Me_2CO (87%). − (d) MCPBA, $NaHCO_3$, CH_2Cl_2 (59%). − (e) $LiAlH_4$, Et_2O. − (f) $Me_2C(OMe)_2$, Me_2CO, TsOH·H_2O (77%, 2 steps). − (g) PCC, NaOAc, MS 3 A, CH_2Cl_2 (70% for **E** and 97% for **F**). − (h) MeMgBr, Et_2O (84%). − (i) TsOH·H_2O, Et_2O/H_2O (81%).

enantiomers of insect juvenile hormone (JH) I (**30**)[44][45] and JH III (**31**)[46]. Only the naturally occurring (+)-JH I (**30**) and (+)-JH III (**31**) were extremely active as insect juvenile hormones[47][48].

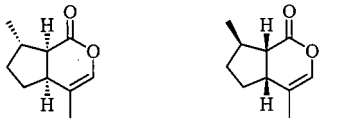
Scheme 11. Bioactive natural products, a single enantiomer of which is extremely bioactive



Another interesting case is that of (+)-nepetalactone (**32**, Scheme 12), which is a monoterpenoid isolated by McElvain et al. in 1941 as the cat attractant in catnip[49]. In 1987 Pickett and his coworkers reisolated this compound as the sex pheromone of the vetch aphid (*Megoura viciae*)[50]. They then clarified that only the (+) isomer is active as the

aphid pheromone. We were curious to find out whether or not both the enantiomers of **32** are active as the cat attractant. The enantiomers **32** and **32′** were synthesized and bioassayed on Japanese cats[51]. Both compounds were extremely active in cats at the 0.01 mg dosage level[51]. Pheromone perception by vetch aphids as a means of distinguishing between **32** and **32′** is a more rigorous process than perception by cats.

Scheme 12. Only (+)-nepetalactone (**32**) is active as the aphid pheromone, whereas both the enantiomers are active as the cat attractant



(+)-Nepetalactone (4a*S*,7*S*,7a*R*)-**32** (−)-Nepetalactone (4a*R*,7*R*,7a*S*)-**32′**

Stereochemistry-Bioactivity Relationships Among Pheromones

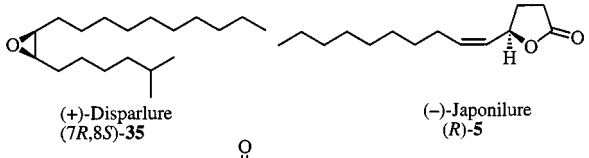
Among various semiochemicals, the relationships between stereochemistry and bioactivity have been most extensively studied in the case of pheromones since the early 1970′s when their pure enantiomers became available by synthesis. As exemplified in Schemes 13−17, the relationships are far from straightforward[3]. It was discovered that organisms utilize chirality to enrich and diversify their communication system. The stereochemistry-bioactivity relationships are divided into ten categories as detailed below.

Scheme 13. Stereochemistry and pheromone activity (1)

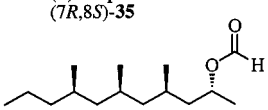
(1) Only a single enantiomer is bioactive, and its opposite enantiomer does not inhibit the response to the active stereoisomer.

Atta texana alarm pheromone (*S*)-**33** (+)-*exo*-Brevicomin (1*R*,5*S*,7*R*)-**2** (−)-Dehydro-*exo*-brevicomin (1*R*,5*S*,7*R*)-**34** etc.

(2) Only one enantiomer is bioactive, and its opposite enantiomer inhibits the response to the pheromone.



(+)-Disparlure (7*R*,8*S*)-**35** (−)-Japonilure (*R*)-**5**



(−)-Lardolure (1*R*,3*R*,5*R*,7*R*)-**36**

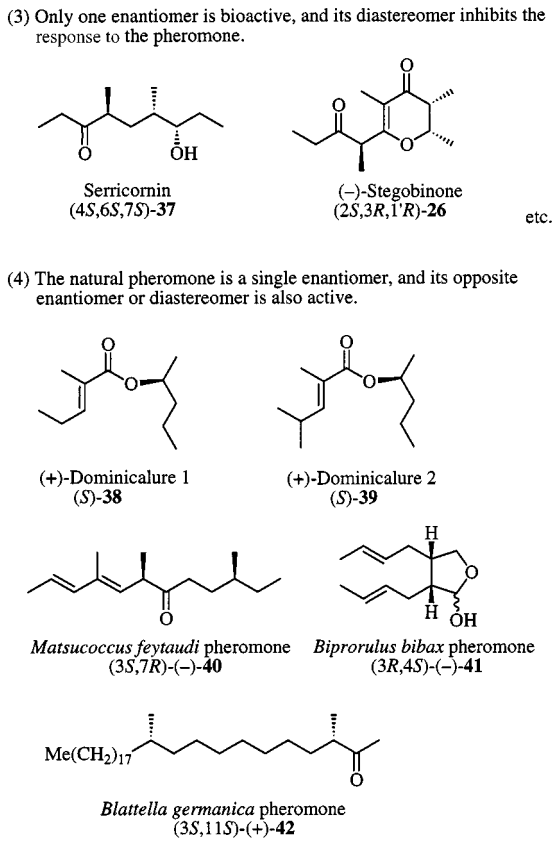
(1) *Only a single enantiomer is bioactive, and its opposite enantiomer does not inhibit the response to the active stereoisomer.* This is the most common relationship, and the majority (about 60%) of the chiral pheromones belong to this category. In 1974, Silverstein and his coworkers synthesized the enantiomers of **33**, the alarm pheromone of the leaf-cutting ant (*Atta texana*), and found (*S*)-**33** to be about 400 times more active than the (*R*) enantiomer[52]. As already described in the Introduction, (1*R*,5*S*,7*R*)-*exo*-brevicomin (**2**) was the bioactive enantiomer[5]. (1*R*,5*S*,7*R*)-Dehydro-*exo*-brevicomin (**34**) is a chemical signal of the male state, and a potential multipurpose pheromone of the house mouse (*Mus musculus*) to show his male state to others. This mammalian chemical communication is also an enantioselective process, and only (1*R*,5*S*,7*R*)-**34** is bioactive[53]. The mouse pheromone **34** shares the same absolute stereochemistry as *exo*-brevicomin (**2**). It is interesting to note that animals as different as the mouse and the pine beetle biosynthesize these acetals with the same absolute configuration.

(2) *Only one enantiomer is bioactive, and its opposite enantiomer inhibits the response to the pheromone.* The enantiomers of disparlure (**35**), the pheromone of the gypsy moth (*Lymantria dispar*), were first synthesized in 1974 by Marumo and his coworkers[54] and then by our group[55]. Electroantennographical (EAG) and behavioral responses of the gypsy moth to the enantiomers showed that (7*R*,8*S*)-(+)-**35** was the most effective, (±)-**35** came second, while (7*S*,8*R*)-(−)-**35′** inhibited the activity of the (+) isomer[54]. Under field conditions, males of the gypsy moth and males of the nun moth (*Lymantria monacha*) responded to (7*R*,8*S*)-**35**. However, the addition of (7*S*,8*R*)-(−)-**35′** significantly suppressed the response by *L. disper*, while (7*S*,8*R*)-(−)-**35′** did not have such an effect on the response of *L. monacha*[56]. EAG studies using the differential receptor saturation technique suggest the existence of one receptor type having greater affinity for (7*S*,8*R*)-**35′** than for (7*R*,8*S*)-**35**[57]. Very strong inhibitory action of the opposite enantiomer (*S*)-**5′** of japonilure [(*R*)-**5**] has already been mentioned in the Introduction. Lardolure [(1*R*,3*R*,5*R*,7*R*)-**36**] is the aggregation pheromone isolated from the acarid mite *Lardoglyphus konoi*. We synthesized both enantiomers of **36**[58]. The bioactive enantiomer is (1*R*,3*R*,5*R*,7*R*)-**36** against *L. konoi*, whereas (1*S*,3*S*,5*S*,7*S*)-**36′** is inhibitory[59]. A mixture of all the possible stereoisomers of **36** is therefore only marginally active against *L. konoi*[59].

(3) *Only one enantiomer is bioactive, and its diastereomer inhibits the response to the pheromone.* Serricornin [(4*S*,6*S*,7*S*)-**37**, Scheme 14] is the female-produced sex pheromone of the cigarette beetle (*Lasioderma serricorne*). Bioactivity of the stereoisomers of **37** was studied carefully by Chuman and his coworkers during the course of developing practical pheromone traps[60]. Only (4*S*,6*S*,7*S*)-**37** was bioactive, and its opposite enantiomer (4*R*,6*R*,7*R*)-**37′** did not inhibit the action of the pheromone. However, 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 with no contamination of the (4*S*,6*S*,7*R*) isomer. As already mentioned in connection with its synthesis, the (2*S*,3*R*,1′*S*) isomer of stegobinone [(2*S*,3*R*,1′*R*)-**26**] is the pheromone inhibitor. Therefore the racemic and diastereomeric mixture of synthetic stegobinone showed only very weak activity.

(4) *The natural pheromone is a single enantiomer, and its opposite enantiomer or diastereomer is also active.* Domini-

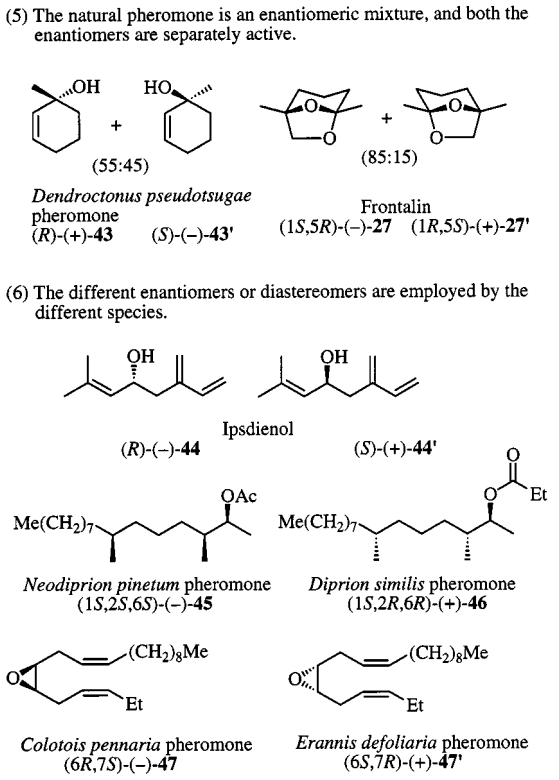
Scheme 14. Stereochemistry and pheromone activity (2)



calure 1 [(*S*)-**38**] and dominicalure 2 [(*S*)-**39**] are the male-produced aggregation pheromone components of the lesser grain borer, *Rhyzopertha dominica*. They are attractive against both sexes of that insect. The natural (*S*)-**38** and (*S*)-**39** were only twice as active as the unnatural (*R*)-**38** and (*R*)-**39**, as assayed by their field test[61]. Females of the maritime pine scale (*Matsucoccus feytaudi*) use (3*S*,7*R*)-**40** as the sex pheromone. Its (3*R*,7*R*) isomer also showed bioactivity similar to the natural pheromone, while *M. feytaudi* males responded very weakly to the two other stereoisomers[62]. It therefore seems that the stereochemistry at C-3 is not important for the expression of bioactivity. The male spined citrus bug (*Biprorulus bibax*) produces (3*R*,4*S*)-**41** as the aggregation pheromone. Our synthetic enantiomers of **41**[63] were bioassayed. The opposite (3*S*,4*R*) isomer of the pheromone was also bioactive, indicating that *B. bibax* does not discriminate between the enantiomers[64]. The female German cockroach (*Blattella germanica*) produces (3*S*,11*S*)-**42** as her contact sex pheromone[65]. The male German cockroaches, however, do not discriminate between the four stereoisomers of **42**, and all of the stereoisomers are bioactive[66].

(5) *The natural pheromone is an enantiomeric mixture, and both the enantiomers are separately active.* Female Douglas fir beetles (*Dendroctonus pseudotsugae*) produce an average of a 55:45 mixture of (*R*)-**43** and (*S*)-**43′** (Scheme 15)[67]. The enantiomers are separately active, but both enantiomers are required for maximum response[67]. Male southern pine beetles (*Dendroctonus frontalis*) produce an 85:15 mixture of (1*S*,5*R*)-frontalin (**27**) and its opposite enantiomer (1*R*,5*S*)-**27′**. In laboratory and field bioassays, the response of *D. frontalis* was greater to the mixture of (1*S*,5*R*)-**27** and α-pinene than to (1*R*,5*S*)-**27′** and α-pinene[68]. EAG studies showed that antennal olfactory receptor cells were significantly more responsive to (1*S*,5*R*)-**27** than to (1*R*,5*S*)-**27′**. Both **27** and **27′** stimulated the same olfactory cells, suggesting that each cell has at least two types of enantioselective receptors.

Scheme 15. Stereochemistry and pheromone activity (3)

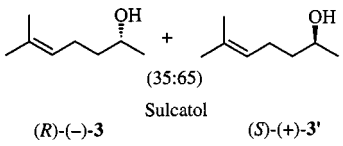


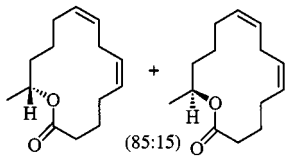
(6) *Different enantiomers or diastereomers are employed by different species.* (*S*)-Ipsdienol (**44′**) is the pheromone component of the California five-spined ips (*Ips paraconfusus*). However, both the bark beetles *I. calligraphus* and *I. avulsus* respond to its opposite enantiomer (*R*)-**44**[69]. The pine engraver *I. pini* in the U.S.A. responds to a mixture of **44** and **44′**. A detailed study on variation of the enantiomeric purity of ipsdienol in *I. pini* was reported recently[70]. Complicated relationships between stereochemistry and bioactivity of the pine sawfly pheromone were studied extensively[13]. For example, the white pine sawfly (*Neodiprion pinetum*) uses (1*S*,2*S*,6*S*)-**45** as its sex pheromone[71][72], while (1*S*,2*R*,6*R*)-**46** is used by the pine sawfly (*Diprion similis*) introduced into the U.S.A.[72]. Chirality of pheromones is important to discriminate between two species of the winter-flying geometrid moths in Central Europe. Thus (6*R*,7*S*)-**47** is the pheromone of *Colotois pennaria*, while *Erannis defoliaria* uses (6*S*,7*R*)-**47′** as its pheromone[73]. In these cases, insects utilize chirality to segregate different species.

(7) *Both enantiomers are necessary for bioactivity.* The synergistic response of the ambrosia beetle *Gnathotrichus sulcatus* based on the enantiomers of sulcatol (**3** and **3′**, Scheme 16) has already been discussed in the Introduction. In the case of the grain beetle *Cryptolestes turcicus*, neither (*R*)-**48** nor (*S*)-**48′** was bioactive as its aggregation pheromone. However, the mixture [(*R*)-**48**/(*S*)-**48′** = 85:15] was bioactive[74].

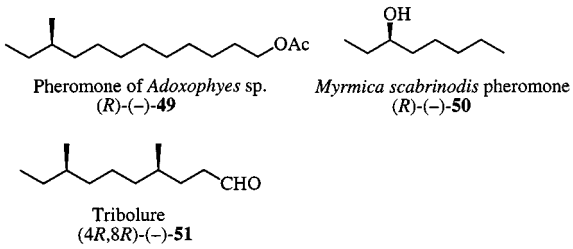
Scheme 16. Stereochemistry and pheromone activity (4)

(7) Both the enantiomers are necessary for bioactivity.





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

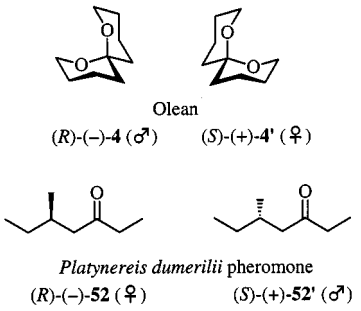


(8) *One enantiomer is more active than the other stereoisomer(s), but an enantiomeric or a diastereomeric mixture is more active than the enantiomer alone.* The smaller tea tortrix moth (*Adoxophyes* sp.) uses **49** as a minor component of its pheromone bouquet, and (*R*)-**49** was found to be slightly more active than the opposite enantiomer (*S*)-**49′**. Further field tests suggested that there is an optimum (*R*)/(*S*) ratio of 95:5 for trapping of males[75]. In the case of the ant *Myrmica scabrinodis*, the naturally occurring mixture of (*R*)-**50** and its opposite enantiomer (*S*)-**50′** [(*R*)/(*S*) = 9:1] was more attractive than the pure (*R*)-**50** or (±)-**50**, while (*S*)-**50′** was inactive[76]. Tribolure [(4*R*,8*R*)-**51**] is the male-produced aggregation pheromone of the red-flour beetle, *Tribolium castaneum*. Suzuki et al. found that (4*R*,8*R*)-**51** was as active as the natural pheromone, while a mixture of (4*R*,8*R*)-**51** and its (4*R*,8*S*) isomer in a ratio of 4:1 was about ten times more active than (4*R*,8*R*)-**51** alone[77].

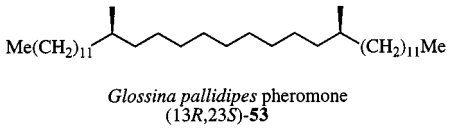
(9) *One enantiomer is active on males, while the other is active on females.* As described in the Introduction, olean (**4**, Scheme 17) shows this unique stereochemistry-bioactivity relationship[10]. 5-Methyl-3-heptanone (**52**) was isolated as a pheromone in the coelomic fluid of gravid specimens of nereid marine polychaetes by Zeeck, Hardege and their coworkers[78]. It is responsible for the induction of the nuptial dance behavior prior to the release of gametes in *Platynereis dumerilii.* Interestingly, the female-produced (*S*)-(+)-**52′** activates the males, while the male-produced (*R*)-(−)-**52** is active on females[79][80].

Scheme 17. Stereochemistry and pheromone activity (5)

(9) One enantiomer is active on males, while the other is active on females.



(10) Only the *meso*-isomer is active.



(10) *Only the meso isomer is active.* In the cases of the tsetse fly sex pheromones, *meso*-alkanes seem to be bioactive. Thus, (13*R*,23*S*)-**53** was active as the sex-stimulant pheromone of the female tsetse fly, *Glossina pallidipes.* Neither the (13*R*,23*R*) nor the (13*S*,23*S*) isomer was bioactive[81].

The ten categories described above were only found through experiments. In all cases, synthesis of pure enantiomers and stereoisomers was followed by bioassay to clarify the matter. A more detailed compilation of the stereochemistry-bioactivity relationships can be found in refs.[24][82].

5. Conclusions

The urgent need for our society to preserve the global ecological system makes it important to understand more about the roles of semiochemicals in the environment. The more we understand these roles, the better we may be able to protect our ecological system. From the standpoint of practical applications of pheromones, their stereochemical problems must be solved prior to any attempt at large-scale use of pheromones. We must not forget that stereoisomers of pheromones can be inhibitors of the pheromone action. At present we cannot predict whether a stereoisomer inhibits the pheromone action or not. The answer can be obtained only through experiments.

For the population-monitoring of the gypsy moth in the U.S.A., trapping of males with (7*R*,8*S*)-dispalure (**35**) has

been used for many years. Only highly enantiomerically pure (7*R*,8*S*)-**35** can work as a powerful trapping agent. For the mass-trapping of the Japanese beetle in the U.S.A. and also in Japan, only the enantiomerically pure (*R*)-japonilure (**5**) works ideally. Both (7*R*,8*S*)-**35** and (*R*)-**5** are commercially available as the pure enantiomers. In the case of sericornin [(4*S*,6*S*,7*S*)-**37**], the cigarette beetle pheromone, it is essential to prepare the commercial product with no contamination of its (4*S*,6*S*,7*R*) isomer. We need highly sophisticated stereoselective synthetic technology to prepare large amounts (kg or ton scales) of pheromones to be used practically.

The importance of chirality is now well established in chemical communications. The progress was made possible by the advance in both analytical and synthetic organic chemistry. The advance in this last quarter of the 20th century is most evident in the fact that we can now synthesize pure enantiomers with even higher enantiomeric purities than those of naturally occurring semiochemicals. This technical advance enabled the unveiling of the biodiversity in pheromone perception. Organisms employ chirality to enrich their communication system and also to secure greater specificity in perception. This holds a strong adaptive advantage for the organisms. The exact enantioselective mechanisms of pheromone perception are now under active investigation. We look forward to witnessing further advances.

I thank my past and present coworkers, especially Dr. *H. Takikawa*, for their help.

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