# Biocatalysis Applied to the Synthesis of Pheromones

J. Aleu, A. J. Bustillo, R. Hernández-Galán and I. G. Collado*

*Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Cádiz, República Saharaui s/n, Apdo. 40, 11510 Puerto Real, Cádiz, Spain*

**Abstract:** The application of biologically derived catalysts to the synthesis of agrochemicals has become increasingly popular in recent years. In most cases, the aim of using a biotransformation is either to introduce chirality into the molecule, to achieve a regioselective functionalization, or to selectively convert a functional group among other groups with similar reactivity. Pheromones, which have recently been commercialized as agrochemicals, are generally used in enantiopure forms with their intentional mixtures. Since they are usually highly effective, only very small quantities are needed to achieve the desired activity. This review, with approximately 200 references covering the period previous to December 2004, describes various efficient means of preparing optically pure pheromones and their precursors with the aid of isolated enzymes and microorganisms serving as catalysts.

## 1. INTRODUCTION

The technique of incorporating biotransformation steps, with microorganisms and/or isolated enzymes, is becoming increasingly common in both industrial and academic synthesis laboratories. The primary consideration for the incorporation of a biotransformation in a synthetic sequence is the regio- and stereo-control that can be achieved with an enzyme-catalyzed reaction. Biotransformations are thus becoming accepted as a method for generating optically pure compounds as well as for developing efficient routes to target compounds.

Most enzymes operate at room temperature, under neutral aqueous conditions, and in the absence of substrate functional-group protection. In organic synthesis, these biocatalysts can be used as the sole catalyst in a reaction, in combination with other enzymes, or with non-biological reagents. In addition, many enzymes accept unnatural substrates, and genetic engineering can further alter their stability, broaden their substrate specificity, and increase their specific activity. Thus, while molecules with several functional groups pose particular challenges to non-biological synthetic methods, they are natural targets for biological techniques. Through the use of biocatalysts, then, otherwise impractical synthetic manipulations of complex molecules can be performed in an environmentally benign manner.

Enzyme-catalyzed chemical transformations are now widely recognized as practical alternatives to traditional (non-biological) organic synthesis, and as convenient solutions to certain intractable synthetic problems. Their application in synthesis thus represents a remarkable opportunity for the development of industrial chemical and pharmaceutical processes [1].

Pheromones and insect hormones have recently been commercialized as agrochemicals, with most of them being used in their enantiopure forms with their intentional mixtures. Different enantiomers can exhibit different, stereospecific biological activities, including positive pheromone activity, inhibitory activity, synergistic activity and so on. Since pheromones and hormones are usually highly effective, only very small quantities are needed to achieve the desired activity. Their preparation as commercial products is thus of great interest, even if it involves a sophisticated, multistep synthetic route on a smaller scale than those of other categories of agrochemicals [2].

Insect sex pheromones that work either by disrupting mating or by leading to mass trapping, for example, are expected to become the next generation of pesticides [3]. These target pheromones are all optically active molecules, with their chiral centers being critical to their activities. In some cases, unnatural enantiomers that correspond to their natural counterparts can strongly inhibit a pheromone's male response. Extremely high optical purity is therefore essential for practical use of a pheromone. Because the utility of pheromones is obvious, many research groups have devoted themselves to developing efficient chemoenzymatic routes for large scale preparation of these compounds [4,5]. This review will highlight the main applications of biocatalysts, isolated enzymes, and whole microorganisms to the synthesis of pheromones and their precursors.

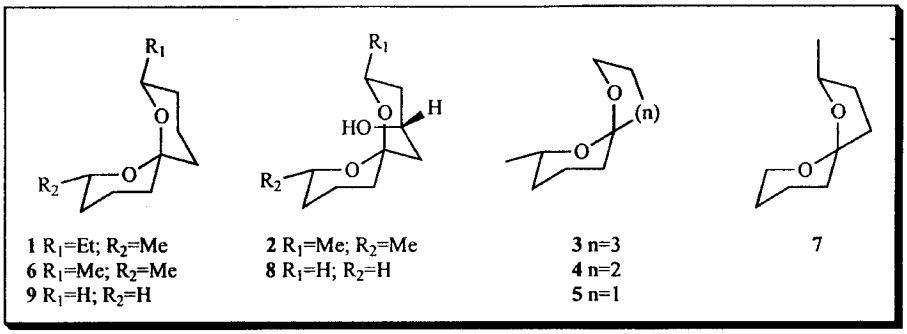
## 2. SYNTHESIS OF SPIROKETAL PHEROMONES

A spiroketal structure is a feature of an expanding variety of naturally occurring compounds, many of which exhibit important physiological activities as pheromones [6].

The sex pheromones with a spiroketal structure for *Bactrocera nigrotibialis*, (2*S*, 6*R*, 8*S*)-2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane (**1**) [7], *Andrena wilkella*, (2*S*, 4*R*, 6*R*, 8*S*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecan-4-ol (**2**) [8], and *Andrena haemorrhoa* F, (2*S*, 6*R*)-2-methyl-1,7-dioxaspiro[5.6]dodecane (**3**) [9], have already been synthesized. The synthetic methods, however, have not always been satisfactory due to their long synthetic pathways and the low optical purities of the target compounds. Still, Kitayama [10] reported the asymmetric synthesis of these pheromones at almost complete enantiomeric purity (>99%) from a chiral nitro alcohol, (*S*)-1-nitropropan-2-ol, prepared

*Address correspondence to this author at the Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Cádiz, República Saharaui s/n, Apdo. 40, 11510 Puerto Real, Cádiz, Spain; Tel: +34-956016368; Fax: +34-956016193; E-mail: isidro.gonzalez@uca.es

1385-2728/07 $50.00+.00 



**1** $R_1$=Et; $R_2$=Me
**6** $R_1$=Me; $R_2$=Me
**9** $R_1$=H; $R_2$=H

**2** $R_1$=Me; $R_2$=Me
**8** $R_1$=H; $R_2$=H

**3** n=3
**4** n=2
**5** n=1

**7**

by means of a lipase-catalyzed stereoselective transesterification of the corresponding racemic compound.

Compound **3** and the other spiroketal pheromones (2*S*, 6*R*)-2-methyl-1,7-dioxaspiro[5.5]undecane (**4**) and (5*S*, 7*S*)-7-methyl-1,6-dioxaspiro[4.5]decane (**5**) had been synthesized previously by Cohen *et al.* [11] from (*S*)-5-phenylthiopentan-2-ol, which had been obtained efficiently in high enantiomeric excess by means of a bakers' yeast-mediated reduction of the corresponding ketone. These authors used the same method for the synthesis of the bee pheromone (2*S*, 6*R*, 8*S*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**6**) [12].

Moreover, Izquierdo *et al.* [13] reported the lipase-mediated resolution of several precursors of the pheromones of the common wasp *Vespula vulgaris* (F.), (5*S*, 7*S*)-7-methyl-1,6-dioxaspiro[4.5]decane (**5**), and of *Paravespula vulgaris* (L.), (2*R*, 5*R*)-2-methyl-1,6-dioxaspiro[4.5]decane (**7**).

In 1996, Mori *et al.* [14] achieved a chemoenzymatic synthesis of (4*R*, 6*R*)-4-hydroxy-1,7-dioxaspiro[5.5]undecane (**8**), the minor component of the pheromone of the olive fruit fly (*Bactrocera oleae*) and a precursor of 1,7-dioxaspiro[5.5]undecane (**9**) (olean). The key step was an asymmetric hydrolysis with pig liver esterase (PLE). Bioassays on the synthetic enantiomers of **9** revealed that (*R*)-**9** is active on male insects while (*S*)-**9** is active on females. The natural olean was racemic [15].

## 3. SYNTHESIS OF BICYCLIC KETAL PHEROMONES

(+)-*Exo*- and (–)-*endo*-brevicomin ((+)-*exo*-**10** and (–)-*endo*-**10**, respectively) are components of the attracting pheromone system of several bark-beetle species belonging to the genera *Dendroctonus* and *Dryocoetes* [16]. In several species, *endo*-**10** is a minor component accompanying (+)-*exo*-**10**. The (–)-*endo* isomer has been reported to be an anti-aggregation pheromone for the southern pine beetle *Dendroctonus frontalis*. In contrast, (+)-*endo*-**10** increases aggregation [17]. *Dentroctonus ponderosae* (Mountain Pine beetle) is known to produce (+)-*exo*-brevicomin with >98% *ee*, whereas the optical purities of the accompanying stereoisomer *endo*-**10** were reported as being in the range of 65–70% *ee* [18]. Only the (1*R*, 5*S*, 7*R*)-isomer of *exo*-brevicomin (**10**) is bio-active, but its opposite enantiomer does not inhibit the action of the pheromone [19].

A short total asymmetric synthesis of (+)-*exo*- and (–)-*endo*-brevicomin (**10**) was accomplished with a chemoenzymatic protocol [20]. The key step consisted of biocatalytic hydrolysis by bacterial epoxide hydrolases of *cis*-configured 2,3-disubstituted oxiranes bearing olefinic side chains. This reaction proceeded in an enantioconvergent fashion, affording a single enantiomeric *vic*-diol from the *rac*-epoxide in up to 92% *ee* and 83% isolated yield.

Myles *et al.* [21] also reported a strategy combining chemical and enzymatic steps for the synthesis of (+)-*exo*-brevicomin ((+)-*exo*-**10**). The commercially available enzyme transketolase (EC 2.2.1.1) catalyzed the condensation of β-hydroxypyruvic acid and 2-hydroxybutyraldehyde to furnish the central intermediate in the sequence, an optically active hydroxyketone.

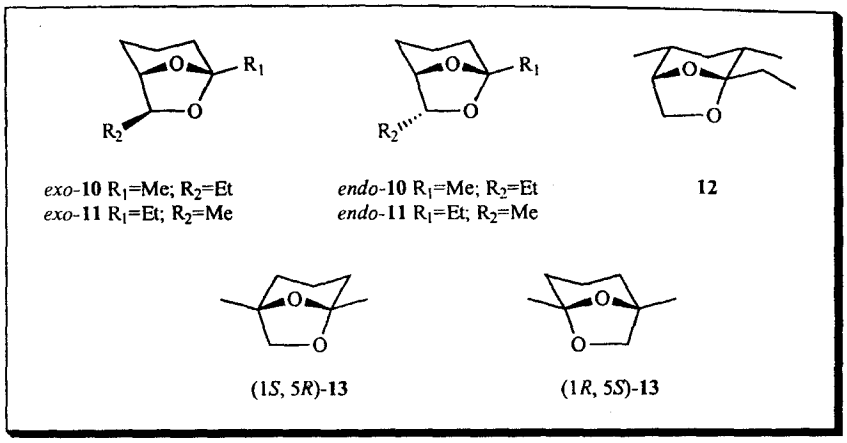
Moreover, the microbial reduction of 3,4-diketones and α-ketothioacetals [22], along with lipase-catalyzed kinetic resolution [23,24] have also been applied to a chemoenzymatic synthesis of the *exo*- and *endo*-brevicomin enantiomers.

In this vein, Mori *et al.* [25] reported an efficient and highly enantioselective chemoenzymatic synthesis of both the *exo*- and *endo*-isomers of isobrevicomin (**11**), which had been isolated by Francke *et al.* [26] in 1996 as components of the volatiles obtained from male mountain pine beetles *(Dendroctonus ponderosae)*. The enzymatic step was a lipase-catalyzed asymmetric acetylation with vinyl acetate and immobilized lipase PS (Amano).

(-)-α-Multistriatin (**12**) is an essential component of the aggregation pheromone of the European elm bark beetle *Scolytus multistriatus* (Marsham), which is the principal vector of Dutch elm disease [27]. Sinha *et al.* [28] carried out the first total synthesis of this compound via antibody catalysis. The key step in the synthesis is an antibody-catalyzed, enantioselective protonolysis of an enol ether to produce a branched ketone. The latter is obtained with an (*S*)-configuration in >99% *ee*.

Another bicyclic ketal pheromone is frontalin (1,5-dimethyl-6,8-dioxabicyclo[3,2,1]octane) (**13**), the aggregation pheromone of pine beetles of the *Dendroctonus* family [29]. Frontalin (**13**) from the pine beetle *Dendroctonus frontalis* is an 85:15 mixture of (1*S*, 5*R*)- and (1*R*, 5*S*)-enantiomers. Bioassays have shown that the (1*S*, 5*R*)-(–) enantiomer of frontalin is much more active than the (1*R*, 5*S*)-(+)-enantiomer [30]. Indeed, the latter isomer was prepared in a practical and highly enantioselective fashion with the help of the commercially available aldolase antibody 38C2 [31].

The more active enantiomer (1*S*, 5*R*)-(-)-**13**, on the other hand, has been synthesized by various authors *via* a chemoenzymatic route in which whole cells [32-34] or lipases [23,35-39] are utilized in the key step. In the synthesis




developed by Nishimura *et al.* [33], the enzymatic step was an asymmetric bakers' yeast-mediated reduction of ethyl 2-oxocyclopentane-1-carboxylate, to afford the target compound with an enantiomeric purity of 89% *ee*.

Ohta *et al.* [34] carried out the kinetic resolution of racemic 1-cyano-1-methylalkyl and alkenyl acetates by incubating them with *Pichia miso* IAM 4682, which selectively hydrolyzed the (*R*)-enantiomer, leaving the (*S*)-enantiomer intact. The chiral 1-cyano-1-methyl-5-hexenyl acetate thus obtained was converted to (1*S*, 5*R*)-(-)-frontalin (**13**). These authors later reported [36] using *Candida cylindracea* lipase for the enzymatic preparation of enantiomerically enriched tertiary α-benzyloxy acid esters as synthetic intermediates for (1*S*, 5*R*)-(-)-**13**.

In addition, Chênevert *et al.* [35] reported the synthesis of (1*S*, 5*R*)-(-)-frontalin (**13**) by means of the stereoselective acylation (desymmetrization) of 2-(4,5-dihydroxy-4-hydroxymethylpentyl)-2-methyl-1,3-dioxolane with vinyl acetate in organic media in the presence of *Pseudomonas* sp. lipase with 90% *ee*.

Finally, Veschambre *et al.* [40] prepared the four stereoisomers of 1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane, the pheromone of the beetle *Trypodendron lineatum*, by means of selective microbiological reduction and subsequent cyclization.

## 4. SYNTHESIS OF HYDROXYLATED PHEROMONES AND RELATED COMPOUNDS

6-Methylhept-5-en-2-ol (**14**), sulcatol, is the male-produced aggregation pheromone of the ambrosia beetle *Gnathotrichus sulcatus*, an economically important pest in the coniferous forests of the Pacific Coast of North America. Neither (*R*)-**14** nor (*S*)-**14** was bioactive. But when combined to give a racemic mixture, synthetic **14** was more active than the natural pheromone, which appeared as a mixture of (*R*)-**14** and (*S*)-**14** in a ratio of 35:65 [41].

Both enantiomers of sulcatol (**14**) can be prepared by means of biocatalytic asymmetric reduction of prochiral 6-methylhept-5-en-2-one [42]; for this purpose, bacteria [43], yeasts [44-46], fungi [47,48] and commercial enzymes [49,50] that give high optical purities can all be used.

In addition, (*S*)-(+)-sulcatol (**14**) has been obtained through yeast reduction of various substrates including ethyl (*S*)-3-hydroxybutanoate [51], a nitroalkane synthon [52], and a β-ketosulfone [53], with excellent enantiomeric excesses.

Moreover, lipase-catalyzed transesterification [54,55] and hydrolysis [56,57] have both been employed extensively in the synthesis of sulcatol (**14**). Thus, Kita *et al.* [58] reported a convenient lipase-mediated resolution of sulcatol (**14**) to obtain both enantiomers with excellent chemical and optical yields using 1-ethoxyvinyl esters as highly reactive acyl donors.

An enantioconvergent synthesis of (*R*)- and (*S*)-sulcatol (**14**) was described by Steinreiber *et al.* [59]. The key steps in the deracemization strategy were sequential combinations of enzymatic resolutions and Mitsunobu inversions. Racemization-free Mitsunobu transformations were carried out with high-speed microwave irradiation to afford the desired sulcatyl acetates with a clean inversion of chirality.

In the commercial sector, Forschungszentrum Jülich GmbH (Germany) has produced (*S*)-sulcatol (**14**) using alcohol-NAD+ oxidoreductase obtained from *Rhodococcus erythropolis*. The cofactor regeneration is carried out with a formate dehydrogenase from *Candida boidinii* and makes use of formate which is oxidized to $CO_2$ [60] (Fig. 1).

In this general context, Steinreiber *et al.* [61] described a short chemoenzymatic synthesis of the (2*R*, 5*S*)- and (2*R*, 5*R*)-stereoisomers of the bark beetle pheromone pityol (**15**)

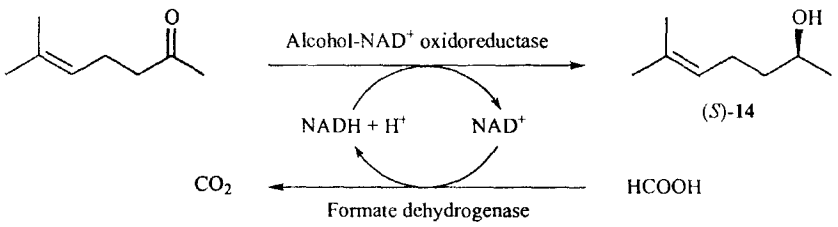
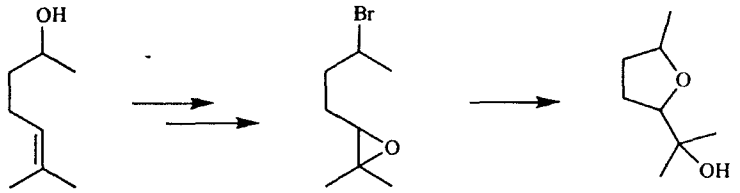



**Fig. (1).** Production of (*S*)-sulcatol (**14**) by Forschungszentrum Jülich GmbH.




14 15

Fig. (2). Chemoenzymatic synthesis of (2*R*, 5*S*)- and (2*R*, 5*R*)-pityol (**15**) from (±)-sulcatol (**14**).

from (±)-sulcatol (**14**). The key steps included a lipase-catalyzed deracemization by means of kinetic resolution coupled to an *in situ* inversion, along with the use of an epoxide-hydrolase for diastereo-convergent hydrolysis and subsequent spontaneous ring closure to form pityol (**15**) (Fig. 2). Archelas *et al.* [62] also reported the synthesis of (2*R*, 5*S*)-pityol (**15**) using a chemoenzymatic route with highly stereoselective, microbiologically mediated reactions.

Other pheromones structurally related to sulcatol (**14**) have been synthesized by means of enzymatic lipase-mediated resolution. For example, (-)-lasiol, (2*S*, 3*S*)-2,3,6-trimethylhept-5-en-1-ol, the major component of the mandibular gland secretion produced by male *Lasius meridionalis* ants, was prepared by means of enzymatic desymmetrization of *meso*-2,3-dimethylbutane-1,4-diol and its acetate [63]. (*R*)-Lavandulol, 5-methyl-2*R*-(2-methylet-1-enil)hex-4-en-1-ol, a component of the aggregation pheromone of the strawberry blossom weevil *Anthonomus rubi* Herbst, and (*S*)-lavandulol, recently identified as the sex pheromone of the vine mealybug *Planococcus ficus*, have both been synthesized with a two-cycle enzymatic transesterification of racemic lavandulol with the aid of lipase [64]. Both enantiomers of rhynchophorol, (*E*)-6-methylhept-2-en-4-ol, the male-produced aggregation pheromone of the American palm weevil *Rhynchophorus palmarum*, were also prepared in a synthesis that included lipase-mediated asymmetric hydrolysis as the key step [65].

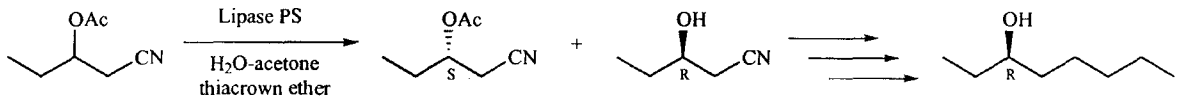



Fig. (3). Chemoenzymatic synthesis of (*R*)-octan-3-ol.

Nagaki *et al.* [66,67] carried out one-pot syntheses of the sex pheromone homologue of the codling moth *Laspeyresia promonella* L., (2*Z*, 6*Z*)-7-methyl-3-propyldeca-2,6-dien-1-ol, by using first a thermophilic enzyme, the thermostable farnesyl diphosphate synthase, and then an alkaline phosphatase.

The stereoisomers of 4-methylheptan-3-ol are major components of both the aggregation pheromones of bark beetles and the trail pheromones of ants. Zada *et al.* [68] studied the synthesis and the biological activity of these compounds; the key step in their synthesis was a stereospecific transesterification with lipase AK catalysis. Mori *et al.* had previously prepared optically active forms of threo-4-methylheptan-3-ol [69] using a microbial acylase obtained from *Aspergillus* while Domínguez *et al.* [70] prepared optically active (*E*)-γ-hydroxy-α,β-unsaturated phenyl sulfones using lipase-mediated acylations. They then successfully applied this process to the synthesis of the aggregation pheromone (3*S*, 4*S*)-4-methylheptan-3-ol.

The two enantiomers of octan-3-ol, the pheromone of a number of species of ants, were synthesized by Kamezawa *et al.* [71] with an enantiomeric purity of almost 100% through an enzymatic two-step hydrolysis of 3-octyl acetate catalyzed by *Pseudomonas cepacia* lipase. Kang *et al.* [72] used the same lipase-mediated resolution to obtain (*S*)-octan-3-ol, the alarm pheromone of the ant species *Crematogaster castanea* and *liengmei*, from 1-(2-thienyl)propyl acetate. In addition, both enantiomers of octan-3-ol were synthesized in >99% *ee* from optically active 3-hydroxyalkanenitriles prepared by means of a lipase-mediated enzymatic resolution with catalytic amounts of thiacrown ether (Fig. 3) [73]. Cammaerts *et al.* [74] studied the stereochemistry-bioactivity relationships of these pheromones of the ant *Myrmica scabrinodis* and showed that the naturally occurring mixture of (*R*)- and (*S*)-octan-3-ol (*R*:*S* = 9:1) was more attractive than either pure (*R*)- or (±)-octan-3-ol. The (*S*)-enantiomer was found to be inactive.

Cruentol, (4*S*, 5*S*)-5-methyloctan-4-ol, the male-produced aggregation pheromone of the palmetto weevil *Rhynchophorus cruentatus*, was synthesized by means of lipase-catalyzed asymmetric hydrolysis with excellent optical yields [75].

(2*S*, 3*S*)-Octane-2,3-diol has been reported to be a major component of the pheromones of the grape borer *Xylotrechus pyrrhoderus*. Ichikawa [76] prepared this compound through the enantiomeric resolution of asymmetric glycol by means of a lipase-catalyzed transesterification reaction, while Takahata *et al.* [77] synthesized it from 3-hydroxy-4-methyl-γ-butyrolactone prepared with chemoenzymatic methods.

Sharma *et al.* applied the lipase-catalyzed acetylation of 2-alkanols to the synthesis of dodecan-2-ol and 2-tridecyl acetate, the pheromones of *Crematogaster* ants and *Drosophila mulleri* flies [78], as well as to the preparation of the key synthon of the oviposition-deterring pheromone of the European cherry fruit fly *Rhagoletis cerasi* L., ethyl (8*RS*, 15*R*)-8-acetoxy-15-hydroxyhexadecanoate [79]. In addition, kinetic resolution of secondary alcohols with *Mucor miehei* lipase was employed in the synthesis of 8-methyldecan-2-ols, precursors of the sex pheromone of the *Diabrotica* spe-

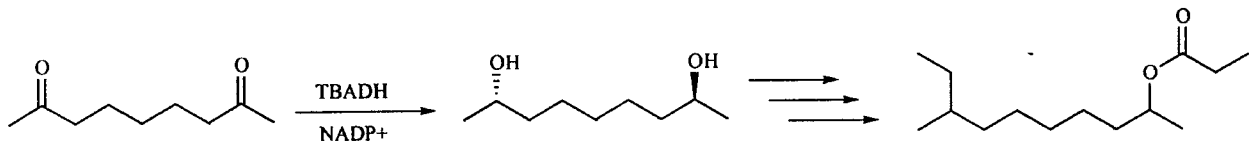



Fig. (4). Chemoenzymatic synthesis of the four isomers of 8-methyldec-2-yl propanoate.

cies, with high enantioselectivity [80,81]. The four isomers of 8-methyldec-2-yl propanoate, the sex pheromone emitted by the female western corn rootworm *Diabrotica virgifera*, were obtained by means of a *Thermoanaerobium brockii* alcohol dehydrogenase-catalyzed reduction (Fig. 4) [82].

Pine sawflies of the *Diprionidae* family are severe pests of conifers, particularly pine trees. Until recently, it was thought that all pine sawfly species used the acetates and/or propionates of the two stereoisomers of diprionol – either (2*S*, 3*S*, 7*S*)- or (2*S*, 3*R*, 7*R*)-3,7-dimethylpentadecan-2-ol – as their sex pheromone [83]. However, in the past few years, researchers have found several pine sawfly species that use sex pheromones with structural types different from that of the diprionyl esters, including various stereoisomers of 3,7,11-trimethyltridecan-2-ol, 3,7-dimethyltridecan-2-ol, or 3,7-dimethylundecan-2-ol derivatives [84]. Indeed, several syntheses of both the actual sex pheromones of pine sawfly species [84-86] and their precursors [87-90] through lipase-catalyzed stereoselective acylation have been described.

Another related compound, (2*R*, 6*S*, 10*S*)-6,10,14-trimethylpentadecan-2-ol, one of the sex pheromones of *Corcyra cephalonica* Stainton, was synthesized by means of stereoselective hydrolysis with *Pseudomonas fluorescens* lipase [91].

Other pheromone acetoxy derivatives that are structurally related to those mentioned above have also been synthesized with biological methods [92,93,94]. For example, both enantiomers of quadrilure, (*E*)-3-methyl-7-acetoxynon-3-ene (**16**), the pheromone of the squarenecked grain beetle, have been prepared in high enantiomeric excess via a stereoselective, lipase-catalyzed route. In this protocol, easily accessible 3-methylpent-1-en-3-ol underwent a Claisen orthoester rearrangement to afford the corresponding ester with exclusive (*E*)-geometry. The key step included a lipase-catalyzed esterification to yield (*R*)-**16** directly while its enantiomer was obtained from the resolved alcohol through chemical acetylation (Fig. 5) [95].

Optically active (*R*)-(+)-2-methylbutan-1-ol was prepared in a chemoenzymatic synthesis in which the key step involved a reduction catalyzed by bakers' yeast. This synthon was then used in the synthesis of (*R*)-10-methyldodecan-1-yl acetate, the chiral methyl-branched pheromone of *Adoxophyes* sp. [96].

Using enantioselective hydrolysis with *Pseudomonas cepacia* lipase, Kamezawa *et al.* carried out the biocatalytic synthesis of (*S*, *E*)-1-methyldodec-9-enyl acetate [97], the sex pheromone of the Hessian fly *Mayetiola destructor*, and (*S*)-2-tridecanyl acetate and (*S*)-2-pentadecanyl acetate, aggregation pheromone components of *Drosophila mulleri* and *Drosophila busckii* [98]. (*S*)-2-Tridecanyl acetate was also synthesized from β-ketoester through enzymatic reduction by bakers' yeast [99].

Gamalevich *et al.* studied the chemoenzymatic approach to the synthesis of all the stereoisomers of 1,6-dimethyloct-1-yl formate [100] and 2,6-dimethyloct-1-yl formate [101], pheromones of the smaller flour beetle. The key step involved enantioselective hydrolysis with porcine pancreatic lipase. Vogel *et al.* [102] reported two synthetic routes to optically pure lardolure precursors. Lardolure, (1*R*, 3*R*, 5*R*, 7*R*)-tetramethyldecyl formate, is the aggregation pheromone of the acarid mite *Lardoglyphus konoi*. The first procedure involved the Baeyer-Villiger oxidation of *cis*-2,4,6-trimethylcyclohexanone with cyclohexanone monooxygenase while the alternative procedure entailed a kinetic resolution by means of enzymatic hydrolysis with guinea pig liver esterase.

The aggregation pheromone of the lesser grain borer *Rhyzopertha dominica* has been identified as a mixture of (*S*)-(+)-2'-pentyl (*E*)-2-methylpent-2-enoate (dominicalur-I, **17**) and (*S*)-(+)-2'-pentyl (*E*)-2,4-dimethylpent-2-enoate (dominicalur-II, **18**). These compounds were obtained in a stereocontrolled synthesis by means of enzymatic reduction with soil yeast [103] and PPL-catalyzed kinetic resolution of secondary alcohols [104].

Another alcohol, in this case the cycloalcohol seudenol, which is the Douglas Fir Beetle pheromone 3-methylcyclohex-2-en-1-ol, was prepared by means of a *Candida antarctica* lipase B-catalyzed kinetic resolution in non-aqueous media of controlled water activity [105].

## 5. SYNTHESIS OF EPOXY PHEROMONES

(+)-Disparlure, *cis*-(7*R*, 8*S*)-7,8-epoxy-2-methyloctadecane (**19**), was identified as the sex pheromone for the gypsy moth *Lymantria dispar* L., which is a harmful forest pest [106]. Under field conditions, researchers found that only this particular enantiomer is bioactive while the opposite

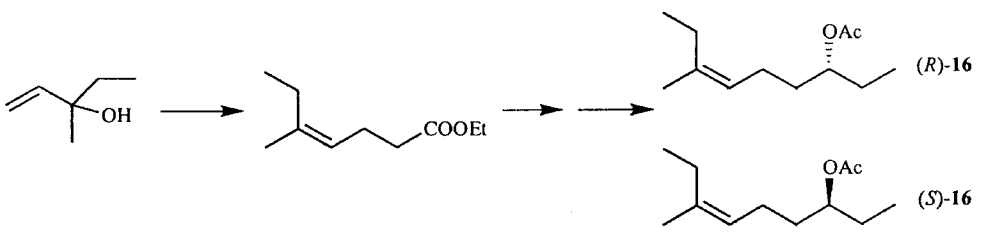
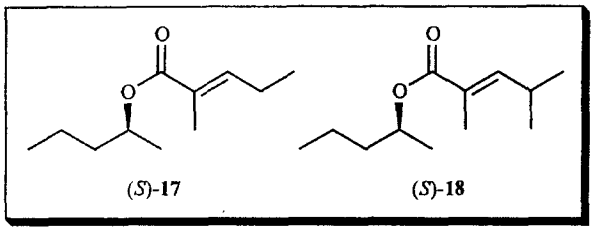



Fig. (5). Chemoenzymatic synthesis of the (*R*)- and (*S*)-quadrilure (**16**).




enantiomer actually inhibits the action of the pheromone [41]. An enzymatic approach to the optically active form of **19** by means of an enantioselective transesterification of its racemate with ethyl acetate as both the acyl donor and the reaction medium was reported [107]. In addition, Otto *et al.* [108] reported a bioorganic synthesis of (+)-disparlure (**19**) starting from *cis*-15-methylhexadec-9-enoic acid through epoxydation of **19** to a racemic mixture, enzymatic stereoselective hydrolysis and physical separation of the required compound (9*S*, 10*R*)-9,10-epoxy-15-methylhexadec-9-enoic acid, followed by Kolbe reaction with butyric acid. The chemical purity of **19** was 95%.

Another synthesis of (+)-disparlure (**19**) based on an enzymatic asymmetric process was reported by Brevet and Mori [109]: Treatment of *meso*-epoxydiacetate A with PPL yielded optically active monoacetate B (90% *ee*), which could then be purified to give crystalline C of approximately 100% *ee*. (+)-Disparlure (**19**) was synthesized from C, as shown in Fig. (**6**).

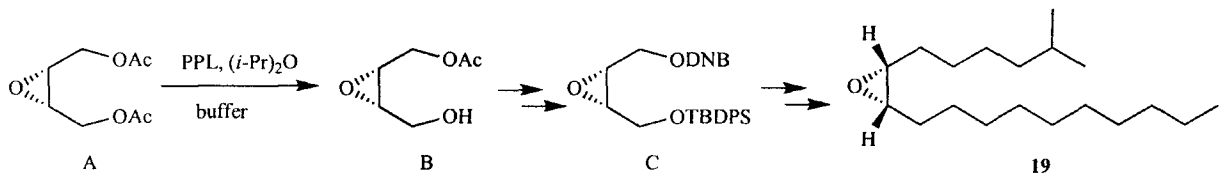
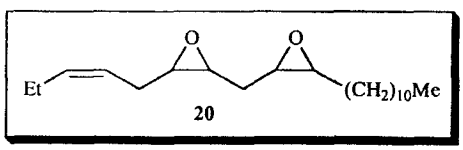



**Fig. (6).** Chemoenzymatic synthesis of (+)-disparlure (**19**).

Fukusaki *et al.* [110,111] carried out a large-scale preparation of (+)-disparlure (**19**) using a practical chemoenzymatic procedure based on the lipase-catalyzed kinetic resolution of 2,3-epoxy-8-methylnonan-1-ol and achieving excellent chemical and optical purity. Pancreatin F, a porcine pancreatic lipase, was found to catalyze the enantioselective acylation to yield the corresponding epoxy esters in a highly enantioselective fashion. Several anhydrides, including acetic, propionic, *n*-butyric, *n*-caproic, and *i*-butyric anhydride, were used as the acylating agent.

Using a lipase-catalyzed transesterification, Tsuboi *et al.* [112] developed a total synthesis of the enantiomer of **19**, (-)-disparlure, from ethyl (2*S*, 3*S*)-3-chloro-2-hydroxytridecanoate.

In addition, Muto *et al.* [113] studied the synthesis of all four stereoisomers of leucomalure, [(3*Z*)-*cis*-6,7-*cis*-9,10-diepoxy-3-henicosene] (**20**), the major component of the female sex pheromone of the satin moth *Leucoma salicis*. Lipase PS-C-catalyzed asymmetric acetylation of (±)-4-(*t*-butyldiphenylsilyloxy)-*cis*-2,3-epoxybutan-1-ol afforded the (2*R*, 3*S*)-epoxy alcohol and the (2*S*, 3*R*)-epoxyacetate, which were then converted into all the stereoisomers of leucomalure (**20**).




## 6. SYNTHESIS OF LACTONIC PHEROMONES AND RELATED COMPOUNDS

The Japanese beetle *Popillia japonica* Newman is a devastating pest of a variety of trees and crops in the United States. Japonilure (*R*)-**21**, its female-produced sex pheromone, was identified as (*R*, *Z*)-(-)-5-(dec-l-enyl)oxacyclopentan-2-one. While the bioactive enantiomer is (*R*)-(+)-**21**, (*S*)-(-)-**21** strongly inhibits the action of the pheromone [114]. The application of this pheromone thus requires extremely high optical purity.

In this context, several authors [115-118] have reported a synthesis of (*R*)-(+)-**21** involving a lipase-catalyzed enantioselective lactonization as the key reaction (Fig. 7).

Lactonic pheromones related to japonilure (*R*)-**21** were synthesized with several biocatalytic methods including lipase-catalyzed resolution [119-125], biotransformations of γ-hydroxyamides with an enzyme expressed in *E. coli* from a cloned amidase gene [126], and from diethyl 3-oxoglutarate with an enzymatic reduction as the key step [127,128].

The cupreous chafer beetle *Anomala cuprea* Hope is a devastating pest to a variety of crops in Japan. Leal has isolated its pheromone from female beetles captured in nature and identified it as (*R*, *Z*)-(-)-5-(oct-1-enyl)oxacyclopentan-2-one [129]. Its structure closely resembles that of the sex pheromone of the Japanese beetle, (*R*)-**21**, and its synthesis involved a lipase-catalyzed enantioselective reaction as the key step [130,131].

Hexan-4-olide (γ-caprolactone) (**22**) was isolated and identified as a component of the sex pheromone from the female dermestid beetle *Trogoderma glabrum* [132], a stored-product pest. Subsequently, Ravid *et al.* [133] reported the synthesis and bioassay of both enantiomers, thus determining the absolute configuration of the natural pheromone as *R*. Early syntheses of optically active hexan-4-olide (**22**) from chiral building blocks as well as by means of chemical or biochemical asymmetric reactions have all been reported. Mori *et al.* [134] achieved the synthesis of highly enantiomerically pure enantiomers of hexan-4-olide (**22**) in 51% overall yield from enantiopure methyl 3-hydroxypentanoate which had been prepared in four steps through microbial asymmetric reduction of octyl 3-oxopentanoate. The pheromone antipode has also been obtained from methyl 3-oxohept-6-enoate by means of a bakers' yeast-mediated reduction in 11% yield [135]. Lipase resolution of the corre-

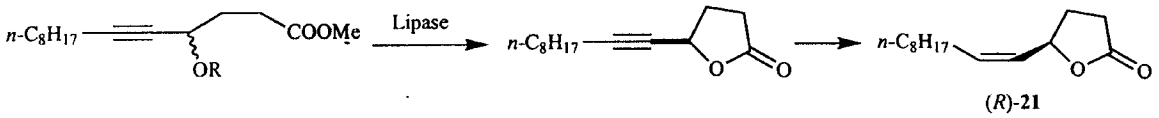



**Fig. (7).** Lipase-catalyzed enantioselective lactonization in the synthesis of japonilure (*R*)-**21**.

sponding hydroxysulfone afforded (*R*)-hexan-4-olide (*R*-**22**) in 15% yield [136].

Using lipase-catalyzed acetylation, Henkel *et al.* carried out the chemoenzymatic synthesis of (5*R*, 6*S*)-6-acetoxyhexadecan-5-olide (**23**), the major component of the mosquito oviposition attractant pheromone [137], and its homologues [138]. Moreover, Japanese beetle and mosquito oviposition attractant pheromones have also been synthesized from a common chiral precursor derived from bakers' yeast reduction [139]. Mori *et al.* reported the synthesis of the enantiomers of hexadecane-5-olide, the pheromone of the queen of the oriental hornet *Vespa orientalis*, with the enzymatic resolution of (±)-2-aminotridecanoic acid as the key step [140]. Other 6-membered lactone pheromones, including (3*S*, 5*R*, 6*S*)-3,5-dimethyl-6-isopropyl-3,4,5,6-tetrahidropyran-2-one, the sex pheromone of the larval parasitoid *Macrocentrus grandii* [141], and (2*R*, 4*R*)-5-(2,4-dimethyl)-3-methyl-2*H*-pyran-2-one (supellapyrone), the female sex pheromone of the brownbanded cockroach *Supella longipalpa* [142], were synthesized with a lipase-catalyzed resolution as the key reaction.

(+)-Eldanolide (**24**) is a sex pheromone of the male African sugarcane borer *Eldana saccharina*. In the past few years, this compound has been synthesized with biocatalytic methods and in excellent optical and chemical yields [143,144]. Thus, Sarmah *et al.* [145,146] carried out an efficient stereoselective synthesis of (+)-eldanolide (**24**) from nitroalkane synthons using a bakers' yeast reduction as the key step.

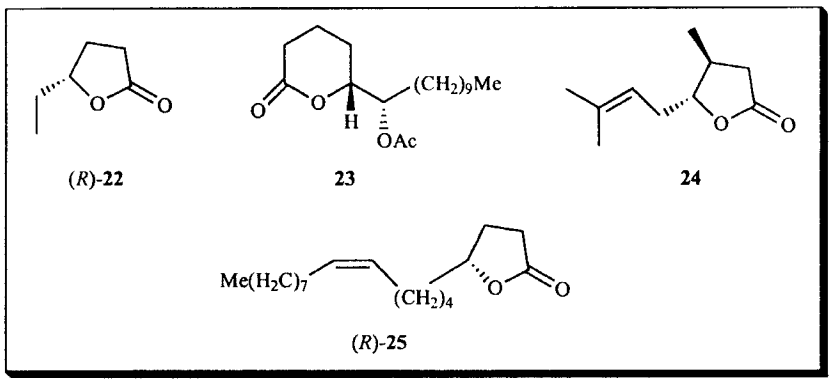
In 2001, Cossé *et al.* [147] isolated and identified (*Z*)-octadec-9-en-4-olide (**25**) as a female-specific, antennally active compound from the currant stem girdler *Janus integer* Norton (Hymenoptera: Cephidae), which is an occasional pest of red currants in North America. These same researchers then synthesized (±)-**25**, demonstrated its sex pheromone properties in field experiments, and showed that natural **25** contains only a single enantiomer, (4*R*, 9*Z*)-**25**. Later, Shibata *et al.* [148] reported the synthesis of (*R*)- and (*S*)-**25** and showed that the (*S*)-enantiomer inhibited the pheromone activity. The key optical step of this synthesis was an asymmetric lipase-catalyzed acetylation.

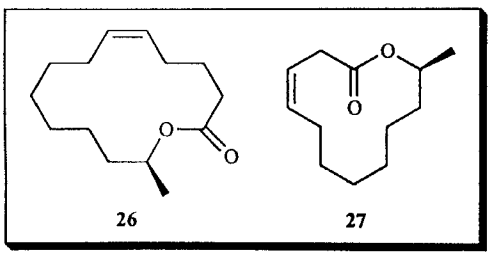
Syntheses of several macrolide pheromones were carried out by means of enzymatic macrolactonization [149,150]. Asymmetric bioreduction with either immobilized bakers' yeast [151] or *Thermoanaerobium brockii* alcohol dehydrogenase [152,153] as catalysts was carried out to synthesize (*S*)-(+)-*Z*-tetradec-5-en-13-olide (**26**) and ferrulactone II, (*S*)-(+)-*Z*-dodec-3-en-11-olide (**27**), synergistic aggregation pheromones of flat grain beetles of the genus *Cryptolestes*.

The lactol pheromone of the spined citrus bug *Biprorulus bibax*, (3*S*, 4*R*, 1'*E*)-3,4-bis(1'-butenyl)tetrahydrofuran-2-ol, was synthesized from buta-1,3-diene and maleic anhydride with the key step being an HLADH-catalyzed enzymatic oxidation [154].

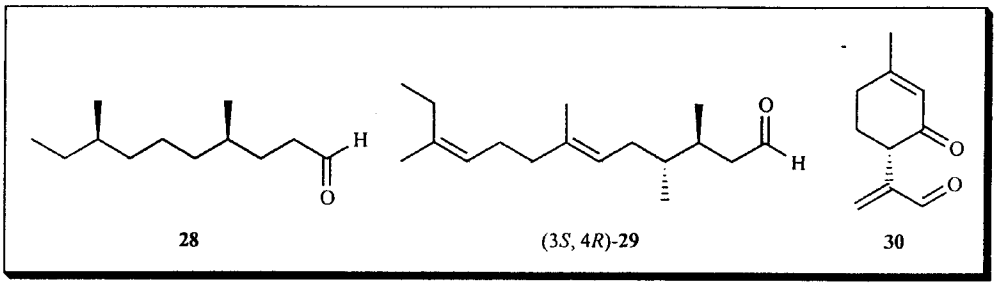
## 7. SYNTHESIS OF ALDEHYDIC PHEROMONES

Tribolure, (4*R*, 8*R*)-dimethyldecanal (**28**), constitutes the aggregation pheromone of the red flour beetle, *Tribolium*




*castaneum*, and is used to effectively control this economically important pest [155]. Interestingly, the racemic pheromone shows very low activity compared to the natural pheromone; hence, its enantiomeric synthesis is extremely important [156,157]. With this in mind, Sankaranarayanan *et al.* [158] reported a convenient synthesis of the 1,5-dimethylic chiron enantiomers, 3,7,11-trimethyldodec-10-en-1-ol, starting from (±)-citronellol and employing a sequential acetylation protocol with two lipases to obtain the pure enantiomer (4*R*, 8*R*)-dimethyldecanal (**28**).




**28** (3*S*, 4*R*)-**29** **30**

Furthermore, Chênevert *et al.* [159] studied the enzymatic desymmetrization of *meso*-2,6-dimethylheptane-1,7-diol with PS lipase in organic medium to obtain the chiral monoester used in the formal synthesis of tribolure (**28**).

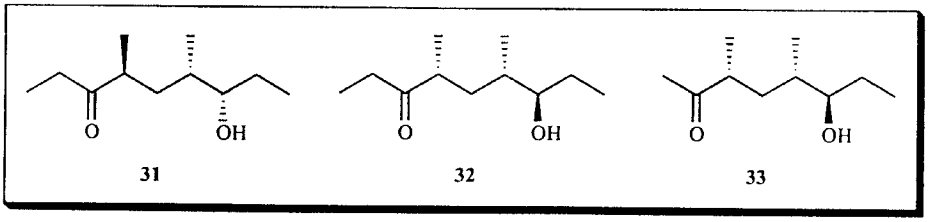
(3*S*, 4*R*)-Faranal (**29**) is the bioactive enantiomer of the trail pheromone of the pharaoh's ant *Monomorium pharaonis* [41]. Kobayashi *et al.* [160,161,162] synthesized all four stereoisomers of faranal (**29**) using the farnesyl pyrophosphate synthetase from pig liver to obtain stereospecifically the *S* or *R* enantiomer of 4-methylfarnesyl pyrophosphate with (*E*)- or (*Z*)-3-methylpent-3-enyl pyrophosphate as substrate. The absolute configuration of the pheromone was determined to be (3*S*, 4*R*, 6*E*, 10*Z*)-faranal (**29**).

Moreover, Poppe *et al.* [163] synthesized (+)-faranal (**29**) and its congener, (+)-13-norfaranal, from a chiral building block. They employed diastereoselective carbon-carbon bond formation, applying a crude pig liver esterase enzyme.

Vesperal, (*S*)-10-oxoisopiperitenone (**30**), is the female sex pheromone of the longhorn beetle *Vesperus xatarti*, a major pest of vineyards in Catalonia, Spain. Fuganti *et al.* [164] carried out the lipase-mediated preparation of enantiomerically pure *p*-menthan-3,9-diols for the synthesis of both enantiomers of **30**, with 97% chemical purity.

## 8. SYNTHESIS OF KETONIC PHEROMONES

Serricornin, the sex pheromone of the females of the cigarette beetle *Lasioderma serricorne*, a pest for stored plant products including tobacco goods, has been identified as (4*S*, 6*S*, 7*S*)-7-hydroxy-4,6-dimethylnonan-3-one (**31**). In the course of developing practical pheromone traps, Mori *et al.* [165] studied the bioactivity of the stereoisomers of **31** and found that only (4*S*, 6*S*, 7*S*)-**31** was bioactive while its (4*S*, 6*S*, 7*R*)-isomer was inhibitory against the action of (4*S*, 6*S*, 7*S*)-**31**. Accordingly, the commercial pheromone must be manufactured without contamination from the (4*S*, 6*S*, 7*R*)-isomer.



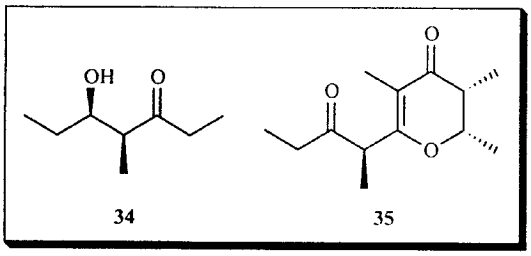

**31** **32** **33**

Biological methods have also been used to synthesize the pure enantiomer (4*S*, 6*S*, 7*S*)-**31** with either a bakers' yeast reduction [166, 167] or a lipase-catalyzed asymmetric resolution [168,169] as the key step. Recently, Masuda *et al.* [170] carried out the synthesis of (4*R*, 6*S*, 7*R*)-7-hydroxy-4,6-dimethylnonan-3-one (**32**) and (3*R*, 5*S*, 6*R*)-6-hydroxy-3,5-dimethyloctan-2-one (**33**), stereoisomers of serricornin (**31**) and nor-serricornin, respectively, using a lipase AK-catalyzed asymmetric acetylation of meso-2,4-dimethylpentane-1,5-diol. Compounds **32** and **33** were found to be the pheromone components of the bostrychid beetle *Dinoderus bifoveolatus*.

Using a lipase-mediated hydrolysis as the key step, Nakazono *et al.* [171] reported the synthesis of (-)-periplanone-B, a sex pheromone component of the American cockroach *Periplaneta Americana*.

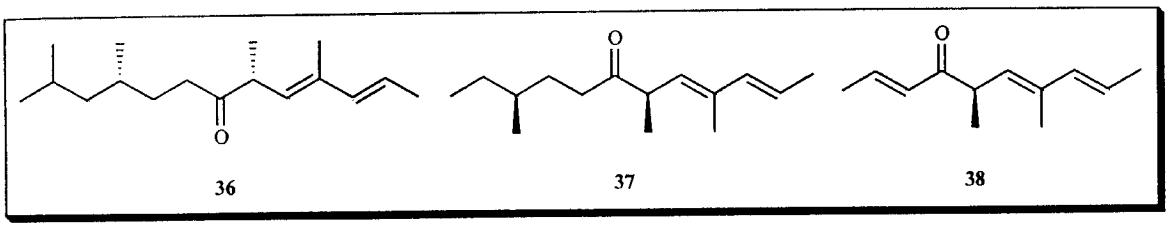
The asymmetric synthesis of (+)-sitophilure (**34**), the aggregation pheromone of *Sitophilus oryzae* L. and *Sitophilus zeamais* M., was carried out by means of the enzymatic reduction of methyl 3-oxopentanoate with bakers' yeast [172].

Stegobinone, (2*S*, 3*R*, 1'*R*)-**35**, is one of the two components of the female-produced sex pheromone of the drugstore beetle *Stegobium paniceum* L., a serious pest of a wide variety of commodities and stored products. Mori *et al.* [173] synthesized this compound using a lipase-catalyzed kinetic resolution as the key step.




**34** **35**

Pine scales of the genus *Matsucoccus* devastate forestlands worldwide. Lanier *et al.* [174] isolated and identified a cross-attractive female sex pheromone component, (2*E*, 4*E*, 6*R*, 10*R*)-4,6,10,12-tetramethyltrideca-2,4-dien-7-one (matsuone, **36**), from *M. resinosae* (USA), *M. matsumurae* (China), and *M. thunbergianae* (South Korea). Lin *et al.* [175] subsequently synthesized matsuone (**36**) using a lipase-catalyzed transesterification of *meso*-2,4-dimethylpropane-1,5-diol as the key reaction. Later, another sex pheromone of



36 37 38

this family was isolated from the maritime pine scale *M. feytaudi* (Africa and Europe) by Einhorn *et al.* [176] and characterized as a mixture of (3*S*, 7*R*, 8*E*, 10*E*)-3,7,9-trimethyldodeca-8,10-dien-6-one (**37**) (major) and its (8*Z*, 10*E*)-isomer (minor). Two closely related compounds, (2*E*, 5*R*, 6*E*, 8*E*)-5,7-dimethyldeca-2,6,8-trien-4-one (**38**) (major) and its (2*E*, 6*Z*, 8*E*)-isomer (minor) have also been reported as sex pheromone components of *M. josephi* (Israel). Synthesis of compounds **37** and **38** was reported by Mori *et al.* [177,178], who employed an enzyme-catalyzed asymmetric hydrolysis as the key step.

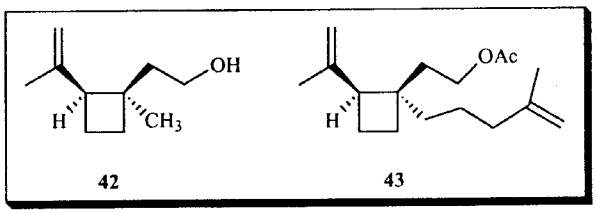
## 9. SYNTHESIS OF ACIDIC PHEROMONES AND RELATED COMPOUNDS

(*S*)-(+)-9-Hydroxydec-2*E*-enoic acid (**39**), a component of the queen pheromone of the honeybee *Apis mellifera*, has been synthesized in two different ways, first by means of the enzymatic reduction of 9-oxodec-2*E*-enoic acid with the aid of bakers' yeast [179], and also through PPL-catalyzed transesterification in an organic medium of straight-chain and branched alkan-2-ols [180].

In addition, Vasilev *et al.* [181] reported the chemoenzymatic synthesis of several acidic insect pheromones. For example, (*Z*)-dec-3-enoic acid (**40**), the aggregation pheromone of the furniture carpet beetle *Anthrenus flavipes* (Dermestidae), otherwise known as the 'museum beetle', was obtained with 99% *ee*; the key step in the synthesis was the PPL-catalyzed hydrolysis of the corresponding ester.

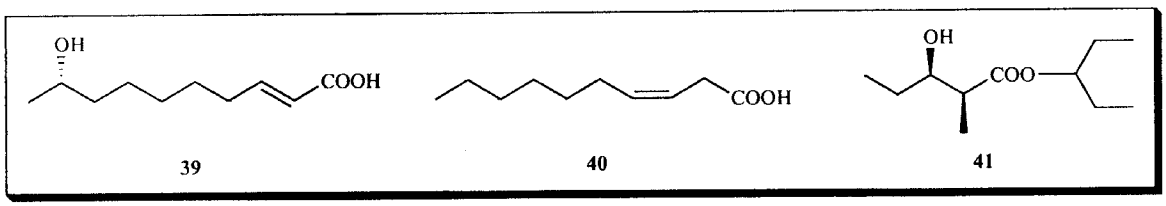
Sankaranarayanan *et al.* [185] reported the preparation of a versatile chiron, (*R*)- and (*S*)-12-(tetrahydropyranyloxy)-3-methyldodecanol, and studied its application through lipase-catalyzed acetylation to the syntheses of the methyl branched insect pheromones (*R*)-10-methyldodecyl acetate (lesser tea tortrix moth), (*R*)-10-methyltridecanone (southern corn rootworm), and (*S*)-14-methyloctadecene (peach leafminer moth).

Formal synthesis of chiral grandisol (**42**), the cotton boll-weevil pheromone, and the oleander scale pheromone **43** have been achieved through a convenient lipase-catalyzed enantiodifferentiation process of the common cyclobutane intermediate (±)-2-(1-hydroxyethyl)-1-(methoxymethyloxy ethyl)cyclobutane-1-carbonitrile. The resolution afforded both enantiomers in almost enantiomerically pure form [186].



42 43

In this context, the use of enzymatic or microbiologically mediated transformations is a promising new strategy for the synthesis of several algae pheromones [187,188]. In many species of marine brown algae, for example, female gametes secrete a complex bouquet of olefinic C11 hydrocarbons as chemical signals to stimulate and attract male gametes and thereby initiate the sexual fusion [189]. Thus, (+)-(*Z*)-(3*S*, 4*S*)-multifidene (**44**) has been identified as the major and most active pheromone of the algae *Cutleria multifida* and *Chorda tomentosa*, (+)-(3*R*, 4*S*)-viridiene (**45**) is the major component in the algae *Desmarestia aculeata* and *D. viridis*, and (+)-(2*R*, 3*R*, 1'*S*, 5'*S*)-caudoxirene (**46**) is the major pheromone found in *Perithalia caudate*. These pheromones have all been synthesized through a novel microbiological Baeyer-Villiger oxidation carried out with the aid of the fungus *Cunninghamella echinulata* [190,191].



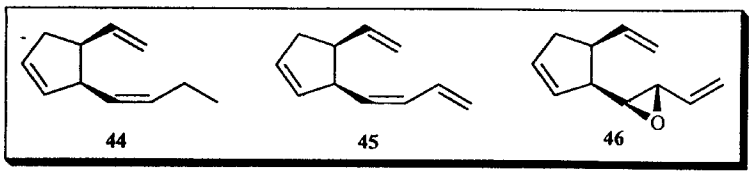
39 40 41

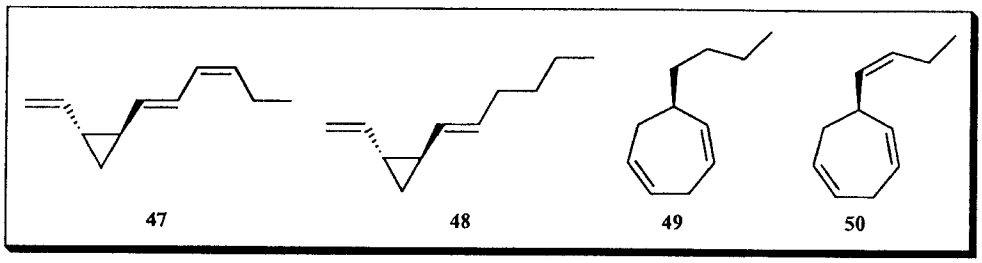
The granary weevil *Sitophilus granarius* is a pest which causes commercially important damage to stored cereal grains. Its male-produced aggregation pheromone sitophilate (**41**) was isolated and identified as l'-ethylpropyl (2*S*)-methyl-(3*R*)-hydroxypentanoate [182]. Sugai *et al.* [183] synthesized **41** through the reduction of the corresponding enol ester by growing cells of the yeast *Pichia farinosa* IAM 4682.

## 10. SYNTHESIS OF OTHER PHEROMONES

A convenient bakers' yeast mediated synthesis of (5*RS*, 9*S*)-5,9-dimethylheptadecane and (5*RS*, 9*S*)-5,9-dimethylpentadecane, the main sex-components of *Leucoptera scitella* and *Perileucoptera coffeella*, was carried out by Poppe *et al.* [184].

The dictyopterenes are a class of C11 hydrocarbons isolated from the essential oil of algae of the genus *Dictyopteris* and other brown algae. Dictyopterene B, [(−)-hormosirene]




(1*R*, 2*R*)-1-((1*E*, 3*Z*)-hexa-1,3-dienyl)-2-vinylcyclopropane (**47**), is the specific sex attractant of several brown algae found along the Australian shelf such as *Scytosiphon lomentaria* and *Colpomenia bullosa*, while dictyopterene A, (1*R*, 2*R*)-1-((1*E*)-hexenyl)-2-vinylcyclopropane (**48**), dictyopterene C' [(-)-(*R*)-6-butylcyclohepta-1,4-diene] (**49**), and dictyopterene D'[(+)-(*S*)-6-(*cis*-but-1'-enyl)cyclohepta-1,4-diene] (**50**) were found in sexually mature thalli of *Scytosiphon lomentaria*. It has also been shown that **50** is the sex attractant produced by the female gametes of the brown alga *Ectocarfius siliculosus*. Cyclopropanes and cycloheptadienes derived from brown algae are secreted as mixtures of enantiomers, often with well defined compositions that depend on species and habitat.

Chemoenzymatic syntheses of these compounds have been carried out through optical resolution of racemic synthons [192,193,194]. For example, enantiomerically pure dictyopterenes A (**48**) and C' (**49**) were synthesized through enzymatic hydrolysis of *cis*-1,2-bis(butyryloxymethyl) cyclopropane to give optically pure *cis*-(1*S*, 2*R*)-1-hydroxymethyl-2-butyryloxymethylcyclopropane, a versatile cyclopropane synthon [195].

## 11. CONCLUSION

Progress in the field of organic chemistry in the past few years is most evident in the fact that we can now synthesize pure enantiomers, often with even higher enantiomeric purity than that of the naturally occurring material. This has been made possible by the development of various methods in both asymmetric synthesis and stereochemical analysis. Biocatalysis has thus proven to be a valuable tool in the production of fine chemicals, particularly of enantiomerically pure compounds.

Modern insect chemistry owes a great deal to this development in fundamental chemistry. We can now determine the absolute configuration of a pheromone or a hormone and investigate the stereochemistry-bioactivity relationship on the basis of a compound's enantioselective synthesis.

As the biodiversity in pheromone perception is evident, chemists and biologists should work toward clarifying these diverse structure-activity relationships. The next task is thus for biochemists and molecular biologists to discover the biochemical mechanisms that make this diversity possible.

## REFERENCES

[1] Loughlin, W.A. *Bioresour. Technol.*, **2000**, *74*, 49. b) Koeller, K.M.; Wong, Ch-H. *Nature*, **2001**, *409*, 232.
[2] Kurihara, N.; Miyamoto, J. *Chirality in Agrochemicals*, John Wiley & sons: Chichester, U.K., **1998**.
[3] Shea, P.J. *ACS Symp. Ser.*, (2nd Ed.), 595, **1995**.
[4] a) Fukusaki, E.; Satoda, S. *J. Mol. Cat. B: Enz.*, **1997**, *2*, 257. b) Mori, K. *Synlett*, **1995**, *11*, 1097. c) Roberts, S.M.; Williamson, N.M. *Curr. Org. Chem.*, **1997**, *1*, 1.
[5] Roberts, S.M. *Pure Appl. Chem.*, **1992**, *64*, 1153.
[6] Davis, H.G.; Green, R.H. *Nat. Prod. Rep.*, **1986**, *3*, 87.
[7] a) Perkins, M.V.; Kitching, W.; Konig, W.A.; Drew, R.A.I. *J. Chem. Soc. Perkin Trans. 1*, **1990**, 2501. b) Perkins, M.V.; Kitching, W.; Drew, R.A.I.; Moore, C.J.; Konig, W.A. *J. Chem. Soc. Perkin Trans. 1*, **1990**, 1111. c) Chen, J.; Fletcher, M.; Kitching, W. *Tetrahedron Asymmetry*, **1995**, *6*, 967.
[8] Bergstrom, G.; Tengo, J.; Reith, W.; Francke, W. *Z. Naturforsch.* **1982**, *37c*, 1124. b) Redlich, H.; Schneider, B. *Liebigs Ann. Chem.*, **1983**, 412.
[9] Nakamura, K.; Kitayama, T.; Inoue, Y.; Ohno, A. *Tetrahedron*, **1990**, *46*, 7471. b) Mori, K.; Katsurada, M. *Liebigs Ann. Chem.*, **1984**, 157. c) Francke, W.; Reith, W.; Bergstrom, G.; Tengo, J. *Z. Naturforsch*, **1981**, *36c*, 928.
[10] Kitayama, T. *Tetrahedron*, **1996**, *52*, 6139.
[11] Liu, H.; Cohen, T. *J. Org. Chem.*, **1995**, *60*, 2022.
[12] Cohen, T.; Tong, S. *Tetrahedron*, **1997**, *53*, 9487.
[13] a) Izquierdo, I.; Plaza, M.T.; Rodriguez, M.; Tamayo, J.A.; Martos, A. *Tetrahedron Asymmetry*, **2001**, *12*, 293. b) Izquierdo, I.; Plaza, M.T.; Rodriguez, M.; Tamayo, J.A. *Tetrahedron Asymmetry*, **2000**, *11*, 1749.
[14] Yokohama, Y.; Takikawa, H.; Mori, K. *Bioorg. Med. Chem.*, **1996**, *4*, 409.
[15] Haniotakis, G.; Francke, W.; Mori, K.; Redlich, H.; Schurig, V. *J. Chem. Ecol.*, **1986**, *12*, 1559.
[16] Hu, S.; Jayaraman, S.; Oehlschlager, A.C. *J. Org. Chem.*, **1999**, *64*, 2524.
[17] Oehlschlager, A.C.; Johnston, B.D. *J. Org. Chem.*, **1987**, *52*, 940.
[18] Francke, W.; Schröder, W. *Curr. Org. Chem.*, **1999**, *3*, 407, and refs. cited therein.
[19] Wood, D.L.; Browne, L.E.; Ewing, B.; Lindahl, K.; Bedard, W.D.; Tilden, P.E.; Mori, K.; Pitman, G.B.; Hughes, P.R. *Science*, **1976**, *192*, 896.
[20] Mayer, S.F.; Mang, H.; Steinreiber, A.; Saf, R.; Faber, K. *Can. J. Chem.*, **2002**, *80*, 362.
[21] a) Myles, D.C.; Andrulis, P.J.; Whitesides, G.M. *Tetrahedron Lett.*, **1991**, *32*, 4835. b) Sprenger, G.A.; Pohl, M. *J. Mol. Cat. B: Enz.*, **1999**, *6*, 145.
[22] Bel-Rhlid, R.; Renard, M.F.; Veschambre, H. *Bulletin de la Societé Chimique de France*, **1996**, *133*, 1011.
[23] Ishiyama, J.; Toi, M.; Ichikawa, Ch.; Ot, S.; Inoue, Y. *Nippon Kagaku Kaishi*, **1993**, *10*, 1162.
[24] Mori, K.; Kiyota, H. *Liebigs Ann.*, **1992**, *9*, 989.

[25] Mori, K.; Takikawa, H.; Nishimura, Y.; Horikiri, H. *Liebigs Ann.*, **1997**, *2*, 327.
[26] Francke, W.; Schröder, F.; Philipp, P.; Meyer, H.; Sinnwell, V.; Gries, G. *Bioorg. Med. Chem.*, **1996**, *4*, 363.
[27] Pearce, G.T.; Gore, W.E.; Silverstein, R.M.; Peacock, J.W.; Cuthbert, P.A.; Lanier, G.N.; Simeone, J.B. *J. Chem. Ecol.*, **1975**, *1*, 115.
[28] a) Sinha, S.C.; Keinan, E. *J. Am. Chem. Soc.*, **1995**, *117*, 3653. b) Sinha, S.C.; Keinan, E. *Isr. J. Chem.*, **1996**, *36*, 185. c) Keinan, E.; Sinha, S.C.; Shabat, D.; Itzhaky, H.; Reymond, J.L. *Acta Chem. Scand.*, **1996**, *50*, 679.
[29] Kinzer, G.W.; Fentiman, A.F.; Page, T.F.; Foltz, R.L.; Vité, J.P.; Pitman, G.B. *Nature*, **1969**, *221*, 447.
[30] Payne, T.L.; Richerson, J.V.; Dickens, J.C.; West, J.R.; Mori, K.; Brisford, C.W.; Hedden, R.L.; Vité, J.P.; Blum, M.S. *J. Chem. Ecol.*, **1982**, *8*, 873.
[31] List, B.; Shabat, D.; Guofu, Z.; Turner, J.M.; Li, A.; Bui, T.; Anderson, J.; Lerner, R.A.; Barbas III, C.F. *J. Am. Chem. Soc.*, **1999**, *121*, 7283.
[32] Kroutil, W.; Osprian, I.; Mischitz, M.; Faber, K. *Synthesis*, **1997**, *2*, 156.
[33] Nishimura, Y.; Mori, K. *Eur. J. Org. Chem.*, **1998**, 233.
[34] Ohta, H.; Kimura, Y.; Sugano, Y.; Sugai, T. *Tetrahedron*, **1989**, *45*, 5469.
[35] Chênevert, R.; Caron, D. *Tetrahedron Asymmetry*, **2002**, *13*, 339.
[36] Sugai, T.; Ohta, H.; Kakeya, H. *J. Org. Chem.*, **1990**, *55*, 4643.
[37] Fang, J-M.; Chen, S-T. *J. Org. Chem.*, **1997**, *62*, 4349.
[38] Ferraboschi, P.; Casati, S.; Grisenti, P.; Santaniello, E. *Tetrahedron Asymmetry*, **1993**, *4*, 9.
[39] Seu, Y.B.; Kho, Y.H. *Nat. Prod. Lett.*, **1994**, *4*, 61.
[40] Dauphin, G.; Fauve, A.; Veschambre, H. *J. Org. Chem.*, **1989**, *54*, 2238.
[41] Mori, K. *Chem. Commun.*, **1997**, 1153.
[42] Belan, A.; Bolte, J.; Fauve, A.; Gourcy, J.G.; Veschambre, H. *J. Org. Chem.*, **1987**, *52*, 256.
[43] Tidswell, E.C.; Salter, G.J.; Kell, D.B.; Morris, J.G. *Enzyme Microb. Technol.*, **1997**, *21*, 143.
[44] Wu, M-H.; Li, Y.; Chen, Z-X.; Yang, G-Ch.; Shi, C-Y. *Yingyong Huaxue*, **2000**, *17*, 224.
[45] Sugai, T.; Ohta, H. *Agric. Biol. Chem.*, **1990**, *54*, 1577.
[46] Sugai, T.; Katoh, O.; Ohta, H. *Tetrahedron*, **1995**, *51*, 11987.
[47] Patil, P.N.; Chattopadhyay, A.; Udupa, S. R.; Banerji, A. *Biotech. Lett.*, **1993**, *15*, 367.
[48] Schwab, E.; Bernreuther, A.; Puapoomchareon, P.; Mori, K.; Schreier, P. *Tetrahedron Asymmetry*, **1991**, *2*, 471.
[49] Da Silva, F.M.; Bastos, F.M.; Oestreicher, E.G.; Pinto, G.F.; Jones Jr, J.; Paiva, L.M.C. *Biotech. Tech.*, **1997**, *11*, 739.
[50] Stampfer, W.; Kosjek, B.; Moitzi, Ch.; Kroutil, W.; Faber, K. *Angew. Chem. Int. Ed.*, **2002**, *41*, 1014.
[51] Mori, K. *Tetrahedron*, **1981**, *37*, 1341.
[52] Sarma, B.; Barua, N.C. *Indian J. Chem.*, **1993**, *32B*, 615.
[53] Li, Y.; Chen, Z-X.; Shi, Ch-Y. *Youji Huaxue*, **2000**, *20*, 388.
[54] Stokes, T.M.; Oehlschlager, A.C. *Tetrahedron Lett.*, **1987**, *28*, 2091.
[55] Fukunaga, K.; Minamijima, N.; Sugimura, Y.; Zhang, Z.; Nakao, K. *J. Biotech.*, **1996**, *52*, 81.
[56] Naoshima, Y.; Kamezawa, M.; Tachibana, H.; Munakata, Y.; Fujita, T.; Kihara, K.; Raku, T. *J. Chem. Soc. Perkin Trans.*, **1993**, *1*, 557.
[57] Liang, S.; Paquette, L.A. *Tetrahedron Asymmetry*, **1990**, *1*, 445.
[58] a) Kita, Y.; Takebe, Y.; Murata, K.; Naka, T.; Akai, S. *J. Org. Chem.*, **2000**, *65*, 83. b) Kita, Y.; Takebe, Y.; Murata, K.; Naka, T.; Akai, S. *Tetrahedron Lett.*, **1996**, *37*, 7369.
[59] Steinreiber, A.; Stadler, A.; Mayer, S.F.; Faber, K.; Kappe, O. *Tetrahedron Lett.*, **2001**, *42*, 6283.
[60] a) Kruse, W.; Kragl, U.; Wandrey, C. Forschungszentrum Jülich GmbH, Germany, DE 4436149 A1, CAN 124:315156, **1996**. b) Liese, A.; Seelbach, K.; Wandrey, C. *Industrial Biotransformations*, Wiley-VCH, Weinheim, Germany, **2000**.
[61] Steinreiber, A.; Edegger, K.; Mayer, S.F.; Faber, K. *Tetrahedron Asymmetry*, **2001**, *12*, 2067.
[62] Archelas, A; Furstoss, R. *Tetrahedron Lett.*, **1992**, *33*, 5241.
[63] Vasilev, A.A.; Vielhauer, O.; Engman, L.; Pietzsch, M.; Serebryakov, E.P. *Russian Chem. Bull., Int. Ed.*, **2002**, *51*, 481.
[64] Zada, A.; Harel, M. *Tetrahedron Asymmetry*, **2004**, *15*, 2339.
[65] Mori, K.; Ishigami, K. *Liebigs Ann. Chem.*, **1992**, 1195.
[66] Nagaki, M.; Takaya, A.; Maki, Y.; Ishibashi, J.; Kato, Y.; Nishino, T.; Koyama, T. *J. Mol. Cat. B: Enz.*, **2000**, *10*, 517.
[67] Nagaki, M. **2002**, Jpn. Pat. JP 2002191390 A2, CAN 137:62273.
[68] Zada, A.; Ben-Yehuda, S.; Dunkelblum, E.; Harel, M.; Assael, F.; Mendel, Z. *J. Chem. Ecol.*, **2004**, *30*, 631.
[69] Mori, K.; Iwasawa, H. *Tetrahedron*, **1980**, *36*, 2209.
[70] Domínguez, E.; Carretero, J.C.; Fernández-Mayoralas, A.; Conde, S. *Tetrahedron Lett.*, **1991**, *32*, 5159.
[71] Kamezawa, M.; Raku, T.; Tachibana, H.; Ohtani, T.; Naoshima, Y. *Biosci. Biotechnol. Biochem.*, **1994**, *58*, 598.
[72] Kang, S-K.; Jeon, J-H.; Yamaguchi, T.; Kim, J-S.; Ko, B-S. *Tetrahedron Asymmetry*, **1995**, *6*, 2139.
[73] Itoh, T.; Mitsukura, K.; Kanphai, W.; Takagi, Y.; Kihara, H.; Tsukube, H. *J. Org. Chem.*, **1997**, *62*, 9165.
[74] Cammaerts, M-C.; Mori, K. *Physiol. Entomol.*, **1987**, *12*, 381.
[75] Mori, K.; Murata, N. *Liebigs Ann. Chem.*, **1995**, 697.
[76] Ichikawa, A. *Chirality*, **1999**, *11*, 338.
[77] Takahata, H.; Uchida, Y.; Momose, T. *J. Org. Chem.*, **1994**, *59*, 7201.
[78] Sharma, A.; Pawar, A.S.; Chattopadhyay, S. *Synth. Commun.*, **1996**, *26*, 19.
[79] Sharma, A.; Chattopadhyay, S. *Tetrahedron Asymmetry*, **1997**, *8*, 4021.
[80] Sonnet, Ph.E.; Baillargeon, M.W. *J. Chem. Ecol.*, **1987**, *13*, 1279.
[81] Sonnet, Ph.E. *ACS Symp. Series*, **1988**, *362*, 230.
[82] Keinan, E.; Sinha, S.C.; Sinha-Bagchi, A. *J. Org. Chem.*, **1992**, *57*, 3631.
[83] Wagner, M.R.; Raffa, K.F. In *Sawfly Life History Adaptations to Woody Plants*, Academic Press, San Diego, **1993**.
[84] Larsson, M.; Nguyen, B-V.; Högberg, H-E.; Hedenström, E. *Eur. J. Org. Chem.*, **2001**, 353.
[85] Lundh, M.; Smitt, O.; Hedenström, E. *Tetrahedron Asymmetry*, **1996**, *7*, 3277.
[86] Nakamura, Y.; Mori, K. *Eur. J. Org. Chem.*, **1999**, 2175.
[87] Hedenström, E.; Edlund, H.; Lund, S.; Abersten, M.; Persson, D. *J. Chem. Soc. Perkin Trans. 1*, **2002**, 1810.
[88] Larsson, M.; Andersson, J.; Liu, R.; Högberg, H-E. *Tetrahedron Asymmetry*, **2004**, *15*, 2907.
[89] Högberg, H-E.; Berglund, P.; Edlund, H.; Faegerhag, J.; Hedenström, E.; Lundh, M.; Nordin, O.; Servi, S.; Voerde, C. *Catal. Today*, **1994**, *22*, 591.
[90] Larcheveque, M.; Sanner, C.; Azerad, R.; Buission, D. *Tetrahedron*, **1988**, *44*, 6407.
[91] Naoshima, Y.; Munakata, Y.; Yoshida, S.; Funai, A. *J. Chem. Soc. Perkin Trans. 1*, **1991**, 549.
[92] Glänzer, B.I.; Königsberger, K.; Berger, B.; Faber, K.; Griengl, H. *Chem. Phys. Lipids*, **1990**, *54*, 43.
[93] Furukawa, A.; Shibata, Ch.; Mori, K. *Biosci. Biotechnol. Biochem.*, **2002**, *66*, 1164.
[94] Mori, K.; Ohtaki, T.; Ohrui, H.; Berkebile, D.R.; Carlson, D.A. *Biosci. Biotechnol. Biochem.*, **2004**, *68*, 1768.
[95] Pawar, A.S.; Chattopadhyay, S. *Tetrahedron Asymmetry*, **1995**, *6*, 463.
[96] Geresh, Sh.; Valiyaveettil, T.J.; Lavie, Y.; Shani, A. *Tetrahedron Asymmetry*, **1998**, *9*, 89.
[97] Kamezawa, M.; Tachibana, H.; Ohtani, T.; Naoshima, Y. *Biosci. Biotechnol. Biochem.*, **1993**, *57*, 1962.
[98] Kamezawa, M.; Tachibana, H.; Ohtani, T.; Naoshima, Y. *J. Chem. Ecol.*, **1994**, *20*, 1057.
[99] Chin, Sh-Z.; Li, Y.; Chen, Z-X. *Yingyong Huaxue*, **2002**, *19*, 85.
[100] Gamalevich, G.D.; Serebryakov, E.P. *Mendeleev Commun.*, **1994**, 40.
[101] Gamalevich, G.D.; Morozov, B.N.; Serebryakov, E.P. *Izv. Akad. Nauk. Khim.*, **1996**, 204.
[102] Vogel, M.; Kordel, A.; Schulze, A. Proceedings of ECSOC-3 and Proceedings of ECSOC-4, **2000**, 1443.
[103] Kharisov, R.Y.; Petuchova, N.I.; Phaifer, L.V.; Davletova, A.R.; Zorin, V.V.; Ishmuratov, G.Y.; Tolstikov, G.A. *Bashkirskii Khimicheskii Zhurnal*, **2000**, *7*, 46.
[104] Morgan, B.; Oehlschlager, A.C.; Stokes, T.M. *J. Org. Chem.*, **1992**, *57*, 3231.

[105] Orrenius, C.; Noria, T.; Hule, K.; Carrea, G. *Tetrahedron Asymmetry*, **1995**, *6*, 3023.
[106] Iwaki, S.; Maruo, S.; Saito, T.; Yamada, M.; Katagiri, K. *J. Am. Chem. Soc.*, **1974**, *96*, 7842.
[107] Bianchi, D.; Cabri, W.; Cesti, P.; Flancalanci, F.; Rama. F. *Tetrahedron Lett.*, **1988**, *29*, 2455.
[108] Otto, P.P.J.H.L.; Stein, F.; Van der Willigen, C.A. *Agr. Ecosyst. Environ.*, **1988**, *21*, 121.
[109] Brevet, J.L.; Mori, K. *Synthesis*, **1992**, 1007.
[110] a) Fukusaki, E.; Senda, S.; Nakazono, Y.; Yuasa, H.; Omata, T. *J. Ferment. Bioeng.*, **1992**, *73*, 280. b) Fukusaki, E.; Senda, S.; Nakazono, Y.; Yuasa, H.; Omata, T. *J. Ferment. Bioeng.*, **1992**, *73*, 284.
[111] Yuasa, H. **1994**, Jpn. Pat. JP 06022778 A2, CAN 121:7458.
[112] Tsuboi, S.; Yamafuji, N.; Utaka, M. *Tetrahedron Asymmetry*, **1997**, *8*, 375.
[113] Muto, S.; Mori, K. *Eur. J. Org. Chem.*, **2003**, 1300.
[114] Tumlinson, J.H.; Kleinn, M.G.; Doolittle, R.; Ladd, T.T.; Proveaux, A.T. *Science*, **1977**, *197*, 789.
[115] Sugai, T.; Ohsawa, S.; Yamada, H.; Ohta, T. *Synthesis*, **1990**, 1112.
[116] Fukusaki, E.; Senda, S.; Nakazono, Y.; Omata, T. *Tetrahedron*, **1991**, *47*, 6223.
[117] Yamada, Y.; Fukusaki, E. *Kagaku to Seibutsu*, **1993**, *31*, 531.
[118] Taylor, S.K.; Atkinson, R.F.; Almli, E.P.; Carr, M.D.; Van Huis, T.J.; Whittaker, M.R. *Tetrahedron Asymmetry*, **1995**, *6*, 157.
[119] Matsumura, Y.; Fukawa, H.; Chiba, M.; Endo, T. **2000**, Jpn. Pat. JP 2000139493 A2, CAN 132:333456.
[120] Satoda, S.; Senda, S.; Komata, T.; Fukusaki, E. **1997**, Jpn. Pat. JP 09028393 A2, CAN 126:224352.
[121] Fukusaki, E.; Senda, S.; Yuasa, H.; Tanaka, H.; Komata, T. **1994**, Jpn. Pat. JP 06217792 A2, CAN 121:279069.
[122] Fukusaki, E.; Senda, S.; Nakazono, Y.; Omata, T.; Hibino, K.; Ota, H.; Sugai, T. **1991**, Eur. Pat. Appl. EP 435293 A2, CAN 115:278160.
[123] Tsuboi, S.; Sakamoto, J.; Uko, M.; Imai, Y. **1990**, Jpn. Pat. JP 02291286 A2, CAN 115:27723.
[124] Sugai, T.; Mori, K. *Agric. Biol. Chem.*, **1984**, *48*, 2497.
[125] Nakayama, T.; Mori, K. *Liebigs Ann.*, **1997**, 839.
[126] Taylor, S.K.; Arnold, C.R.; Gerds, A.T.; Ide, N.D.; Law, K.M.; Kling, D.L.; Pridgeon, M.G.; Simons, L.J.; Vyvyan, J.R.; Yamaoka, J.S.; Liao, M-K.; Goyne, T.E. *Tetrahedron Asymmetry*, **2004**, *15*, 3819.
[127] Naoshima, Y.; Nishiyama, T.; Nakamura, A. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu*, **1988**, *30*, 111.
[128] Naoshima, Y.; Ozawa, H.; Kondo, H.; Hayashi, S. *Agric. Biol. Chem.*, **1983**, *47*, 1431.
[129] Leal, W.S. *Naturwissenschaften*, **1991**, *78*, 521.
[130] Fukusaki, E.; Senda, S.; Nakazono, Y.; Omata, T. *Biosci. Biotech. Biochem.*, **1992**, *56*, 1160.
[131] Fukusaki, E.; Satoda, S.; Senda, S.; Omata, T. *J. Ferment. Bioeng.*, **1998**, *86*, 508.
[132] Yarger, R.G.; Silverstein, R.M.; Burkholder, W.E. *J. Chem. Ecol.*, **1975**, *1*, 323.
[133] Ravid, U.; Silverstein, R.M.; Smith, L.R. *Tetrahedron*, **1978**, *34*, 1449.
[134] Mori, K.; Mori, H.; Sugai, T. *Tetrahedron*, **1985**, *41*, 919.
[135] Ghosh, S.K.; Chattopadhyay, S.; Mamdapur, V.R. *Tetrahedron*, **1991**, *47*, 3089.
[136] Jacobs, H.K.; Mueller, B.H.; Gopalan, A.S. *Tetrahedron*, **1992**, *48*, 8891.
[137] Henkel, B.; Kunath, A.; Schick, H. *Liebigs Ann.*, **1995**, 921.
[138] Henkel, B.; Kunath, A.; Schick, H. *J. Prakt. Chem. Chem. Ztg.*, **1997**, *339*, 434.
[139] Ramaswamy, S.; Oehlschlager, A.C. *Tetrahedron*, **1991**, *47*, 1145.
[140] Mori, K.; Otsuka, T. *Tetrahedron*, **1985**, *41*, 547.
[141] Lin, G-Q.; Xu, W-Ch. *Tetrahedron*, **1996**, *52*, 5907.
[142] Fujita, K.; Mori, K. *Eur. J. Org. Chem.*, **2001**, 493.
[143] Suemune, H.; Hizuka, M.; Kamashita, T.; Sakai, K. *Chem. Pharm. Bull.*, **1989**, *37*, 1379.
[144] Butt, S.; Davies, H.G.; Dawson, M.J.; Lawrence, G.C.; Leaver, J.; Roberts, S.M.; Turner, M.K.; Wakefield, B.J.; Wall, W.F.; Winders, J.A. *J. Chem. Soc. Perkin Trans. 1*, **1987**, 903.
[145] Sarmah, B.K.; Barua, N.C. *Tetrahedron*, **1993**, *49*, 2253.
[146] Fang, J-M. *Pure Appl. Chem.*, **1996**, *68*, 581.
[147] Cossé, A.A.; Bartelt, R.J.; James, D.G.; Petroski, R.J. *J. Chem. Ecol.*, **2001**, *27*, 1841.
[148] Shibata, Ch.; Mori, K. *Eur. J. Org. Chem.*, **2004**, 1083.
[149] Mori, K.; Tomioka, H. *Liebigs Ann. Chem.*, **1992**, 1011.
[150] Pawar, A.S.; Chattopadhyay, S.; Chattopadhyay, A.; Mamdapur, V.R. *J. Org. Chem.*, **1993**, *58*, 7535.
[151] Naoshima, Y.; Nakamura, A.; Nishiyama, T.; Haramaki, T.; Mende, M.; Munakata, Y. *Chem. Lett.*, **1989**, 1023.
[152] Keinan, E.; Seth, K.K.; Lamed, R.; Ghirlando, R.; Singh, S.P. *Biocatalysis*, **1990**, *3*, 57.
[153] Keinan, E.; Sinha, S.C.; Singh, S.P. *Tetrahedron*, **1991**, *47*, 4631.
[154] Mori, K.; Amaike, M.; Oliver, J.E. *Liebigs Ann. Chem.*, **1992**, 1185.
[155] Suzuki, T. *Agric. Biol. Chem.*, **1981**, *45*, 1357.
[156] Suzuki, T. *Appl. Entomol. Zool.*, **1983**, *18*, 134.
[157] Fuganti, C.; Grasselli, P.; Servi, S.; Hoegberg, H.E. *J. Chem. Soc. Perkin Trans. 1*, **1988**, 3061.
[158] Sankaranarayanan, S; Sharma, A.; Chattopadhyay, S. *Tetrahedron Asymmetry*, **2002**, *13*, 1373.
[159] Chênevert, R.; Desjardins, M. *J. Org. Chem.*, **1996**, *61*, 1219.
[160] Kobayashi, M.; Koyama, T.; Ogura, K., Seto, S. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu*, **1979**, *22*, 164.
[161] Kobayashi, M.; Koyama, T.; Ogura, K., Seto, S.; Ritter, F.J.; Brüggemann-Rotgans, I.E.M. *J. Am. Chem. Soc.*, **1980**, *102*, 6602.
[162] Koyama, T.; Kobayashi, M.; Matsubara, M.; Ogura, K., Ritter, F.J.; Brüggemann-Rotgans, I.E.M. *Nippon Kagaku Kaishi*, **1983**, 1377.
[163] Poppe, L.; Novák, L.; Kolonits, P.; Bata, A.; Szántay, C. *Tetrahedron*, **1988**, *44*, 1477.
[164] Serra, S.; Fuganti, C. *Helv. Chim. Acta*, **2002**, *85*, 2489.
[165] Mori, M.; Mochizuki, K.; Kohno, M.; Chuman, T.; Ohnishi, A.; Watanabe, H.; Mori, K. *J. Chem. Ecol.*, **1986**, *12*, 83.
[166] Pilli, R.A.; Riatto, V.B. *J. Braz. Chem. Soc.*, **1998**, *9*, 571.
[167] Hayakawa, R.; Shimizu, M. *Synlett*, **1999**, 1298.
[168] Ha, H-J.; Yim, Y-G. *Synth. Commun.*, **2000**, *30*, 581.
[169] Fujita, K.; Mori, K. *Biosci. Biotech. Biochem.*, **2001**, *65*, 1429.
[170] Masuda, Y.; Fujita, K.; Mori, K. *Biosci. Biotech. Biochem.*, **2003**, *67*, 1744.
[171] Nakazono, Y.; Komata, T.; Senda, S.; Fukusaki, E.; Yuasa, H. **1994**, Jpn. Pat. JP 06007181 A2, CAN 121:7463.
[172] Pilli, R.A.; Riatto, V.B. *J. Braz. Chem. Soc.*, **1999**, *10*, 363.
[173] Mori, K.; Sano, S.; Yokoyama, Y.; Bando, M.; Kido, M. *Eur. J. Org. Chem.*, **1998**, 1135.
[174] Lanier, G.N.; Qi, Y-T.; West, J.R.; Park, S.C.; Webster, F.X.; Silverstein, R.M. *J. Chem. Ecol.*, **1989**, *15*, 1645.
[175] Lin, G-Q.; Xu, W-Ch. *Bioorg. Med. Chem.*, **1996**, *4*, 375.
[176] Einhorn, J.; Menussieu, P.; Malosse, C.; Ducrot, P.H. *Tetrahedron Lett.*, **1990**, *31*, 6633.
[177] Mori, K.; Furuuchi, T.; Kiyota, H. *Liebigs Ann.*, **1994**, 971.
[178] Mori, K.; Amaike, M. *J. Chem Soc. Perkin Trans.*, **1994**, *1*, 2727.
[179] Odinokov, V.N.; Botsman, L.P.; Saranova, L.V.; Syutkina, E.V.; Emel'yanova, G.A. *Chem. Nat. Compd.*, **1998**, *33*, 687.
[180] Morgani, B.; Oehlschlager, A.C.; Stokes, T.M. *Tetrahedron*, **1991**, *47*, 1611.
[181] Vasil'ev, A.A.; Vlasyuk, A.L.; Gamalevich, G.D.; Serebryakov, E.P. *Bioorg. Med. Chem.*, **1996**, *4*, 389.
[182] Phillips, J.K.; Miller, S.P.F.; Andersen, J.F.; Fales, H.M.; Burkholder, W.E. *Tetrahedron Lett.*, **1987**, *28*, 6145.
[183] Sugai, T.; Sakuma, D.; Kobayashi, N.; Ohta, H. *Tetrahedron*, 1991, *47*, 7237.
[184] Poppe, L.; Novák, L.; Dévényi, J.; Szántay, C. *Tetrahedron Lett.*, **1991**, *32*, 2643.
[185] Sankaranarayanan, S.; Sharma, A.; Kulkarni, B.A.; Chattopadhyay, S. *J. Org. Chem.*, **1995**, *60*, 4251.
[186] Petschen, I.; Bosch, M.P.; Guerrero, A. *Tetrahedron Asymmetry*, **2000**, *11*, 1691.
[187] Boland, W.; Mertes, K.; Jaenicke, L.; Müller, D.G.; Foelster, E. *Helv. Chim. Acta*, **1983**, *66*, 1905.
[188] Boland, W.; Niedermeyer, U.; Jaenicke, L.; Goerisch, H. *Helv. Chim. Acta*, **1985**, *68*, 2062.
[189] Maier, I.; Müller, D.G.; Gassmann, G.; Boland, W.; Marner, F-J.; Jaenicke, L. *Naturwissenschaften*, **1984**, *71*, 48.
[190] Lebreton, J.; Alphand, V.; Furstoss, R. *Tetrahedron Lett.*, **1996**, *37*, 1011.
[191] Lebreton, J.; Alphand, V.; Furstoss, R. *Tetrahedron*, **1997**, *53*, 145.

[192] Schotten, T.; Boland, W.; Jaenicke, L. *Helv. Chim. Acta*, **1985**, *68*, 1186.

[193] Yamamoto, Y.; Akakabe, Y.; Matsui, K.; Shimidzu, H.; Kajiwara, T. *Z. Naturforsch., [C]*, **1999**, *54*, 1027.

[194] Kajiwara, T.; Yamamoto, Y.; Akakabe, Y.; Matsui, K.; Shimizu, H.; Kawai, T. *Z. Naturforsch. [C]*, **2003**, *58*, 109.

[195] Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron*, **1991**, *47*, 1215.