Chiral Methyl-branched Pheromones

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Insect pheromones are some of the most interesting natural products because they are utilized for interspecific communication between various insects, such as beetles, moths, ants, and cockroaches. A large number of compounds of many kinds have been identified as pheromone components, reflecting the diversity of insect species. While this review deals only with chiral methyl-branched pheromones, the chemical structures of more than one hundred non-terpene compounds have been determined by applying excellent analytical techniques. Furthermore, their stereoselective syntheses have been achieved by employing trustworthy chiral sources and ingenious enantioselective reactions. The information has been reviewed here not only to make them available for new research but also to understand the characteristic chemical structures of the chiral pheromones. Since biosynthetic studies are still limited, it might be meaningful to examine whether the structures, particularly the positions and configurations of the branched methyl groups, are correlated with the taxonomy of the pheromone producers and also with the function of the pheromones in communication systems.

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1 Introduction

Reflecting the diversity of insect species, many kinds of pheromone compounds have been identified, such as aromatic compounds, terpenes, and non-terpene-based aliphatic compounds.[1] Methyl-branched pheromones, which include terpenes and non-terpenes, make one of the most interesting chemical groups, because they are utilized for the species-specific communication of beetles, moths, ants, cockroaches, scales, sawflies, stink bugs, spiders, mites, and so on. They include stereogenic centres, and the absolute configuration has been determined by applying new analytical techniques with enantioselective GC and HPLC columns. Furthermore, many reports have been published regarding their enantioselective syntheses to understand the stereochemistry of the natural pheromones.[2-5] Natural pheromone content is usually very low, and it may be difficult to achieve an instrumental analysis; however, the structures can be estimated using a bioassay with a set of optically pure stereoisomers. Not only the stereochemistry, but determination of the positions of the methyl groups is very important for structural analysis of the non-terpenes. In the case of pheromones with three or more methyl groups and with an additional functional group, the determination is not easy, because the mass spectra are not expected to produce reliable fragment ions that indicate positions of the branches.

In addition to a useful database,[1] insect pheromones have been reviewed for several insect orders, such as Coleoptera,[6] Lepidoptera,[7] Hymenoptera,[8] and Heteroptera,[9] in studies published

a decade ago. Subsequently, an excellent review written by Drs. Francke and Schulz covered all chiral and achiral insect pheromone compounds identified until the end of 2008.[10] On the basis of these works, this review deals only with chiral methyl-branched pheromones, mainly non-terpene compounds, highlighting studies of the identification and stereoselective synthesis carried out in this century. Together with normal hydrocarbons, insect cuticles consist of many methyl-branched hydrocarbons,[11] and the biosynthetic study showed that an origin of the branch is attributed to methylmalonyl-CoA.[12] The pheromones dealt with here are mainly "propanogenins",[10] which are biosynthesized *via* the analogous incorporation of methylmalonyl-CoA (a propanoate unit) in a simple saturated fatty acid biosynthesis or a polyketide biosynthesis. Besides the propanoate, some methyl groups may be introduced by incorporation of an isoprene unit or by other biosynthetic routes, such as chain methylation with a C_1 unit.[10] While many interesting pheromones have been identified from mealybugs and scale insects in the order Homoptera, this review excludes them because they are described in another review by Dr. Millar in this issue.[13] The species in Coleoptera produce many polyunsaturated hydrocarbons with methyl- and ethyl-branches,[14] which are also not discussed here because there are no stereogenic centres in the pheromones.

The methyl-branched pheromones are classified into six groups according to the main functional group and listed separately as follows: 1) hydrocarbons (Table 1), 2) primary alcohols and their derivatives (Table 2), 3) secondary alcohols and their esters (Table 3), 4) ketones (Table 4), 5) carboxylic acids and their derivatives (Table 5), and 6) dihydropyrans, spiroacetals, and others (Table 6). In Tables 1–5, pheromone compounds are arranged in order of the length of main chains. Since the pheromones are mainly acyclic compounds, they are abbreviated as follows: Me = methyl branch, Δ = double bond, the number before the hyphen = the position of the methyl branch or the double bond, the number after the hyphen = the carbon number of the main chain, H = hydrocarbon, OH = alcohol, OFo = formate, OAc = acetate, OPr = propionate, Ald = aldehyde, one = ketone, and acid = carboxylic acid. The position of a functional group is indicated by inserting the number before its symbol, such as 3-OH for a hydroxyl group at the 3-position, except in the case of a terminal position without the number. The tables show the absolute configurations of the methyl-branched pheromones, the scientific names and classifications of the producers, and references to the identification and stereoselective synthesis of the pheromones. The publication years are given to indicate which studies are current or well known.

2 Overview of the natural pheromones identified

2.1 Hydrocarbons

Table 1 shows methyl-branched hydrocarbons (**1**–**21**) that were produced by insects for intraspecific-interindividual communication. The hydrocarbons have been identified mainly from lepidopteran females as a sex pheromone component, and the saturated and monounsaturated moth pheromones (**2**–**12**) include one or two methyl branches connected to a C_{15}–C_{21} main chain. Almost all of the branches are located at odd-numbered positions in the chain; a methyl group at the 5-position is particularly characteristic. In the unsaturated pheromones (**9** and **10**) of two *Lyonetia* species in the family Lyonetiidae, a methyl group at the 14-position is considered to be the same as that at the 5-position by counting from the opposite side. These pheromones are expected to be biosynthesized by elongating a small acyl-CoA to produce the long-chain fatty acyl intermediate that is then converted to hydrocarbon by decarboxylation, as in the case of the cuticular hydrocarbons that cover an insect's body.[8] While the number of the known pheromones is limited, the common branch position in chains with different lengths suggests a starting acyl compound and subsequent units for constructing the carbon skeletons. Namely, 5,9-dimethyl hydrocarbons (**2** and **5**) may be constructed as follows: acetyl-CoA + malonyl-CoA + methylmalonyl-CoA + malonyl-CoA + methylmalonyl-CoA + several malonyl-CoA. Lyonetiidae is a primitive group that includes small moths whose larvae mine into leaves. In addition to the Lyonetiidae species, some species in the families Noctuidae and Geometridae exceptionally utilize the branched hydrocarbons for mating communication.

Lepidopteran sex pheromones are usually composed of straight chain compounds, such as unsaturated fatty alcohols and their derivatives (Type I) and unsaturated hydrocarbons and their epoxides (Type II).[3] Many Noctuidae and Geometridae species frequently secrete Type I and Type II pheromones, respectively. These families are comprised of highly evolved large moths. It is interesting that some taxonomically unrelated species have established the same system for biosynthesizing similar branched pheromones. Due to the low content in a pheromone gland and insufficient separation of the isomers by an enantioselective GC column, the absolute configurations of the natural pheromones were estimated by field evaluation of synthetic stereoisomers. Furthermore, hydrocarbons (**17** and **18**) with long C_{23} and C_{25} main chains were identified as a scent from the female body scales of a Gelechiidae species and as a male sex pheromone of a Pyralidae species.

In addition to the lepidopteran pheromones, some novel sex pheromones have been identified from insects in other orders. Females of a parasitoid wasp in Hymenoptera produce 4,6,8,10-tetramethyl-2,4-diene with a C_{13} chain (**1**) and the corresponding primary alcohol (**35**). The positions of the branched methyl groups were revised from a 2,6,8,12-tetramethyl structure, and the absolute configuration was determined by enantioselective GC analysis after ozonolysis of a natural sample. Recently, a male sex pheromone (**13**) with a C_{21} 5,9,17-trimethyl structure was found from a true bug in Heteroptera, but its stereochemistry is unknown. Major cuticular hydrocarbons that were identified from female scarab beetles in Coleoptera, interestingly, include a C_{22} 4,6,8,10,16,18-hexamethyl structure (**14**) or a 4,6,8,10,16-pentamethyl structure (**15**). The physiological roles of these compounds are unclear, but some enantioselective syntheses have been accomplished to determine their stereochemistry. The *anti,anti* configuration was assigned for the 6,8,10-trimethyl moiety of **14** and **15**, while the same moiety of **1** bears the *syn,syn* configuration. As contact pheromones, simple monomethyl hydrocarbons (**16**, **20**, and **21**) with a C_{23}–C_{33} chain and a dimethyl derivative of **21** have been identified from the cuticles of many insects in Thysanoptera, Coleoptera, Hymenoptera, and Diptera, while the stereochemistry is unknown. Long-chain cuticular hydrocarbons of the queens regulate worker reproduction in

several social insects, such as wasps, ants, and bees. The 3-methyl hydrocarbons with a C_{25} chain (**18**) and the longer chains act as key components of the queen pheromone.

<Table 1>

2.2 Primary alcohols and their derivatives

Table 2 shows methyl-branched primary alcohols and their derivatives (**22**–**40**), which act as pheromones of insects and mites. A long-horned beetle and a flour beetle in Coleoptera produce a C_4 2-methyl alcohol (**22**) and a C_{10} 4,8-dimethyl aldehyde (**29**), respectively, as an aggregation pheromone. On the other hand, adult females of a mealworm and hide beetles of this order use primary alcohols (**28** and **39**), an aldehyde (**40**), and a methyl ester of carboxylic acid with one methyl branch in a C_9 or C_{16} main chain to communicate with conspecies males. Females of a seed beetle species release an aldehyde (**31**) with two methyl and one ethyl branches in a C_{12} main chain and C_{11} analogues as a sex pheromone. In the order Heteroptera, an assassin bug species produces C_4 2-methyl and C_7 4-methyl sex pheromone components (**22** and **23**), and a stink bug produces a C_{14} 6,10,13-trimethyl aggregation pheromone (**37**). A C_6 2-methyl alcohol (**26**) was found in the mandibular gland of an ant species in Hymenoptera, and a C_{13} 3,4,7,11-tetramethyl aldehyde (faranal, **36**) was identified as a trail pheromone of another ant species. Bumblebee males in this order produce a marking pheromone composed of a C_{12} unsaturated 3,7,11-trimethyl alcohol (dihydrofarnesol, **33**) and its aldehyde derivative.

In Lepidoptera, an isobutyl ester of C_{15} 10,14-dimethyl alcohol (**38**) was identified from females of two tussock moth species as an unusual main sex pheromone, and an acetate of C_{12} 10-methyl alcohol (**30**) acts as an important minor pheromone component of a leafroller moth to establish reproductive isolation from sibling species. Recently, a C_{13} 3,5,9-trimethyl aldehyde (stylopsal, **34**) was identified from two European species of a twisted-wing parasite of Strepsiptera, an unfamiliar and small order of insects with approximately 600 known species. The larval stage is spent as endoparasites in other insects, such as wasps and leafhoppers. Adult males resemble a small fly, but females are neotenic in form, lacking wings, legs, and eyes. The sex pheromone is necessary for virgin females to mate. In addition to the insects, C_7 2,6-dimethyl alcohol (**27**) and its aldehyde were identified from an acarid mite in Astigmata of Arachnida as a female sex pheromone. Another species produced esters of C_5 2-methyl and C_6 2,4-dimethyl alcohols (**24** and **25**) with common fatty acids, while their functions were unknown.

All branches of the mono- and dimethyl primary alcohols and their derivatives are located at even-numbered positions, indicating that their biosynthetic precursors might be the corresponding fatty acyl-CoA that incorporated one or two C_3 units derived from methylmalonyl-CoA. In the case of 2-methyl compounds, the incorporation proceeds at the final step. On the contrary, trimethyl pheromones possess branches at odd-numbered positions, indicating a different biosynthesis. C_{12} 3,7,11-trimethyl compounds are typical sesquiterpenes, such as the dihydrofarnesol (**33**) of a bumblebee, and the sex pheromone of a seed beetle (**31**) is a unique homologue with an ethyl group at the 7-position. Nerol, farnesol, and some related compounds, which possess no chiral methyl branches, have also been identified as pheromone components from many insects and mites.[1] On the other hand, it is speculated that stylopsal (**34**) with a novel 3,5,9-trimethyl structure might incorporate an isoprene unit at the final step to build the branched carbon skeleton, but a recent study denied the possibility.[109] Faranal (**36**) includes one more methyl branch at the 4-position. Since **37** has a C_{14}-chain skeleton, the methyl branch at the 13-position might be caused by the incorporation of valine, leucine, or an isoprene unit at the beginning of its biosynthesis. Studies in this century have usually clarified the stereochemistry of natural pheromones, mainly using an enantioselective GC column. Interestingly, opposite configurations were assigned to 2-methylbutan-1-ol (**22**), which is produced by the long-horned beetle and the assassin bug.

<Table 2>

2.3 Secondary alcohols and their esters

Table 3 shows methyl-branched secondary alcohols and their esters (**41**–**63**), which act as pheromones in insects and a mite. Four secondary alcohols (**43**–**46**) with one methyl branch in a C_7–C_9 main chain have been identified as an aggregation pheromone of weevils in Coleoptera. Their hydroxyl groups are located at different 3–5-positions; **43**–**45** are considered to be the same 5-hydroxy compounds when their positions are counted from the opposite chain terminal. The methyl branch is fixed at the α-position of the hydroxyl group, which is commonly located at the 5- or ω5-position. While **43** also works as a trail pheromone of an ant species in Hymenoptera, this compound is a diastereomer of the aggregation pheromone of a weevil species. A C_6 3-hydroxy-4-methyl compound (**42**) and its keto derivative (**64** in Table 4) were identified from a head extract of another species of ant, while its function was unknown. Recently, C_6 3,5-dimethyl alcohol (**41**) with a male attraction activity was found in headspace volatiles collected from mating pairs of an assassin bug species. Leaf beetle females of Coleoptera secrete a C_{12} 8-methyl-2-propioxy compound (**47**) as a sex pheromone.

A structure of propionate is frequently found in sex pheromones of sawflies in Hymenoptera. The common name comes from the saw-like appearance of the ovipositor, which the females use to cut into the plants where they lay their eggs. Larvae are defoliators, and many species cause serious agricultural and forestry damage. The pheromones are propionates or acetates of secondary alcohols with one, two, or three methyl branch(es) in a C_{11}–C_{15} chain (**50**–**59**). Compounds of another type have been scarcely reported as pheromones of the sawfly in the family Diprionidae. Since the pheromones are stored as alcohol precursors in the female body and the precursors are esterified at the moment of release from females, structural analysis was usually accomplished with the parent alcohols included in a whole-body extract of females, and the acyl moiety was determined by the biological activity of the synthetic candidates. The pheromones universally possess an acyl group at the 2-position and a methyl branch at the 3-position. Other branches are located at the 7-, 9-, and/or 11-positions. While the *S* configuration at the 2-position is fixed and 2*S*,3*R*,7*R* configuration

was frequently assigned for 3,7-dimethyl pheromones, the diastereomer with 2*S*,3*S*,7*S* configuration was also identified in the cases of **56** and **57**. The diversity of the sawfly pheromones resulted not only from the kind of the acyl moiety, the length of the main chain, and number and position of the branch but also from the configuration of the branch. Since some species produce the same component, additional factors might play a role in achieving strict species-specific mating communication.

A trimethyl secondary alcohol (**48**) and a formate (**49**) with a C_{11} main chain were found as tergal gland secretions of female cockroaches in Dictyoptera and as an aggregation pheromone of an acarid mite, respectively. While **48** is a dienyl compound and **49** is a saturated compound with the functional group at a different position, the two compounds identified from species in different orders, interestingly, bear the branches at the same 4-, 6-, and 8-positions. In Lepidoptera, novel C_{15} 6,10,14-trimethyl and C_{17} 5-methyl secondary alcohols (**60** and **61**) were identified from females of a pyralid moth and a lichen moth, respectively. While **60** acts as a short-range signal, **61** effectively attracts males in the field similar to many other moth pheromones. As a contact sex pheromone, C_{29} 19-methyl-6-acetoxy and 15-methyl-7-acetoxy compounds (**62** and **63**) and some analogues were found in body wax extracted from adult females of the New World screwworm, a blowfly in Diptera.

<Table 3>

2.4 Ketones

Volatile methyl-branched ketones (**64**–**79**) with a C_6–C_{18} main chain and contact pheromones (**80** and **81**) with a C_{27} or C_{29} main chain have been identified from several insects, a spider and a mite, as shown in Table 4. Most of the C_6–C_9 pheromones (**64**–**68, 71**, and **72**) are 3-ketones indicating polyketide biosynthesis, and some components bear a double bond and/or a hydroxyl group. On the contrary, all pheromones with a chain longer than C_{10} (**73**–**81**) are saturated 2-ketones. Almost all branches are located at even-numbered positions and some compounds characteristically include two branches that are separately located at an interval of five methylene carbons or more. These structural distinctions suggest the biosynthetic route of each pheromone component, particularly the formation step of the carbonyl group.

Ants secrete C_6 and C_7 4-methyl-3-ketones (**64** and **65**), C_8 6-methyl-3-ketone (**69**), and monounsaturated C_8 4,6-dimethyl-3-ketone (**68**) as an alarm pheromone. The former two pheromone components are keto derivatives of 3-hydroxyl-4-methyl compounds (**42** and **43**), which have been identified in other ant species. The same *S* configuration was assigned for carbons at the 4-position of the ketones and the secondary alcohols. **65** also acts as a trial pheromone of another ant species and, furthermore, is utilized as a sex pheromone of a caddis fly in Trichoptera and as allomones (defensive substances) of a wasp and a spider. The monounsaturated and 5-hydroxy derivatives (**66** and **67**) are an allomone of a walking stick in Phasmatodea and an aggregation pheromone of weevils, respectively. The caddis fly also produces C_9 4,6-dimethyl-3-ketone (**71**), whose 7-hydroxyl derivative (serricornin, **72**) is a sex pheromone of a deathwatch beetle in Coleoptera. While a C_8 1,3-dihydroxy-2-ketone (**70**) produced by leaf beetle females (Colorado potato beetle) is an aggregation pheromone with a monoterpene skeleton, C_{13} 10-methyl- and C_{15} 6,12-dimethyl-2-ketones (**74** and **76**) are sex pheromones identified from females of two other leaf beetle species.

Recently, it was demonstrated that insects in Heteroptera and Lepidoptera also secrete sex pheromones with the 2-keto structure, *i.e.*, C_{14} 6,10,13-trimethyl-2-ketone (pallantione, **75**) from stink bug males and a mixture of C_{18} 6-methyl, 14-methyl, and 6,14-dimethyl 2-ketones (**77**–**79**) from female lichen moths. Low-volatile **80** and **81** are well-known contact pheromone components produced by females of a cockroach species, which are responsible for male wing-raising in a characteristic sequence of courtship behaviour. In addition to the insect pheromones, C_{10} 4,6,8-trimethyl-2-ketone (chortolure, **73**) was identified as an aggregation pheromone of a storage mite species. Chortolure is an oxidized nor-derivative of lardolure (**49**) with a formyloxy group at the 2-position, another aggregation pheromone with the same 4*R*,6*R*,8*R* configuration as that produced by an acarid mite species.

<Table 4>

2.5 Carboxylic acids and their derivatives

Table 5 shows methyl-branched carboxylic acids and their structure-related compounds (**82**–**97**) that act as insect pheromones. Carboxylic acids and their ester derivatives with one, two, or three methyl branch(es) in a C_5–C_{15} main chain have been identified from insects, mainly in Coleoptera. In addition to methanol, ethanol, and butan-1-ol, branched propan-1-ol has been identified as an alcohol moiety of the esters. Some insects also produce unique lactones derived from hydroxyl acids with a methyl-branched skeleton. The branches are usually located at even-numbered positions, indicating a general biosynthesis based on incorporation of methylmalonyl-CoA, while some exceptions are known.

Coleoptera, the largest order in Insecta, includes about 400,000 described species; structural variation in the pheromone components is very high.[2] Since the volatility of a free acid is low, a carboxyl group is not a common functional group of insect pheromones. Hide beetles, however, utilize several unsaturated carboxylic acids with a straight chain as a species-specific female sex pheromone, and different carboxylic acids (**86**, **87**, and **92**) with a C_7 or C_{12} main chain exceptionally branched at odd-numbered positions have been identified from males of two scarab species and females of a long-horned beetle, respectively. While γ-lactones derived from hydroxyl acids with a straight chain, such as japonilure and buibuilactone, are well-known female sex pheromones of scarabs, males of two scarab species release ethyl esters of C_7 and C_8 4-methyl acids (**88** and **89**) as an aggregation pheromone. A 1-ethylpropyl ester of a C_5 2-methyl acid (sitophilate, **82**) identified from a weevil as an aggregation pheromone bears the same acyl motif with α-methyl and β-hydroxyl groups as a C_7 4-methyl-3-ketone (sitophinone, **67**), which was released by another weevil species. On the other hand, a novel structure of a β-lactone (vittatalactone, **91**) derived from a C_{11} pentamethyl 3-hydroxyl acid was identified as an aggregation pheromone of a leaf beetle.

In Hymenoptera, a δ-lactone (**84**) derived from a C_6 5-hydroxyl-2,4-dimethyl acid acts as a trail pheromone of an ant species, and

another ant species releases different δ-lactone (invictolide, **90**) derived from a C_9 5-hydroxyl-2,4,6-trimethyl acid as a queen-recognition pheromone. A parasitoid wasp species produce anther δ-lactone (**85**) derived from the corresponding C_7 acid as a sex pheromone. In the case of Heteroptera, a pheromone of a broad-headed bug is an *n*-butyl ester of a C_6 4-methyl acid (**83**), while pheromones of stink bugs are methyl esters of C_{12}-C_{15} trimethyl acids (**93**–**96**). Furthermore, females in Lepidoptera and Dictyoptera also produce unique sex pheromones with methyl branches, *i.e.*, a 1-ethyl-2-methylpropyl ester of a C_{15} dimethyl acid (**97**) of a bagworm moth and a 3,5-dialkyl-substitured α-pyrone (supellapyrone, **98**) of a cockroach. Other α-pyrones with a pentyl or a pentenyl group at the 6-position are trail and queen-recognition pheromones of ants, respectively, but α-pyrones have infrequently been found in insects.[1]

Some carboxylic acids and their derivatives might be expected to include a branched structure similar to the known pheromones with a primary hydroxyl group. Alcohols or aldehydes corresponding to the compounds in Table 5, however, are not easy to find in Table 2. Only a few common structures are listed as follows: the C_6 2,4-dimethyl structure for **84** and **25**, the C_7 2,6-dimethyl-5-enyl structure for **87** and **27**, and the C_{12} 3,5-dimethyl structure for **92** and **34**. Alcohols **25** and **27** are produced by acarid mites, and aldehyde **34** is released by a twisted-wing parasite. These similarities, which are promoted by two species classified far apart in the taxonomy, might be coincidental. In the cases of **82** and **67**, which are produced by two different weevil species in the same genus, both compounds act as aggregation pheromones, indicating structural modification by speciation of the insects.

<Table 5>

2.6 Dihydropyrans, spiroacetals, and others

In addition to the lactones mentioned above, some insects produce cyclic compounds in other chemical groups as a pheromone or an allomone. Table 6 shows dihydropyrans (**100**–**104**), spiroacetals (**105**–**111**), and their related compounds (**99** and **112**) with methyl branches on the ring. After identification of serricornin (**72**) with an acyclic structure from females of one death watch beetle species, cyclic anhydroserricornin (**99**) and dihydropyrans (**100**–**102**) were found in the same females as another sex pheromone component. Bifunctional **101** and **102** also work as marking pheromones that deters oviposition of other individuals. Females of another deathwatch beetle species produce similar dihydropyrans (**103** and **104**). All of the pheromone components are estimated to be biosynthesized *via* cyclization of polyketides with a C_9–C_{11} chain. On the other hand, spiroacetals have been isolated from a number of species of Coleoptera, Diptera, Hymenoptera, Heteroptera, and Phasmatodea.[330]

The first insect spiroketal is chalcogran with no methyl branches but an ethyl branch released from a bark beetle.[331] The methyl-branched spiroacetals act as a male sex pheromone of fruit flies and bark beetles (**105**, **106**, and **109**), a female sex pheromone of wild bees (**109**), an aggregation pheromone of a shield bug (**110**), and a defense substance of wasps, walking sticks, and rove beetles (**107**, **108**, and **111**). Mono- and dimethyl spiroacetals (**105**–**109**) are biosynthesized by cyclization of unbranched 2-ketones,[332,333] but biosynthetic precursors of the trimethyl spiroacetals (**110** and **111**) have a methyl branch. Furthermore, bark beetles produce a bicyclo[3.2.1] compound with an intramolecular acetal structure, α-multistriatin (**112**), which might be biosynthesized by cyclization of a polyketide with a C_8 chain.

<Table 6>

3 Structual determination of natural pheromones

3.1 Determination of the branch positions of mono-, di-, and trimethyl compounds

Since pheromone titers are very low, GC-MS is most frequently used for structural determination. In addition to the mass spectra that include molecular ions, the analysis informs the chromatographic behavior of pheromone components, such as Kovats retention index (KI) values.[7] Upon analysis using electron impact (EI) ionization, monomethylalkanes (R_1-$CHCH_3$-R_2) give characteristic secondary fragment ions by cleavage at the branch position, *i.e.*, $[R_1\text{-}CHCH_3]^+$ (= $[M - R_2]^+$) and $[R_2\text{-}CHCH_3]^+$ (= $[M - R_1]^+$). These secondary ions are produced more abundantly than are other primary ions. Similarly, dimethylalkanes (R_1-$CHCH_3$-$(CH_2)_n$-$CHCH_3$-R_2) produce four secondary ions, *i.e.*, $[R_1\text{-}CHCH_3]^+$, $[M - R_1]^+$, $[R_2\text{-}CHCH_3]^+$, and $[M - R_2]^+$.[334] The chain length between two branches, however, cannot be clarified by spectral analysis. These ions narrow down two possible structures; C_{25} dimethyl pheromone (**19**) showed ions at *m/z* 323, 224, 183, and 85, indicating 5,11- and 5,14-dimethyl structures (Fig. 1A).[70] Both candidates were synthesized, and the former structure was assigned for the pheromone because the relative intensities of the four ions produced by the 5,14-dimethyl compound were smaller than those of the natural pheromone.

On the other hand, the branch positions of functionalized compounds are not considered to be determined directly by their mass spectra because the EI ionization predominantly proceeds at a π-bond and on a hetero atom. To detect the informative secondary fragment ions, pheromones with a functional group are usually converted into alkanes by micro-chemical reactions. A mass spectrum of the 7-hydroxy-5-methyl pheromone (**61**) showed ions at *m/z* 171 and 129, indicating the position of the hydroxyl group, and a hydrocarbon derived by tosylation and $LiAlD_4$ reduction showed ions at *m/z* 198 and 85, indicating the position of the methyl group (Fig. 1B).[184] While analysis of the deuterated hydrocarbon did not deny the possibility of the 8-hydroxy-13-methyl structure, and synthetic confirmation was conducted, further GC-MS analysis of a series of synthetic analogues revealed that **61** abundantly showed a diagnostic ion of the 5-methyl structure at *m/z* 85.[185] In the case of 2-ketones (**77**–**79**),[235] which commonly produce a characteristic ion at *m/z* 58 (base peak) by the McLafferty rearrangement, the 6- and 14-positions of branches were determined from mass spectra of the hydrocarbons produced by the Wolff-Kishner reduction (Fig. 1C). Spectral analysis of several synthetic branched 2-ketones indicated that the 6-methyl-2-ketone with characteristic ions at *m/z* 113 and 95 (113–H_2O) was differentiated from the 4-, 5-, and 7-methyl-2-ketones, but differentiation of the mass spectra of the 13-, 14-, and 15-methyl-2-ketones was difficult.[236]

Structural determination of the 3,13-dimethyl pheromone (**97**) was also conducted using a mass-spectral analysis of the pheromone

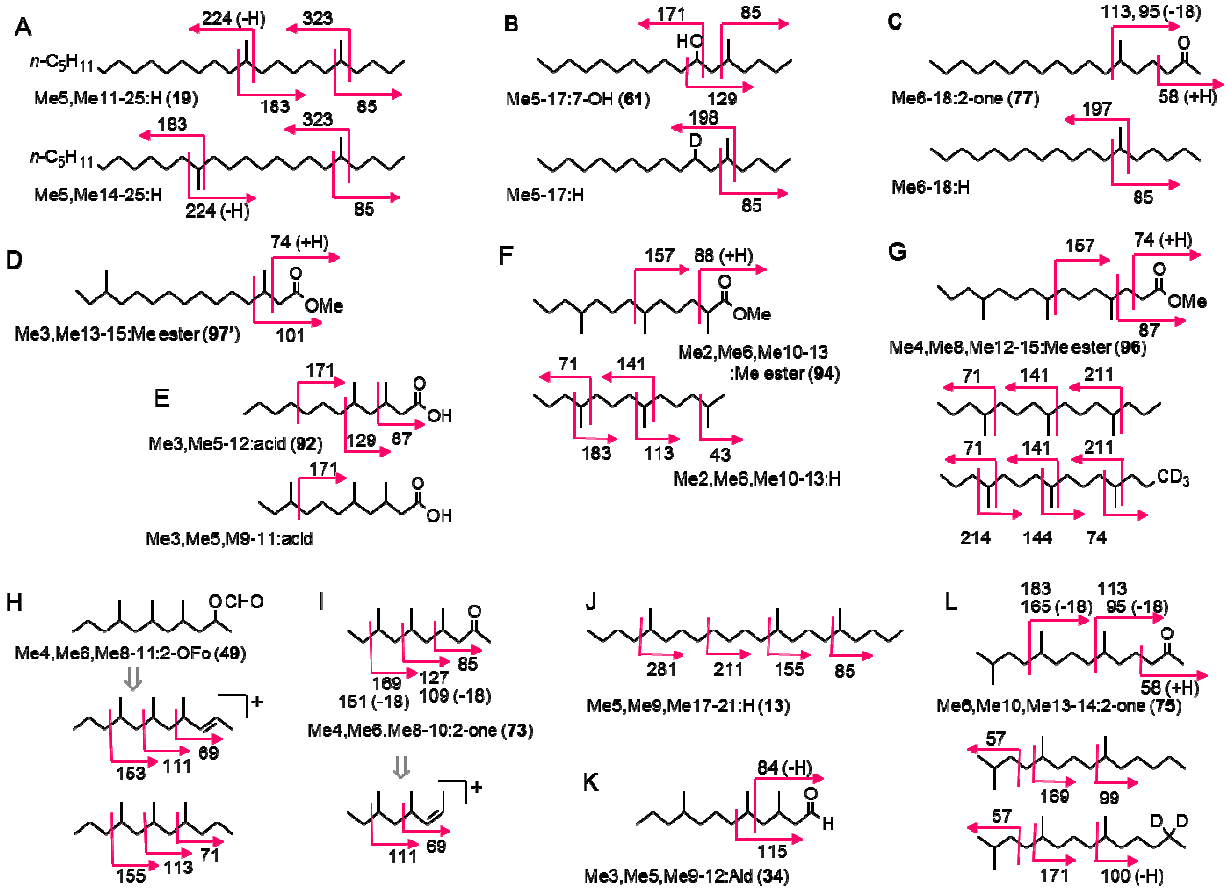


Fig. 1. Characteristic fragment ions detected by EI-MS analysis of mono-, di-, and trimethyl pheromones

derivative and some synthetic candidates.[286] By transesterification with KOH in MeOH, the novel ester was converted into the methyl ester (**97'**), which showed ions at *m/z* 101 (base peak) and 74, indicating a 3-methyl structure (Fig. 1D). The mass spectrum of the synthetic 3-methyl ester was similar to that of **97'** but different from those of the 4-, 5-, 13-, 14-, and 15-methyl esters. As the 13-, 14-, and 15-methyl branches had a small effect on the spectral patterns, the position of the second methyl branch was speculated to be widely separated from the carboxylate carbon. Among some synthetic dimethyl compounds, the pheromone activity of **97** with the 3,13-dimethyl structure was observed.

Carboxylic acid (**92**) was initially expected to be a trimethyl compound based on three remarkable ions at *m/z* 171, 129, and 87 (base peak), which are different from each other by 42 mass units (Fig. 1E).[278] However, the spectra of synthetic 3,5,9- and 3,5,7-trimethyl carboxylic acids are similar but not quite identical to that of the insect pheromone. While the fragmentation mechanism to produce the ion at *m/z* 171 was unknown, GC-MS data of the synthetic 3,5-dimethyl carboxylic acid (**92**), interestingly, coincided well with those of the natural component. On the contrary, the 2,6,10-trimethyl structure of ester pheromone (**94**), which showed characteristic ions at *m/z* 157 and 88 (base peak) (Fig. 1F), was a revised version of the initially assigned 2,6-dimethyl structure.[282] The third branch was overlooked because the methyl branch at the 10-position scarcely affected the spectral pattern. In a reexamination study, the pheromone extract was sealed with $LiAlH_4$ and Pt-Al_2O_3 and heated at 250°C. The hydrogenation/hydrolysis reaction gave a hydrocarbon, which showed a mass spectrum with ions at *m/z* 183, 141, 113, 71, and 43, indicating the trimethyl structure. The homologous ester pheromone with the same 1,5,9-trimethyl motif as **96** showed ions at *m/z* 157 and 87 (base peak), but the ion at *m/z* 74 that was produced by the McLafferty rearrangement indicated no branch at the 2-position (Fig. 1G).[285] The hydrocarbons were prepared by three steps: $LiAlH_4$ reduction, mesylation, and a second reduction with $LiAlH_4$ or $LiAlD_4$. In addition to the ions at *m/z* 211, 141, and 71 also produced by the unlabelled hydrocarbon, the deuterated hydrocarbon showed corresponding ions at *m/z* 214, 144, and 74, confirming methyl branches at the 4-, 8-, and 12-positions.

As compared with the 1,5,9-trimethyl motif, pheromones with another 1,3,5-trimethyl ("skipped" trimethyl) motif exhibited mass spectra that more clearly indicated the branch positions. A mite pheromone with a 4,6,8-trimethyl structure (**49**) showed characteristic secondary ions at *m/z* 153, 111 (base peak), and 69, which are different from each other by 42 mass units and might be produced after losing the formate moiety located at the 2-position (Fig. 1H).[150] In support of fragmentation, a hydrocarbon prepared from the pheromone by a three-step reaction showed ions at *m/z* 155, 113, and 71 (base peak). Since another mite pheromone (**73**)

includes a 2-keto structure, the relative intensities of the expected secondary ions at *m/z* 169 and 127 were very weak, but the corresponding ions that were losing water were definitely detected at *m/z* 151 and 109 (Fig. 1I).[221] The secondary ion at *m/z* 85 was detected as the base peak instead of the base peak at *m/z* 58 of the 6-methyl-2-ketone (**77**).[235] Furthermore, the spectrum showed other characteristic ions at *m/z* 111 and 69, which might be derived from a moiety losing the 1–3-positions by the McLafferty rearrangement, indicating the 4,6,8-trimethyl structure.[221]

Additionally, several insect products with different branching have been identified. The studies illustrated the difficulty of determining unique branch positions. Since the cuticular hydrocarbon (**13**) showed characteristic ions at *m/z* 281, 211, 155, and 85, a 5,9,12,16-tetramethyl structure was initially assigned to it (Fig. 1J).[59] Mass spectra of the synthetic tetramethyl candidate and the 5,9-dimethyl analogue were similar to that of the natural pheromone, and their Kovats retention index (KI) values informed the existence of three methyl branches. The 12- and 17-positions were estimated for the third branch, and the 5,9,17-trimethyl structure was finally confirmed by a synthetic approach. In the case of the 3,5,9-trimethyl pheromone (**34**), the 3- and 5-positions of two branches at a side of the functional group were estimated by mass spectral analysis of the natural aldehyde and derivatives, but no information was obtained for the third position (Fig. 1K).[107,108] Methyl and deuterated methyl esters of the acid derivative showed $[M–57]^+$ at *m/z* 199 and 202 with similar intensities. This result equated the loss of a C_4 moiety at the terminal side of the ester, *i.e.*, the third methyl branch might not be placed at the 9-position. Surprisingly, only the 3,5,9-trimethyl aldehyde was active in the field among some synthetic trienes. The trimethyl 2-ketone (**75**) produced a characteristic ion at *m/z* 58 (base peak) by the McLafferty rearrangement, and two sets of ions at *m/z* 113 and 95 and *m/z* 183 and 165 suggested the methyl branches at the 6- and 10-positions, respectively (Fig. 1L).[229] These positions were confirmed by spectral comparison of two hydrocarbons produced by $LiAlH_4$ and $LiAlD_4$ reduction of a tosylhydrazone derived from the natural pheromone. Base peaks of both hydrocarbons were, likewise, observed at *m/z* 57, and relative intensities of the ion at *m/z* 59 were equally low in their spectra, indicating the presence of a branched C_4 moiety at a higher position. Two candidates with a 6,10,12- or 6,10,13-trimethyl structure were synthesized, and the latter matched the natural pheromone.

3.2 Determination of the branch positions of tetra-, penta-, and hexamethyl compounds

An unsaturated primary alcohol with four methyl branches and the corresponding hydrocarbon (**1**) were found as sex pheromone components of a parasitoid wasp. A 2,6,8,12-tetramethyl structure was initially proposed for their branched skeletons,[15] and the positions of two branches were revised later.[16] A crude pheromone extract was treated with a silylation reagent (TBSTFA with 1% TMCS), and silylated alcohol was characterized by a base peak at *m/z* 169 on the GC-MS analysis. This fragment was estimated to be a stable six-membered oxonium ion ($MeC_5H_4O^+SiMe_3$), which indicated that the parent alcohol was 2,4-dien-1-ol. The structure of this allylic alcohol with a conjugated dienyl motif was also confirmed by spectral analysis of the adduct with a dienophile, 4-methyl-1,2,4-triazoline-3,5-dione (MTAD). On the other hand, a mass spectrum of the hydrocarbon showed characteristic ions at *m/z* 109 (base ion) and 82 (Fig. 2A). Based on these experiments, a 2,4-dienyl-2,6,8,12-tetramethyl structure was tentatively proposed for both components.[15] The mass spectrum of the synthetic hydrocarbon, however, did not coincide with that of the natural component, while the difference was observed for the fragment ions with very small relative intensities. Ions at *m/z* 180 and 153 were absent and present in the spectrum of the natural hydrocarbon, respectively, but opposite data were obtained from the synthetic 2,6,8,12-tetramethyl compound. Another synthetic candidate with a 2,6,8,10-tetramethyl structure showed the same difference, and final congruence was recognized from the 4,6,8,10-tetramethyl 2,4-diene (**1**).[16]

Vittatalactone (**91**) is a novel β-lactone with five methyl branches that has been identified as an aggregation pheromone of a leaf beetle.[271] High resolution EI-MS analysis of M^+ at *m/z* 254 established its molecular formula as $C_{16}H_{30}O_2$. The pheromone had two degrees of unsaturation but micro-chemical reactions showed that it was not an aldehyde or a ketone and had no C-C double bonds. Acid methanolysis produced a methyl ester of the acid with a 3-hydroxy-2-methyl structure, which showed a mass spectrum with a base peak at *m/z* 117 (an ion produced by α-cleavage next to the hydroxyl group) and a prominent peak at *m/z* 88 (an ion produced by the McLafferty rearrangement of the ester) (Fig. 2B). This result indicated a β-lactone moiety in the pheromone; this was supported by a strong absorption at 1853 cm^{-1} recorded by GC-FT-IR measurement. In addition to $[M–CO_2]^+$ at *m/z* 210, the GC-MS analysis of **91** showed characteristic ions at *m/z* 156 and 153 suggesting the branch positions. Furthermore, an unsaturated hydrocarbon, which was produced by thermal decarboxylation in the GC injector, showed fragment ions at *m/z* 153, 111, and 69, indicating the branch positions in the chain moiety of **91**. The identification was confirmed by ^1H, ^{13}C, and 2D NMR experiments with 0.8 mg of the natural pheromone. The ^{13}C NMR spectrum, which showed 16 carbon signals without overlapping, is an important datum for confirming the diasteromeric purity of its enantioselective synthesis.[272-274]

Females of a scarab beetle species produce cuticular hydrocarbons with unprecedented hexamethyl and pentamethyl structures (**14** and **15**). Their mass spectra exhibited molecular ions at *m/z* 394 and 380, respectively, and the formulas $C_{28}H_{58}$ and $C_{27}H_{56}$ were confirmed by accurate mass measurements. The mass spectral fragmentation pattern of each component demonstrated the presence of multiple methyl branches bearing a skipped motif, *i.e.*, **14** showed ions at *m/z* 309, 267, and 225, which were different from each other by 42 mass units (Fig. 2C).[60] Further structural determination of **14** was carried out by ^{13}C NMR analysis, which showed resonances of two terminal methyl carbons at 14.2 and 14.4 ppm, six branched methyl carbons at 19.6–20.3 ppm, four methylene carbons attached to one branch at 36.6–40.2 ppm, and four methylene carbons between two branches at 45.2–46.5 ppm. Calculated ^{13}C chemical shifts in best agreement with the natural hydrocarbon indicated two candidates with a 4,6,8,10,16,18- or

5,7,9,11,17,19-hexamethyl structure, which includes the first methyl branches at the 4- and 5-positions counting from the chain terminals.

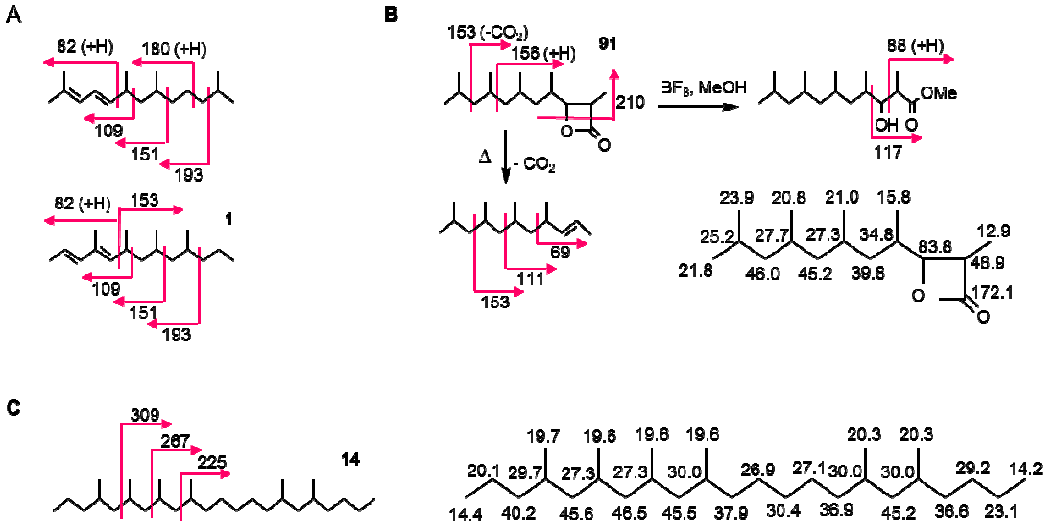


Fig. 2. Characteristic fragment ions detected by EI-MS analysis and ^{13}C NMR assignment of tetra-, penta-, and hexamethyl insect compounds; (A) (2*E*,4*E*)-2,6,8,12-tetramethyltridecadiene and (2*E*,4*E*)-4,6,8,10-tetramethyltridecadiene (**1**), (B) vittatalactone (**91**), and (C) 4,6,8,10,16,18-hexamethyldocosane (**14**)

Two-dimensional NMR experiments, particularly HMBC measurement, provided a clear distinction in favor of the former structure for **14** and 4,6,8,10,16-pentamethyl structure for **15**. Since branched methyl carbons of synthetic *syn*- and *anti*-7,9-dimethylhexadecane resonated at 20.3 ppm (unresolved) and 19.6 ppm (unresolved), respectively, an *anti,anti,anti* configuration of the 4,6,8,10-tetramethyl moiety in **14** and **15** and a *syn* configuration of the 16,18-dimethyl moiety in **14** were proposed.[60] The relative stereochemistry was confirmed by comparing ^{13}C NMR data of the natural components with those of several synthetic diastereomers,[61,65] indicating the usefulness of high resolution ^{13}C NMR. Some carbons of positional isomers and diastereomers have detectably different chemical shifts.

3.3 Determination of absolute configurations

In addition to indirect determination based on the biological activities of synthetic stereoisomers, absolute configurations of many natural pheromones have been directly determined by using an enantioselective GC column, as shown in Tables 2–6. While resolution of hydrocarbons seems to be difficult, separation of two enantiomers has been definitely accomplished in the case of functionalized monomethyl pheromone components whose methyl branch is positioned close to a functional group. Furthermore, some successful separation of dimethyl compounds has been reported. The columns with a γ-cyclodextrin-based stationary phase separated four stereoisomers of the 4,8-dimethyl aldehyde (tribolure, **29**) [elution order: (4*R*,8*R*)-, (4*R*,8*S*)-, (4*S*,8*S*)-, and (4*S*,6*R*)-isomers],[96] the 4,6-dimethyl-3-ketone (**71**) [elution order: (4*R*,6*R*)- or (4*R*,6*S*)-, (4*S*,6*S*)-, and (4*S*,6*R*)-isomers],[195] and supellapyrone (**98**) [elution order: (2*S*,4*S*)-, (2*S*,4*R*)-, (2*R*,4*R*)-, and (2*R*,4*S*)-isomers].[291] The column with a β-cyclodextrin-based stationary phase, interestingly, separated three stereoisomers of the 7,11-dimethyl hydrocarbon (**8**) [elution order: (*S,S*)-, (*R,R*)-, and *meso*-isomers].[43] In the case of the 6,10,14-trimethyl-2-ketone (pallantione, **75**) with two stereogenic centres, a mixture of four synthetic stereoisomers showed only two peaks on the GC analysis with a β-cyclodextrin-based column [elution order: (6*S**,10*S**)- and (6*R**,10*S**)-isomers].[229] In order to determine the absolute configuration, the natural pheromone with the longer Rt was reduced with $LiAlH_4$ and acetylated to yield the 2-acetoxy derivative, which was composed of two diastereomers with the third stereogenic centre but was expected to benefit from the interaction between the acetoxy group and the stationary phase. Four peaks were detected on the GC analysis of the secondary acetates derived from the synthetic (6*R**,10*S**)-isomer, a mixture of the (6*R*,10*S*)- and (6*S*,10*R*)-isomers. The diastereomers derived from the former isomer showed the same chromatographic behaviours as those from the natural pheromone, revealing the 6*R*,10*S* configuration of **75**. On the other hand, a mixture of eight stereoisomers of the 4,6,8-trimethyl-2-ketone (chortolure, **73**) showed seven peaks and their peak areas indicated that the sixth peak consisted of two isomers.[221] The Rt of the natural pheromone coincided with that of the (4*R*,6*R*,8*R*)-isomer eluted as the second peak.

The sawfly pheromones (**50**–**59**) include 2–4 stereogenic centres. Absolute configuration of the 2-acetoxy-3,7,9-trimethyl compound (**53**) was determined by comparing its GC data with those of synthetic stereoisomers.[165] The GC analyses were conducted with two achiral-phase and one chiral-phase columns. The first analysis with all sixteen stereoisomers of the alcohol derivative demonstrated a 2*S**,3*R** configuration of the natural component, and then a

2*S**,3*R**,7*R**,9*S** configuration was revealed by a second analysis with eight stereoisomers of the propionate derivative containing the 2*S**,3*R** configuration. Finally, a 2*S*,3*R*,7*R*,9*S* configuration was confirmed by the experiment using a column with an (*S*)-valine-2-phenylethylamine-based stationary phase. Recently, GC separation of the stereoisomers of several methyl-branched secondary alcohols was systematically examined after esterification with (*S*)-2-acetoxypropionic (AP) acid.[162] Among eight columns with an achiral or a chiral phase, a high polar achiral-phased column showed the best separation for diastereomers of each acetoxypropionate of the branched alcohols, such as esters of the 2-hydroxy-3-methyl compound (**59**) [elution order: (2*R*,3*R*)-, (2*R,*3*S*)-, (2*S,*3*S*)-, and (2*S,*3*R*)-isomers] and the 2-hydroxy-3,7-dimethyl compound (**58**) [elution order: (2*R*,3*R*,7*R*)-, (2*R*,3*R*,7*S*)-, (2*R*,3*S*,7*R*)-, (2*R*,3*S*,7*S*)-, (2*S*,3*S*,7*S**)-, (2*S*,3*R*,7*S*)-, and (2*S*,3*R*,7*R*)-isomers]. The separation of the (2*S*,3*S*,7*S*)- and (2*S*,3*S*,7*R*)-isomers was accomplished with another achiral-phased column after esterification with 2-naphthoyl chloride. Application of this method revealed that two sawfly species produced pheromones with the same 2-hydroxy-3,7-dimethyl structure but with different chain skeletons (C_{13} and C_{15}) and configurations (2*S*,3*R*,7*R* and 2*S*,3*S*,7*S*). While elution order was not examined, the separation of sixteen diastereomers was recorded on the GC analysis of the acetoxypropionate derived from the 3,7,9-trimethyl pheromone (**53**).

The separation of stereoisomers was also examined with enantioselective HPLC columns, and successful resolution was found for sex pheromones of a lichen moth, which could not be resolved by chiral-phase GC columns.[236] A normal-phase HPLC column packed with silica gel coated with an amylose derivative showed good resolution ability for the 6-methyl-2-ketone (**77**) [elution order: (*R*)- and (*S*)-isomers]. Its moderate ability was also exhibited for the 14-methyl-2-ketone (**78**), whose methyl branch was positioned far from the carbonyl group [elution order: (*S*)- and (*R*)-isomers]. While a mixture of (*R*)-**77** and (*S*)-**78** effectively attracted male moths, analysis of the pheromone extract revealed that females produced some amounts of the enantiomers. In the case of 7-hydroxy 5-methyl compound (**61**), structural determination was achieved by a pheromone extract from only one female moth. The 5*R*,7*R* configuration was estimated by field evaluation of four synthetic stereoisomers, and no experiments were conducted for the determination. Direct analysis, however, might be possible because the synthetic isomers showed different Rts on an HPLC column with silica gel coated with another amylase derivative [elution order: (5*R*,7*R*)-, (5*R*,7*S*)-, (5*S,*7*S*)-, and (5*S,*7*R*)-isomers].[184] Enantioselective HPLC columns were also utilized to measure the enantiomeric excess (*ee*) of synthetic intermediates with a methyl branch, such as 3-methyl primary alcohols and 2-methyl-1-sulfonyl compounds.[32,230,289]

Major pheromone components of a blowfly, 6-acetoxy-19-methyl and 7-acetoxy-15-methyl compounds (**62** and **63**), include two stereogenic centres separated by many methylene carbons. Separation of four synthetic stereoisomers was carried out after converting the acetates into esters with a chiral and fluorescent derivatizing reagent,[188] (1*R*,2*R*)-2-(2,3-anthracenedicarboximido)cyclohexanecarboxylic acid (Fig. 3, R =CO_2H), which was designed to promote highly sensitive detection and interaction with an asymmetric carbon widely separated from a functional group. The use of a column-switching HPLC system equipped with two reversed-phase columns of different polarities allowed good separation of the stereoisomers of each methyl-branched compound at a low temperature [elution order of the 19-methyl ester: (6*S,*19*R*)-, (6*S,*19*S*)-, (6*R,*19*R*)-, and (6*R,*19*S*)-isomers; elution order of the 15-methyl ester: (7*R*,15*S*)-, (7*S,*15*S*)-, (7*S,*15*R*)-, and (7*R,*15*R*)-isomers]. Experiments with the natural components clarified a 6*R,*19*R* configuration for **62** and 7*R,*15*R* and 7*R*,15*S* configurations for **63**. This method was also applied for analysis of the 4,8-dimethyl aldehyde (**29**).[96] Four stereoisomers of the alcohol corresponding to **29** were esterified with the (1*R*,2*R*)-acid, but analysis of a mixture of four diastereomers on the same HPLC system showed their elution as three broad peaks. On the other hand, four diastereomers of another ester between the acid corresponding to **29** and (1*R*,2*R*)-2-(2,3-anthracenedicarboximido)cyclohexanol (Fig. 3, R = OH) could be separated with HPLC analysis [elution order: (4*R*,8*R*)-, (4*R,*8*S*)-, (4*S,*8*S*)-, and (4*S,*8*R*)-isomers]. An experiment with the natural pheromone clarified the presence of the four stereoisomers in a ratio of approximately 4:4:1:1, and bioassay of the synthetic pheromone in a wind tunnel demonstrated high potency of the reconstituted natural blend.[83]

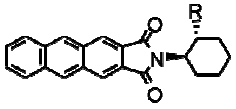


Fig. 3. Chemical structures of fluorescent reagents, (1*R*,2*R*)-2-(2,3-anthracenedicarboximido)cyclohexanecarboxylic acid (R = CO_2H) and (1*R*,2*R*)-2-(2,3-anthracenedicarboximido)cyclohexanol (R = OH).

4 Synthesis of chiral pheromones

4.1 Employment of chiral sources

Many enantioselective syntheses of chiral methyl-branched pheromones have been accomplished by employing a chiral source. In addition to optically active natural products with a branched methyl group, several industrial chiral compounds are available as a starting material for the pheromone syntheses. Table 7 shows the chiral sources and brief synthetic routes for their conversion to some targeted pheromones. Citronellol (**S1a**) is one of the most important starting materials for various organic syntheses,[335] and both enantiomers of **S1a** [(*S*)-(-)- and (*R*)-(+)-isomers] with a high *ee* are commercially available. **S1a** and citronellal (**S1b**) are also most frequently used for pheromone synthesis because of their beneficial structure; *i.e.*, two alkyl groups functionalized differently are attached to a methyl-branched asymmetric carbon. Generally, they are converted into a C_6 bifunctional chiral synthon, C_2-CHMe-C_3, which is incorporated into a long-chain skeleton of the insect pheromone as a key part, such as a moiety at the 7–12 positions in C_{12} monomethyl acetate (**30**),[99] and two moieties at the 4–9- and 10–15-positions in C_{15} dimethyl 2-ketone (**76**).[233] In the case of the syntheses of **29** and **94**, citronellyl benzyl ether was converted to an

allylic alcohol by means of organoselenium chemistry, and another chiral C_5 chain synthon, C_2-CHMe-C_2, was prepared.[90,284]

Several pheromone syntheses, mainly conducted in the 1980s, started from isopulegol (**S2**) or pulegone, which were converted to the C_6 synthon *via* citronellic acid (**S1c**). In contrast, the (5*S*,9*S*)-isomer of 5,9-dimethyl hydrocarbon (**2**) was synthesized by inserting the whole molecule of **S2**.[19] Two diastereomers of a diol, which were formed in a 7:1 ratio through stereoselective hydroboration of (-)-**S2**, were readily separated by chromatography and the main isomer was changed to a dimethyl C_8-chain compound by several steps, including oxidation of a secondary hydroxyl group and Baeyer-Villiger oxidation of the resulting ketone. Furthermore, C_9 4-methyl alcohol (**28**) was synthesized utilizing dihydromyrcene (**S3**),[85] which was derivatized to a bromide with a structure similar to that of **S1**. (*S*)-**S3** contributed to building a moiety at the 1–6-positions of (*R*)-**28**. As another natural chiral source, aromadendrene (**S4**) was used for the monomethyl hydrocarbon (**11**) and 2-ketone (**74**).[55] A chiral methyl-branched C_{10}-chain intermediate was prepared from (+)-**S4** in nine steps that included Baeyer-Villiger oxidation and Grob fragmentation as the key reactions.

Resolution of 3-methylglutaric acid monomethyl ester (**S5**) with cinchonidine provides enantiomerically pure (*R*)-**S5**. This C_5 chiral synthon with a structure of C_2-CHMe-C_2 was utilized for monomethyl pheromones (**47** and **74**).[147,228] Roche ester (**S6**) is another useful bifunctional chiral synthon, considered to be the most compact building block, C_1-CHMe-C_1, with two different functional groups. Both enantiomers with a high *ee* [(*S*)-(+)- and (*R*)-(-)-isomers] are commercially available and have been widely applied for many pheromone syntheses from a simple hydrocarbon (**17**)[67] to a novel β-lactone (vittatalactone, **91**).[272,273] Four methyl-branched carbons in **91** are stereogenic centres and the enantioselective synthesis was started from **S6**. The enantiomeric purity of **S6** made the total synthesis successful (see Fig 4, Route 5) because unexpected diastereomers produced by subsequent stereoselective reactions could be removed at each step. 3-Bromo-2-methylpropanol (**S7**) is a similar chiral synthon that is utilized for syntheses of trimethyl aldehyde (stylopsal, **34**)[108] and supellapyrone (**98**).[292] In the case of pheromones with a methyl branch at the 3- or ω3-position, such as C_{15} 3,13-dimethyl ester (**97**)[287,288] and C_{10} 4,8-dimethyl aldehyde (**29**),[96] C_4 chiral synthons with an ethyl group (**S8a**–**S8c**) are useful for the enantioselective syntheses. (*R*)-**S8a** was prepared from D-isoleucine and used as a chiral source for the synthesis of the C_{10} 8-methyl pheromone (**47**).[146] While optically active methyl-4-butanolide (**S9**) is not commercially available, it is an interesting building block with a structure of C_2CHMe-C_1. After DIBAL-H reduction of (*R*)-**S9**, the produced lactol was treated with an ylide to yield a C_8 chiral 2-methyl alcohol, which was used as a moiety for the 8–15-positions in the C_{15} 5,9-dimethyl pheromone (**2**).[20] (*R*)-**S9** was also converted into a C_{12} chiral 2-methyl alcohol by one-pot alkylation followed by in site silylation and modified Arimoto-Clemmensen reduction with excess amounts of trimethylsilyl chloride and Zn dust, and the alcohol was used for the synthesis of the monomethyl hydrocarbon (**11**).[56]

Malic acid (**S10**), which has no methyl groups but a secondary hydroxyl group, was concisely employed for synthesis of the C_{15} 3,7-dimethyl 2-acetoxy pheromone (**56**) with three stereogenic centres.[176,178] Tosylation and $LiAlH_4$ reduction of the dimethyl ester of (*S*)-**S10** produced a C_4 diol with an inverted configuration, and its secondary tosylate was coupled with a Grignard reagent to make a C_{11} monomethyl moiety with an *S* configuration associated stereoselective inversion again. Another C_4 moiety with a 2*S*,3*S* configuration was also made from (*S*)-**S10** by stereoselective methylation with LiHMDS as a base and $LiAlH_4$ reduction as a key reaction, and then linked with the C_{11} moiety to yield (2S,3S,7S)-**56**.

Some α-methyl secondary alcohols have been synthesized from 2,3-epoxyalkan-1-ol (**S11**). The (2*S*,3*R*)-isomer of C_5 epoxy synthon (**S11a**, R = Me) prepared by Sharpless asymmetric epoxidation of (*Z*)-2-pentan-1-ol using (+)-DET was methylated with $AlMe_3$ to yield (2*R*,3*S*)-3-methyl-1,2-diol, which was converted into a (3*S*,4*S*)-isomer of the 4-hydroxy-3-methyl pheromone (**44**).[135] The methylating reagent selectively attacked a carbon at the 3-position behind the epoxy ring. By the same route, other stereoisomers were synthesized by employing (-)-DET and/or (*E*)-2-pentan-1-ol. Furthermore, a 4-hydroxy-5-methyl pheromone (**45**) was prepared from a C_6 epoxy synthon (**S11b**, R = Et) derived from (*Z*)-2-hexan-1-ol.[135] Sitophilate (**82**) with a 3-hydroxy-2-methyl structure was also synthesized from **S11a**.[246] The chiral source was converted into a carboxylate, and methylation with Me_2CuLi proceeded stereoselectively at the 2-position. **44** was synthesized from another chiral epoxy synthon, the (2*R*,3*S*)-isomer of (3-hydroxymethyloxiranyl)methyl acetate (**S12**), which was prepared from *meso*-diacetate by asymmetric hydrolysis catalyzed with porcine pancreatic lipase (PPL).[136] After transformation of the protective group, the chiral epoxy compound was treated with Me_2CuLi to yield 2-methyl-1,3-diol with the 2*S*,3*R* configuration as a major product, which was converted into (3*S*,4*S*)-**44**. The (4*S*,5*S*)-isomer of 5-hydroxy-4-methyl pheromone (**46**) was also synthesized from the same 1,3-diol.[142]

Both enantiomers with a high *ee* [(*S*)-(-)- and (*R*)-(+)-isomers] of propylene oxide (**S13**) are also commercially available and recently utilized as a chiral source of some branched pheromones. The coupling reaction between **S13** and a Grignard reagent formed a chiral 2-hydroxy compound, and the tosylate was converted into two kinds of methyl-branched building blocks with an inversed configuration by S_N2 reaction with appropriate alkylating reagents, such as the enolate of dimethyl malonate and the anion of methyl phenyl sulfone.[32] The product of the former reaction supplied a chiral block that branched at the 3-position and after decarboxylation; another block that branched at the 2-position was the product of the latter. Pheromones (**5**, **10**, and **75**) that possess two stereogenic centres at a distance of three carbons were formed by the coupling of these two blocks (see Table 9, R-8).[32,53,230]

Allylstanate, which was prepared in amount of grams from cyclopronanol, was coupled with (benzyloxy)acetaldehyde in the presence of (*S*)-BINOL/Ti(O-iPr)$_4$ to yield an α,β-unsaturated lactone. Diastereoselective reduction of the C-C double bond and deprotection of the hydroxyl group led to a chiral *cis*-β-methyl-δ-lactone (**S14**), which was utilized as a building block for the synthesis of faranal (**36**),[113] and some other pheromone components (**10**, **30**, **40**, and **110**).[54,103,322]

<Table 7>

4.2 Application of stereoselective reactions

To data, various stereoselective reactions have been developed to create chiral compounds without a living specimen, and many chiral methyl-branched pheromones have been synthesized by applying the reactions shown in Table 8. These syntheses are classified in the following five groups based on the types of reactions used for a key step: 1) C-C coupling of a chiral intermediate, 2) reaction of an epoxy compound, 3) chelation-controlled reaction, 4) reaction with a chiral catalyst, and 5) chemoenzymatic reaction.

1) Synthesis via C-C coupling of a chiral intermediate: In the synthesis of (2*S*,3*S*,7*S*)-**56**, a methyl branch at the 7-position in a C_{15} chain was constructed by alkylation of a chiral 2-ethyloxazoline (R-1-1),[174] which was prepared by condensing (1*S*,2*S*)-1-phenyl-2-amino-1,3-propanediol and an imino ether. Acidic hydrolysis and $LiAlH_4$ reduction of 2-(1'-methylnonyl)oxazoline produced (*S*)-2-methyldecan-1-ol, which was used as a moiety at the 5–15-positions in **56**. For the synthesis of (3*R*,4*S*)-**42**, (*R*)-2,3-cyclohexylideneglyceraldehyde, which was prepared from D-mannitol, was utilized (R-1-2a).[129] Crotylation of the aldehyde dominantly produced a *threo*-alcohol that included a tertiary carbon with an *S* configuration, which was benzylated and, subsequently, deketalized to produce 3-benzyloxy-4-methyl-5-hexene-1,2-diol, a key intermediate of the pheromone. (*S*)-**70** with a methyl branch at the 3-position in a C_8 chain was synthesized from glyceraldehyde acetonide, which also prepared from D-mannitol (R-1-2b).[213] A keto intermediate was treated with a combination of MeLi and Lewis acid ($SnCl_4$), and the desired *anti*-isomer of a tertiary alcohol was obtained as a single product. (*S*)-1-Amino-2-(methoxymethyl)pyrrolidine (SAMP) and its enantiomer (RAMP), which are prepared from L- and D-proline, respectively, are useful chiral auxiliaries for the synthesis of chiral pheromones, such as 7,11-dimethyl hydrocarbon (**8**) (R-1-3).[42] Treatment of SAMP with *n*-propanal formed the hydrazone, which was deprotonated with Li tetramethylpiperidide (LiTMP) and stereoselectively coupled with *n*-hexyliodide to produce α-alkylated SAMP-hydrazone with an *S,S* configuration. Cleavage of SAMP with O_3 or 4M HCl yielded (*S*)-2-methyloctanal, a half moiety of (7*S*,11*S*)- and (7*S*,11*R*)-**8**. This Enders method has been applied for the syntheses of other insect pheromones, such as **43** and **71**.[133,195]

Some chiral oxazolidinyl compounds and their thio-derivatives are used for many enantioselective syntheses as Evans' chiral auxiliaries because of the simplicity of their preparation from amino acids or their derivatives, the economic merit of recycling them after hydrolysis, and the effectiveness of chiral induction for a high *ee*.[336] (*R*)-**20** with a methyl branch at the 7-position in a long chain was synthesized utilizing (*R*)-4-isopropyloxazolidin-2-one prepared from D-valinol (R-1-4a).[72] Coupling of deprotonated oxazolidinone with octanoyl chloride produced the imide, which was methylated with MeI at the α-position after another deprotonation with NaHMDS. Reduction of the product with $LiBH_4$ afforded (*R*)-2-methyloctan-1-ol, a moiety at the 1–8-positions in **20**, along with recovery of the oxazolidinyl auxiliary. (*S*)-**20** was synthesized by the same route that included (*S*)-isopropyloxazolidinone prepared from L-valinol. 4-Benzyloxazolidin-2-one prepared from phenylalanine was utilized in some other cases, such as the synthesis of chiral (*S*)-2-methylhexan-1-ol, a key intermediate of (*S*)-**9** (R-1-4b).[49] Since L-amino acid was used, the chiral alcohol with a desired configuration was obtained. In the synthesis of (5*R*,9*R*)-**5**, (*R*)-2-methylhexan-1-ol was prepared using 4-benzyloxazolidine-2-thione prepared from D-phenylalanine (R-1-4c).[31] While the coupling reagent was butylbromide, with a longer chain than MeI, configuration at the newly induced stereogenic centre was controlled by configuration at the hetero ring that was fixed by the parent amino acid. The methyl group at the ω4-position of (*R*)-**74** was generated by an asymmetric Michael addition using (*S*)-4-benzylthiazolidinethione as a chiral auxiliary (R-1-4d).[227] The reaction of an organo-Cu reagent with the *N*-crotonyl derivative produced a compound with the *R* configuration at the methyl-branched ω4-position. (*R*)-**28** and (*S*)-**69** were synthesized by the similar reaction.[86,209] Furthermore, α-methyl secondary alcohols (**44**–**46**) were synthesized by asymmetric aldol condensation with an imide of another chiral oxazolidinone (R-1-4e).[137] The boron enolate derivative from the imide was treated with *n*-pentanal or *n*-butanal to afford *syn* adducts. Cleavage of the auxiliary by $LiBH_4$ produced C_7 and C_6 1,3-diols with a methyl group at the same 2-position, which were converted to pheromones with an *S,S* configuration. Evans' chiral auxiliaries were also utilized in the syntheses of tri- and pentamethyl pheromones (**49**, **90**, and **91**) to induce asymmetry at one of the methyl-branched stereogenic centers.[158,266,274]

2) Synthesis via a reaction of an epoxy compound: Several interesting pheromone syntheses *via* chiral epoxy intermediates have been published. The synthesis of (S)-**70** was accomplished from geraniol, which was converted to (2*R*,3*R*)-epoxy alcohol by Sharpless asymmetric epoxidation with D-(-)-diethyl tartrate (R-2-1a).[215] After acetylation, the chiral epoxide was treated with aqueous solutions of perchloric acid and K_2CO_3 to yield a triol with an *S* configuration at a tertiary carbon. Another synthesis used 2-fluoronerol, which was prepared from 6-methyl-5-hepten-2-one, and a (2*R*,3*R*)-2-fluoroepoxy alcohol was produced by the reaction with L-(+)-diethyl tartrate (R-2-1b).[214] Epoxy ring opening of the acetate derivative under an acidic condition promoted defluorination and formation of ketone functionality. Starting from a chiral 2,3-epoxy alcohol, (*S*)-**7** was synthesized by applying a different reaction, intramolecular hydride transfer, from a secondary γ-benzyloxy group (R-2-2).[37] A chiral 1,3-diol derived from the epoxide was converted to a diastereomeric mixture of an acetylene alcohol with a methyl group at the 7-position. The intramolecular reaction produced a chiral synthetic intermediate of (*S*)-7. In the same procedure, (7*S*,11*S*)-**8** and the *meso*-form were synthesized.[37]

In addition to the asymmetric epoxidation, Jacobsen's hydrolytic kinetic resolution (HKR)[337] was widely applied as a key step in the syntheses of the branched pheromones, such as a C_{17} 5,9-dimethyl hydrocarbon (**5**) (R-2-3a).[31] Reaction of the (±)-benzyl glycidyl ether with (*R,R*)-salenCo^{III}OAc produced the (*S*)-isomer. The chiral terminal epoxide was alkylated, and a tosylate of the resulting secondary alcohol was treated with Me_2CuLi to yield a benzyl ether of (*R*)-2-methylhexan-1-ol, a building block of the (5*R*,9*R*)-isomer. In the case of (7*R*,11*R*)-**8** bearing the same C_6 chain at both stereogenic centres, the diastereomeric mixture of a C_7 diepoxy compound was subjected to HKR with the (*R,R*)-catalyst, and the

(7*R*,11*R*)-isomer was obtained as a synthetic intermediate (R-2-3b).[43] Mono- and dimethyl chiral pheromones (**30**, **47**, **74**, and **76**) were similarly synthesized *via* chiral epoxides prepared by HKR.[102,225] Furthermore, in the synthesis of (3*S*,4*R*)-faranal (**36**), the 3,4-dimethyl structure was constructed by asymmetric cleavage of an epoxy ring with a chiral lithium amide (R-2-4).[112] A *meso*-epoxide of 4,5-dimethylcyclohexene was converted into (1*S*,4*S*,5*S*)-4,5-dimethylcyclohex-2-enol, which was converted to dimethyl triol by ozonolysis and the subsequent reductive workup. The C_6 triol with a 1,2-dihydro structure was used as a C_5 moiety at the 1–5-positions of **36**.

3) Synthesis via a chelation-controlled reaction: The (4*R*,8*R*)-isomer of 4,8-dimethyl aldehyde (**29**) was synthesized utilizing a chelation-controlled radical reaction of ethyl (*R*)-5-iodo-3-methylpentanoate (R'I) with (*S*)-α-methylene-γ-benzyloxycarboxylic acid ester, which was prepared by the Reformatsky reaction of (*R*)-acetonide of glyceraldehyde with ethyl 2-(bromomethyl)propenoate (R-3).[94] The ethoxycarbonyl group in the resulting *syn*-adduct was converted into a branched-methyl group at the 4-position of **29**. The *meso*-form of 7,11-dimethyl hydrocarbon (**8**) was selectively synthesized by applying the same reaction as a key step.[44] The symmetric branched chain skeleton was constructed from diethyl 4-benzyloxy-2,6-dimethyleneheptanedioate.

4) Synthesis via a reaction with a chiral catalyst: Some methyl-branched pheromones were synthesized by reactions with a chiral catalyst. Enantioselective reduction of α,β-unsaturated ccarboxylate was accomplished by using $NaBH_4$ and a cobalt complex with a chiral ligand, (1*S*,9*S*)-1,9-bis[(*t*-butyldimethylsiloxy)methyl]-5-cyanosemicorrin. The (*R*)-(**93**) was synthesized from farnesoate by this reduction (R-4-1).[281] The methyl ketone (*S*)-**66** was synthesized by catalytic hydrogenation over an Ru catalyst, (*S*)-H8-BINAP-$Ru(OAc)_2$, as a key step (R-4-2a).[200] This catalyst reduced more enantioselectively the prochiral acrylic acid to (*S*)-2-methylpentanoic acid than that with (*S*)-BINAP did. The produced chiral acid was converted into the pheromone in three steps, including C_2-chain elongation with vinylmagnesium bromide. As a total synthesis of hexamethyl hydrocarbon (**14**) was achieved by connecting two building blocks that included a tetramethyl or dimethyl moiety (R-4-2b),[63] configuration of one of the methyl groups in each block was fixed by catalytic hydrogenation over a chiral Ir Crabtree catalyst derived from L-asparatic acid. Methyl branches with *anti* and *syn* configurations were formed from the (*E*)-allylic ester and (*Z*)-allylic alcohol, respectively. The same (4*S*,6*R*,8*R*,10*S*,16*R*,18*S*)-isomer was synthesized by the Zr-catalyzed asymmetric carboalumination of alkenes (ZACA reaction) (R-4-3).[64] Five of the six asymmetric carbon centres were generated stereoselectively by iterative repetition of the reaction five times using the (+)- or (-)-ZACA catalyst (see Fig. 4, Route 7).

The Cu-catalyzed asymmetric Michael addition of organometallic reagents is also an important method for creating chiral molecules, and several types of the ligand have been developed to improve the stereospecificity of the reaction. Reaction of Me_2Zn with cycloocta-2,7-dione twice produced a dimethyl intermediate for the synthesis of (5*R*,9*R*)-**5** (R-4-4a).[30] The ligand (L_1) of the first addition was composed of (*S,S*)-bis(1-phenylethyl)amine and (*R*)-2,2'-binaphthol, and that of the second was the enantiomer. For the synthesis of (2*R*,4*R,*6*R*,8*R*)-lardolure (**49**), a Josiphos ligand was used for the reaction of MeMgBr with an α,β-unsaturated thioester, and a branched methyl group was directly introduced at the β-position (R-4-4b).[157] The resulting thioester was used as a terminal part of the tetramethyl pheromone, and three other methyl branches were also introduced by applying the same reaction. Recently, this reaction was used for the synthesis of (6*S*,8*S*,10*S*)-**35**.[110] Commercially available Tol-BINAP [2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl] is another useful ligand that was employed for synthesizing the (3*R*,5*S*)-3,5-dimethyl pheromone (**92**) (R-4-4c).[278] The first methylation of (*E*)-2-decenoate used the (*S*)-ligand, and the second methylation of (*E*)-5-methyl-1-dodecenoate, which was obtained by a two-step reaction, used the (*R*)-ligand. This reaction was also employed for enantioselective introduction of a methyl branch at the 3-position of 3,5,9-trimethyl aldehyde (**34**),[109] and three methyl branches of 3,7,9-trimethyl propionate (**53**).[166]

The Roskamp reaction, a Lewis acid catalysed reaction of alkyl diazoesters with aldehydes, was developed to asymmetric transformation using a chiral oxazaborolidinium ion. The asymmetric reaction between propanal and 2-azopropionate produced (*S*)-α-methyl-β-ketoester, which was reduced with $Zn(BH_4)_2$ to afford (2*S*,3*R*)-**82** (R-4-5).[251]

5) Synthesis via chemoenzymatic reaction: The synthetic route for (4*R*,8*R*)-**29** was designed by applying a lipase-catalyzed resolution at two steps (R-5-1a).[93] In the reaction of racemic citronellol (**S1a**) with vinyl acetate and porcine pancreatic lipase (PPL), the (*R*)-isomer was selectively acetylated. The unreacted (*S*)-isomer was converted into a diastereomeric mixture of tetrahydrofarnesol by a three-step reaction, and the alcohol was acetylated using another enzyme, *Candida rugosa* lipase (CRL), to yield only the (3*S*,7*R*)-isomer of the 3,7,11-trimethyl acetate. Branches at the 3- and 7-positions of the C_{12}-chain compound correspond to those at the 8- and 4-positions in the C_{10} chain of **29**. In the case of the synthesis of **55**, CRL was used for resolution of α-methyl carboxylic acid, a building block from the 6- to 14-positions of the (2S,3*R*,7*R*)- isomer (R-5-1b).[171] A mixture of the racemic acid and *n*-icosanol was treated with CRL, and the unreacted (*R*)-isomer could be recovered. Kinetic resolutions with lipases have also been carried out to prepare key chiral intermediates for other enantioselective pheromone syntheses, *i.e.*, β-methyl primary alcohol with CRL in the synthesis of **9**,[48] β-methyl-α,β-epoxy alcohol with lipase PS in the synthesis of **70**,[212] and α-methyl secondary alcohol with lipase AK in the synthesis of **43**.[133] In the cases of **54**, **60**, and **94** with a *syn*-1,5-dimethyl structure, the *meso*-form of 2,6-dimethylheptane-1,7-diol was treated with lipase PS to make a single stereoisomer of the monoacetate (R-5-1c).[169,182] The acetylation occurred at the hydroxyl group next to the asymmetric carbon with the *R* configuration. Similar selective acetylation of the *meso*-form of 2,4-dimethylpentane-1,5-diol with lipase was carried out in the syntheses of **85** and **98** with a *syn*-1,3-dimethyl structure.[259,293]

Baker's yeast reduction of the α,β,-unsaturated aldehyde derived from furfural led to the preparation of a chiral α-methyl primary alcohol (R-5-2a).[92] This alcohol was utilized for the synthesis of (4*R*,8*R*)-**29** as a bifunctional synthon with the C_2-CHMe-C_1 structure because the 2-furyl group could be converted to a carbinol carbon by ozonolysis and reductive work-up. In the synthesis of (*R*)-10-methyl

acetate (**30**), (*R*)-2-methylbutan-1-ol (**S8b**) was prepared with this reduction as a key step (R-5-2b).[101] 2-Methyl-3-oxobutyrate was prepared from ethyl acetoacetate, and the keto carbonyl group was stereoselectively reduced using baker's yeast to yield a 3-hydroxy derivative with the *R* configuration. By removing the hydroxyl group at the 3-position, (*R*)-**S8b** was obtained. In the synthesis of the 3,7-dimethyl pheromone (**51**), 2-methyloctan-1-ol with the same *R* configuration was prepared by baker's yeast reduction of an acetal of acrylaldehyde (R-5-2c).[164]

Stereoselective reduction was also achieved with isolated NADPH-dependent ketoreductases (KRED). After methylation of 3,5-heptadedione, (4*S*,5*R*)- and (4*S*,5*R*)-isomers of sitophinone (**67**) was synthesized by the reduction utilizing KRED-A1C and KRED-119, respectively, in the presence of a glucose/glucose hydrogenase system for NADPH recycling (R-5-3).[205] For syntheses of sitophilate (**82**), stegobinone (**103**), and stegobiol (**104**), the 2*S*,3*R* configuration was formed by the reduction of methyl 2-methyl-3-oxopentanoate with KRED-A1B and B1E.[250,306] On the other hand, its enantioselective fungal reduction with a strain of *Aureobasidium pullulans* formed the (2*S*,3*S*)-isomer.[252] (2*S*,3*R*)-**82** was obtained by a Mitsunobu inversion at the 3-positiona and by transesterification with *Candida antarctica* B lipase.

Furthermore, *Aspergillus* amino acylase was used for the kinetic resolution of an amino acid with a methyl branch at the α-position in the synthesis of invictolide (**90**) (R-5-4).[268] A diastereomeric mixture of the amino acid prepared from racemic 2-methylpentanal was treated with chloroacetyl chloride. The produced amide was hydrolyzed with the enzyme, and an amino acid with a 2*S*,3*S* configuration was obtained in quantitative yield. After changing the functionalities, the resulting diol was employed as a chain moiety of **90**.

<Table 8>

4.3 Linkage of two chiral blocks for dimethyl pheromones

Many dimethyl pheromones have been synthesized by linking two chiral building blocks (Table 9). 10,14-Dimethyl hydrocarbon (**10**) was prepared using Grignard coupling reaction of a β-methyl aldehyde with a Mg derivative of 1-bromo-2-methylhexane (R-6a).[28] After mesylation of the resulting secondary alcohol, the mesyl group was removed by reduction with $LiBEt_3H$. The coupling of a Grignard reagent with a tosylate in the presence of Li_2CuCl_4 (Schlosser's Cu-catalyzed Grignard coupling reaction) directly produced a hydrocarbon, such as synthetic intermediates of 3,11-dimethyl 2-ketone (**80**) (R-6b)[241] and 4,8-dimethyl aldehyde (**29**).[95] The same coupling reaction was used to construct the 3,7,11-trimethyl skeleton of a propionate (**54**).[169] Synthesis of all 16 stereoisomers of the propionate was accomplished *via* Julia olefinations by applying a fluorous mixture-synthesis approach.[170] Wittig reaction of a chiral ylide derived from **S7** and a β-methyl aldehyde produced a chiral 2,6-dimethyl intermediate for the synthesis of 3,5,9-trimethyl aldehyde (**34**) (R-7).[108] Coupling of an alkyl phenyl sulfone and an alkyl halide has been widely used for the syntheses of several pheromones, such as 5,9-dimethyl hydrocarbon (**5**) (R-8),[27] 3,13-, 4,8-, 6,12-, and 10,14-dimethyl, and 2,6,10- and 6,10,13-trimethyl pheromones (**97**,[289] **29**,[89] **76**,[233,234] **10**,[53] **94**,[284] and **75**[230]). Reductive removal of the sulfonyl group was achieved with Na amalgam in EtOH or Li in liquid $EtNH_2$; also, another procedure utilizing Mg activated with a catalytic amount of MeMgBr has recently been reported.[32] The sulfonyl compound was prepared from the corresponding tosylate by treatment with PhSNa and successive oxidation of the produced phenylthio derivative by a peracid in the synthesis of **5**; it was also prepared directly by S_N2 reaction with the anion of methyl phenyl sulfone associating chain elongation by one carbon (R-11-1).[52]

For the synthesis of **29**, Kolbe electrolysis has been employed as a key step (R-9).[90] A 5:1 mixture of two acids was electrolyzed at 28 V with Pt electrodes in the presence of NaOMe to yield a dimethyl product as a main component. By-products generated by self-coupling were removed using chromatography. Recently, a 6,14-dimethyl pheromone (**79**) was synthesized by employing olefin cross metathesis reaction with a Grubbs' 1st generation catalyst, $(Cy_3P)_2Ru(=CHPh)Cl_2$ (R-10).[237] A 6:1 mixture of two olefins was heated in an Ar atmosphere. The progress of the reaction was monitored by the evolution of ethylene, which enlarged the Ar balloon. After removing the by-products generated by self-coupling, the dimethyl olefin was reduced by hydrogenation over Pd-C. This coupling reaction was applied not only for the synthesis of **97**,[287,288] a pheromone with two methyl groups located separately, but also for a 3,7,9-trimethyl pheromone (**53**),[166] and furthermore, for monomethyl pheromones (**74**, **77**, and **78**) in order to elongate the carbon chains of chiral branched building blocks.[228,237]

In addition to the direct linkages of the two chiral blocks, some syntheses mediated with an achiral linchpin have been published. The linchpin is a compound with an ability to accept double alkylation or a compact bifunctional compound. Using methyl phenyl sulfone as a linchpin, a new synthetic route for **10** was designed (R-11-1),[52] and **5** was synthesized with the same synthetic strategy,[29] which was different from R-8. The alkyl phenyl sulfone in R-8 was prepared by a reaction of the corresponding iodo compound and $NaSO_3Ph$. As the linchpin results in the insertion of one carbon between two chiral building blocks, a synthetic intermediate with a 1,5-dimethyl structure in the C_7-chain was constructed with two different iodides bearing the same 2-methyl structure of the C_3-chain derived from Roche ester (**S6**). Double alkylations were carried out step by step using *n*-BuLi as a base. Furthermore, **10** was also synthesized using tosylmethyl isocyanide (TosMIC) as another linchpin (R-11-2).[31] The first alkylation proceeded in a 40% aqueous solution of NaOH and CH_2Cl_2 in the presence of a phase transfer catalyst, and NaH was used as a base for the second alkylation. After the coupling, the TosMIC moiety was removed by treatment with Li in liquid NH_3.

1,3-Dithiane and its derivative were used for the syntheses of the 7,11-dimethyl hydrocarbon (**8**) and the monomethyl secondary propionate (**47**), respectively (R-11-3a and 3b).[42,145] While *t*-BuLi was used as a base for the both alkylations in the synthesis of **8** and desulfonization was carried out by hydrogenation over Raney-Ni, *n*-BuLi was used and desulfonization was conducted by heating over Raney-Ni without H_2 gas in the case of **47**. On the other hand, the 5,11-dimethyl hydrocarbon (**6**) was synthesized using methyl acetoacetate as a linchpin with a C_3 chain (R-11-4).[35] The first

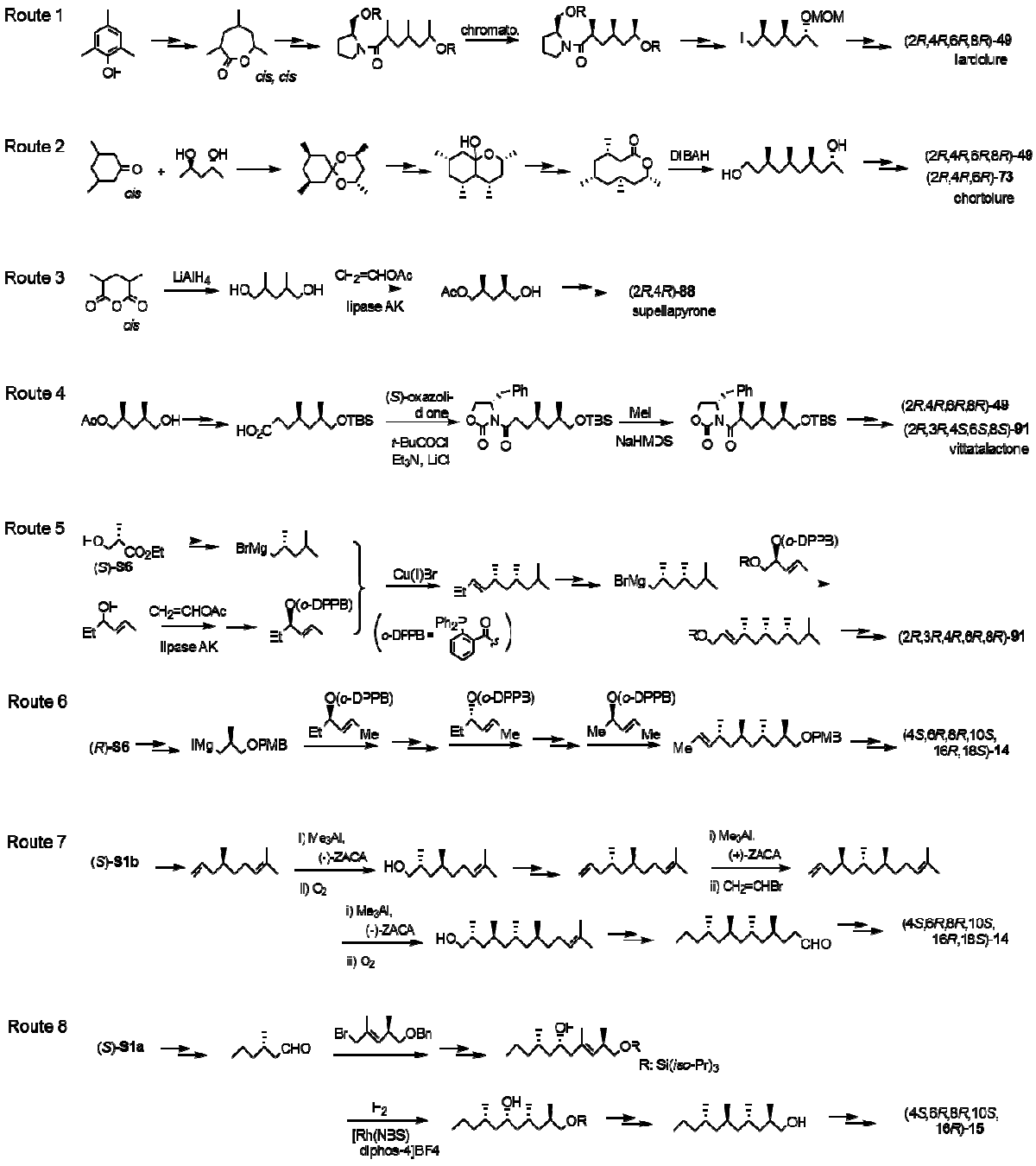
alkylation, which used NaH and *n*-BuLi as bases to make a dianion, proceeded at the 4-position of the linchpin, and the second alkylation with K_2CO_3 as a base was carried out at the 2-position. The coupled product was hydrolyzed and decarboxylated under a basic condition, and the remaining keto group was converted into a methylene unit by three steps: $NaBH_4$ reduction, mesylation, and $LiBEt_3H$ reduction.

<Table 9>

4.4 Syntheses of 1,3-dimethyl and more branched pheromones

Syntheses of pheromones with a 1,3-dimethyl ("skipped" dimethyl) motif, have been achieved with a strategy quite different from those for 1,5-dimethyl pheromones (Fig. 4). Particularly, 1,3,5-trimethyl and the more branched pheromones with several stereogenic centres are interesting targets for many synthetic chemists. Optically active lardolure (**49**), with the 1,3,5-trimethyl structure, was first synthesized starting from *cis,cis*-trimethyl lactone, which was prepared from 2,4,6-trimethylphenol (Route 1).[151] Ring opening of the lactone with (*S*)-prolinol produced a diastereomeric mixture of the diol. Their bis-3,5-dinitrobenzoates were separable, and their

Fig. 4. Synthetic routes for chiral methyl-branched compounds with a skipped motif.



absolute configurations were determined by derivatization to a known compound. The more polar isomer with an *R,R,R* configuration was converted into the MOM ether of a secondary alcohol, which corresponded to a C_7 2,4-dimethyl moiety of **49** and was coupled with methyl (*S*)-3-hydroxypentanoate to construct the whole carbon skeleton of the (2*R*,4*R*,6*R*,8*R*)-isomer. Another synthetic route to the same isomer was began at the acetal of *cis*-3,5-dimethylcyclohexanone with (2*R*,4*R*)-pentane-2,4-diol (Route 2).[154,156] The hemiacetal, which was derived from the acetal by treatment with *i*-Bu_3Al and triflic anhydride, was converted into the C_{10} 2,4,6-trimethyl diol *via* a lactone by ring opening with iodobenzene diacetate, deiodination with *n*-Bu_3SnH, and reduction with DIBAH. In addition to (2*R*,4*R*,6*R*,8*R*)-**49**, the trimethyl diol was used as a key intermediate for the synthesis of (4*R*,6*R*,8*R*)-chortolure (**73**),[221] another aggregation pheromone of mites.

On the other hand, a chain moiety with the 1,3-dimethyl structure of supellapyrone (**98**) was synthesized by applying a chemoenzymatic reaction (Route 3)[293] similar to the 1,5-dimethyl moiety of **60** (R-5-1c).[182] Reduction of *cis*-2,4-dimethylglutaric anhydride furnished achiral 2,4-dimethylpentane-1,5-diol, which was desymmetrized by treatment with lipase AK and vinyl acetate. Since the chiral monoacete is a useful synthon for synthesizing skipped polymethyl-branched compounds with a *syn* configuration, it has been employed for the total synthesis of **49** and vittatalactone (**91**) (Route 4).[158,274] After chain elongation by means of Wittig reaction, the resulting carboxylic acid was coupled with Evan's chiral oxazolinone using pivaloyl chloride in the presence of Et_3N and LiCl. Enantioselective methylation of the enolate with MeI (R-1-4b) furnished a compound with the 1,3,5-trimethyl structure, which was further modified to chain moieties of (2*R*,4*R*,6*R*,8*R*)-**49** and (2*R*,3*R*,4*S*,6*S*,8*S*)-**91**. Furthermore, **49** was synthesized by repeating the Cu-catalyzed asymmetric Michael addition to α,β-unsaturated thioester with a Josiphos ligand (R-4-4b).[157] In the case of 3,5-dimethyldodecanoic acid (**92**), two asymmetric carbons with an *anti* configuration were introduced by properly using (*S*)- and (*R*)-Tol-BINAP (R-4-4c).[278]

Enantioselective total synthesis of another stereoisomer of vittatalactone, (2*R*,3*R*,4*R*,6*R*,8*R*)-**91**, was accomplished by employing enantioselective *o*-diphenylphosphanyl benzoyl (*o*-DPPB)-directed allylic substitution (Route 5).[272,273] The (*R*)-isomer of (*E*)-3-hydroxy-4-hexene was prepared by kinetic resolution with lipase AK, and the *o*-DPPB ester was coupled with a Grignard reagent of (*R*)-1-bromo-2,3-dimethylpentane prepared from the Roche ester (**S6**). The Cu-mediated alkylation proceeded enantioselectively at the 5-position of the ester, and 5,7,9-trimethyl-3-decene with *R,R* configuration was obtained. After conversion of the olefin into a bromide, a 4,6,8,10-tetramethyl alcohol was prepared with a second *o*-DPPB-directed allylic substitution. The C_{11}-chain length and configurations at the 4-, 6-, and 8-positions are the same as those expected of (2*R*,3*R*,4*R*,6*R*,8*R*)-**91**. The same allylic substitution was also used as a key reaction for the total synthesis of the 4,6,8,10,16,18-hexamethyl hydrocarbon (**14**) (Route 6).[62] Starting from a chiral methyl-branched Grignard reagent protected as a 4-methoxybenzyl (PMB) ether, a set of two steps, its coupling reaction with the *o*-DPPB ester and the conversion of the resulting olefin to a halide, was repeated three times. By couplings conducted in the order of (*R*)-, (*S*)-, and (*R*)-*o*-DPPB esters, the tetramethyl moiety at the 1–11-positions of **14** with all *anti* configurations was constructed.

(4*S*,6*R*,8*R*,10*S*,16*R*,18*S*)-**14** was also synthesized by hydrogenation over a chiral Ir Crabtree catalyst as a key step (R-4-2b).[63] Furthermore, the same stereoisomer of **14** was synthesized by employing ZACA reaction of a terminal olefin starting from (*S*)-citronellal (Route 7).[64] In addition to the short-chain moiety with an 2,4-dimethyl structure (R-4-3), the enantioselective methylation was conducted three times for the synthesis of the long-chain moiety with a 4,6,8,10-tetramethyl structure. Methylation in the presence of O_2 and vinyl bromide produced a methylated primary alcohol and a methylated terminal olefin, respectively. All *anti* configurations were assured by the reactions catalyzed with the (-)-, (+)-, and (-)-ZACA reagents in this order. In addition to these total syntheses, a new approach for the 4,6,8,10,16-pentamethyl analogue (**15**) was recently published (Route 8).[65] Bi(0)-mediated coupling reaction of a chiral aldehyde derived from (*S*)-citronellol with (4*R*,2*E*)-1,5-benzyloxy-1-bromo-2,4-dimethylpent-2-ene yielded a 6-hydroxyl-2,4,8-trimethyl alkene with a 2,6-*anti* configuration. After changing the protecting group from the benzyl ether to the monotri-*iso*-propylsilyl ether, hydroxyl-directed hydrogenation using [Rh(NBD)diphos-4]BF_4 as the catalyst was conducted to make a new stereogenic centre with an *anti* configuration at the 4-position. The coupling of the tetramethyl moiety with a monomethyl moiety furnished (4*S*,6*R*,8*R*,10*S*,16*R*)-**15**.

5 Biosynthetic studies

It has been reported that methyl branches at terminal positions of sex pheromones are derived from amino acids with a branched structure; 2-methylheptadecane of arctiid moths from leucine *via* 3-methylbutyryl-CoA,[338] and 2-methyl-7,8-epoxyoctadecane (disparlure) of a lymantrid moth from valine *via* isobutyryl-CoA.[339] On the other hand, most of the other branches, which are attached to an asymmetric carbon and dealt with in this review, are expected to be formed by incorporation of propanoate chains (propanogenins) derived from methylmalonyl-CoA in the biosynthesis catalyzed by polyketide synthases (PKS) or fatty acid synthases (FAS). Although PKS of microorganisms and plants are known, no insect PKS involved in the biosynthesis of pheromones or allomones (defensive substances) have yet been found, and it still remains unclear whether the structures that are formed from propanogenins are PKS or FAS products.[340]

In addition to the branched cuticular hydrocarbons of insects,[12,341] some biosynthetic pathways of branched pheromones have been studied by using labelled compounds. The first study was carried out with ants that produced δ-lactones (**84** and invictolide, **90**) as a trail pheromone. GC-MS analysis of the pheromone from ants fed [3,3,3-D_3]-propionic acid showed M^+ of D_6-**84** at *m/z* 148 and M^+ of D_9-**90** at *m/z* 210, indicating incorporation of two and three propionic (C_3) units, respectively (Fig. 5A).[342] Another feeding experiment with [1-^{13}C]-fatty acids and salts, such as sodium

propionate, potassium pentanoate, and 2-methylheptanoic acid, revealed incorporation of two C_3 units into the 4-methyl primary alcohol (**28**) with an odd-numbered chain skeleton, a sex pheromone of a mealworm beetle species (Fig. 5B).[343] In the mass spectra of the C_{10} main chain, was examined with [3,3,3-D_3]-propionate.[221] After one week of feeding, GC-MS analysis of the headspace extract of a mite culture showed M^+ of D_{12}-**73** at *m/z* 210, indicating incorporation of up to four C_3 units. A biosynthetic precursor was

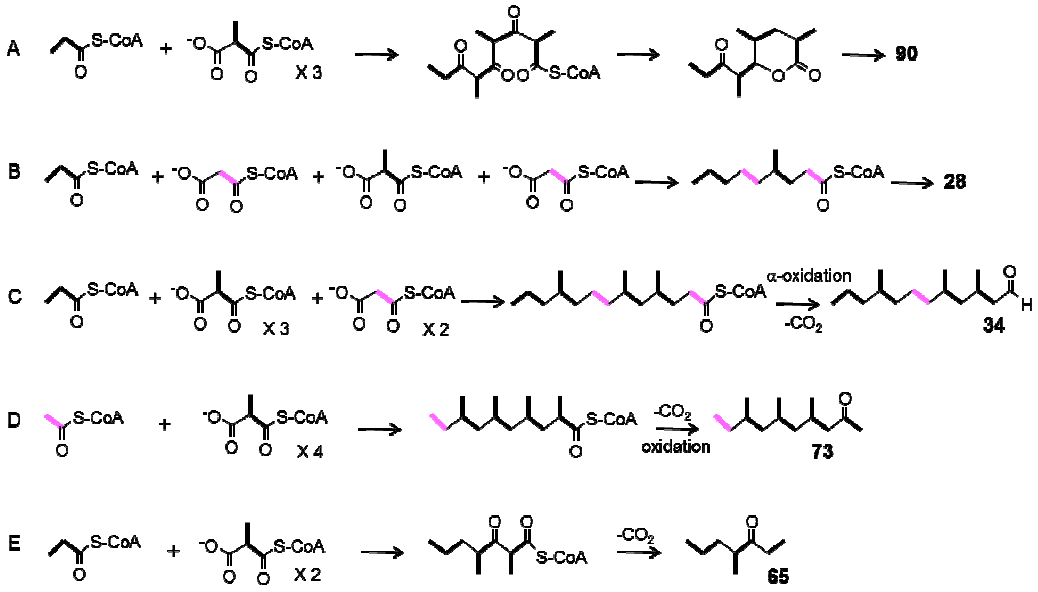


Fig. 5. Proposed biosynthetic routes to methyl-branched pheromones; (A) invictolide (90), (B) a primary alcohol (28), (C) stylopsal (34), (D) chortolure (73), and (E) a 3-ketone (65).

labelled pheromones, $[M-18]^+$ and some other fragment ions were recorded at *m/z* values higher than those of the natural pheromone by a few mass units. Biosynthesis of the pheromone of 3,5,9-trimethy aldehyde (stylopsal, **34**) with a C_{12} chain skeleton is interesting because the methyl branches of the pheromone are located at unusual odd-numbered positions. While incorporation of a labelled precursor has not been examined, it has recently been proposed that **34** is formed by α-oxidation and decarboxylation of a 4,6,10-trimethyl C_{13} acid derivative (Fig. 5C). The acid was found in substantial amounts in the fat body of the twisted-wing parasite female but not in the host bee.[109]

In the case of methyl-branched ketones, different routes for the introduction of the carbonyl group have been proposed in three types of pheromone compounds, while branched skeletons were commonly constructed by incorporation of the C_3 units derived from methylmalonyl-CoA. In addition to the 3,13-dimethyl-2-keto pheromone (**80**) with a C_{29} main chain, the cuticle of the German cockroach contains the corresponding 3,13-dimethyl hydrocarbon, whose incorporation of [1-^{13}C]-propionate was confirmed by ^{13}C NMR analysis.[344] Further experiments with [11,12-$^3H_2$]-labelled hydrocarbon and the 2-hydroxy derivative, which were topically applied to the ventral abdomen, revealed that they were precursors of **80**. The keto group in a long chain was formed by hydroxylation and oxidation at the 2-position of the major cuticular component.[345] An enzyme for the oxidation might recognize a target site of the precursor using the branch at the 3-position as a clue. Biosynthesis of the storage mite pheromone (**73**), 4,6,8-thrimethyl-2-ketone with a estimated to be 2,4,6,8,-tetramethyldodecanoic acid, which could be converted into **73** by oxidative decarboxylation (Fig. 5D). A 4,6,8-trimethyl (= 3,5,7-trimethyl) hydrocarbon corresponding to **73** might not be a precursor because of the similarity of the two terminal parts in the short chain. Although experimentally unproved, structures of three 2-keto components of a moth pheromone (**77**–**79**) with a C_{18} main chain also deny the possibility of their biosynthesis *via* branched hydrocarbons. If 6-methyl (= 13-methyl), 14-methyl (= 5-methyl), and 6,14-dimethyl (= 5,13-dimethyl) hydrocarbons are precursors, the pheromone might become a mixture of six 2-ketones.

On the other hand, pheromone components (**64**–**69, 71**, and **72**) with C_6–C_9 are 3-ketones. Feeding experiments with [Me]-D_3- and [Me]-D_3-[1,3]-$^{13}C_2$-methylmalonic acids proposed an interesting biosynthetic route to the ant pheromone (**65**).[346] GC-MS analysis of mandibular gland extracts of ants showed M^+ of D_9-**65** at *m/z* 137 and D_9,$^{13}C_2$-**65** at *m/z* 139. Furthermore, comparison of fragment ions in three mass spectra of the natural and two labelled pheromones clarified the positions of the incorporated ^{13}C, indicating construction with three C_3 units and decarboxylation at the final step of biosynthesis (Fig. 5E). It is noteworthy that the origin of the carbonyl carbon is different from that of the carbons at the 1- and 2-positions, which is another propionic unit rather than an acetic unit. In addition to the related 3-ketones, 3-hydroxy pheromones (**42** and **43**) are also expected to be produced by a similar route. Since branched pheromones in the group of secondary alcohols and their derivatives possess functionalities at various positions, how they are formed is interesting. No biosynthetic routes, however, have been reported.

6 Conclusion

Many insects produce pheromones for species-specific communication. The specificity is based on structural diversities of the chemical signals, which are the result of modifying the carbon skeletons and the kind of functionalities. Particularly, methyl branches derived from C_3 units play an important role because numerous modifications could be created by differences in the number, positions, and configurations of the branches. While the biosynthetic routes restrict the branch positions, combining C_3 and C_2 units would extend the possibilities of the positions. As listed in Tables 1–6, more than one hundred methyl-branched insect pheromones, which make one interest group of natural products, have been identified. Regarding the diversities of insect species, however, our knowledge is still very limited; it is difficult to correlate all of the chemical structures with taxonomy of the pheromone producers and also with function of the pheromones in communication systems. While several methyl-branched pheromones had already been identified in the 1970s, approximately 40 compounds have been found in this century, indicating that the structural determination of the new pheromones and further research on their synthesis and biosynthesis are topics for current and future studies. It is expected that pheromone studies will be increasingly developed by close collaboration between organic chemists and entomologists.

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Figure Legends

Fig. 1. Characteristic fragment ions detected by EI-MS analysis of mono-, di-, and trimethyl pheromones

Fig. 2. Characteristic fragment ions detected by EI-MS analysis and ^{13}C NMR assignment of tetra-, penta-, and hexamethyl insect compounds; (A) (2*E*,4*E*)-2,6,8,12-tetramethyltridecadiene and (2*E*,4*E*)-4,6,8,10-tetramethyltridecadiene (**1**), (B) vittatalactone (**91**), and (C) 4,6,8,10,16,18-hexamethyldocosane (**14**).

Fig. 3. Chemical structures of fluorescent reagents, (1*R*,2*R*)-2-(2,3-anthracenedicarboximido)cyclohexanecarboxylic acid (R = CO_2H) and (1*R*,2*R*)-2-(2,3-anthracenedicarboximido)cyclohexanol (R = OH).

Fig. 4. Synthetic routes for chiral methyl-branched compounds with a skipped motif.

Fig. 5. Proposed biosynthetic routes to methyl-branched pheromones; (A) invictolide (**90**), (B) a primary alcohol (**28**), (C) stylopsal (**34**), (D) chortolure (**73**), and (E) a 3-ketone (**65**).

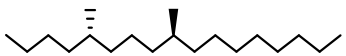
Graphic abstract

A large number of chiral methyl-branched pheromones have been identified reflecting the diversity of insect species. This deals with mainly non-terpene compounds, highlighting studies of the identification, stereoselective synthesis, and biosynthesis carried out in this century.

Table 1. Hydrocarbons: Pheromones and related compounds identified from insects. [a]

Pheromone				Insect		Reference [e]	
	Structure	Configuration [b]		Group [c]	Species [d]	Identification	Stereoselective synthesis
C_{13}	Δ2,Me4, Δ4,Me6,Me8,Me10-13:H (**1**) + primary alcohol (**35**)	2*E*,4*E*,*syn*,*syn*	B1	[Hymenoptera]	*Trichogramma turkestanica*	15 [05], 16 (14)	16 (14)
C_{15}	Me5,Me9-15:H (**2**)	5*S*,9*R*	A	Lyonetiidae	*Perileucoptera coffeella*	17 [88], 18 (09)	19 (03), 20 (08)
C_{17}	Me2,Me5-17:H (**3**)	*S*	A	Geometridae	*Lambdina fiscellaria*	21 (91)	22 (93)
	Me3,Me13-17:H (**4**)	3*S*,13*R*	A	Geometridae	*Nepytia freemani*	23 [93], 24 (95)	24 (95)
	Me5,Me9-17:H (**5**)	5*S*,9*S*	A	Lyonetiidae	*Leucoptera scitella* #1	25 [87], 26 (89)	27 (91), 28 (99), 29 (00), 30 (05), 31 (09), 32 (12)
	Me5,Me11-17:H (**6**)	5*R*,11*S*	A	Geometridae	*Lambdina fiscellaria*	33 [93], 34 (93)	35 (96)
	Me7-17:H (**7**)	*S*	A	Noctuidae	*Anomis texana*	36 (93)	22 (93), 37 (00), 38 (01)
		S	A	Geometridae	*Lambdina athasaria* #2	39 [94], 40 (01)	40 (01)
	Me7,Me11-17:H (**8**)	7*S*,11*R*	A	Geometridae	*Lambdina pellucidaria* #3	41 [98], 40 (01)	42 (02), 43 (04), 44 (07)
C_{18}	Δ1,Me14-18:H (**9**) (= Me5,Δ17-18:H)	*S*	A	Lyonetiidae	*Lyonetia clerkella*	45 [84], 46 (85)	47 (85), 48 (95), 49 (13)
	Δ1,Me10,Me14-18:H (**10**) (= Me5,Me9,Δ17-18:H)	10*S*,14*S*	A	Lyonetiidae	*Lyonetia prunifoliella*	50 [97], 51 (02)	28 (99), 52 (00), 31 (09), 53 (14), 54 (14)
C_{19}	Me9-19:H (**11**)	*S*	A	Noctuidae	*Alabama argillacea*	36 (93)	55 (03), 56 (13)
C_{21}	Δ6,Me13-21:H (**12**)	6*Z*,13*S*	A	Noctuidae	*Scoliopteryx libatrix*	57 [00], 58 (03)	58 (03)
	Me5,Me9,Me17-21:H (**13**)		B2	[Heteroptera]	*Phthia picta*	59 [12]	
C_{22}	Me4,Me6,Me8,Me10,Me16,Me18-22:H (**14**) + Me4,Me6,Me8,Me10,Me16-22:H (**15**)	4*S*,6*R*,8*R*,10*S* $[\alpha]_D$ (+10.7), 16*R*,18*S*	B3	[Coleoptera]	*Antitrogus parvulus*	60 [03], 61 [05], 62 (07)	62 (07), 63 (07), 64 (08) 65 (12)

C_{23}	Me7-23:H (**16**)		B4	Thysanoptera	*Frankliniella occidentalis*	66 [13]	
	Me11-23:H (**17**)	*SR*	B5	Gelechiidae	*Anarsia lineatella*	67 (05)	67 (05)
C_{25}	Me3-25:H (**18**) + Me3-27:H + Me3-29:H		B6	[Hymenoptera]	*Camponotus floridanus*	68 [04], 69 [14]	
	Me5,Me11-25:H (**19**)		B7	Pyralidae	*Galleria mellonella*	70 [14]	
C_{27}	Me7-27:H (**20**)		B8	[Coleoptera]	*Neoclytus acuminatus* #4	71 [08]	72 (13)
C_{33}	Me15-33:H (**21**) + Me15,Me19-33:H		B9	[Diptera]	*Stomoxys calcitrans* #4	73 [75], 74 [77]	75 (84), 76 (87)



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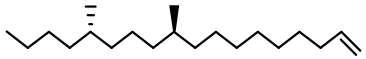

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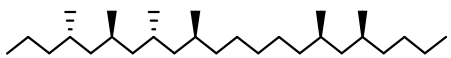


14

[a] Compounds are arranged in order of length of the main chains. A, sex pheromones of female moths; B1, sex pheromone from females of a parasitoid wasp; B2, sex pheromone from males of a true bug; B3, cuticular hydrocarbon from females of a scarab beetle; B4, sex pheromone from males of a thrip; B5, scent in body scales of female moths; B6, queen pheromone from several social insects; B7, sex pheromone from males of a moth; B8, cuticular hydrocarbon from females of a longhorn beetle; B9, cuticular hydrocarbon from females of a fly.

[b] Configurations of moth pheromones were mainly assigned by biological activity (field evaluation of synthetic isomers).

[c] Family in Lepidoptera or [order of other insects].

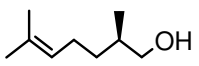
[d] Also identified from *Lyonetia prunifoliella* (#1); *Lambdina pellucidaria.* (#2); *Lambdina athasaria* (#3); and several species in Coleoptera and Hymenoptera (#4).

[e] (Year of publication, 19XX or 20XX). [ ] indicates year when the publication was reported before determination of the absolute configuration.

Table 2. Primary alcohols and their derivatives (aldehydes and esters): Pheromones and related compounds identified from insects and mites. [a]

Pheromone					Insecta and [Arachnida]		Reference [e]	
	Structure [Trivial name]	Configuration and analytical method [b]		Function (Producer)	Order [c]	Species [d]	Identification	Stereoselective synthesis
C_4	Me2-4:OH (**22**)	*R*	GC* #A	aggregation (M)	Coleo.	*Phymatodes lecontei* (long-horned beetle)	77 (07)	77 (07)
	Me2-4:OH (**22**) + Me4-7:OH (**23**)	*S* *R*	GC* #B	sex (F)	Hetero.	*Triatoma brasiliensis* (assassin bug)	78 (09)	78 (09)
C_5	Me2-5:OR (ester) (**24**) + Me2,Me4-6:OR (ester) (**25**)	*S* 2*S*,4*S*	HPLC* #C		[Astigmata]	*Sancassania shanghaiensis* (acarid mite)	79 (01)	79 (01)
C_6	Me2-6:OH (**26**)	*S*	GC* #D	(mandibular gland)	Hymeno.	*Cataglyphis bicolor* #1 (ant)	80 [92], 81 (96)	81 (96)
C_7	Me2,Δ5,Me6-7:OH (**27**) + Ald derivative	*R*	GC* #E	sex (F)	[Astigmata]	*Tyreophagus* sp (acarid mite)	82 (09)	82 (09)
C_9	Me4-9:OH (**28**)	*R*	HPLC #F	sex (F)	Coleo.	*Tenebrio molitor* (mealworm)	83 [86], 84 (89)	84 (89), 85 (03), 86 (10)
C_{10}	Me4,Me8-10:Ald (**29**) [tribolure]	4*R*,8*R* mixture	HPLC #J	aggregation	Coleo.	*Tribolium castaneum* #2 (flour beetle)	87 [81], 88 (83), 89 (11)	90 (83), 91 (85), 92 (88), 93 (02), 94 (06), 95 (06), 96 (11)
C_{12}	Me10-12:OAc (**30**)	*R*		sex (F)	Lepido.	*Adoxophyes honmai* (leafroller moth)	97 [79], 98 (83)	99 (79), 100 (85), 48 (95), 101 (98), 102 (01), 103 (14)

	Me3,Δ6,Et7,Δ10,Me11-12:Ald (**31**) + C11 analogue (**32**)	3*S*,6*E*	GC* #G	sex (F)	Coleo.	*Callosobruchus rhodesianus* (seed beetle)	104 (10), 105 (10)	104 (10)
	Me3,Δ6,Me7,Δ10,Me11-12:OH (**33**) [dihydrofarnesol] + Ald derivative	3*S*,6*E*	GC* #H	marking (M)	Hymeno.	*Bombus jonellus* #3 (bumblebee)	106 (04)	106 (04)
	Me3,Me5,Me9-12:Ald (**34**) [stylopsal]	3*R*,5*R*,9*R*		sex (F)	Strepsi.	*Stylops melittae* *S. muelleri* (twisted-wing parasite)	107 (12) 108 [12], 109 (13)	107 (12), 109 (13)
C_{13}	Δ2,Me4,Δ4,Me6,Me8,Me10-13:OH (**35**)	2*E*,4*E*,*syn*, *syn*		sex (F)	Hymeno.	*Trichogramma turkestanica* (parasitoid wasp)	15 [05], 16 (14)	110 (14)
	Me3,Me4,Δ6,Me7, Δ10,Me11-13:Ald (**36**) [faranal]	3*S*,4*R*, 6*E*,10*Z*	NMR #I	trail	Hymeno.	*Monomorium pharaonis* (ant)	111 (77)	111 (77), 112 (95), 113 (10)
C_{14}	Me6,Me10,Me13-14:OH (**37**)			aggregation (M)	Hetero.	*Stiretrus anchorago* (stink bug)	114 [86], 115 [89]	
C_{15}	Me10,Me14-15:OisoBu (**38**)	*R*		sex (F)	Lepido.	*Arna pseudoconspersa* *Artaxa subflava* (tussock moth)	116 [94], 117 (96), 118 (07)	119 (95)
C_{16}	Δ8,Me14-16:OH (**39**) + Me ester of acid derivative	8*EZ*,14*R*	$[\alpha]_D$ (-)	sex (F)	Coleo.	*Trogoderma inclusum* (hide beetle)	120 [69], 121 (80)	122 (74)
	Δ8,Me14-16:Ald (**40**) [trogodermal]	8*EZ*,14*R*		sex (F)	Coleo.	*Trogoderma glabrum* #4 (hide beetle)	123 [76], 121 (80)	124 (77), 125 (78), 126 (82), 103 (14)



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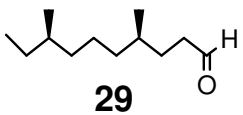

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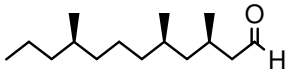

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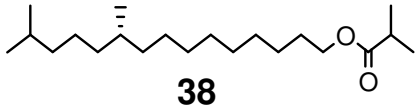


38

[a] Compounds are arranged in order of length of the main chains.

[b] GC* and HPLC* indicate analyses with the following enantioselective columns; #A, Cyclodex-B; #B, CycloSil-B (30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyl dimethylsilyl)-ß-cyclodextrin in DB-1701); #C, Shiseido Ceramospher chiral RU-1 S-5; #D, octakis(6-*O*-methyl-2,3-di-*O*-phenyl)-γ-cyclodextrin; #E, CP-cyclodextrin-β-2,3,6-M-19; #G, β–DEX 225; #H, heptakis(2,3-di-*O*-acetyl-6-*O*-TBDMS)-β–cyclodextrin. #F: Analysis after oxidation and derivatizaiton with (*R*)-1-phenylethylamine. #I: The coupling constant ($J_{3,4}$ = 4 Hz) indicates *syn* configuration.

[c] Coleo. = Coleoptera, Hetero. = Heteroptera, Hymeno. = Hymenoptera, Lepido. = Lepidoptera, Strepsi. = Strepsiptera.

[d] Also identified from *Cataglyphis diehlii, C. savignyi,* and *C. viaticus* (#1); *Tribolium audax, T. brevicornis, T. confusum, T. destructor, T. freemani,* and *T. madens* (#2); *Bombus impatiens and B. terrestris* (#3); and *Trogoderma granarium, T. inclusum*, and *T. variabile* (#4).

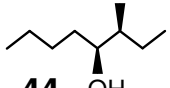
[e] (Year of publication, 19XX or 20XX). [ ] indicates year when the publication was reported before determination of the absolute configuration.

Table 3. Secondary alcohols and their esters: Pheromones and related compounds identified from insects and mites. [a]

Pheromone					Insecta and [Arachnida]		Reference [e]	
	Structure [Trivial name]	Configuration and analytical method [b]		Function (Producer)	Order [c]	Species [d]	Identification	Stereoselective synthesis
C_6	Me3,Me5-6:2-OH (**41**)			sex	Hetero.	*Triatoma dimidiata* (assassin bug)	127 [13]	
	Me4-6:3-OH (**42**) + Me4-6:3-one (**64**)	3*R*,4*S*	GC #A		Hymeno.	*Tetramorium impurum* (ant)	128 (81)	129 (00)
C_7	Me4-7:3-OH (**43**) (= Me4-7:5-OH)	3*R*,4*S*	GC* #B	trail	Hymeno.	*Leptogenys diminuta* (ant)	130 (88)	
		3*S*,4*S*	GC* #C	aggregation	Coleo.	*Scolytus multistriatus* #1 (bark beetle)	131 [75], 132 (77)	133 (04)
C_8	Me3-8:4-OH (**44**) (= Me6-8:5-OH) [phoenicol]	3*S*,4*S*	GC* #D	aggregation (M)	Coleo.	*Rhynchophorus phoenicis* #2 (weevil)	134 [93], 135 (94)	136 (93), 135 (94), 137 (99), 138 (11)
	Me5-8:4-OH (**45**) (= Me4-8:5-OH) [cruentol]	4*S*,5*S*	GC* #D	aggregation (M)	Coleo.	*Rhynchophorus cruentatus* (weevil)	139 [94], 135 (94)	135 (94), 137 (99)
C_9	Me4-9:5-OH (**46**) [ferrugineol]	4*S*,5*S*	GC* #D	aggregation (M)	Coleo.	*Rhynchophorus ferrugineus* #3 (weevil)	140 [93], 141 (95)	142 (93), 137 (99), 138 (11)
C_{10}	Me8-10:2-OPr (**47**)	2*R*,8*R*		sex (F)	Coleo.	*Diabrotica virgifera* (leaf beetle)	143 [82], 144 (84)	145 (84), 146 (85), 147 (86), 225 (02)
C_{11}	Me4,Me6,Δ7,Me8,Δ9-11:5-OH (**48**)	4*R**,5*R**,6*S**, 7*E*,9*E*#a		(F, tergal gland)	Dictyo.	*Cryptocercus punctulatus* #4 (cockroach)	148 [91]	149 (90)
	Me4,Me6,Me8-11:2-OFo (**49**)	2*R*,4*R*,6*R*,		aggregation	[Astigmata]	*Lardoglyphus konoi*	150 [82],	153 (86), 154 (90),

	[lardolure]	8*R*				(acarid mite)	151 (86), 152 (94)	155 (95), 156 (96), 157 (05), 158 (12)
	Me3,Me9-11:2-OPr (**50**)	2*S*,3*R*,9*S*		sex (F)	Hymeno.	*Diprion nipponica* (sawfly)	159 (98), 160 (02)	
C_{13}	Me3,Me7-13:2-OAc (**51**) + Me3,Me7-13:2-OPr (**52**) < Me3,Me7-13:2-OH>[f]	2*S*,3*R*,7*R* 2*S*,3*R*,7*R*	GC #A	sex (F)	Hymeno.	*Diprion pini* #5 (sawfly)	161 (95), 162 (11)	163 (04), 164 (06)
	Me3,Me7,Me9-13:2-OAc (**53**) <Me3,Me7,Me9-13:2-OH>[f]	2*S*,3*R*,7*R*, 9*S*	GC* #E	sex (F)	Hymeno.	*Macrodiprion nemoralis* (sawfly)	165 (00)	166 (11)
	Me3,Me7,Me11-13:2-OPr (**54**) <Me3,Me7,Me11-13:2-OH>[f]	2*S*,3*S*,7*S*, 9*R*		sex (F)	Hymeno.	*Microdiprion pallipes* (sawfly)	167 [98], 168 (03)	169 (99), 170 (04)
C_{14}	Me3,Me7-14:2-OPr (**55**)	2*S*,3*R*,7*R*		sex (F)	Hymeno.	*Gilpinia pallida* (sawfly)	171 (06)	171 (06)
C_{15}	Me3,Me7-15:2-OAc (**56**) [diprionyl acetate] + Me3,Me7-15:2-OPr (**57**) <Me3,Me7-15:2-OH>[f] (**58**)	2*S*,3*S*,7*S* 2*S*,3*S*,7*S*	GC #A	sex (F)	Hymeno.	*Neodiprion sertifer* #6 (sawfly)	172 [76], 173 (00), 162 (11)	174 (81), 175 (01), 176 (04), 177 (12), 178 (12)
	<Me3-15:2-OH>[f] (**59**) <Me3,Me7-15:2-OH>[f] (**58**)	2*S*,3*R* 2*S*,3*R*,7*R*	GC* #E	sex (F)	Hymeno.	*Gilpinia frutetorum* #7 (sawfly)	179 (09)	179 (09)
	Me6,Me10,Me14-15:2-OH (**60**)	2*R*,6*R*,10*R*		sex (F)	Lepido.	*Corcyra cephalonica* (pyralid moth)	180 [87], 181 (91)	182 (00), 183 (11)
C_{17}	Me5-17:7-OH (**61**)	5*R*,7*R*		sex (F)	Lepido.	*Miltochrista calamine* (lichen moth)	184 (11)	185 (14)
C_{29}	Me19-29:6-OAc (**62**)	6*R*,19*R*	HPLC #F	sex (F)	Diptera	*Cochliomyia hominivorax*	186 [93],	189 (04), 190 (04)

+ Me15-29:7-OAc (**63**)	7*R*,15*SR*	(blowfly)	187 [07], 188 (09)



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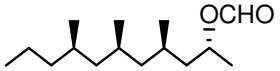

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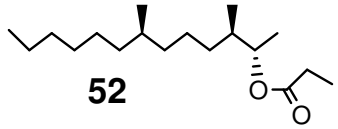

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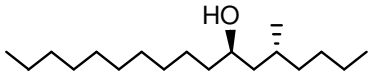


61

[a] Compounds are arranged in order of length of the main chains.

[b] #A, Analyzed after derivatization with (*S*)-2-acetoxypropionyl chloride. GC* indicates analyses with the following enantioselective columns;.#B, Mn(II)-bis[3-heptafluorobutyryl-(1*R*)-camphorate] in methylsilicone OV-101; #C, Lipodex G, octakis-(2,3-di-*O*-pentyl-6-*O*-methyl)-γ-cyclodextrin; #D, Cyclodex-B; #E, XE-60-(*S*)-valine-(*S*)-2-phenylethylamide. #G, Synthetic alcohol intermediates were analyzed after derivatizaiton with (1*R*,2*R*)-2-(2,3-anthracenedicarboximido)cyclohexanecarboxylic acid.

[c] Coleo. = Coleoptera, Dictyo. = Dictyoptera, Hymeno. = Hymenoptera, Lepido. = Lepidoptera.

[d] Also identified from *Scolytus scolytus* and *S. amygdali* (#1); *Rhynchophorus cruentatus* (#2); *Rhynchophorus bilineatus, R. vulneratus, Dynamis borassi,* and *Metamasius hemipterus* (#3); *Cryptocercus kyebangensis* (#4); *Diprion jingyuanensis* (#5); *Neodiprion lecontei, N. nannulus, N. pinetum, N. pratti, N. taedae,* and *Diprion similis* (#6); and *Gilpinia socia* (#7).

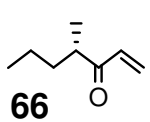
[e] (Year of publication, 19XX or 20XX). [ ] indicates year when the publication was reported before determination of the absolute configuration.

[f] Identification of alcohols as biosynthetic precursors.

Table 4. Ketones: Pheromones and related compounds identified from insects, spiders, and mites. [a]

Pheromone					Insecta and [Arachnida]		Reference [e]	
	Structure [Trivial name]	Configuration and analytical method [b]		Function (Producer)	Order [c]	Species [d]	Identification	Stereoselective synthesis
C_6	Me4-6:3-one (**64**)	*S*		alarm	Hymeno.	*Manica mutica* #1 (ant)	191 [72], 192 (92)	129 (00)
C_7	Me4-7:3-one (**65**)	*S*	$[\alpha]_D$ (+)	alarm	Hymeno.	*Atta texana* #2 (ant)	193 (74)	198 (74)
		S	GC* #A	trail	Hymeno.	*Aphaenogaster cockerelli* #3 (ant)	194 (95)	
		S	GC* #B	sex (F)	Tricho.	*Potamophylax latipennis* #4 (caddis fly)	195 (01)	
				allomone	Hymeno.	*Dasymutilla occidentalis* #5 (wasp, velvet ant)	196 (80)	
				allomone	[Opiliones]	*Leiobunum vittatum* (spider: harvestman)	197 (71)	
	Δ1,Me4-7:3-one (**66**) [chichimol ketone]	*S*	$[\alpha]_D$ (+)	allomone	Phasmatodea	*Agathemera elegans* (walking stick)	199 (06)	200 (09)
	Me4-7:5-OH,3-one (**67**) [sitophinone]	4*S*,5*R*		aggregation	Coleo.	*Sitophilus oryzae* #6 (weevil)	201 [84], 202 (87)	203 (86), 204 (88), 205 (06)
C_8	Δ4,Me4,Me6-8:3-one (**68**) [manicone]	4*E*,6*S*	GC* #C	alarm	Hymeno.	*Manica mutica* #1 (ant)	191 [72], 206 (88)	
	Me6-8:3-one (**69**)			alarm	Hymeno.	*Crematogaster ashmeadi* #7 (ant)	207 [72]	208 (88), 209 (10), 210 (13)

	Me3,Δ6,Me7-8:1-OH,3-OH,2-one[f] (**70**)	*S*	GC* #D	aggregation (M)	Coleo.	*Leptinotarsa decemlineata* (leaf beetle)	211 (02)	212 (05), 213 (09), 214, (13), 215 (14)
C_9	Me4,Me6-9:3-one (**71**) + C7, C8 derivatives	4S,6S	GC* #B	sex (F)	Tricho.	*Potamophylax latipennis* #4 (caddis fly)	195 (01)	195 (01)
	Me4,Me6-9:7-OH,3-one (**72**) [serricornin]	4*S*,6*S*,7*S*		sex (F)	Coleo.	*Lasioderma serricorne* (deathwatch beetle)	216 [79], 217 (84), 218 (01)	219 (85), 220 (11)
C_{10}	Me4,Me6,Me8-10:2-one (**73**) [chortolure]	4*R*,6*R*,8*R*	GC* #E	aggregation (F &M)	[Astigmata]	*Chortoglyphus arcuatus* (storage mite)	221 (04)	221 (04)
C_{13}	Me10-13:2-one (**74**)	*R*		sex (F)	Coleo.	*Diabrotica undecimpunctata* (leaf beetle)	222 (83)	223 (82), 224 (83), 225 (02), 226 (03), 55 (03), 227 (09), 228 (12)
C_{14}	Me6,Me10,Me13-14:2-one (**75**) [pallantione]	6*R*,10*S*	GC* #F	sex (M)	Hetero.	*Pallantia macunaima* (stink bug)	229 (13)	230 (13)
C_{15}	Me6,Me12-15:2-one (**76**)	6*R*,12*R*		sex (F)	Coleo.	*Diabrotica balteata* (leaf beetle)	231 [87], 232 (91)	233 (88), 234 (95), 225 (02)
C_{18}	Me6-18:2-one (**77**) + Me14-18:2-one (**78**) + Me6,Me14-18:2-one (**79**)	*S* *S*	HPLC* #G	sex (F)	Lepido.	*Lyclene dharma* (lichen moth)	235 [07], 236 (10)	237 (09), 238 (12)
C_{29}	Me3,Me11-29:2-one (**80**) + Me3,Me11-27:2-one (**81**)	3*S*,11*S* 3*S*,11*S*	ORD #H	sex (F)	Dictyo.	*Blattella germanica* (cockroach)	239 [74], 240 (79) 243 (04)	241 (81), 242 (08) 242 (08)



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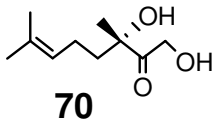

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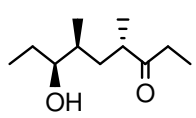

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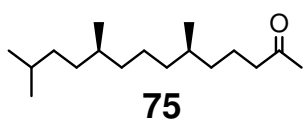

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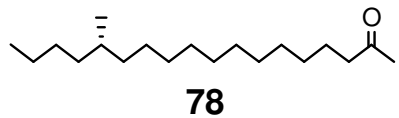


78

[a] Compounds are arranged in order of length of the main chains.

[b] GC* and HPLC* indicate analyses with the following enantioselective columns; .#A, 6-*O*-methyl-2,3-di-*O*-pentyl-γ-cyclodextrin; #B, 60% octakis-(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin in OV1701, #C, FSCC coated with OV-1 containing 1% nickel(II) bis[3-(heptafluorobutyryl)-(1*R*)-camphorate]; #D, Chiraldex™ B-DM; #E, heptakis(2,6-di-*O*-dimethyl-3-*O*-pentyl)-β-cyclodextrin; #F, β-DEX 325 (2,3-di-*O*-methyl-6-*O*-TBDMS-β-cyclodextrin, after $LiAlH_4$ reduction); #G, Chiralpak AD-H. #H: ORD measurement and NMR analysis with a chiral shift reagent.

[c] Coleo. = Coleoptera, Dictyo. = Dictyoptera, Hymeno. = Hymenoptera, Lepido. = Lepidoptera, Tricho. = Trichoptera.

[d] Also identified from mandibular glands of *Manica bradleyi* and a head of *Tetramorium impurum* (#1, see Table 3); a head of *Atta capiguara* (**#2**); *Aphaenogaster albisetosus* (#3); *Potamophylax cingulatus* and *Glyphotaelius pellucidus* (#4); several species in Hymenoptera and Coleoptera (#5); *Sitophilus zeamai*s (#6); and several species in Hymenoptera and Trichoptera (#7).

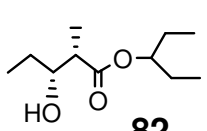
[e] (Year of publication, 19XX or 20XX). [ ] indicates year when the publication was reported before determination of the absolute configuration.

[f] 1,3-Dihydroxy-3,7-dimethyl-6-octen-2-one

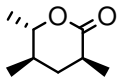
Table 5. Carboxylic acids and their derivatives: Pheromones identified from insects. [a]

Pheromone				Insecta		Reference [e]	
	Structure [trivial name]	Configuration and analytical method [b]	Function (Producer)	Order [c]	Species [d]	Identification	Stereoselective synthesis
C_5	Me2-5:3-OH, Et-Pr ester [f] (**82**) [sitophilate]	2*S*,3*R* NMR #A	aggregation (M)	Coleo.	*Sitophilus granaries* (weevil)	244 (87), 245 (89)	246 (89), 247 (89), 248 (96), 249 (01), 250 (07), 251 (12), 252 (13)
C_6	Me4-6:*n*-Bu ester (**83**)	S	aggregation	Hetero.	*Neomegalotomus parvus* (broad-headed bug)	253 (12)	
	Me2,Me4-6:δ-lactone [g] (**84**)	2*S*,4*R*,5*S*	trail	Hymeno.	*Camponotus herculeanus* #1 (ant)	254 [95], 255 (99)	255 (99)
C_7	Me2,Me4,Me6-7:δ-lactone [h] (**85**)	2*S*,4*R*,5*S*	sex (F)	Hymeno.	*Macrocentrus grandii* (parasitoid wasp)	256 [93], 257 (94)	258 (93), 259 (96), 260 (11)
	Me3-7:acid (**86**)	*R* GC* #B	sex (M)	Coleo.	*Kheper nigroaeneus* (scarab)	261 (02)	261 (02)
	Me2,Δ5,Me6-7:acid (**87**)		sex (M)	Coleo.	*Kheper lamarcki* (scarab)	262 [83]	
	Me4-7:Et ester (**88**)		aggregation (M)	Coleo.	*Oryctes rhinoceros* #2 (scarab)	263 [95]	
C_8	Me4-8:Et ester (**89**) [oryctelure]		aggregation (M)	Coleo.	*Oryctes monoceros* #3 (scarab)	264 [94]	
C_9	Me2,Me4,Me6-9:δ-lactone [i] (**90**) [invictolide]	2*R*,4*R*,5*S*, 6*R*	queen recognition	Hymeno.	*Solenopsis invicta* (ant)	265 [83], 266 (86)	266 (86), 267 (86), 268 (87), 269 (96), 270 (12)

C_{11}	Me2,Me4,Me6,Me8,Me10-11: β-lactone [j] (**91**) [vittatalactone]	2*R*,3*R*,4*S*, 6*S*,8*S*	NMR #A	aggregation (M)	Coleo.	*Acalymma vittatum* (leaf beetle)	271 [05]	272 (09), 273 (10), 274 (11), 275 (11), 276 (12)
C_{12}	Me3,Me5-12:acid (**92**)	3*R*,5*S*		sex (F)	Coleo.	*Prionus californicus* (long-horned beetle)	277 [09], 278 (11), 279 (11)	278 (11)
	Me3, Δ6,Me7, Δ10,Me11-12:Me ester (**93**) [methyl 2,3-dihydrofarnesoate]	3*R*,6*E*	GC #C	sex (M)	Hetero.	*Chlorochroa ligata* #4 (stink bug)	280 [01], 281 (01)	281 (01)
C_{13}	Me2,Me6,Me10-13:Me ester (**94**) + Me2,Me6,Me10-12:Me ester (**95**)			aggregation (M)	Hetero.	*Euschistus heros* #5 (stink bug)	282 [94], 283 [00]	284 (94) 182 (00)
C_{15}	Me4,Me8,Me12-15:Me ester (**96**)			sex (M)	Hetero.	*Edessa meditabunda* (stink bug)	285 (12)	
	Me3,Me13-15:Et-Me-Pr ester [k] (**97**)	3*R*,13*R*,1'*S*		sex (F)	Lepido.	*Clania variegate* (bagworm moth)	286 [06], 287 (10)	288 (09), 287 (10), 289 (13)
C_{7+5}	Me2,Me4-7:α-pyrone [l] (**98**) [supellapyrone]	2*R*,4*R*	GC* #D	sex (F)	Dictyo.	*Supella longipalpa* (cockroach)	290 [93], 291 (95)	292 (95), 293 (01)



82



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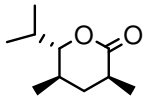

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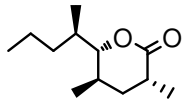

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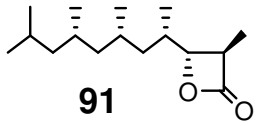

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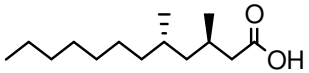

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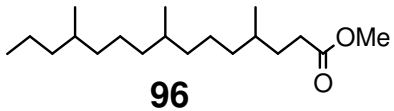

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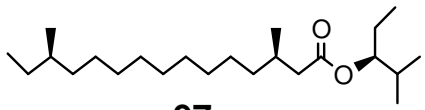

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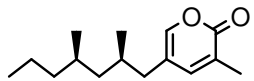


98

[a] Compounds are arranged in order of length of the main chains.

[b] #A, determination by Mosher's method. GC* indicates analyses with the following enantioselective columns;#B, 10% heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin in OV-1701-OH; #C, analysis after hydrolysis and derivatization with (*S*)-methylbenzylamine; #D, trifluoroacetylated γ-cyclodextrin phase, Chiraldex GTA.

[c] Coleo. = Coleoptera, Hetero. = Heteroptera, Hymeno. = Hymenoptera, Lepido. = Lepidoptera, Dictyo. = Dictyoptera.

[d] Also identified from *Camponotus socius, C. ligniperdus, C. vagus, and C. pennsylvanicus* (#1); *Nicrophorus vespilloides* (#2); *Oryctes elegans* and *O. rhinoceros* (#3); *Chlorochroa sayi* and *C. uhleri* (#4), and *Euschistus obscurus* and *Piezodorus guildini*i (#5).

[e] (Year of publication, 19XX or 20XX). [ ] indicates year when the publication was reported before determination of the absolute configuration.

[f] 1-Ethylpropyl 2-methyl-3-hydroxypentanoate.

[g] 2,4-Dimethyl-5-hexanolide.

[h] Tetrahydro-3,5-dimethyl-6-isopropyl-2*H*-pyran-2-one.

[i] Tetrahydro-3,5-dimethyl-6-(1-methylbutyl)-2*H*-pyran-2-one.

[j] 3-Methyl-4-(1,3,5,7-tetramethyloctyl)oxetan-2-one.

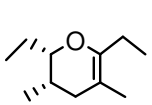
[k] 1-Ethyl-2-methylpropyl 3,13-dimethylpentadecanoate.

[l] 5-(2',4'-Dimethylheptanyl)-3-methyl-2*H*-pyran-2-one.

Table 6. Dihydropyrans, spiroacetals, and related compounds: Pheromones and allomones identified from insects.

Pheromone	Configuration and analytical method [a]	Function (Producer)	Insecta Order [b]	Species [c]	Reference [d] Identification	Stereoselective synthesis
anhydroserricornin (**99**) [e]	2*S*,3*S*	sex (F)	Coleo.	*Lasioderma serricorne* (deathwatch beetle)	294 [81], 295 (86)	296 (84), 297 (85)
dihydropyran						
Serricorole (**100**) [f]	2*S*,3*R*,1'*S*,2'*S*	sex (F)	Coleo.	*L. serricorne*	298 [83], 299 [85], 300 (87)	300 (87)
α-serricorone (**101**) [g] + β-serricorone (**102**)	2*S*,3*R*,1'*S* CD 2*S*,3*R*,1'*R*	sex (F) + marking	Coleo.	*L. serricorne*	298 [83], 301 (90)	300 (87)
stegobinone (**103**) [h]	2*S*,3*R*,1'*S*	sex (F)	Coleo.	*Stegobium paniceum* #1 (deathwatch beetle)	302 [78], 303 (81)	304 (79), 305 (81), 306 (12)
Stegobiol (**104**) [i]	2*S*,3*R*,1'*S*	sex (F)	Coleo.	*S. paniceum*	307 (87)	308 (86), 306 (12)
spiroacetal						
conophthorin [j]						
(**105**)	5*R*,7*S*	sex (M)	Diptera	*Bactrocera xanthodes* (fruit fly)	309 (92)	309 (92)
(**106**)	5*S*,7*S*	sex (M)	Coleo.	*Conophthorus coniperda* #2 (bark beetle)	310 (98)	311 (81)

2-methyl-1,7-dioxaspiro[5,5]undecane (**107**)	2*R*,6*S*	GC* #A	(mandibular gland)	Hymeno.	*Goniozus nephantidis* #3 (wasp)	312 (08)	312 (08)
(**108**)	2*S*,6*R*	GC* #B	allomone	Phasmatodea	*Asceles glaber* #4 (walking sticks)	313 (12)	313 (12)
2,8-dimethyl-1,7-dioxaspiro-[5,5]undecane (**109**)	2*S*,6*R*,8*S*	GC* #C	sex (F)	Hymeno.	*Andrena wilkella* #5 (wild bee)	314 [80], 315 (90)	316 (81), 317 (87), 318 (89)
			sex (M)	Diptera	*Bactrocera kirki* #6	309 (92)	
2,4,8-trimethyl-1,7-dioxaspiro-[5,5]undecane (**110**)	2*S*,4*R*,6*R*,8*S*		aggregation	Hetero.	*Cantao parentum* (shield bug)	319 (94)	320 (95), 321 (01), 322 (14)
2,2,8-trimethyl-1,7-dioxaspiro [5,5] undecane (**111**)	6*R*,8*S*	GC* #D	allomone	Coleo.	*Ontholestes murinus* #7 (rove beetle)	323 (99)	323 (99)
α-multistriatin (**112**) [k]	1*S*,2*R*,4*S*,5*R*		aggregation	Coleo.	*Scolytus multistriatus* #8 (bark beetle)	131 (75), 132 (77)	324 (76), 325 (77), 326 (79), 327 (79), 328 (82), 329 (87)



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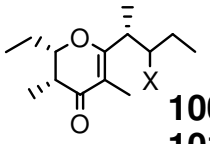
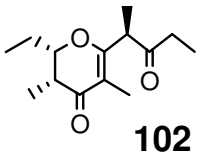


100 X: OH
101 X: =O



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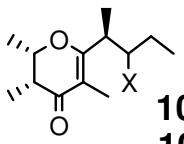
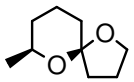


103 X: =O
104 X: OH



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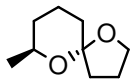

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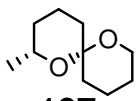

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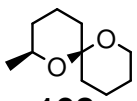

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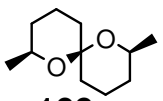

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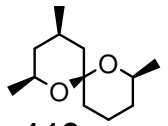

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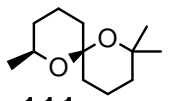

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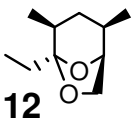


112

[a] GC* indicates analyses with the following enantioselective columns: #A, 1:1 mixture of OV1701 and hexakis(6-*tert*-butyl-2,3-dimethyl)-β-cyclodextrin; #B, Beta DEX 120 column; #C, per-*n*-hexyl-α-cyclodextrin; #D, Cyclodex-B.

[b] Coleo. = Coleoptera, Hetero. = Heteroptera, Hymeno. = Hymenoptera.

[c] Also identified from *Anobium punctatum* (#1); *Conophthorus ponderosae, Pityophthorus carmeli*, and *Pityophthorus nitidulus* (#2); *Goniozus legneri* (#3); *Goniozus legneri* and *G. nephantidis* as a minor component (#4); *Polybia occidentalis* and several species in Hymenoptera (#5); *Bactrocera cucumis, B. kraussi, B. latifrons, B. nigrotibialis* (Diptera), *Ontholestes murinus*, and *O. tesselatus* (Coleoptera) (#6); *Ontholestes tesselatus* (#7); *Scolytus pygmaeus and S. scolytus* (#8).

[d] (Year of publication, 19XX or 20XX). [ ] indicates year when the publication was reported before determination of the absolute configuration.

[e] 2,6-Diethyl-3,5-dimethyl-3,4-dihydro-2*H*-pyran

[f] 2,3-Dihydro-3,5-dimethyl-2-ethyl-6-(1-methyl-2-hydroxybutyl)-4*H*-pyran-4-one

[g] 2,3-Dihydro-3,5-dimethyl-2-ethyl-6-(1-methyl-2-oxobutyl)-4*H*-pyran-4-one

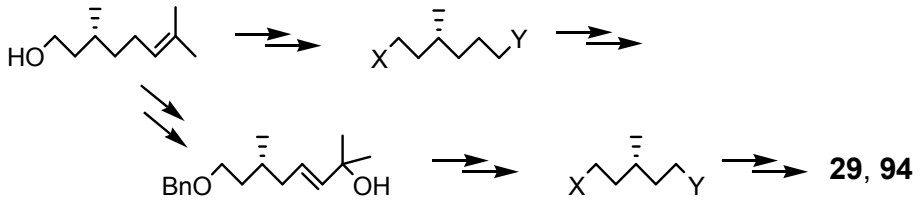
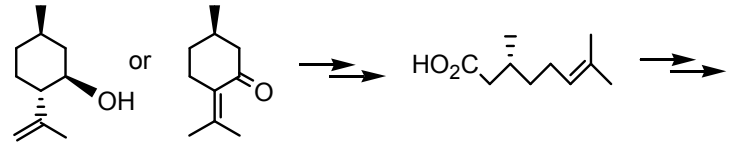
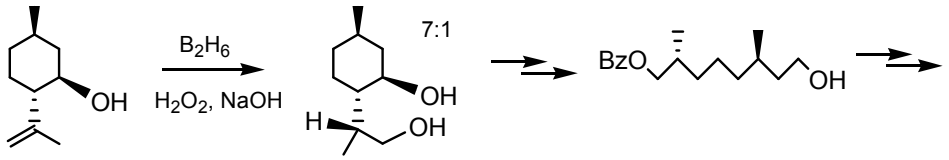
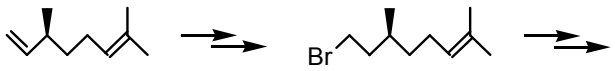
[h] 2,3-Dihydro-2,3,5-trimethyl-6-(1-methyl-2-oxobutyl)-4*H*-pyran-4-one

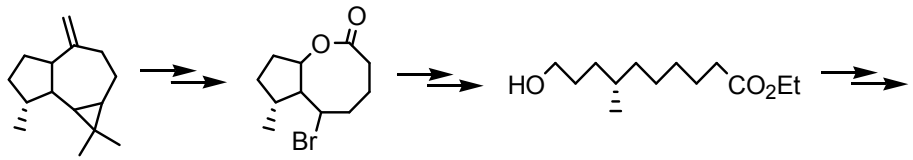
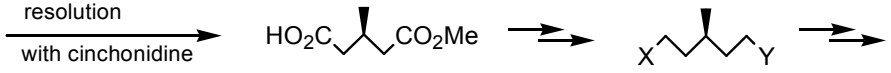
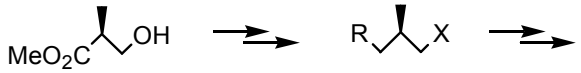
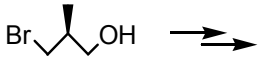
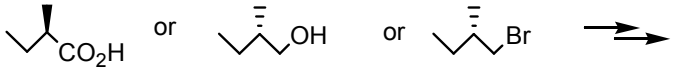
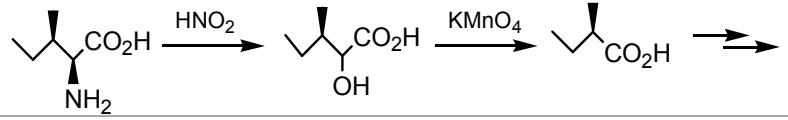
[i] 2,3-Dihydro-2,3,5-trimethyl-6-(1-methyl-2-hydroxybutyl)-4*H*-pyran-4-one

[j] 7-Methyl-1,6-dioxaspiro[4.5]decane

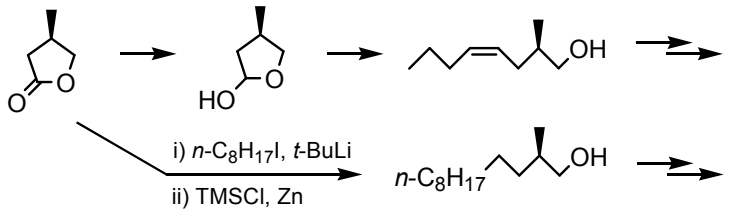
[k] 5-Ethyl-2,4-dimethyl-6,8-dioxabicyclo[3.2.1]octane

Table 7. Chiral synthons (**S1** – **S14**) for enantioserective syntheses of methyl-branched pheromones.

Synthon Chemical structure and the synthetic route	Targeted pheromone
1a. Citronellol (**S1a**) or citronellal (**S1b**) 	Me10-12:OAc (**30**)[99] Me6,Me12-15:2-one (**76**)[233] and **2**[20], **5**[27], **10**[52], **28**[83], **29**[90,95,96], **38**[119], **62**[189], **63**[190], **74**[224], **77**–**79**[237,238], **80**[242], **86**[261], **94**[284], **97**[287,288], **112**[325]
1b. Citronellic acid (**S1c**) derived from isopulegol or pulegone 	Δ8,Me14-16:Ald (**40**)[125,126] Me8-10:2-OPr (**47**)[145] Me3,Me11-29: 2-one (**80**)[242] and **21**,[76] **69**,[208] **110**[320]
2. Isopulegol (**S2**) or neoisopulegol 	Me5,Me9-15:H (**2**)[19]
3. Dihydromyrcene (**S3**) 	Me4-9:OH (**28**)[85]

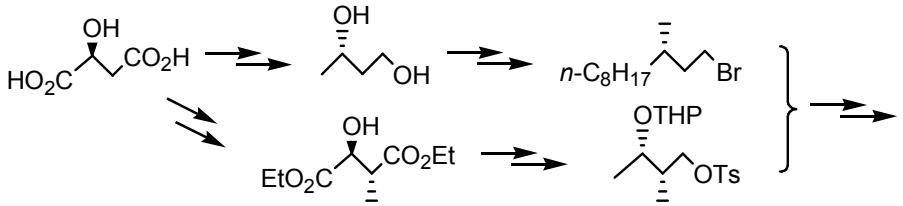
4. Aromadendrene (**S4**) 	Me9-19:H (**11**)[55] Me10-13:2-one (**74**)[55]
5. 3-Methylglutaric acid monomethyl ester (**S5**) 	Me8-10:2-OPr (**47**)[147] Me10-13:2-one (**74**)[228]
6. 3-Hydroxy-2-methylpropionate (Roche ester, **S6**) 	Me11-23:H (**17**)[67] vittatalactone (**91**)[272,273] and **5**[27-29], **6**[35], **9**[47], **10**[53], **29**[94], **74**[228], **78**[237], **79**[237], **94**[284]
7. 3-Bromo-2-methylpropanol (**S7**) 	Me3,Me5,Me9-12:Ald (**34**)[108] supellapyrone (**98**)[292]
8a. 2-Methylbutanoic acid (**S8a**), 2-methylbutan-1-ol (**S8b**), or 1-bromo-2-methylbutane (**S8c**) 	Me3,Me13-15: ester (**97**)[287,288] and **29**[96], **39**[122], **40**[124], **68**[206]
8b. (*R*)-2-Methylbutanoic acid [(R)-**S8a**] from L-isoleucine 	Me8-10: 2-OPr (**47**)[146]

9. 3-Methyl-4-butanolide (**S9**)



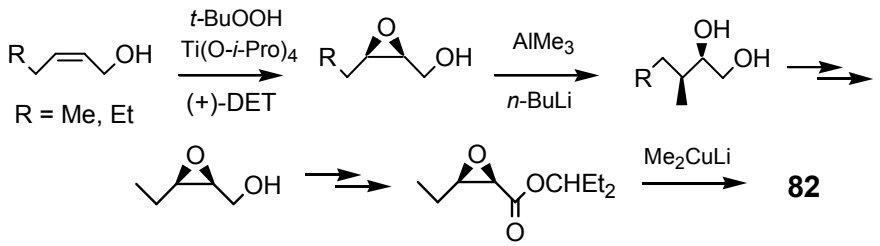
Me5,Me9-15:H (**2**)[20]
invictolide (**90**)[267]
Me9-19:H (**11**)[56]

10. Malic acid (**S10**)



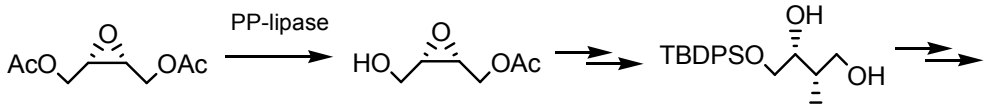
Me3,Me7-15:2-OAc (**56**)[176,178]

11. Chiral epoxide: 2,3-Epoxyalkan-1-ol (**S11**) produce by Sharpless asymmetric epoxidation



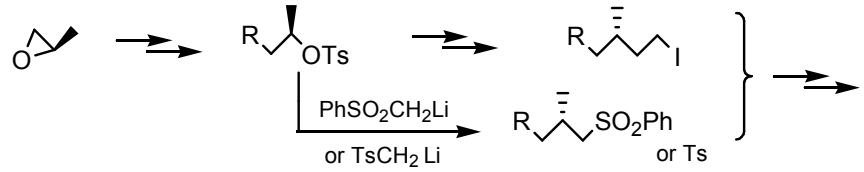
Me3-8:4-OH (**44**)[135]
Me5-8:4-OH (**45**)[135]
sitophilate (**82**)[246]
invictolide (**90**)[266]

12. Chiral epoxide: (3-Hydroxymethyloxiranyl)methyl acetate (**S12**)



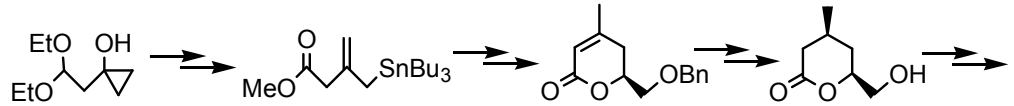
Me3-8:4-OH (**44**)[136]
Me4-9:5-OH (**46**)[142]

13. Chiral epoxide: Propylene oxide (**S13**)



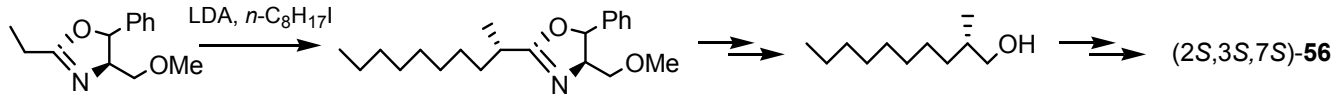
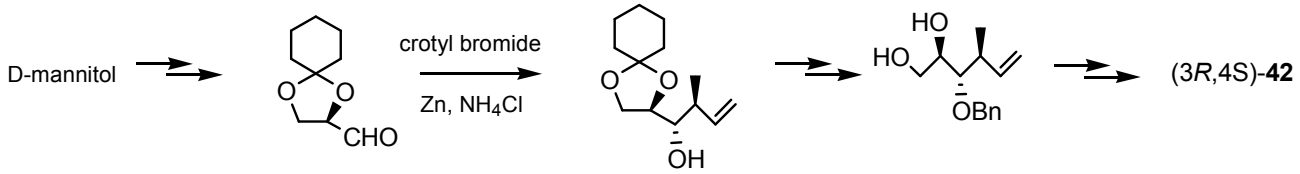
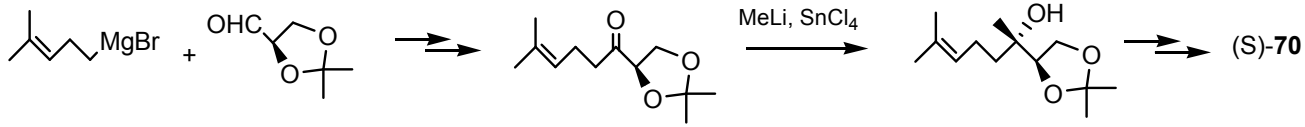
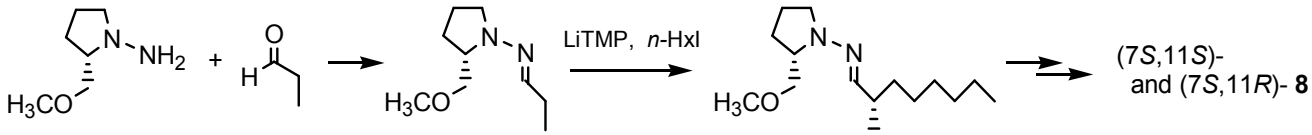
Me5,Me9-17:H (**5**)[32]
Δ1,Me10,Me14-18:H (**10**)[53]
Me5-17:7-OH (**61**)[185]
and **75**[230], **97**[289]

14. Chiral lactone (**S14**)



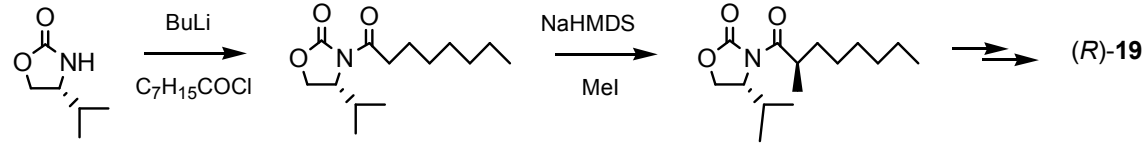
Δ1,Me10,Me14-18:H (**10**)[54]
Me10-12:OAc (**30**)[103]
faranal (**36**)[113]
and **40**[103], **110**[322]

Table 8. Syntheses of methyl-branched pheromones applying an enantioselective organic or biochemical reaction (R-1 – R-5).

Reaction type
Synthetic route for a targeted chiral pheromone
1. C-C coupling with a chiral intermediate
R-1-1. 2-Oxazoline derivative
Me3,Me7-15:2-OAc (**56**)[174]

R-1-2. [1,3]Dioxolane-4-carbaldehyde and a keto derivative
a. Me4-6:3-OH (**42**)[129]

b. Me3,Δ6,Me7-8:1-OH,3-OH,2-one (**70**)[213]

R-1-3. Enders SAMP/RAMP hydrazone-alkylation reaction
Me7,Me11-17:H (**8**)[42]


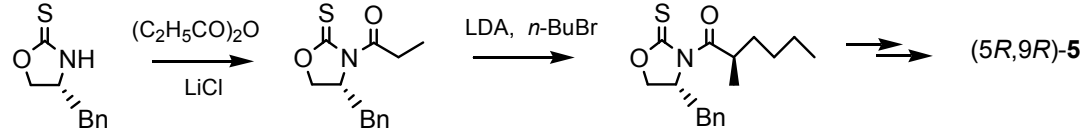
R-1-4. Evans' chiral auxiliaries

a. Me7-27:H (**20**)[72]

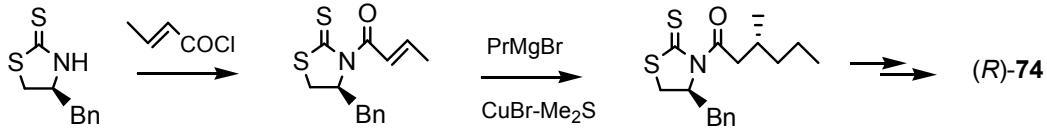


b. Δ1, Me14-18:H (**9**)[49]

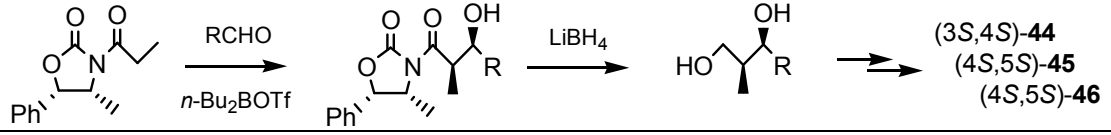
c. Me5,Me9-17:H (**5**)[31]



d. Me10-13:2-one (**74**)[227]



e. Me3-8:4-OH (**44**)[137] etc.

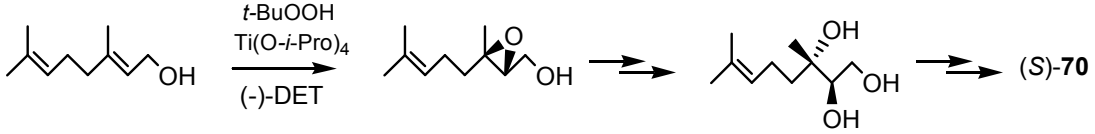


2. Reaction *via* an epoxy compound

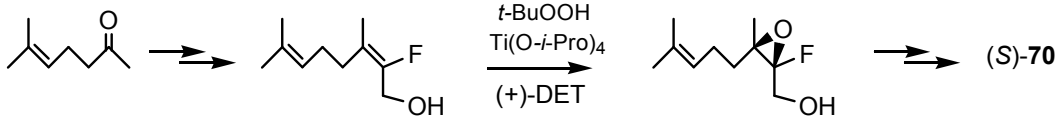
R-2-1. Sharpless asymmetric epoxydation

Me3,Δ6,Me7-8:1-OH,3-OH,2-one (**70**)[214,215]

a

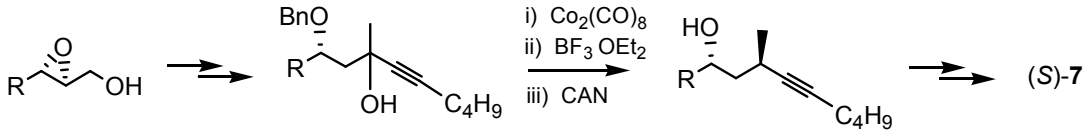


b



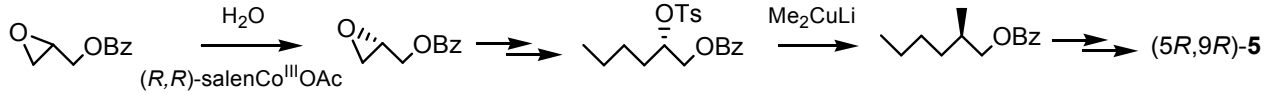
R-2-2. Intermolecular hydride transfer

Me7-17:H (**7**)[37]

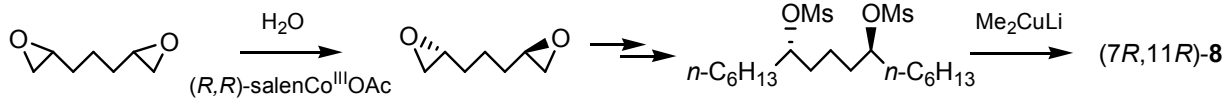


R-2-3. Hydrolytic kinetic resolution (HKR)

a. Me5,Me9-17:H (**5**)[31]

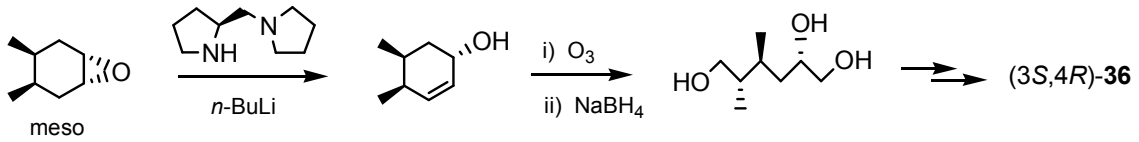


b. Me7,Me11-17:H (**8**)[43]



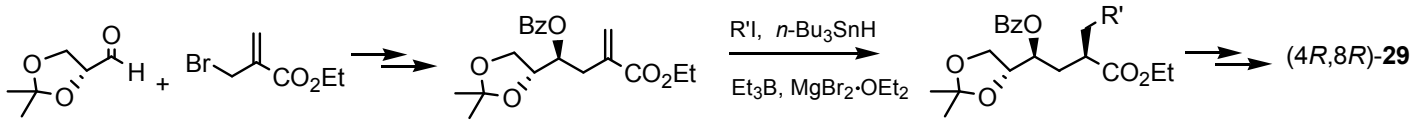
R-2-4. Asymmetric cleavage of an epoxy ring

faranal (**36**)[112]



3. Chelation-controlled radical reaction

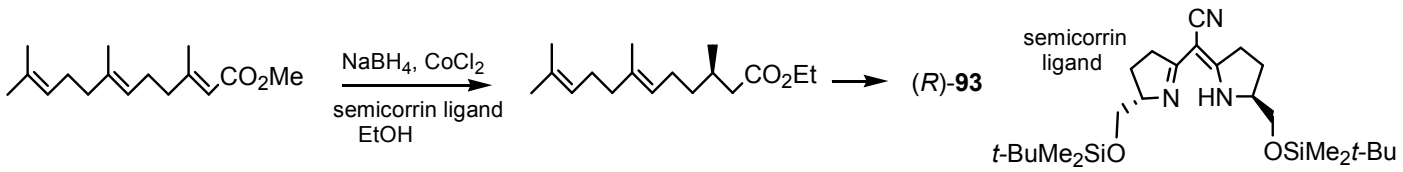
R-3 Me4,Me8-10:Ald (**29**)[94]



4. Reaction with a chiral catalyst

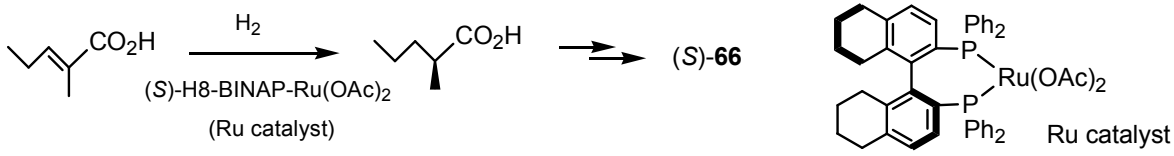
R-4-1. $NaBH_4$ reduction with a chiral cobalt semicorrin complex

dihydrofarnesoate (**93**)[281]

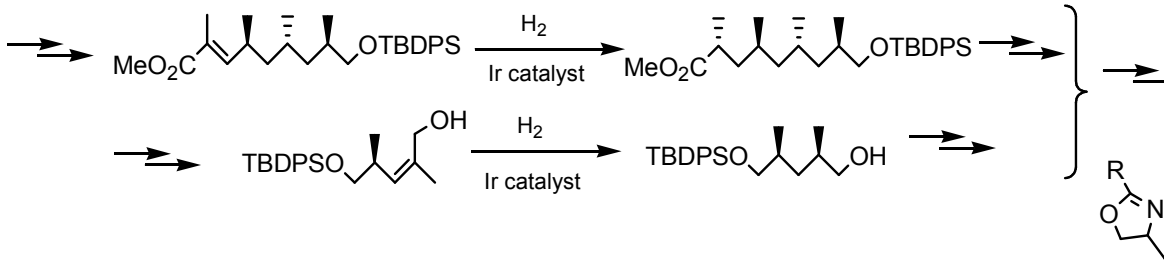


R-4-2. Hydrogenation over a chiral catalyst

a. Δ1,Me4-7:3-one (**66**)[200]

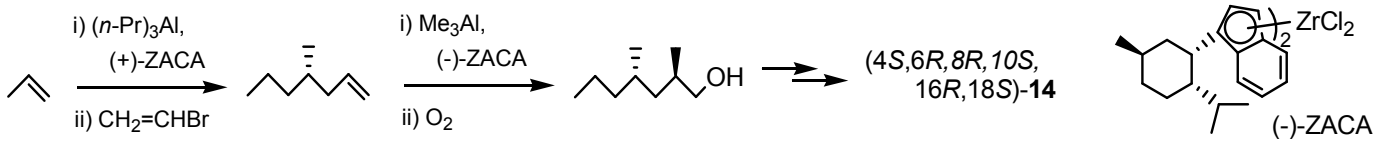


b. Me4,Me6,Me8,Me10,Me16,Me18-22:H (**14**)[63]



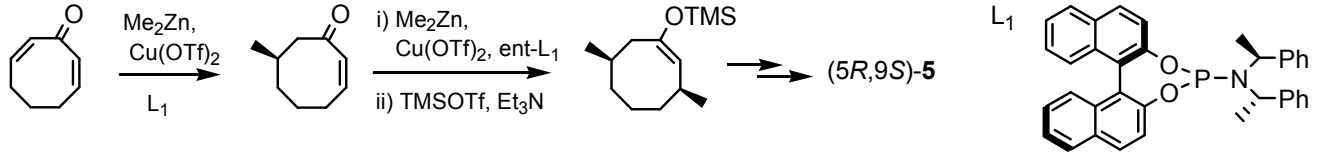
R-4-3. Zr-catalyzed asymmetric carboalumination of alkenes (ZACA reaction)

Me4,Me6,Me8,Me10,Me16,Me18-22:H (**14**)[64]

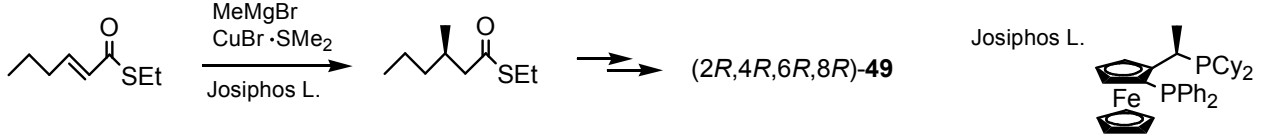


R-4-4. Cu-catalyzed asymmetric Michael addition of organometallic reagents

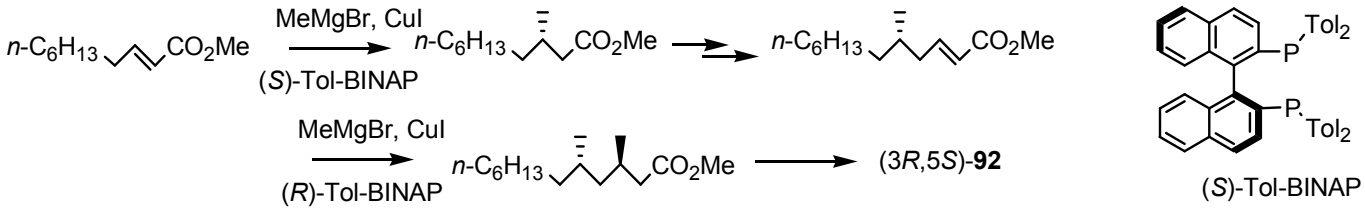
a. Me5,Me9-17:H (**5**)[30]



b. lardolure (**49**)[157]

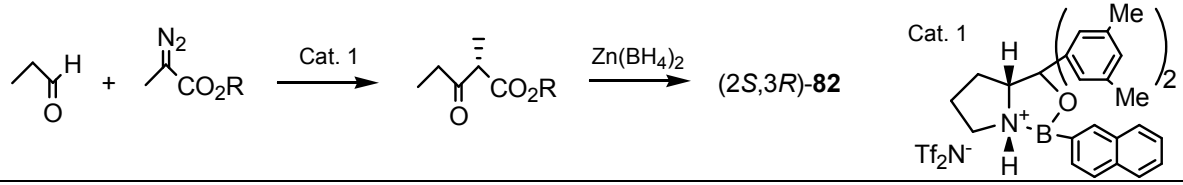


c. Me3,Me5-12:acid (**92**)[278]



R-4-5. Asymmetric Roskamp reaction catalyzed by an oxazaborolidium ion

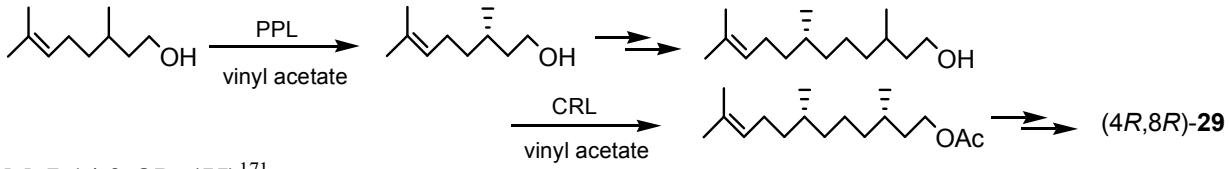
sitophilate (**82**)[251]



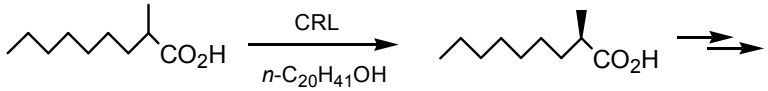
5. Chemoenzymatic reaction

R-5-1. Lipase-catalyzed kinetic resolution

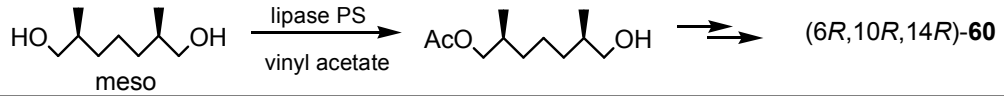
a. Me4,Me8-10:Ald (**29**)[93]



b. Me3,Me7-14:2-OPr (**55**)[171]

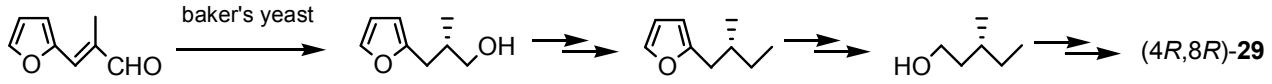


c. Me6,Me10,Me14-15:2-OH (**60**)[182]

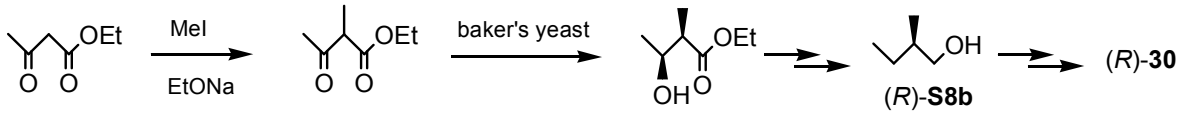


R-5-2. Reduction by baker's yeast

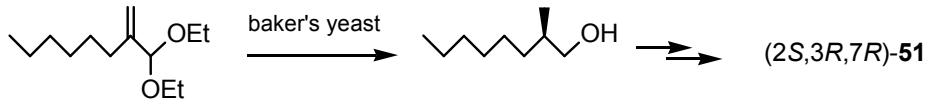
a. Me4,Me8-10:Ald (**29**)[92]



b. Me10-12:OAc (**30**)[101]

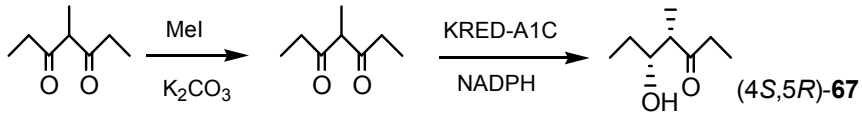


c. Me3,Me7-13:2-OAc (**51**)[164]



R-5-3. Reduction by isolated ketoreductase

sitophinone (**67**)[205]



R-5-4. *Aspergillus* amino acylase

invictolide (**90**)[268]

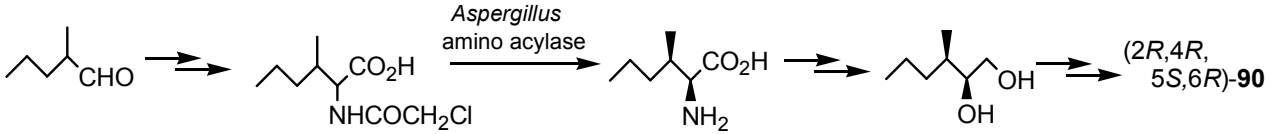
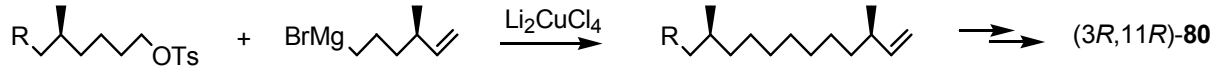
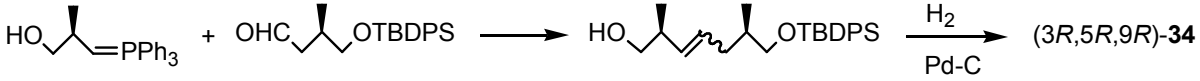
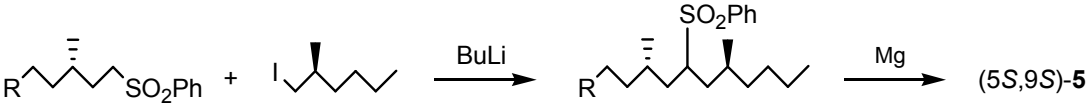
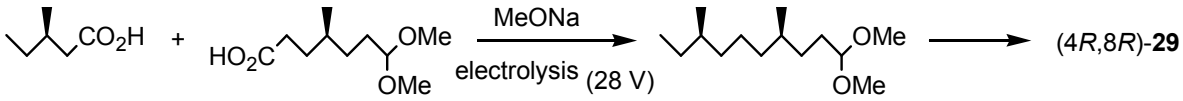
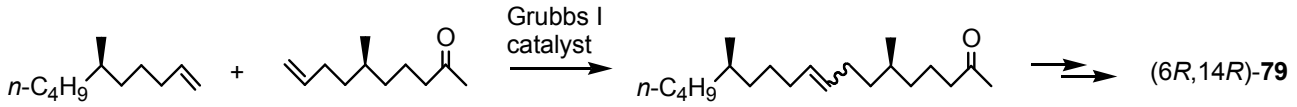


Table 9. Coupling reactions of two chiral blocks (R-6 – R-11) for the syntheses of dimethyl pheromones.

Reaction type Synthetic route for a targeted chiral pheromone
R-6. Reaction of a Grignard reagent a. Δ1,Me10,Me14-18:H (**10**)[28]    b. Me3,Me11-29:2-one (**80**)[241] 
R-7. Wittig reaction Me3,Me5.Me9-12:Ald (**34**)[108] 
R-8. Coupling of RSO_2Ph with R'I Me5,Me9-17:H (**5**)[27] 
R-9. Kolbe electrolysis Me4,Me8-10:Ald (**29**)[90] 

R-10. Olefin cross metathesis

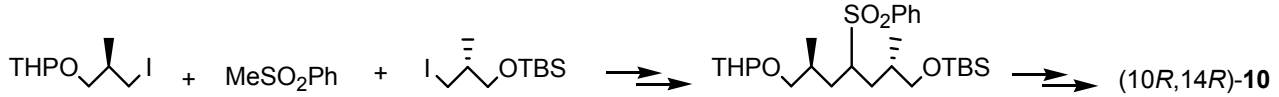
Me6,Me14-18:2-one (**79**)[237]



R-11. Coupling with a linchpin

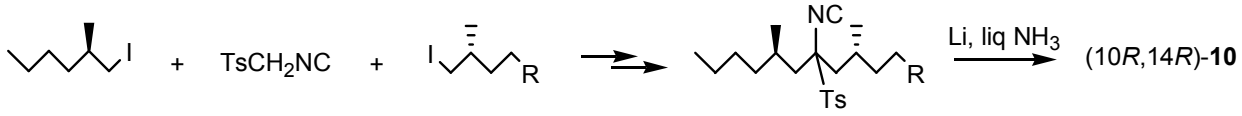
11-1. Methyl phenyl sulfone ($MeSO_2Ph$)

Δ1,Me10,Me14-18:H (**10**)[52]



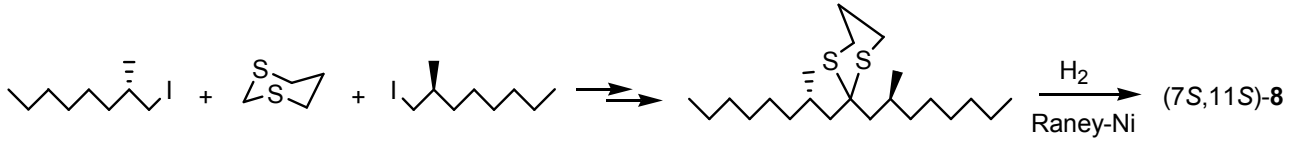
11-2. *p*-Toluenesulfonylmethyl isocyanide [$CH_2(NC)SO_2Ts$, TosMIC]

Δ1,Me10,Me14-18:H (**10**)[31]

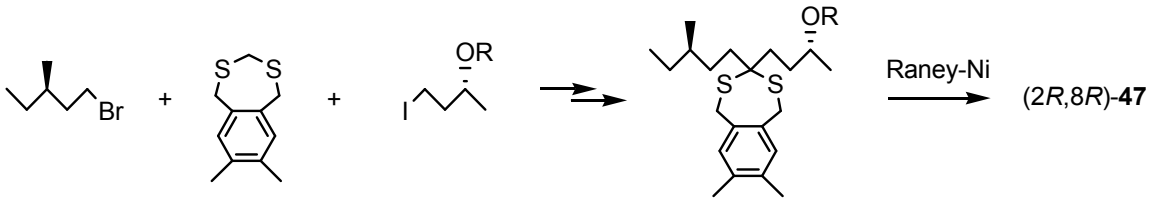


11-3. 1,3-Dithiane

a. Me7,Me11-17:H (**8**)[42]



b. Me8-10:2-OPr (**47**)[145]



11-4. Methyl acetoacetate

Me5,Me11-17:H (**6**)[35]