SYNTHESES OF INSECT SEX PHEROMONES. A REVIEW OF THE LITERATURE 1990–1998

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The term "insect sex pheromones" denotes compounds used for chemical communication between sexual partners in the insect kingdom. The aim of this review covering the literature 1990–1998 is to survey papers on their syntheses. A review with 201 references.
Key words: Insects; Sex pheromones; Sex attractants; Insect semiochemicals.

1. INTRODUCTION

Insect pheromones are defined as a general class of chemical messengers secreted to the outside by an insect individual and received by another individual of the same species, thereby releasing a specific reaction. Of them, insect sex pheromones which have evolved as an efficient means for bringing the two sexes of the same species together for the purpose of reproduction, are probably the largest group. Over the past three decades, insect pheromones have gained considerable interest as alternatives to conventional insecticides and became a significant part of natural product chemistry. The rationale for this interest includes a negligible environmental impact of pheromones and increasing evidence of their effectiveness in pest control. Reflecting these

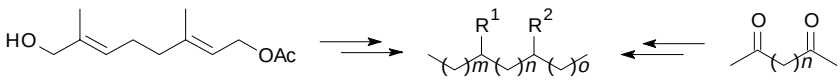
facts, there has been considerable effort towards developing methods for pheromone synthesis.

General strategies and methods employed in synthesizing insect pheromones constitute a collection almost as broad as the entire scope of organic synthesis. A number of timely reviews on the synthesis of pheromones have been published, the last and most comprehensive of them being the excellent book by Mori[1] which covers the literature through 1990. Since then, several more specialized papers dealing with various aspects of insect pheromone chemistry have also appeared[2–10]. Our review focuses on syntheses published from 1990 to mid 1998. It is structured according to types of the compounds and covers about 200 references obtained mainly from electronic media. The abbreviations used for the respective reactants and/or protective groups follow those frequently employed in chemical journals and listed, *e.g.* in the book of Greene and Wuts[11].

2. HYDROCARBONS

Pheromones used for sexual attraction by e.g. some insect species of Lepidopteran family comprise linear and branched hydrocarbons with 15–29 carbon atoms in the molecule[12]. Their preparation usually does not represent any complication except for the synthesis of compounds containing chiral centers. For instance, Kovalev and Sorochinskaya[13] have shown that the hydroxyacetate 2.1 (easily accessible from geranyl acetate by successive oxidation with tert-butyl peroxide, selenium oxide and PCC) can be used as the key intermediate in the preparation of racemic 5,9-dimethylheptadecane (**2.2**), the sex pheromone of *Leucoptera scitella*.

A widely applicable strategy based on molecular symmetry considerations has been elaborated by Mori *et al.*[14] for preparation of 13,25-dimethylheptatriacontane (**2.3**) and 11,23-dimethylheptatriacontane (**2.4**), the major components of the tsetse fly (*Glossina tachinoides*) contact sex pheromone, as well as 11,21-dimethylheptatriacontane (**2.5**), the minor component. In this synthesis, methyl acetoacetate served as starting material for alkylation with bifunctional $Br(CH_2)_nBr$, and the prepared diketones **2.7** were then treated with corresponding Grignard compounds. Stereoisomeric mixtures of pheromones **2.3**, **2.4**, and **2.5** were thus obtained in five steps and 38% overall yield (Scheme 1).



2.1

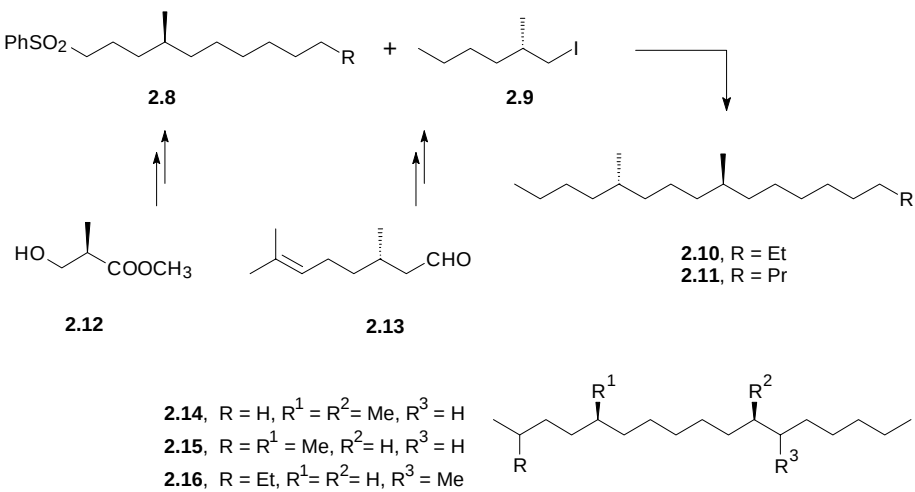
2.2, $m = 3$, $n = 3$, $o = 7$, $R^1 = R^2 = Me$
2.3, $m = 11$, $n = 11$, $o = 11$, $R^1 = R^2 = Me$
2.4, $m = 9$, $n = 11$, $o = 13$, $R^1 = R^2 = Me$
2.5, $m = 9$, $n = 9$, $o = 15$, $R^1 = R^2 = Me$
2.6, $m = 0$, $n = 7$, $o = 7$, $R^1 = Me$, $R^2 = H$

2.7

SCHEME 1

Ballini *et al.* have published several papers on synthesis of hydrocarbons using suitable nitro-group-containing intermediates. A two-step synthesis of 2-methylheptadecane (**2.6**), the sex pheromone of the tiger moth, includes condensation of tridecanal and 3-methyl-1-nitrobutane, the latter compound acting as an alkyl anion[15]. The subsequent tandem denitration–deoxygenation afforded **2.6**. A practical synthesis of (*Z*)-tricos-9-ene, sex pheromone of the housefly (*Musca domestica*), was based on a similar principle[16].

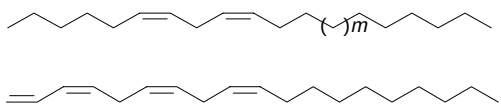
While hydrocarbons containing no chiral atoms in the molecule or those in racemic form can be relatively easily prepared, synthesis of the corresponding optical isomers may lead to some difficulties due to the similarity of functional groups (alkyl groups) attached to the chiral center. Thus, Mori and Wu[17] combined the chiral building blocks, derived from methyl (2*R*)-3-hydroxy-2-methylpropanoate (**2.12**) and (*S*)-citronellal (**2.13**) to obtain optically pure **2.2** by coupling **2.8** and **2.9** under the catalysis of Li_2CuCl_4. They were able to prepare **2.10** and **2.11**, the major and the minor components of the sex pheromone of the *Leucoptera* species (Scheme 2).



SCHEME 2

Another approach was published by Poppe *et al.* who used the baker's yeast mediated synthesis of both **2.10** and **2.11**, enriched in the 9*S*-isomers[18]. Poppe utilized (*R*)-citronellal, obtained by baker's yeast incubation of racemic citronellal, for creating the (9*S*)-9-methyl center in **2.10**. A similar strategy was used by Mori and Horikiri[19] in the synthesis of (5*R*,11*S*)-5,11-dimethylheptadecane (**2.14**) and (5*S*)-2,5-dimethylheptadecane (**2.15**), the major and the minor components of the female-produced sex pheromone of the western hemlock looper (*Lambdina fiscellaria lugubrosa*). Mori based his synthesis on the enantiomers of methyl 3-hydroxy-2-methylpropanoate (**2.12**) and (*S*)-citronellal (**2.13**).

Synthesis of four stereoisomers of 3,13-dimethylheptadecane (**2.16**), the major sex pheromone component of the western false hemlock looper, was also performed by Mori *et al.*[20] who used the enantiomers of citronellol and 2-methylbutan-1-ol as chiral building blocks. The stereogenic centers of (*R*)- and (*S*)-citronellol, and (2*R*)- and (2*S*)-2-methylbutan-1-ol served as the centers of chirality of reaction intermediates, *i.e.*, (9*R*)- or (9*S*)-9-methyltridecyl tosylate and (2*R*)- or (2*S*)-2-methylbutyl iodide. Having coupled the respective intermediates under conditions avoiding racemization of the stereogenic centers, Mori prepared all isomers of **2.16** in purities enabling biological tests.



2.17, *m* = 1
2.18, *m* = 2

2.19

SCHEME 3

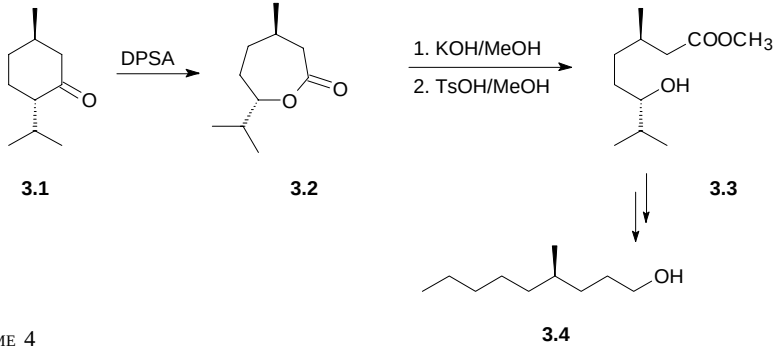
Vig *et al.*[21] have reported the stereoselective synthesis of (6*Z*,9*Z*)-nonadeca-6,9-diene (**2.17**) and (6*Z*,9*Z*)-henicosa-6,9-diene (**2.18**), sex pheromones of *Bupalus piniarius* and *Utethesia ornatrix*. The almost pure *Z*-products were prepared by using (*Z*)-oct-2-enyl bromide for alkylation of either 1-(tetrahydropyran-2-yloxy)prop-2-yne or 2-(chloromethyl)tetrahydrofuran with subsequent hydrogenation of the reaction intermediates over the Lindlar catalyst (Scheme 3).

Synthesis of a four-double-bond-containing sex pheromone was described in a paper of Nikolaeva *et al.*[22]. Repeated coupling of appropriate propargylic compounds followed by hydrogenation over the Lindlar catalyst gave a mixture of products from which **2.19** was obtained by chromatography.

3. ALCOHOLS

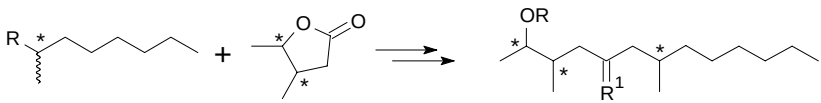
Odinokov *et al.* synthesized a number of methyl substituted chirons starting from (–)-menthone[23,24]. To prepare the required intermediates, they elaborated a novel, efficient and selective oxidation with decaneperoxysulfonic acid (DPSA). This method has been applied to the synthesis of optically pure (4*R*)-4-methylnonan-1-ol (**3.4**), the sex pheromone of the yellow mealworm (*Tenebrio molitor*). The reaction sequence started with (–)-**3.1** which, after oxidation with DPSA, afforded the product of Baeyer–Villiger reaction (**3.2**) in high yield. Opening the lactone **3.2** to hydroxy ester **3.3** led to an intermediate of required stereochemistry (Scheme 4).

Both enantiomers of 4-methylnonan-1-ol (**3.4**) with high optical purity (*ca* 100% e.e.) were also prepared from methyl 3-methyloctanoate by Kitahara and Kang[25].



SCHEME 4

A Swedish group[26] had revealed that the sex pheromone secretion of the pine sawfly (*Diprion pini*) from insects collected both in Finland and France contains stereoisomers of **3.11** (Scheme 5). To confirm the assumed structure, the threo and erythro acetates and propionates of 3,7-dimethyltridecan-2-ol (**3.10**) were synthesized from enantiomerically highly enriched (>99% e.e.) building blocks. First, racemic 2-methyloctanoic acid (**3.6**) was subjected to enzyme-catalyzed esterification using commercial lipase. Two additional esterification cycles led to an easily separable mixture of (*R*)-**3.6** and (*S*)-**3.7** which after reduction afforded the desired enantiomeric alcohols of more than 98% e.e. Then, the pure alcohols were separately converted to the tosylates and bromides and, subsequently, by reaction with (*R*,*R*)- or (*S*,*S*)-**3.8**, to the ketone intermediate **3.9**, structurally close to **3.11**.



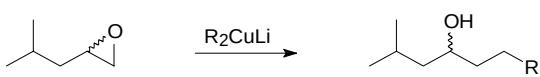
3.5, R = CH_2OH
3.6, R = COOH
3.7, R = COOn-$C_{12}H_{25}$

3.8

3.9, R = H, R^1 = O
3.10, R = H, R^1 = H_2
3.11, R = Ac, COEt, R^1= H_2

SCHEME 5

Takenaka *et al.*[27] published the synthesis of enantiomers of 2-methylheptan-4-ol (**3.13**) and 2-methyloctan-4-ol (**3.14**), the components of the West Indian sugarcane borer pheromone (Scheme 6). Starting from (*S*)- and (*R*)-**3.12**, prepared from (*S*)- and

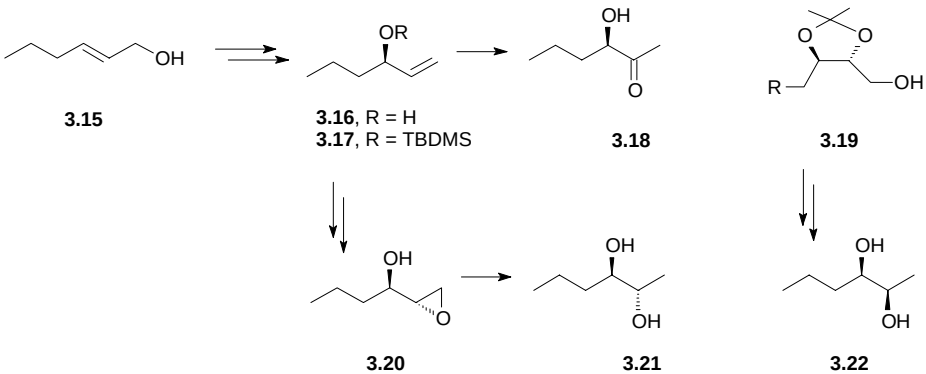


3.12

3.13, R = Me
3.14, R = Et

SCHEME 6

(*R*)-leucine, they obtained compounds **3.13** and **3.14** by reaction with dialkyl lithiocuprates.

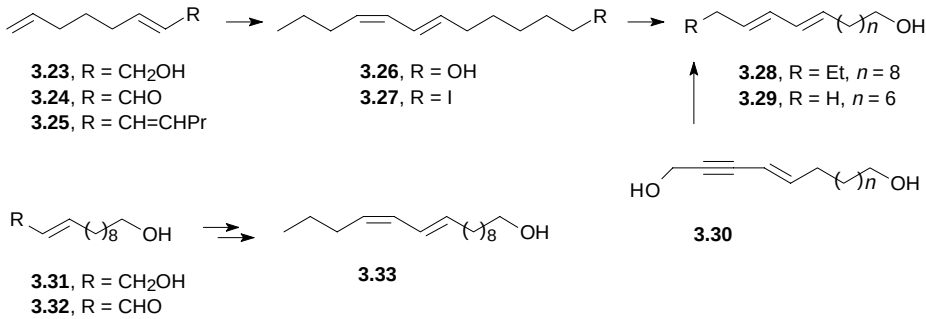


SCHEME 7

The male pheromone components of the longhorn beetles (*Hylotrupes bajulus* and *Pyrrhidium sanguineum*) have been identified by Francke and collaborators[28]. An unambiguous structural assignment of (3*R*)-3-hydroxyhexan-2-one (**3.18**), (2*R*,3*R*)-hexane-2,3-diol (**3.21**) and (2*S*,3*R*)-hexane-2,3-diol (**3.22**) was based on the synthesis of enantiomerically pure standards purified by chiral gas chromatography (Scheme 7). Thus, the commercially available (2*E*)-hex-2-en-1-ol (**3.15**) was subjected to Sharpless epoxidation giving the chiral epoxy alcohol (97% e.e. by chiral GC). This alcohol was transformed into the bromide which, after dehydrobromination, afforded compound **3.16**. Its Wacker oxidation resulted in the ketone **3.18**. Using a similar reaction sequence, the diol **3.21** was prepared from the epoxy alcohol **3.20**. Finally, the synthesis of 2*R*-enantiomer of **3.22** originated from diethyl (2*S*,3*S*)-tartrate and proceeded *via* the intermediate **3.19**, where R = OH → OTs → Et.

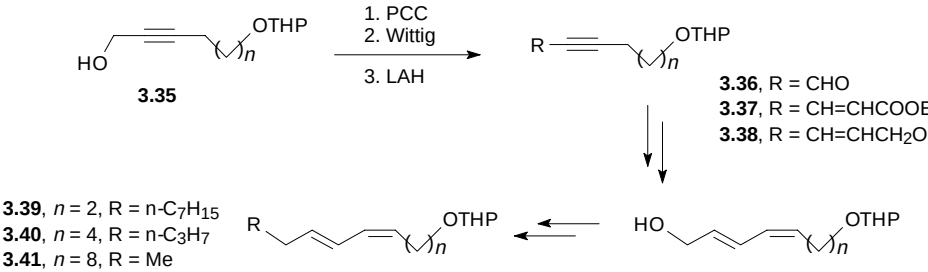
Many pheromone alcohols contain two or more conjugated and/or nonconjugated double bonds. While the conjugated *E*,*E*-unsaturated system can be prepared relatively easily, synthesis of pheromones with conjugated one or more *Z*-double bonds makes some troubles mainly due to an easy isomerization to the more stable *E*,*E*-isomers. Odinokov *et al.* have chosen (2*E*)-octa-2,7-dien-1-ol (**3.23**) as a convenient starting material to prepare (10*E*,12*Z*)- and (10*E*,12*E*)-hexadeca-10,12-dien-1-ols as well as (10*E*,12*Z*)-hexadeca-10,12-dienal, the components of the mulberry silkworm sex pheromone[29]. While the sequence **3.23** → **3.24** → **3.25** followed by hydroboration proceeded without problems, alkylation of **3.27** with 1-(tetrahydropyran-2-yloxy)butylmagnesium bromide under catalysis with CuBr resulted in reversal of configuration ((*Z*) → (*E*)) and compound **3.28** was obtained as the only product (Scheme 8). Therefore, Odinokov had to modify his original strategy and to choose **3.31** as the synthetic source for **3.33**.

Synthesis of (8*E*,10*E*)-dodeca-8,10-dien-1-ol (**3.29**) by Khrimyan *et al.*[30] uses **3.30** as the key structure. Khrimyan found that **3.30** can be reduced by lithium dimethoxy-



SCHEME 8

aluminium hydride (prepared *in situ* from $LiAlH_4$ and methanol in THF) giving good yield of the (*E*,*E*)-**3.29** while with $LiAlH_4$ alone the yield was low because of an increased amount of by-products. Reductive removal of the terminal hydroxy group *via* the mesylate was the last step in this preparation.



SCHEME 9

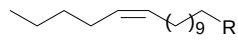
In an attempt to elaborate a general stereoselective synthesis of insect pheromone components possessing conjugated *Z*,*E*-dienes, Vig *et al.*[31] based their synthesis on the utilization of 1,3-enynes (generated by *in situ* alkylation of prop-2-yn-1-ol dianion followed by Wittig–Horner reaction). Thus, the dianion was coupled with $Br(CH_2)_nOTHP$ yielding **3.35** (n = 2, 4, 8) which was oxidized by PCC to give **3.36**. Subsequent Wittig reaction (**3.37**), reduction with $LiAlH_4$ (**3.38**), hydrogenation over the Lindlar catalyst, and coupling of the terminal mesylate with alkyl bromide under Li_2CuCl_4 catalysis gave **3.39**–**3.41** (Scheme 9). The synthesis also applies to the aldehydes and acetates.

Russian chemists[32] accomplished the synthesis of (8*E*,10*E*)-dodeca-8,10-dien-1-ol, the sex pheromone of *Laspeyresia pommonella*, by acetolysis of 4-propenyl-1,3-dioxane

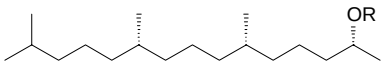
(**3.47**). Thus, **3.47** was converted to diacetyl derivative whose pyrolysis afforded hexa-2,4-dien-1-yl acetate. This compound is widely used in the synthesis of (*E*,*E*)-dienoates.

Guo *et al.*[33] synthesized all geometrical isomers of the poplar pole clearwing moth (*Sphecia siningensis*) pheromone (**3.42**) in purities higher than 95%. For instance, the *Z*,*Z*-isomer was obtained from the dianion of prop-2-yn-1-ol and an alkynyl halide, the *Z*-geometry being created by hydrogenation over P–2 Ni catalyst (Scheme 10).

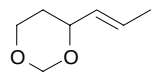
3.42



3.43, R = $B(Me)_2$
3.44, R = OH



3.45, R = H
3.46, R = $OCOCH_2CCl_3$



3.47

SCHEME 10

A new route to hexadec-11-en-1-ol (**3.44**), a sex pheromone of *Chilo infuscatellus*, has been presented by Narasimhan and Ganeshwarprasad[34]. The authors started from undecenal, which with pentyltriphenylphosphonium bromide afforded (11*Z*)-hexadeca-1,11-diene. Selective hydroboration of the terminal double bond was achieved by a new hydroborating procedure with $Ca(BH_4)_2$ and the formed borane **3.43** on a simple work-up afforded uncontaminated compound **3.44**.

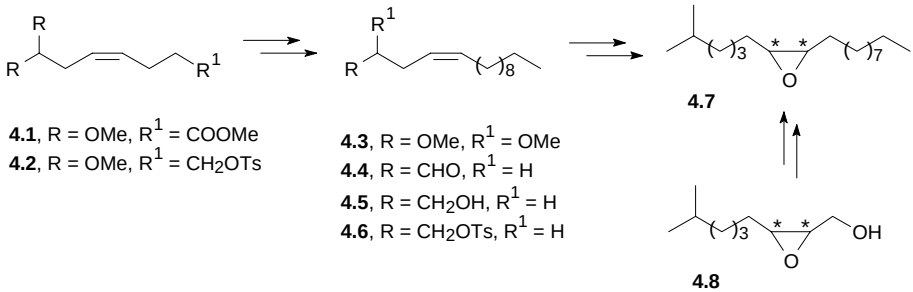
Synthesis of optically pure (2*R*,6*S*,10*S*)-6,10,14-trimethylpentadecan-2-ol (**3.45**), one of the stereoisomers of the rise moth (*Corcyra cephalonica)* sex pheromone, was performed using an enzyme-catalyzed hydrolysis by *Pseudomonas fluorescens* lipase[10]. The ester **3.46** was repeatedly resolved furnishing almost optically pure alcohol **3.45**.

4. ETHERS AND EPOXIDES

cis-(7*R*,8*S*)-7,8-Epoxy-2-methyloctadecane, disparlure (**4.7**), was identified as a gypsy moth (*Lymantria dispar)* sex pheromone. Though it seems that the other isomers do not decrease the biological activity in the field, optically pure **4.7** is an interesting object for synthetic chemists. Also syntheses of racemic disparlure are being continuously published (Scheme 11).

Odinokov *et al.*[35] have reported the ozonolysis of (*Z*,*Z*)-cycloocta-1,5-diene and conversions of the functional groups attached to the carbon chain as outlined in the scheme (**4.1** → **4.6**): *e.g.*, reaction with heptylmagnesium bromide in the presence of Li_2CuCl_4

gave **4.3**. Further conversion of this compound to tosylate **4.6** and subsequent reaction with isobutylmagnesium bromide/Li_2CuCl_4 and MCPBA led finally to the racemic *cis*-**4.7**.

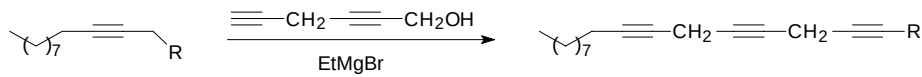


4.1, R = OMe, R^1 = COOMe
4.2, R = OMe, R^1 = CH_2OTs

4.3, R = OMe, R^1 = OMe
4.4, R = CHO, R^1 = H
4.5, R = CH_2OH, R^1 = H
4.6, R = CH_2OTs, R^1 = H

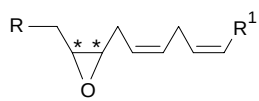
SCHEME 11

Fukusaki *et al.*[36] applied lipase-catalyzed enantioselective acylation to 2,3-epoxy-8-methylnonan-1-ol (**4.8**) which served as a useful intermediate in the disparlure synthesis. The enzymatic acylation was performed in acetic anhydride/diisopropyl ether yielding the acetates of (2*S*,3*R*)-**4.8** and (2*R*,3*S*)-**4.8**. The optical purity was further improved up to 95% e.e. by lipase-catalyzed alcoholysis. To optimize the e.e., various anhydrides were checked as acylating agents.



4.9, R = CH(Me)OEt
4.10, R = OH
4.11, R = I

4.12, R = CH_2OH
4.13, R = Li

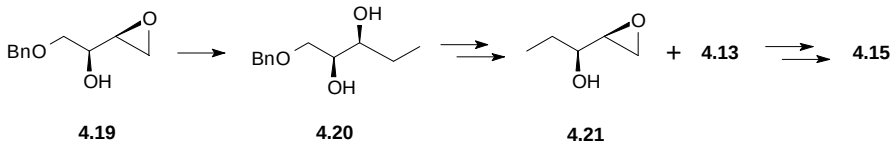


4.14, R = OH, R^1 = n-C_9H_{19}
4.15, R = Me, R^1 = n-C_9H_{19}
4.16, R = n-C_9H_{19}, R^1 = Et
4.17, R = n-$C_{10}H_{21}$, R^1 = Et
4.18, R = n-$C_{10}H_{21}$, R^1 = $CH=CH_2$

SCHEME 12

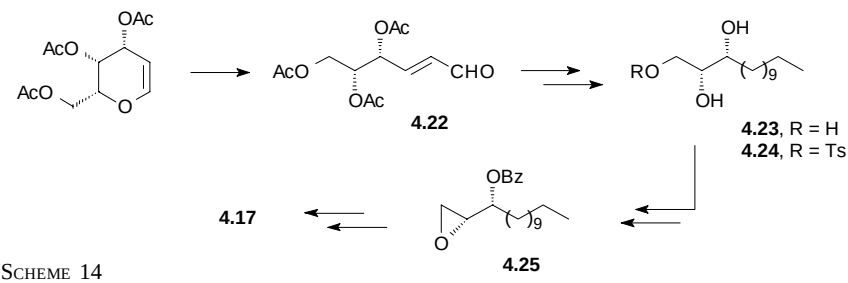
The major constituent of the giant looper (*Boarmia selenaria*) sex pheromone, **4.15**, has been synthesized by Cosse *et al.*[37,38]. The alcohol **4.10**, obtained as a product of nonyl bromide and lithium/prop-2-yn-1-ol coupling, was transformed into the iodide **4.11** which then reacted with hexa-2,5-diyn-1-ol in the presence of 2 equivalents of ethylmagnesium bromide. The obtained alcohol **4.12** as a template structure of the pheromone, was converted into **4.15** by partial hydrogenation and Sharpless epoxidation (Scheme 12).

A general method for the synthesis of chiral *cis*-epoxides bearing both saturated and unsaturated chain, elaborated by Soulie *et al.*, has been applied to the synthesis of structurally similar pheromones[39,40]. The synthetic strategy can be understood from the sequence **4.19** → **4.21** (Scheme 13). Thus, the epoxide **4.19** was treated with lithium dimethyl cuprate under the specific protection of hydroxy groups, the result of which was the compound **4.21**. Subsequent reaction with lithium acetylide **4.13** and alkaline work-up afforded unsaturated (3*S*,4*R*)-**4.15**. Compound **4.16** was prepared similarly.



SCHEME 13

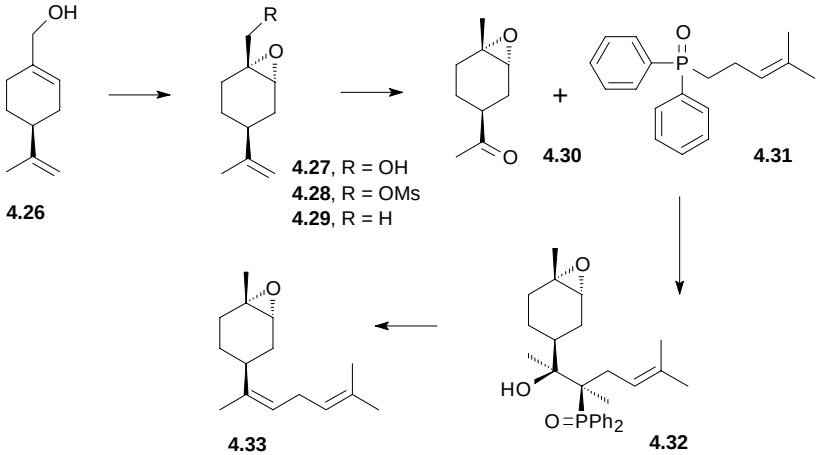
Glycals for the stereospecific synthesis of (3*Z*,6*Z*,9*Z*,10*R*)-**4.17**, the component of sex pheromone of the American white butterfly, has been used by Tolstikov *et al.*[41]. The synthesis originated from the aldehyde **4.22**. Its eight carbon atoms homologation using octyltriphenylphosphonium ylide and subsequent hydrogenation resulted in **4.25**. This oxirane was treated with lithium hepta-1,4-diynide and the product converted to (9*S*,10*R*)-**4.17** by means of a base (Scheme 14).



SCHEME 14

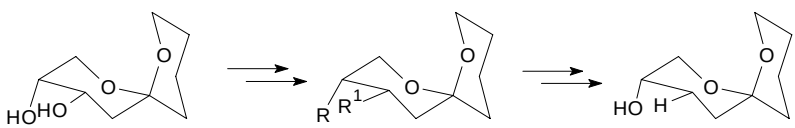
Within the framework of synthetic studies on insect sexual attractants, Nikolaeva and Kovalev[42] published preparation of racemic **4.18**, a component of the *Hyphantria cunea* sex pheromone. In this synthesis, acetylenic chemistry and triple bond hydrogenation was mainly used.

(–)-(*Z*)-(1*S*,2*R*,4*S*)-Epoxybisabolene (**4.33**), the major component of the green stink bug (*Nezara viridula*) sex pheromone, was prepared from (*S*)-(–)-perillyl alcohol (**4.26**) starting with Sharpless epoxidation[43]. Of the two possible products, **4.27**, predominanted. Oxidation of **4.29** with $KMnO_4$ gave the substrate for Wittig–Horner reaction (**4.30**) where the erythro isomer **4.32** resulted as a separable compound. Then the base-induced elimination simply afforded **4.33** (Scheme 15).



SCHEME 15

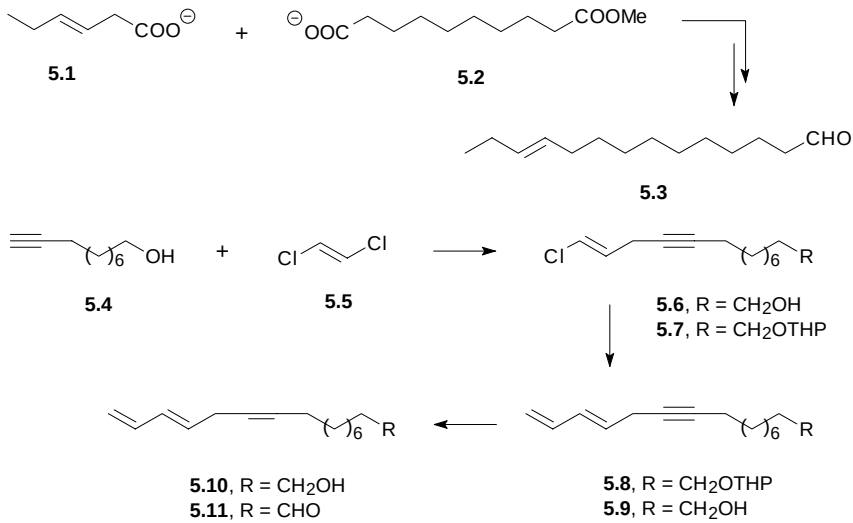
Enantiospecific synthesis of spiroketals **4.40** and **4.43**, the minor components of olive fruit fly pheromone, was accomplished by Spanish chemists[44] (Scheme 16). Their interesting synthetic approach is based on D-fructose which determines the stereochemistry of the final product. Compounds **4.40** and **4.43** have arisen as a result of reactions affected by different chemical properties of both hydroxy groups. Thus, having started from **4.34**, the compound **4.35** was obtained by the action of dibutyltin oxide. Subsequent reaction with benzyl bromide occurred with high stereoselectivity giving the monobenzyl compound **4.36**. Several other steps where stereo- and regioselective protection–deprotection procedures were included, led finally to **4.40**. The isomeric compound **4.43** was obtained similarly by conversion of **4.36** into **4.41** and **4.42**, making use of Barton's reduction and deprotection procedures.



SCHEME 16

5. ALDEHYDES

Dzumakulov and Kadyrova[45] synthesized (9*Z*)-hexadec-9-enal, one of the components of *Heliothis armigera* sex pheromone. The three-step synthesis involved Wittig reaction of 8-acetoxyoctanal with heptyltriphenylphosphonium bromide, $LiAlH_4$ reduction of the ester and PCC oxidation to the desired aldehyde. (11*Z*)-Octadec-11-enal was prepared similarly[46].



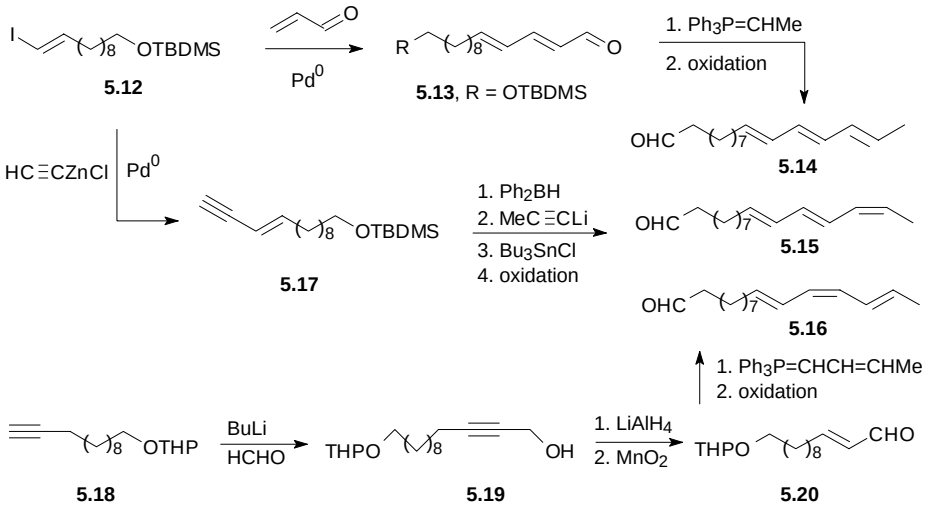
SCHEME 17

(11*E*)-Tetradec-11-enal (**5.3**), the sex pheromone of the eastern spruce budworm, was prepared by Singh *et al.*[47] (Scheme 17). Employing Kolbe's anodic cross-coupling of (3*E*)-hexen-3-oic acid (**5.1**) and methyl hydrogen decanedioate (**5.2**), the authors devised a simple way for obtaining the title compound. Millar described a short and efficient synthesis of (9*Z*,11*E*)-tetradeca-9,11,13-trienal (**5.11**), the major component of sex pheromone of the carob moth[48] (*Ectomyelois ceratoniae*). The key step included Pd^0-catalyzed coupling of **5.4** (obtained from dec-3-yn-1-ol by the zipper reaction) and (*E*)-1,2-dichloroethene (**5.5**) with subsequent coupling with vinylmagnesium bromide to form **5.7**. The triple bond in **5.9** was reduced with high stereoselectivity using zinc granules in aqueous propan-1-ol with no detectable isomerization of the double bonds present. The synthesis was completed by Swern oxidation to aldehyde **5.11** in 50% total yield.

(11*E*)-Octadec-11-enal, (14*E*)-octadec-14-enal, (11*E*,14*E*)-octadeca-11,14-dienal and octadecanal, the components of female tea cluster caterpilar (*Andraca bipunctata*) sex pheromone, were synthesized by Ho *et al.*[49]. For the purpose of identification, Ho also synthesized *Z*-isomers of the above mentioned compounds as GC/MS standards. The

synthetic strategy was based on the consecutive alkylation of terminal acetylenic intermediates with appropriate alkynes giving compounds of required length. The *Z*- or *E*-configuration of products was achieved by hydrogenation or reduction of the triple bond with $LiAlH_4$ in diglyme.

Synthesis of long-chain aldehydes with several conjugated double bonds in the molecule is certainly a troublesome preparation because the compounds undergo easy degradation and extensive isomerization. Therefore, the reaction procedure had to be carefully chosen according to the individual compounds' properties and possible separation of products from by-products.



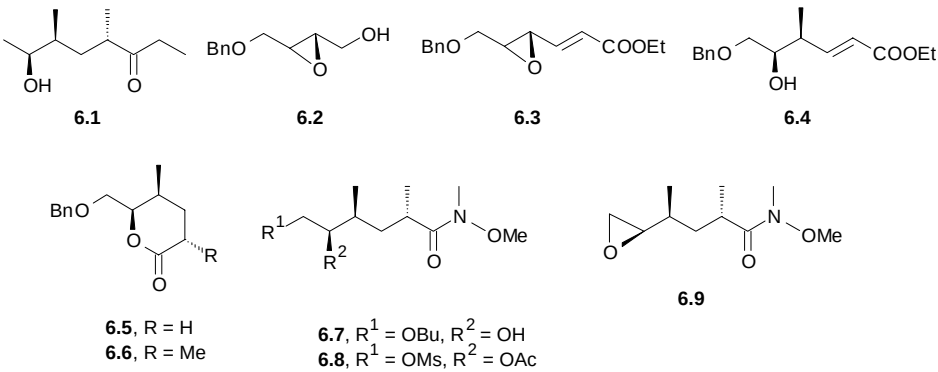
SCHEME 18

A report by Doolitle *et al.*[50] described a stereoselective synthesis of (10*E*,12*E*,14*E*)-, (10*E*,12*E*,14*Z*)-, and (10*E*,12*Z*,14*E*)-hexadeca-10,12,14-trienals (**5.14**, **5.15**, **5.16**), two of them being the components of *Manduca sexta* pheromone (Scheme 18). Aldehydes **5.14** and **5.15** were prepared from iodide **5.12** (obtained by catecholborane–iodine conversion of undec-10-yn-1-ol) which was further coupled with either prop-2-enal or acetylene-zinc chloride giving **5.13** and **5.17**, respectively. Dess–Martin periodinane oxidation proved to be the most suitable method for converting alcohols into the final aldehydes. The products of the preceding reactions were mostly obtained as mixtures of geometric isomers. Rather surprisingly, the isomers could be separated by reverse-phase HPLC.

6. KETONES

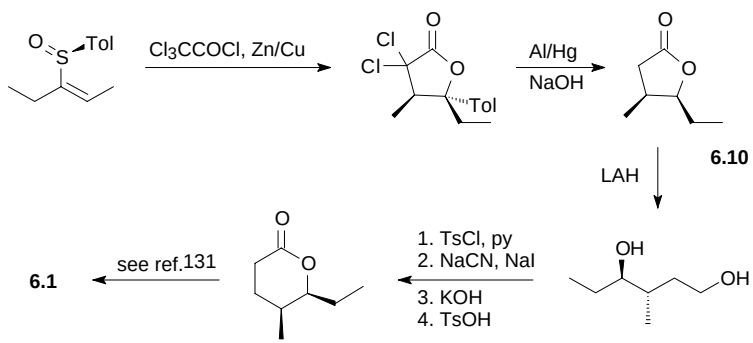
For the synthesis of the already known (2*R*,3*S*)-4-benzyloxy-2,3-epoxybutanol[52] (**6.2**), the Katsuki–Sharpless asymmetric epoxidation[51] of a starting material for the synthesis

of serricornin and, sex pheromone of the cigarette beetle *(Lasioderma serricorne)*, **6.1**, was used[53]. The general strategy for obtaining the pheromone included oxidation of the hydroxy group in **6.2** and Horner–Emmons reaction of the resulting aldehyde giving epoxyhexenoate **6.3**, the methylation of which with trimethylaluminum led to the alcohol **6.4**. Hydrogenation of **6.4** followed by methylation of the formed lactone **6.5** afforded the dimethyl lactone **6.6**. To avoid isomerization of the α-methyl group, the lactone was converted[54] to the amide **6.7**. Acetylation, hydrogenation and mesylation gave the mesylate **6.8**. Conversion of the mesylate to the epoxide **6.9** followed by reaction with lithium dimethylcuprate and then with ethyllithium led to serricornin (**6.1**) (Scheme 19).



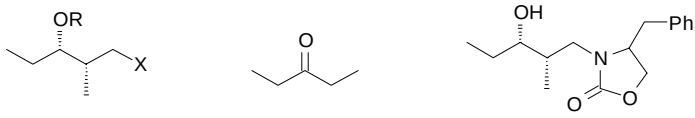
SCHEME 19

For the synthesis of serricornin, Ferreira *et al.*[55] used (4*S*,5*S*)-4-methyl-5-ethylpentano-5-lactone (**6.10**) instead of β-homoallylic alcohols as described by Sato *et al.*[56]. The key step for creating the chiral centers involved an enantioselective lactonization of optically active vinyl sulfoxides[57] (Scheme 20).



SCHEME 20

Synthesis of serricornin (**6.1**) by Chan *et al.*[58], suitable for preparing gram quantities of material, was based on coupling of pentan-3-one (**6.14**) with **6.12** prepared by a shorter route than described by Mori[59]. The authors turned to the aldol methodology developed earlier[60,61]. They used crystalline adduct **6.15** with phenylalanine-derived oxazolidine providing an excellent diastereoselectivity of the reaction intermediate. The five-step sequence leading to the iodide **6.13** involved routine steps and was used to produce hundreds of grams of the final product (Scheme 21).



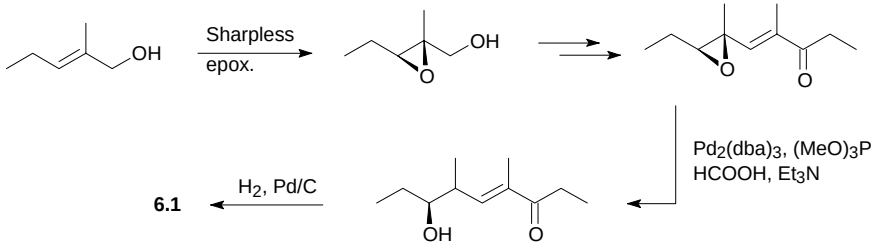
6.12, R = H, X = I
6.13, R = TBS, X = I

6.14

6.15

SCHEME 21

Earlier, the Japanese authors[62] presented a (–)-serricornin (**6.1**) synthesis using palladium-catalyzed stereoselective hydrogenolysis of an alkenyloxirane (Scheme 22).

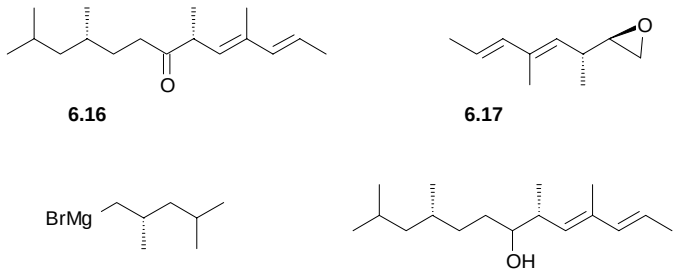


SCHEME 22

Among the scale pests, the *Matsucoccus* scales play an important role in damaging the host pine population in Europe (*M. feytaudi*), U.S.A. (*M. resinosae*), Asia (*M. matsumurae* and *thunbergianae*), and in Israel *(M. josephi)*. They were found to use branched and unsaturated ketones as sex pheromones. Except for the European and Israel endemites, they use (2*E*,4E,6*R*,10*R*)-4,6,10,12-tetramethyltrideca-2,4-dien-7-one (matsuone) (**6.16**) as a main sex pheromone component.

An attractive strategy for the synthesis of matsuone presented by Cywin *et al.*[63] included (2*S*,3*R*,4*E*,6*E*)-1,2-epoxy-3,5-dimethylocta-4,6-diene (**6.17**) as a key compound. The copper-assisted addition of the Grignard reagent **6.18** to the epoxide **6.17** gave rise to the alcohol **6.19** which, after oxidation with tetrapropylammonium perruthenate led to the final product **6.16**. Using the same reaction sequence, the C_{10}-epimeric (6*R*,10*S*)-product was also prepared (Scheme 23).

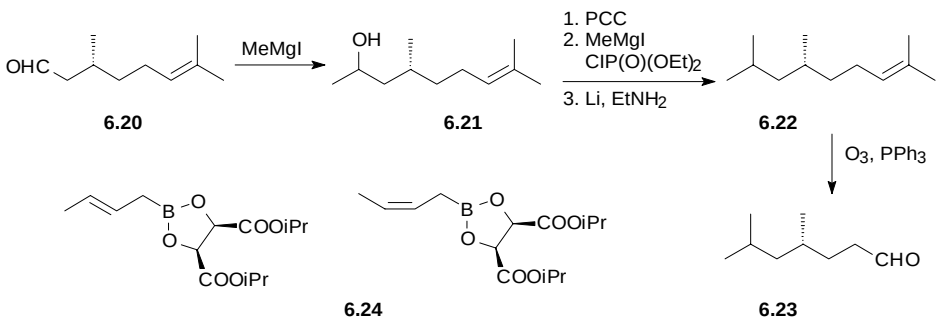
The Chinese authors[64] synthesized all four stereoisomers of the ketone **6.16** in order to assign the absolute configuration to the natural sex pheromone. Starting from (*S*)-citronellal to build the aldehyde **6.23** with known configuration, the set of reactions was



6.16 **6.17** **6.18** **6.19**

SCHEME 23

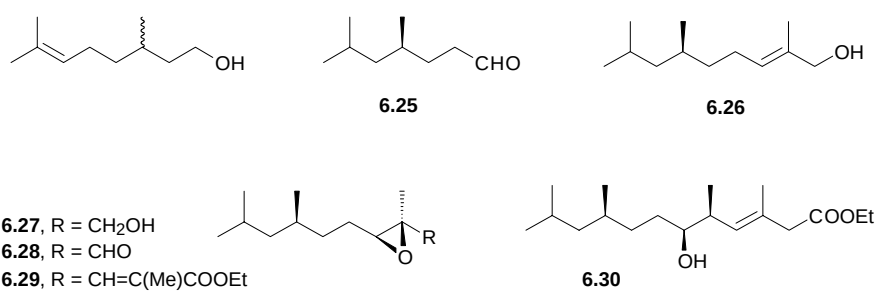
followed by aldol condensation of the aldehyde **6.23** with the boronates **6.24** to build the configuration at C-6 of **6.16** (Scheme 24).



6.20 **6.21** **6.22** **6.24** **6.23**

SCHEME 24

The *R*- or *S*-configuration on C-6 was achieved by condensation of **6.23** with (*E*)- or (*Z*)-boronates **6.24**. In a similar way, Mori and Harashima[65] prepared matsuone (**6.16**) and its antipode starting from (*R*)- and (*S*)-citronellol, respectively (Scheme 25). They



6.25 **6.26**

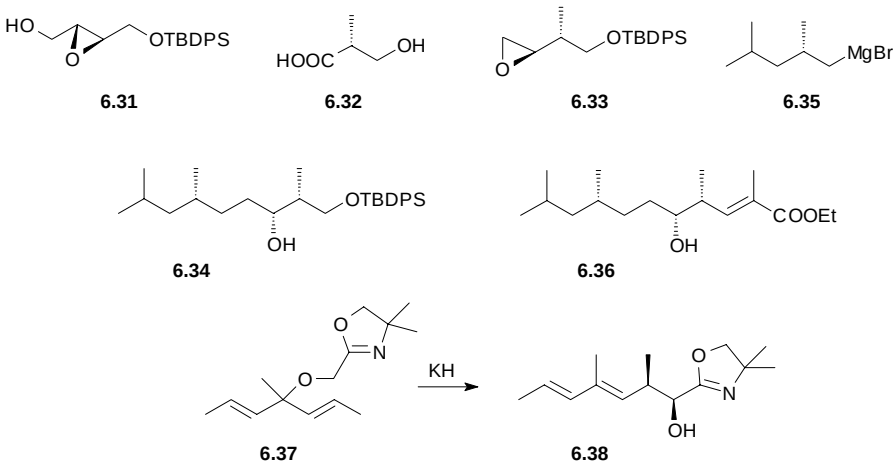
6.27, R = CH_2OH
6.28, R = CHO
6.29, R = CH=C(Me)COOEt

6.30

SCHEME 25

used asymmetric epoxidation[51] of the allyl alcohol **6.26** to **6.27** and palladium-catalyzed reductive cleavage of the epoxy ring of **6.29** to **6.30** as the key steps. The remaining reactions, namely **6.25** to **6.26**, **6.27** to **6.29**, and **6.30** to **6.16** are routine.

In 1995, a new and effective synthesis of matsuone was performed by Mori *et al.*[66] (Scheme 26). Their synthesis started from (2*R*,3*S*)-4-(*tert*-butyldiphenylsilyloxy)-2,3-epoxybutan-1-ol (**6.31**) and methyl (*R*)-3-hydroxy-2-methyl propanoate (**6.32**). The epoxide **6.33** was derived from the epoxide **6.31** and furnished the hydroxy compound **6.34** by alkylating cleavage of the epoxide ring with the Grignard compound **6.35**. The synthesis of matsuone **6.16** was then finished in the following way: **6.35** → **6.36** → **6.16**.

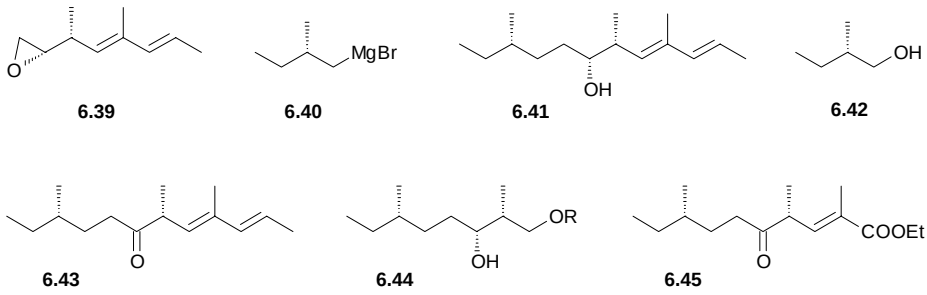


SCHEME 26

Four possible stereoisomers of matsuone (**6.16**) were prepared[67,68] in order to bioassay them with the natural pheromone. The authors applied a newly developed, diastereoselective (2,3)-Wittig rearrangement of tertiary biallylic ether **6.37** → **6.38** for this purpose[69]. Surprisingly enough, the laboratory bioassays on *M. resinosae*, which helped to determine the absolute configuration of the natural matsuone to be (6*R*,10*R*)-**6.16**, revealed that the unnatural 6*R*,10*S*-isomer also shows significant activity. The question whether *M. matsumurae* and *M. thunbergianae* also respond to this unnatural (6*R*,10*S*)-isomer remains still unanswered.

The synthesis of (2*E*,4*E*,6*R*,10*S*)-4,6,10-trimethyldodeca-2,4-dien-7-one (**6.43**), an assumed major component of a sex pheromone blend of the maritime pine scale (*Matsucoccus feytaudi*), was performed by Cywin and Kallmerten[70]. It was based on the coupling of epoxide **6.39** with Grignard reagent **6.40** (easily obtained from **6.42**) giving alcohol **6.41**, which by oxidation with tetrapropylammonium perruthenate afforded the desired (6*R*,10*S*)-ketone **6.43** (Scheme 27). Comparison of the NMR spectra confirmed its identity with the native *M. feytaudi* pheromone.

Mori and Harashima[71] also synthesized the ketone **6.43** and its (6*S*,10*S*)-stereoisomer in a way analogous to the synthesis of matsuone as described in the paper of Mori[65] and – after re-examination of the NMR spectra[72] – confirmed the conclusion that the natural *M. feytaudi* pheromone has actually 6*R*,10*S*-configuration.

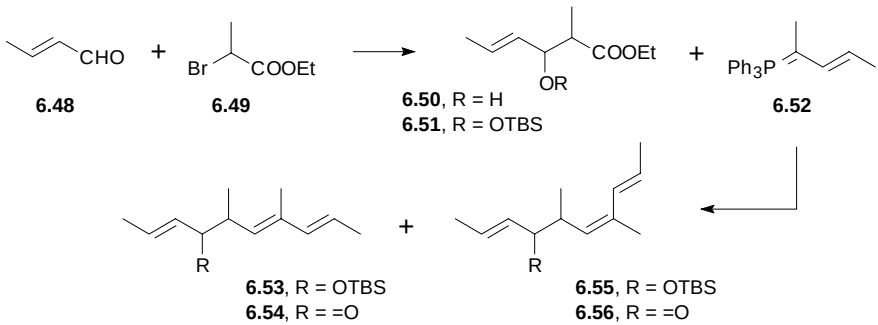


6.39 **6.40** **6.41** **6.42** **6.43** **6.44** **6.45**

SCHEME 27

Mori *et al*.[73] published an improved way of preparing the above pheromone starting from the epoxide **6.39** which, after treating with Grignard reagent **6.40**, gave the alcohol **6.41**. Routine oxidation and Wittig reaction steps furnished the ketoester **6.45** and finally, the pheromone **6.43**.

The Israeli pine bast scale (*M. josephi*), is assumed to use two main pheromone components, **6.54** and **6.56**, the former being more important as far as the activity is concerned. The synthesis was based on the $C_4 + C_3 + C_5$ approach using crotonaldehyde (**6.48**), ethyl 2-bromopropanoate (**6.49**) and the Wittig ylide **6.52** derived from (3*E*)-pent-3-en-2-ol[74] (Scheme 28). Of the two possible isomers, (5*R*)-**6.54** and (5*S*)-**6.56**, the former, having supposedly the same stereochemistry at the α-keto position as the pheromones of other *Matsucoccus* species, was synthesized preferentially.

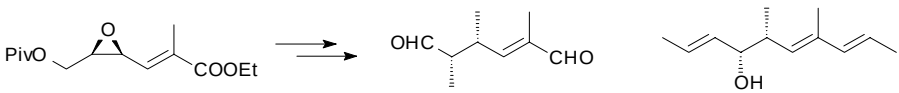


6.48 **6.49** **6.50**, R = H **6.51**, R = OTBS **6.52**

6.53, R = OTBS **6.54**, R = =O **6.55**, R = OTBS **6.56**, R = =O

SCHEME 28

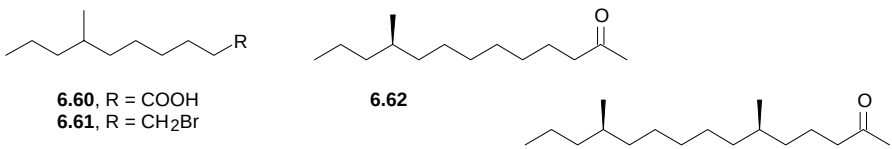
Compound (5*R*)-**6.54** was also prepared[75] starting from the epoxy ester **6.57** (Scheme 29). The cleavage of the oxirane ring in **6.57** gave the dialdehyde **6.58** which on Wittig chain extension furnished the alcohol **6.59** and further the final product (5*R*)-**6.54**.



6.57 **6.58** **6.59**

SCHEME 29

Racemic form of the spotted cucumber beetle (*Diabrotica undecimpunctata*) sex pheromone (**6.62**) was prepared from 7-methyldecanoic acid (**6.60**) *via* acetoacetic ester condensation with the bromo compound **6.61** (ref.[76]) (Scheme 30).



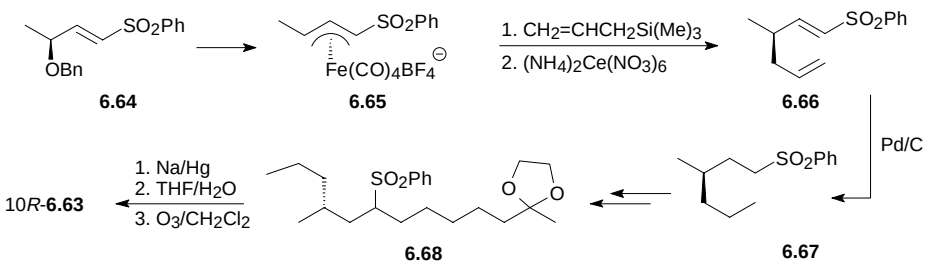
6.60, R = COOH
6.61, R = CH_2Br

6.62

6.63

SCHEME 30

The biologically active enantiomer, (10*R*)-10-methyltridecan-2-one (**6.62**), was synthesized by Enders and Jandeleit[77] using enantiopure chiral tetracarbonyliron derivative **6.65** (Scheme 31). This intermediate was obtained from (*S*)-(–)-lactic acid *via* the vinyl sulfone[78] **6.64**.

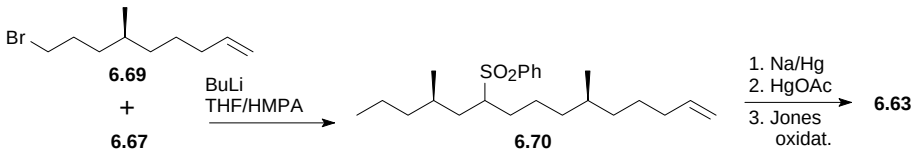


6.64 **6.65** **6.66** **6.67** **6.68**

SCHEME 31

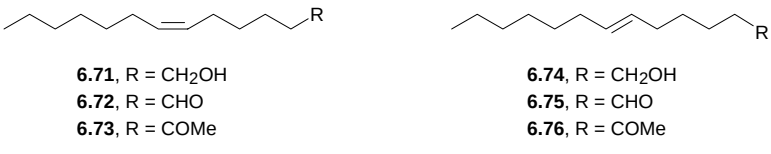
The synthesis of (6*R*,12*R*)-6,12-dimethylpentadecan-2-one[79] (**6.63**), the sex pheromone of the *Diabrotica balteata,* was based on the same principle as shown in the previous paper of Enders[77]. However, the intermediate **6.67** was coupled with the

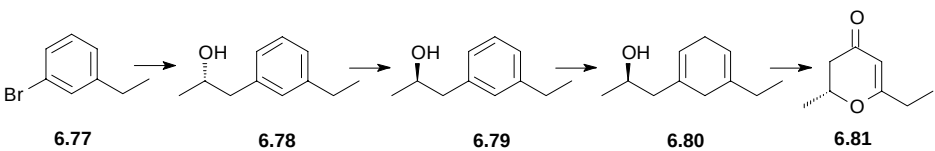
bromo derivative **6.69** in order to introduce the second methyl group into the carbon skeleton (Scheme 32).



SCHEME 32

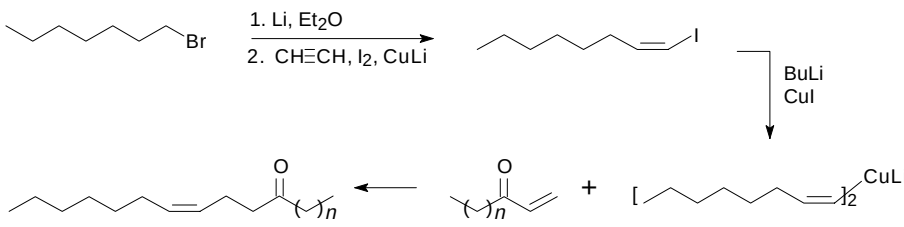
Females of the oriental beetle (*Anomala orientalis*) use the 9 : 1 blend of (7*Z*)- and (7*E*)-tetradec-7-en-2-one ((*Z*)-**6.73** and (*E*)-**6.76**) as sex pheromone. Zhang *et al.*[80] synthesized both isomers for flight-tunnel bioassays, starting from (6*Z*)- and (6*E*)-tridec-6-en-1-ol (**6.71** and **6.74**, respectively), *via* the corresponding aldehydes **6.72** and **6.75**, using MeMgBr as the methylating agent (Scheme 33).





SCHEME 33

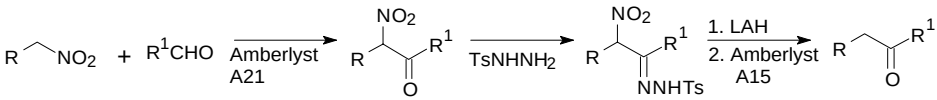
The male swift moth (*Hepialus hecta*) sex pheromone, (+)-(2*R*)-6-ethyl-2-methyl-2,3-dihydro-4*H*-pyran-4-one (**6.81**), was prepared from 1-bromo-3-ethylbenzene (**6.77**) which was further converted to alcohol **6.78** by means of (–)-(*S*)-methyloxirane[81]. After inversion of the chiral center in the alcohol **6.78** to **6.79** according to Mitsunobu[82], the resulting isomer **6.79** was partially reduced and the obtained alcohol **6.80** was treated with Li/NH_3 and ozonized to give the final (+)-**6.81**.



SCHEME 34

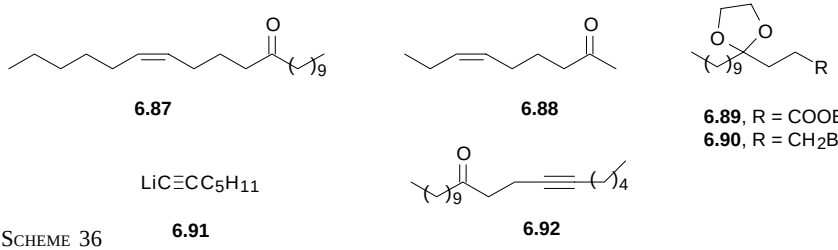
Sex pheromones of the peach fruit moth (*Carposina nipponensis*) and the Douglas fir tussock moth (*Orgyia pseudotsugata*) were found to be straight-chain γ,δ-unsaturated ketones[83]. A procedure based on the reaction of di((*Z*)-alkenyl) cuprate **6.82** with vinyl ketones **6.83** or **6.84** was used to prepare (7*Z*)-nonadec-7-en-11-one (**6.85**) for *C. nipponensis*, and (7*Z*)-heneicos-7-en-11-one (**6.86**) which the authors erroneously presented as an *O. pseudotsugata* sex pheromone[83] (Scheme 34).

In 1991, Ballini[84] published the synthesis of both (6*Z*)-henicos-6-en-11-one (**6.87**), the Douglas fir tussock moth *(Orgyia pseudotsugata)* sex pheromone and (6*Z*)-non-6-en-2-one (**6.88**), an intermediate for the synthesis of brevicomin, the sex pheromone of the Western pine beetle (*Dentroctonus brevicomis*). The functionalized nitroalkanes explored for this purpose have been prepared from commercial alkenols by conversion into the corresponding bromides and substitution with sodium nitrite in DMF. The α-nitroketones were denitrated by $LiAlH_4$ reduction of their 4-methylbenzenesulfonohydrazones (Scheme 35).



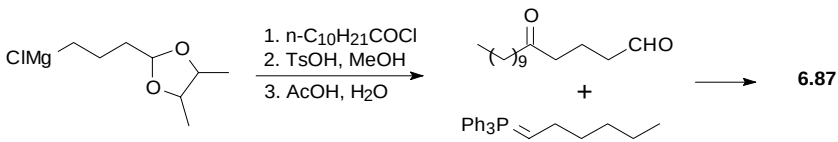
SCHEME 35

The synthesis of the *Orgyia* pheromone **6.87** published by Kovalev *et al.*[85] was based on ethyl 4-oxotetradecanoate which, after protecting the keto group (**6.89**), was transformed into the bromide **6.90** by conventional methods (Scheme 36). Treatment of the bromide with lithium acetylide **6.91**, deprotection and partial reduction of the triple bond in the ketone **6.92** gave the expected product **6.87**.



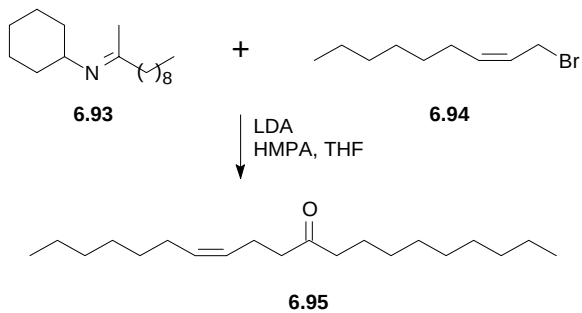
SCHEME 36

Stowell and Pelito[86] applied the δ–ketoaldehyde synthesis for the preparation of the above sex pheromone **6.87** (Scheme 37).



SCHEME 37

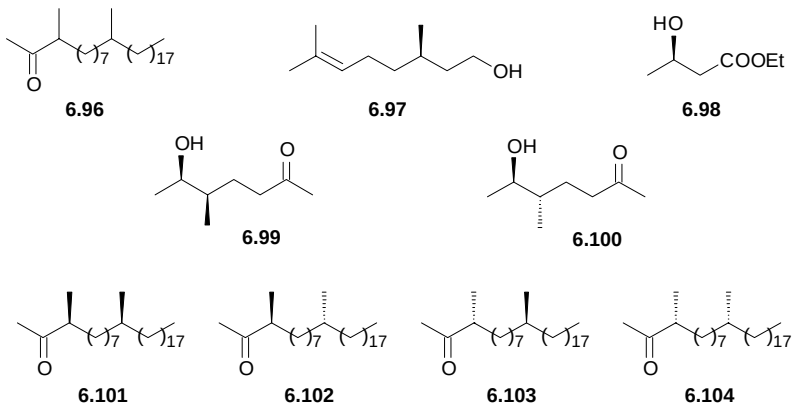
(7*Z*)-Eicos-7-en-11-one **(6.95)**, the main component of the peach fruit moth (*Carposina nipponensis*) pheromone blend, was prepared by Kang and Lee[87]. This synthesis involved the reaction of the imine **6.93** with (2*Z*)-1-bromonon-2-ene (**6.94**) (Scheme 38).



6.93 **6.94** **6.95**

SCHEME 38

(*R*)-Citronellol (**6.97**) and ethyl (3*R*)-3-hydroxybutanoate (**6.98**) were the starting materials for preparation of 3,11-dimethylnonacosan-2-one (**6.96**), the female-produced sex pheromone of the German cockroach (*Blatella germanica*). For the synthesis of all four stereoisomers of **6.96** (**6.101**–**6.104**), the key step was chromatographic separation of (5*RS*,6*R*)-6-hydroxy-5-methylheptan-2-one isomers[88] to give pure **6.99** and **6.100** (Scheme 39).



6.96 **6.97** **6.98**

6.99 **6.100**

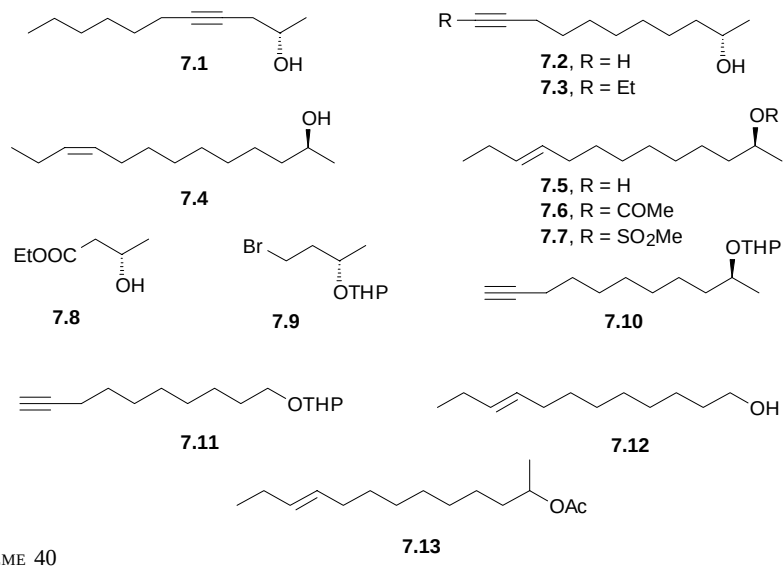
6.101 **6.102** **6.103** **6.104**

SCHEME 39

7. ACETATES

The Hessian fly (*Mayetiola destructor*) has been reported to be one of the most destructive insect pests of wheat. The identity of the main component of the native pheromone with (2*S*,10*E*)-tridec-10-en-2-yl acetate (**7.6**) was reported by Foster *et al.*[89].

Millar *et al.*[90] started the synthesis of the Hessian fly pheromone, in addition to its 10*Z*- isomer and its 2*R*-enantiomer, from (–)-(*S*)-propylene oxide and oct-1-yne to obtain (2*S*)-unde-4-cyn-2-ol (**7.1**) in high optical purity (Scheme 40). To move the triple bond, a modified zipper reaction[91] was used resulting in the alcohol **7.2**, which on ethyl bromide alkylation furnished (*S*)-tridecynol (**7.3**). Reduction of the triple bond with either P–2 Ni or Na/NH_3 gave (10*Z*)- and (10*E*)-tridecen-2-ols (**7.4** or **7.5**), respectively. The acetylation was the final step to obtain **7.6**. For comparative evaluations of biological activity, the 2*R*-antipode of **7.6** was also prepared *via* stereoselective nucleophilic displacement of the mesylate group in **7.7**.

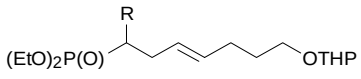


SCHEME 40

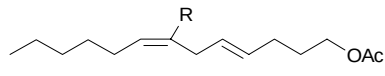
There are two more papers dealing with the synthesis of the Hessian fly pheromone **7.6** differing in the way of creating the chiral (*S*)-acetate center. For instance, Takeuchi and Mori[92] have chosen yeast reduction of ethyl acetoacetate and then converted the product of reduction (**7.8**) to the bromide[93] **7.9**. Alkylation of hept-1-yne with **7.9** gave, after acetylene zipper reaction[94], the protected (*S*)-undec-9-yne-2-ol (**7.10**) which, after alkylation with ethyl iodide, subsequent $LiAlH_4$ reduction and acetylation, afforded the desired final product in a good yield and 95% e.e.

Kamezawa *et al.*[95] synthesized (2*S*,10*E*)-tridec-10-en-2-yl acetate (**7.6**) in a highly enantiomerically pure form. Thus, alkylation of 9-(tetrahydropyranyloxy)dec-1-yne (**7.11**), deprotection and $LiAlH_4$ reduction of the triple bond, furnished (9*E*)-dodec-9-en-1-ol (**7.12**), which was further oxidized and coupled with MeMgBr. Subsequent acetylation gave the racemic acetate **7.13**. The racemate was hydrolyzed by *Pseudomonas cepacia* lipase to afford **7.6** in 100% e.e. (overall yield 10.3%).

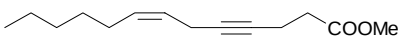
(*E*)-γ,δ-Unsaturated phosphonate **7.14** was chosen[96] as a key intermediate for the synthesis of (4*E*,7*Z*)-trideca-4,7-dienyl acetate (**7.17**), a sex pheromone component of the potato tuberworm, (*Phtorimaea operculella*) (Scheme 41). The methylsulfanyl group in **7.14** was oxidized with MCPBA to the more reactive and easily removable methanesulfonyl group furnishing, after Horner–Wadsworth–Emmons reaction with hexanal, compound **7.16**, and after chromatographic purification, desulfonylation with sodium hydrogensulfite, deprotection and acetylation, the acetate **7.17**.



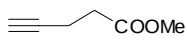
7.14, R = SMe
7.15, R = SO_2Me



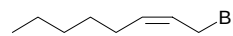
7.16, R = SO_2Me
7.17, R = H



7.18



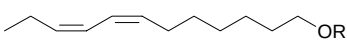
7.19



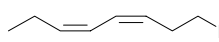
7.20

SCHEME 41

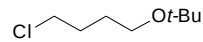
Another synthesis of **7.17**, which is also a component of the *Lithocolletis corylifoliella* pheromone, was described by the Roumanian authors[97]. They used methyl (7*Z*)-tridec-7-en-4-ynoate (**7.18**; prepared by Grignard-promoted coupling of **7.19** and (2*Z*)-1-bromooct-2-ene (**7.20**)), as the key compound. An $LiAlH_4$ reduction of both the triple bond and the ester group followed by acetylation gave the acetate **7.17**. For the synthesis of (7*Z*,9*Z*)-dodeca-7,9-dienyl acetate (**7.21**), a sex pheromone component of the leafrollers of *Epinotia* and *Eucosma* sp., (3*Z*,5*Z*)-1-bromoocta-3,5-diene (**7.23**) was found to be the intermediate of choice[98]. The organocuprate coupling with 4-*tert*-butoxy-1-chlorobutane (**7.24**) gave (7*Z*,9*Z*)-1-*tert*-butoxydodeca-7,9-diene (**7.22**) and, after acetolysis, the target pheromone **7.21** with the configurational purity of 87% (Scheme 42).



7.21, R = Ac
7.22, R = *t*-Bu



7.23

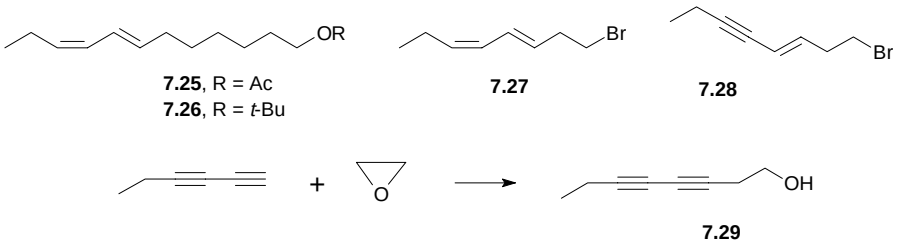


7.24

SCHEME 42

Chrelashvili *et al.*[99] performed the synthesis of **7.25**, the *Lobesia botrana* pheromone, using (3*E*,5*Z*)-1-bromoocta-3,5-diene (**7.27**) as the main building block. The 3*E*,5*Z*-double bond configuration was achieved by stepwise reduction of the diacetylenic alcohol **7.29** by means of $LiAlH_4$ reduction of the Δ^3 bond followed by the Zn/Cu/ i-PrOH reduction of the other. The obtained *tert*-butoxydodecadiene **7.26** was transformed to acetate in the way mentioned earlier[98] (Scheme 43).

Alternatively, **7.25** was prepared in 45% yield and 84.7% configurational purity by $Ac_2O/FeCl_3$ acetylation of (7*E*,9*Z*)-1-*tert*-butoxydodeca-7,9-diene (**7.26**; obtained by Li_2CuCl_4 catalyzed cross-coupling of 4-*tert*-butoxybutylmagnesium chloride with the enyne[100] **7.28**.



7.25, R = Ac
7.26, R = *t*-Bu

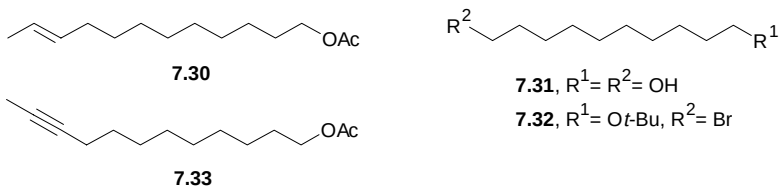
7.27

7.28

7.29

SCHEME 43

In these papers (refs[98–100]), the advantage of the *tert*-butyl over the tetrahydropyranyl protection has been emphasized because of the stability and ability of the former of direct transformation into the acetyl group (see also: Tellier and Descoins[101]) (Scheme 44).



7.30

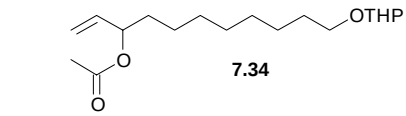
7.33

7.31, $R^1 = R^2 = OH$
7.32, $R^1 = O$*t*-Bu, $R^2 = Br$

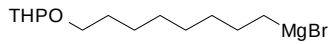
SCHEME 44

The Roumanian authors[102] described the synthesis of (10*E*)-dodec-10-en-1-yl acetate (**7.30**), the sex pheromone of the spotted tentiform moth (*Lithocolletis blancardella*) based on a $C_{10} + C_2$ coupling scheme. They used decane-1,10-diol (**7.31**) as starting material. Reaction of 1-bromo-10-*tert*-butoxydecane (**7.32**) with sodium acetylide furnished a compound with terminal acetylene group which was isomerized to **7.33** by means of KOH/ethylene glycol at 160 °C. Subsequent $LiAlH_4$ reduction and acetylation gave **7.30**.

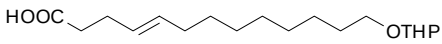
Ireland–Claisen rearrangement[103] of 3-acetoxy-11-(tetrahydropyranyloxy)undec-1-ene (**7.34**) followed by oxidative decarboxylation[104] were the principal reactions of the synthesis of the red bollworm (*Diparopsis catenea*) sex pheromone[105]. Thus, the synthon **7.34**, prepared by reaction of 1-bromo-8-(tetrahydropyranyloxy)octylmagnesium bromide (**7.35**) with acrolein and subsequent acetylation, was converted *via* rearrangement and hydrolysis of a silyl ether into the γ,δ-unsaturated acid **7.36** which was further decarboxylated[104] at 80 °C with lead tetraacetate and acetylated to give the final product, (9*E*)-dodeca-9,11-dien-1-yl acetate (**7.37**) (Scheme 45).



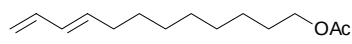
7.34



7.35



7.36

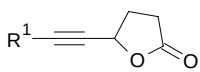


7.37

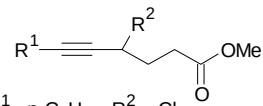
SCHEME 45

(5*Z*)-Tetradec-5-en-1-yl acetate (**7.42**), the major component of a pheromone mixture, produced by a polyphagous pest, *Agrotis exclamationis*, was prepared starting from dodec-1-en-3-yne[106] (**7.38**) (Scheme 46). This was converted into methyl 4-chlorotetradec-5-ynoate (**7.40**) by Mn (III) acetate oxidation followed by treatment of the obtained lactone **7.39** with $SOCl_2$/MeOH. Dicobalthexacarbonyl complex[107] of the chloroester **7.40** was regioselectively reduced to give methyl tetradec-5-ynoate (**7.41**).

7.38, R^1= n-C_8H_{17}

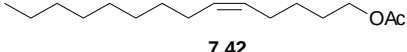


7.39, R^1= n-C_8H_{17}



7.40, R^1= n-C_8H_{17}, R^2 = Cl

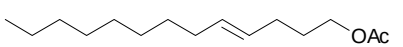
7.41, R^1= n-C_8H_{17}, R^2 = H



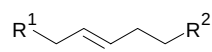
7.42

SCHEME 46

The synthesis of the sex pheromone of *Keiferia lycopersicella*, (4*E*)-tridec-4-en-1-yl acetate (**7.43**) (Scheme 47), was based on undec-1-en-3-yne (**7.44**) prepared from vinylacetylene and n-heptyl bromide[108]. Reaction of **7.44** with acetic acid and man-



7.43

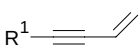


7.46, R^1= n-C_7H_{15}, R^2= COOH

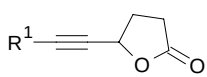
7.47, R^1= n-C_7H_{15}, R^2= CH_2OH

7.48, R^1= n-C_7H_{15}, R^2= CHO

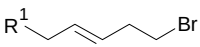
7.49, R^1= n-C_7H_{15}, R^2= COOEt



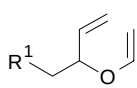
7.44, R^1= n-C_7H_{15}



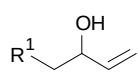
7.45, R^1= n-C_7H_{15}



7.50, R^1= n-C_7H_{15}



7.51



7.52

SCHEME 47

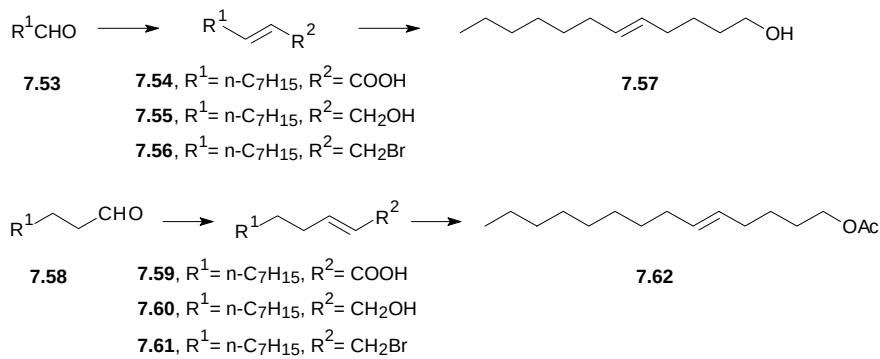
ganese(III) acetate afforded the lactone **7.45** which was converted by partial hydrogenation of the acetylenic bond and opening of the lactone ring to the acid **7.46**. $LiAlH_4$ reduction of the carboxy group of **7.46** and subsequent acetylation (according to Vinczer *et al.*[114]) resulted in the pheromone **7.43**.

A Tashkent group of chemists[109] prepared the sex pheromone of *Keiferia lycopersicella* starting from (3*E*)-1-bromododec-3-ene (**7.50**) the synthesis of which was published by the same authors elsewhere[110]. The C_{13} alcohol **7.47** prepared *via* Grignard reaction[111] furnished the expected pheromone **7.43** on acetylation.

Alternatively, Claisen rearrangement of vinyl ether **7.51** was used by Odinokov *et al.*[112] to create the *E*-double bond of the same pheromone (**7.43**). Rearrangement of the ether **7.51** afforded the aldehyde **7.48** as the only product, its reduction and acetylation led to the expected **7.43**.

Similarly, Claisen rearrangement of undec-1-en-3-yl orthoacetate (derived from **7.52**) yielding the (4*E*)-tridec-4-enoate (**7.49**) followed by the $LiAlH_4$ reduction and acetylation was also used[113] to prepare **7.43**.

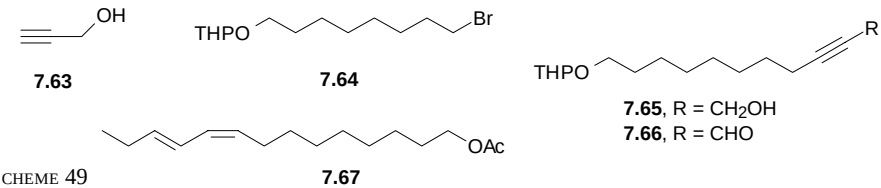
Verba and coworkers[110] prepared (5*E*)-dodec-5-en-1-ol (**7.57**) and (5*E*)-tetradec-5-en-1-yl acetate (**7.62**), the pheromone components of the dipteran *Tricimba cincta* and the lepidopteran *Rhynchopacha* sp., respectively. The synthesis was based on the Knoevenagel condensation (Scheme 48). Thus, condensation of the octanal (**7.53**) and decanal (**7.58**) with malonic acid and the subsequent series of reactions of the respective unsaturated C_{10} (**7.54** → **7.55** → **7.56**) and C_{12} (**7.59** → **7.60** → **7.61**) intermediates, gave – after reaction of the bromides **7.56** and **7.61** with malonic ester and subsequent decarboxylation, $LiAlH_4$ reduction and acetylation – the desired pheromone compounds **7.57** and **7.62**.



SCHEME 48

(9*Z*,11*E*)-Tetradeca-9,11-dien-1-yl acetate (**7.67**), the major sex pheromone component of *Spodoptera littoralis* and *S. litura* and of other species, was synthesized by Indian authors[115] starting from propargyl alcohol (**7.63**) and 1-bromo-8-(tetrahydropyranyloxy)octane (**7.64**). Their combination afforded the acetylenic derivative **7.65**,

which was further oxidized to **7.66**. Subsequent reaction of **7.66** with propyltriphenylphosphonium bromide followed by hydrogenation over Lindlar catalyst and acetylation led to **7.67** (Scheme 49).

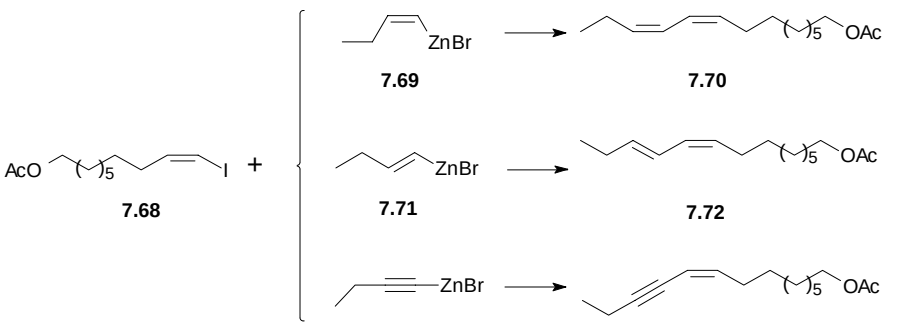


7.63 **7.64** **7.65**, R = CH_2OH; **7.66**, R = CHO

7.67

SCHEME 49

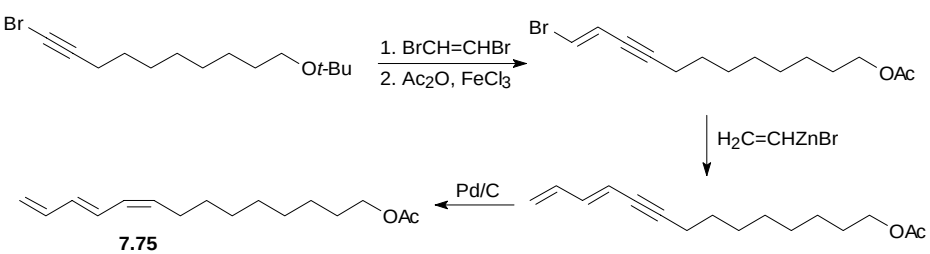
The potential sex pheromones of *Stenoma cecropia*, (9*Z*,11*Z*)-, (9*Z*,11*E*)-tetradeca-9,11-dienyl, and (9*Z*)-tetradec-9-en-11-yn-1-yl acetates (**7.70**, **7.72**, **7.74**) were prepared by Ramiandrasoa and Tellier[116]. The synthesis was based on the iodoacetate **7.68**, using tetrakis(triphenylphosphine) palladium-catalyzed cross-coupling reaction with the respective organozinc reagents **7.69**, **7.71**, and **7.73** (Scheme 50).



7.68 **7.69** **7.70** **7.71** **7.72** **7.73** **7.74**

SCHEME 50

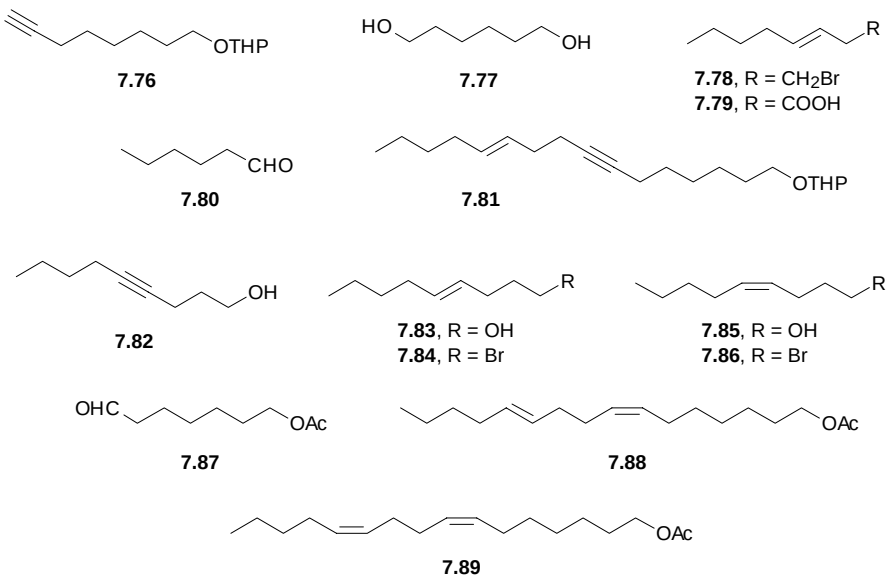
A similar strategy consisting in palladium-catalyzed cross-coupling reaction of the organozinc compound, followed by partial hydrogenation of the acetylenic intermediate, was adapted for the stereospecific synthesis of (9*Z*,11*E*)-tetradeca-9,11,13-trien-1-yl acetate (**7.75**), the sex pheromone component of *Stenoma cecropia* and *Ectomyelois ceratoniae*[117] (Scheme 51).



7.75

SCHEME 51

Pink bollworm moth (*Pectinophora gossypiella)* ranks among to the most important destructive cotton pests. The essential components of its sex pheromone, (7*Z*,11*Z*)- and (7*Z*,11*E*)-hexadeca-7,11-dien-1-yl acetates, act as a synergistic mixture ("gossyplure") in the ratio of about 1 : 1. Extending the series of stereospecific syntheses described earlier (see, *e.g.*, refs[118,119]), Odinokov *et al.*[120] performed synthesis of (7*Z*,11*E*)-hexadeca-7,11-dien-1-yl acetate (**7.88**) (Scheme 52). Cross-coupling of two eight-carbon units, namely that of 8-(tetrahydropyranyloxy)oct-1-yne (**7.76**; prepared from diol **7.77**) and of (3*E*)-oct-3-enyl bromide (**7.78**; prepared from hexanal (**7.80**) *via* (3*E*)-oct-3-enoic acid (**7.79**)), gave the C_{16} acetylenic alcohol **7.81**. Hydrogenation of **7.81** and subsequent acetylation were the final steps in the preparation of **7.88.**



7.76 **7.77** **7.78**, R = CH_2Br; **7.79**, R = COOH

7.80 **7.81**

7.82 **7.83**, R = OH; **7.84**, R = Br **7.85**, R = OH; **7.86**, R = Br

7.87 **7.88**

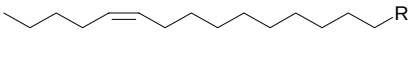
7.89

SCHEME 52

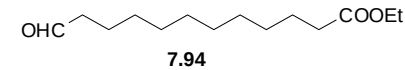
The acid **7.79** was also prepared from the aldehyde **7.80** by modified Knoevenagel condensation[121]. Later on, both the 7*Z*,11*E*- and 7*Z*,11*Z*-isomers **7.88** and **7.89** were synthesized[122] using non-4-yn-1-ol (**7.82**) as the key intermediate which enabled the formation of either **7.83** or **7.85** isomers depending on how the triple bond was reduced ($LiAlH_4$ or P–2 Ni). For instance, the corresponding Wittig compound prepared from **7.84** furnished (7*Z*,11*E*)-hexadeca-7,11-dien-1-yl acetate (**7.88**) by reaction with aldehyde **7.87**. (7*Z*,11*Z*)-Hexadeca-7,11-dien-1-yl acetate (**7.89**) was prepared in a similar way from **7.85** or **7.86**.

(11*Z*)-Hexadec-11-en-1-ol, its acetate and the corresponding aldehyde (**7.90**, **7.91** and **7.92**, respectively) the pheromone components of *Mamestra* and *Heliothis* sp., were synthesized by Odinokov *et al.*[123], starting from cyclododecene (Scheme 53). The ester

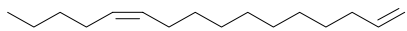
aldehyde **7.94 o**btained by its ozonolysis was subjected to reaction with pentyltriphenylphosphonium ylide and subsequent decarboxylation/oxidation of the C_{17} acid **7.93** furnished (11*Z*)-hexadeca-1,11-diene (**7.95**). This was hydroborated and the obtained **7.90** on acylation afforded the acetate **7.91** or, on oxidation, the aldehyde **7.92**.



7.90, R = CH_2OH
7.91, R = CH_2OAc
7.92, R = CHO
7.93, R = CH_2COOH



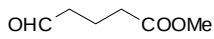
7.94



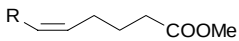
7.95

SCHEME 53

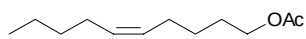
Methyl 5-oxopentanoate **(7.96**) was used by Odinokov *et al.*[124] in the synthesis of (5*Z*)-dec-5-en-1-yl acetate (**7.98**), the pheromone of the moths of *Agrotis* sp. In this synthesis (Scheme 54), the ester **7.96** reacted with pentyltriphenylphosphonium ylide to give **7.97** (R = $CH_3(CH_2)_4$) which, on reduction and acetylation, furnished the acetate **7.98**.



7.96



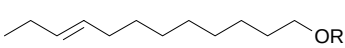
7.97



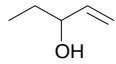
7.98

SCHEME 54

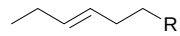
For the synthesis of (9*E*)-dodec-9-en-1-ol (**7.99**) and its acetate (**7.100**), the sex pheromone components of the vinyard pest[125] (*Sparganothis pilleriana*), Claisen rearrangement of pent-1-en-3-ol (**7.101**) was employed in the first step to obtain ethyl (4*E*)-hept-4-enoate (**7.102**). Conversion into the bromide **7.103** followed by reaction with 5-(tetrahydropyranyloxy)pentylmagnesium bromide, hydrolysis and acetylation furnished the final products **7.99** and **7.100** (Scheme 55).



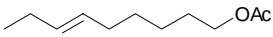
7.99, R = H
7.100, R = Ac



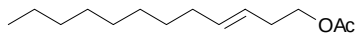
7.101



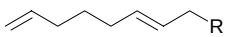
7.102, R = COOEt
7.103, R = CH_2Br



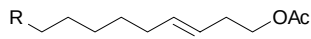
7.104



7.105



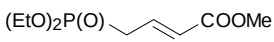
7.106, R = COOiPr
7.107, R = CH_2OAc



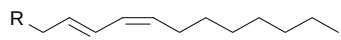
7.108, R = OH
7.109, R = Br

SCHEME 55

Odinokov and coworkers[126] described the synthesis of isopropyl (3*E*)-nona-3,8-dienoate (**7.106**), the key compound for a variety of pheromone components. It was used, for instance, for the synthesis of acetates **7.104** and **7.105**, the pheromone components of various *Lepidopteran* species. The terminal double bond in **7.106** allows the introduction of a hydroxy group into this position making thus easy to perform reactions on either end of the chain. Thus, hydroboration of the ester **7.106** led to the 9-hydroxy derivative, and subsequent reduction of the ester group to the pheromone **7.104**. This applies also to the synthesis of the pheromone **7.105** from acetate **7.107** *via* compounds **7.108** and **7.109**. Sex pheromone of the leafroller moth (*Phterochroa cranaodes*), (3*E*,5*Z*)-dodeca-3,5-dien-1-yl acetate[127] (**7.112**), was prepared using Horner–Wadsworth–Emmons reaction of methyl diethyl [3-(methoxycarbonyl)prop-2-en-1-yl]phosphonate (**7.110**) with octanal, followed by a strong base-induced deconjugation of the 2,4-dienoate to its 3,5-isomer. Compound **7.111** after DIBALH reduction and acetylation furnished **7.112** (Scheme 56).



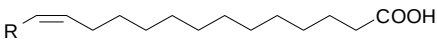
7.110



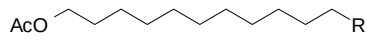
7.111, R = COOMe
7.112, R = CH_2OAc

SCHEME 56

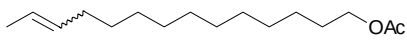
Another dienoate synthesis was published by Chinese authors[128]. The synthesis of (12*E*,*Z*)-**7.116**, pheromone mixture of the Asian corn borer (*Ostrinia furnacalis*) harming mostly on maize, wheat, barley *etc*., started from (13*Z*)-docos-13-enoic acid (**7.113**) which was converted to **7.114** by ozonization and subsequent sodium borohydride reduction and acetylation (Scheme 57). Decarboxylation of the acid in the presence of red mercuric oxide and bromine afforded the bromo derivative **7.115**. Wittig ylide derived from **7.115** was reacted with acetaldehyde to give **7.116**.



7.113, R = $(CH_2)_7CH_3$

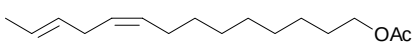


7.114, R = CH_2COOH
7.115, R = CH_2Br

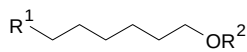


7.116

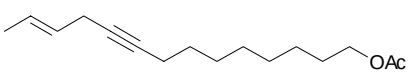
SCHEME 57



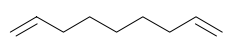
7.117



7.118, R^1 = OH, R^2 = H
7.119, R^1 = Br, R^2 = THP



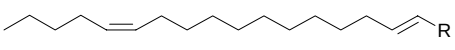
7.120



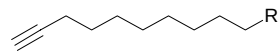
7.121

SCHEME 58

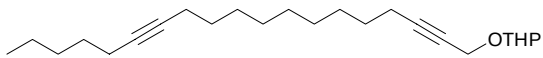
(9*Z*,12*E*)-Tetradeca-9,12-dien-1-yl acetate (**7.117**), a pheromone component of several *Lepidopteran* species, was prepared by Odinokov *et al.*[129] (Scheme 58). Odinokov started his synthesis from hexane-1,6-diol (**7.118**) prepared *via* octa-1,7-diene (**7.121**). Then the *O*-protected bromoalcohol **7.119** was subjected to the reaction with sodium



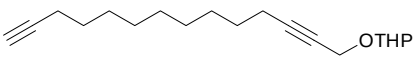
7.122, R = CH_2OAc
7.123, R = COOEt



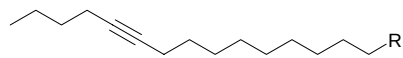
7.124, R = CH_2OH
7.125, R = CH_2Br
7.126, R = CHO



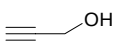
7.127



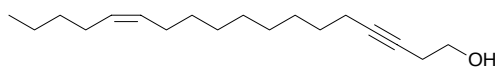
7.128



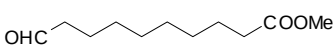
7.129, R = CHO
7.130, R = CH_2OH



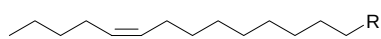
7.131



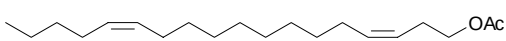
7.132



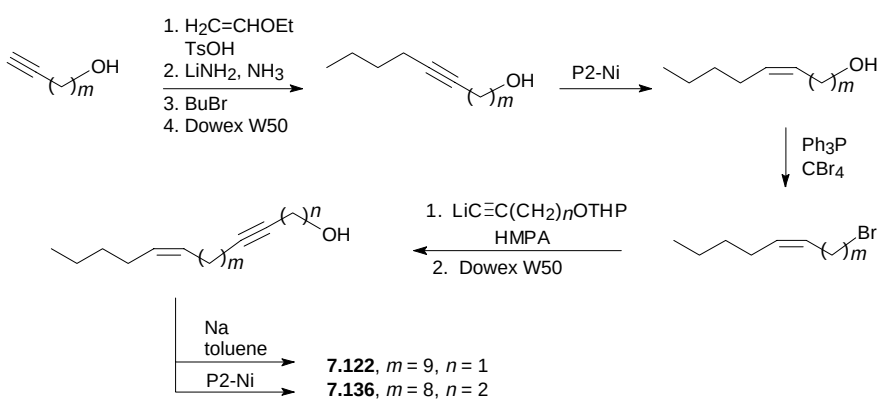
7.133



7.134, R = COOMe
7.135, R = CH_2Br



7.136



SCHEME 59

acetylide first and then with but-2-en-1-yl bromide giving the acetate **7.120**, a template structure of **7.117**.

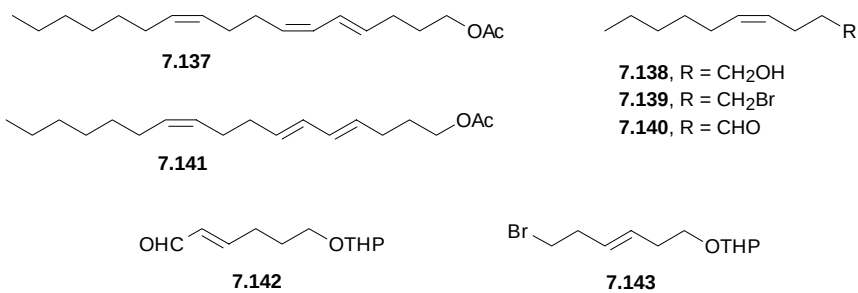
Octadeca-2,13-dien-1-yl and octadeca-3,13-dien-1-yl acetates are the most common components of the sex pheromone blend of the moths of *Synanthedon* species. Their syntheses are mainly based on acetylenic intermediates as a source of double bonds; also, the Wittig–Horner reaction has been used for this purpose. For instance, the synthesis of (2*E*,13*Z*)-octadeca-2,13-dienyl acetate[130] (**7.122**) involves **7.127** as the key intermediate, prepared by the following coupling strategy: **7.124** → **7.125** + 3-(tetrahydropyranyloxy)prop-1-yne → → **7.127** → **7.122**.

Another synthetic approach was published by Sorochinskaya and Kovalev[131] where the pheromone **7.122** was obtained from ester **7.123 (**formed by Wittig olefination from hexadec-11-ynal, **7.129**, prepared from the acetylenic alcohol **7.130**).

Narasimhan *et al.*[132] performed the synthesis of (3*Z*,13*Z*)-octadeca-3,13-dienyl acetate (**7.136**) from the readily available undec-10-yn-1-ol (**7.125**). In this synthesis, the corresponding aldehyde **7.126** was subjected to the reaction with pentyltriphenylphosphonium ylide and the product was coupled with 1-bromo-2-(tetrahydropyranyloxy)ethane to give (13*Z*)-octadec-13-en-3-yn-1-ol (**7.132**).

The compound **7.136** was also prepared by Vinczer *et al.*[133] by a series of Wittig reactions. The double bond in the ester **7.134** was formed from the ester-aldehyde **7.133** and pentyltriphenylphosphonium ylide, the obtained **7.134** was converted into the bromide **7.135** and this was again subjected to Wittig reaction with 3-acetoxypropanal, yielding **7.136** (Scheme 59).

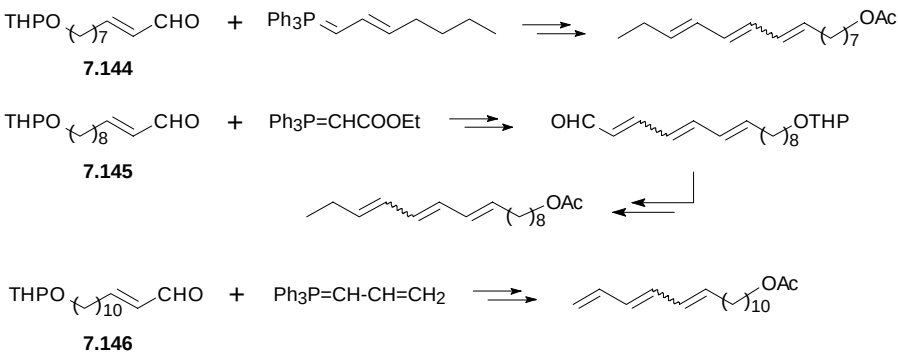
An alternative general way[134] leading to octadecadienyl acetates **7.122** and **7.136**, was based on the acetylenic route of chain lengthening. For instance, the synthesis of sex pheromones of cocoa pod borer moth (*Conopomorpha cramerela*), (4*E*,6*Z*,10*Z*)-hexadeca-4,6,10-trienyl acetate (**7.137**) and its 4*E*,6E,10*Z*-isomer **7.141**, published by Chinese authors[135], started from (4*Z*)-dec-4-en-1-ol[136] (**7.138**) (Scheme 60).



SCHEME 60

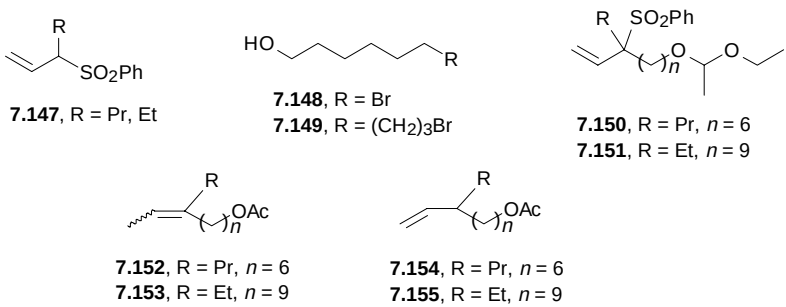
The corresponding bromide **7.139** was converted into a Wittig ylide and subsequently subjected to reaction with 6-(tetrahydropyranyloxy)hex-2-enal (**7.142**) to give, after deprotection and acetylation, **7.137**. Similarly, **7.141** was obtained from

[6-(tetrahydropyranyloxy)hex-2-en-1-yl]triphenylphosphonium bromide and (4*Z*)-dec-4-enal[137] (**7.140**). Sex pheromone compounds with a conjugated triene system with double bonds in positions 8,10,12, 9,11,13, and 11,13,15 were synthesized by introducing stereospecifically two double bonds of the *E*-configuration[138]. The mixture of *E*- and *Z*-isomers of the third double bond was then separated using the HPLC technique (Scheme 61).



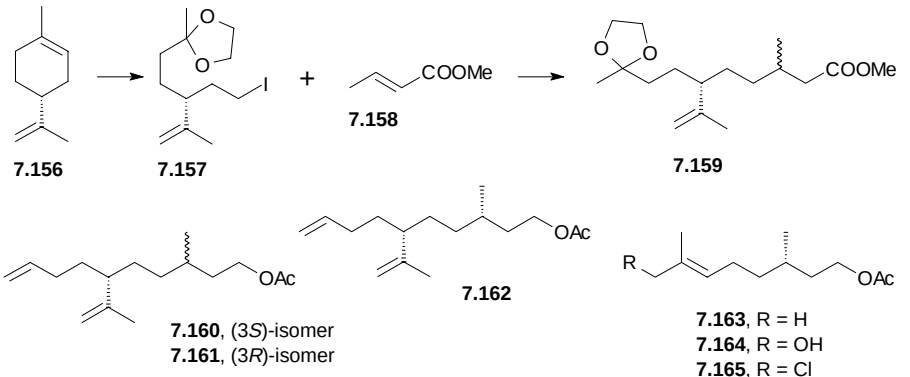
SCHEME 61

The synthetic strategy is outlined in the scheme with **7.144**–**7.146** as the key intermediates. Synthesis of vinyl-branched pheromone analogs by Koutek *et al.*[139] was based on the chemistry of allyl sulfones. Generation of allyl sulfonyl carbanion from allyl phenyl sulfone (**7.147**) and its reactions with haloalkanes led to new C–C bonds. Thus, **7.147** was combined with protected 6-bromohexan-1-ol or 6-bromononan-1-ol (**7.148** and **7.149**, respectively) and then alkylated with 1-iodopropane or 1-iodoethane producing the dialkylated sulfones **7.150** and **7.151** (Scheme 62). Subsequent reductive removal of the benzenesulfonyl group and photo-oxidation of the by-products (**7.152**,



SCHEME 62

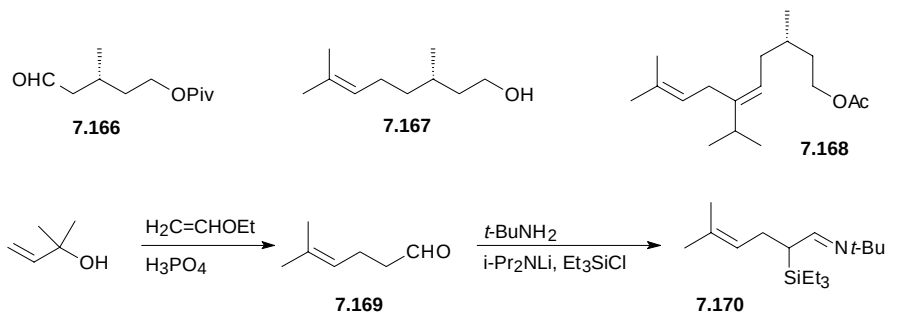
7.153) to achieve easier separation, afforded 99.5% pure pheromone analogs **7.154** and **7.155**.



SCHEME 63

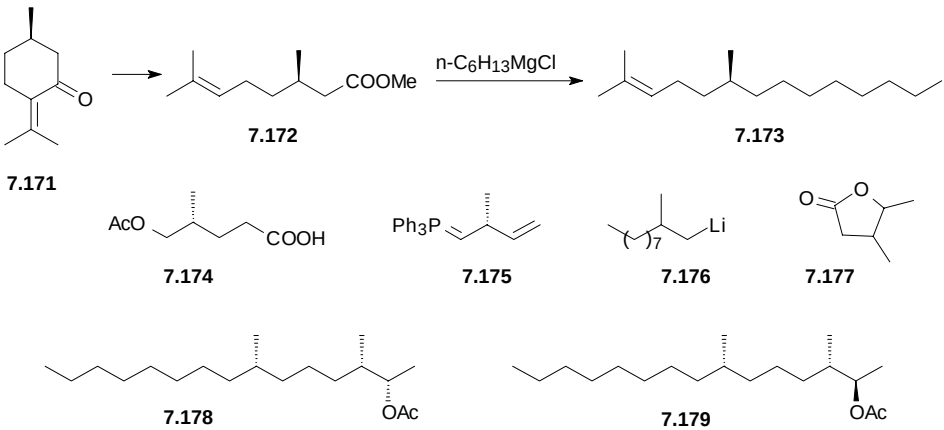
California red scale (*Aonidiella aurantia*) pheromone component, **7.160**, was obtained in 14 steps by a Swiss group[140] as a mixture with its 3*R*,6*R*-isomer (**7.161**) (Scheme 63). The synthesis started from (+)-(*R*)-limonene (**7.156**), the key step of the reaction being the reductive coupling of (*R*)-5-(2-iodoethyl)-6-methylhept-6-en-2-one ethylene acetal (**7.157**) with methyl but-2-enoate (**7.158**) leading to the ester **7.159**.

(*S*)-Citronellyl acetate (**7.163**) was the starting material for an efficient synthesis[141] of one of the *Aonidiella aurantia* sex pheromone components, (3*S*,6*R*)-6-isopropenyl-3-methyldec-9-en-1-yl acetate (**7.162**). The key feature of the synthesis was a highly stereoselective attack of but-4-enylmagnesium bromide to the γ-site of the chloroallylic system of (3*S*)-8-chloro-3,7-dimethyloct-6-en-1-yl acetate (**7.165**; prepared from citronellyl acetate **7.163** *via* the hydroxy derivative **7.164**). The final compound was obtained as a stereoisomeric mixture at C_6 atom. The guiding idea of the stereoselective



SCHEME 64

synthesis[142] of the *Aonidiella citrina* sex pheromone, (3*S*,5*E*)-6-isopropyl-3,9-dimethyldeca-5,8-dien-1-yl acetate (**7.168**) consisted in the condensation of the aldehyde **7.166** (prepared from (*S*)-(–)-citronellol (**7.167**)), with the α-silylaldimine **7.170**. The silylaldimine was synthesized from 2-methylbut-3-en-2-ol according to the Scheme 64.

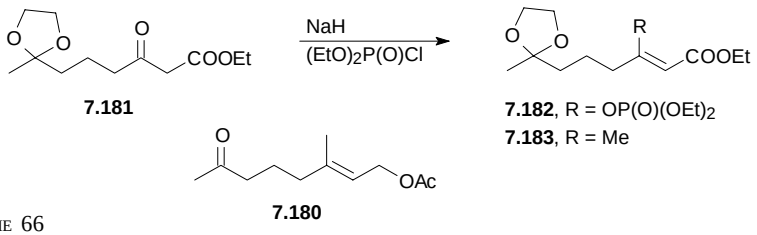


SCHEME 65

Sex pheromones of the pine sawfly (*Neodiprion sertifer*), (2*S*,3*S*,7*S*)-3,7- and (2*R*,3*S*,7*S*)-3,7-dimethylpentadec-2-yl acetates (**7.178** and **7.179**, respectively), were prepared according to the following procedure[143] (Scheme 65). Using (*R*)-pulegone (**7.171**) and compounds **7.172**–**7.177** as reaction intermediates, a mixture of (2*S*,3*S*,7*S*)- and (2*R*,3*S*,7*S*)-3,7-dimethylpentadecan-2-ols separable by HPLC, was obtained. Acetylation of the respective alcohols afforded the acetates **7.178** and **7.179**. Synthesis and gas chromatographic separation of the sex pheromone components of the *Diprionidae* saw flies were performed by Swedish authors[144]. They described syntheses of eight possible stereoisomeric 3,7-dimethylpentadecan-2-ols and their corresponding acetates (see also the structure **3.11**). Chiral starting materials or products of asymmetric synthesis were used as key intermediates for this purpose. For instance, in the preparation of the threo series of four stereoisomers, two enantiomers of 1-lithio-2-methyldecane (**7.176**) and two *cis*-dimethyllactone enantiomers **7.177** were used. The four erythro stereoisomers were prepared by the Mitsunobu reaction[82] which is known to proceed with complete inversion of configuration providing in this case a tool for stereospecific preparation of the erythro from threo isomers.

A stereospecific five-step synthesis of (6*E*)-8-acetoxy-6-methyloct-6-en-2-one (**7.180**), the main component of the Mexican and Caribbean fruit fly sex pheromones, was described in 1996 (ref.[145]). The key intermediate, ethyl (2*Z*)-3-[(diethoxyphosphoryl)oxy]-7,7′-ethylenedioxyoct-2-enoate (**7.182**), prepared from the ketoester **7.181**

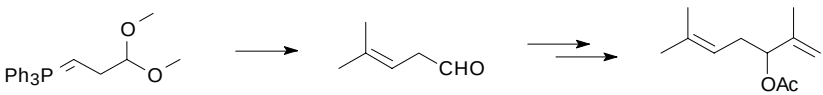
(Scheme 66), was transformed to the protected keto ester **7.183** by reaction with MeMgCl/MeCu. The final product **7.180** was obtained from the ester **7.183** by a standard reaction sequence (Scheme 66).



7.181 **7.182**, R = $OP(O)(OEt)_2$ **7.183**, R = Me **7.180**

SCHEME 66

The synthesis of the racemic sex pheromone of the comstock mealybug (*Pseudococcus comstocki*) (*R*,*S*)-3-acetoxy-2,6-dimethylhepta-1,5-diene (**7.186**) was announced by Korean authors[146]. The principal reaction path is given in the scheme. Reaction of the ylide **7.184** with acetone gave **7.185** which on treatment with isopropylmagnesium bromide afforded **7.186** (Scheme 67).



7.184 **7.185** **7.186**

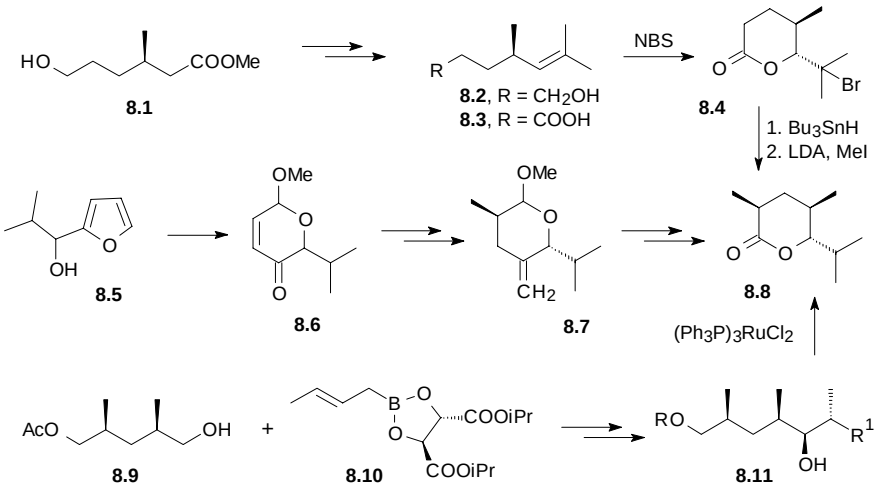
SCHEME 67

8. LACTONES

The heptanolide **8.8** is a component of the sex pheromone of *Macrocentrus grandii*. This wasp is a larval parasitoid for the European corn borer (*Ostrinia nubilalis*) and as such it is used, *e.g.*, in the U.S.A. to control the pest. Due to the possible role in the insect pest management much effort was devoted to the understanding of chemical ecology of this parasitoid. Therefore, several syntheses of the active compound **8.8** have been published (Scheme 68).

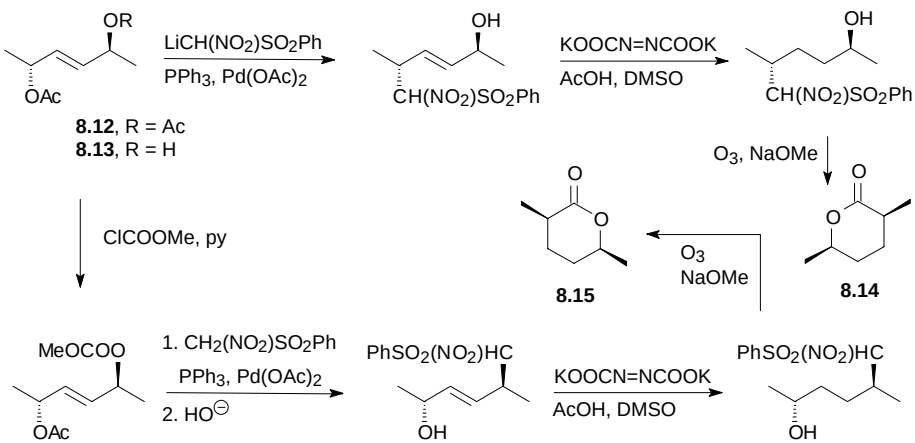
Kiyota and Mori[147] offered a relatively short synthetic approach, with stereoselective halolactonization (**8.3** → **8.4**) as the key reaction. Starting with ozonolysis of methyl (*R*)-citronellate affording **8.1**, subsequent protection and reaction with methylmagnesium iodide, *etc.* led to the alcohol **8.2**. An exo methylene derivative arising as by-product was separated on Ag^+-modified silica gel. As already mentioned, the key reaction in this synthesis was the stereoselective conversion of the acid **8.3** to the bromolactone **8.4**. Debromination and alkylation with methyl iodide in the presence of LDA resulted in **8.8**, together with its stereoisomer. Although the alkylation was not stereoselective,

both products were easily separated by chromatography thus offering a simple access to the pheromone.



SCHEME 68

Raju and Pandey[148] based their synthesis of **8.8** on the readily available isobutyraldehyde and furan, the compounds simply convertable to **8.5**. Oxidation with MCPBA yielded quantitatively **8.6** (after methylation with methyl iodide and silver nitrate) and subsequent cuprate addition introduced regio- and stereoselectively another methyl group into the desired position. Wittig reaction yielded **8.7**, and subsequent hydrogenation and Jones oxidation led finally to **8.8**.

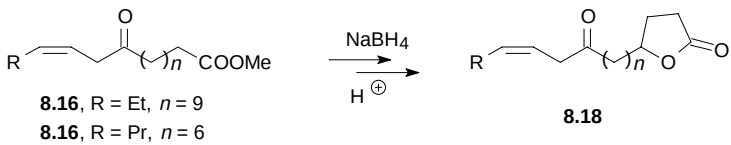


SCHEME 69

Lin and Xu[149] synthesized **8.8** from the monoacetate **8.9** which was obtained by PPL acetylation of the corresponding meso diol (98% e.e.). Oxidation with PDC and asymmetric aldol reaction with **8.10** afforded **8.11** (R = Ac, R^1 = CH=CH_2) in 88% d.e. This compound was converted to the diol **8.11** (R = H, R^1 = Me) from which **8.8** was obtained by oxidative lactonization with $(Ph_3P)_3RuCl_2$.

Enantioselective enzymatic hydrolysis of diacetate **8.12** has been used by Schink and Backvall[150] for the preparation of the carpenter bee (*Xylocopa hirutissima*) pheromone **8.15** and its 2*R*,5*S*-enantiomer, **8.14**. In this synthesis, the meso diacetate is hydrolyzed by acetylcholinesterase. The resulting **8.13** was converted into the respective enantiomers **8.14** and **8.15** by reaction routes outlined in the scheme with significant improvements upon the previously reported preparations (Scheme 69).

The lactone analogs of *Ostrinia nubilalis* and *Cydia molesta* pheromones were synthesized by Koutek *et al.*[151,182] (Scheme 70). They expected that similar lactones can

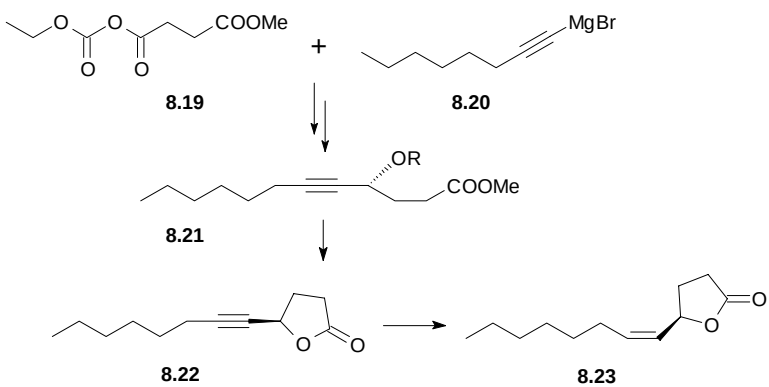


8.16, R = Et, *n* = 9
8.16, R = Pr, *n* = 6

8.18

SCHEME 70

alkylate serine-containing enzymes and thus block irreversibly the pheromone receptor sites. The key intermediates of the synthesis were the keto esters **8.16** and **8.17**, prepared by coupling of the corresponding acyl chloride and Grignard compound under catalysis with $Fe(acac)_3$. The analogs **8.18** were obtained from **8.16** and **8.17** by a simple synthetic procedure involving $NaBH_4$ reduction and closing of the lactone ring under acid conditions.



8.19 **8.20**

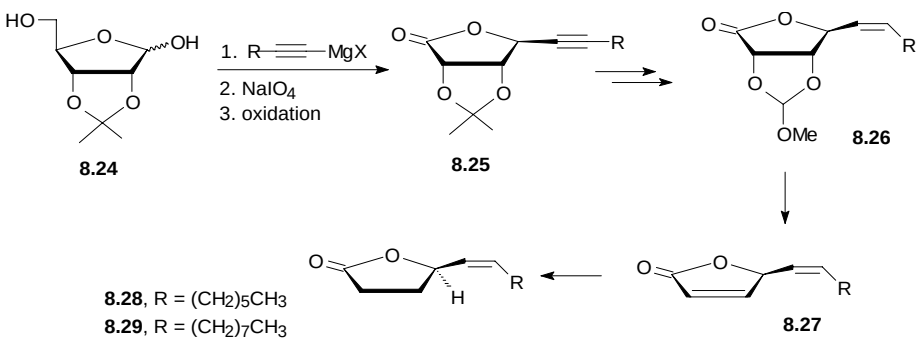
8.21

8.22 **8.23**

SCHEME 71

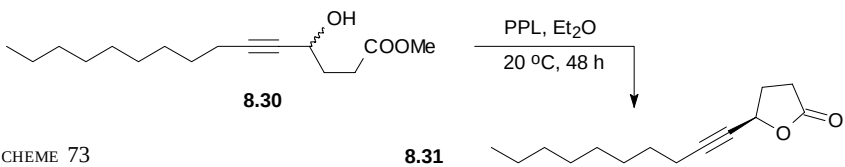
Fukusaki *et al.*[152] prepared (5*Z*)-5-(oct-1-en-1-yl)tetrahydrofuran-2-one (**8.23**), a sex pheromone of the cupreous chafer beetle. This compound is structurally close to the Japanese beetle pheromone (the side chain is by two carbon atoms longer) and the unnatural enantiomer was assumed to be a pheromone inhibitor. Therefore, Fukusaki also synthesized the antipode of **8.23**. The synthetic strategy included the lipase-catalyzed acylation of **8.21** as the key step. The lipase-mediated acylation in a mixture of n-butyric acid/diisopropyl ether afforded (*R*)-acyloxy ester **8.21** (R = COPr) in 93% e.e. Fukusaki further improved the optical purity by repetitive enzymatic acylation/hydrolysis. Subsequent distillation and hydrogenation over Lindlar catalyst afforded pure **8.23**. The *S*-derivative was prepared in a similar manner starting from the (*S*)-enantiomer of **8.21** (R = H) (Scheme 71).

Another synthetic approach leading to the sex pheromone of the cupreous chafer beetle **8.28** was published by Koseki *et al.*[153] and the procedure was also applied to the synthesis of the Japanese beetle pheromone (**8.29**). D-Ribose was used as the starting material and the final products were prepared in eight steps. Koseki used **8.27** (obtained *via* **8.24**, **8.25**, and **8.26**) as the key compound in his synthesis. Then the lactone **8.27** was reduced with Bu_3SnH/TMSCl/LiCl giving **8.28** and **8.29** of high purity as checked by chiral GLC (Scheme 72). The method was claimed by Koseki to be a new procedure for the preparation of (*R*,*Z*)-alk-5-en-4-olides of high optical purity.



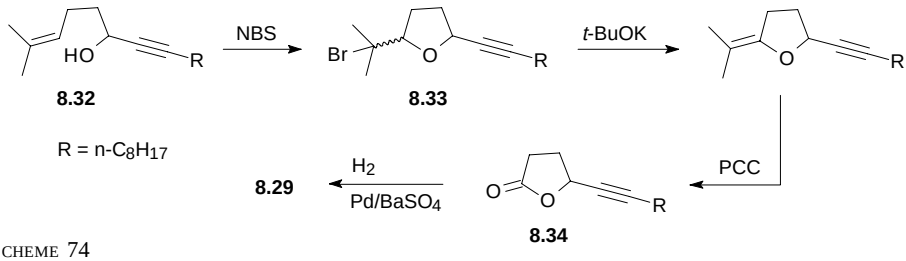
SCHEME 72

In the synthesis of Japanese beetle pheromone, Sugai *et al.*[154] obtained the enantiomerically enriched intermediate **8.31** by lipase-catalyzed enantioselective lactonization of **8.30**. Sugai further improved the optical yield by opening the lactone and repeating the enzyme lactonization (Scheme 73).



SCHEME 73

Baskaran *et al.*[155] developed a general approach to the synthesis of butanolides and applied it to the synthesis of the racemic Japanese beetle pheromone. The procedure was based on bromoetherification of **8.32** with NBS (**8.33**). Base-induced elimination of the halogen atom, treatment with PCC and hydrogenation gave racemic **8.29** (Scheme 74).



SCHEME 74

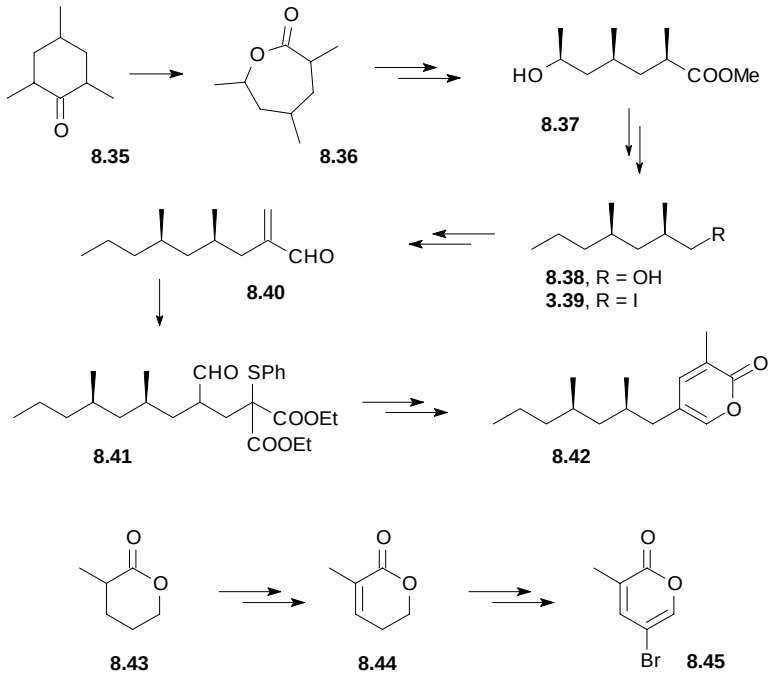
Mori and Takeuchi[156], and independently Shi *et al.*[157], determined the absolute configuration of supellapyrone (**8.42**), the sex pheromone of the brownbanded cockroach (*Supella longipalpa*) by comparing the natural material with synthetic standards.

Mori *et al*. started the synthesis from 2,4,6-trimethylphenol which was converted to methyl 5-hydroxy-1,3-dimethylheptanoate *via* **8.35** and **8.36** as the reaction intermediates[156]. Under the conditions of lipase acylation (vinyl acetate in hexane), only the 2*S*,4*S*,6*R*-isomer of **8.37** was acylated while its antipode remained intact. The enantiomeric purity of the products was 100 and 98%, respectively.

Conversion of (–)-5-hydroxy-1,3-dimethylheptanoate (**8.37**) to tosylate, subsequent reduction with $LiAlH_4$ **(8.38**) and iodination gave compound **8.39** which was further used for alkylation of diethyl malonate. The alkyl malonate, after treatment with $LiAlH_4$/NaH in DME and MnO_2, afforded **8.40**, the molecule with the structure pattern of the side chain. Closure of the pyranone ring led finally to **8.42** (Scheme 75).

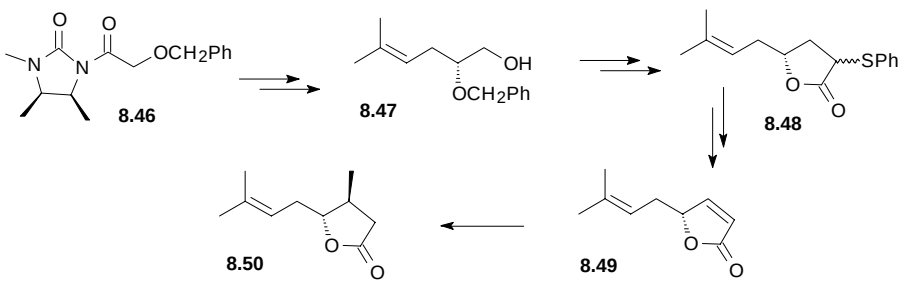
Meinwald's and Shi's synthesis[157] consists in the direct attachment of the alkyl side chain to the pyranone ring, the method which has not been used so far. The alkyl side chain preparation resulting in the iodide **8.39** was similar to that described in Mori's paper[156]. The second part of the general synthetic strategy consisted in the preparation of pyranone bromide **8.45** (R = Br), which was obtained from pentano-2-lactone by several reactions involving alkylation of pentano-2-lactone enolate, reaction with PhSeCl, photobromination and reaction with Et_3N. Meinwald and Shi finally tried several methods of direct coupling of **8.39** and **8.45** (R = Br) and have found that the best results were obtained by coupling an appropriate zinc derivative of **8.39** with **8.45** under the catalysis of $PdCl_2$(dppf). The coupling afforded **8.42** (the assignment of the absolute configuration is also given in this paper). Imidazolidin-2-one proved to be a versatile chiral auxiliary for the preparation of optically pure alcohols. The method was

elaborated by Mobbili *et al.*[158] and has been applied to the synthesis of *Eldana saccharina* pheromone **8.50**. The lithium salt of **8.46** was alkylated with 1-bromo-3-methylbut-2-ene and cleaved afterwards with LiBH4 leading to **8.47**. The key reaction



SCHEME 75

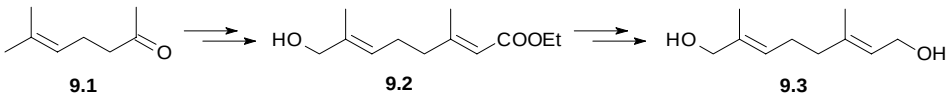
step here was the reaction of **8.49** with Me_2CuLi giving (+)-eldanolide (**8.50**) in high optical purity (Scheme 76).



SCHEME 76

9. OTHER ESTERS

Diisovaleryl ester of (2*E*,6*E*)-2,6-dimethylocta-2,6-diene-1,8-diol (**9.3**), a sex pheromone of *Agriotes tauricus*, was synthesized[159] from 6-methylhept-5-en-2-one (**9.1**). This compound was converted to the ester **9.2** and diol **9.3** which, after esterification, afforded the above-mentioned bis(3-methylbutanoate) (Scheme 77).

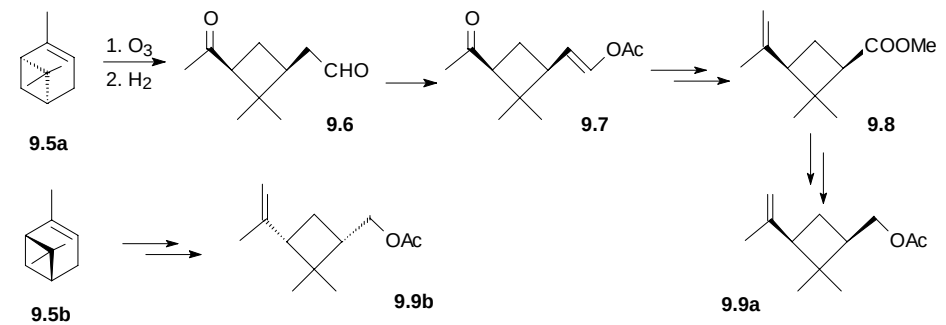


9.1 **9.2** **9.3**

SCHEME 77

(+)-α- and (–)-α-Pinenes (**9.5a** and **9.5b**) were the starting materials for the synthesis of **9.9a** and **9.9b**, citrus mealybug (*Planococcus citri*) sex pheromones[160].

Thus, ozonization of (+)-α-pinene furnished the keto aldehyde **9.6**, which was converted into enol acetate **9.7** on treatment with organic base. One more ozonization, reaction of the carbonyl group in **9.7** with $Ph_3P{=}CH_2$, reduction and acetylation, resulted in **9.9a**. The same reaction sequence was used for the enantiomeric **9.9b** (Scheme 78).

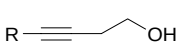


9.5a **9.6** **9.7** **9.8**

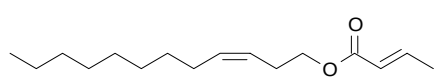
9.5b **9.9b** **9.9a**

SCHEME 78

Another synthesis of the *Planococcus* pheromone (**9.9**) was also published using the same starting materials, however, with a slightly different reaction sequence[161]. A three-step synthesis of (3*Z*)-dodec-3-en-1-yl ester of (2*E*)-but-2-enoic acid (**9.12**), the sex pheromone of the Sweet potato weevil (*Cylas formicarius*), was described by Indian authors[162]. Dodec-3-yn-1-ol (**9.11**), prepared from but-3-yn-1-ol (**9.10**) in a routine way, furnished the final product **9.12** on partial hydrogenation of the triple bond and esterification (Scheme 79).



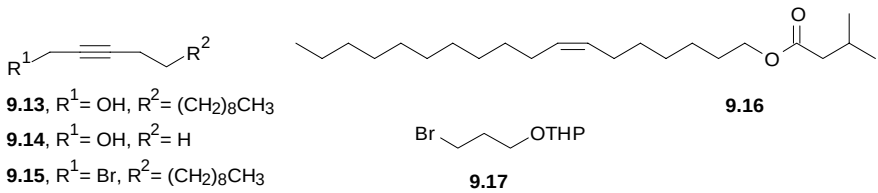
9.10, R = H
9.11, R = $(CH_2)_6CH_3$



9.12

SCHEME 79

A synthesis of (7*Z*)-octadec-7-en-1-yl 3-methylbutanoate (**9.16**), the sex pheromone of *Euproctic similis*, was described by Sharma and Verma[163]. The key compound, pentadec-4-yn-1-ol (**9.13**) was obtained through the reaction of 1-bromodecane with the dianion of pent-4-yn-1-ol (**9.14**; prepared *in situ* from furfuryl chloride and lithium amide in liquid ammonia). The bromide **9.15** (**9.13** → **9.15**) gave, after coupling with 3-bromo-1-(tetrahydropyran-2-yloxy)propane (**9.17**) followed by the deprotection and esterification steps, the title compound **9.16** (Scheme 80).



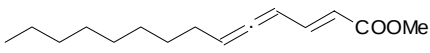
9.13, R^1= OH, R^2= $(CH_2)_8CH_3$
9.14, R^1= OH, R^2= H
9.15, R^1= Br, R^2= $(CH_2)_8CH_3$

9.16

9.17

SCHEME 80

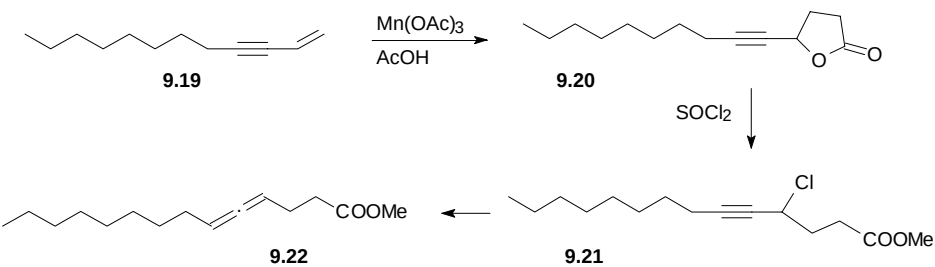
For the synthesis of methyl (2*E*)-tetradeca-2,4,5-trienoate (**9.18**), the sex pheromone of *Acanthoscelides obtectus*, dodec-1-en-3-yne (**9.19**) was employed as starting material[164]. The chloroester **9.21** was prepared from the acetylenic compound **9.19** *via* the lactone **9.20** (ref.[165]). Reduction of **9.21** with Zn/Cu gave the allenic ester **9.22** which on allylic oxidation with sodium periodate[166] afforded the pheromone **9.18** (Scheme 81).



9.18

SCHEME 81

Ichikawa *et al.*[167] synthesized both (10*R*)- and (10*S*)-10,14-dimethylpentadec-1-yl 3-methylbutanoates (**9.26**) from (*S*)- and (*R*)-citronellols (**9.23**) in order to determine the absolute configuration of the sex pheromone of *Euproctis pseudoconspersa*. The synthesis involved hydrogenation of the double bond (Scheme 82), oxidation to the



9.19

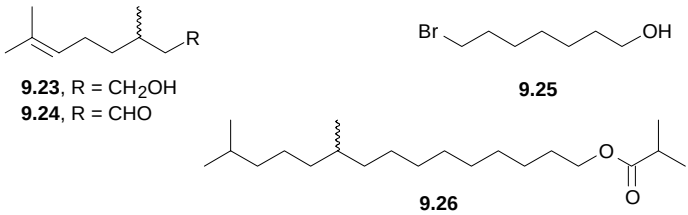
9.20

9.22

9.21

SCHEME 82

aldehyde **9.24** and reaction with (7-hydroxyheptyl)triphenylphosphonium bromide (prepared from **9.25**). The final double bond reduction with hydrazine and esterification afforded, *e.g.*, (10*R*)-**9.26** (Scheme 83).



9.23, R = CH_2OH
9.24, R = CHO

9.25

9.26

SCHEME 83

Synthesis of racemic 8-methyl-2-decyl propionate (**9.27**), the sex pheromone of several *Diabrotica* sp., was performed by a Moldavian group of chemists[168]. The authors started from (4*E*)-7-methyl-non-4-en-1-ol (**9.28**) and 2-methylbutylmagnesium bromide. Hydrogenation and oxidation of the alcohol **9.28** furnished the aldehyde **9.33** which gave, by reaction with MeMgBr and subsequent esterification, the expected product **9.27** (Scheme 84).

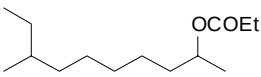
All four stereoisomers of the western corn rootworm (*Diabrotica virgifera*) sex pheromone, **9.27**, were synthesized from nona-1,8-diene (**9.32**) by means of the Sharpless asymmetric dihydroxylation[169,170]. (2*R*,8*R*)-Nonane-1,2,8,9-tetrol (**9.29**), obtained from diene **9.32** in this way, was capable of desymmetrization by modifying any of the two ends of the molecule, thus producing one diastereomer only. The *S*,*S*-isomer **9.30**, prepared from the tetrol **9.29** *via* dibromide **9.31**, was then converted to give all the four isomers of **9.27**: (2*R*,8*S*)- and (2*R*,8*R*)- were produced from **9.30**, while the isomeric (2*S*,8*R*)- and (2*S*,8*S*)-8-methyl-2-decyl propanoates were generated from the first two by inversion of the carbinol center according to Mitsunobu[82].

A synthesis leading to the four stereoisomers of **9.27** using *Thermoanaerobium* alcohol dehydrogenase was described in detail by Keinan *et al.*[171]. Nonane-2,8-dione as a substrate for the enzyme as well as the Mitsunobu method[82] for epimerizing the carbinol centers in the esters **9.37**–**9.41** were chosen as a basic reaction principle.

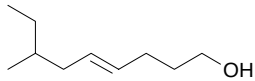
Synthesis of the pure (2*R*,8*R*)-8-methyl-2-decyl propionate (**9.34**), a component of the sex pheromone of *D. virgifera virgifera*, was performed through the enzyme-catalyzed hydrolysis of the racemic **9.35** using *Pseudomonas fluorescens* lipase. Repeated operations gave the alcohol **9.36** in high optical purity. Esterification[172] and chromatographic purification furnished finally the pheromone **9.34**.

Three isomeric components of the San Jose scale (*Quadraspidiotus perniciosus*) pheromone, **9.42**–**9.44**, were synthesized from the common β-ketoester intermediate **9.45** (obtained from methyl acetoacetate and 3-methylbut-3-en-1-ol)[173] (Scheme 85). The trisubstituted double bond-containing compounds in **9.42** and **9.43** were prepared stereospecifically *via* copper-catalyzed coupling of methylmagnesium bromide with the

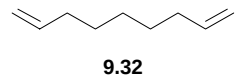
(*E*)- or (*Z*)-enol phosphates **9.47** and **9.49** and the respective esters were converted into the final pheromone components **9.42** and **9.43** by a standard reaction sequence. For the third component, **9.44**, the ketoester **9.45** was reduced to the alcohol **9.46** and then esterified and transformed to the pheromone **9.44** with the Tebbe reagent[174].



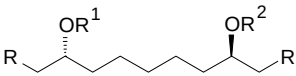
9.27



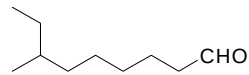
9.28



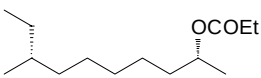
9.32



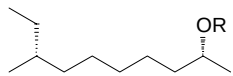
9.29, R = OH, $R^1 = R^2 = H$
9.30, R = $R^1 = R^2 = H$
9.31, R = Br, $R^1 = R^2 = Ac$



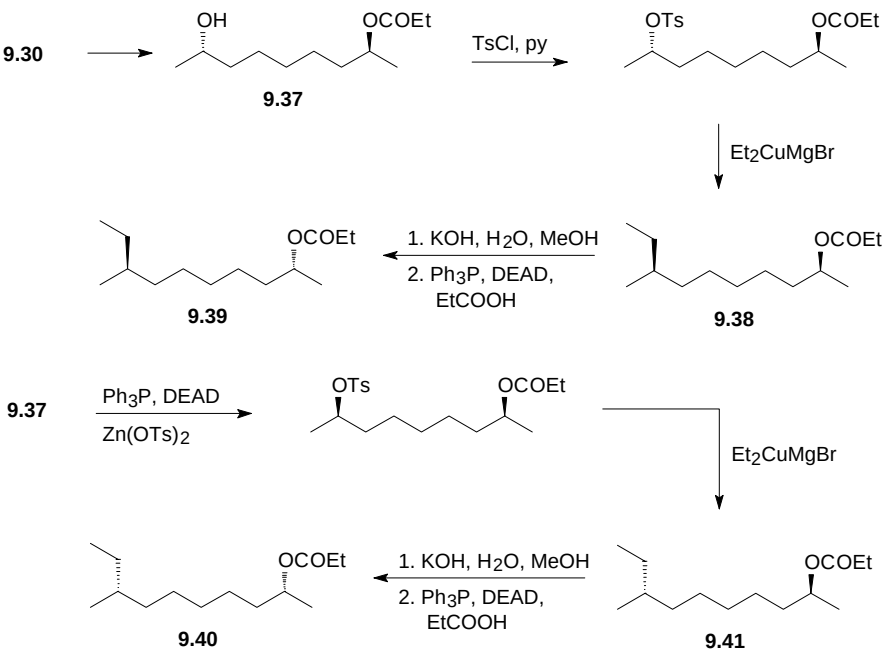
9.33



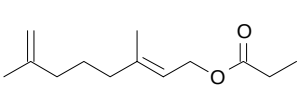
9.34



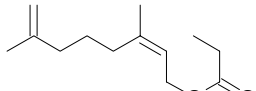
9.35, R = $COCH_2CCl_3$
9.36, R = H



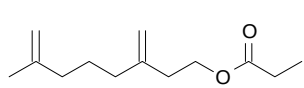
SCHEME 84



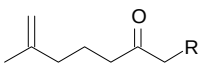
9.42



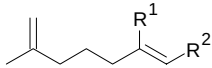
9.43



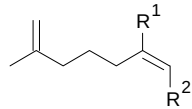
9.44



9.45, R = COOMe
9.46, R = CH_2OH



9.47, R^1= $OP(O)(OEt)_2$, R^2= COOMe
9.48, R^1= Me, R^2= CH_2OCOEt

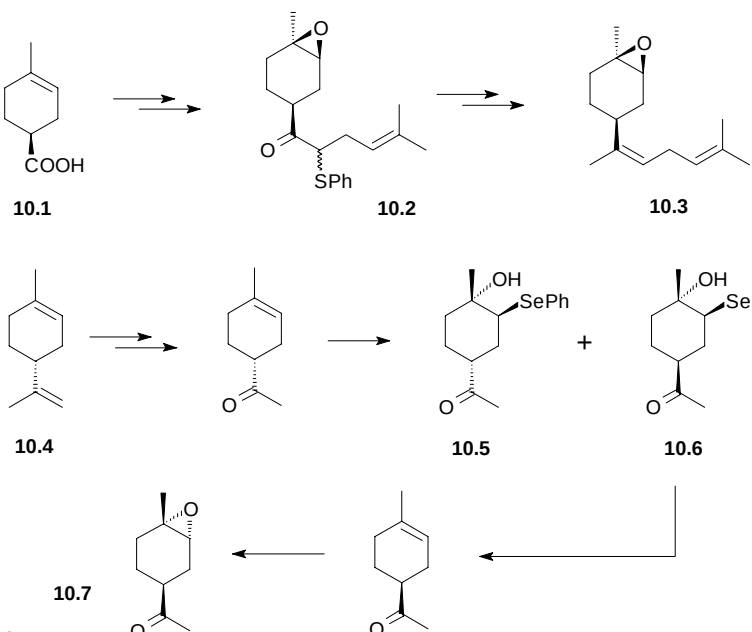


9.49, R^1= $OP(O)(OEt)_2$, R^2= COOMe
9.50, R^1= Me, R^2= CH_2OCOEt

SCHEME 85

10. CONCLUDING REMARKS

During the preparation of the manuscript many more papers dealing with the synthesis of insect sex pheromones have appeared. A brief survey of the most recent synthetic effort is included in this section. For instance, a new synthesis of *Nezara viridula* sex pheromone blend and the intermediate for its preparation can be found in the papers of Kuwahara *et al.*[175] and Ceccherelli *et al.*[176]. While the former authors based their syntheses on the similar principle as Baptistella[43] did (see also the sequence **4.26** to **4.33**) with reaction intermediate **10.2** involved, the latter concentrated their effort on the synthesis of ketone **10.7** (Scheme 86) as a suitable compound for preparation of **4.33**.



10.1 **10.2** **10.3**

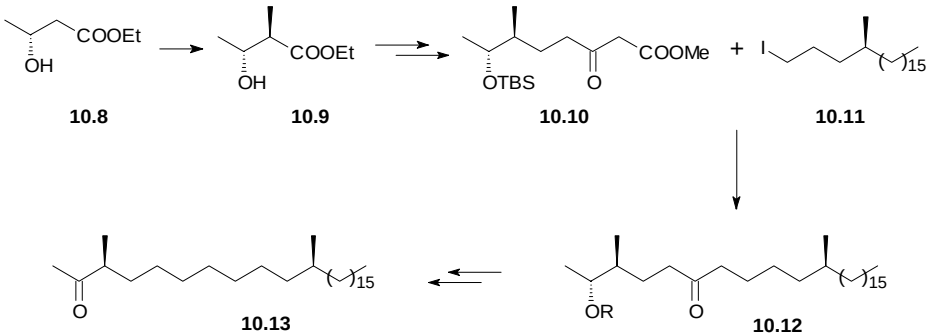
10.4 **10.5** **10.6**

10.7

SCHEME 86

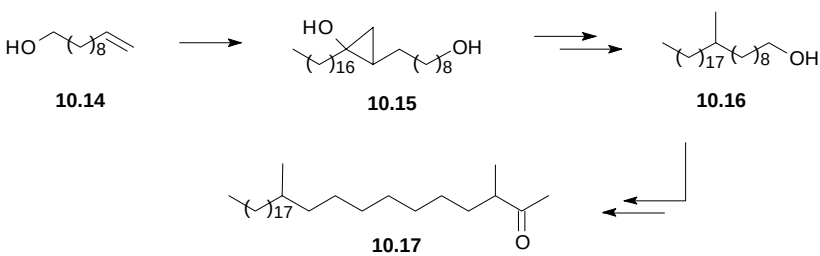
Ceccherelli started his synthesis from (+)-(*R*)-limonene (**10.4**) to obtain selenides **10.5** and **10.6**. Since the compounds could not be separated by chromatography, the authors utilized the fact that selenide **10.6** does not undergo the retrohydroxyselenenylation with 4-methylbenzenesulfonic acid while **10.5** does. Then the ketone **10.7** was selectively gained from **10.6** by conversion with Oxone® oxidizing reagent *via* corresponding selenone.

The fourth component of the female sex pheromone of *Blatella germanica*, **10.13**, was synthesized by Mori *et al.*[177]. The synthesis is based on alkylation of the ketoester **10.10** with iodide **10.11** (Scheme 87).



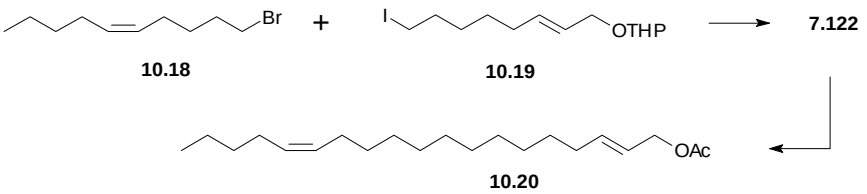
SCHEME 87

Titanium-mediated formation of 1,2-disubstituted cyclopropanols from esters and alkenes as a new approach to the synthesis of 3,11-dimethylnonacosan-2-one (**10.17**), a component of the sex pheromone of *Blatella germanica*, was elaborated by Epstein *et al.*[178]. They used disubstituted cyclopropanol (obtained from **10.14** by treatment with an alkylmagnesium halide in the presence of $Ti(OisoPr)_4$) as the key intermediate (Scheme 88).



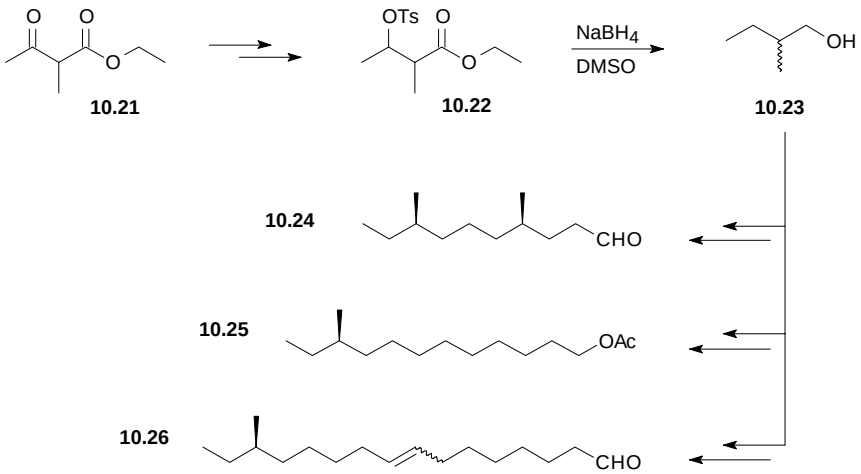
SCHEME 88

The synthesis of dienic acetate **10.20**, the component of *Synanthedon tipuliformis* pheromone, was published by Tolstikov *et al.*[179]. The authors coupled the halides **10.18** and **10.19** to obtain the corresponding alcohol **7.122** which was further acetylated to **10.20** (Scheme 89).



SCHEME 89

The chemoenzymatic access to (+)-(*R*)-2-methylbutan-1-ol ((*R*)-**10.23**) as a chiral synthon for the synthesis of optically active methyl-branched pheromones, was published by Geresh *et al.*[180]. The authors subjected acetoacetate **10.21** to the baker's-yeast reduction to obtain, after subsequent $NaBH_4$/DMSO reduction and chromatography, (*R*)-**10.23** (Scheme 90).

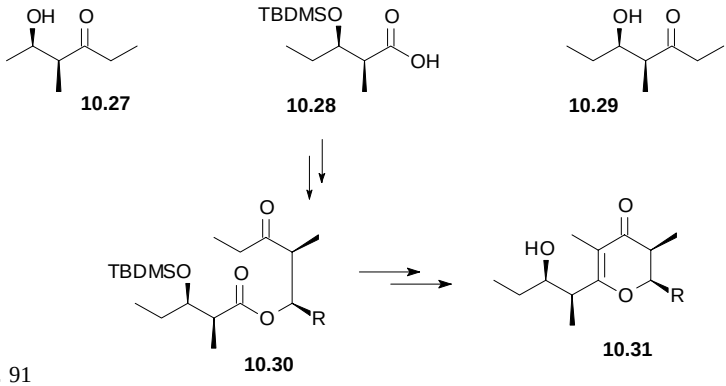


SCHEME 90

Gil *et al.*[181] described the preparation of stegobiol (**10.31**; R = H) and serricorol (**10.31**; R = Me), pheromones of *Stegobium paniceum* and *Lasioderma serricorne*, respectively. The preparation consists in condensation of **10.28** with either **10.27** (stegobiol) or **10.29** (serricorol), and closure of the ring (Scheme 91).

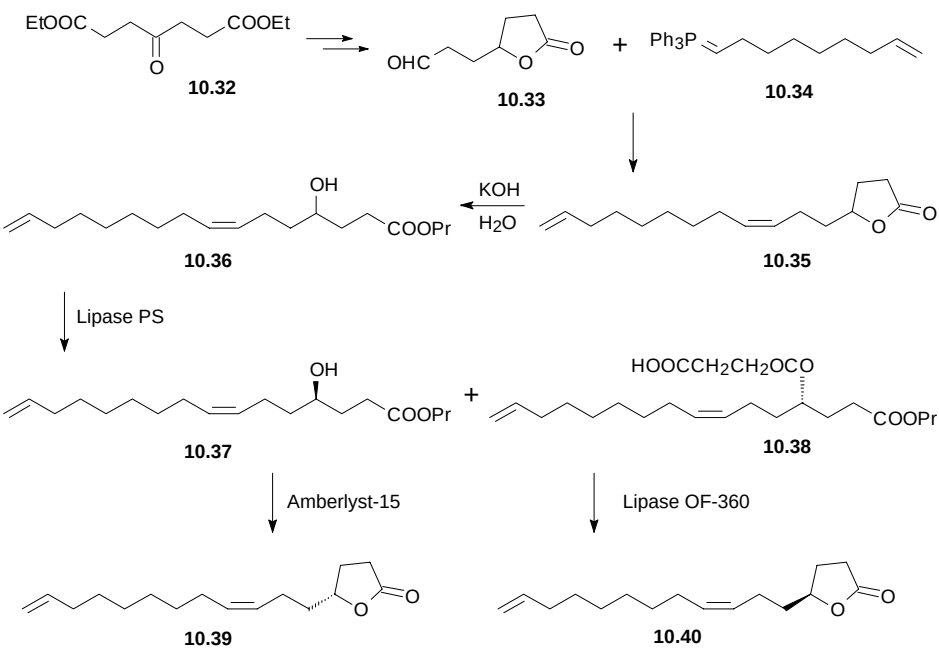
The female-produced pheromone of the yellowish elongate chafer (*Heptophylla picea*), **10.39**, as well as the isomeric **10.40**, was published by Mori and Nakayama[183]. The synthesis proceeded as outlined in the scheme. For resolving the compounds, several lipases were used to obtain products with different degree of optical purity (Scheme 92).

The enantiospecific synthesis of (+)-(*S*)-3-methylhenicosan-2-one, the sex pheromone analog of *Blatella germanica* pheromone, can be found in the paper of Ishmuratov *et al.*[184], while the synthesis of (11*E*)-tetradec-11-en-1-ol and its acetate appeared in



SCHEME 91

ref.[185]. Fukusaki *et al.*[186] published the preparation of 21-methylpentatriacont-8-ene and Matsuo *et al.* the key intermediate for grandisol synthesis[187]. Identification and synthesis of vesperal is described in ref.[188] and some common approaches to the synthesis of pheromones can be found in refs[189,190].



SCHEME 92

The synthesis of the pine bast scale pheromone (dienic ketone)[191] and a new component of the German cockroach female pheromone have been reported[192] as well as the syntheses of koiganal, the sex pheromone component of the webbing clothes moth[193].

Also the *Phtorimaea operculella* sex pheromone[194] and enantiomers of lactonic pheromones[195,196] have been described.

During the prepartion of the manuscript, several microreviews have appeared[197–200], dealing mainly with the enantioenriched syntheses of the discussed compounds. A microreview describing synthesis, stereochemistry, and bioactivity of semiochemicals *incl*. pheromones has been recently published by Mori[201].

Recent years have generally witnessed an increased interest in the preparation of nonracemic bioactive compounds. Accordingly, the flurry of recent activity in the field of pheromone synthesis has expanded some of the traditional synthetic methods to allow preparation of nonracemic pheromones. Reflecting the general quest for more efficient, more specifically targeted enantiopure pheromones, a number of new strategies for stereocontrolled pheromone synthesis is being published. Although considerable progress has been made in this direction, further advances in asymmetric synthesis are expected to make these strategies even more amenable to large-scale pheromone synthesis.

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