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OZONOLYSIS OF UNSATURATED COMPOUNDS IN THE SYNTHESIS OF INSECT PHEROMONES AND JUVENOIDS

G. Yu. Ishmuratov,* Yu. V. Legostaeva, L. R. Garifullina, L. P. Botsman, M. P. Yakovleva, and G. A. Tolstikov†

Research from the last 20 years on the use of ozonolysis of cyclic and acyclic mono- and dienes and aromatic compounds in various steps of the total synthesis of insect pheromones and juvenoids was reviewed.

Keywords: unsaturated compounds, ozonolysis, insect pheromones, juvenoids, synthesis.

Rampant use of pesticides has destroyed the natural ecological equilibrium such that the application of compounds that act selectively on the insect hormonal system remains critical in the battle with insect pests.

Pheromones are produced by insects for intraspecies communication and can be used to observe and control their population. Juvenoids are natural juvenile hormone analogs and affect insect development in the larval stage and subsequent metamorphosis into adults. Insect pheromones and juvenoids are harmless to mammals, including man, and are broadly used as ecologically safe agents for battling agricultural pests [1–6].

Aliphatic compounds with functional groups at the ends of the carbon chains are usually required to synthesize pheromones and juvenoids for many insect species. Ozonolysis of olefins is one of the most promising synthetic pathways to such synthons [7–9]. Ozone is an effective and ecologically friendly oxidant that is broadly used in organic synthesis, including in targeted synthesis of biologically active compounds, because of the capability to transform selectively the α,ω-bifunctional oxygen-containing compounds that are formed during ozonolysis of olefins.

Research from the last 20 years on the use of ozonolytic transformations of cyclic and acyclic mono- and dienes and aromatic compounds in various steps of the total synthesis of insect pheromones and juvenoids was reviewed. This review continued a previous one [10].

1. Selective Ozonolysis of Cyclic and Acyclic Dienes and Aromatic Compounds in the Synthesis of Insect Pheromones and Juvenoids

Oxidative cleavage of olefins became especially useful owing to the success of metal-complex catalysis, as a result of which cyclic and acyclic oligomers and co-oligomers of 1,3-dienes became available.

Products from selective ozonolysis of cyclic butadiene oligomers are widely used to synthesize insect pheromones. Partial ozonolysis of available cyclic oligomers and co-oligomers of butadiene [(1*Z*,5*Z*)-cyclooctadiene (**1**) and (1*E*,5*Z*)-cyclodecadiene (**2**)] represented a new approach to the synthesis of 1,8-octane- (**3**) and 1,10-decanediol (**4**), selective bromination of which followed by condensation of the obtained bromides (**5** and **6**) with lithium acetylenide synthesized **7** and **8** with a terminal triple bond. Then, alkylation and hydrogenation of the disubstituted alkynes (**9** and **10**) produced the target (9*E*)-dodecen-1-ylacetate (**11**), which was identified, like the corresponding alcohol, in the sex pheromone of *Sparganothis pilleriana*, and (11*E*)-tetradecen-1-ylacetate (**12**), the sex pheromone of *Loxostege sticticalis* [11] (Scheme 1).

†Deceased.

Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, Ufa, e-mail: insect@anrb.ru.
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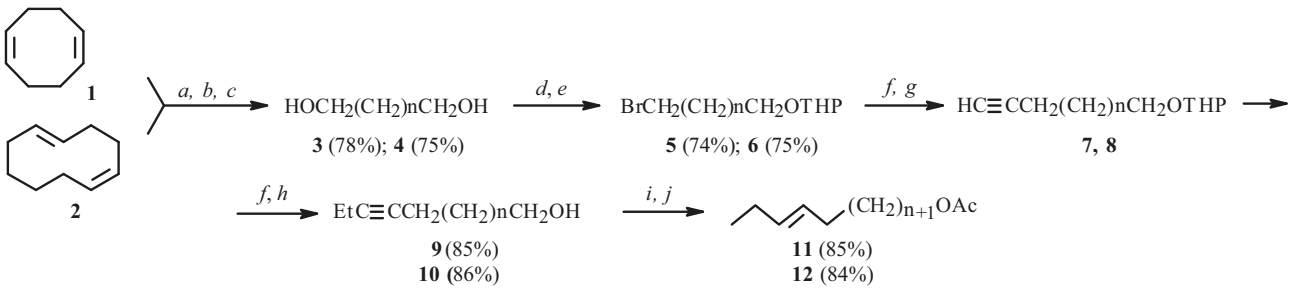
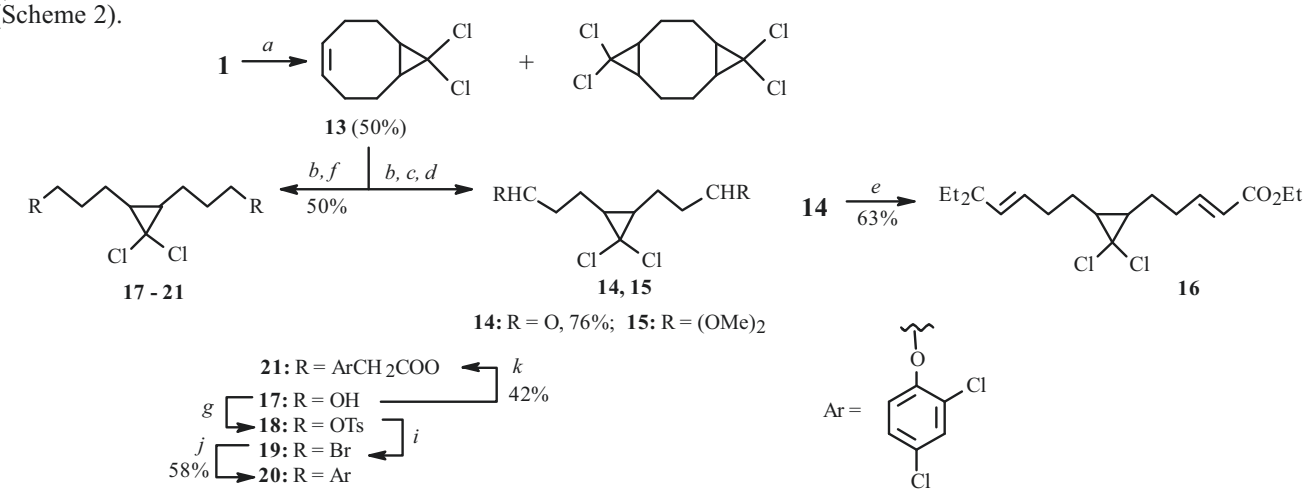


n = 6 (**3**, **5**, **7**, **9**, **11**); n = 8 (**4**, **6**, **8**, **10**, **12**)

a. O_3, *cyclo*-C_6H_{12}, MeOH; *b.* H_2, Pd, C; *c.* $NaBH_4$; *d.* HBr; *e.* DHP, TsOH; *f.* Li, NH_3; *g.* C_2H_2, THF; *h.* EtBr; *i.* $LiAlH_4$; *j.* Ac_2O, Py

Scheme 1

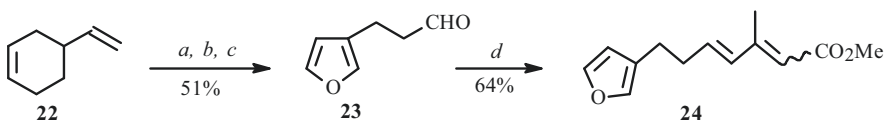
Ozonolysis of monocyclopropanation product **13**, which was synthesized via reaction of 1,5-cyclooctadiene (**1**) with dichlorocarbene using phase-transfer catalysis or ultrasonic irradiation, produced convenient synthons containing a *gem*-dichlorocyclopropane ring. Depending on the reductant, α,ω-dialdehyde **14**, which was characterized as dimethylacetal **15**, or diol **17**, which was converted through tosylate **18** into corresponding bromide **19**, was isolated. Horne–Wadsworth–Emmons olefination of **14** with a stabilized phosphonate produced the potential juvenoid dienoate **16** as a mixture of *E*- and *Z*-isomers in an 85:15 ratio. Reaction of bromide **19** with potassium 2,4-dichlorophenoxide in the presence of tetrabutylammonium bromide gave 1,3-*bis*-[3-(2,4-dichlorophenoxy)propyl]-2,2-dichlorocyclopropane (**20**), which exhibited juvenoid activity. Another juvenoid **21** was prepared by treating diol **17** with 2,4-dichlorophenoxyacetylchloride. The yields in all steps of the proposed syntheses were ~40–60%. Therefore, the overall yields of target juvenoids **20** and **21** were low [12] (Scheme 2).



a. $CHCl_3$, CH_2Cl_2, NaOH, $(C_4H_9)_4N^+Br^-$ or ultrasonic radiation; *b.* O_3, MeOH; *c.* Me_2S; *d.* MeOH, NH_4Cl; *e.* $(MeO)_2P(O)CH_2CO_2Et$, NaH; *f.* $NaBH_4$; *g.* TsCl, Py; *i.* NaBr, $(CH_3)_2CO$; *j.* ArOK/$(C_6H_9)_4N^+Br^-$; *k.* $ArCH_2COCl$

Scheme 2

Another butadiene cyclodimerization product [13], vinylcyclohexene (**22**), was also used to synthesize low-molecular-weight insect bioregulators. Thus, a new approach based on exhaustive ozonolysis of **22** was proposed [14] for synthon **23** for furan-containing analogs of native juvenile hormones and more effective juvenoids with a 2,4-dienoate system (**24**) (Scheme 3).

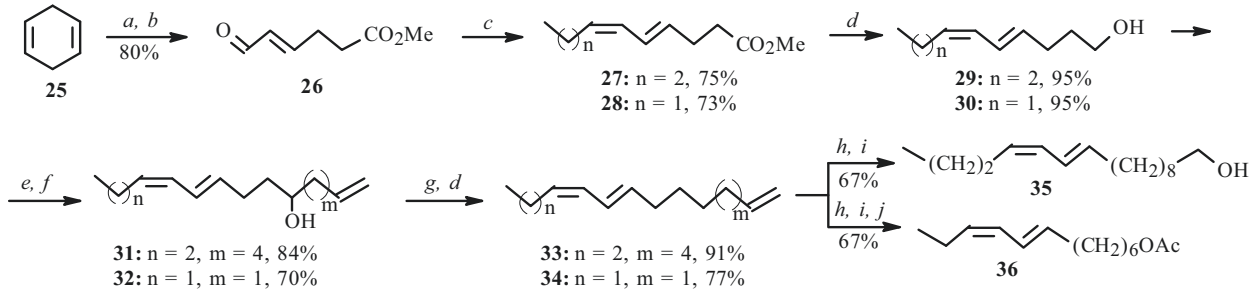


a. O_3, MeOH; *b.* Me_2S; *c.* Al_2O_3, Δ; *d.* $(Et_2O)_2P(O)CH_2C(Me)=CHCO_2Me$, NaH

Scheme 3

Partial ozonolysis of 1,4-cyclohexadiene (**25**) synthesized (10*E*,12*Z*)-hexadecadienol (bombykol) (**35**) and (7*E*,9*Z*)-dodecadien-1-ylacetate (**36**), sex pheromones of *Bombix mori* [15] and *Lobesia botrana* [16, 17]. Wittig olefination of the reductive ozonolysis product **26** gave the corresponding methyl esters of (4*E*,6*Z*)-decane- (**27**) and (4*E*,6*Z*)-nonane-4,6-dienoic acid (**28**), which then were reduced by $LiAlH_4$ to alcohols **29** and **30**. The key step was extension of the carbon chain by

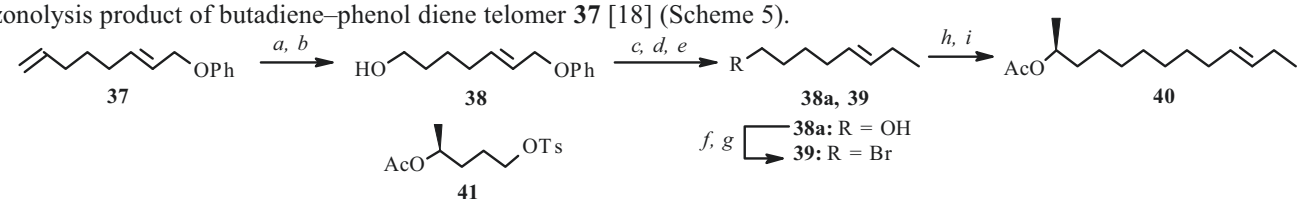
reacting the oxidation products of alcohols **29** and **30** with the corresponding Grignard reagents. Resulting alcohols **31** and **32** were de-oxygenated by $LiAlH_4$ through the mesylate intermediates. Chemo- and regiospecific hydroboration by 9-BBN followed by H_2O_2 oxidation converted trienes **33** and **34** into target alcohol **35** and then acetate **36** (Scheme 4).



a. O_3, MeOH, CH_2Cl_2; *b.* Et_3N, Ac_2O; *c.* $[Ph_3P^+CH_2Pr]Br^-$, $(Me_3Si)_2NNa$ (for **27**), $[Ph_3P^+Pr]Br^-$, $(Me_3Si)_2NNa$ (for **28**); *d.* $LiAlH_4$; *e.* PCC; *f.* $CH_2=CH(CH_2)_4MgBr$ (for **31**), $CH_2=CHCH_2MgCl$ (for **32**); *g.* MsCl, Et_3N; *h.* 9-BBN; *i.* H_2O_2, NaOH; *j.* Ac_2O, Py

Scheme 4

The key step in the synthesis of (2*S*)-acetoxytridec-10-ene (**40**) (sex pheromone of *Mayetiola destructor*) was catalyzed cross-coupling of chiral **41** and achiral **39** block synthons. The latter was obtained from phenoxy derivative **38**, the partial ozonolysis product of butadiene–phenol diene telomer **37** [18] (Scheme 5).

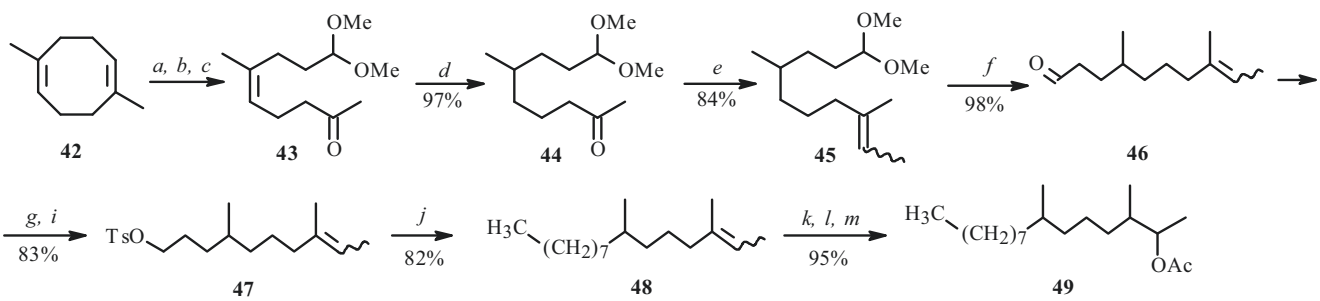


a. O_3, CH_2Cl_2, MeOH, $NaHCO_3$; *b.* $NaBH_4$; *c.* DHP, TsOH, Et_2O; *d.* MeMgI, Li_2CuCl_4, THF; *e.* TsOH, MeOH, H_2O; *f.* TsCl, Py; *g.* LiBr, Me_2CO; *h.* Mg, THF; *i.* Li_2CuCl_4, THF, **41**

Scheme 5

One approach to synthesizing terpenoid insect pheromones with a tri-substituted double bond was to use regularly constructed oligomers, co-oligomers, and isoprene telomers, the preparation of which is now well developed, in addition to natural terpenoids with tri-substituted double bonds as starting materials. If this approach was used, the problem consisted of choosing selective methods for the required transformation of the starting material so that the carbon skeleton required for the pheromone could be constructed using the resulting functional block synthon. The starting cyclic isoprenoid was transformed into the α,ω-bifunctional synthon by opening the ring. A suitable method for converting a starting acyclic compound with the given geometry of the double bonds into an intermediate that was convenient for further use in preparing the target pheromone was selected [10].

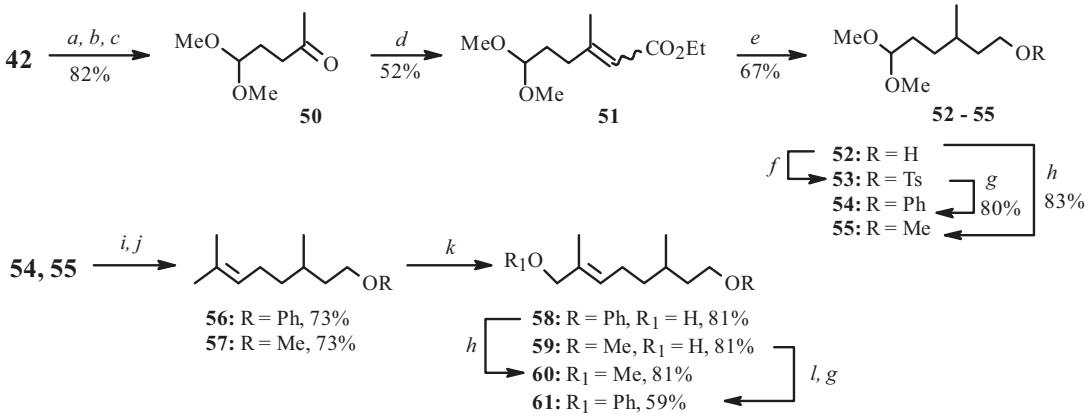
The most available isoprene cyclooligomer is (1*Z*,5*Z*)-dimer **42**, selective ozonolysis of which produced unsaturated ketoacetal **43**, which was used to synthesize insect pheromones [10], e.g., (±)-3,7-dimethylpentadec-2-ylacetate (diprionylacetate) (**49**) [19, 20], which was a racemic analog of sex pheromones from four species of pine sawflies in the genera *Diprion* and *Neodiprion*. The key synthetic step was Wittig olefination of saturated ketone **44**, the product from catalytic hydrogenation of enone **43**, which gave an ~4:1 mixture of the *Z*- and *E*-isomers of 1,1-dimethoxy-4,8-dimethyldec-8-ene (**45**). Construction of the carbon skeleton of pheromone **49** was completed by Li_2CuCl_4-catalyzed cross-coupling of *n*-amylmagnesiumbromide and tosylate **47**, which was obtained via selective transformations of unsaturated acetal **45** along the path **46** → **47** → **48**. The secondary acetoxy group was introduced by regiospecific hydration using an organoboron intermediate followed by acetylation (Scheme 6).



a. O_3, *cyclo*-C_6H_{12}, MeOH; *b.* H_2, Pd, $CaCO_3$, PbO, MeOH; *c.* MeOH, NH_4Cl; *d.* H_2, Pd, C; *e.* $CH_2=CHPPh_3$, THF; *f.* H_3O^+; *g.* $NaBH_4$; *i.* TsCl, Py; *j.* *n*-$C_5H_{11}MgBr$, Li_2CuCl_4, THF; *k.* B_2H_6; *l.* H_2O_2, NaOH; *m.* Ac_2O, Py

Scheme 6

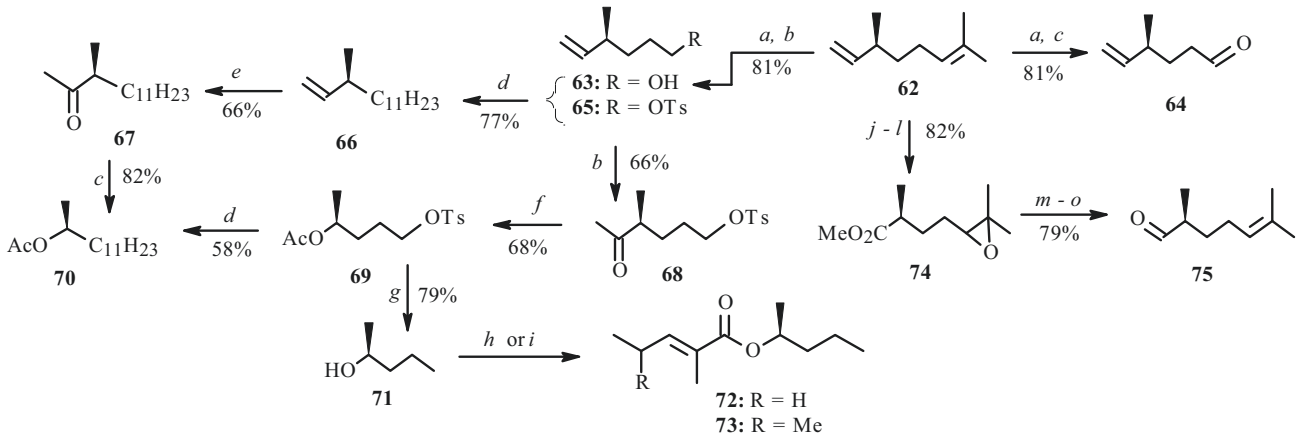
2,6-Dimethyl-(2*E*)-octene-1,8-diol diethers (**60** and **61**), which were active against *Culex* mosquito larvae, were synthesized in ~16% overall yield from the product of exhaustive ozonolysis of 1,5-dimethyl-1,5-cyclooctadiene (**42**), i.e., the dimethylacetal of levulinic aldehyde (**50**) [21]. Petersen olefination of **50** added ethoxycarbonylmethylene to give unsaturated ethyl ester **51**, subsequent reduction of the ester of which by Li in liquid NH_3 was accompanied by simultaneous hydrogenation of the Δ^2-bond to afford alcohol **52**. Phenyl ether **54** was prepared by treating its 6-tosyl derivative (**53**) with sodium phenoxide. Methyl ether **55** was prepared by alkylating alcohol **52** with methyliodide through an intermediate sodium alkoxide. Acid hydrolysis of acetals **54** and **55** followed by olefination of the free aldehydes by isopropylidenetriphenylphosphorane gave 1-phenoxy- (**56**) and 1-methoxy-3,7-dimethyl-6-octene (**57**), allylic oxidation of which gave 8-phenoxy- (**58**) and 8-methoxy-2,6-dimethyl-(2*E*)-octen-1-ol (**59**), which were transformed into target diethers **60** and **61**, respectively (Scheme 7).

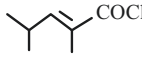


a. O_3, *cyclo*-C_6H_{12}, MeOH; *b.* H_2, Pd, $CaCO_3$, PbO; *c.* MeOH, NH_4Cl; *d.* $Me_3SiCH_2CO_2Et$, BuLi, C_6H_{14}; *e.* Li, NH_3; *f.* TsCl, Py; *g.* NaH, DMSO, C_6H_5OH; *h.* NaH, MeI; *i.* Py, TsOH, Me_2CO; *j.* $Ph_3P{=}CMe_2$; *k.* *t*-BuOOH, SeO_2; *l.* PBr_3

Scheme 7

Partial ozonolysis of dihydromyrcene (**62**), which occurred preferentially at the tri-substituted double bond, produced alcohol **63** (R = OH) or aldehyde **64**, which are widely used to synthesize insect pheromones, depending on the decomposition conditions for the intermediate peroxides (Scheme 8) [22, 23].



a. O_3, $NaHCO_3$, CH_2Cl_2, MeOH; *b.* $NaBH_4$; *c.* H_2, Pd, $CaCO_3$, PbO; *d.* *n*-$C_8H_{17}MgBr$, Li_2CuCl_4; *e.* O_2, $PdCl_2$, Cu_2Cl_2; *f.* *m*-CPBA; *g.* $LiAlH_4$; *h.*  COCl; *i.*  COCl; *j.* *t*-BuOOH, $Mo(CO)_6$; *k.* O_3, MeOH, CH_2Cl_2; *l.* Ac_2O, Et_3N, *m.* AlI_3, PhH; *n.* DIBAH; *o.* PCC

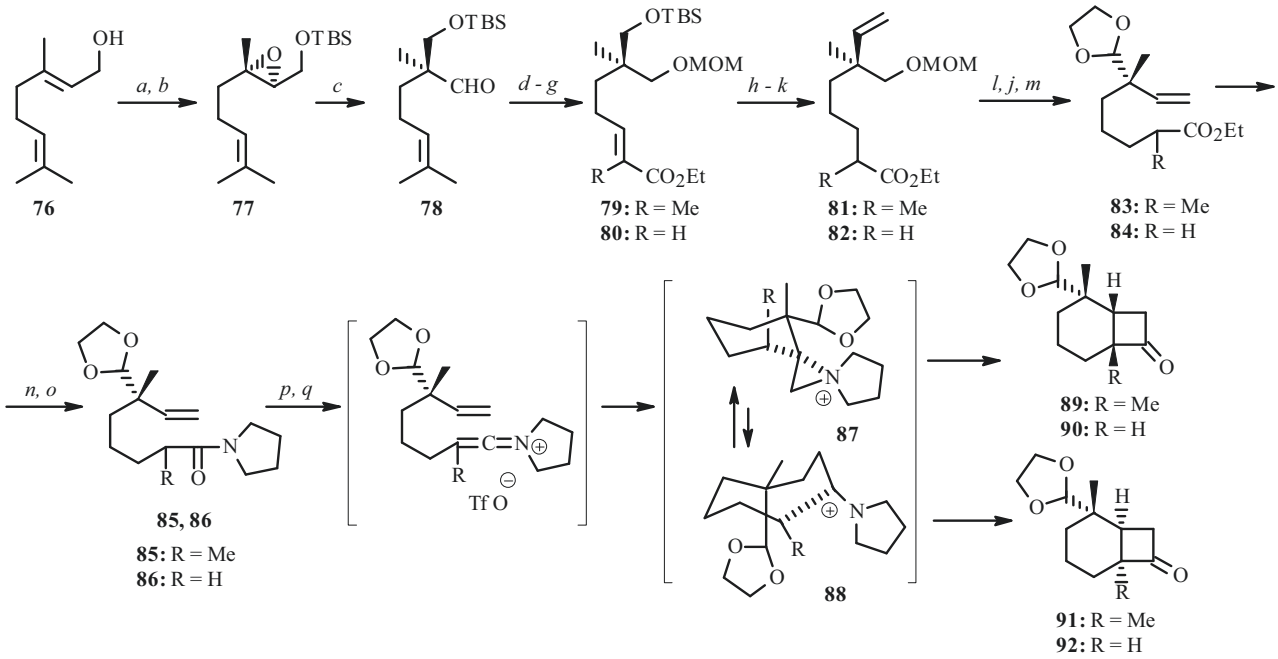
Scheme 8

Thus, the synthetic capabilities of unsaturated alcohol **63** were studied using preparation of the three insect pheromone components **70**, **72**, and **73** as examples [24, 25]. One of the proposed synthetic approaches was based on catalytic cross-coupling of tosylate **65** with *n*-octylmagnesiumbromide. Successive Wacker–Tsuji oxidation of alkene **66** and Baeyer–Villager oxidation of the obtained (*S*)-3-methyltetradecan-2-one (**67**) gave *Drosophila mulleri* pheromone **70** in 40% overall yield. An alternative and less effective (20% overall yield) synthetic route to chiral acetate **70** consisted of Wacker–Tsuji oxidative transformation of vinyl tosylate **65** into ketone **68** and then Baeyer—Villager oxidation into acetoxytosylate **69**, which underwent

chemoselective cross-coupling with a magnesium-cuprate reagent generated from *n*-octylbromide. Reduction of diester **69** by $LiAlH_4$, which occurred with configuration retention of the chiral center, produced enantiomerically enriched (*S*)-pentan-2-ol (**71**), which could be readily converted into components of the *Rhyzopertha dominica* aggregation pheromone, i.e., dominicalur-1 (**72**, 94%) and dominicalur-2 (**73**, 95%) (Scheme 8).

The terminal vinyl group in (*S*)-(+)-dihydromyrcene (**62**) had to be cleaved in order to synthesize a component of the smaller yellow ant *Acanthomyops claviger* sex pheromone (**75**). Diene **62** was epoxidized in order to protect the isopropylidene group, which was more sensitive to electrophiles. Further ozonolysis and treatment of the peroxide with $Et_3N–Ac_2O$ gave key epoxyester **74** in high yield [26] (Scheme 8).

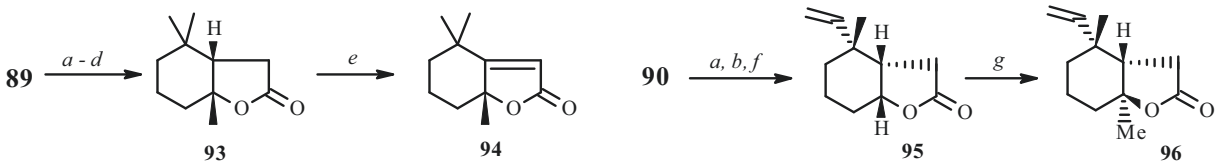
A synthesis of intermediates **93** and **95** was developed [27] in order to prepare (–)-dihydroactinidiolide (**94**) and (–)-anastrephin (**96**), pheromone components of *Solenopsis invicta* Buren and *Anastrepha suspense* Loew, respectively. Starting geraniol **76** [28] was converted by Sharpless asymmetric epoxidation in the presence of L-(+)-DET and subsequent silylation into epoxysilyl ether **77**. Rearrangement of **77** through the action of methylaluminum *bis*(4-bromo-2,6-di-*t*-butylphenoxide) gave (*S*)-aldehyde **78** (*ee* 95%), which was transformed by several sequential reactions first into the two unsaturated esters **79** and **80** and then into **81** and **82**. Removal of the protection in the last two and Swern oxidation produced the corresponding aldehydes, which underwent Noyori acetalization to form esters **83** and **84**, which were then converted to amides **85** and **86**. Treatment of **85** and **86** with trifluoroacetic anhydride in the presence of collidine in refluxing benzene caused 1,2-asymmetric induction during [2+2]-cycloaddition to form after hydrolysis a chromatographically separable mixture of cyclobutanone diastereomers **89**/**90** and **91**/**92** in 5:1 and 3:1 ratios, respectively. The configuration of the new asymmetric center (C-1) was established using the NOE-effect between the C-2 methyl and the C-1 methine proton in principal diastereomers **89** and **90**. According to the researchers, the diastereoselectivity of the cycloaddition was explained by ketenimine cyclization through eight-membered enamine intermediates **87** and **88** (Scheme 9).



a. (+)-DET, $(i\text{-PrO})_4Ti$, *t*-BuOOH; *b.* TBSOTf, $i\text{-Pr}_2NEt$, CH_2Cl_2, 0°C; *c.* methylaluminum *bis*(4-bromo-2,6-di-*t*-butylphenoxide); *d.* $NaBH_4$, EtOH, 0°C; *e.* MOMCl, $i\text{-Pr}_2NEt$; *f.* O_3, CH_2Cl_2, then Me_2S, –78°C; *g.* $Ph_3P{=}C(R)CO_2Et$, C_6H_6, Δ; *h.* H_2, Pd, C, EtOH; *i.* $n\text{-Bu}_4NF$, THF; *j.* DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, –78°C; *k.* $Ph_3P{=}CH_2$, THF, 0°C; *l.* HCl, EtOH, Δ; *m.* $TMSO(CH_2)_2OTMS$, TMSOTf, CH_2Cl_2, –78°C; *n.* LiOH, THF, H_2O, Δ; *o.* pyrrolidine, Py, BOP®, HOBT, Et_3N, DMF; *p.* Tf_2O, collidine, C_6H_6, Δ; *q.* hydrolysis

Scheme 9

Baeyer–Villager oxidation of **89** gave a lactone, which was hydrolyzed to form **93**, which was transformed into (–)-dihydroactinidiolide (**94**) as before [29]. Also, **90** was transformed into lactone **95**, a key intermediate in the synthesis of (–)-anastrephin (**96**) [30], by successive Baeyer–Villager oxidation, acid hydrolysis, and olefination (Scheme 10).

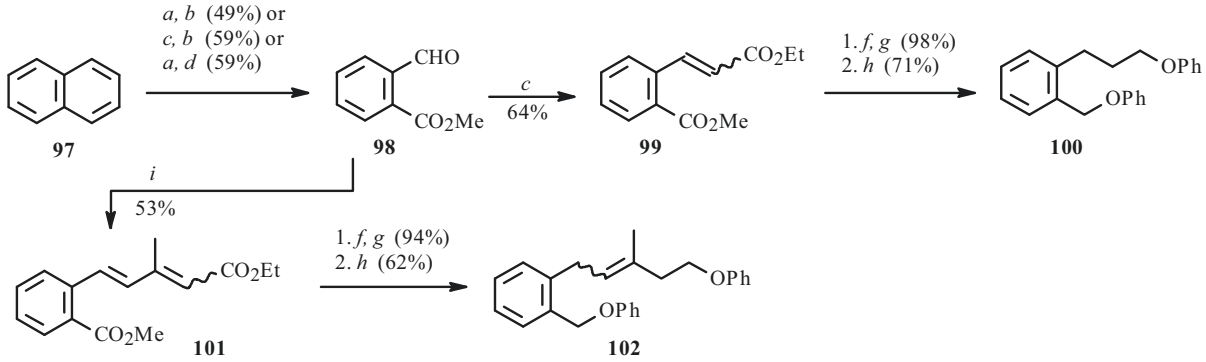


a. *m*-CPBA, $KHCO_3$, CH_2Cl_2; *b.* AcOH, H_2O, 90°C; *c.* $TsNHNH_2$, THF, Δ; *d.* $NaBH_3(CN)$, TsOH, DMF, sulfolane, 140°C; *e.* [29]; *f.* $Ph_3P{=}CH_2$-THF; *g.* [30]

Scheme 10

Juvenoids often include aromatic moieties in their structures. Therefore, ozonolytic cleavage of substrates containing aromatic systems was used to synthesize them.

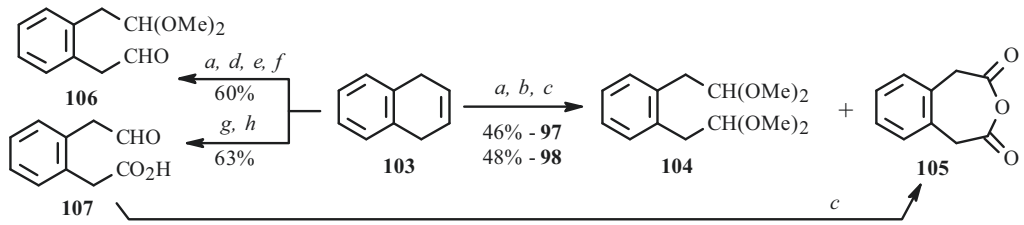
Ozonation of naphthalene (**97**) in MeOH formed primarily aldehydoester **98**, regardless of the reductant. Horner–Wittig olefination of **98** produced mono- (**99**) and diene (**101**) esters, which were intermediates in the synthesis of *bis*-phenyl ethers **100** and **102**, aromatic analogs of *Culex* and *Pectinophora gossypiella* juvenile hormones [31, 32] (Scheme 11).



a. O_3, MeOH; *b.* Me_2S; *c.* O_3, MeOH, H_2O; *d.* KI, AcOH; *e.* $(Et)_2P(O)CH_2COOEt$, NaH; *f.* $LiAlH_4$, Et_2O; *g.* PBr_3; *h.* NaOPh, $Bu_4N^+Cl^-$; *i.* $(i\text{-}PrO)_2P(O)CH_2C(Me){=}CHCO_2Et$, NaH

Scheme 11

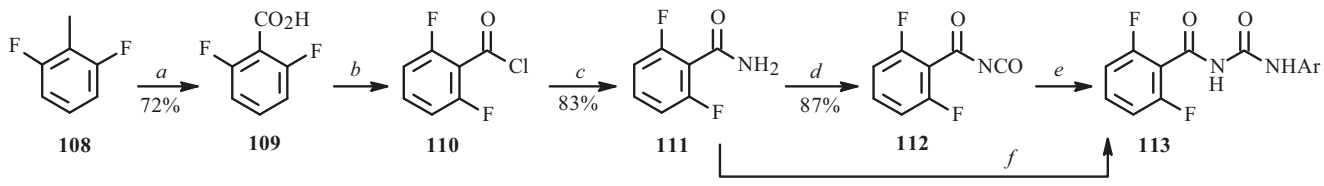
Ozonolysis by various methods of 1,4-dihydronaphthalene (**103**), a readily available product from partial Birch reduction of naphthalene, produced functionalized benzene derivatives **104**–**107**, which were used to synthesize juvenoids [33] (Scheme 12).



a. O_3, CH_2Cl_2, MeOH; *b.* H_2, Pd, $CaCO_3$, PbO; *c.* MeOH, TsOH; *d.* TsOH; *e.* $NaHCO_3$; *f.* Me_2S; *g.* O_3, *cyclo*-C_6H_{12}, AcOH; *h.* Ac_2O, H_2O

Scheme 12

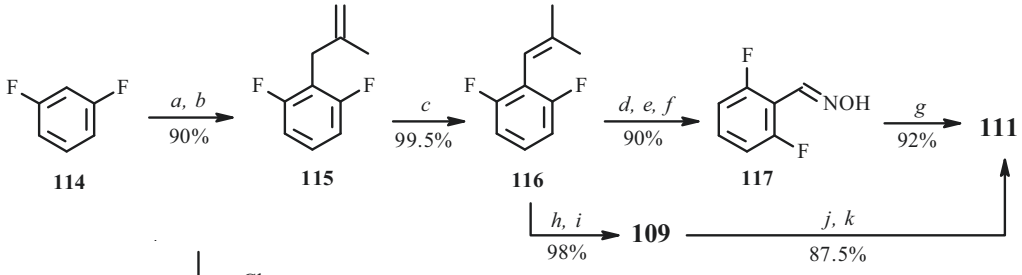
N-(2,6-Difluorobenzoyl)-*N*′-arylureas (**113**) are highly touted as effective insect chitin biosynthesis inhibitors. The most convenient pathways for synthesizing them were the reaction of 2,6-difluorobenzamide (**111**) with arylisocyanates or the reaction of 2,6-difluorobenzoylisocyanate (**112**) with arylamines. An approach to the synthesis of **112** was developed based on 2,6-difluorobenzoic acid (**109**), which was synthesized via O_3–O_2 oxidation of 2,6-difluorotoluene (**108**) in the presence of $Co(OAc)_2$. Transformation of **109** into acid chloride **110** and treatment of **110** with NH_4OH gave 2,6-difluorobenzamide (**111**), which was converted to isocyanate **112** by reaction with oxalylchloride [34] (Scheme 13).

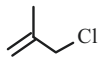


a. O_3, O_2, $Co(OAc)_2$; *b.* $SOCl_2$; *c.* NH_4OH; *d.* $(COCl)_2$; *e.* $ArNH_2$; *f.* ArNCO

Scheme 13

An alternative synthetic route to benzamide **111** [33] was based on alkylation of available *m*-difluorobenzene (**114**) by the action of methylallylchloride on its sodium derivative, which was generated using sodium amide in liquid NH_3. Subsequent transformations of the alkylation product, 1-(2-methyl-2-propen-1-yl)-2,6-difluorobenzene (**115**), gave eventually amide **111** with high yields in each step. Olefin **115** isomerized readily on heating in benzene in the presence of TsOH to styrene derivative 1-(2-methyl-1-propen-1-yl)-2,6-difluorobenzene (**116**), ozonolysis of which and subsequent treatment of the peroxide ozonolysis product with $NH_2OH{\cdot}HCl$ gave 2,6-difluorobenzaldoxime (**117**), which was transformed under Beckmann reaction conditions into benzamide **111**. The overall yield of **111** from difluorobenzene (**114**) was 80%. Ozonation of alkene **116** in AcOH followed by oxidative decomposition of the ozonide in the presence of SeO_2 gave 2,6-difluorobenzoic acid (**109**), which was converted into amide **111** by the usual route (Scheme 14).



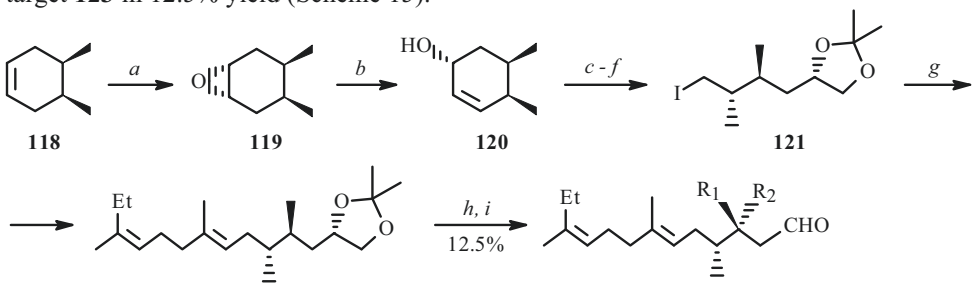
a. $NaNH_2$, NH_3; *b.*  ; *c.* TsOH; *d.* O_3, MeOH; *e.* $NH_2OH{\cdot}HCl$; *f.* Na_2CO_3; *g.* H_2SO_4; *h.* O_3, AcOH; *i.* AcOH, Ac_2O, SeO_2; *j.* $SOCl_2$; *k.* NH_4OH

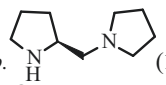
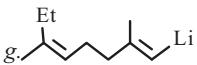
Scheme 14

2. Synthesis of Pheromones and Juvenoids Based on Ozonolysis Products of Cyclic and Acyclic Alkenes

Ozonolysis of monoenes afforded saturated oxygen-containing compounds that were of interest for synthesizing pheromones and juvenoids.

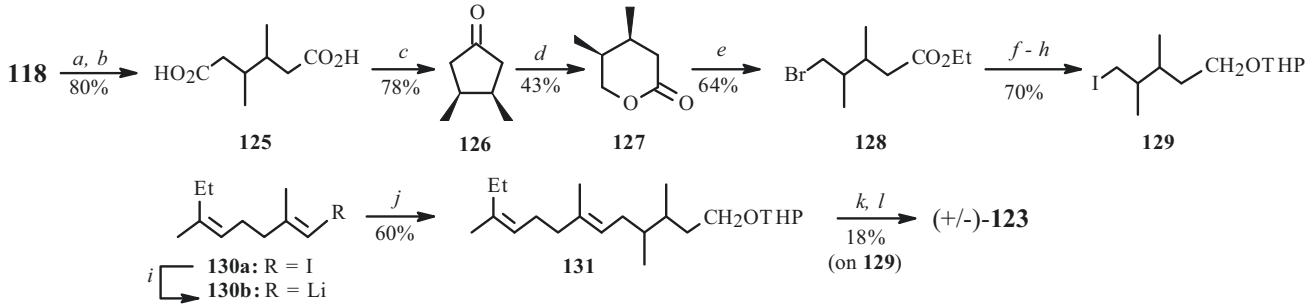
The trail pheromone (pharanal) of *Monomorium pharaonis*, a food pest and dangerous infection vector, was identified as 3,4,7,11-tetramethyldeca-(6*E*,10*Z*)-dienal (**123**) although natural pharanal has the (3*S*,4*R*)-configuration [35]. A synthesis of **123** starting from *cis*-dimethylcyclohexene (**118**) was proposed. Asymmetric cleavage of *meso*-epoxide **119** using (*S*)-(pyrrolidin-2-ylmethyl)pyrrolidine (**124**) gave allyl alcohol **120**, reductive ozonolysis of which and protection of the C-1 and C-2 hydroxyls in the obtained triol followed by replacement of the C-6 OH gave iodide **121**. Condensation of **121** with a lithium derivative produced enantiomerically pure acetal **122**, hydrolysis of which and subsequent periodate oxidation completed the synthesis of target **123** in 12.5% yield (Scheme 15).



a. *m*-CPBA; *b.*  (**124**); *c.* O_3, CH_2Cl_2; *d.* $NaBH_4$; *e.* TsOH, Me_2CO; *f.* I_2, Ph_3P, imidazole; *g.*  ; *h.* H_3O^+; *i.* $NaIO_4$

Scheme 15

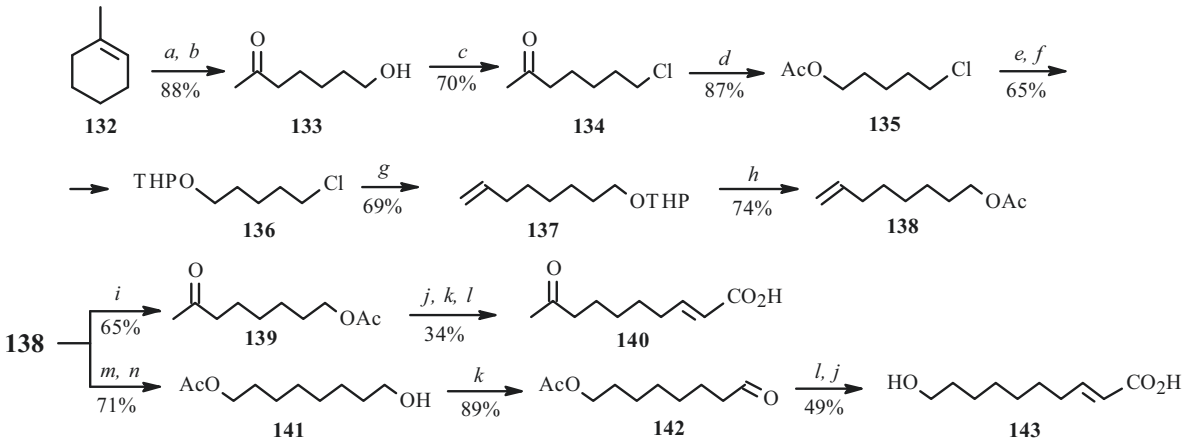
An alternative pathway for preparing racemic (±)-pharanal (**123**) starting from *cis*-dimethylcyclohexene (**118**) was proposed [35]. The key synthon of the proposed synthesis was iodide **129**. Ozonolysis of **118** followed by Jones oxidation produced diacid **125**, pyrolysis of which in the presence of $Ba(OH)_2$ afforded cyclic ketone **126**. Baeyer–Villager oxidation of **126** to lactone **127** and treatment with anhydrous HBr in EtOH gave bromoester **128**, which then was transformed into key iodide **129**. Further condensation of **129** with Li-derivative **130b** gave tetrahydropyranyl ether **131**, which was transformed by standard reactions into (±)-pharanal (**123**) in 18% overall yield from iodide **129** (Scheme 16).



a. O_3, CH_2Cl_2; *b.* CrO_3; *c.* $Ba(OH)_2$, Δ; *d. m*-CPBA; *e.* HBr, EtOH; *f.* $LiAlH_4$; *g.* DHP, TsOH; *h.* LiI, MeCN; *i. t*-BuLi, Et_2O; *j.* (**129**), Et_2O, THF; *k.* H_3O^+; *l.* PCC, CH_2Cl_2

Scheme 16

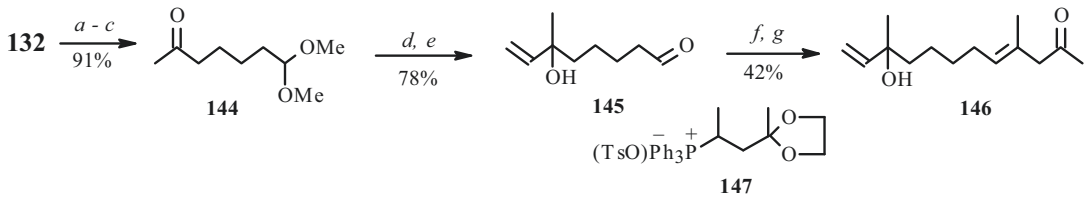
The most important components of queen substance and royal jelly of *Apis mellifera* L., 9-oxo- (**140**) and 10-hydroxy-2*E*-decenoic acid (**143**), were synthesized starting with an ozonolytic cleavage product of methylcyclohexene (**132**), 7-hydroxyheptan-2-one (**133**) [36]. The key synthon for both target acids **140** and **143** was unsaturated acetate **138**, which was synthesized by standard transformations of ketoalcohol **133** along the route **133**→**134**→**135**→**136**→**137**→**138**. Further transformation of alkenylacetate **138** that was directed at oxoacid **140** consisted of single-step Wacker–Tsuji transformation into ketoacetate **139**. Building block **142** for hydroxyacid **143** was constructed from intermediate monoester **141** using chemo- and regioselective oxidative hydroboration (Scheme 17).



a. O_3, CH_2Cl_2, AcOH; *b*. $NaBH(OAc)_3$; *c.* $SOCl_2$; *d. m*-CPBA; *e*. MeOH, TsOH; *f.* DHP, TsOH; *g*. Mg, CH_2=$CHCH_2Br$, CuI, 2,2′-bipy; *h*. AcCl, AcOH; *i*. O_2, $PdCl_2$, Cu_2Cl_2; *j*. NaOH, H_2O; *k*. PCC, CH_2Cl_2; *l*. $CH_2(CO_2H)_2$, Py+Pyp; *m*. 9-BBN; *n*. H_2O_2, AcONa

Scheme 17

1,1-Dimethoxy-6-oxoheptane (**144**), another reductive ozonolysis product of 1-methyl-1-cyclohexene (**132**), was used to synthesize a racemic mixture of echinolone *Z*- and *E*-isomers (**146**), which exhibited higher juvenile hormone activity than each of the isomers. Transformation of ketoacetal **144** into vinyl alcohol **145** and condensation of the latter with the complementary phosphorane generated from phosphonium tosylate **147** gave target compound **146** [37] (Scheme 18).

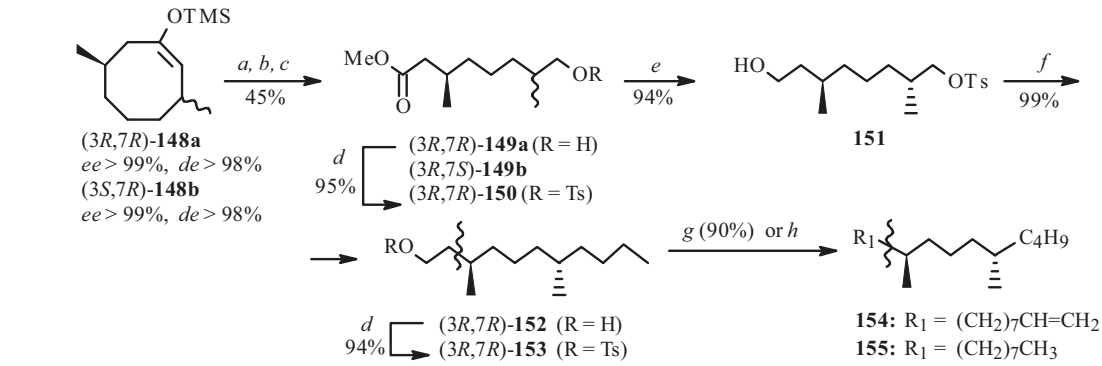


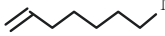
a. O_3, MeOH; *b.* H_2, Pd, $CaCO_3$, PbO; *c.* MeOH, NH_4Cl; *d.* CH_2=$CHMgBr$; *e.* H_2O, TsOH, Py; *f.* **147**, $(Me_3Si)_2NNa$; *g.* H_2O, TsOH, Me_2CO

Scheme 18

Ozonolytic ring opening of optical isomers of silylenol ethers **148a** or **148b** followed by $NaBH_4$ reduction and treatment with MeOH in the presence of TMSCl gave ω-hydroxyesters **149a** and **149b**, which were used to synthesize **154** and **155**, two female sex pheromones of *Lyonetia prunifoliella*, a pest endemic to the eastern regions of North America [38]. The

carbon chain of **149a** was lengthened from the side of the primary hydroxyl in three steps, i.e., transformation into tosylate **150**, chemoselective hydride reduction of the ester to alcohol **151**, and final cross-coupling with an excess of *n*-propylmagnesiumbromide in the presence of stoichiometric amounts of $CuBr{\cdot}SMe_2$ to branched dimethylalcohol **152**. The last was transformed into tosylate **153**, which underwent $CuBr{\cdot}SMe_2$-catalyzed reaction with 6-heptenyl- or *n*-hexylmagnesiumbromide to form target pheromones **154** and **155**, respectively (Scheme 19).

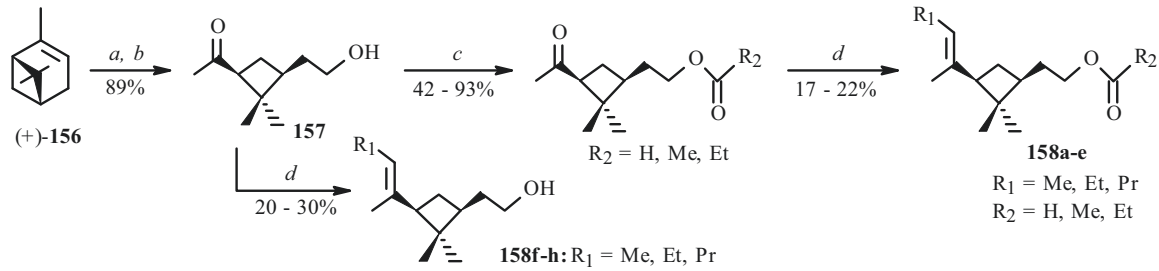


a. O_3, MeOH, CH_2Cl_2; *b.* $NaBH_4$; *c.* MeOH, TMSCl; *d.* TsCl, Py; *e.* DIBAH, Et_2O; *f.* $CuBr{\cdot}SMe_2$, *n*-PrMgBr, THF; *g.* $CuBr{\cdot}SMe_2$, 
MgBr, THF; *h.* $CuBr{\cdot}SMe_2$, *n*-$C_6H_{13}MgBr$, THF

Scheme 19

The availability of starting compounds in addition to the preparation of chemically and optically pure target compounds in yields as high as possible and the economic feasibility and ease of carrying out the proposed pathway often remain problematical for planning targeted organic syntheses. The problem is often solved in practice by using renewable natural raw material that is available from essential oils, turpentine, and other sources.

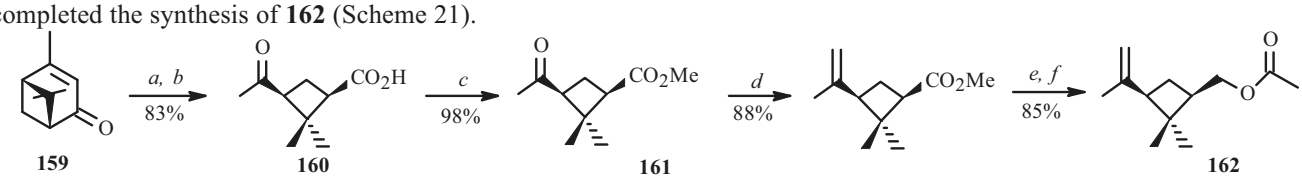
Ozonolysis of α-pinene (**156**), which was isolated from turpentine from sap of various coniferous *Pinus* species [28], was used to demonstrate [39] its synthetic capabilities for synthesizing pheromones. (+)-*cis*-(1*R*)-2,2-Dimethyl-3-acetylcyclobutanylethanol (**157**), a product from ozonolysis of α-pinene [(+)-**156**] followed by $NaBH(OAc)_3$ [40, 41] or $NaBH_4$–NaOH–H_2O [42] reduction, was proposed for synthesizing several structural analogs (**158a-h**) of a *Planococcus citri* (Risso) pheromone via acylation and Wittig olefination (Scheme 20).



a. O_3, CH_2Cl_2, 0°C or O_3, *i*-PrOH, –2°C; *b.* $NaBH(OAc)_3$, CH_2Cl_2 or $NaBH_4$, NaOH, H_2O; *c.* $R_2COOCOMe$, R_2COCl, Py; *d.* $R_1P^+Ph_3Br^-$, NaH, DMSO

Scheme 20

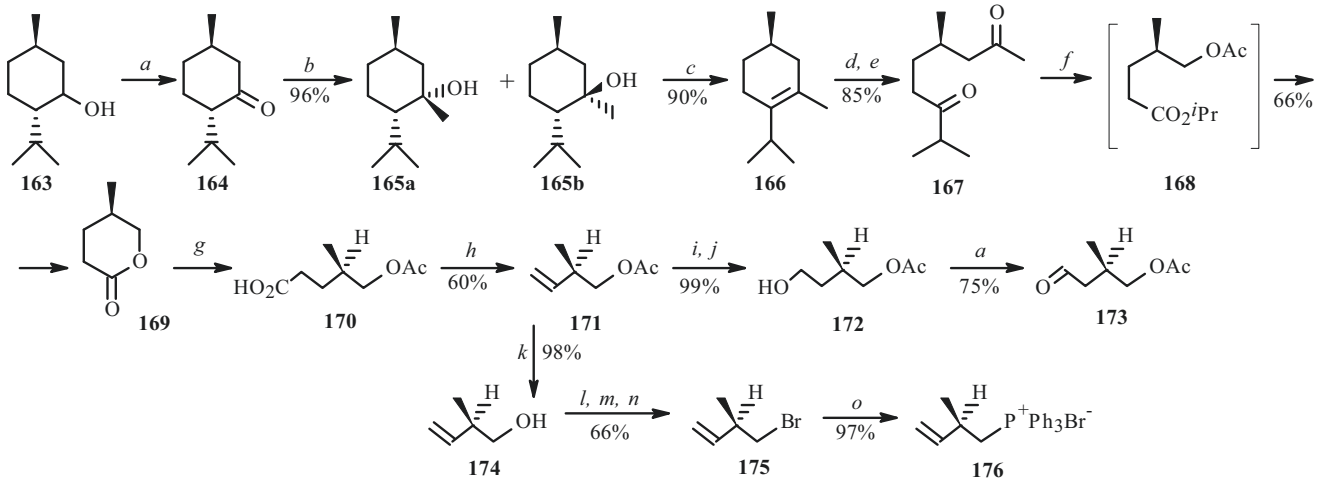
A convenient synthesis in a few steps of a *Planococcus citri* (Risso) sex pheromone (**162**) that was based on ozonolysis of an α-pinene oxidation product (**156**), verbenone [(1*R*,5*R*)-**159**], in MeCN was proposed [43]. Reaction with an excess of ozone at –40°C caused simultaneous cleavage of the double bond in **159** and oxidative degradation of the side chain, which resulted in ketoacid **160**, which was converted to ketoester **161**. Olefination of the last, hydride reduction, and acylation completed the synthesis of **162** (Scheme 21).



a. O_3, MeCN; *b.* Me_2S; *c.* CH_2N_2, Et_2O; *d.* $MeP^+Ph_3Br^-$, BuLi; *e.* DIBAH; *f.* Ac_2O, Py

Scheme 21

Optically pure pentanolide **169**, an intermediate in the synthesis of aggregation pheromone components of *Tribolium* flour beetles [(4*R*,8*R*)- and (4*R*,8*S*)-stereoisomers of 4,8-dimethyldecanal (**181**)], was synthesized from *l*-menthol (**163**), the principal component of *Mentha piperita* [44–46]. Lactone **169** was obtained by intramolecular re-esterification of **168**, a product from exhaustive Baeyer–Villager oxidation of chiral diketone **167**. The last was synthesized using reductive ozonolysis of (3*R*)-methylmenthene (**166**), which was prepared in turn by regiospecific acidic dehydration of Grignard coupling intermediate products [**165a** and **b** (94:6)] of menthone (**164**) and methylmagnesiumiodide (Scheme 22).

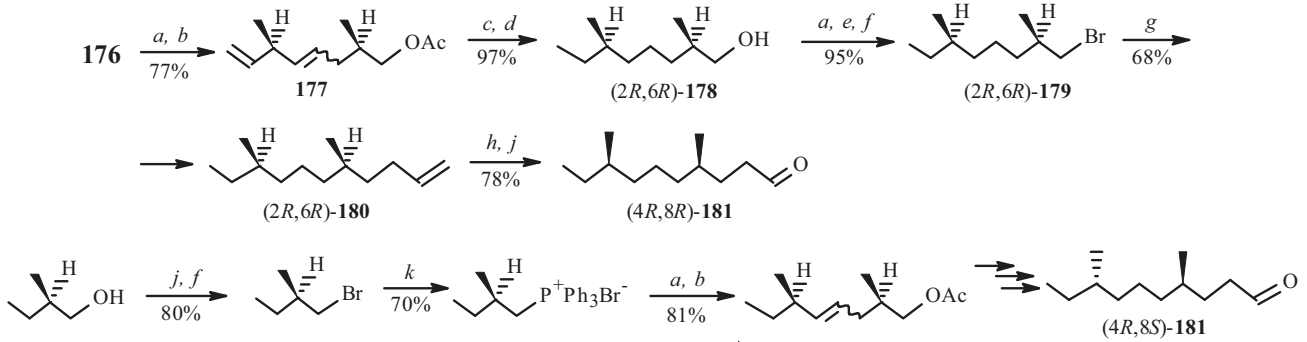


a. PCC, CH_2Cl_2; *b.* MeMgI, Et_2O, Δ *c.* H_3O^+; *d.* O_3, CH_2Cl_2, AcOH; *e.* $NaBH(OAc)_3$; *f.* H_2SO_5; *g.* AcOH, [47]; *h.* $Pb(OAc)_4$, $Cu(OAc)_2$; *i.* 9-BBN, THF; *j.* H_2O_2, AcONa; *k.* KOH, H_2O, Et_2O, MeOH; *l.* *n*-BuLi; *m.* TsCl; *n.* NaBr, DMF; *o.* Ph_3P, THF, 14 kbar

Scheme 22

Pheromones (4*R*,8*R*)- and (4*R*,8*S*)-**181** were approached using acidic opening of lactone **169** to acetoxyacid **170** [47], oxidative decarboxylation to unsaturated acetate **171**, oxidative hydroboration in acetate buffer to give quantitatively alcohol **172**, and PCC oxidation into one of the required fragments, acetoxyaldehyde **173**. The second required structural unit, phosphonium salt **176**, was synthesized from the same acetate **171** by saponification into alcohol **174** and standard two-step transformation of the latter into bromide **175** without isolating the intermediate tosylate (Scheme 22).

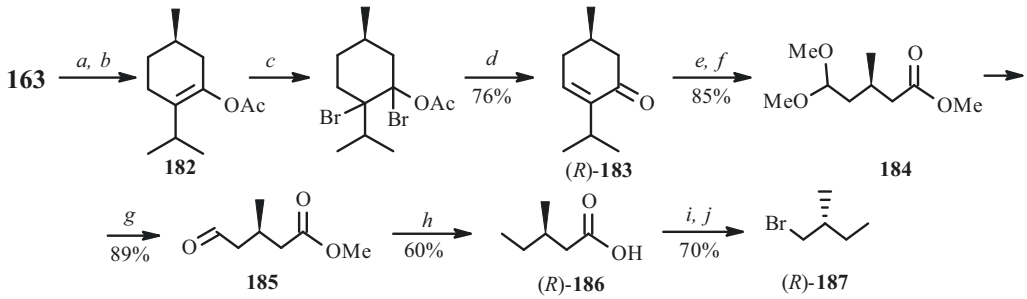
Phosphonium salt **176** was used to construct monoterpene fragment **177** of target (4*R*,8*R*)-**181** from key synthons **173** and **176** according to Wittig without affecting the chiral centers. Catalytic hydrogenation of **177** followed by saponification of the intermediate saturated acetate gave alcohol **178**, which was transformed in high yield into bromide **179**. The concluding step in the synthesis of pheromone (4*R*,8*R*)-**181** involved extending the carbon chain of **179** by a CH_2CHO fragment, which was achieved in two steps by CuI-catalyzed condensation of a Grignard reagent prepared from **179** and allylbromide and subsequent ozonolysis of olefin **180**. The overall yield of (4*R*,8*R*)-**181** was 10% from starting acid **170**. The (4*R*,8*S*)-isomer was synthesized analogously (Scheme 23).



a. *n*-BuLi; *b.* (**173**); *c.* H_2, Pd; *d.* KOH; *e.* TsCl; *f.* NaBr, DMF; *g.* Mg, CuI,  ; *h.* O_3, CH_2Cl_2, Py; *i.* Me_2S; *j.* TsCl, Py; *k.* Ph_3P, THF, 14 kbar

Scheme 23

Another method for functionalizing *l*-menthol (**163**) through (–)-menthone (**164**) ended with the conversion of the latter into (*R*)-4-menthenone (**183**) and was based on halogenation–dehydrohalogenation of the corresponding enolacetate **182** [48, 49] (Scheme 24).



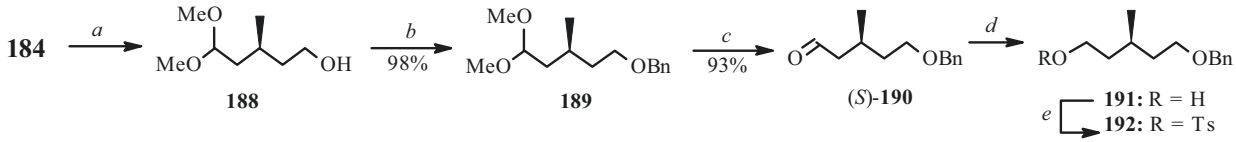
a. PCC, CH_2Cl_2; *b.* Ac_2O, TsOH; *c.* Br_2, CCl_4; *d.* MeOH; *e.* O_3, MeOH, CCl_4, –20°C or *cyclo*-C_6H_{12}, 5°C; *f.* MeOH, TsOH; *g.* PPTs, H_2O; *h.* $N_2H_4 \cdot H_2O$, KOH; *i.* Ag_2O; *g.* Br_2

Scheme 24

(*R*)-4-Menthenone (**183**) was transformed ozonolytically into acetalester **184** [50] in order to use **183** as a substrate for synthesizing optically pure biologically active compounds. Compound **184** was a promising bifunctional synthon for synthesizing several optically active pheromones and juvenoids [51–53] (Scheme 24).

A key step in the synthesis of (4*R*,8*R*)-dimethyldecanal (**181**) and its (4*R*,8*S*) stereoisomer was cross-coupling of bromide (*R*)-**187** and tosylate **192**, products of chemoselective transformations of chiral synthon **184** [54, 55]. The first block [(*R*)-**187**] was synthesized from acetalester **184** via Huang–Minlon deoxygenation of intermediate aldehydoester **185**. Hydrolysis of the ester occurring during this allowed key bromide (*R*)-**187** to be obtained after Hunsdiecker decarboxylation of **186** (Scheme 24).

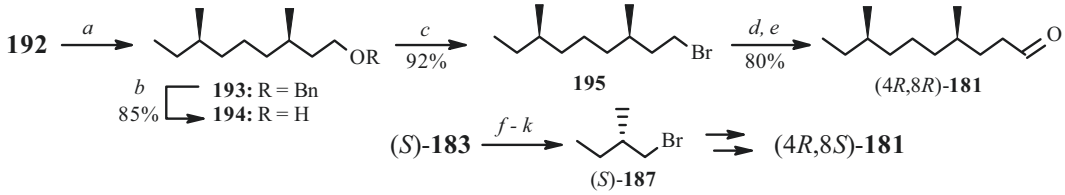
The second block **192** was synthesized using a product from hydride reduction of **184**, i.e., hydroxyacetal **188**, in which the hydroxyl had to be protected for further transformations. This was achieved by converting it into benzyl ether **189**, deprotection of the oxo group in which gave aldehyde (*S*)-**190**. Sequential reduction and then esterification of mono-substituted diol **191** gave the required methyl-branched synthon **192** (Scheme 25).



a. DIBAH; *b.* BnCl, KOH; *c.* PPTs, H_2O; *d.* $NaBH_4$, MeOH; *e.* TsCl, Py

Scheme 25

Benzyl ether **193** was prepared in the key step via alkylation of the tosyl group in **192** by the Grignard reagent of bromide (*R*)-**187**. The carbon chain was lengthened by converting alcohol **194** to bromide **195** followed by formylation of the corresponding Grignard reagent to complete the synthesis of (4*R*,8*R*)-**181** (Scheme 26).



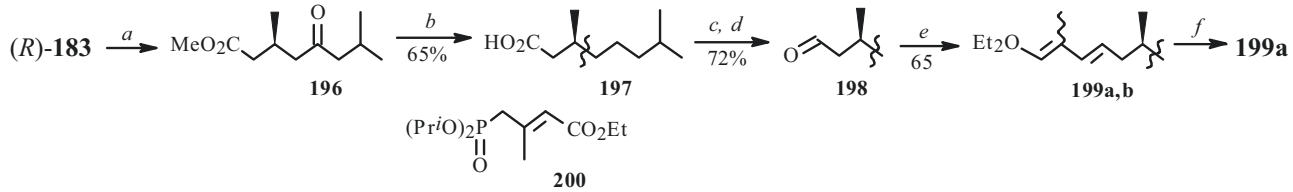
a. Mg, (*R*)-(**187**), Li_2CuCl_4; *b.* H_2, $PdCl_2$; *c.* PBr_3, Py; *d.* Mg; *e.* DMF; *f.* O_3, CCl_4 or *cyclo*-C_6H_{12}, MeOH; *g.* MeOH, TsOH; *h.* PPTs, H_2O; *i.* $N_2H_4 \cdot H_2O$, KOH; *j.* Ag_2O; *k.* Br_2

Scheme 26

The (4*R*,8*S*)-**181** isomer could be synthesized analogously using chiral synthon (*S*)-**187**, which was obtained from (*S*)-4-menthen-3-one [(*S*)-**183**], instead of the (*R*)-**187** isomer [55] (Scheme 26).

Optically pure (*S*)-(+)-hydroprene (**199**), an juvenile hormone analog from insects with incomplete metamorphosis [56], was synthesized from methyl (3*S*)-3,7-dimethyl-5-oxooctanoate (**196**), an ozonolysis product of (*R*)-4-menthen-3-one (**183**) in the presence of Py or Et_3N in CH_2Cl_2–MeOH (1:1) [57, 58]. Subsequent Huang–Minlon deoxygenation of **196**, which was accompanied by saponification of the ester, gave (3*S*)-3,7-dimethyloctanoic acid (**197**), which was converted by sequential hydride reduction and Corey oxidation into aldehyde **198**. Condensation of the last with phosphonate **200** in the

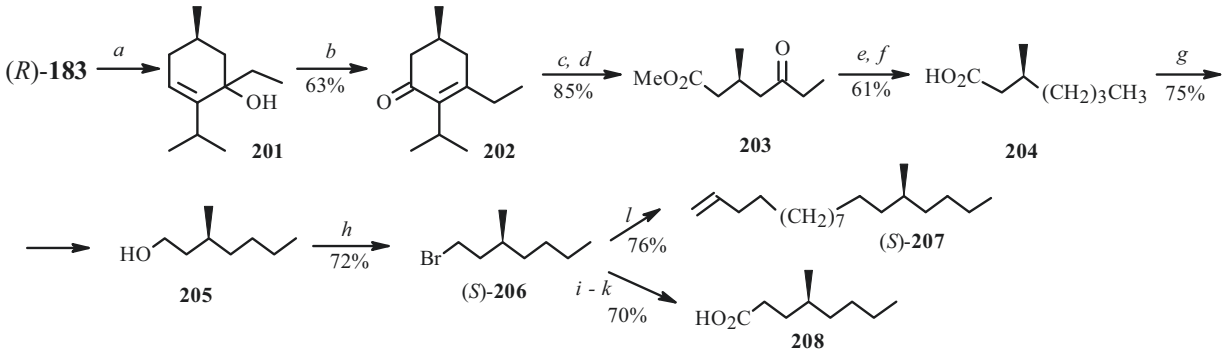
presence of KOH and [*n*-Bu_4N]OH as before [59] formed target (*S*)-(+)-hydroprene (**199**) as a 9:1 mixture of the (2*E*,4*E*)-**199a** and (2*Z*,4*E*)-**199b** isomers in 32% overall yield from ester **196** (Scheme 27).



a. O_3, Py or NEt_3, CH_2Cl_2, MeOH (1:1) [59]; *b.* $N_2H_4 \cdot H_2O$ then KOH, Δ; *c.* $LiAlH_4$, Et_2O; *d.* PCC, CH_2Cl_2; *e.* **200**, [*n*-Bu_4N]OH, KOH; *f.* SiO_2

Scheme 27

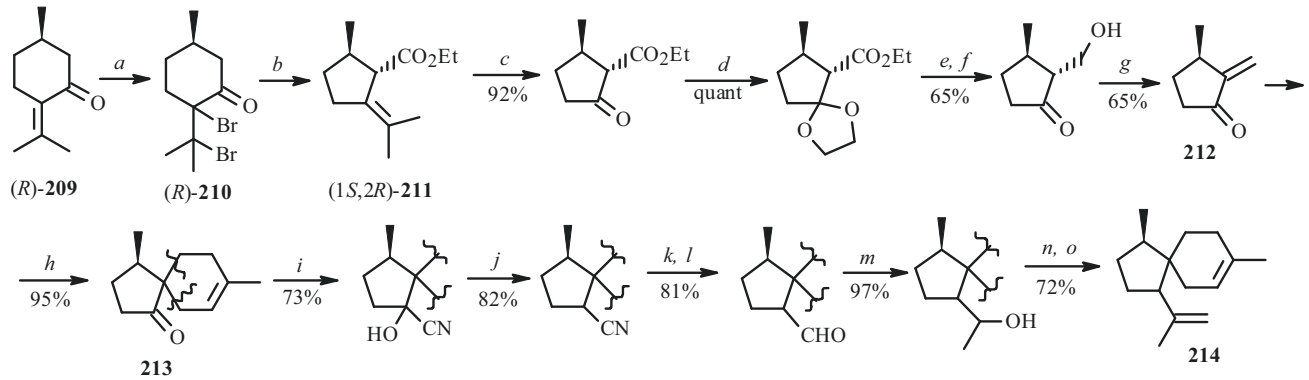
The conjugated enone system in (*R*)-4-menthenone (**183**) enabled it to undergo regioselective 1,2-addition of organometallic reagents. Condensation of enone (*R*)-**183** with ethyllithium produced tertiary allylic alcohol **201** [60], oxidation of which by Cr(VI) with allylic rearrangement gave 5-ethylmenthenone (**202**). Huang–Minlon reduction of the oxo group in ketoester **203**, which was obtained by ozonolysis of enone **202**, to a methylene was accompanied by hydrolysis of the ester to afford (*S*)-3-methylheptanoic acid (**204**), a *Coleoptera scarabaeidae* pheromone. Its reduction product, alcohol **205**, was converted to bromide (*S*)-**206**, which was transformed by standard reactions into (4*S*)-methyloctanoic acid (**208**), a component of an *Oryctes* rhinoceros beetle aggregation pheromone. Alkylation of bromide (*S*)-**206** by a Grignard reagent generated from 10-undecenylbromide resulted in (*S*)-14-methyloctadecene [(*S*)-**207**], a *Lyonetia clerkella* sex pheromone [61, 62] (Scheme 28).



a. EtLi, Et_2O; *b.* PCC, CH_2Cl_2; *c.* O_3, MeOH, CH_2Cl_2; *d.* MeOH, TsOH; *e.* $N_2H_4 \cdot H_2O$; *f.* KOH; *g.* $LiAlH_4$, Et_2O; *h.* PBr_3, Py; *i.* Mg, THF; *j.* CO_2; *k.* H_2O; *l.* $H_2C{=}CH(CH_2)_9MgBr$, CuI, 2,2′-bipy

Scheme 28

Derivatives of *R*-(+)-pulegone [(*R*)-**209**], which is available from *Mentha pulegium* L. essential oil [28], are often used to synthesize insect pheromones. The ring of (*R*)-**209** was contracted using Favorskii rearrangement of the corresponding isomer of dibromo-derivative **210** to produce the (1*S*,2*R*)-isomer of unsaturated cyclic ester **211** [63] (Scheme 29).

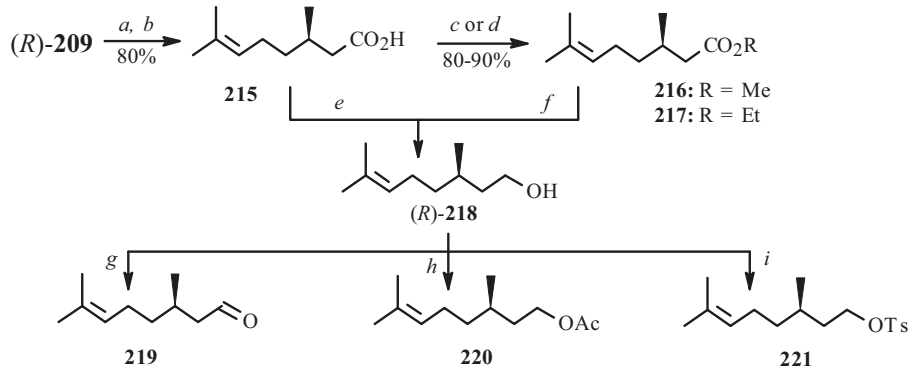


a. Br_2, AcOH, 0°C; *b.* EtONa, EtOH, 0°C; *c.* O_3, EtOAc, –90°C then Zn, AcOH, 0°C; *d.* $(CH_2OH)_2$, TsOH, C_6H_6, Δ; *e.* $LiAlH_4$, Et_2O; *f.* HCl, H_2O; *g.* DCC, Cu_2Cl_2, Et_2O, Δ; *h.*  , $SnCl_4 \cdot 5H_2O$; *i.* NaCN, AcOH, EtOH; *j.* $POCl_3$, Py; *k.* Mg, MeOH; *l.* DIBAH, CH_2Cl_2; *m.* MeMgBr, THF; *n.* Dess-Martin periodinate, CH_2Cl_2; *o.* $MePPh_3Br$, *i*-BuLi, THF

Scheme 29

This process was employed to synthesize 1,8-dimethyl-4-(1′-methylethenyl)spiro[4,5]dec-7-ene [(+)-acoradiene] (**214**), a stereoisomer of which is an aggregation pheromone of the flour beetle *Gnatocerus cornutus* [64]. Ozonolytic cleavage of the double bond of unsaturated ester (1*S*,2*R*)-**211** followed by simple transformations produced conjugated ketone **212**, which underwent a Diels–Alder reaction to construct the required structure with spiro-connected five- and six-membered rings. The regiospecific but not stereospecific course of the last reaction explained the formation of an equimolar mixture of stereoisomers of both the resulting spiroketone **213** and acoradiene (**214**) obtained from it (Scheme 29). The resulting mixture of **214** stereoisomers was separated using preparative GC. The two isomers with retention times closest to that of the natural compound were selected for convergent synthesis.

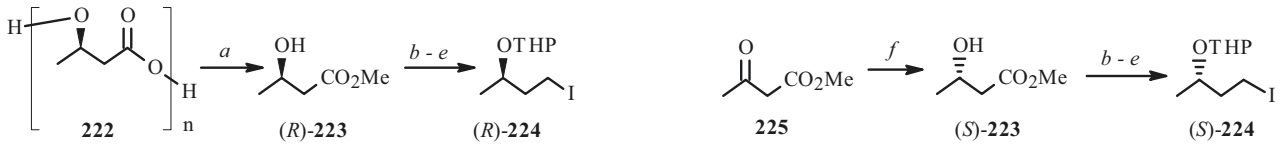
Citronellic acid (**215**) was formed in two steps via recyclization of pulegone [(*R*)-**209**] [65]. It could be reduced to (*R*)-citronellol [(*R*)-**218**] by $LiAlH_4$ or DIBAH after conversion into ester **216** or **217**. Alcohol (*R*)-**218** was readily transformed into citronellal (**219**), citronellylacetate (**220**), citronellyltosylate (**221**) [65], and other derivatives used to synthesize insect pheromones. (*R*)-**218** and its oxidation products (aldehyde **219** and acid **215**) were natural compounds in citrus and eucalyptus essential oils [28] (Scheme 30).



a. HCl; *b.* NaOH, H_2O; *c.* MeOH, H_2SO_4, 60°C; *d.* K_2CO_3, EtI, DMF, 0°C; *e.* $LiAlH_4$, Et_2O, Δ; *f.* $LiAlH_4$, Et_2O or DIBAH, Et_2O, 0°C; *g.* PCC, CH_2Cl_2; *h.* Ac_2O, Py; *i.* TsCl, Py, 0°C

Scheme 30

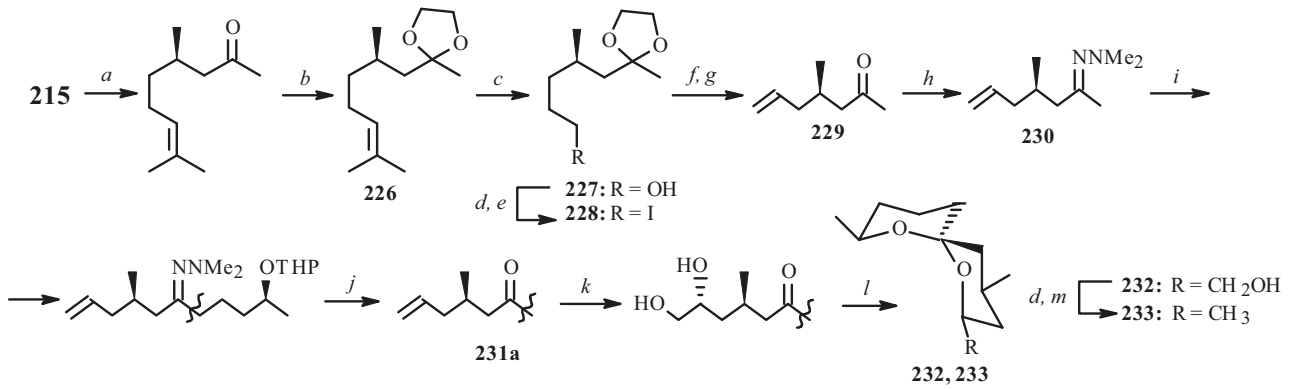
A synthesis based on citronellic acid (**215**) was proposed for synthesizing the principal component of *Cantao parentum* abdominal gland secretion, which was identified as (2*S*,4*R*,6*R*,8*S*)-trimethyl-1,7-dioxaspiro[5.5]undecane (**233a**). This was the first example of a branched spiroacetal in insects [66]. This unique compound was synthesized enantioselectively [67] through the intermediate acetonide of unsaturated ketone **226**. Successive ozonolysis of the double bond of **226** and reduction of the peroxide products gave hydroxyketal **227**, dehydration of which through the corresponding iodide **228** gave ketoolefin **229** after acid hydrolysis. The required carbon chain was constructed by alkylation of the lithium derivative of the corresponding hydrazone (**230**) using optically active protected iodohydrin (*S*)-**224**, which was prepared from intermediate hydroxyester (*S*)-**223** [68]. The (*R*)-enantiomer of the last was synthesized by hydrolysis of poly[(*R*)-β-hydroxybutyrate] (**222**); (*S*)-**223**, by enzymatic reduction of ketoester **225** using *Candida cylindracea* lipases or porcine pancreas lipase (PPL) as before [69]. Furthermore, (*S*)-**223** was obtained from asymmetric hydrogenation of ketoester **225** on catalysts modified with chiral ligands [70] (Scheme 31).



a. hν, HCl, H_2O; *b.* DHP, TsOH, Et_2O; *c.* $LiAlH_4$, Et_2O, 0°C; *d.* TsCl, Py, 0°C; *e.* NaI, Me_2CO, Δ; *f.* enzyme, PhMe, $PhCO_2CH{=}CH_2$, 65°C

Scheme 31

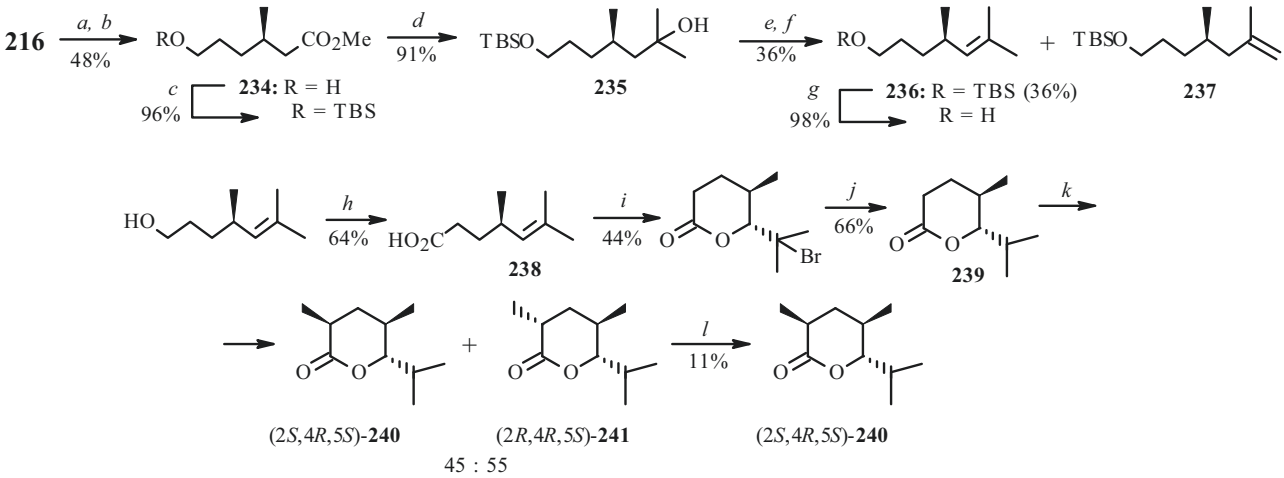
The hydroxyl was introduced by oxidizing the double bond of **231a** using the chiral osmium reagent AD-mix β. The appearance in the precursor of alcohols in the δ and δ′ positions relative to the oxo group was accompanied by simultaneous ketalization to give hydroxyketal **232**, deoxygenation of which gave target spiroketal **233** (Scheme 32). Other diastereomers of **233** that were minor components in the insect isolates were also obtained [70].



a. MeLi, Et_2O, –78°C; *b.* $(CH_2OH)_2$, TsOH, C_6H_6, Δ; *c.* O_3, CH_2Cl_2, –78°C, then $NaBH_4$; *d.* TsCl, Py, –15°C; *e.* NaI, Me_2CO, D; *f. t*-BuOK; *g.* AcOH, H_2O, 80°C; *h.* H_2NNMe_2, AcOH; *i.* LDA, –78°C, then (*S*)-(**224**); *j.* SiO_2; *k.* AD-mix *β*, 0°C; *l.* HCl, H_2O; *m.* $LiAlH_4$, Et_2O

Scheme 32

The key step in the synthesis [71] of (2*S*,4*R*,5*S*)-2,4,6-trimethyl-5-heptanolide (**240**), a sex pheromone component of *Macrocentrus grandii*, a larval parasite of *Ostrinia nubilaris*, was stereoselective bromolactonization of unsaturated acid **238**, which was obtained from alcohol **234**, an ozonolysis product of methylcitronelloate **216**. The carbon chain of **234** was grown using a Grignard reagent (after protecting the hydroxyl). Dehydration of tertiary alcohol **235** produced a mixture of required **236** and its regioisomer **237**, from which it was separated by chromatography. The second methyl was introduced into lactone **239** using MeI in the presence of LDA. Pheromone **240** was separated from side product **241** using HPLC (Scheme 33).

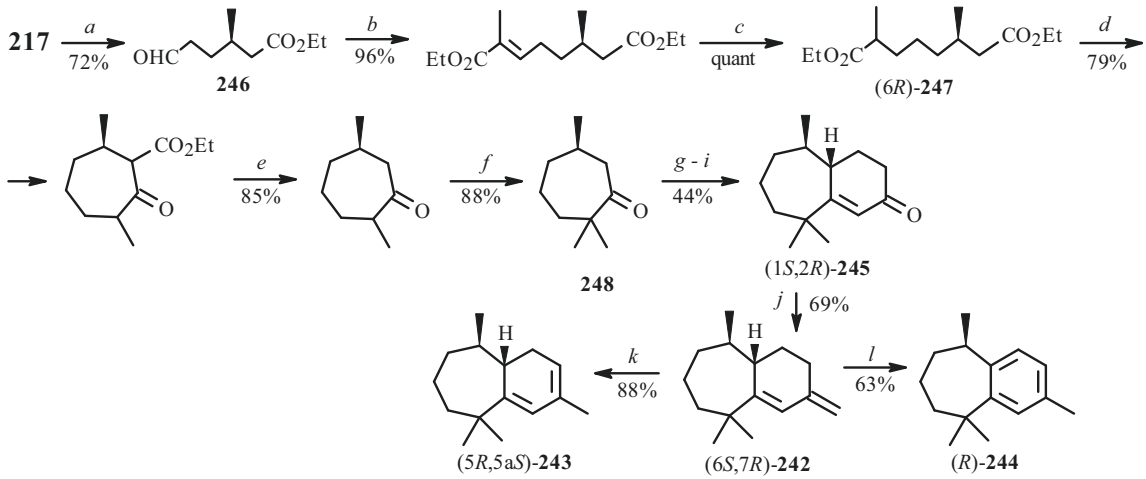


a. O_3, MeOH, CH_2Cl_2, –78°C; *b.* $NaBH_4$; *c.* TBSCl, imidazole, DMF; *d.* MeMgI, Et_2O; *e.* $POCl_3$, Py, 0°C; *f.* purification; *g. n*-Bu_4NF, THF; *h.* PDC, MS 4Å, DMF; *i.* NBS, THF; *j. n*-Bu_3SnH, C_6H_6, 70°C; *k.* LDA, MeI, THF, HMPA, –78°C; *l.* HLPC

Scheme 33

Pheromones that were isolated from *Aphthona flava* and *Phyllotreta cruciferae* included (6*R*,7*S*)-2,2,6-trimethyl-10-methylenebicyclo[5.4.0]undec-1(11)-ene (**242**), (5*R*,5a*S*)-1,1,5,8-tetramethyl-1,2,3,4,5,6,5a-heptahydrobenzo[1,2-*a*][7]annulene (**243**), and (*R*)-1,1,5,8-tetramethyl-1,2,3,4,5-pentahydrobenzo[a][7]annulene (**244**). All these compounds were prepared from one precursor, (1*S*,2*R*)-2,2,6-trimethylbicyclo[5.4.0]undec-7-en-9-one (**245**) [72].

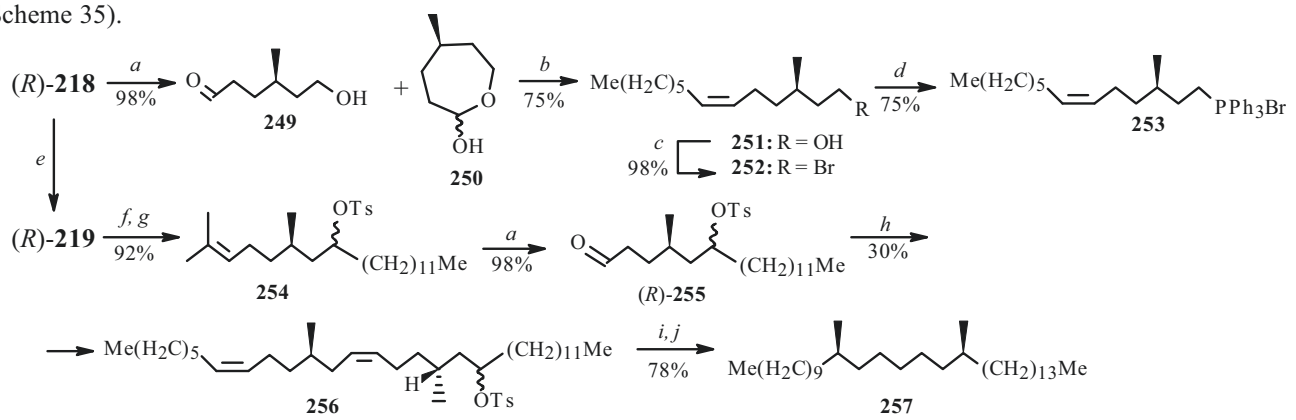
Ozonolytic cleavage of the double bond in ethylcitronelloate (**217**) and Horner–Emmons olefination of resulting aldehyde **246** produced diester **247**, Dieckmann condensation of which created the required seven-membered ring. Subsequent Robinson annelation of ketone **248** introduced the six-membered ring of **245** [72]. Wittig olefination converted the last into component **242**. Compound **243** was the product from migration of the double bond in **242**. Component **244** was obtained via aromatization of the six-membered ring by chloranil (tetrachlorobenzoquinone) (Scheme 34).



a. O_3, MeOH, –78°C, then Me_2S; *b.* $(EtO)_2P(O)CHMeCO_2Et$, NaH, THF, –30°C; *c.* H_2, PtO_2, EtOAc; *d. t*-BuOK, *m*-xylene, 150°C; *e.* NaOH, MeOH, H_2O, Δ; *f. t*-BuOK, *t*-BuOH, MeI, 0°C; *g.* LDA, TMSCl, THF, –78°C; *h.* MeLi, CH_2=C(TMS)COMe, THF; *i.* NaOMe–MeOH; *j.* Ph_3PMeBr, *n*-BuLi, THF, 0°C; *k.* HCO_2H, MeOH; *l.* C_6H_6, tetrachloro quinone, 75°C

Scheme 34

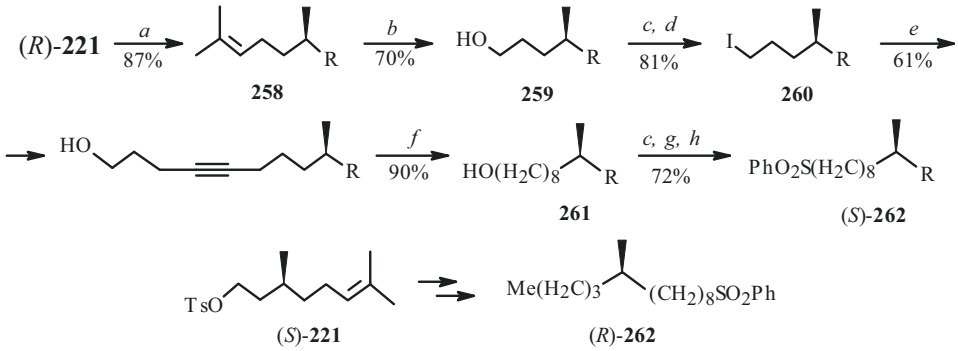
(*R*)-Citronellol (**218**) was used to prepare both synthons **253** and **255** in a convergent synthesis of (11*R*,17*S*)-dimethyltriacontane (**257**), a *Camponotus vagus* communication pheromone [73]. Reductive ozonolysis of alcohol (*R*)-**218** in the synthesis of phosphonium salt **253** gave a mixture of hydroxyaldehyde **249** and hemiacetal **250**, Wittig olefination of which produced (*Z*)-unsaturated alcohol (*R*)-**251**, which was transformed through bromide **252** into salt **253**. The second synthon **255** was obtained from ozonolytic cleavage of intermediate tosylate **254**, the esterified alkylation product of *n*-dodecylmagnesiumbromide and (*R*)-**219**, which was prepared via oxidation of citronellol (*R*)-**218** [65] or incubation of racemic citronellal (**219**) with baker's yeast enzymes [74]. Resulting aldehyde (*R*)-**255** underwent Wittig olefination by the phosphorane from phosphonium salt **253**. Reduction of tosyloxydiene **256** completed the synthesis of target pheromone **257** (Scheme 35).



a. O_3, Sudan Red 7B, CH_2Cl_2, –78°C, then Me_2S; *b.* $Me(CH_2)_6P^+Ph_3Br^-$, *n*-BuLi, THF, –78°C; *c.* CBr_4, PPh_3, CH_2Cl_2, 0°C; *d.* PPh_3, MeCN, 70°C; *e.* Py·CrO_3, CH_2Cl_2; *f.* Mg, $Me(CH_2)_{11}Br$, $(CH_2Br)_2$, THF, 30°C; *g.* TsCl, Py, 0°C; *h.* **253**, *n*-BuLi, THF, –78°C; *i.* $LiAlH_4$, NaH; *j.* H_2, Pd, C

Scheme 35

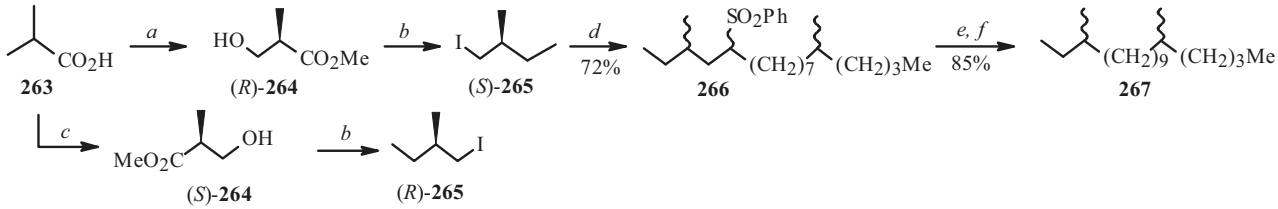
3,13-Dimethylheptadecane (**267**) was identified in 1993 as the principal female sex pheromone component of *Nepytia freemani* [75], a conifer pest that is broadly distributed in the northwestern USA and in southeastern Canada. The key step in the synthesis of all stereoisomers of 3,13-dimethylheptadecane (**267a**–**d**) was alkylation of phenylsulfones **262**, which had active α-methylenes [76]. The aforementioned organosulfur compounds were synthesized by first alkylating citronellyltosylate enantiomers **221** with EtMgBr using Grignard–Schlosser cross-coupling. The double bond of synthesized alkene **258** underwent ozonolytic cleavage. The resulting alcohol **259** was transformed into iodide **260**, which was alkylated by the lithium derivative of 4-pentyn-1-ol. Exhaustive hydrogenation followed by phenylthiylation of **261** and oxidation by *m*-CPBA gave the corresponding (*R*)- and (*S*)-isomers of **262** (Scheme 36).



a. EtMgBr, Li_2CuCl_4, THF, –78°C; *b.* O_3, MeOH, 0°C then $NaBH_4$; *c.* TsCl, Py, 0°C; *d.* NaI, Me_2CO, Δ; *e.* *n*-BuLi, HC≡CH$(CH_2)_3$OH, THF, HMPA; *f.* H_2, PtO_2, EtOH; *g.* PhSH, NaOH, MeOH; *h.* *m*-CPBA, CH_2Cl_2

Scheme 36

The second building block, 2-methylbutyliodide (**265**) [77], was synthesized using the required enantiomer of methyl 2-methyl-3-hydroxybutanoate (**264**), the (*R*)-isomer of which was a product of microbiological oxidation of isobutanoic acid (**263**) by *Candida rugosa* IFO 0750 [78]. Its antipode (*S*)-**264** was produced by *Pseudomonas putida* ATCC 21244 [79] (Scheme 37).

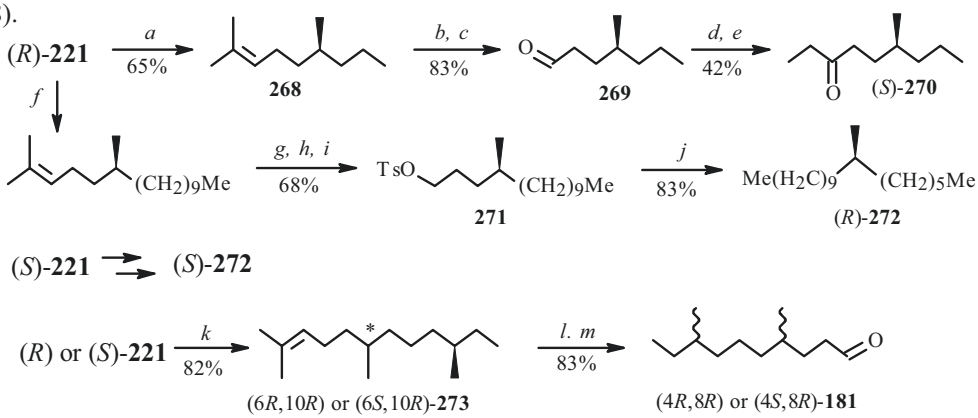


a. [78]; *b.* [77]; *c.* [79]; *d.* **262**, *n*-BuLi, THF, HMPA; *e.* Na, Hg, Na_2HPO_4, EtOH; *f.* H_2, PtO_2

Scheme 37

Various combinations of lithium derivatives of sulfone **262** (*R* and *S*) and iodide **265** (*R* and *S*) isomers cross coupled to give sulfone **266** with two optically pure chiral centers. Desulfurization and hydrogenation completed the synthesis of target pheromones **267** (*RS*, *RR*, *SR*, *SS*) (Scheme 37).

The absolute configuration of the *Hesperophylax occidentalis* sex pheromone was elucidated using simple syntheses of both enantiomers (*S* or *R*)-**270**. For this, citronellyltosylate (*R*)-**221** was treated with Me_2CuLi and transformed into alkene **268**, ozonolysis of which gave aldehyde **269**. Treatment of the last with EtMgBr and subsequent oxidation completed the synthesis of (*S*)-ketone **270**. (*S*)-Citronellyltosylate [(*S*)-**221**] was transformed analogously into the (*R*)-enantiomer of **270** [80] (Scheme 38).



a. Me_2CuLi, Et_2O, –30°C; *b.* O_3, MeOH, $NaHCO_3$, 0°C; *c.* Me_2S; *d.* EtMgBr, Et_2O; *e.* H_2CrO_4, Me_2CO; *f.* $Me(CH_2)_7MgBr$, Li_2CuCl_4, THF, –78°C; *g.* O_3, MeOH, CH_2Cl_2, *n*-C_6H_{14}; *h.* $NaBH_4$; *i.* TsCl, Py; *j.* $Me(CH_2)_2MgBr$, Li_2CuCl_4, THF, –78°C; *k.* Mg, (*R*)-(**187**), Li_2CuCl_4, THF; *l.* O_3, CH_2Cl_2; *m.* Me_2S

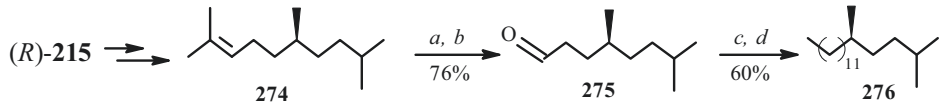
Scheme 38

Both stereoisomers of 7-methylheptadecane (**272**), a *Lambdina athasaria* and *L. pellucidaria* sex pheromone, were synthesized and tested [81]. The approach was based on two sequential Schlosser reactions of the (*R*)- or (*S*)-enantiomer of citronellyltosylate (**221**) with $Me(CH_2)_7MgBr$ and tosylate **271** with $Me(CH_2)_2MgBr$. Biological tests showed that the (*S*)-isomer of **272** was active (Scheme 38).

A concise and effective synthesis of (4*R*,8*R*)- or (4*S*,8*R*)-**181**, components of the *Tribolium confusium* and *T. castaneum* aggregation components, was proposed using ozonolysis in the final step to transform the isopropylidene into an aldehyde [82, 83]. The key synthetic step was the Li_2CuCl_4-catalyzed cross-coupling of tosylates (*R*)- and (*S*)-**221** with (*R*)-2-methyl-1-bromobutane (**187**). This led to olefins (6*R*,10*R*)- and (6*S*,10*R*)-**273**, ozonolysis of which produced pheromones (4*R*,8*R*)- and (4*S*,8*R*)-**181** (Scheme 38).

Ozonolysis of mono-unsaturated carboxylic acids and their derivatives represented a convenient route to α,ω-bifunctional reagents that were used to synthesize insect pheromones.

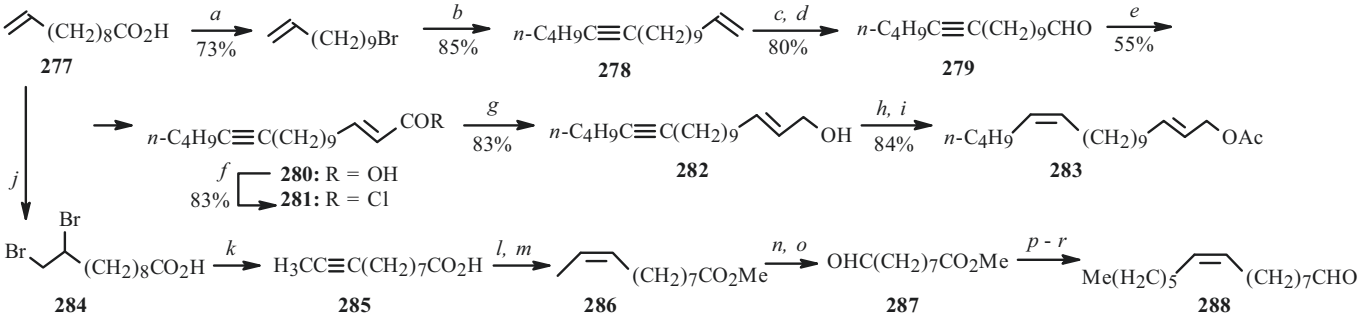
(*S*)-2,5-Dimethylheptadecane (**276**) is a minor component of the *Lambdina fiscellaria lugubrosa* sex pheromone. Ozonolytic fragmentation of (*R*)-2,6,9-trimethyldec-1-ene (**274**), which was obtained from (*R*)-citronellic acid (**215**), gave (4*R*,7)-dimethyloctanal (**275**), coupling of which with *n*-nonylidenetriphenylphosphorane followed by catalytic hydrogenation led to target pheromone **276** [84] (Scheme 39).



a. O_3, CH_2Cl_2, MeOH; *b.* Me_2S; *c*. $Me(CH_2)_8P^+Ph_3Br^-$, *n*-BuLi; *d.* H_2, Pd, C

Scheme 39

10-Undecenoic acid (**277**), which is available via destructive distillation of castor oil isolated from castor beans [85], was used for a series of syntheses of octadeca-2*E*,13*Z*-dienylacetate (**283**) [86, 87], a pheromone component of the hazardous garden pests *Synanthedon tipuliformis* and *Zeuzera pyrina*. Ozonolysis of enyne **278** occurred selectively at the double bond because the acetylene group was less reactive toward ozone than the vinyl group. Reduction of the peroxide products by Me_2S gave hexadec-11-ynal (**279**) in high yield. Use of the Doebner reaction allowed the required carbon chain to be constructed and the 2*E*-double bond to be introduced. Resulting acid **280** was converted to the chloride (**281**), which was reduced by $LiAlH_4$ to octadec-2*E*-en-13-yn-1-ol (**282**). Catalytic hydrogenation of the triple bond in **282** and subsequent acetylation completed the synthesis of target diene pheromone **283** in 16% overall yield from starting acid **277** (Scheme 40).

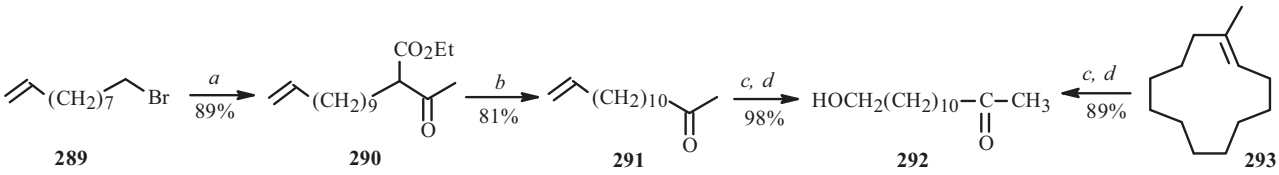


a. [87]; *b.* *n*-$C_4H_9C{\equiv}CH$, Li-NH_3; *c.* O_3, *cyclo*-C_6H_{12}, MeOH; *d.* Me_2S; *e.* $CH_2(CO_2H)_2$, Py+Pyp; *f.* $SOCl_2$; *g.* $LiAlH_4$; *h.* H_2, Ni, Pd; *i.* AcCl, Py; *j.* Br_2; *k.* KOH, PEG,150°C; *l.* MeOH, TsOH; *m.* H_2, Pd, $CaCO_3$, PbO; *n.* O_3, MeOH, CH_2Cl_2; *o.* Me_2S; *p.* $Me(CH_2)_6P^+Ph_3Br^-$, $NaNH_2$, THF; *q.* $LiAlH_4$; *r.* PCC, CH_2Cl_2

Scheme 40

Alkaline dehydrohalogenation at 150°C of dibromo-derivative **284** of acid **277** synthesized with high regioselectivity 9-undecynoic acid (**285**), reductive ozonolysis of the olefin analog of which (**286**) gave aldehydoester **287**, a key compound for (9*Z*)-hexadecenal (**288**), a minor component of the *Heliothis armigera* sex pheromone [88] (Scheme 40).

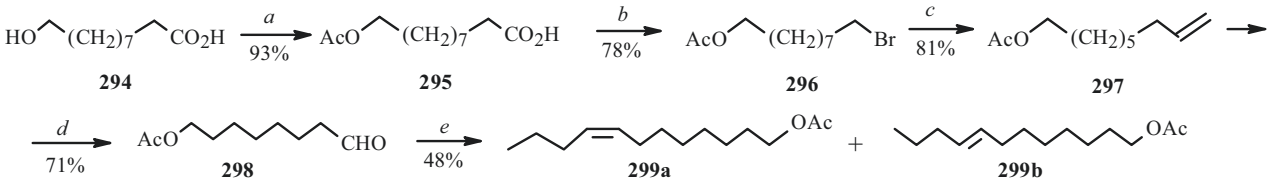
13-Hydroxy-2-oxotridecane (**292**) that was isolated from fruit extracts of *Evodia hupehensis* Dode was an active attractant for honeybees. New approaches to the synthesis of this attractant were developed. The first was based on selective transformations of the monoalkylation product of acetoacetic ester by bromide **289**. Decarbethoxylation of unsaturated ketoester **290** gave the key intermediate tetradec-13-en-2-one (**291**), ozonolysis of which followed by $NaBH(OAc)_3$ reduction, which reduced selectively existing or formed aldehydes without affecting the ketones, produced target compound **292**. An alternative version used reductive ozonolysis of 1-methylcyclododecene (**293**). The yield of attractant in this instance was 89% [89, 90] (Scheme 41).



a. AcC(O)OEt, NaOEt, EtOH; *b.* LiI, DMF; *c.* O_3, AcOH, CH_2Cl_2; *d.* $NaBH(OAc)_3$

Scheme 41

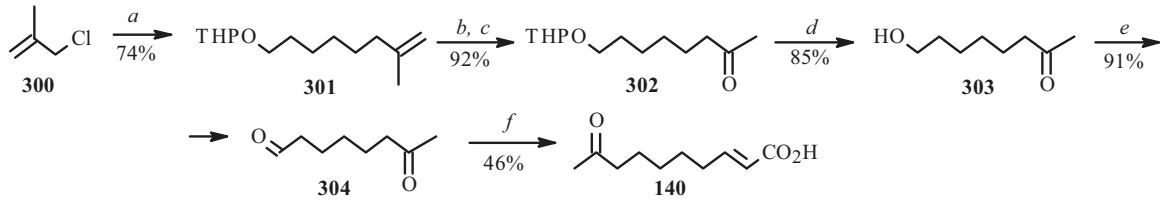
The sex pheromone of *Grapholitha molesta*, a pest of peaches, apples, pears, and apricots, was identified as (*Z*)-8-dodecylacetate (**299a**). It was observed that an impurity (up to 10%) of the (*E*)-isomer (**299b**) did not inhibit its activity. A short synthetic scheme [91] for a mixture (72.5:27.5) of acetates **299a** and **b** started from 10-hydroxydecanoic acid (**294**) and used ozonolysis of 9-nonenylacetate (**297**) to prepare aldehyde **298** and Wittig olefination of the last. In turn, the carbon chain of starting hydroxyacid **294** was shortened by dehydrobromination of **296**, which was obtained by Hunsdiecker decarboxylation from acetoxyacid **295** (Scheme 42).



a. Ac_2O, Py; *b.* HgO, Br_2, CCl_4; *c.* LiBr, Li_2CO_3, DMF; *d.* O_3, CH_2Cl_2 then Zn, H_2O, AcOH; *e.* BuLi, *n*-Bu$P^+Ph_3Br^-$, THF

Scheme 42

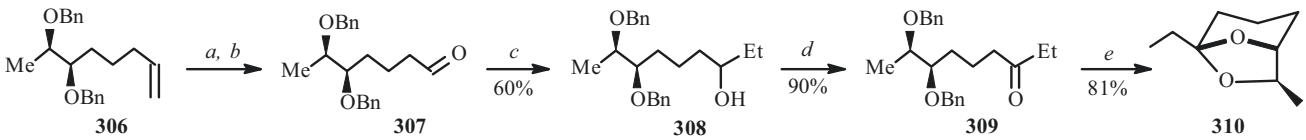
A new approach to the synthesis of 9-oxo-2*E*-decenoic acid (**140**), the queen substance of *Apis mellifera* L., started from available methylallylchloride **300**, coupling of which with 5-(2-tetrahydropyranyloxy)pentanemagnesiumbromide (**305**) gave the 2-tetrahydropyranyl ether of 7-methyl-7-octen-1-ol (**301**) in high yield [92, 93]. The ketone in terminal alkene **301** was generated by reductive ozonolysis. The resulting tetrahydropyran ether **302** was hydrolyzed to hydroxyketone **303**, oxidation of which by PCC gave the key ketoaldehyde **304**, which was transformed as usual into acid **140** in 24% overall yield (Scheme 43).



a. $THPO(CH_2)_5MgBr$ (**305**), CuI, 2,2′-bipy; *b.* O_3, MeOH; *c.* H_2, Pd, $CaCO_3$, PbO; *d.* H_3O^+; *e.* PCC, CH_2Cl_2; *f.* $CH_2(CO_2H)_2$, Py+Pyp

Scheme 43

Ozonolytic cleavage of dibenzyl ether **306** followed by reduction of the peroxide products by Me_2S and reaction of intermediate aldehyde **307** with EtMgBr under Grignard conditions produced alcohol **308**, further oxidation of which by 2-iodoxybenzoic acid into ketone **309** gave (+)-*iso*-exo-brevicomin (**310**), a *Dendroctonus ponderosae* aggregation pheromone, after removal of the benzyl protection [94] (Scheme 44).

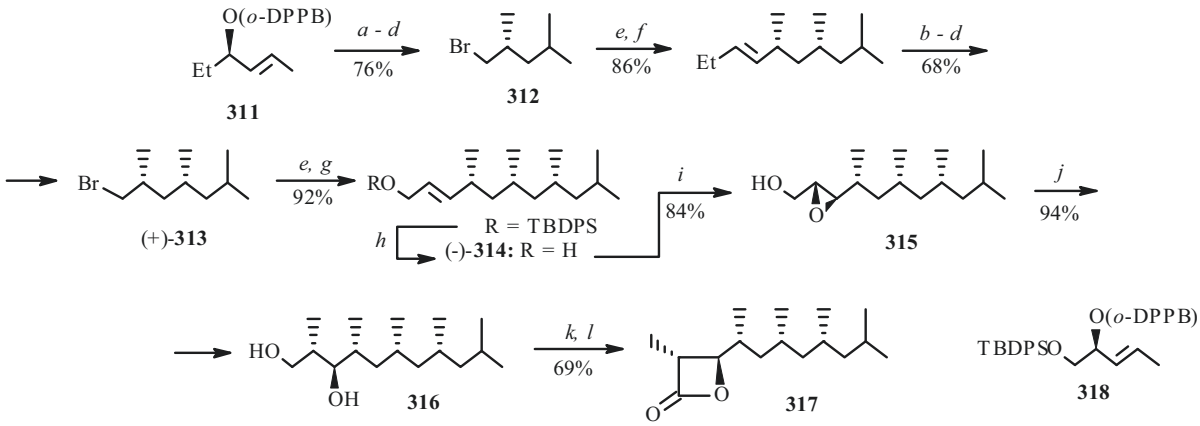


a. O_3, CH_2Cl_2, MeOH; *b.* Me_2S; *c.* EtMgBr, THF; *d.* IBX, DMSO; *e.* 10% H_2, Pd, C, MeOH, HCl

Scheme 44

A total asymmetric synthesis of the aggregation pheromone (vittatalactone) **317** of *Acalymma vittatum*, the principal grain and melon pest in North America, was proposed [95, 96]. Key synthon **314** was obtained by repeating the reaction sequence of Cu-catalyzed allyl substitution to the corresponding *syn*-S_N2' products, their ozonolysis followed by borohydride reduction, bromination of the intermediate alcohols, conversion of bromides **312** and **313** to the Grignard reagents, and coupling

of them with the corresponding ethers **311** and **318**. Transformation of intermediate **314** toward target pheromone **317** concluded with stereoselective Sharpless epoxidation, conversion of epoxide **315** into 1,3-diol **316** by treatment with cyanodimethylcuprate, chemo- and stereoselective oxidation of the primary alcohol to produce the corresponding β-hydroxyaldehyde, which was oxidized to the β-hydroxyacid and then converted into target lactone **317** (Scheme 45).



a. CuBr·SMe_2, *i*-BuMgBr; *b.* O_3, CH_2Cl_2, MeOH; *c.* $NaBH_4$; *d.* NBS, PPh_3; *e.* Mg, Et_2O; *f.* CuBr·SMe_2, **(311)**; *g.* CuBr·SMe_2, **318**; *h.* TBAF, THF; *i.* D-DET-Ti(O-*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2; *j.* $Me_2Cu(CN)Li_2$, Et_2O; *k.* 4-methoxy-TEMPO, NaClO, CH_2Cl_2, H_2O then $NaClO_2$, *t*-BuOH, H_2O; *l.* TsCl, Py

Scheme 45

Thus, the literature review indicated that ozonolysis of unsaturated compounds in various steps of total syntheses of insect pheromones and juvenoids has great potential and often determines the success of implementing the selected pathway.

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