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Ozonolysis of unsaturated compounds in the synthesis of insect pheromones and juvenoids

G Yu Ishmuratov, R Ya Kharisov, V N Odinokov, G A Tolstikov

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Abstract. The review surveys data on the use of the ozonolysis of cyclic and acyclic monoenes, dienes, and trienes in various stages of the total synthesis of insect pheromones and juvenoids. The bibliography includes 178 references.

I. Introduction

In a review published in 1981,[1] we presented the results of studies on the structures of peroxide ozonolysis products and the path followed in their transformation into the final oxygen-containing compounds without a peroxide fragment. As a result of progress in this field, the ozonolysis of alkenes has become not only a recognised analytical method for the determination of the structures of the initial unsaturated compounds but also a procedure for the highly selective introduction of oxygen-containing functional groups into organic molecules. The development of the ozone generation technique and of the control over ozonolysis have reached a level such that this reaction has advanced sufficiently to be included in the class of modern methods which are not only of preparative value but also of interest for industry.

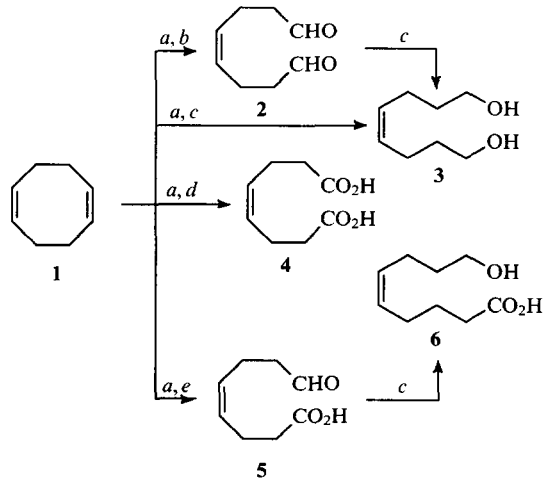
During the last decade, a considerable number of studies have been published on the use of ozonolysis of unsaturated compounds in the synthesis of insect pheromones and juvenoids. The present review is devoted to a survey of the results of these investigations.

II. Use of selective ozonolysis of cyclic and acyclic dienes and trienes in the synthesis of pheromones and juvenoids

The problems arising in the intensification of agricultural production and in the expansion and improvement of measures for the protection of nature and human health may be solved only with the aid of integrated systems for the protection of cultivated plants, forests, and agricultural and forestry produce. An indissoluble component of these measures in the fight against insect pests is the partial or complete replacement of the traditional chemical poisons by ecologically clean new generation insecticides, which include pheromones and juvenile hormones regulating arthropod behaviour and development.

The primary tasks in the synthesis of insect pheromones, juvenile hormones, and their analogues include the development of preparatively convenient methods of synthesis of the key intermediates, such as the α,ω-bifunctional compounds capable of undergoing selective chemical transformations. One of the promising ways of synthesising such compounds is the ozonolysis of alkenes.[1–57] The study of the oxidative cleavage of alkenes has become especially timely in connection with advances in metal complex catalysis, by virtue of which cyclic and acyclic oligomers and cooligomers of 1,3-dienes have become available.

The products of ring opening of cyclic butadiene oligomers are widely used in the synthesis of pheromones and other natural products. Thus the partial ozonolysis of one of the most readily available butadiene oligomers — (1*Z*, 5*Z*)-cyclo-octadiene **1** — as well as other cyclic butadiene oligomers and cooligomers provides a simple and effective path to bifunctional unsaturated compounds containing terminal functional groups which are of the same or different nature depending on the procedure used in the treatment of the peroxide ozonolysis product.[1,58–64]

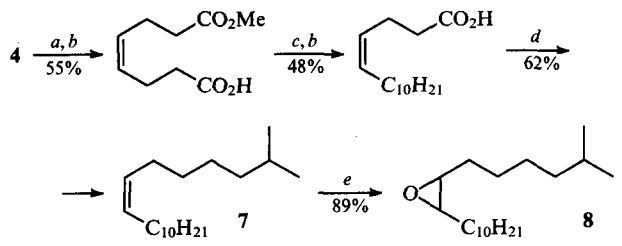


(*a*) O_3; (*b*) H_2–Pd–$CaCO_3$–PbO; (*c*) $NaBH_4$; (*d*) H_2CrO_4; (*e*) AcONa–AcOH–Ac_2O.

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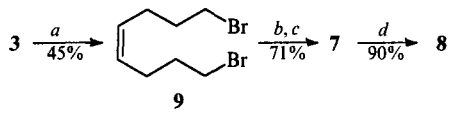
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A whole series of Lepidoptera pheromones have been obtained from α,ω-bifunctional alkenes **2–6**. Disparlure **8**—the pheromone of the gypsy moth (*Porthetria dispar*)—has been synthesised from (*Z*)-oct-4-ene-1,8-dioic acid **4**. The Kolbe condensation was used in two stages of this process (*c*, *d*).[65,66]



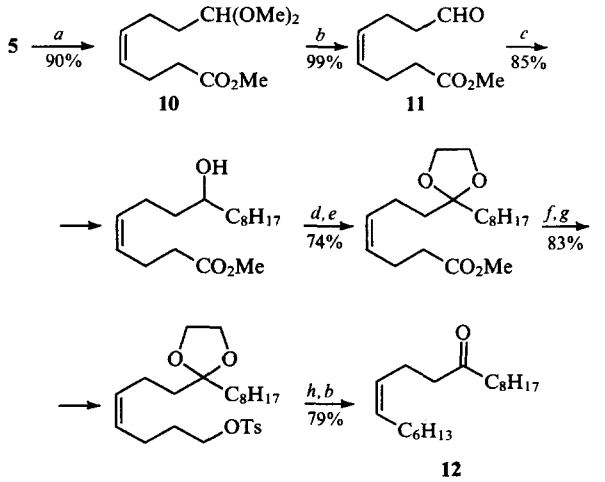
(*a*) MeOH–H^+; (*b*) KOH–MeOH;
(*c*) $Me(CH_2)_7CO_2H$–Pt/anode–MeOH;
(*d*) $Me_2CHCH_2CH_2CO_2H$–Pt/anode–MeOH;
(*e*) MCPBA (*m*-chloroperbenzoic acid)–CH_2Cl_2.

The simpler synthesis of disparlure from (*Z*)-oct-4-ene-1,8-diol **3** involves its transformation into the dibromo-derivative **9** and two successive stages in which it is coupled with n-heptyl- and isobutyl-magnesium bromides.[67–69]



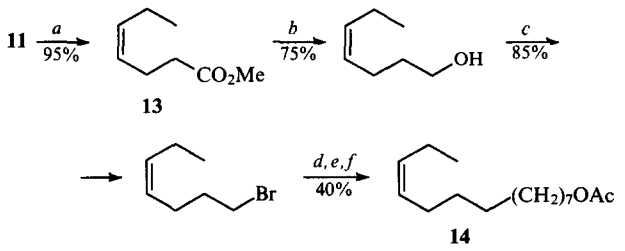
(*a*) PBr_3–Py; (*b*) n-$C_7H_{15}MgBr$; (*c*) Bu^iMgBr; (*d*) $ArCO_3H$ (Ar = 3-ClC_6H_4, 2-$HO_2CC_6H_4$).

The aldehydoacid **5** can be converted into the acetal-ester **10**, which has served as a convenient reagent for the synthesis of certain insect pheromones. For example, the synthesis of the sex pheromone **12** of the peach fruit moth (*Carposina niponensis Walsingham*) is based on the selective hydrolysis of the acetal **10** to the aldehydoester **11** and its interaction with n-octylmagnesium bromide.[70]



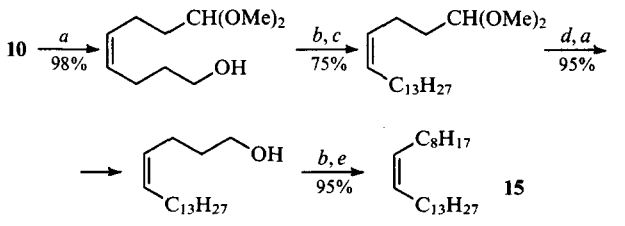
(*a*) MeOH–H^+; (*b*) H_3O^+; (*c*) n-$C_8H_{17}MgBr$; (*d*) PCC (Py·$HCrO_3Cl$, pyridinium chlorochromate); (*e*) $(CH_2OH)_2$–TsOH; (*f*) DIBALH (Bu^i_2AlH); (*g*) TsCl–Py; (*h*) PrMgBr–Li_2CuCl_4.

Yet another variant of the transformation of the aldehydoester **11** leads to the sex pheromone **14** of the oak moth (*Tortrix viridana*). The decarbonylation of compound **11** by treatment with tris(triphenylphosphine)rhodium chloride takes place under mild conditions, affording a high yield of the methyl ester of the (4*Z*)-heptenoic acid **13**, which determines the subsequent success of the entire synthesis.[71]



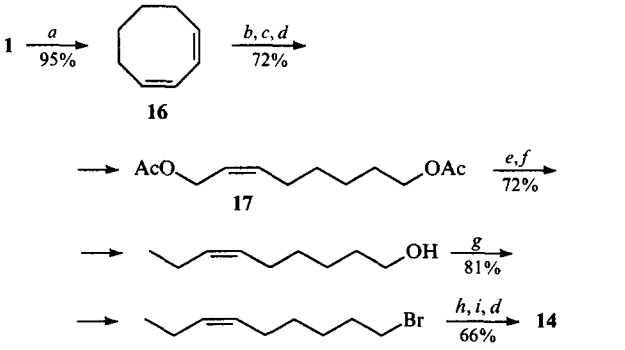
(*a*) $(Ph_3P)_3RhCl$; (*b*) DIBALH; (*c*) $Br_2·PPh_3$;
(*d*) $EtOCH(Me)O(CH_2)_7MgBr$–CuI–2,2′-Bipy;
(*e*) TsOH–MeOH–H_2O; (*f*) Ac_2O–Py.

The stereospecific syntheses of (9*Z*)-tricosene **15** [a component of the sex pheromone of the housefly (*Musca domestica*)[72,73]] and of (9*Z*)-tetradec-1-enyl acetate and (9*Z*)-hexadecenal[74] [the components of the sex pheromones of the pine moth (*Panolis flammea*) and the cotton bollworm (*Heliothis armigera*) respectively] have been achieved by the successive transformations of the acetal-ester **10** involving the ester and acetal groups and two cross-couplings with the corresponding organomagnesium and organolithium reagents catalysed by copper salts.



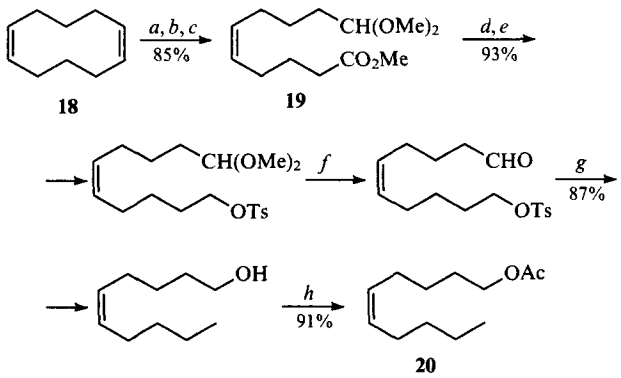
(*a*) DIBALH; (*b*) TsCl–Py; (*c*) n-$C_{10}H_{21}MgBr$–Li_2CuCl_4;
(*d*) H_3O^+; (*e*) n-$C_5H_{11}MgBr$–Li_2CuCl_4.

After reduction and acetylation, the product of the partial ozonolysis of cycloocta-1,3-diene **16** gave rise to (2*Z*)-1,8-diacetoxyoct-2-ene **17**, capable of regio- and stereo-selective coupling with Grignard reagents via the allylacetoxy-groups, which has been used in the regio- and stereo-selective synthesis of the oak moth pheromone **14**.[71]



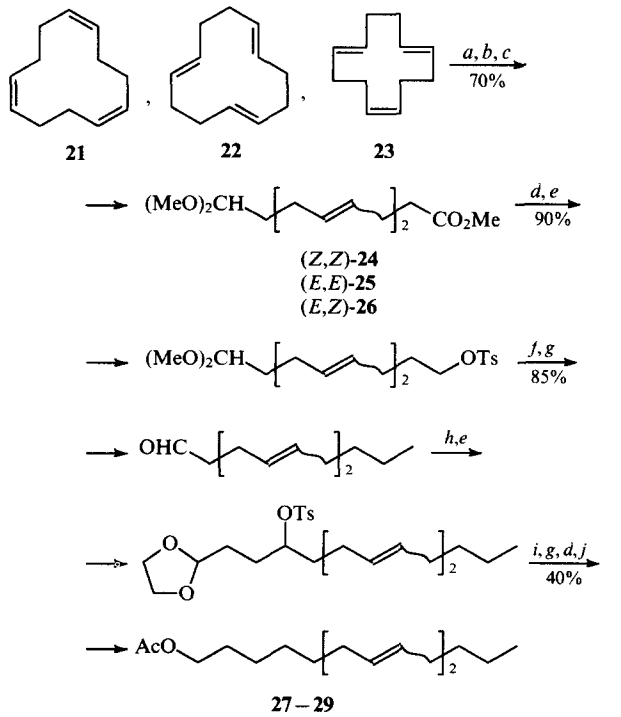
(*a*) Bu^tOK–DMSO; (*b*) O_3–cyclo-C_6H_{12}–MeOH;
(*c*) $NaBH_4$–MeOH; (*d*) Ac_2O–Py; (*e*) MeMgI–Li_2CuCl_4;
(*f*) DIBALH; (*g*) $Br_2·PPh_3$;
(*h*) $EtOCH(Me)O(CH_2)_5MgBr$–CuI–2,2′-Bipy;
(*i*) TsOH–MeOH–H_2O.

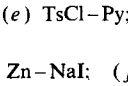
The carbon skeleton of the (*Z*)-C_{10} block **19**, obtained from the products of the selective ozonolysis of (1*Z*,6*Z*)-cyclodecadiene **18**, is identical to the skeleton of the component of the pheromone of the turnip moth (*Agrotis segetum*) — (5*Z*)-dec-1-enyl acetate **20**; the latter was therefore synthesised via chemoselective transformations of the functional groups.[75,76]



(*a*) O_3–cyclo-C_6H_{12}–AcOH; (*b*) AcONa–AcOH–Ac_2O; (*c*) TsOH–MeOH; (*d*) DIBALH; (*e*) TsCl–Py; (*f*) H_2O–PPTS (Py·HOTs, pyridinium *p*-toluenesulfonate); (*g*) $LiAlH_4$; (*h*) Ac_2O–Py.

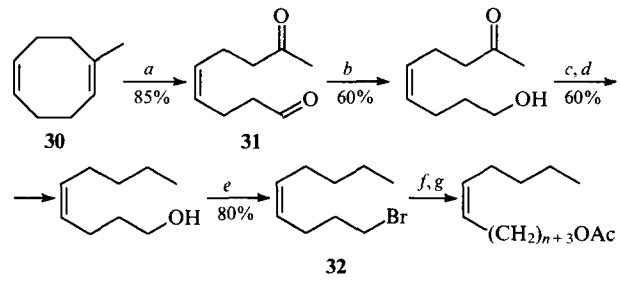
The C_{12} α,ω-bifunctional compounds **24**–**26**, obtained by the selective ozonolysis of (1*Z*,5*Z*,9*Z*)-cyclododecatriene **21**, (1*E*,5*E*,9*E*)-cyclododecatriene **22**, and (1*E*,5*E*,9*Z*)-cyclododecatriene **23**, are of evident interest for the synthesis of the diene components **27**–**29** of the pheromone of the pink bollworm (*Pectinophora gossypiella*).[77,78]



(*a*) O_3–cyclo-C_6H_{12}–AcOH; (*b*) AcONa–AcOH–Ac_2O; (*c*) TsOH–MeOH; (*d*) DIBALH; (*e*) TsCl–Py; (*f*) Me_2CuLi; (*g*) HCl; (*h*) ; (*i*) Zn–NaI; (*j*) Ac_2O–Py.

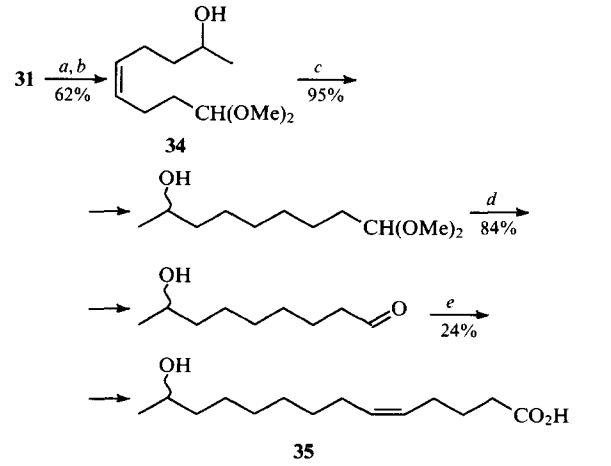
One of the approaches to the solution of the problem of the synthesis of pheromones with a terpenoid structure and a trisubstituted double bond involves the use as the starting compounds of regularly constructed oligomers, cooligomers, and telomers of isoprene, the methods of synthesis of which have now been thoroughly worked out, as well as natural terpenoids with trisubstituted double bonds. When this approach is employed, the task reduces to the choice of selective methods for the necessary transformation of the initial compound for the subsequent construction from the resulting functional block-synthon of the required carbon skeleton of the pheromone. The transformation of the initial cyclic isoprenoid into the α,ω-bifunctional synthon is achieved by opening its ring[79–81] and, in the case of an acyclic initial compound with a specified geometry of the double bond, a suitable method is chosen for its conversion into an intermediate which is suitable for subsequent employment in the formation of the target pheromone.[82–86]

A series of pheromones have been synthesised from 1-methyl-(1*Z*,5*Z*)-cyclooctadiene **30**. The partial ozonolysis of this isoprene — butadiene codimer proceeds selectively via the trisubstituted double bond, which makes it possible to obtain (*Z*)-alk-1-enyl acetates — the pheromones of the order Lepidoptera.[87,88] (*Z*)-Non-4-enyl bromide **32** was obtained by successive transformations of the functional groups of the ozonolysis products of compound **31**. Compound **32** was converted into the corresponding Grignard reagent and the latter was subsequently coupled with the acetoxybromo-derivatives **33**.



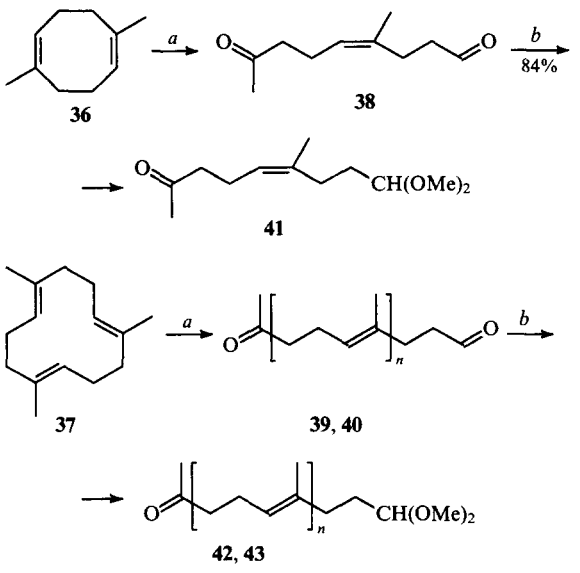
(*a*) O_3–cyclo-C_6H_{12}–MeOH; H_2–Pd–$CaCO_3$–PbO; (*b*) $KBH(OAc)_3$; (*c*) $TsNHNH_2$; (*d*) $NaBH_3CN$; (*e*) PBr_3–Py; (*f*) Mg; (*g*) $AcO(CH_2)_nBr$ (**33**).

After a two-stage reaction (selective protection of the aldehyde functional group and subsequent reduction of the keto-group to give the hydroxyacetal **34**), the ketoaldehyde **31** affords the key intermediate for the synthesis of (13*RS*)-hydroxy-(*Z*)-tetradec-5-enoic acid **35** — the acyclic precursor of the racemic form of the macrolide component of the aggregation pheromone of the flat grain beetle (*Cryptolestes pusillus*).[89]



(*a*) MeOH–NH_4Cl; (*b*) $NaBH_4$–MeOH; (*c*) H_2–Raney Ni; (*d*) PPTS–H_2O; (*e*) $HO_2C(CH_2)_4PPh_3Br$, $NaN(SiMe_3)_2$.

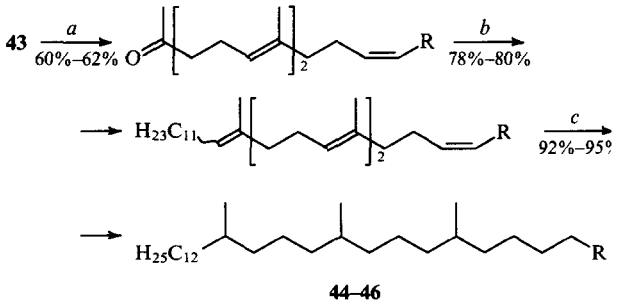
The most readily available cyclooligomers of isoprene are its (1*Z*,5*Z*)-dimer **36** and the (1*E*,5*E*,9*E*)-trimer **37**. The products of their selective ozonolysis have been used widely in the synthesis of pheromones.[59,60,79–81] The ozonolysis of (1*Z*,5*Z*)-1,5-dimethylcycloocta-1,5-diene **36** gives the monoterpene ketoaldehyde **38** with the (*Z*)-configuration, while ozonolysis of (1*E*,5*E*,9*E*)-1,5,9-trimethylcyclododeca-1,5,9-triene **37** affords the ketoaldehydes **39** and **40** with the (*E*)-configuration. The easily achieved selective protection of the aldehyde group in the ketoaldehydes **38**–**40** led to the corresponding monoacetals **41**–**43**, from which the target pheromones were synthesised.



n = 1 (**39**, **42**), 2 (**40**, **43**)

(*a*) O_3–cyclo-C_6H_{12}–MeOH, H_2–Pd–$CaCO_3$–PbO; (*b*) MeOH–NH_4Cl.

The subsequent conversion of compound **43** into an alkene via the aldehyde group and then the keto-group and subsequent hydrogenation led to the diastereoisomeric (±)-13,17,21-trimethyltriacontane and its homologues **44**–**46**.[90,91]

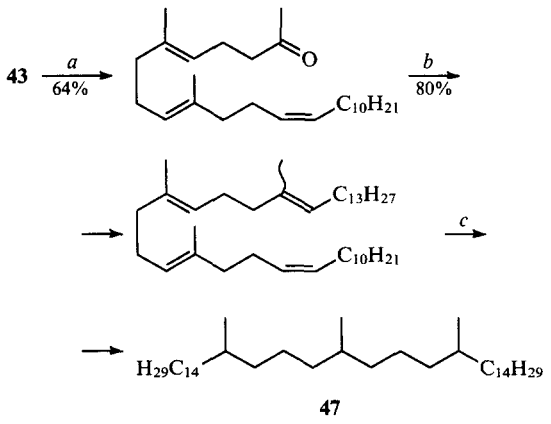


R = n-C_8H_{17} (**44**), n-$C_{10}H_{21}$ (**45**), n-$C_{12}H_{25}$ (**46**)

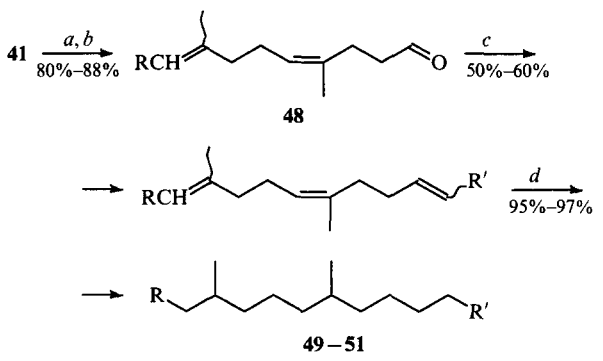
(*a*) RCH=PPh_3; (*b*) n-$C_{11}H_{23}$CH=PPh_3; (*c*) H_2–Pd/C.

A similar approach has been used in the synthesis of 15,19,23-trimethylheptatriacontane **47** — a component of the pheromone of the tsetse fly (*Glossina morsitans morsitans*).[92]

The carbon skeletons of the diastereoisomeric (±)-7,11-dimethyloctadecane **49**, (±)-15,19-dimethyltritriacontane **50**, and (±)-17,21-dimethylheptatriacontane **51** — the components of the egg-laying pheromones of the yellow-fever mosquito (*Aedes aegypti*), the stable fly (*Stomoxys calcitrans*), and the tsetse fly respectively, have been constructed by the introduction of double bonds into the unsaturated ketoacetal **41** with the (*Z*)-configuration via the keto-group and then the aldehyde-group (in compound **48**).[93–95]



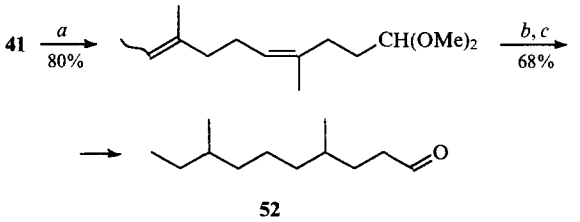
(*a*) n-$C_{10}H_{21}$CH=PPh_3; (*b*) n-$C_{13}H_{27}$CH=PPh_3; (*c*) H_2–Pd/C.



49: R = n-C_5H_{11}, R′ = n-C_3H_7;
50: R = n-$C_{13}H_{27}$, R′ = n-$C_{10}H_{21}$;
51: R = n-$C_{15}H_{31}$, R′ = n-$C_{12}H_{25}$.

(*a*) RCH=PPh_3; (*b*) H_3O^+; (*c*) R′CH=PPh_3; (*d*) H_2–Pd/C.

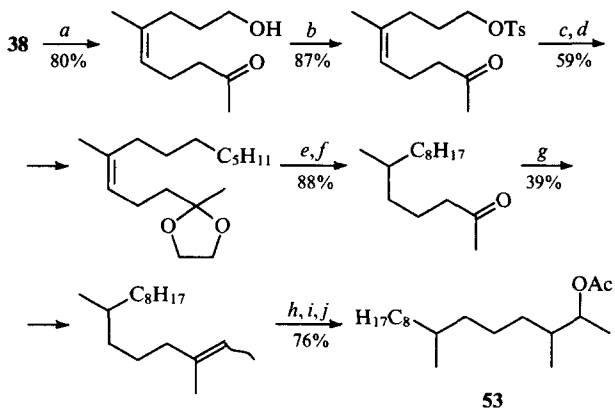
4,8-Dimethyldecanal **52** — the aggregation pheromone of the flour beetles (*Tribolium confusum* and *Tribolium castaneum*) — has been conveniently synthesised from the ketoacetal **41** by increasing its carbon chain length by two atoms via the keto-group with subsequent hydrogenation and hydrolysis.[96]



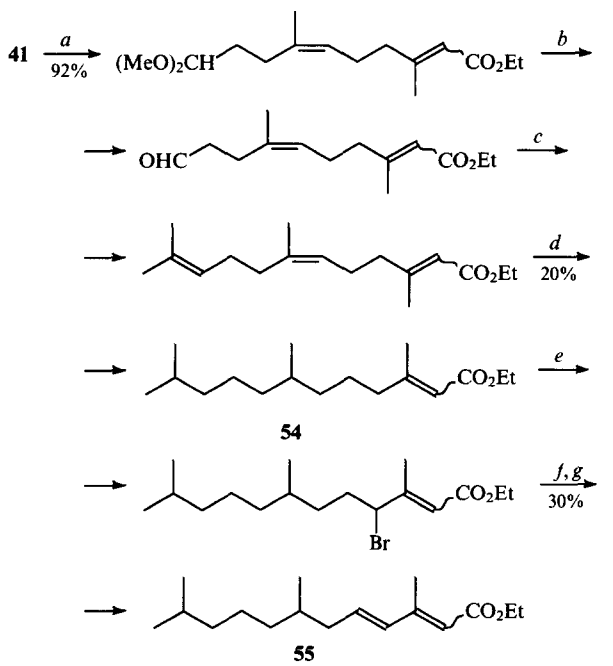
(*a*) MeCH=PPh_3; (*b*) H_2–Pd/C; (*c*) H_3O^+.

By use of the difference between the reactivities of the carbonyl groups of the ketoaldehyde **38**, it proved possible to achieve selective transformations leading to the racemic 3,7-dimethylpentadec-2-yl acetate **53** — the sex pheromone of the pine sawflies of the genera *Diprion* and *Neodiprion*.[97]

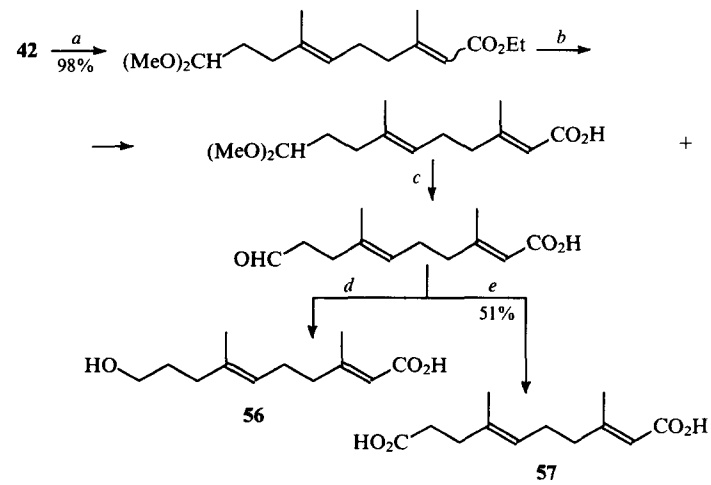
The synthesis of the ethyl ester of (2*E*,4*E*)-3,7,11-trimethyldodeca-2,4-dienoic acid (hydroprene) **55**, which has found extensive application as a juvenoid, is based on selective transformations of the unsaturated ketoacetal **41**, involving ethoxycarbonylmethylenation of the keto-group, conversion of the formyl group into an alkene by treatment with isopropylidenetriphenylphosphorane, ionic hydrogenation to the α,β-unsaturated ester **54**, and then transformation (via allylic bromination–dehydrobromination) into the target hydroprene.[98]



(*a*) $NaBH(OAc)_3$; (*b*) TsCl–Py; (*c*) $(CH_2OH)_2$–TsOH; (*d*) n-$C_5H_{11}MgBr$–Li_2CuCl_4; (*e*) H_2–Pd/C; (*f*) H_3O^+; (*g*) $MeCH{=}PPh_3$; (*h*) B_2H_6; (*i*) H_2O_2–NaOH; (*j*) Ac_2O–Py.



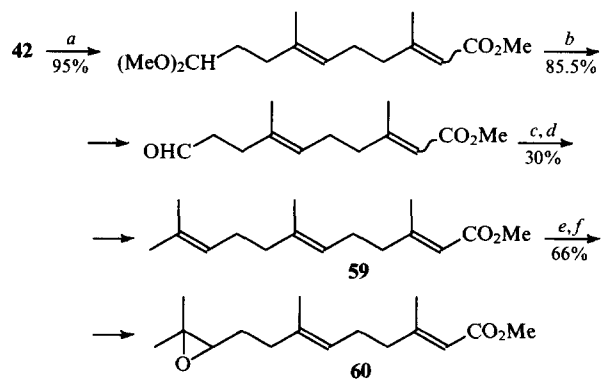
(*a*) $Me_3SiCH_2CO_2Et$–LDA ($LiNPr^i_2$); (*b*) PPTS–H_2O; (*c*) $Me_2C{=}PPh_3$; (*d*) Et_3SiH–CF_3CO_2H; (*e*) NBS (*N*-bromosuccinimide)–$(PhCO_2)_2$; (*f*) Li_2CO_3–LiBr; (*g*) HPLC.



(*a*) $Me_3SiCH_2CO_2Et$–LDA; (*b*) Pr^iONa–Pr^iOH; (*c*) H_3O^+; (*d*) $NaBH_4$; (*e*) H_2CrO_4; (*f*) $LiAl(OBu^i)H_2$.

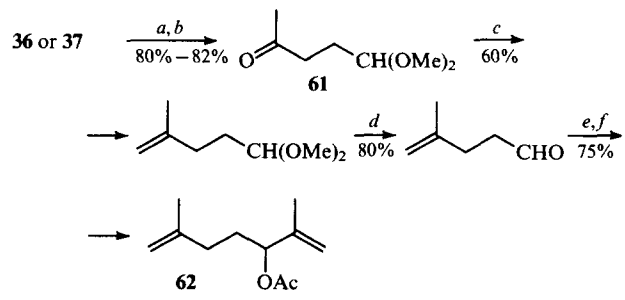
The ketoacetal **42** proved to be a convenient starting compound in the stereospecific synthesis of (2*E*,6*E*)-3,7-dimethyldeca-10-hydroxy-2,6-dienoic acid **56** and (2*E*,6*E*)-3,7-dimethyldeca-2,6-diene-1,10-dioic acid **57**, as well as the diol **58** — the terpenoid components of the pheromone of the danaid butterflies (*Danaus plexippus* and *Danaus chrysippus*) (Scheme 1).[99]

The racemic juvenile hormone YuG-III **60** has been synthesised stereospecifically from the ketoacetal **42** by means of its successive Petersen methoxycarbonylmethylenation, hydrolysis, coupling of the resulting aldehyde to isopropylidene-triphenylphosphorane, and the selective epoxidation of the intermediate triene ester **59** at the terminal double bond.[100]



(*a*) $Me_3SiCH_2CO_2Et$–LDA; (*b*) PPTS–H_2O; (*c*) $Me_2C{=}PPh_3$; (*d*) SiO_2–$AgNO_3$; (*e*) NBS; (*f*) K_2CO_3.

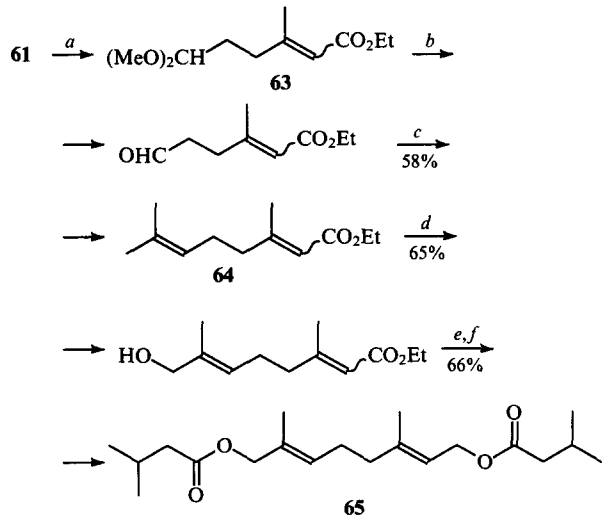
1,1-Dimethoxy-4-oxopentane **61**, obtained by the exhaustive ozonolysis of the isoprene oligomers **36** and **37** and the selective formation of acetal groups, has been used in the synthesis of 2,6-dimethylhepta-1,6-diene-3-yl acetate **62** — the attractant of the Comstock mealybug (*Pseudococcus comstoki*).[101]



(*a*) O_3–cyclo-C_6H_{12}–MeOH, H_2–Pd/$CaCO_3$–PbO; (*b*) MeOH–NH_4Cl; (*c*) $CH_2{=}PPh_3$; (*d*) H_3O^+; (*e*) $H_2C{=}C(Me)MgBr$; (*f*) AcCl.

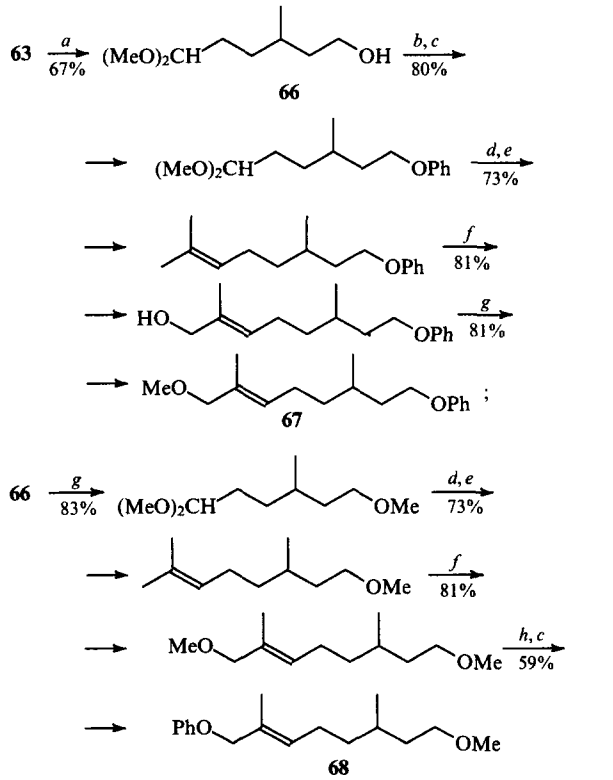
Scheme 1

(2*E*,6*E*)-2,6-Dimethylocta-2,6-diene-1,8-diyl diisovalerate **65**—the sex pheromone of the Crimean click beetle (*Agriotes tauricus*)—has been synthesised from the dimethyl acetal of levulinic aldehyde **61**.[102] The synthesis includes, among others, stages involving the epoxycarbonylmethylenation of the product and the introduction of double bonds into the latter to give the α,β-unsaturated ester **64** and subsequent allylic oxidation with a mixture of *tert*-butyl hydroperoxide and selenium dioxide.



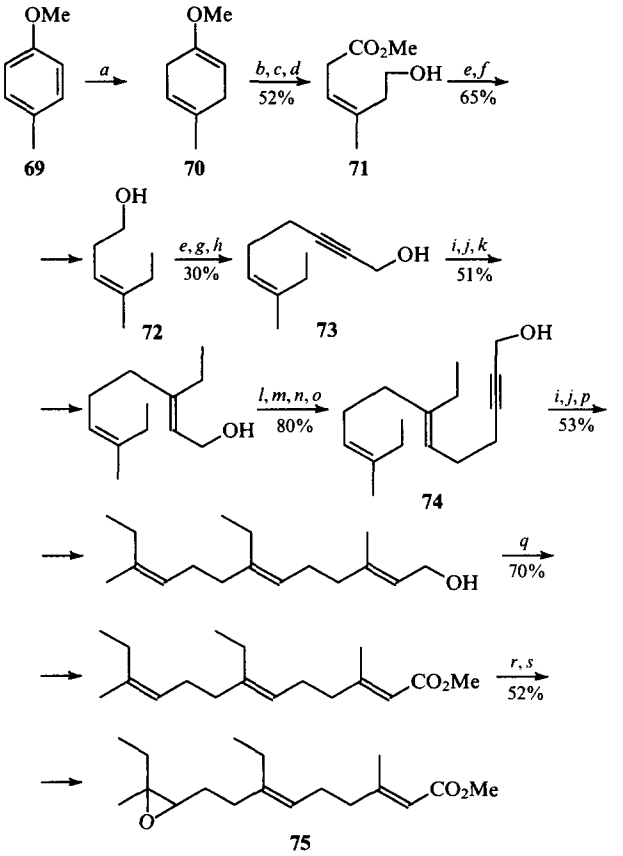
(*a*) $Me_3SiCH_2CO_2Et$–LDA; (*b*) H_3O^+; (*c*) $Me_2C{=}PPh_3$; (*d*) Bu^tOOH–SeO_2; (*e*) $LiAl(OBu^i)H_3$; (*f*) Me_2CHCH_2COCl–Et_3N.

The product of the Petersen ethoxycarbonylmethylenation of the ketoacetal **61**, namely the ester **63**, served as a convenient intermediate in the synthesis of (2*E*)-1-methoxy-8-phenoxy- and (2*E*)-1-phenoxy-8-methoxy-2,6-dimethyloct-2-enes **67** and **68**, which exhibit a juvenoid activity.[103]



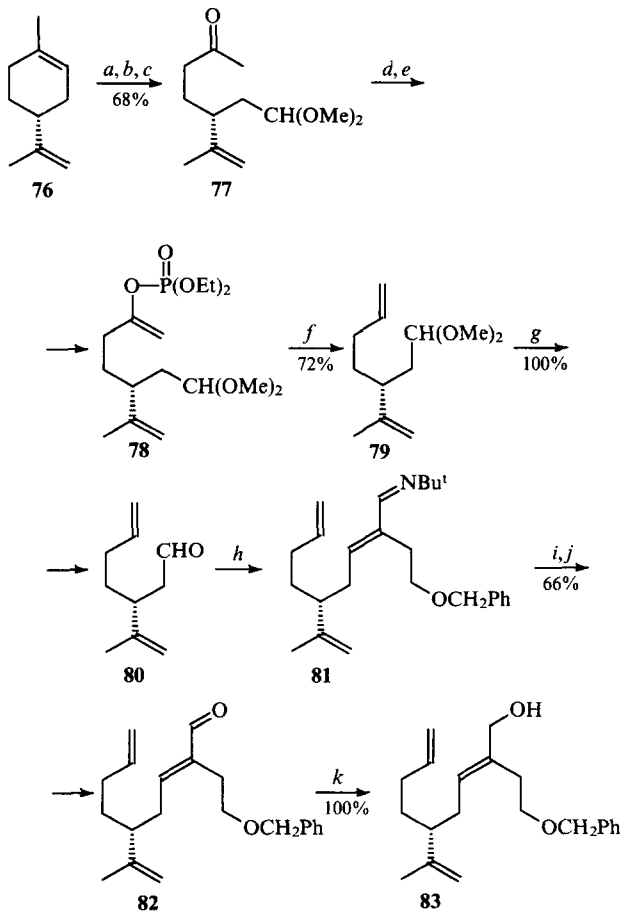
(*a*) Li–NH_3; (*b*) TsCl–Py; (*c*) PhONa; (*d*) PPTS–H_2O; (*e*) $Me_2C{=}PPh_3$; (*f*) Bu^tOOH–SeO_2; (*g*) NaH, MeI; (*h*) PBr_3–Py.

Ozonisation proved to be very effective in the conversion of the vinyl ether **70**—the readily available product of the Birch reduction of the methyl ether of *p*-cresol **69**—into the precursor for the synthesis of the juvenile hormone YuG-I **75**—the alcohol **72**.[104] The selectivity of the ozonolysis of compound **70** to give compound **71** is due to the significantly higher reactivity of the methoxy-substituted double bond. The illustrated sequence of stages in the conversion of compound **70** into compound **72** ensured automatically the required (*Z*)-configuration of the terminal unit of the chain of the juvenile hormone **75**. The transition from the C_7 block **72** to the target compound **75** is achieved by increasing the length of the carbon chain by means of the regio- and stereo-selective alkylation of the propargyl alcohols **73** and **74** via the corresponding vinyl iodides.



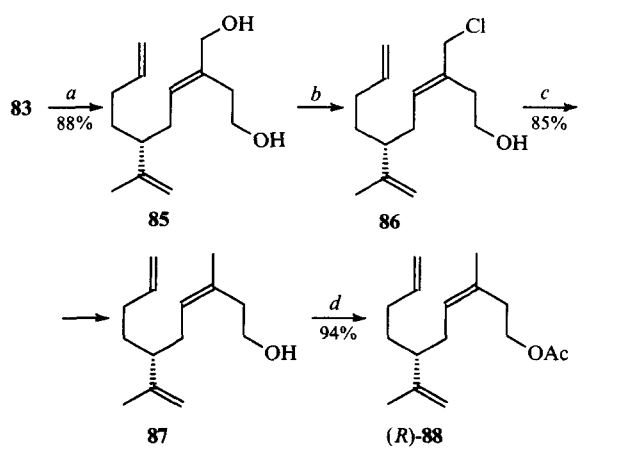
(*a*) Li–NH_3–$EtCMe_2OH$–THF; (*b*) O_3–MeOH; (*c*) Me_2S; (*d*) $NaBH_4$; (*e*) TsCl–Py; (*f*) $LiAlH_4$; (*g*) $LiC{\equiv}CCH_2OTHP$ (THP = tetrahydropyran-2-yl); (*h*) HCl; (*i*) $LiAlH_4$–NaOMe; (*j*) I_2; (*k*) Et_2CuLi; (*l*) PBr_3; (*m*) $LiCH_2C{\equiv}CSiMe_3$; (*n*) Ag^+, CN^-; (*o*) BuLi, CH_2O; (*p*) Me_2CuLi; (*q*) MnO_2, NaCN–MeOH; (*r*) HOBr; (*s*) Pr^iONa.

Limonene proved to be a convenient starting material for the synthesis of pheromones containing a chiral centre. (6*R*)-3-methyl-6-(2-propenyl)deca-3,9-dien-1-yl acetate (*R*)-**88**—the sex pheromone of the California red scale (*Aonidiella aurantii*)—has been synthesised from (*R*)-limonene **76**.[105] This was possible as a result of partial ozonolysis of limonene **76**, which takes place selectively and involves the endocyclic double bond. This gave ketoaldehyde **77**, in which the aldehyde group was protected selectively. The enolisation of the ketone **77** by a strong base and the fixation of the enolic form as the diethyl phosphate **78** followed by treatment with lithium in ammonia gave the diene acetal **79**. The deblocking and Petersen condensation of the aldehyde **80** with the silane **84** led to the imine **81**, from which the allyl alcohol **83** was obtained by successive hydrolysis and reduction.



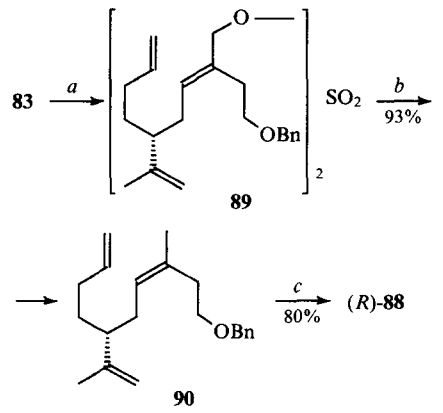
(*a*) O_3–MeOH; (*b*) $(H_2N)_2CS$; (*c*) $HC(OMe)_3$–$CeCl_3 \cdot 6H_2O$; (*d*) LDA; (*e*) $ClPO(OEt)_2$; (*f*) Li–NH_3; (*g*) $HClO_4$–H_2O–THF; (*h*) Et_3Si(NBu^t)CH_2OCH_2Ph (**84**) + BuLi; (*i*) $(CO_2H)_2$–H_2O; (*j*) PCC; (*k*) $LiAlH_4$.

The alcohol **83** was transformed into the target pheromone (*R*)-**88** in two ways. The first involved the removal of the benzyl protecting group under mild conditions (the conditions of the Birch reaction) and the subsequent substitution of the allylic OH group of the resulting diol **85** by chlorine. The hydrogenolysis of the chlorohydrin **86** afforded the pheromone precursor **87**, the acetylation of which completed the synthesis.



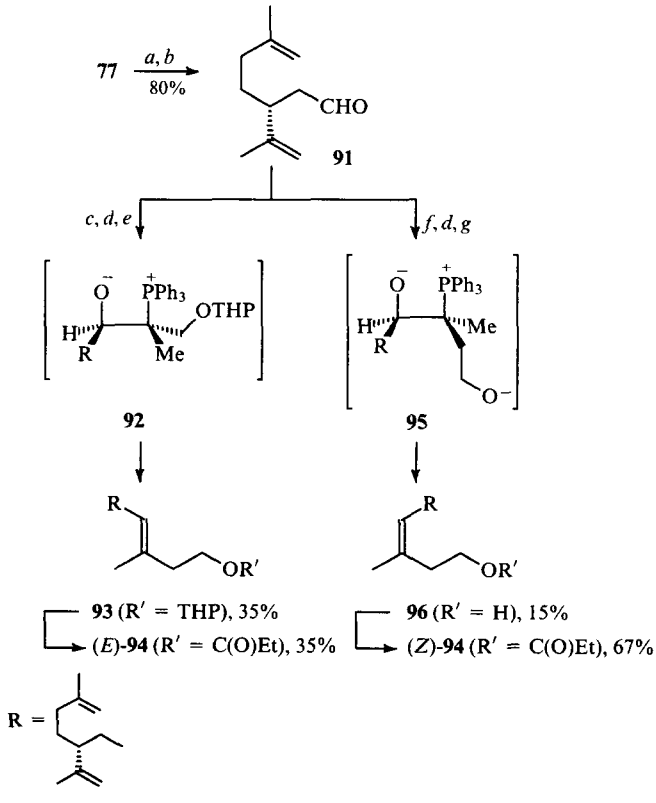
(*a*) Li–NH_3; (*b*) NCS (*N*-chlorosuccinimide)–Me_2S; (*c*) $LiAlH_4$; (*d*) Ac_2O–Py.

The alternative procedure for the transformation of compound **83** into the acetate **88** included the stage in which the sulfate **89** was formed and was subsequently reduced to the benzyl ether **90** and the benzyl group in the latter was replaced by the acetate group.



(*a*) SO_3–Py; (*b*) $LiAlH_4$; (*c*) Ac_2O–$HClO_4$.

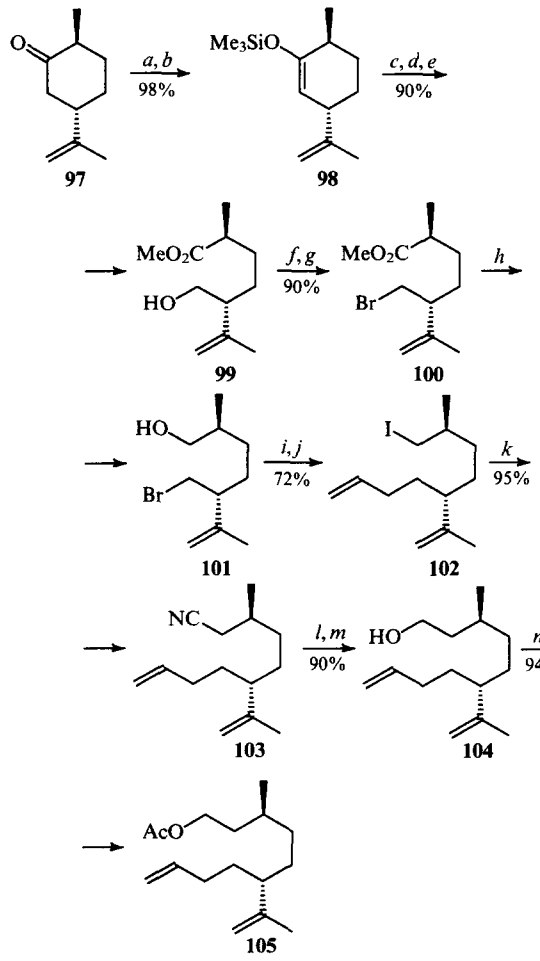
The optically active bifunctional reagent **77** has been used successfully in the stereospecific synthesis of the (*E*)- and (*Z*)-stereoisomers of (6*R*)-3,9-dimethyl-6-(2-propenyl)deca-3,9-dien-1-yl propionate **94** — the components of the sex pheromone of the white peach scale (*Pseudaulacaspis pentagona*).[106] In the synthesis of the pheromone component having the (*E*)-configuration (*E*)-**94**, the product of the methylenation of the ketoacetal **77** and subsequent hydrolysis (the dienal **91**) was converted by means of a modified Wittig reaction via the intermediate betaine **92** into the trisubstituted alkene pheromone precursor **93** (*E* ⩾ 97%). The deprotonation of the betaine **95**, generated from ethylidenetriphenylphosphorane and the chiral



(*a*) $CH_2{=}PPh_3$; (*b*) H_3O^+; (*c*) $THPO(CH_2)_2CH{=}PPh_3$; (*d*) BuLi; (*e*) MeI; (*f*) $MeCH{=}PPh_3$; (*g*) ; (*h*) EtCOCl–Et_3N.

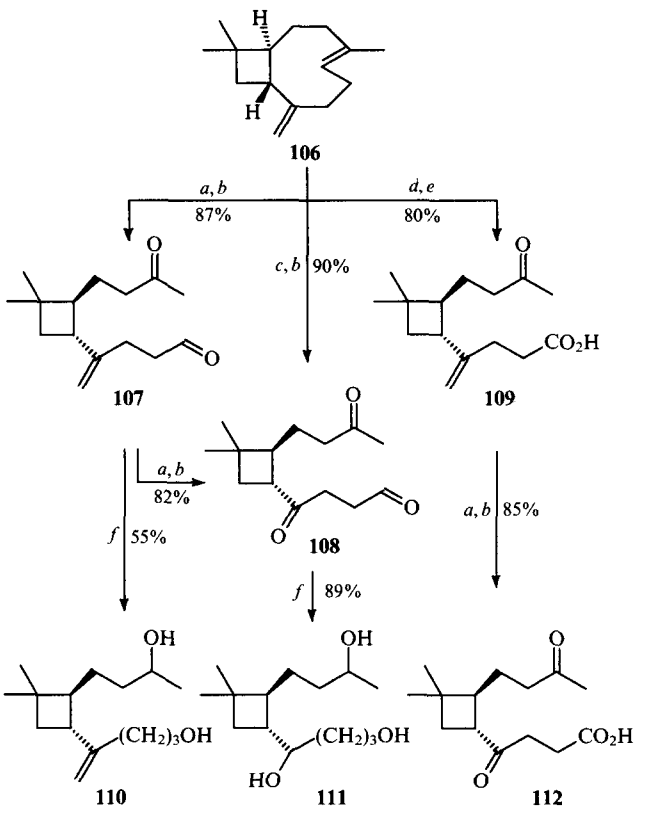
aldehyde **91**, and treatment of the resulting anion with epoxyethane led to the (*Z*)-homoallyl alcohol **96**, which was converted into the target pheromone component with the (*Z*)-configuration (*Z*)-**94**, in which the content of the principal stereoisomer was ⩾98%.

Dihydrocarvone **97** proved convenient for the synthesis of (3*S*,6*R*)-3-methyl-6-(2-propenyl)dec-9-en-1-yl acetate **105** — the sex pheromone of the California red scale (*Aonidiella aurantii*).[107] In order to open the ring in the cyclic ketone **97**, the latter was converted into the silyl enol ether **98**, the ozonolysis of which afforded the hydroxyester **99**. The iodo-derivative **102** was obtained via the bromoester **100** and bromohydrin **101** stages by coupling with allylmagnesium chloride and by the replacement of the alcoholic functional group by the halogen. Conversion into a higher homologue (by reaction with cyanide) and transformation of the functional group led to the target pheromone **105**.



(*a*) LDA; (*b*) Me_3SiCl; (*c*) O_3–MeOH–CH_2Cl_2; (*d*) $NaBH_4$; (*e*) CH_2N_2; (*f*) MsCl–Py; (*g*) Bu_4NBr; (*h*) DIBALH; (*i*) $H_2C{=}CHCH_2MgCl$–CuI; (*j*) $I_2 \cdot PPh_3$; (*k*) NaCN; (*l*) NaOH; (*m*) $LiAlH_4$; (*n*) Ac_2O–Py.

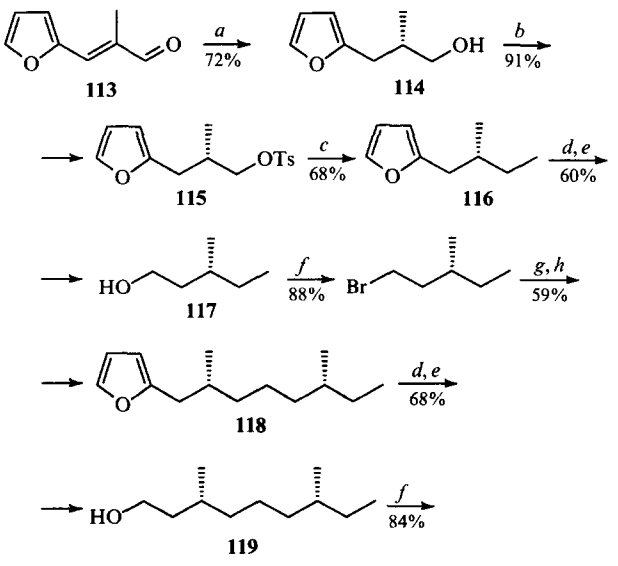
It has been established[108] that the ozonolysis of caryophyllene **106** takes place preferentially at the endocyclic double bond. On treatment with an equimolar amount of ozone and subsequent reduction of the peroxide ozonolysis products, the dicarbonyl derivative **107** was obtained, whereas exhaustive ozonolysis leads to the tricarbonylcyclobutane derivative **108**. The reduction of the keto- and diketoaldehydes **107** and **108** with sodium tetrahydroborate affords the di- and tri-hydroxy-*trans*-alkylcyclobutanes **110** and **111** respectively. The hydrolytic cleavage of the peroxide products of the partial ozonolysis of caryophyllene leads to the ketoacid **109**, the subsequent ozonolysis of which leads to the carboxylic deketoacid **112**.

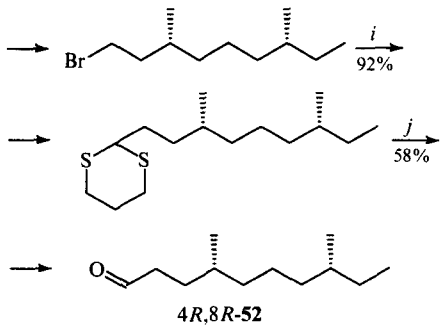


(*a*) O_3–MeOH; (*b*) H_2–Pd–$CaCO_3$–PbO; (*c*) excess O_3–MeOH; (*d*) O_3–cyclo-C_6H_{12}–AcOH; (*e*) AcONa–AcOH–Ac_2O; (*f*) $NaBH_4$.

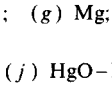
Laboratory biological tests on the cyclobutane derivatives synthesised demonstrated the likely usefulness of the search for analogues of juvenile hormones among compounds of this series.

The natural aggregation pheromone of the confused and red flour beetles (*Tribolium confusum* and *Tribolium castaneum*), namely (4*R*,8*R*)-4,8-dimethyldecanal **52**, has been synthesised from 3-(2-furyl)-2-methylacrolein **113** by means of enzymic reduction.[109] The optical purity of the resulting alcohol **114** was ⩾99%. Other key stages of this synthesis employed the ozonolysis of the 2-substituted furans **116** and **118** (obtained by alkylating the tosylate **115**), which led to the optically active alcohols **117** and **119** respectively.

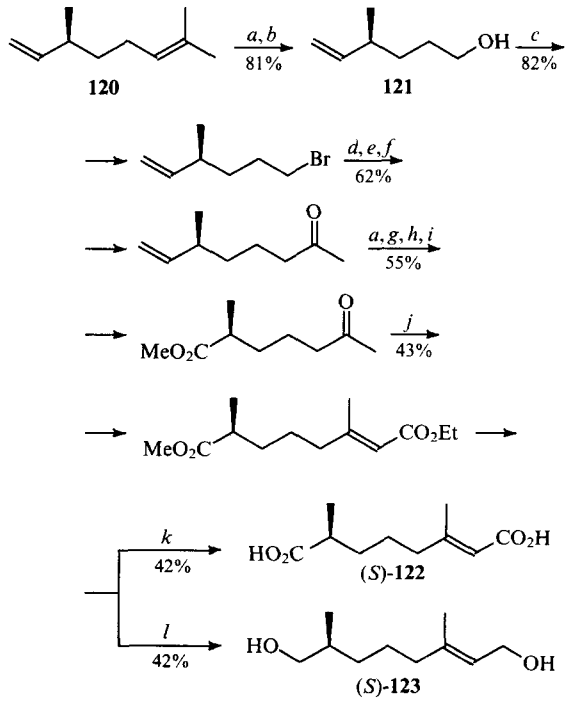




4*R*,8*R*-**52**

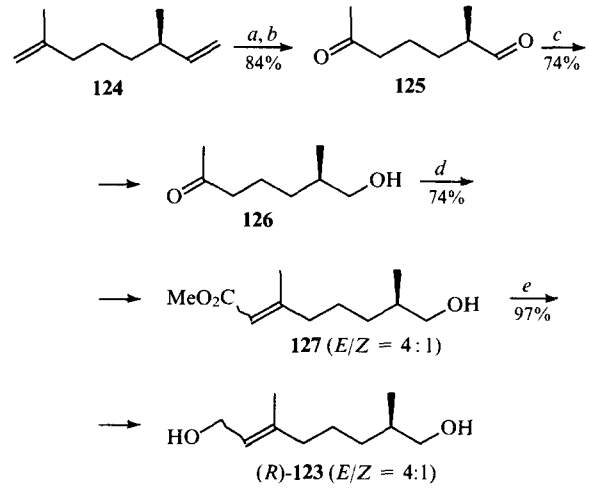
(*a*) baker's yeast; (*b*) TsCl–Py; (*c*) MeMgI–Li_2CuCl_4; (*d*) O_3; (*e*) $LiAlH_4$; (*f*) NBS–PPh_3; (*g*) Mg; (*h*) **115**–Li_2CuCl_4; (*i*) –BuLi; (*j*) HgO–$BF_3 \cdot OEt_2$.

The enantiomerically enriched alcohol **121** has been synthesised from (*S*)-(+)-dihydromyrcene **120** by means of ozonolysis, which involves preferentially the trisubstituted double bond. The alcohol **121** was subjected to selective transformations leading to the unsaturated dicarboxylic acid **122** and the diol **123**—the pheromone components of the Chinese bean weevil (*Callosobruchus chinesis*) and the monarch butterfly respectively.[110]



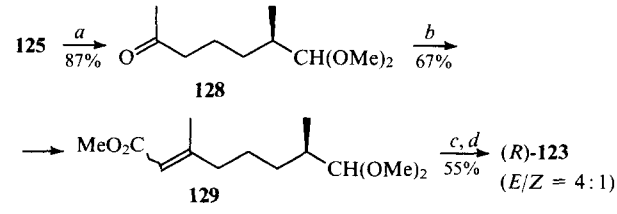
(*a*) O_3–$NaHCO_3$–CH_2Cl_2–MeOH; (*b*) $NaBH_4$; (*c*) PBr_3–Py; (*d*) Mg; (*e*) MeCHO; (*f*) PCC; (*g*) H_2–Pd–$CaCO_3$–PbO; (*h*) Ag_2O; (*i*) CH_2N_2; (*j*) $(MeO)_2P(O)CH_2CO_2Et$–EtONa; (*k*) NaOH; (*l*) DIBALH.

The initial chiral structural block in the syntheses of the (*R*)- and (*S*)-enantiomers of (2*E*)-3,7-dimethyloct-2-ene-1,8-diol **123** (the product secreted by the monarch butterfly) and (2*E*)-3,7-dimethyloct-2-ene-1,8-dicarboxylic acid **122** (the sex pheromone of *Callosobruchus chinesis*) is 2,6-dimethyloctadiene **124** (regioisomeric with respect to dihydromyrcene **120**) with the corresponding (*R*)- or (*S*)-configuration.[111] The schemes presented here indicate the transformations of the (*R*)-enantiomers of the diene **124**, the ozonolysis of which led to the chiral ketoaldehyde **125**. The carbonyl groups in the latter were differentiated (for the subsequent selective conversion into alkene groups) in two ways: by the selective hydride reduction of the aldehyde group, yielding the hydroxyketone **126**, or by blocking the aldehyde group, which leads to the ketoacetal **128**. The involvement of the hydroxyketone **126** in the Wittig–Horner reaction with trimethyl phosphonoacetate gave a mixture of the geometrical isomers of the hydroxyester **127** with respect to the Δ^2-double bond; reduction with lithium tetrahydroaluminate led to the corresponding mixture of the (*E*)- and (*Z*)-diols (*R*)-**123**.



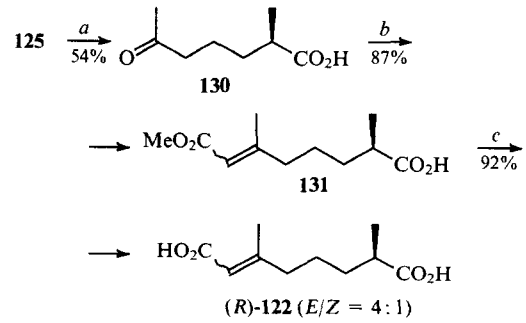
(*a*) O_3; (*b*) Me_2S; (*c*) $NaBH_4$; (*d*) $(MeO)_2P(O)CH_2CO_2Et$–NaH; (*e*) $LiAlH_4$.

The transformation of the ketoacetal **128** into the diol (*R*)-**123** involved the Wittig–Horner reaction, which led to a mixture of the (*E*)- and (*Z*)-isomeric esters **129**. The deblocking of the aldehyde group and subsequent hydride reduction afforded a mixture of the (*E*)- and (*Z*)-isomers of the diol (*R*)-**123**.



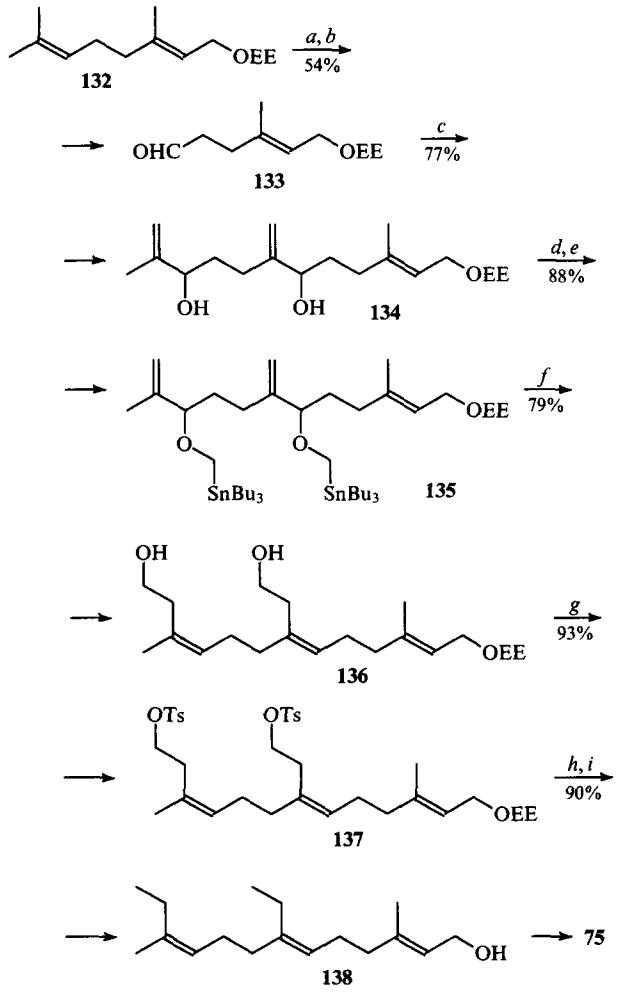
(*a*) MeOH–TsOH; (*b*) $(MeO)_2P(O)CH_2CO_2Me$–NaH; (*c*) HCO_2H–H_2O; (*d*) $LiAlH_4$.

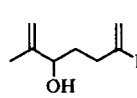
The synthesis of (*Z*,*E*)-(7*R*)-3,7-dimethyloct-2-ene-1,8-dioic acid (*R*)-**122** involves the oxidation of the aldehyde group in the ketoaldehyde **125** and the Wittig–Horner coupling of the ketoacid **130** with trimethyl phosphonoacetate, which leads to the monoester **131** in the form of a mixture of the (*E*)- and (*Z*)-isomers.[111]



(*a*) $AgNO_3$–EtOH–H_2O; (*b*) $(MeO)_2P(O)CH_2CO_2Et$–NaH; (*c*) NaOH.

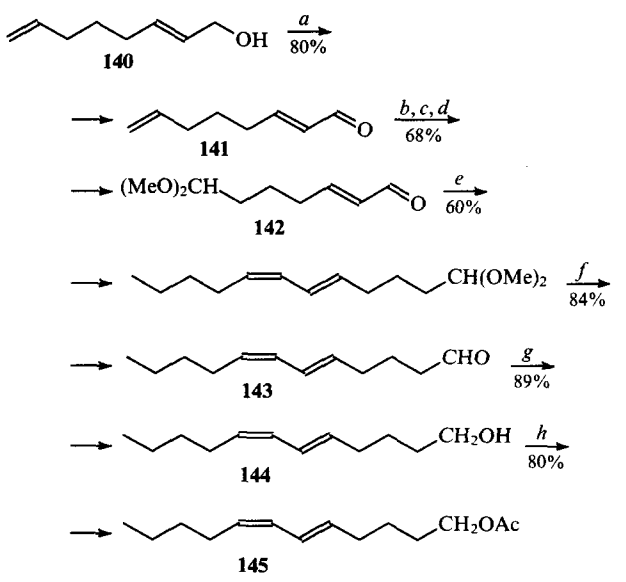
A highly stereoselective method of synthesis of bishomofarnesol **138** — an intermediate in the synthesis of the juvenile hormone YuG-1 **75** — has been achieved by means of the partial ozonolysis of the ethoxyethyl (EE) derivative of geraniol **132** at the isopropylidene group. The interaction of the resulting aldehyde **133** with the dianion derived from the diene bromohydrin **139** yields the monosubstituted trisallyl alcohol **134**; its distannyl derivative **135** is converted by means of a 2,3-sigmatropic rearrangement with high (*E*)-stereoselectivity into the bishomoallyl alcohol **136** and further, via the corresponding ditosylate **137**, into the target trienol **138**.[112]



(*a*) O_3–CH_2Cl_2–Py; (*b*) Zn; (*c*)  Br (**139**) + BuLi;

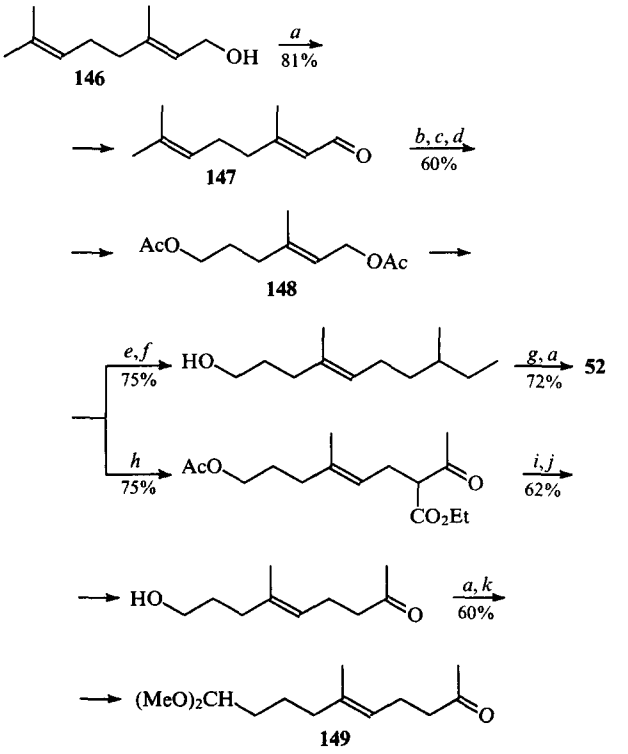
(*d*) KH; (*e*) Bu_3SnCH_2I; (*f*) BuLi; (*g*) TsCl–Py; (*h*) $LiAlH_4$; (*i*) AcOH–H_2O.

An isolated double bond is known to have a reactivity an order of magnitude higher towards ozone than a double bond conjugated with the aldehyde group. This enabled us to expand the possibilities, discovered previously,[113] for the preparative application of the partial ozonolysis of acyclic polyenes as a method of synthesis of bifunctional unsaturated compounds. It was established[114] that (2*E*)-2,7-octadienal **141**, which can be readily obtained from the telomer **140** of butadiene and water, is converted into (2*E*)-7,7-dimethoxyhept-2-enal **142** in a satisfactory yield on interaction with ozone. The target compounds — (5*E*, 7*Z*)-5,7-dodecadienal **143** and the corresponding alcohol **144** and acetate **145** [the components of the sex pheromone of the lackey moth (*Malacosoma neustria* L.)] — were synthesised from compound **142**.



(*a*) PCC; (*b*) O_3–cyclo-C_6H_{12}–MeOH; (*c*) Me_2S; (*d*) MeOH–NH_4Cl; (*e*) $HO_2C(CH_2)_4PPh_3Br$, $NaN(SiMe_3)_2$; (*f*) H_2SO_4–MeOH; (*g*) $LiAlH_4$; (*h*) AcCl–Py.

(2*E*)-1,6-Diacetoxy-3-methylhex-2-ene **148** has been obtained by the partial ozonolysis of (2*E*)-3,7-dimethylocta-2,6-dienal **147** (the product of the oxidation of geraniol **146**) at the isopropylidene group. The aggregation pheromone **52** of the confused and red flour beetles and (4*E*)-1,1-dimethoxy-4-methylnon-4-en-8-one **149** — the intermediate for the synthesis of the components of the sex pheromone of the danaid butterflies (*Danaus plexippus* and *Danaus chrysippus*) — were synthesised from compound **148**.[114]

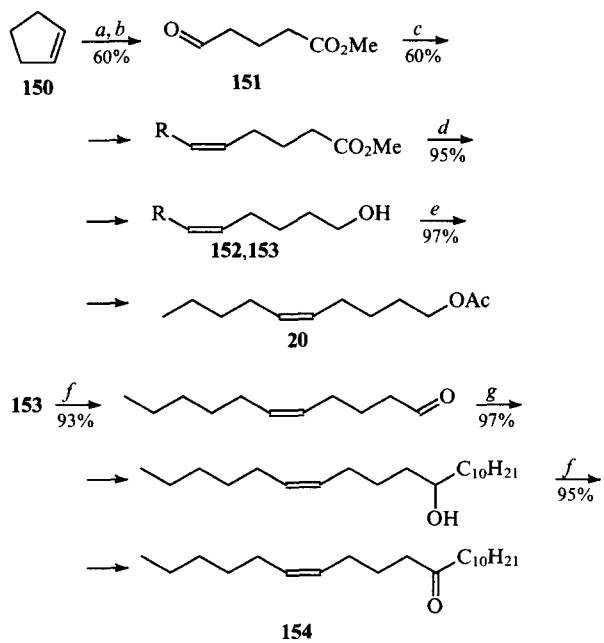


(*a*) PCC; (*b*) O_3–cyclo-C_6H_{12}–MeOH; (*c*) $NaBH_4$; (*d*) Ac_2O–Py; (*e*) EtCH(Me)CH_2Br–Mg–CuI; (*f*) KOH–MeOH; (*g*) H_2–Pd/C; (*h*) $MeCOCH_2CO_2Et$–NaH–$Pd(OAc)_2$–PPh_3; (*i*) NaOH; (*j*) H_2SO_4; (*k*) MeOH–NH_4Cl.

The decisive stages in these syntheses were the catalytic cross-coupling reactions between the diacetate **148** and the corresponding organomagnesium and organosodium reagents, which take place regio- and stereo-specifically with respect to the allylic acetoxy-group.

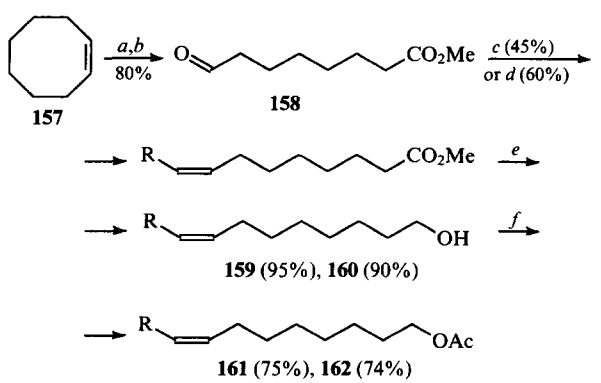
III. Synthesis of pheromones and juvenoids from the ozonolysis products of cyclic and acyclic alkenes

The ozonolysis of monoenes leads to saturated oxygen-containing compounds which are of interest for the synthesis of pheromones and juvenoids. Thus (5*Z*)-dec-5-enol **152** and (5*Z*)-undec-5-enol **153** have been synthesised from methyl 5-oxopentanoate **151** — the product of the functionally differentiated ozonolysis of cyclopentene **150**.[115] The acetate **20** of compound **151** is part of the composition of the pheromones of insects belonging to the genus *Agrotis*. (6*Z*)-Heneicos-6-en-11-one **154** — the sex pheromone of the tussock moth of the genus *Orgyia* which are pests on conifer forests — have been synthesised from compound **153**.



R = Bu (**152**, **155**), n-C_5H_{11} (**153**, **156**).

(*a*) O_3–$NaHCO_3$–CH_2Cl_2–MeOH; (*b*) Ac_2O–Et_3N; (*c*) RCH=PPh_3 (**155**, **156**); (*d*) DIBALH; (*e*) Ac_2O–Py; (*f*) PCC; (*g*) n-$C_{10}H_{21}MgBr$.

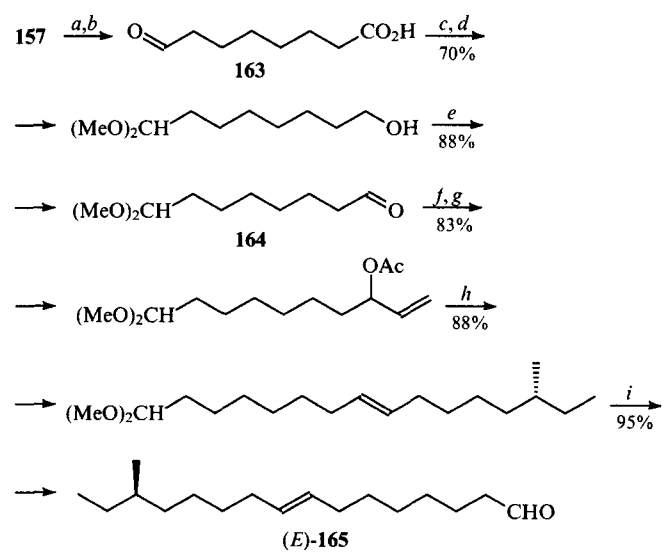


R = Pr (**159**, **161**), n-C_5H_{11} (**160**, **162**).

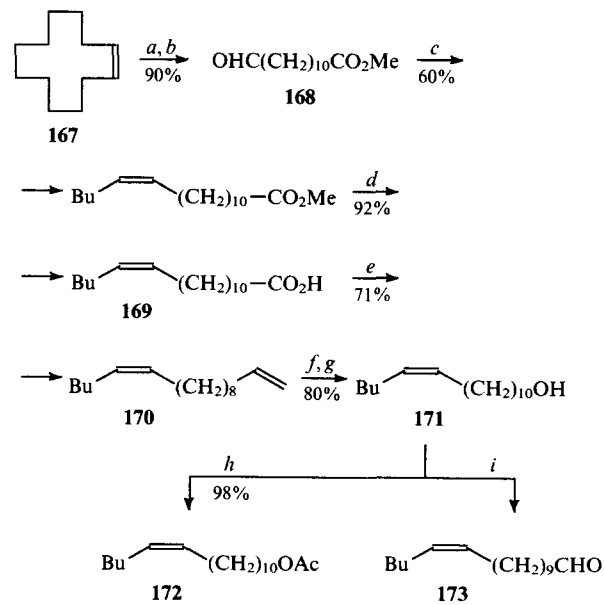
(*a*) O_3–$NaHCO_3$–CH_2Cl_2–MeOH; (*b*) Ac_2O–Py; (*c*) PrCH=PPh_3; (*d*) n-$C_5H_{11}CH$=PPh_3; (*e*) DIBALH; (*f*) Ac_2O–Py.

The ozonolysis of cyclooctane **157** under the conditions described by Odinokov et al.[115] led to a high yield of methyl 8-oxooctanoate **158**, which was used in the Wittig reaction with n-alkylidenetriphenylphosphoranes. This led to the discovery of a simple path to insect pheromones having the structure of (*Z*)-alk-8-enols **159** and **160** and their acetates **161** and **162**.[116]

In the synthesis of the optically active component (*E*)-**165** of the aggregation pheromone of the khapra beetle (*Trogoderma granarium*), the product of the ozonolysis of cyclooctene **157** and of the hydrolytic cleavage of the peroxide ozonolysis product — the aldehydoacid **163** — was converted in three stages into the monoacetal **164**, which reacted with the chiral bromo-derivative **166** obtained from dihydromyrcene **120**.[117]



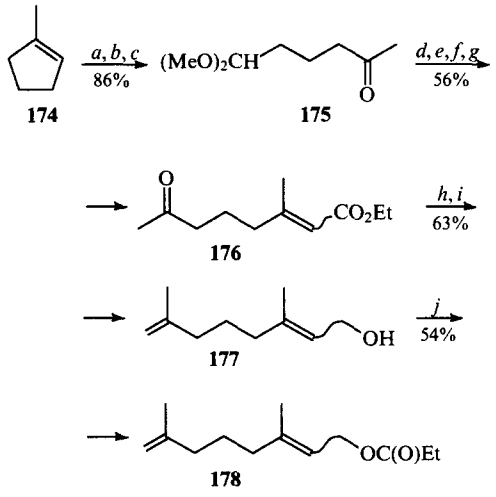
(*a*) O_3–cyclo-C_6H_{12}–AcOH; (*b*) AcONa–AcOH–Ac_2O; (*c*) TsOH–MeOH; (*d*) DIBALH; (*e*) PCC; (*f*) H_2C=CHMgBr; (*g*) Ac_2O; (*h*)  (**166**) + Mg + CuI; (*i*) PPTS–H_2O.



(*a*) O_3–$NaHCO_3$–CH_2Cl_2–MeOH; (*b*) Ac_2O–Et_3N; (*c*) BuCH=PPh_3; (*d*) KOH; (*e*) $Pb(OAc)_4$–$Cu(OAc)_2$·H_2O; (*f*) BBN {9-borabicyclo 3.3.1 nonane}; (*g*) H_2O_2–NaOH; (*h*) Ac_2O–Py; (*i*) PCC.

Methyl 12-oxododecanoate **168**, obtained by the ozonolysis of cyclododecene **167**, has been used to synthesise (11*Z*)-hexadec-11-en-1-ol **171**, its acetate **172**, and (11*Z*)-hexadec-11-enal **173** — the components of the sex pheromone of the noctuid moths belonging to the genera *Mamestra* and *Heliothis*. The key stages in this synthesis[118] are the Wittig conversion of the aldehyde **168** into an alkene, oxidative decarboxylation of the acid **169**, and selective hydroboration of the diene **170** at the terminal double bond.

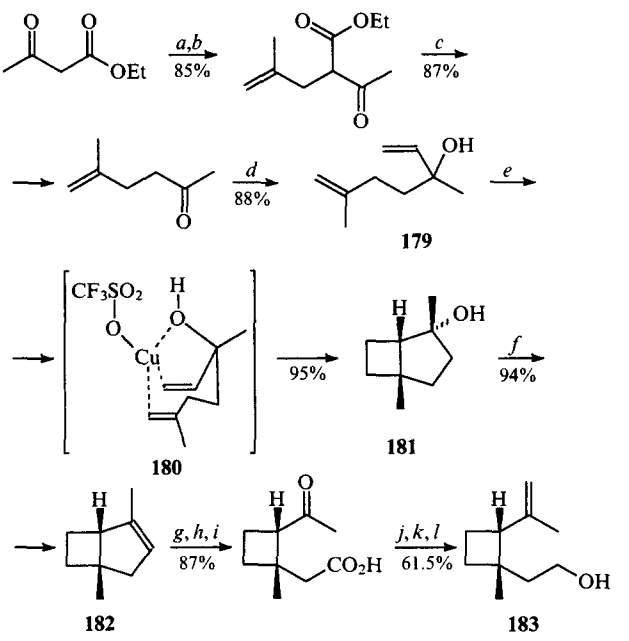
The ketoester **176** has been synthesised by the ozonolysis of 1-methylcyclopent-1-ene **174** and subsequent selective transformations of 1,1-dimethoxy-5-oxo-hexane **175**, including the conversion of the keto-group into an ethoxycarbonylalkene group and the alkylation of the formyl group by methylmagnesium iodide followed by oxidation. Compound **176** was converted in two stages into 3,7-dimethylocta-2,7-dien-1-ol **177** (isomer ratio $E/Z = 85 : 15$), the propionate **178** of which is a component of the sex pheromone of the San Jose scale *Quadraspidiotus perniciosus*.[119]



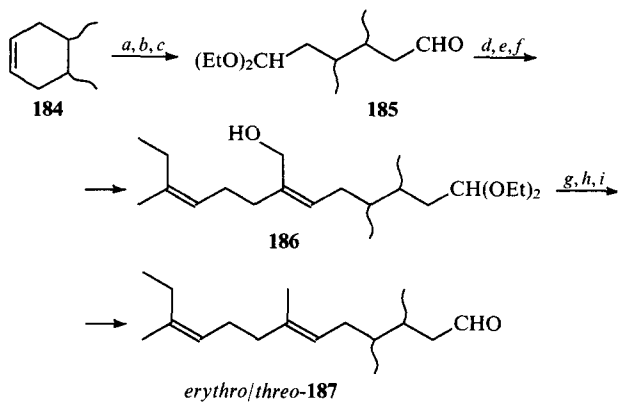
(*a*) O_3–MeOH; (*b*) H_2–Pd–$CaCO_3$–PbO; (*c*) MeOH–NH_4Cl; (*d*) $Me_3SiCH_2CO_2Et$–LDA; (*e*) PPTS–H_2O; (*f*) MeMgI; (*g*) PCC; (*h*) CH_2Br_2–$TiCl_4$–Zn; (*i*) $LiAl(OBu^t)H_3$; (*j*) EtCOCl–Et_3N.

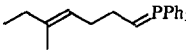
Application of the copper-salt-catalysed 2π + 2π photocycloaddition reaction to terminal 1,6-dienes leads to photobicyclisation products, which has been used in the synthesis of grandisol **183** — the sex pheromone of the cotton-boll weevil (*Anthonomus grandis*).[120] It has been suggested[121] that, in the presence of copper trifluoromethanesulfonate, the dienol **179** gives rise to the tridentate complex **180**, which ensures the stereoselective formation of the bicyclic compound **181**. The latter is readily converted subsequently into the target pheromone **183** by ozonolysis of the product of its regioselective dehydration — the bicyclene **182**.

erythro-(3*S*,4*R*,6*E*,10*Z*)-3,4,7,11-Tetramethyltrideca-6,10-dienal (pharanal) **187** has been identified as the pheromone of the pharaoh ant (*Monomorium pharaonis L.*), which is a carrier of pathogenic bacteria. Several methods have been developed for the synthesis of racemic analogues of pharanal on the basis of the Wittig reaction. Thus 6,6-diethoxy-3,4-dimethylhexanol **185**, obtained by the ozonolysis of a mixture of the *cis*- and *trans*-isomers of dimethylcyclohexene **184**, was converted into an alkene by treatment with the phosphorane **188** and subsequent Cory hydroxymethylation of the intermediate; this led to the hydroxyacetal **186**, which was subsequently converted into the pheromone **187** as a mixture of the *erythro*- and *threo*-isomers.[122]



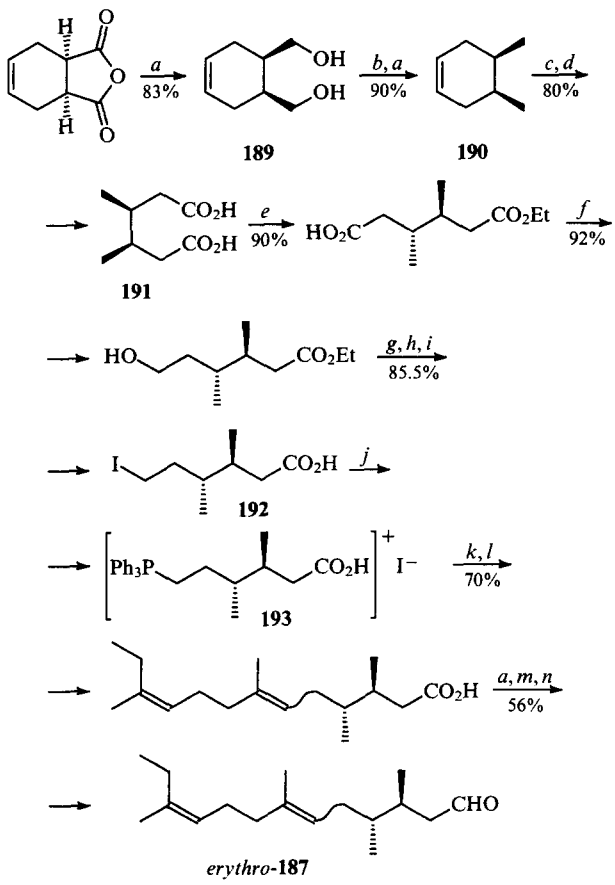
(*a*) EtONa; (*b*) $H_2C=C(Me)CH_2Cl$; (*c*) NaOH, Δ; (*d*) $H_2C=CHMgBr$; (*e*) *hν*, CuOTf; (*f*) HMPA (hexamethylphosphoramide); (*g*) O_3–AcOH; (*h*) Zn; (*i*) H_2CrO_4; (*j*) Me_3SiCH_2MgCl; (*k*) $SOCl_2$; (*l*) $LiAlH_4$.

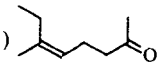


(*a*) O_3; (*b*) Me_2S; (*c*) $HC(OEt)_3$–HCl; (*d*)  (**188**); (*e*) *s*-BuLi; (*f*) $(CH_2O)_n$; (*g*) Py·SO_3; (*h*) $LiAlH_4$; (*i*) H_2SO_4.

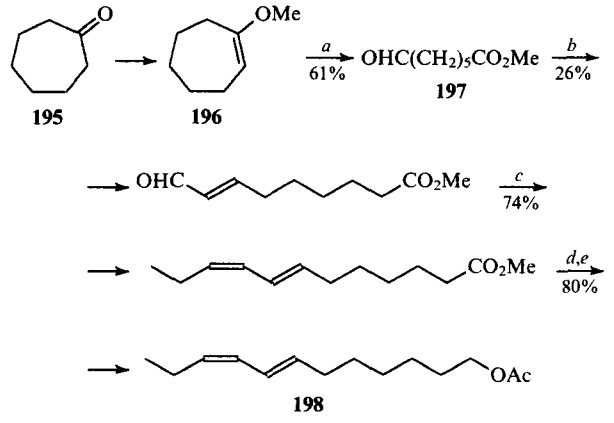
The racemic *erythro*-(3*SR*,4*RS*)-pharanal was synthesised from *cis*-1,2,3,6-tetrahydrophthalic anhydride, which was converted into *cis*-4,5-dimethylcyclohexene **190** via the diol **189**. This cycloalkene was converted by ozonolysis into *erythro*-3,4-dimethyladipic acid **191** and further, via the iodo-derivative **192**, into the phosphonium salt **193**. Coupling of the phosphorane generated from the salt **193** with the ketone **194** yielded an aldehyde with the *erythro*-configuration in the form of a mixture of Δ^6-Z/E-isomers (46 : 54); *erythro*-pharanal **187** was isolated from the latter by preparative gas–liquid chromatography (GLC).[123]

Methods of synthesis of a series of insect pheromones having the structure of unsaturated alcohol acetates have been developed on the basis of the products of reductive ring opening of the ozonides of the alkyl ethers of the enolic form of cycloheptanone.[124,125] Thus the aldehydoester **197**, obtained from 1-methoxycycloheptene **196**, was made to undergo an (*E*)-stereoselective alkene formation reaction (by treatment with formylmethylidenetriphenylphosphorane) and the product was then



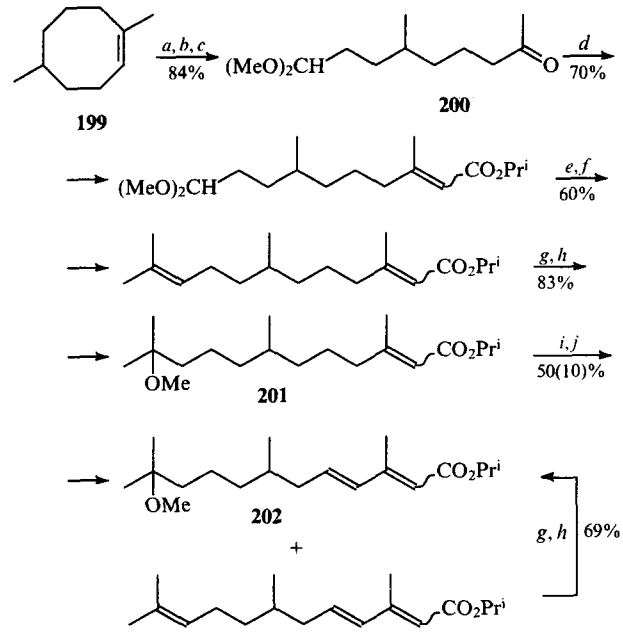
(*a*) $LiAlH_4$; (*b*) MsCl–Py; (*c*) O_3; (*d*) H_2CrO_4; (*e*) EtOH–H_2SO_4; (*f*) B_2H_6; (*g*) TsCl–Py; (*h*) NaI; (*i*) KOH; (*j*) PPh_3; (*k*) NaH; (*l*)  (**194**); (*m*) PCC; (*n*) preparative GLC.

converted by means of a (*Z*)-stereoselective alkene formation reaction (by treatment with propylidenetriphenylphosphorane) into the pheromone **198** of the grape leafcurler (*Lobesia botrana*) containing 92% of the principal stereoisomer.[125]



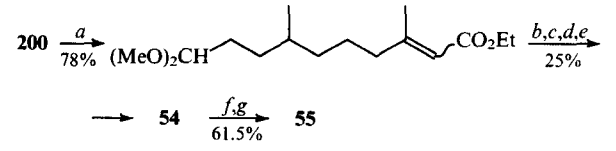
(*a*) O_3–PPh_3–CH_2Cl_2; (*b*) OHC–CH=PPh_3; (*c*) EtCH=PPh_3; (*d*) $LiAlH_4$; (*e*) Ac_2O–Py.

The isopropyl ester of (2*E*)-11-methoxy-3,7,11-trimethyldodec-2-enoic acid **201** has been obtained by the ozonolysis of 1,5-dimethylcyclooct-1-ene **199** and the subsequent transformations of the ketoacetal **200**, including isopropoxycarbonylmethyleneation at the keto-group and then conversion of the aldehyde group into an alkene component by treatment with isopropylidenetriphenylphosphorane and methoxylation of the isopropylidene group.[126] The allylic bromination of compound **201** and subsequent dehydrobromination led to the familiar juvenoid methoprene **202** in the form of an 82:18 mixture of the (2*E*,4*E*)- and (2*Z*,4*Z*)-isomers.



(*a*) O_3–MeOH; (*b*) H_2–Pd/$CaCO_3$–PbO; (*c*) MeOH–NH_4Cl; (*d*) $Me_3SiCH_2CO_2Pr^i$–LDA; (*e*) PPTS–H_2O; (*f*) $Me_2C{=}PPh_3$; (*g*) $Hg(OAc)_2$–MeOH; (*h*) $NaBH_4$–NaOH; (*i*) NBS–$(PhCO_2)_2$; (*j*) LiBr–Li_2CO_3.

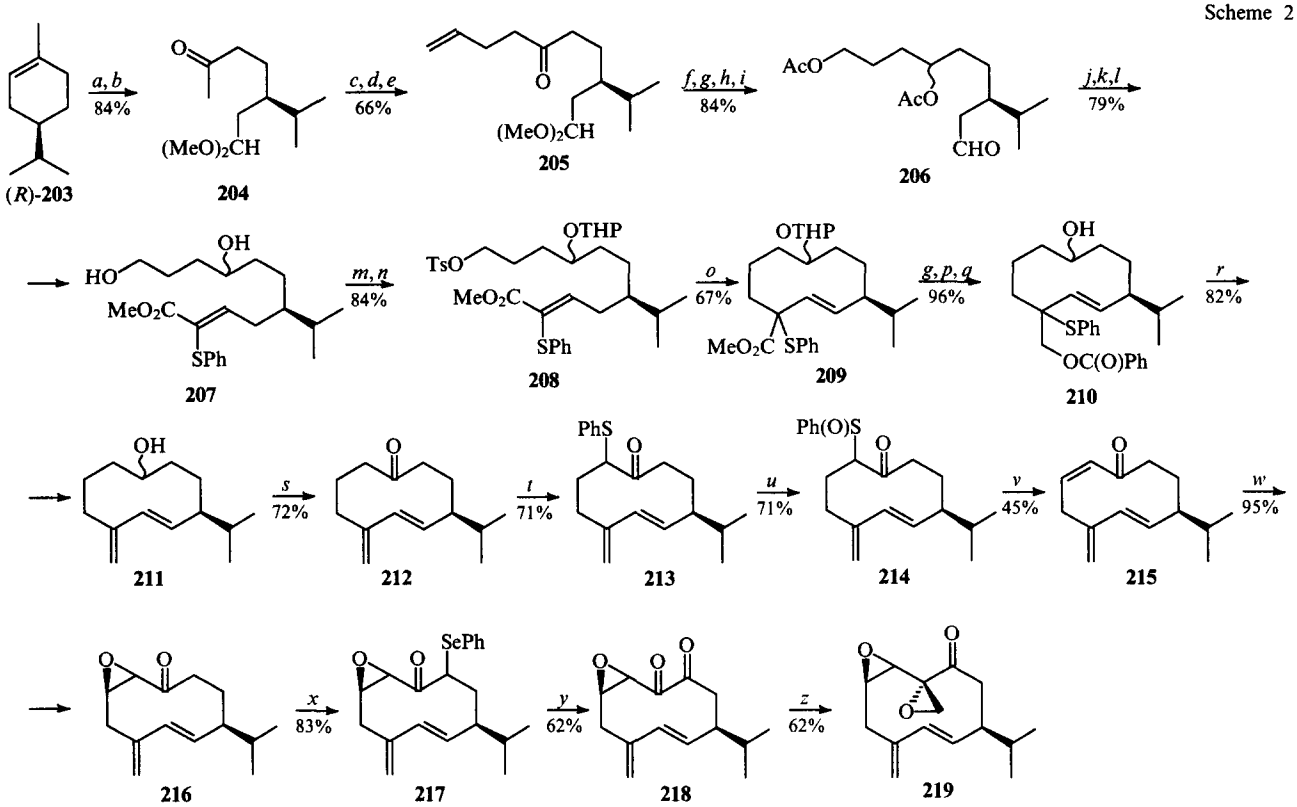
Hydroprene **55** has been obtained in the form of a 77:23 mixture of the (2*E*,4*E*)- and (2*Z*,4*E*)-isomers by the selective transformations of the ketoacetal **200**, including the ethoxycarbonylmethylenation of the keto-group, alkylation of the formyl group by isopropylmagnesium bromide with subsequent deoxygenation, and allylic bromination-dehydrobromination.[98]



(*a*) $Me_3SiCH_2CO_2Et$–LDA; (*b*) PPTS–H_2O; (*c*) Pr^iMgBr; (*d*) TsCl–Py; (*e*) Zn–NaI; (*f*) NBS–$(PhCO_2)_2$; (*g*) LiBr–Li_2CO_3

(+)-Dihydrolimonene (*R*)-**203** has served as the source of one of the chiral centres in the synthesis of (–)-periplanone B **219**—the sex pheromone of the American cockroach (*Periplaneta americana*).[127–129] The synthesis (Scheme 2) begins with the ozonolysis of the terpene (*R*)-**203** and the subsequent selective protection of the aldehyde group. The interaction of the carbanion generated from the dimethyl acetal of the ketoaldehyde **204** with allyl bromide led to the product **205**. Oxidative cleavage of the double bond in the latter, the subsequent reduction of the intermediate ketoaldehyde, and the acetylation and deblocking of the carbonyl group led to the aldehyde **206**. The latter was converted into the diol **207** by condensation with the carbanion generated from methyl benzenesulfonylacetate and subsequent dehydration and hydrolysis. The tosylation of the primary alcoholic group of the latter, accompanied by the blocking of the secondary hydroxy-group, afforded compound **208**, the deprotonation of which led to cyclisation. The product **209** was converted in several stages into the dienol **211** with endocyclic and exocyclic conjugated double bonds. The oxidation of the dienol **211** to the corresponding ketone **212** and its

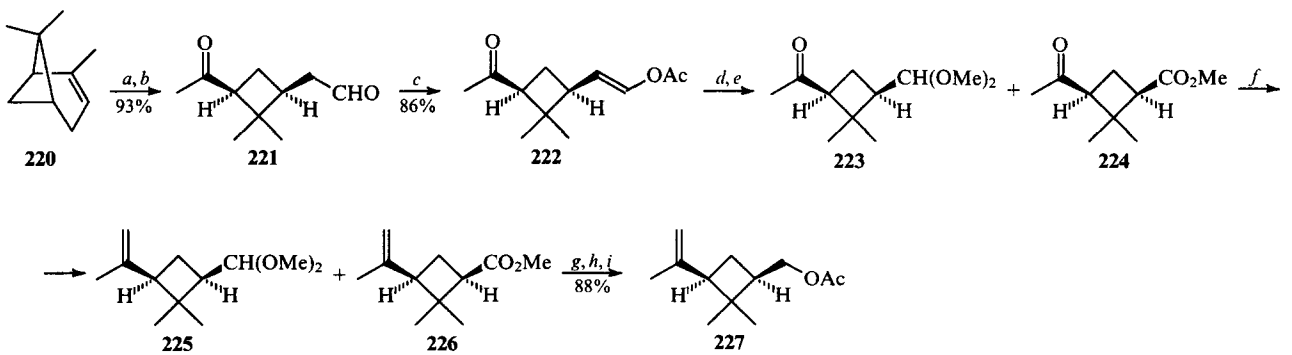
Scheme 2



(*a*) O_3–MeOH; (*b*) Me_2S, TsOH; (*c*) $(MeO)_2CO$, NaH; (*d*) $H_2C{=}CHCH_2Br$; (*e*) KOH–MeOH; (*f*) OsO_4–$NaIO_4$; (*g*) $LiAlH_4$; (*h*) Ac_2O–Py; (*i*) HCl; (*j*) $PhSCH_2CO_2Me$–LDA; (*k*) Ac_2O–AcONa; (*l*) MeONa–MeOH; (*m*) TsCl–DMAP (4-4-dimethylaminopyridine)–Et_3N; (*n*) DHP (dihydropyran)–PPTS; (*o*) $NaN(SiMe_3)_2$; (*p*) PhCOCl–DMAP–Py; (*q*) Dowex 50W (H^+); (*r*) Na–$C_{10}H_8$ (naphthalenesodium); (*s*) PCC–NaOAc; (*t*) $PhSSO_2Ph$–$LiN(SiMe_3)_2$; (*u*) $NaIO_4$; (*v*) $CaCO_3$, 110 °C; (*w*) Bu^tOOH–KH; (*x*) PhSeBr–$LiN(SiMe_3)_2$; (*y*) H_2O_2–Ac_2O–AcONa, K_2CO_3; (*z*) $Me_2S{=}CH_2$.

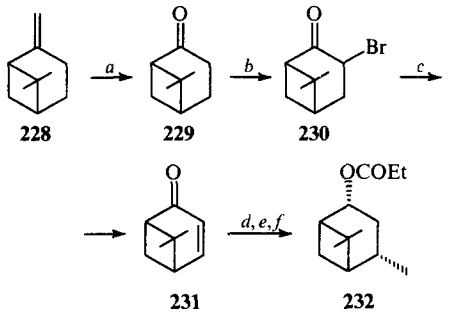
α-phenylsulfanylation afforded the sulfide **213**, which was oxidised to the sulfoxide **214**; the thermal elimination of PhSOH led to the cyclic ketotriene **215**. Its epoxidation by the *tert*-butyl hydroperoxide–base system[130] took place regioselectively with the preferential formation of the epoxide **216**. The latter was oxidised via the phenyl selenide **217** to the diketone **218**, the interaction of which with methylidenedimethyl-λ^4-sulfane took place selectively at one of the keto-groups and led to the target diepoxide **219**.

The readily available (+)-α-pinene **220** served as the initial compound for the synthesis of (+)-*cis*-(1*R*, 3*R*)-1-acetoxymethyl-3-isopropenyl-2,2-dimethylcyclobutane **227** — the sex pheromone of the grape mealybug (*Planococcus citri*).[131] The ozonolysis of compound **220** gives rise to the ketoaldehyde **221** in which the configurations of the asymmetric centres correspond to those of the natural pheromone. The necessary shortening of the side chain was achieved via the enol acetate **222** with its subsequent ozonolysis, which led to a mixture of the acetal **223** and the ester **224**. A mixture of compounds **225** and **226** was obtained by Wittig methylenation and was then converted in three stages into the acetate **227**. The optical isomer of the pheromone was synthesised in accordance with the same scheme from (–)-α-pinene.[132]



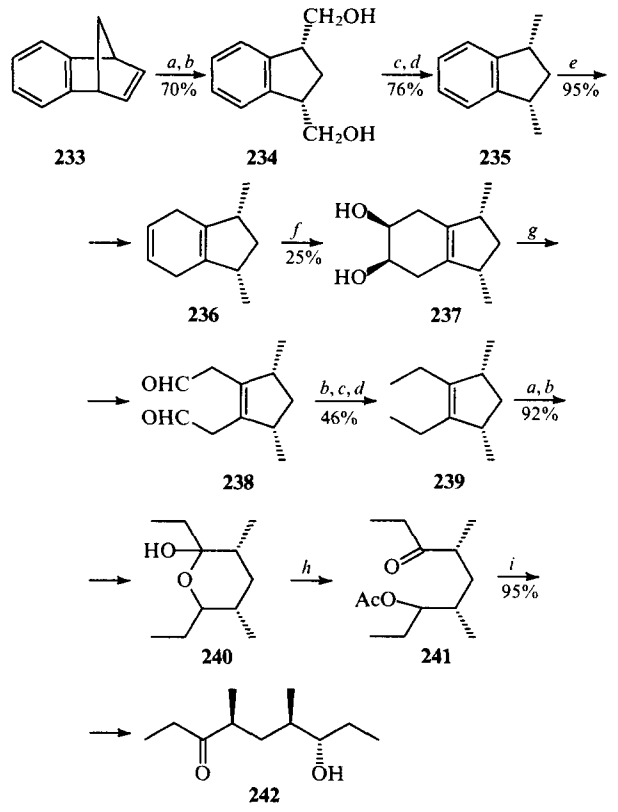
(*a*) O_3–MeOH; (*b*) H_2–Pd–$CaCO_3$–PbO; (*c*) Ac_2O–Et_3N; (*d*) O_3–SiO_2; (*e*) MeOH–TsOH; (*f*) $H_2C{=}PPh_3$; (*g*) PPTS–H_2O; (*h*) DIBALH; (*i*) Ac_2O–Py.

The product of the ozonolysis of β-pinene **228** — nopinone **229** — has found extensive application in the synthesis of insect pheromones.[133–135] For example, it is known that the bicyclic propionate **232** possesses sex pheromone activity for cockroaches. Transformation of ketone **229** gives apoverbenone **231**, converted into the sex pheromone **232** by stereoselective coupled addition of the lithium cuprate reagent and subsequent Meerwein – Ponndorf – Verley reduction of the carbonyl group.[133]



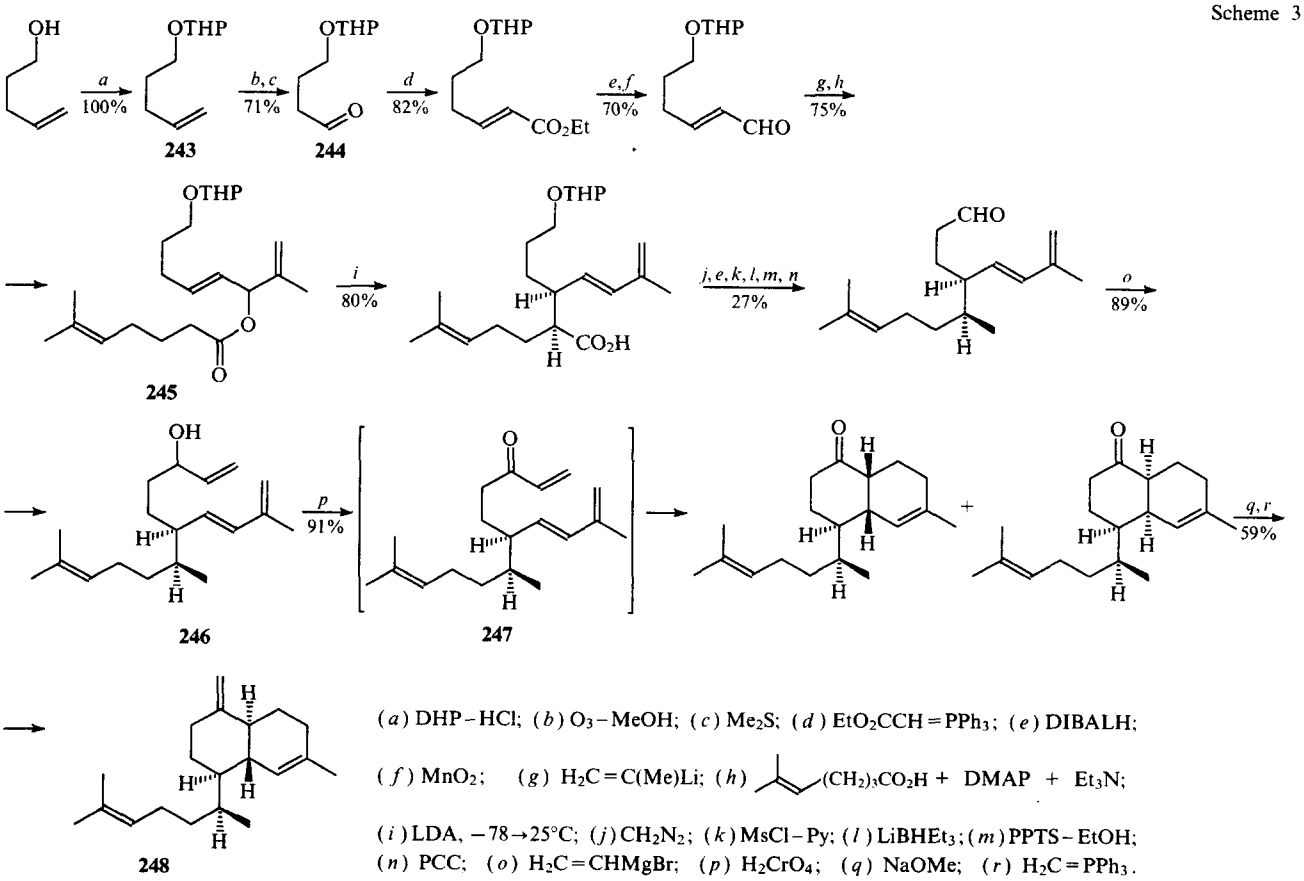
(*a*) O_3–MeOH; (*b*) Br_2; (*c*) DBU {1,8-diazabicyclo[5.4.0]undec-7-ene}; (*d*) Me_2CuLi; (*e*) $(Pr^iO)_3Al$–Pr^iOH; (*f*) $(EtCO)_2O$.

A recently developed approach[136] to the synthesis of (±)-serricornine **242** — the sex pheromone of the tobacco beetle (*Lasioderma serricorne*) — is based on the ozonolysis of benzonorbornadiene **233** to the diol **234**, which is converted via the corresponding methanesulfonate into *cis*-1,3-dimethylindane **235**. Its reduction (via the Birch reaction) gives rise to the diene **236**, the *cis*-hydroxylation of which and subsequent oxidative degradation of the resulting 1,2-diol **237** lead to the dialdehyde **238**. The latter is converted by the reduction–methanesulfonation–reduction procedure into the tetrasubstituted cyclopentene **239**. Repeated ozonolysis of compound **239** leads to the lactol **240**, which is converted into the target ketoalcohol **242** via the ketoacetate **241**.



(*a*) O_3–CH_2Cl_2; (*b*) $NaBH_4$; (*c*) MsCl–Et_3N; (*d*) $LiAlH_4$; (*e*) Li–NH_3– EtOH; (*f*) OsO_4–*N*-methylmorpholine *N*-oxide; (*g*) $Pb(OAc)_4$; (*h*) Ac_2O–DMAP; (*i*) DBU.

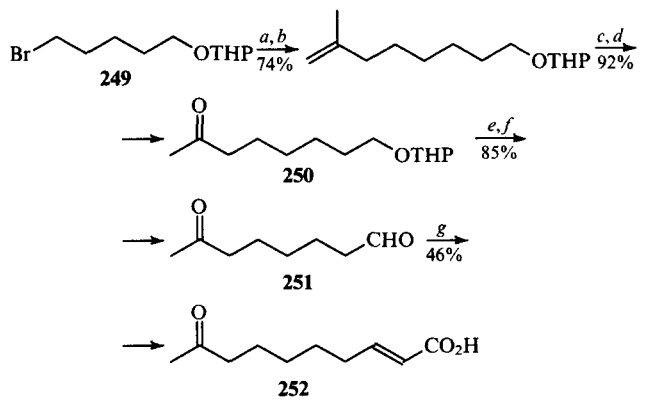
Scheme 3



(*a*) DHP–HCl; (*b*) O_3–MeOH; (*c*) Me_2S; (*d*) $EtO_2CCH{=}PPh_3$; (*e*) DIBALH; (*f*) MnO_2; (*g*) $H_2C{=}C(Me)Li$; (*h*) + DMAP + Et_3N; (*i*) LDA, −78→25°C; (*j*) CH_2N_2; (*k*) MsCl–Py; (*l*) $LiBHEt_3$; (*m*) PPTS–EtOH; (*n*) PCC; (*o*) $H_2C{=}CHMgBr$; (*p*) H_2CrO_4; (*q*) NaOMe; (*r*) $H_2C{=}PPh_3$.

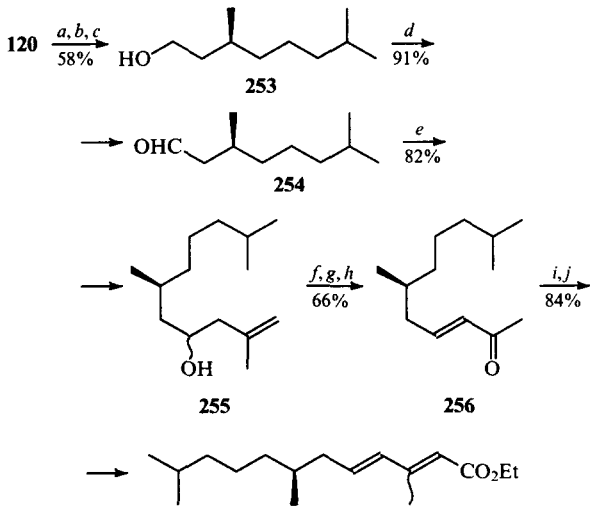
The bicyclic diterpene component of the protective secretion of termites (*Cubitermes umbratus*) (compound **248**) has been synthesised stereoselectively[137] (Scheme 3) from the product of the ozonolysis of the tetrahydropyranyl ether of pent-4-enol **243**. The key stages are the stereoselective Claisen rearrangement of the (*Z*)-enolate of the ether of the 2,8-disubstituted 1,4-dien-3-ol **245** and the spontaneous intramolecular Diels–Alder reaction of the oxidation product of the alcohol **246**.

In the majority of the syntheses of (2*E*)-9-oxodec-2-enoic acid **252** — the 'royal jelly' of honey bees (*Apis mellifera*) — the concluding stage is the condensation of 7-oxooctanal **251** with malonic acid via the Doebner reaction. An effective method has been proposed for the synthesis of the ketoaldehyde **251** on the basis of the coupling of the THP ether of 5-bromopentanol **249** with methylallyl chloride and subsequent ozonolysis of the resulting terminal alkene.[138]



(*a*) Mg; (*b*) $H_2C=C(Me)CH_2Cl$–CuI–2,2′-bipy; (*c*) O_3–MeOH; (*d*) H_2–Pd–$CaCO_3$–PbO; (*e*) TsOH–MeOH–H_2O; (*f*) PCC; (*g*) $H_2C(CO_2H)_2$–Py–piperidine.

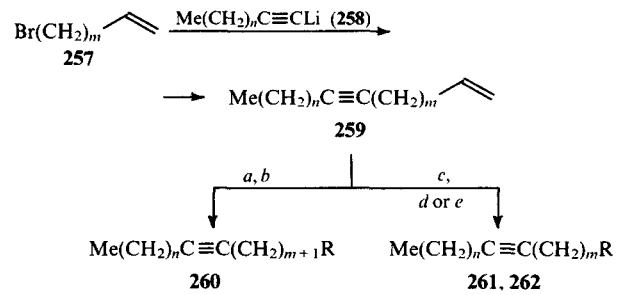
The synthesis of the enantiomerically enriched juvenoid hydroprene.[139] (*S*)-**55** in the form of a 7:3 mixture of the (2*E*,4*E*)- and (2*Z*,4*E*)-stereoisomers has been achieved by the selective transformations of the readily available tetrahydrogeraniol **253** [obtained from (*S*)-dihydromyrcene **120**], involving the ozonolysis of the homoallyl alcohol **255**, in the preparation of the key conjugated enone **256**.



(*a*) Bu^i_3Al; (*b*) O_2; (*c*) H_2–Pd/C; (*d*) PCC; (*e*) $H_2C=C(Me)CH_2MgCl$; (*f*) O_3–CH_2Cl_2–MeOH; (*g*) Me_2S; (*h*) TsOH–Na_2SO_4; (*i*) EtMgBr–$HC\equiv COEt$; (*j*) H_2SO_4.

In the synthesis of Lepidoptera pheromones, which consist as a rule of unsaturated alcohols, acetates, and aldehydes,[35] the so called 'acetylenic' path is usually employed. It consists in the coupling of alkali metal alkynylides with alkyl halides having an oxygen-containing functional group in the ω-position; the subsequent stereoselective reduction of the triple bond affords alkenes with either (*Z*)- or (*E*)-configurations.[34,35]

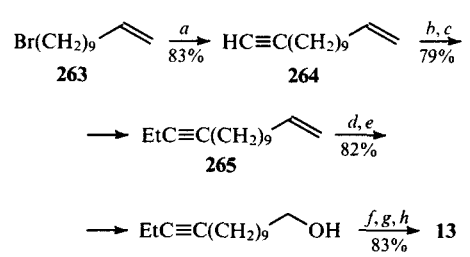
An alternative approach, based on the condensation of lithium alkynylides **258** with ω-bromoalkenes **257** and expanding significantly the synthetic possibilities of the 'acetylenic' path, has been developed recently.[140,141] The terminal double bond in the coupling product **259**, introduced with the aid of the ω-bromoalkene **257**, is smoothly transformed into the required oxygen-containing functional group. This is achieved, for example, by hydration via an organoboron intermediate to the corresponding ethyne alcohol **260** or by ozonolysis with formation (depending on the method of treatment of the peroxide product) of the alkyn-1-ol **261** or the alkynal **262** with a carbon chain shorter by one atom than in the alkenyne precursor **259**.



R = CH_2OH (**260**, **261**), CHO (**262**).

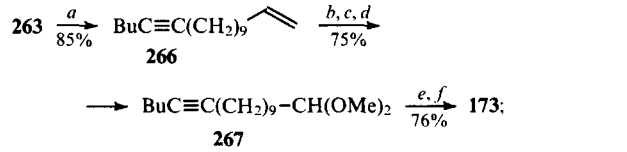
(*a*) BBN; (*b*) H_2O_2–NaOH; (*c*) O_3; (*d*) $NaBH_4$; (*e*) Me_2S.

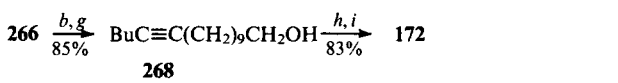
This approach has been used in the synthesis[141] of the sex pheromone **13** of the green oak moth based on the ozonolytic cleavage of the double bond in pentadec-1-en-12-yne **265**, obtained by the ethynylation of undecenyl bromide **263** with subsequent ethylation of the terminal alkenyne **264**.



(*a*) $HC\equiv CLi$; (*b*) $LiNH_2$; (*c*) EtBr; (*d*) O_3–cyclo-C_6H_{12}–MeOH; (*e*) $NaBH_4$; (*f*) BBN; (*g*) AcOH; (*h*) Ac_2O–Py.

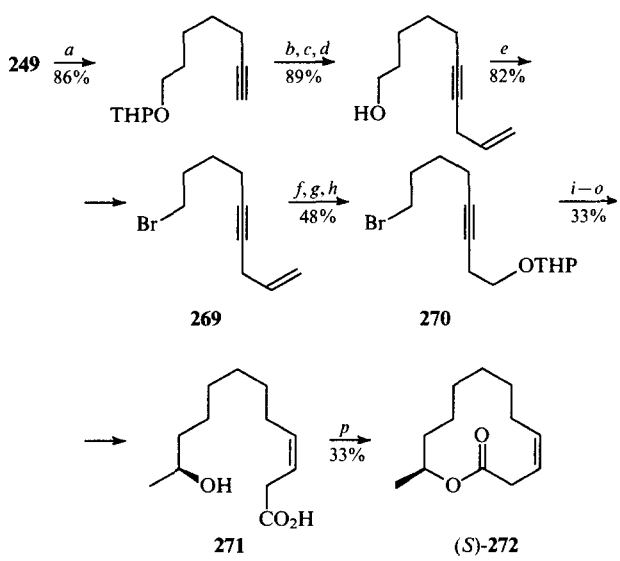
The components of the pheromones of the cabbage moth (*Mamestra brassicae*) and the cotton bollworm (*Heliothis armigera*) (compounds **172** and **173**) have been synthesised[140,141] via heptadec-1-en-12-yne **266**, obtained by the reaction of the bromo-derivative **263** with lithium hex-1-ynylide. The ozonolysis of the enyne **266** led (depending on the reductant employed) either to the alkyne acetal **267** or to the alcohol **268**, which are readily transformable into the target aldehyde **173** or the acetate **172** respectively.





(*a*) $C_4H_9C{\equiv}CLi$; (*b*) O_3–cyclo-C_6H_{12}–MeOH; (*c*) Me_2S; (*d*) MeOH–TsOH; (*e*) H_2–Pd–$CaCO_3$–PbO; (*f*) PPTS–H_2O; (*g*) $NaBH_4$; (*h*) Bu^iMgBr–Cp_2TiCl_2 (Cp = η^5-cyclopentadienyl); (*i*) Ac_2O–Py.

An effective synthesis of the optically pure (*S*)-(3*Z*)-dodec-3-en-11-olide (*S*)-**272** [ferrulactone II — a component of the aggregation pheromone of the rusty grain beetle (*Cryptolestes ferrugineus*)] is based on the macrolactonisation of the acid (*S*)-**271**, obtained by the cross-coupling of the protected bromohydroxy-derivative **270** with the optically active epoxide **273**. The ethyne C_8 block **270** was synthesised by the partial ozonolysis of the 1,4-enynyl bromide **269** — the product of the successive increase in the length of the linear chain of the precursor **249** by reaction with lithium ethynylide and allyl bromide.[142]

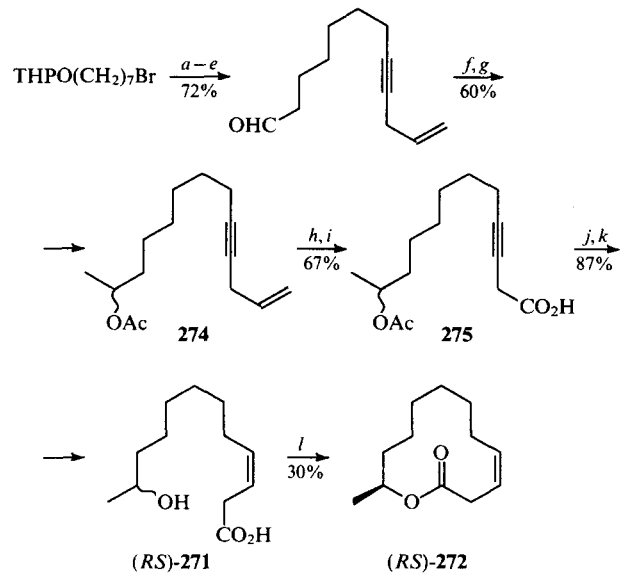


(*a*) HC≡CLi; (*b*) EtMgBr–CuI; (*c*) $H_2C{=}CHCH_2Br$; (*d*) TsOH–MeOH–H_2O; (*e*) $Br_2{\cdot}PPh_3$; (*f*) O_3–cyclo-C_6H_{12}–MeOH; (*g*) $NaBH_4$; (*h*) DHP–TsOH; (*i*) Mg, CuBr–Me_2S; (*j*)  (**273**); (*k*) Ac_2O–Py–DMAP; (*l*) PPTS–EtOH; (*m*) H_2CrO_4; (*n*) K_2CO_3–MeOH; (*o*) H_2–P2-Ni ($NaBH_4$-reduced nickel with ethylenediamine); (*p*) BPDS (2,2′-bipyridyl disulfide)–PPh_3–$AgClO_4$.

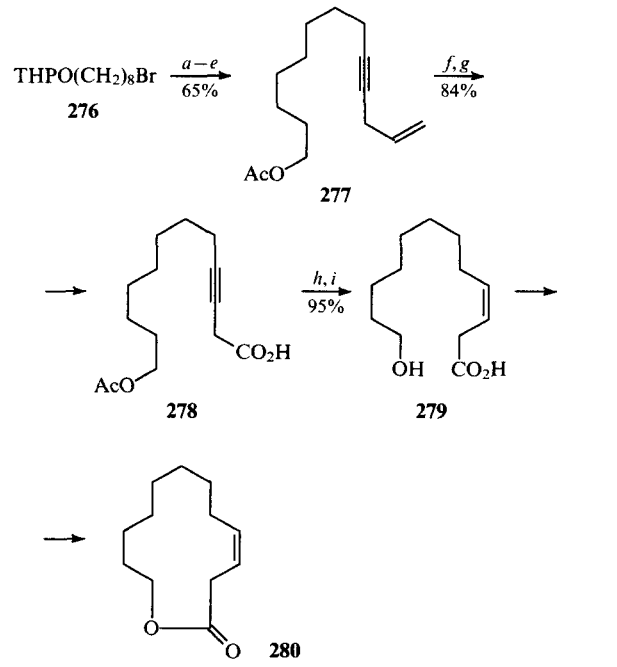
Since the racemic ferrulactone II (*RS*)-**272** is also biologically active, its synthesis is likewise of practical value. A new synthesis has been proposed[143,144] for the acyclic precursor (*RS*)-**271** of the pheromone, in which the acetoxyenyne **274** is used in one of the key stages of the selective ozonolysis. The ozonolysis involves exclusively the double bond and leads (after the oxidation of the peroxide product by the Jones reagent) to the ethyne acetoxyacid **275**, which is converted into the target macrolide (*RS*)-**272** by a standard method.

(3*Z*)-12-Hydroxydodec-3-enoic acid **279** — the acyclic precursor of (3*Z*)-dodec-3-en-12-olide **280** [a component of the aggregation pheromone of the flat grain beetle (*Cryprolestes pusillis)*] has been synthesised, by means of analogous transformations but in a smaller number of stages, from the THP ether of 8-bromooctan-1-ol **276**.

A method proposed for the synthesis of the stereoisomeric components of the sex pheromone of the southern green stink bug (*Nezara viridula*) (compounds **288** and **289**) is based on the

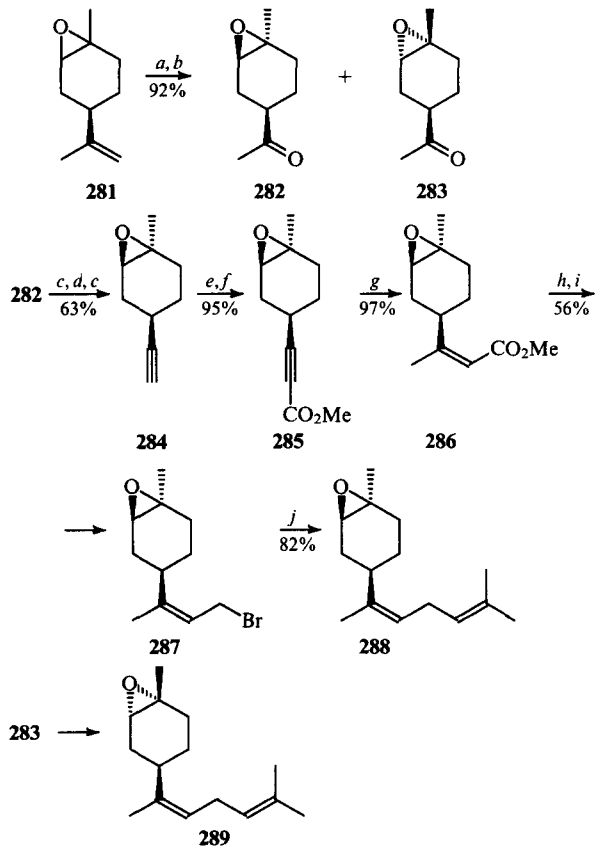


(*a*) HC≡CLi; (*b*) EtMgBr–CuI; (*c*) $H_2C{=}CHCH_2Br$; (*d*) TsOH–MeOH–H_2O; (*e*) PCC; (*f*) MeMgI; (*g*) Ac_2O; (*h*) O_3–cyclo-C_6H_{12}–MeOH; (*i*) H_2CrO_4; (*j*) K_2CO_3–MeOH; (*k*) H_2–P2-Ni; (*l*) DDS–PPh_3–$AgClO_4$.



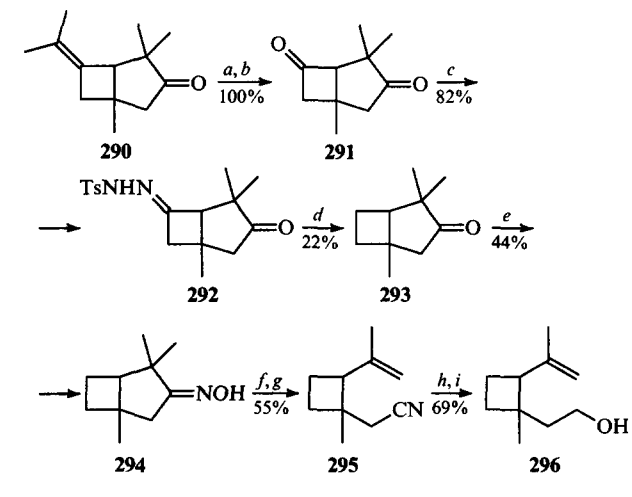
(*a*) HC≡CLi; (*b*) EtMgBr–CuI; (*c*) $H_2C{=}CHCH_2Br$; (*d*) TsOH–MeOH–H_2O; (*e*) Ac_2O–Py; (*f*) O_3–cyclo-C_6H_{12}–AcOH; (*g*) H_2CrO_4; (*h*) K_2CO_3–MeOH; (*i*) H_2–P2-Ni.

ozonolysis of (*R*)-(+)-limonene oxide **281**, which is available as an equimolar mixture of the α- and β-epoxides. The product of the reduction of the ozonide is the corresponding mixture of the ketones **282** and **283**, which was separated chromatographically. In order to obtain the component **288**, the diastereoisomer **282** was converted via the corresponding vinyl phosphate into the terminal ethyne **284** and further into the ester **285**. The regio- and stereo-specific coupled addition of dimethyllithium cuprate led to the (*Z*)-alkene **286**, which was converted into the bromide **287** via the corresponding alcohol. The target *endo*-epoxide **288** was obtained in the concluding stage — the condensation of the bromide **287** with 1-lithio-2-methylpropene. The component **289** has been synthesised similarly from the diastereoisomer **283**.[145]



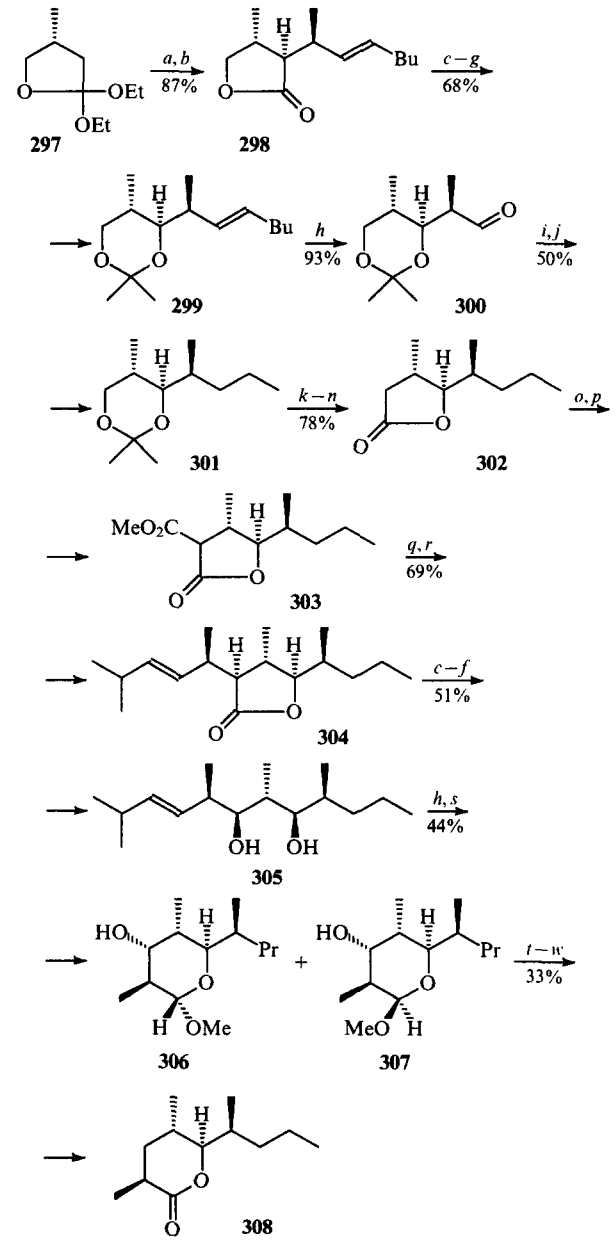
(*a*) O_3; (*b*) PPh_3; (*c*) LDA; (*d*) $(EtO)_2P(O)Cl$; (*e*) BuLi; (*f*) $ClCO_2Me$; (*g*) Me_2CuLi; (*h*) DIBALH; (*i*) CBr_4-PPh_3; (*j*) $Me_2C=CHBr-Bu^tLi$.

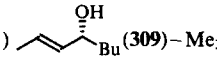
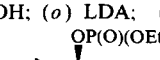
The synthesis of 1,4,4-trimethylbicyclo[3.2.0]heptan-3-one **293** — a key intermediate[146] in the synthesis of grandisol **296** [a component of the sex pheromone of the cotton-boll weevil (*Anthonomus grandis*)] — was based on the ozonolysis of the bicyclic compound **290**, which was converted quantitatively into the diketone **291** with subsequent selective reduction of one of the carbonyl groups via the corresponding tosylhydrazone **292**. The bicyclic ketone **293** was subsequently converted into the oxime **294**, in the tosylate of which regioselective fragmentation occurred on deprotonation of one of the methyl groups with the opening of the five-membered ring and the formation of the unsaturated nitrile **295**.[147] Two-stage reduction (via an intermediate aldehyde) completed the synthesis of grandisol **296**.



(*a*) $O_3-MeOH-CH_2Cl_2$; (*b*) Me_2S; (*c*) $TsNHNH_2$; (*d*) $NaBH_4$; (*e*) $H_2NOH\cdot HCl$, KOH; (*f*) TsCl–2,6-lutidine; (*g*) Py–5% NaOH; (*h*) DIBALH; (*i*) $LiAlH_4$.

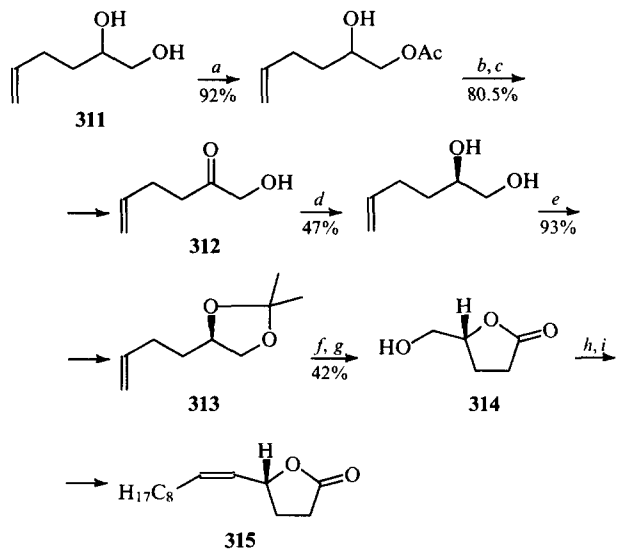
In the synthesis of (+)-invictolide **308** — the optical isomer of the pheromone of the fire ant (*Solenopsis invicta*) [developed on the basis of (*R*)-3-methyl-γ-butyrolactone], the ozonisation was effectively used in three stages.[148] In the first of these, the unsaturated ketal **299** was ozonolysed. Compound **299** was obtained from the diethylortholactone **297** by transesterification with the alcohol **309**, the Claisen rearrangement, epimerisation, the Baeyer–Villiger oxidation of the lactone **298**, and protection of the diol. The ozonolysis product — the aldehyde **300** — was converted into the unsaturated ketal **301** via alkene formation and hydrogenation stages and then into the lactone **302**. The latter was converted into the methoxycarbonyl derivative **303** and was



(*a*)  (**309**)–Me_3CCO_2H; (*b*) Bu^tOK-Bu^tOH; (*c*) MeLi; (*d*) H_2O_2-AcOH; (*e*) $Ac_2O-DMAP-Et_3N$; (*f*) KOH–MeOH; (*g*) $Me_2C(OMe)_2-TsOH$; (*h*) O_3-MeOH, Me_2S; (*i*) $MeCH=PPh_3$; (*j*) H_2–Ra-Ni; (*k*) HCl; (*l*) TsCl–Py; (*m*) NaCN; (*n*) HCl–MeOH; (*o*) LDA; (*p*) $NCCO_2Me$; (*q*) $NaH-Pd(PPh_3)_4-PPh_3$,  (**310**); (*r*) LiCl–DMSO–H_2O; (*s*) $HC(OMe)_3-TsOH$; (*t*) BuLi–PhOSCl; (*u*) Bu_3SnH–AIBN (azobisisobutyronitrile); (*v*) O_3–EtOAc; (*w*) $TsOH-CH_2Cl_2$.

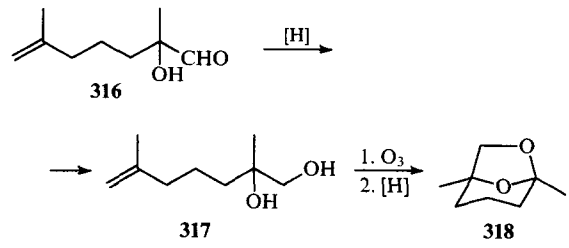
alkylated by the allyl phosphate **310** with subsequent demethoxycarbonylation; this led to the unsaturated lactone **304**, which was oxidised, by a procedure similar to that used for the oxidation of compound **298**, to the diol **305**. Its ozonisation, followed by treatment of the peroxide product with dimethyl sulfate and methyl orthoformate, led to a mixture of the axial (compound **306**) and equatorial (compound **307**) cyclic methoxyacetals, the last of which was oxidised by ozone to the target invictolide **308** after deoxygenation.

An effective procedure has been proposed for the preparation of the key hydroxylactone **314** in the synthesis of the sex pheromone **315** of the Japanese beetle (*Popilia japonica*).[149] It is based on the ozonolysis of the monoene acetal **313**, obtained by enzymic reaction involving the regio-specific acylation of the vicinal diol **311** and the enantioselective reduction of the intermediate ketoalcohol **312**.

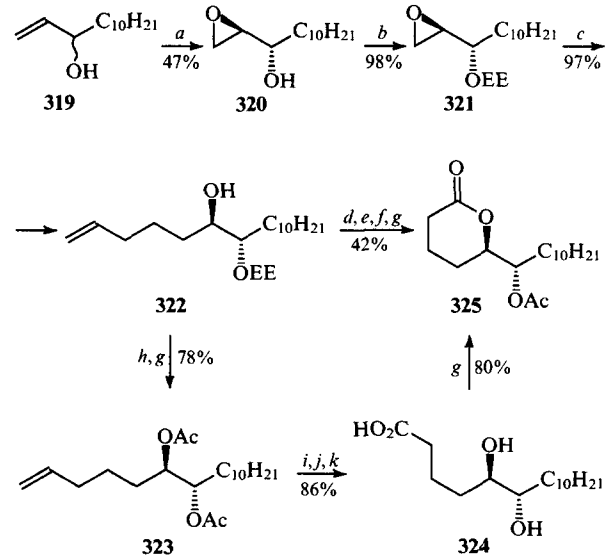


(*a*) Ac_2O–PPL (pig pancreas lipase); (*b*) H_2CrO_4; (*c*) NaOH; (*d*) Baker's yeast; (*e*) $H_2C{=}C(Me)OMe{-}H^+$; (*f*) O_3, Me_2S; (*g*) $Ag_2O{-}OH^-$; (*h*) PCC; (*i*) $C_8H_{17}CH{=}PPh_3$.

Frontaline **318** — the aggregation pheromone of insects of the genus *Dendroctonus* — has been synthesised by ozonising the unsaturated vicinal diol **317** (readily obtainable from the aldehydoalcohol **316**) with subsequent reduction of the peroxide ozonolysis product accompanied by cyclisation.[150]

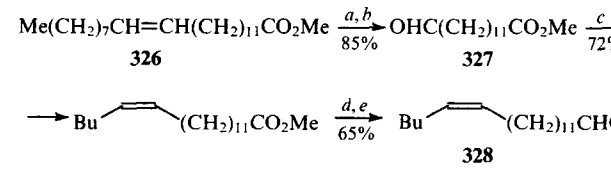


(2*R*,3*S*)-(+)-1,2-Epoxytridecan-3-ol **320** has been obtained by a modified reaction involving the enantioselective epoxidation of tridec-1-en-3-ol **319**. A short path to the conversion of compound **320** into the main component of the egg-laying pheromone **325** of the mosquito *Culex pipiens* has been found. The key stage of this transformation is the ozonolysis of compound **322** — the product of the coupling of the epoxyether **321** with but-3-en-1-ylmagnesium bromide, which proceeds with complete retention of the configuration of the asymmetric centres. The pheromone **325** and its optical isomer have also been synthesised by the ozonolysis of the diacetate **323**.[151–153]



(*a*) $Ti(OPr^i)_4$–(+)-DET (diethyl tartrate)–Bu^tOOH; (*b*) $H_2C{=}CHOEt$–TsOH; (*c*) $H_2C{=}CH(CH_2)_2MgBr$–CuBr; (*d*) O_3–AcOH; (*e*) H_2O_2–SeO_2–Ac_2O; (*f*) TsOH–PhH; (*g*) Ac_2O–Py; (*h*) HCl; (*i*) O_3–MeOH; (*j*) H_2O_2–HCO_2H; (*k*) K_2CO_3.

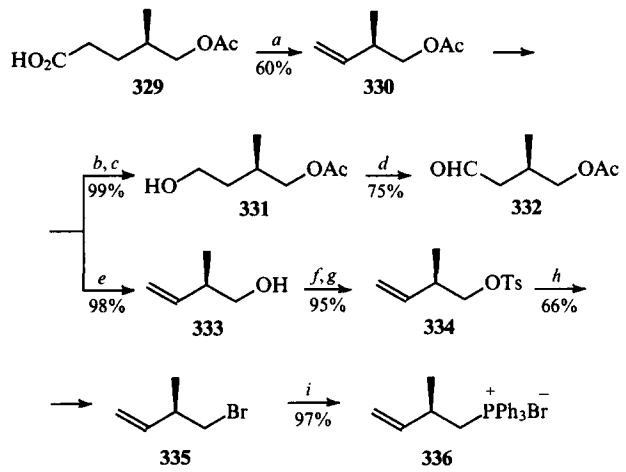
A convenient procedure for the preparation of α,ω-bifunctional reagents used in the synthesis of insect pheromones involves the ozonolysis of derivatives of higher monounsaturated carboxylic acids, for example, oleic and undecenoic.[154–158] Thus, methyl 12-formyldodecanoate **327**, which is necessary for the construction of the carbon skeleton of (*Z*)-octadec-13-enal **328** [a component of the pheromone of the Asiatic rice borer (*Chilo suppressalis*)], has been synthesised by the ozonolysis of the methyl ester of brassidic (or erucic) acid **326**.[154]



(*a*) O_3–CH_2Cl_2; (*b*) PPh_3; (*c*) $BuCH{=}PPh_3$; (*d*) $LiAlH_4$; (*e*) PCC.

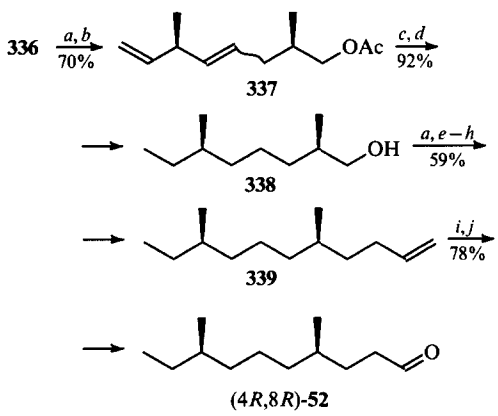
(*R*)-(+)-5-Acetoxy-4-methylpentanoic acid, isolated from the products of the oxidative degradation of the side chain of the (25*R*)-series sapogenins in the manufacture of steroid medicinal preparations, provides extensive possibilities for the synthesis of optically pure chiral pheromones.[159] This bifunctional chiral block has been used to synthesise pheromones with one or several asymmetric carbon atoms. Thus, (*R*)-2-methylbut-3-en-1-yl acetate **330** (the product of the oxidative decarboxylation of the acid **329**) and (*S*)-2-methylbutan-1-ol **340** (a readily available product of the fermentation of sugar) served as a basis[160] for the synthesis of two optically pure stereoisomers of 4,8-dimethyldecanal **52**.

The synthesis of the (4*R*,8*R*)-stereoisomer **52** includes[160] the independent syntheses of the acetoxyaldehyde **332** and the phosphonium salt **336**. The aldehyde **332** was obtained from the alkene **330** via the acetoxyalcohol **331**. The alkene has also been used in the synthesis of the bromo-derivative **335** via the intermediate alcohol **333** and the tosylate **334**. The bromo-derivative **335** was converted into compound **336** by a high-pressure method.



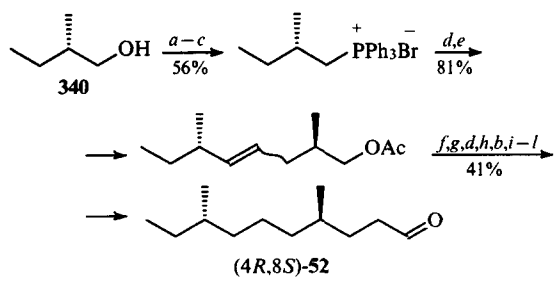
(*a*) $Pb(OAc)_4$, $Cu(OAc)_2 \cdot H_2O$; (*b*) BBN; (*c*) H_2O_2–AcONa; (*d*) PCC; (*e*) KOH; (*f*) BuLi; (*g*) TsCl; (*h*) NaBr; (*i*) PPh_3, 14 kbar.

The Wittig coupling of the aldehyde **332** to the ylide generated from the salt **336** led to the dienyl acetate **337**, which was converted in two stages into the alcohol **338** and further, via the corresponding bromo-derivative, into the alkene **339**. The latter was transformed into the pheromone (4*R*,8*R*)-**52** by ozonisation.



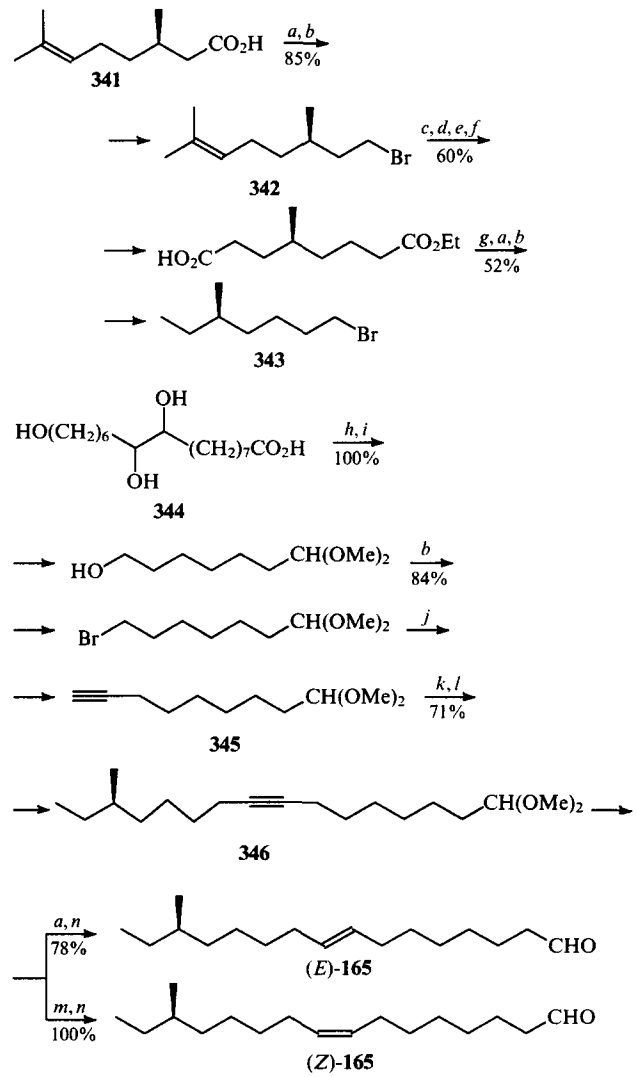
(*a*) BuLi; (*b*) **332**; (*c*) H_2–Pd/C; (*d*) KOH; (*e*) TsCl; (*f*) NaBr; (*g*) Mg; (*h*) $H_2C{=}CHCH_2Br$; (*i*) O_3–CH_2Cl_2; (*j*) Me_2S.

The (4*R*,8*S*)-stereoisomer of compound **52** was synthesised by a procedure in which the chiral alcohol **340** was used in the construction of the (8*S*)-asymmetric centre and this synthesis does not differ fundamentally from that described above.[160]



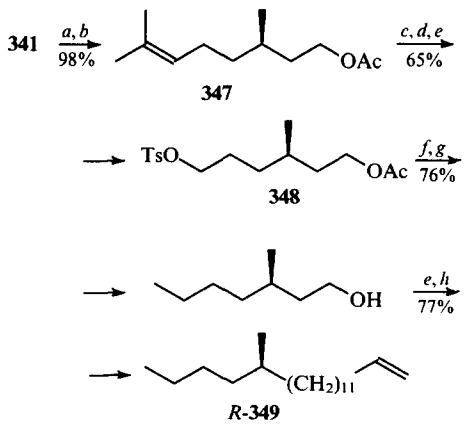
(*a*) Ts–Py; (*b*) NaBr; (*c*) PPh_3; (*d*) BuLi; (*e*) **332**; (*f*) H_2–Pd/C; (*g*) KOH; (*h*) TsCl; (*i*) Mg; (*j*) $H_2C{=}CHCH_2Br$; Me_2S.

(*R*)-(+)-Citronellic acid **341**, obtained by the acid cleavage of the readily available (*R*)-(+)-pulegone, has found extensive application as an optically active unit.[161] (*R*)-5-Methylhept-1-yl bromide **343** has been used as the chiral block in the syntheses of the (*R*)-trogodermals with the (*Z*)- or (*E*)-configuration of the double bond [compound (*Z*)-**165** or (*E*)-**165**]. Compound **343** was obtained by converting the acid **341** in two stages into (*R*)-citronellyl bromide **342**, the subsequent transformations of which included stages involving malonic ester synthesis and ozonolysis with oxidative cleavage of the ozonide. The achiral unit **345** was obtained by the oxidative cleavage of aleuritic acid **344**. Its subsequent alkylation by the bromo-derivative **343** with the (*R*)-configuration afforded the ethyne precursor of the target pheromone **346**.[162,163]



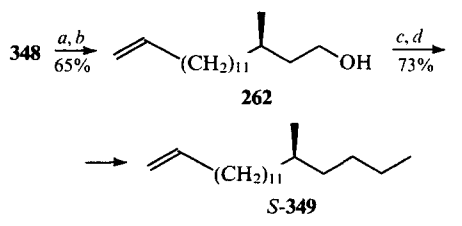
(*a*) $LiAlH_4$; (*b*) Br_2–PPh_3; (*c*) $NaCH(CO_2Et)_2$; (*d*) LiCl–H_2O; (*e*) O_3–MeOH; (*f*) H_2CrO_4; (*g*) $AgNO_3$–$K_2S_2O_8$; (*i*) MeOH–HCl; (*j*) HC≡CNa; (*k*) BuLi; (*l*) **343**; (*m*) H_2–P2-Ni; (*n*) PPTS–H_2O.

The bifunctional nature of (*R*)-citronellic acid **341** made it possible to synthesise from the latter both optical isomers of 14-methyloctadec-1-ene **349** — the sex pheromone of the peach mining moth (*Lyonetia clerckella*).[164] In the synthesis of the (*R*)-enantiomer of compound **349**, citronellyl acetate **347** was converted, after ozonolysis, into the α,ω-acetoxytosylate **348**, the subsequent alkylation of which with dimethyl- and di(undec-10-enyl)-lithium cuprates completed the synthesis of the target pheromone.



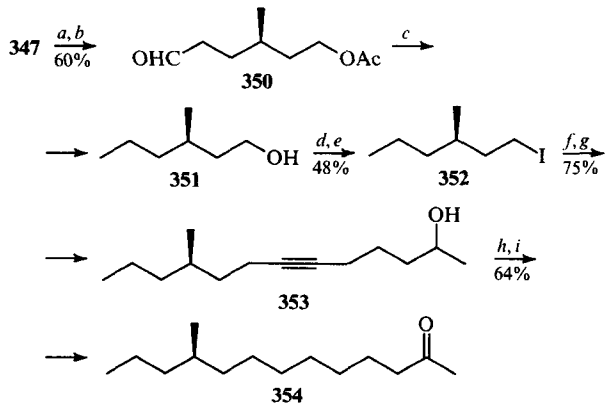
(*a*) $LiAlH_4$; (*b*) Ac_2O–Py; (*c*) O_3–MeOH–CH_2Cl_2; (*d*) $NaBH_4$; (*e*) TsCl–Py; (*f*) Me_2CuLi; (*g*) NaOH; (*h*) $[H_2C{=}CH(CH_2)_9]_2CuLi$.

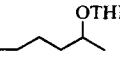
In order to obtain the (*S*)-optical isomer (*S*)-**349**, the intermediate acetoxytosylate **348** was alkylated in the reverse order. i.e. the alkene component of the target molecule was constructed initially.



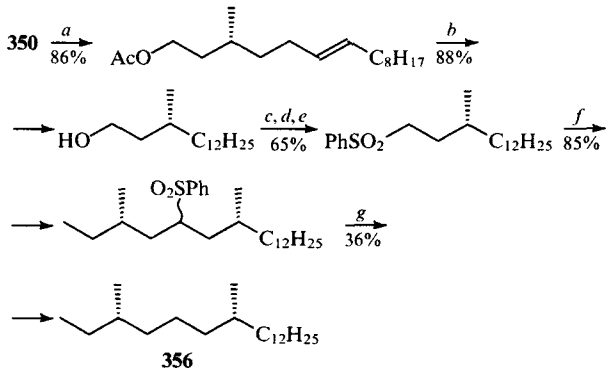
(*a*) $[H_2C{=}CH(CH_2)_8]_2CuLi$; (*b*) NaOH; (*c*) TsCl–Py; (*d*) Et_2CuLi.

10-Methyltridecan-2-one **354**—the optically active pheromone of the spotted cucumber beetle (*Diabrotica undecimpunctata*) with the (*R*)-configuration—has been synthesised from citronellyl acetate **347**, the ozonolytic cleavage of which afforded the acetoxyaldehyde **350**. The Kishner reduction of the latter led to (*R*)-3-methylhexan-1-ol **351**, which was converted into the iodide **352** and the alkynol **353** was obtained by coupling with the ethynylide **355**. Hydrogenation and oxidation of compound **353** led to the target pheromone.[165]



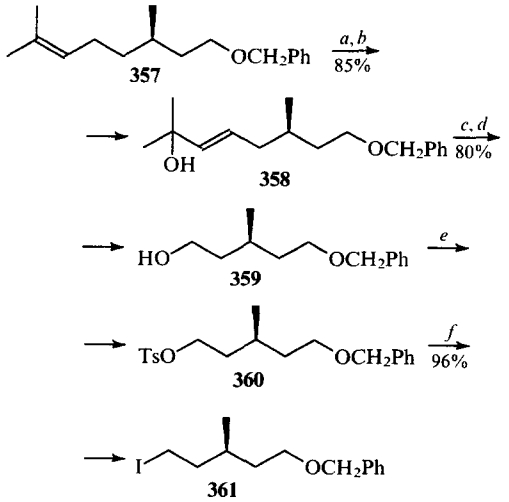
(*a*) O_3–MeOH–CH_2Cl_2; (*b*) Me_2S; (*c*) $N_2H_4 \cdot H_2O$–KOH; (*d*) TsCl–Py; (*e*) NaI; (*f*)  (**355**); (*g*) TsOH–MeOH; (*h*) H_2–Pd/C; (*i*) H_2CrO_4.

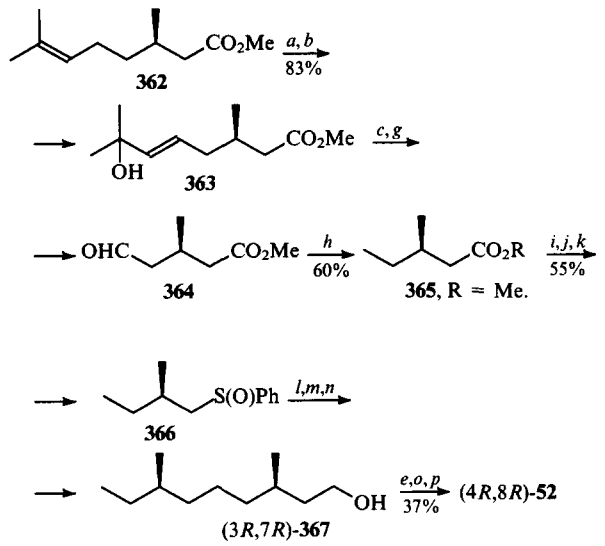
The chiral acetoxyaldehyde **350** has found an application in the synthesis of the sex pheromone **356** of the alfalfa blotch leafminer (*Agromyza frontella Rondarni*) in the construction of the (7*R*)-asymmetric centre.[166]



(*a*) $H_{17}C_8CH{=}PPh_3$; (*b*) $LiAlH_4$–$CoCl_2$; (*c*) TsCl–Py; (*d*) PhSNa; (*e*) MCPBA; (*f*) BuLi,  ; (*g*) Na–Hg–EtOH.

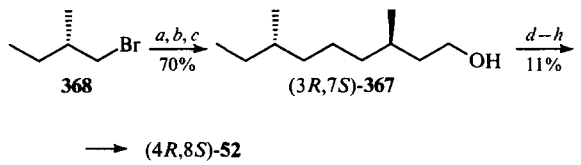
All four stereoisomers of 4,8-dimethyldecanal **52** have been synthesised from the acid **341**.[167] In the synthesis of (4*R*,8*R*)-**52** and (4*R*,8*S*)-**52**, the initial benzyl ether of citronellol **357** was oxidised to the allyl alcohol **358**, the ozonolysis of which (after reductive treatment) afforded the alcohol **359**. Its tosylate **360** and iodide **361** were used to construct the (4*R*)-asymmetric centre in the molecule of compound **52**. The sulfoxide **366**, obtained from the allyl alcohol **363** [the product of the oxidation of (*R*)-methyl citronellate **362**], was used to form the (8*R*)-centre. The ozonolysis of compound **363** yielded the aldehydoester **364**, which was subjected to the Huang-Minlon reduction to the acid **365**. The latter was converted in three stages into the sulfoxide **366**. Its coupling with the iodide **361** and subsequent hydrogenolysis led to the alcohol (3*R*,7*R*)-**367**, the increase in the chain length of which to give the target aldehyde (*R*,*R*)-**52** was carried out via the intermediate nitrile.





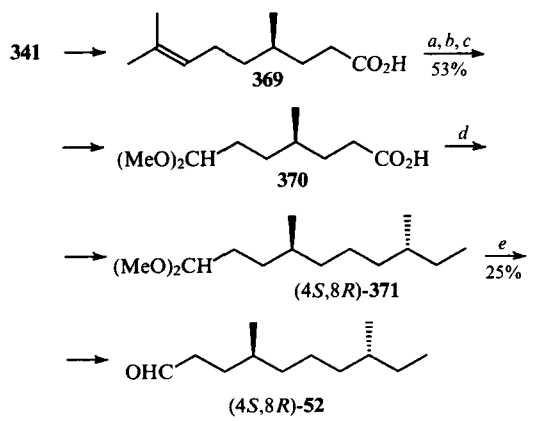
(*a*) $Ph_2Se_2-H_2O_2$; (*b*) Bu^tOOH; (*c*) $O_3-CH_2Cl_2-MeOH-NaHCO_3$; (*d*) $NaBH_4$; (*e*) TsCl–Py; (*f*) NaI; (*g*) Me_2S; (*h*) $N_2H_4 \cdot H_2O-KOH$; (*i*) $Pb(OAc)_4-I_2$; (*j*) PhSNa; (*k*) MCPBA; (*l*) BuLi; (*m*) **361**; (*n*) $Li-EtNH_2$; (*o*) NaCN; (*p*) DIBALH.

The (8*S*)-centre in the (4*R*,8*S*)-stereoisomer of compound **52** was constructed with the aid of the readily available (*S*)-2-methylbutyl bromide **368**, the coupling of which with the tosylate **360** led to the alcohol (3*R*,7*S*)-**367**. It was converted into the pheromone with the (4*R*,8*S*)-configuration via the corresponding nitrile.[167]



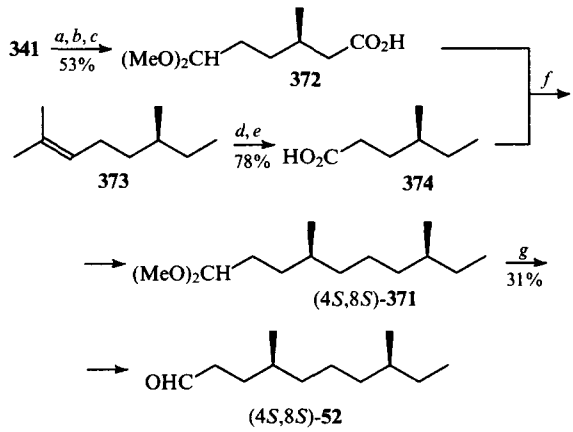
(*a*) Mg; (*b*) **360**–Li_2CuCl_4; (*c*) H_2–Pd/C; (*d*) TsCl–Py; (*e*) NaCN; (*f*) NaOH; (*g*) $LiAlH_4$; (*h*) PCC.

In the synthesis of the (4*S*,8*R*)-isomer, the chiral units for the construction of the skeleton of the sex pheromone were the acids **365** (R = H) and **370**. The latter was obtained by the ozonolysis of homocitronellic acid **369**. The Kolbe condensation of the acid correspondimg to **365** and **370** led to the acetal (4*S*,8*R*)-**371**, the hydrolysis of which afforded the aldehyde **52** with the (4*S*,8*R*)-configuration.[168]



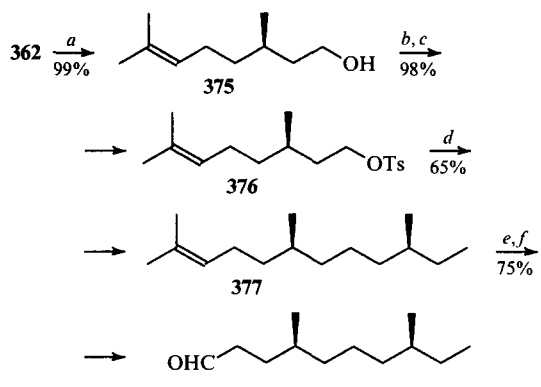
(*a*) O_3–MeOH; (*b*) Me_2S; (*c*) TsOH–MeOH; (*d*) NaOMe–MeOH, **365** (R = H) + e^- (Pt, 24 V, 0.8–1.2 A); (*e*) $HClO_4$.

The (*S*,*S*)-isomer of the pheromone **52** was synthesised in accordance with the same principle. The chiral units were the acids **372** and **374**, obtained by the ozonolysis of citronellic acid **341** and tetrahydromyrcene **373** respectively. The acetal (4*S*,8*S*)-**371**, obtained in the electrolysis of an equimolar mixture of the acids **372** and **374**, was readily converted into the target aldehyde (4*S*,8*S*)-**52**.



(*a*) O_3–MeOH; (*b*) Me_2S; (*c*) TsOH–MeOH; (*d*) O_3-Me_2CO; (*e*) H_2CrO_4; (*f*) NaOMe–MeOH, e^- (Pt, 24 V, 1.5 A); (*g*) 35% $HClO_4$–THF.

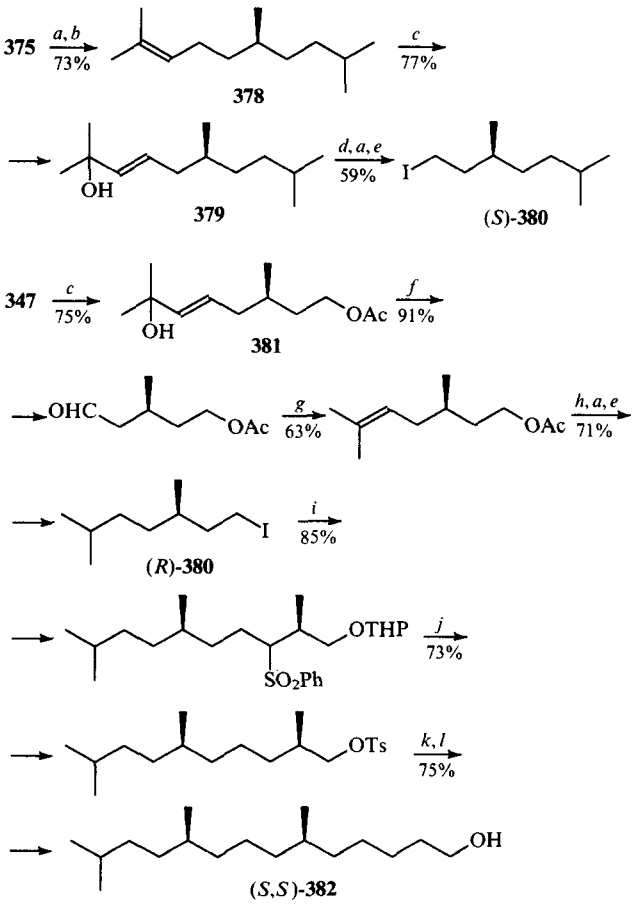
Yet another short path to the synthesis[169] of the enantiomerically pure (4*S*,8*S*)-dimethyldecanal involves the use of readily available chiral units—(*R*)-methyl citronellate **362** and (*S*)-2-methylbutan-1-ol **340**. The former reagent was converted in two stages, via the intermediate (*R*)-citronellol **375**, into the tosylate **376**, while the latter was converted into the bromide **368**, the Wurtz cross-coupling of these precursors afforded 2,6,10-trimethyldodec-2-ene **377**, which was converted by ozonolysis into the aldehyde **52** with the (4*S*,8*S*)-configuration.



(*a*) DIBALH; (*b*) BuLi; (*c*) TsCl; (*d*) **368** + Mg–Li_2CuCl_4; (*e*) O_3–MeOH–CH_2Cl_2; (*f*) Me_2S.

The phenyl sulfone (*S*)-**383** and the iodide **380** with the (*R*)- and (*S*)-configurations were used as the chiral building blocks in the syntheses of all four stereoisomers of 6,10,13-trimethyltetradecan-1-ol **382**—the aggregation pheromone of the predatory stink bug (*Stiretrus anchorago*).[170] [The reactions leading to (6*S*,10*S*)-**382** are shown in the scheme below.]

The carbon skeleton of (*S*)-**380** was constructed by converting (*R*)-citronellol **375** into 2,6,9-trimethyldec-2-ene **378**, its allylic oxidation (with rearrangement), and the subsequent ozonolysis of the product **379**. The iodide **380** with the (*R*)-configuration was synthesised by the ozonolytic cleavage of the allyl alcohol **381**, which can be readily obtained from citronellyl acetate **347** by the method described by Hori and Sharpless.[168]

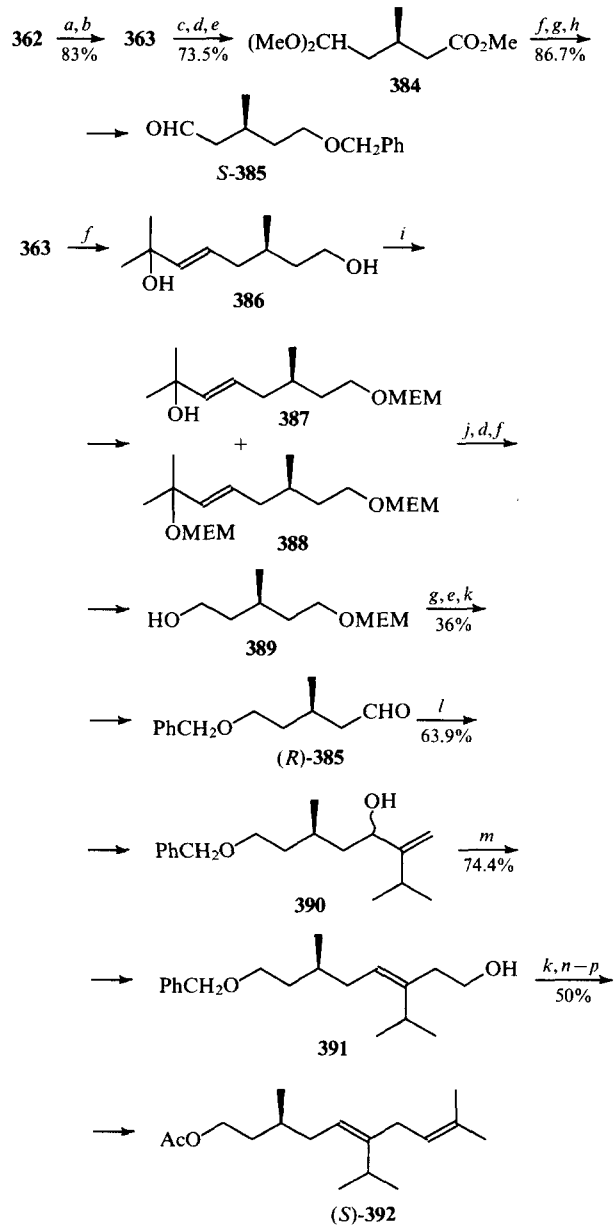


(*a*) TsCl–Py; (*b*) $Me_2CHMgBr-Li_2CuCl_4$; (*c*) $Ph_2Se_2-H_2O_2$, Bu^tOOH; (*d*) O_3, $NaBH_4$; (*e*) NaI; (*f*) O_3, Me_2S; (*g*) $Me_2C=PPh_3$; (*h*) $LiAlH_4-CoCl_2$;

(*i*) THPO–(C)–SO_2Ph [(*S*)-**383**]–BuLi; (*j*) Na–Hg–EtOH; (*k*) $Cl(CH_2)_4OTHP-Mg-Li_2CuCl_4$; (*l*) TsOH–MeOH.

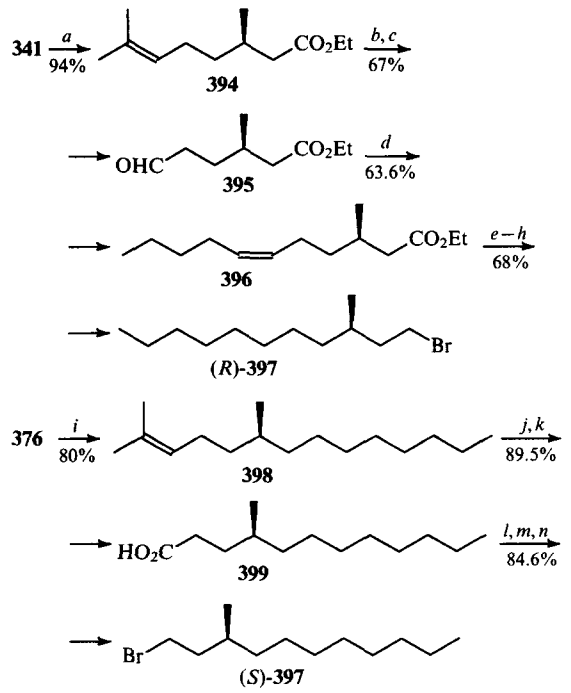
The allyl alcohol **363** — the product of the allylic oxidation of (*R*)-methyl citronellate **362** by a diselenide — has been used to synthesise the (*R*)- and (*S*)-enantiomers of (5*E*)-6-isopropyl-3,9-dimethyldeca-5,8-dienyl acetate **392** — the sex pheromone of the yellow scale (*Aonidiella citrina*).[171] The (3*R*)-centre in the molecule of compound **392** was formed by the conversion of the allyl alcohol **363**, by ozonolysis with reductive cleavage of the ozonide, into the dimethyl acetal **384**, which was converted by means of standard procedures into the key aldehydoester (*S*)-**385**. The optical isomer of the latter — the aldehyde (*R*)-**385** — was obtained from the same allyl alcohol **363** by its transformation via the diol **386** into a mixture of the mono- and di-esters **387** and **388**, the ozonolysis of which and two-stage reduction afforded the monosubstituted diol **389**. The latter was converted via its benzyl ether into the other key aldehydoester (*R*)-**385**. The further transformations of the aldehydes† (*S*)-**385** and (*R*)-**385** included stages involving interaction with the Grignard reagent derived from 2-bromo-3-methylbut-1-ene **393** and the 2,3-sigmatropic rearrangement of the resulting allyl alcohols **390** via their stannyl derivatives to the (*E*)-homoallyl alcohols **391**. The latter were oxidised to the corresponding aldehyde and were converted into the target (*S*)- or (*R*)-**392** by means of the Wittig alkene formation reaction.

† The scheme below indicates the reaction leading to the biologically active (*S*)-enantiomer of compound **392**.



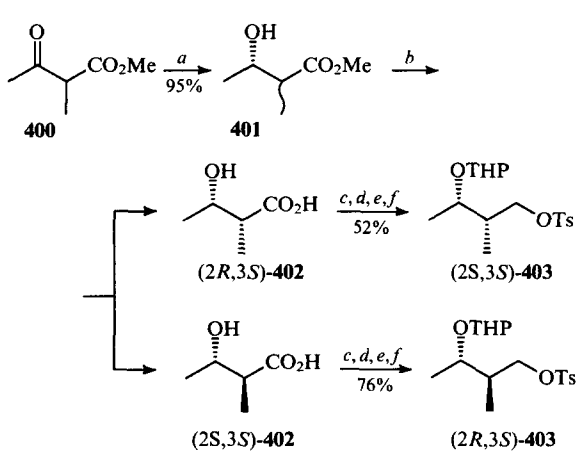
(*a*) $Ph_2Se_2-H_2O_2$; (*b*) Bu^tOOH; (*c*) O_3–MeOH; (*d*) Me_2S; (*e*) TsOH–MeOH; (*f*) $LiAlH_4$; (*g*) $PhCH_2Br-NaH$; (*h*) $HClO_4$; (*i*) NaH–MEMCl ($MeOCH_2CH_2OCH_2Cl$); (*j*) $O_3-CH_2Cl_2$–MeOH–$NaHCO_3$; (*k*) $CrO_3 \cdot 2Py$; (*l*) $H_2C=C(Pr^i)MgBr$ (**393**); (*m*) Bu_3SnCH_2I-KH, BuLi; (*n*) $Me_2C=PPh_3$; (*o*) $Li-NH_3$; (*p*) Ac_2O–Py.

Citronellic acid **341** has also been used in the synthesis of the isomers of 3,7-dimethylpentadec-2-yl acetate **53**, which forms part of the composition of the sex pheromone of the pine sawflies belonging to the genera *Diprion* and *Neodiprion*.[172] The synthesis consists of two stages. In the first of these, the C_{12} and C_5 blocks (**397** and **403** respectively) are formed simultaneously, while in the second they are coupled and the product is subjected to further transformation to give the target compounds. The acid **341** serves as the starting material for the synthesis of the C_{12} block **397** having both the (*R*)- and (*S*)-configurations. Compound (*R*)-**397** was synthesised by the ozonolysis of its ethyl ester **394** to give the aldehydoester **395** and its subsequent conversion into the unsaturated ester **396**. The optical isomer (*S*)-**398** was synthesised by alkylating (*R*)-citronellyl tosylate **376** and by the ozonolysis of the resulting alkene **398** to the acid **399**, which was then subjected to the Hunsdiecker reaction.



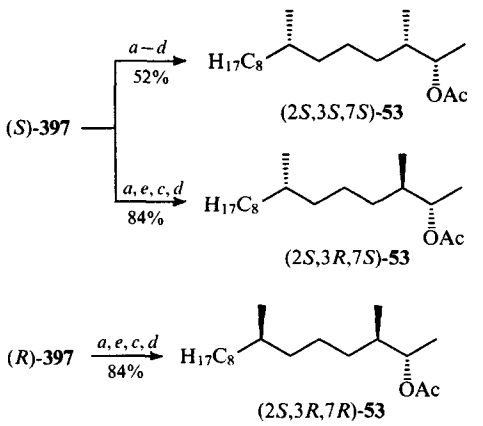
(*a*) EtBr; (*b*) O_3–MeOH; (*c*) H_2–Pd/C; (*d*) $BuCH=PPh_3$; (*e*) H_2–PtO_2; (*f*) $LiAlH_4$; (*g*) TsCl–Py; (*h*) LiBr; (*i*) n-$C_6H_{13}MgCl$–CuI; (*j*) O_3–CH_2Cl_2; (*k*) H_2O_2–HCO_2H; (*l*) NaOH; (*m*) $AgNO_3$; (*n*) Br_2.

The synthesis of the C_5 block with two chiral centres requires greater effort. The diastereoselective asymmetric reduction of methyl 2-methyl-3-oxobutyrate **400** led to a 3:1 mixture of the optically active *erythro*- and *threo*-alcohols **401**, which was separated by fractional crystallisation initially of their sodium salts and then of their ammonium salts. The products of such fairly laborious operations — the hydroxyacids (2*R*,3*S*)-**402** and (2*S*,3*S*)-**402** — were converted in four stages into the corresponding differentially protected diols (2*S*,3*S*)-**403** and (2*R*,3*S*)-**403**, which are necessary for the synthesis of the target products.



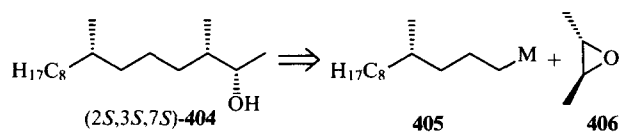
(*a*) H_2–Ni–(*S*,*S*)-$(HO_2CCHOH)_2$; (*b*) crystallisation; (*c*) CH_2N_2; (*d*) DHP–TsOH; (*e*) $LiAlH_4$; (*f*) TsCl–Py.

By combining the stereoisomers of the C_5 and C_{12} blocks in coupling reactions of the organomagnesium derivatives with the tosylates, three optically pure stereoisomers of diprionyl acetate **53** were obtained.

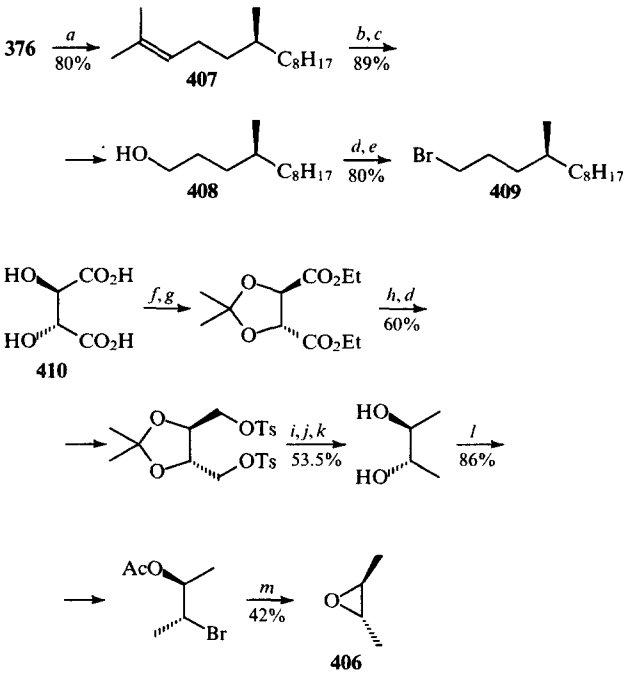


(*a*) Mg; (*b*) (2*S*,3*S*)-**403**–CuI; (*c*) TsOH–MeOH; (*d*) Ac_2O–Py; (*e*) (2*R*,3*S*)-**403**–CuI.

The retrosynthetic analysis of the structure of diprionol (2*S*,3*S*,7*S*)-**404** showed that it can be obtained by the reaction of the organometallic nucleophile **405** with (*S*,*S*)-2,3-epoxybutane **406**.

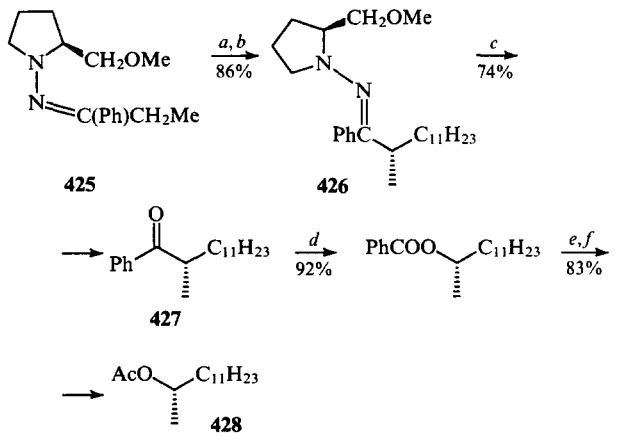


The real chiral building block corresponding to the fragment **405** — (*S*)-(+)-1-bromo-4-methyldodecane **409** — has been synthesised[173] from (*R*)-(+)-citronellyl tosylate **376** by coupling the latter with dihexyllithium cuprate and subsequent ozonolysis of the alkene **407** to the alcohol **408**. The complementary epoxide **406** was obtained from L-(+)-tartaric acid **410** in nine stages. On reaction with the epoxide **406**, the dialkyllithium cuprate prepared from compound **409** afforded the target diprionol **404** with a high configurational homogeneity of all three chiral centres.



The proposed method of synthesis[177] of the pheromone component **423** of the small wood ant (*Formica polyctena*) and the red wood ant (*Formica rufa*) was based on the Michael addition of the azaenolate generated from the hydrazone (*S*)-**419** to the (2*E*)-methyl pent-2-enoate **424** with the asymmetric induction of two chiral centres. The subsequent ozonolysis of the hydrazone **420** led to the aldehyde **421**, which was converted into the target pheromone **423** via the dithioacetal **422**.

A similar approach has been used in the enantioselective synthesis[178] of a component of the aggregation pheromone **428** of the fruit fly *Drosophila mulleri*, the key stages of which are the asymmetric α-alkylation of the azaenolate derived from the hydrazone **425**, the ozonolysis of the hydrazone **426**, and the Baeyer–Villiger oxidation of the ketone **427** accompanied by the inversion of the configuration.



(*a*) LDA; (*b*) $C_{11}H_{23}Br$; (*c*) $O_3-CH_2Cl_2$; (*d*) MCPBA; (*e*) $LiAlH_4$; (*f*) Ac_2O-Py.

Thus the present review of literature gives grounds for the conclusion that there is a growing interest in the use of the ozonolysis of unsaturated compounds at various stages of the total synthesis of insect pheromones and juvenoids, which frequently determine the success in the application of the chosen procedure.

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