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Monoterpenoids in the synthesis of optically active insect pheromones

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Abstract. The data on the application of cyclic and acyclic monoterpenoids in the synthesis of optically active insect pheromones are summarised. The bibliography includes 99 references.

I. Introduction

Studies on pheromones have posed many challenging problems to synthetic chemists the solution of which has broadened the range of methods employed in modern organic synthesis. One of these problems is the study of effects of the absolute configuration of chiral molecules on biological activity, since chemical communication in many insect species is mediated by optically active compounds. More than 100 chiral insect pheromones have been identified so far. As the amount of the pheromone produced by each individual species is negligibly small, the accumulation, isolation, and purification of an individual natural substance is a very labourious problem.[1] Therefore, the determination of the absolute configuration of chiral pheromones is based on a stereocontrolled straightforward synthesis of enantiomerically pure compounds rather than on chemical degradation of natural material accessible with difficulty (together with a combination of physicochemical methods). As a rule, the elucidation of the absolute configuration of a natural pheromone requires the synthesis of all of its possible stereoisomers in enantiomerically pure forms and assay of the biological activity of each of them.

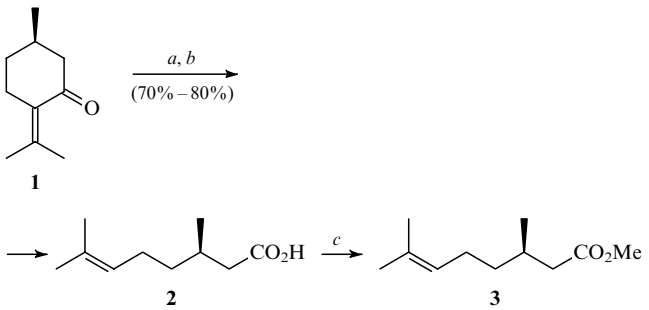
Studies of specific responses of insects to each of these possible stereoisomers have demonstrated that the efficiency of attraction of many species increases 2- to 1000-fold if an enantiomer with the absolute configuration of a natural pheromone or a synergistic mixture of enantiomers is used instead of a racemic compound. Obviously, the use of enantiomerically pure or enantiomerically enriched pheromones makes it possible to considerably reduce the expenditure of materials and the scale of manufacture. However, in order to make the application of these optically active low-molecular-weight bioregulators economically expedient, it is necessary to use the available and inexpensive initial products and simple, practical synthetic schemes.

The currently known chiral insect pheromones are relatively simple molecules (they contain not more than four asymmetric centres and not more than four functional groups). Their structural fragments are sometimes rather peculiar, but the conglomeration of chiral centres and functional groups as in the molecules of carbohydrates, prostanoids, and macrolide antibiotics is not typical of pheromones. Therefore, the 'ideal' chiral building block (CBB) seems to be a moderately functionalised compound devoid of numerous chiral centres. Monoterpenoids, amino acids, and hydroxy acids are the most consistent with this ideal structure. The former are especially suitable for the synthesis of compounds with a branched hydrocarbon skeleton, first of all, of pheromones having an isoprenoid structure. The range of chiral terpenoids is rather wide. All of them are the products of wood-chemical, perfume, food, and pharmaceutical industries.

This review considers the synthetic potentialities of monoterpenoids and the corresponding CBB exemplified in syntheses of optically pure and enantiomerically enriched insect pheromones.

II. Syntheses on the basis of (*R*)-pulegone

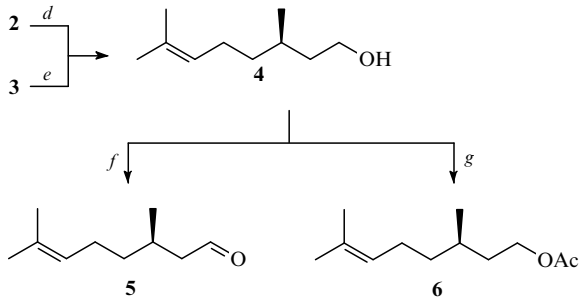
Several chiral building blocks can be synthesised from (*R*)-pulegone **1** by simple transformations. Thus the two-step retrocyclisation of pulegone gives citronellic acid **2**. The latter can be converted into methyl ester **3** and reduced to citronellol **4** with diisobutyl aluminium hydride DIBAH. It can also be obtained directly from the acid **2** by reduction with $LiAlH_4$. The alcohol **4** is easily converted into citronellal **5** or citronellyl acetate **6**.[2]



1 **2** **3**

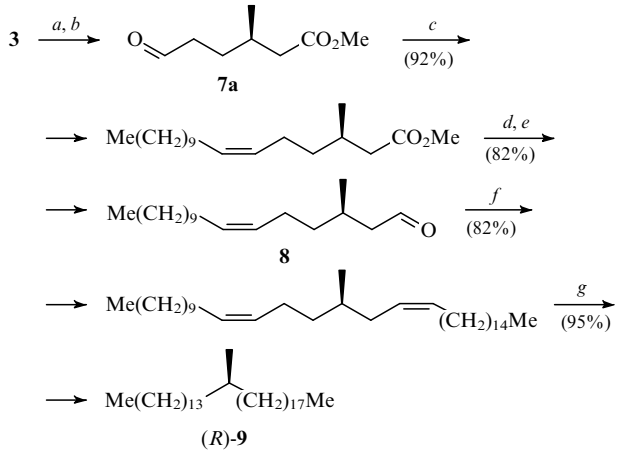
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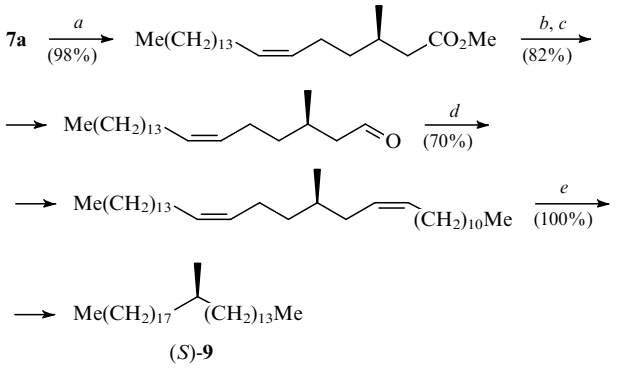
Reagents: (*a*) HCl; (*b*) NaOH; (*c*) MeOH/TsOH; (*d*) $LiAlH_4$; (*e*) Bu^i_2AlH; (*f*) $Py \cdot CrO_3 \cdot HCl$ (PCC); (*g*) Ac_2O/Py.

A scheme for the synthesis of the both enantiomers of 15-methyltritriacontane **9**, the pheromone of the stable fly (*Stomoxys calcitrans*), from the oxo ester **7a**, which is the product of ozonolysis and reduction of methyl citronellate **3**, has been proposed.[3] The (*R*)-**9** enantiomer was synthesised as follows. At the first stage, the aldehydo ester **7a** reacts with C_{11}-phosphorane; then the reaction product is converted in two steps into the aldehyde **8,** which interacts with another phosphorane to give (*R*)-**9** following hydrogenation.



Reagents: (*a*) O_3/MeOH; (*b*) Me_2S; (*c*) $Me(CH_2)_9CH=PPh_3$; (*d*) $LiAlH_4$; (*e*) PCC; (*f*) $Me(CH_2)_{14}CH=PPh_3$; (*g*) H_2/Pd/C.

In an analogous scheme of the synthesis of (*S*)-**9**, C_{15}- and C_{12}-triphenylphosphoranes have been employed.[3]

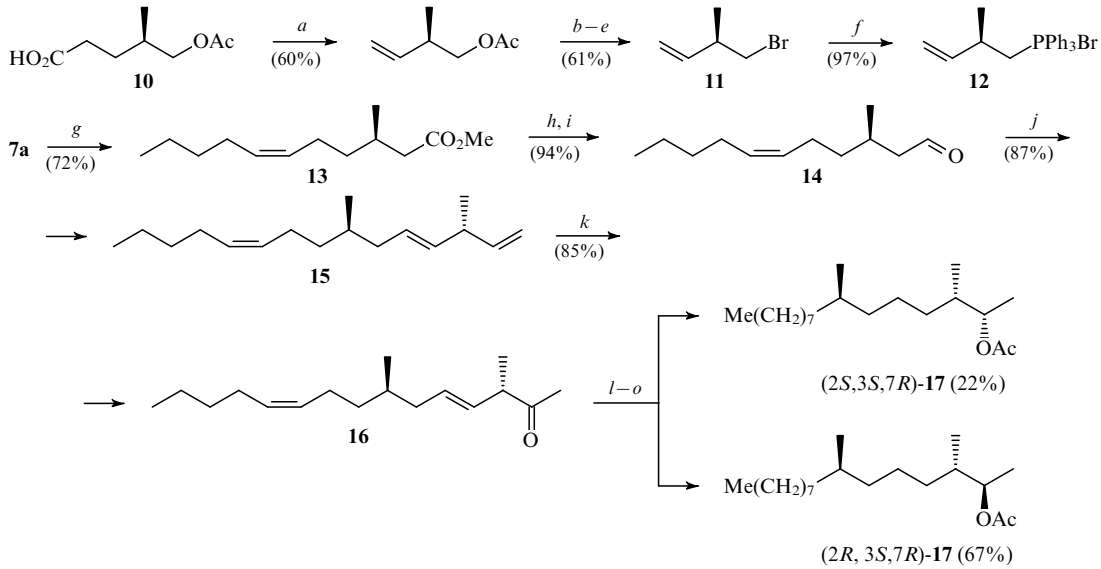


Reagents: (*a*) $Me(CH_2)_{13}CH=PPh_3$; (*b*) $LiAlH_4$; (*c*) PCC; (*d*) $Me(CH_2)_{10}CH=PPh_3$; (*e*) H_2/Pd/C.

Pathways for the synthesis of two diastereomers of 2-acetoxy-3,7-dimethylpentadecane **17**, the analogues of diprionyl acetate, the sex pheromone of the sawflies related to the *Diprion* and *Neodiprion* genera, on the basis of the aldehydo ester **7a** and (4*R*)-methyl-5-acetoxypentanoic acid **10**, have been proposed. The C(7)-chiral centre of the target molecule, which has the (*R*)-configuration, was introduced *via* the building block **7a**. Another CBB, the compound **11**, was used for the creation of the C(3)-chiral centre after its conversion into the phosphonium salt **12**. The chiral C(2)-centre is formed in the reduction of the methyl ketone **16** corresponding to the target structure. Thus, the synthesis of the compound **17** was carried out essentially in two steps. In the first step, the alkenoate **13** obtained by alkenation of **7a** was converted into the aldehyde **14** by a two-step procedure.[4,5] The second part of this synthesis involves the interaction of the aldehyde **14** with the phosphorane prepared from the salt (*R*)-**12** and subsequent selective transformations of the triene **15**: the oxidation of the terminal double bond and borohydride reduction of the methyl ketone **16** into a mixture of diastereoisomers in which the *threo*-isomer predominates (Scheme 1). They were separated by HPLC.

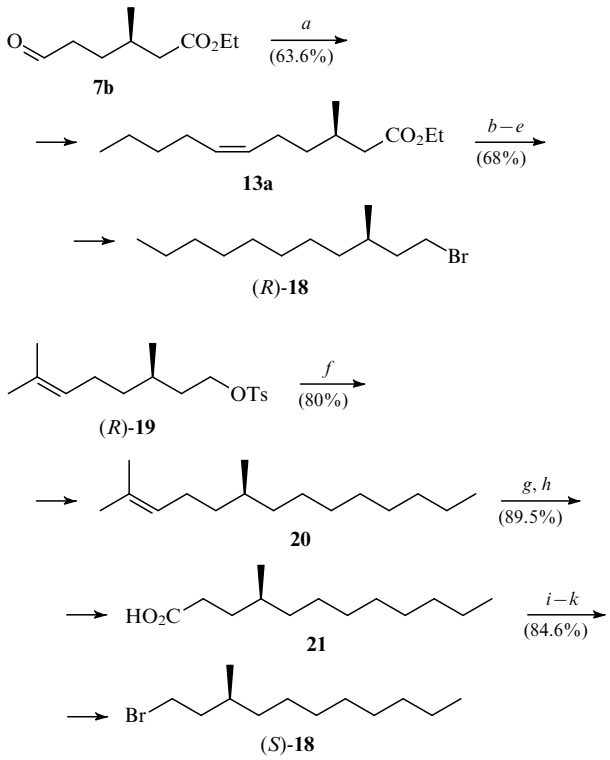
The synthesis of three diastereomers of diprionyl acetate **17** from the aldehydo ester **7b** is based on the coupling of the C_{12}- and C_5-building blocks **18** and **24** of the respective configuration.[6] The

Scheme 1



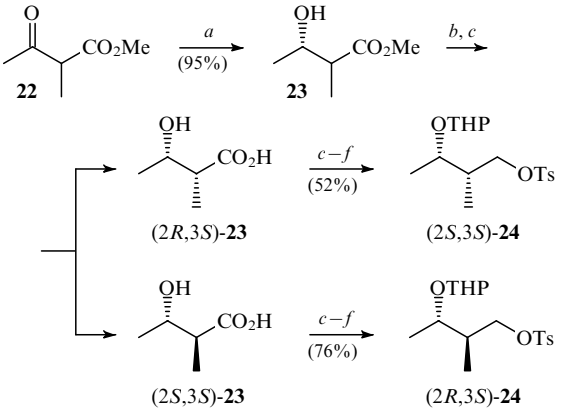
Reagents: (*a*) $Pb(OAc)_4/Cu(OAc)_2 \cdot H_2O$; (*b*) KOH; (*c*) Bu^nLi; (*d*) TsCl; (*e*) NaBr; (*f*) PPh_3/14 kbar; (*g*) $BuCH=PPh_3$; (*h*) Bu^i_2AlH; (*i*) PCC; (*j*) **12**/Bu^nLi; (*k*) $O_2/PdCl_2 - CuCl$; (*l*) $NaBH_4$; (*m*) H_2/Pt; (*n*) HPLC; (*o*) Ac_2O/Et_3N/4-dimethylaminopyridine (DMAP).

key stage in the scheme of synthesis of the C_{12}-block of the (*R*)-configuration is the condensation of the aldehyde **7b** with pentylidenephosphorane resulting in the ester **13a**. Its optical antipode, (*S*)-**18**, was synthesised through alkylation of (*R*)-citronellyl tosylate **19**, the ozonolysis of the resulting alkene **20** into the acid **21,** and its conversion into the bromide by the Hunsdiecker reaction.



Reagents: (*a*) $BuCH=PPh_3$; (*b*) H_2/PtO_2; (*c*) $LiAlH_4$; (*d*) TsCl/Py; (*e*) LiBr; (*f*) $Me(CH_2)_5MgCl/CuI$; (*g*) O_3/CH_2Cl_2; (*h*) H_2O_2/HCO_2H; (*i*) NaOH; (*j*) $AgNO_3$; (*k*) Br_2.

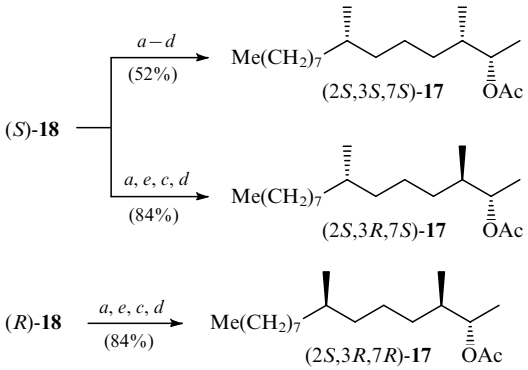
The synthesis of the C_5-blocks **24** having two chiral centres was carried out by diastereoselective asymmetric reduction of methyl 2-methyl-3-oxobutyrate **22** and subsequent fractional crystallisation of first sodium and then ammonium salts. This rather labourious procedure yielded the hydroxy acids (2*R*,3*S*)-**23** and (2*S*,3*S*)-**23**, which were then converted in four steps into the protected diols (2*S*,3*S*)-**24** and (2*R*,3*S*)-**24** required for the synthesis of target products.



Reagents: (*a*) H_2/Ni-(*S,S*)-$[HO_2CCH(OH)]_2$; (*b*) NaOH; (*c*) recrystallisation, H_3O^+; (*d*) CH_2N_2; (*e*) dihydropyrane (DHP)/TsOH; (*f*) $LiAlH_4$; (*g*) TsCl/Py.

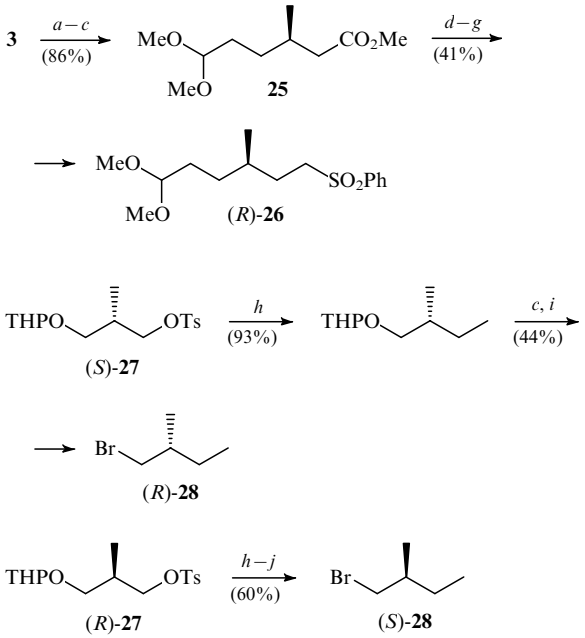
Three optically pure diastereomers of diprionyl acetate **17** were obtained by a Wurtz-type reaction by coupling the stereoisomeric C_5-**24** and C_{12}-**18** blocks (Scheme 2).

Scheme 2



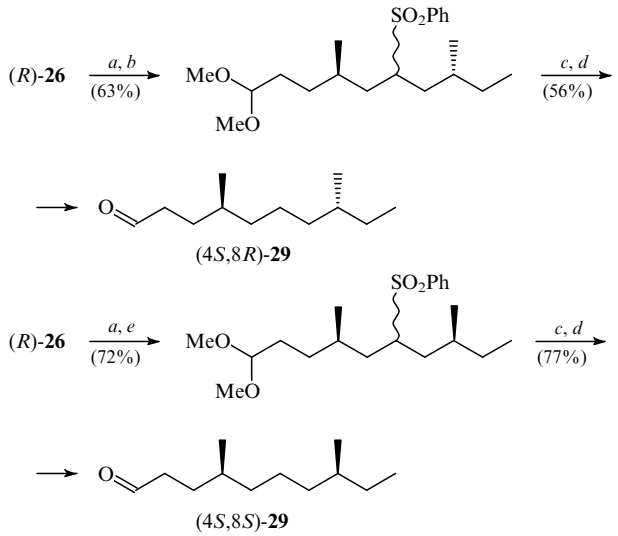
Reagents: (*a*) Mg; (*b*) (2*S*,3*S*)-**24**/CuI; (*c*) TsOH/MeOH; (*d*) Ac_2O/Py; (*e*) (2*R*,3*S*)-**24**/CuI.

Dimethyl acetal **25**, another product of ozonolysis and reduction of methyl citronellate **3**, was used in the synthesis of (4*S*,8*R*)- and (4*S*,8*S*)-4,8-dimethyldecanals **29** manifesting attractant activity against *Tribolium confusum* and *T. castaneum* meal worms. The starting acetal **25** was converted by conventional procedures into the sulfone **26** required for the formation of the (4*S*)-chiral centre of the pheromone **29**. The corresponding enantiomeric, selectively protected diols **27** were converted into bromides **28** and used for the introduction of (8*R*)- and (8*S*)-chiral centres.[7]



Reagents: (*a*) O_3/MeOH; (*b*) Me_2S; (*c*) TsOH, MeOH; (*d*) $LiAlH_4$; (*e*) TsCl/Py, (*f*) $NaI/NaHCO_3$; (*g*) $PhSO_2Na$; (*h*) $MeMgI/Li_2CuCl_4$; (*i*) TsOH/MeOH; (*j*) Br_2/PPh_3.

The alkylation of the sulfone (*R*)-**26** with the bromides (*R*)-**28** or (*S*)-**28** followed by desulfonation of the condensation products and hydrolysis yields the (4*S*,8*R*)- and (4*S*,8*S*)-stereoisomers of the compound **29**, respectively.

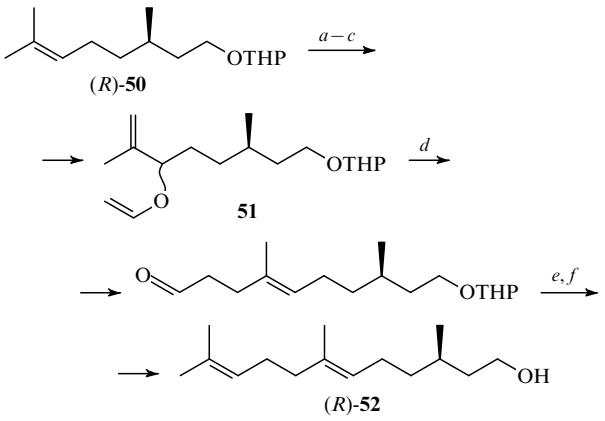


Reagents: (*a*) Bu^nLi; (*b*) (*R*)-**28**; (*c*) Na – Hg; (*d*) H_3O^+; (*e*) (*S*)-**28**.

The allylic alcohol **30**, the product of the Sharpless oxidation [8] of the compound **3**, was used as the starting material in the synthesis of both enantiomers of (5*E*)-isopropyl-3,9-dimethyldeca-5,8-dienyl acetate **39** the (*S*)-isomer of which is the sex pheromone of the yellow scale (*Aonidiella citrina*).[9] The building block (*S*)-**32** obtained from the methyl ester **30** *via* the acetal **31** was used for the creation of the (3*R*)-centre in the molecule of **39.** Its optical antipode, the aldehyde (*R*)-**32**, was obtained from the same allylic alcohol **30** by converting it into a mixture of mono- and di-ethers (**34** and **35**, respectively) *via* the diol **33**. The ozonolysis and reduction of this mixture gave the monosubstituted diol **36,** which was converted *via* the benzyl derivative into another key aldehydo ester, (*R*)-**32**. Further transformations of (*S*)- and (*R*)-**32** involved the condensation with the Grignard reagent **40** and a 2,3-sigmatropic rearrangement of the resulting allylic alcohols **37** into the *E*-homoallylic alcohols **38** *via* their stannyl derivatives (Scheme 3). The alcohols **38** were further converted into the corresponding aldehydes; their alkenation gave the target products, (*S*)- or (*R*)-**39**. The synthesis of the biologically active (*S*)-enantiomer **39** is shown in Scheme 3.

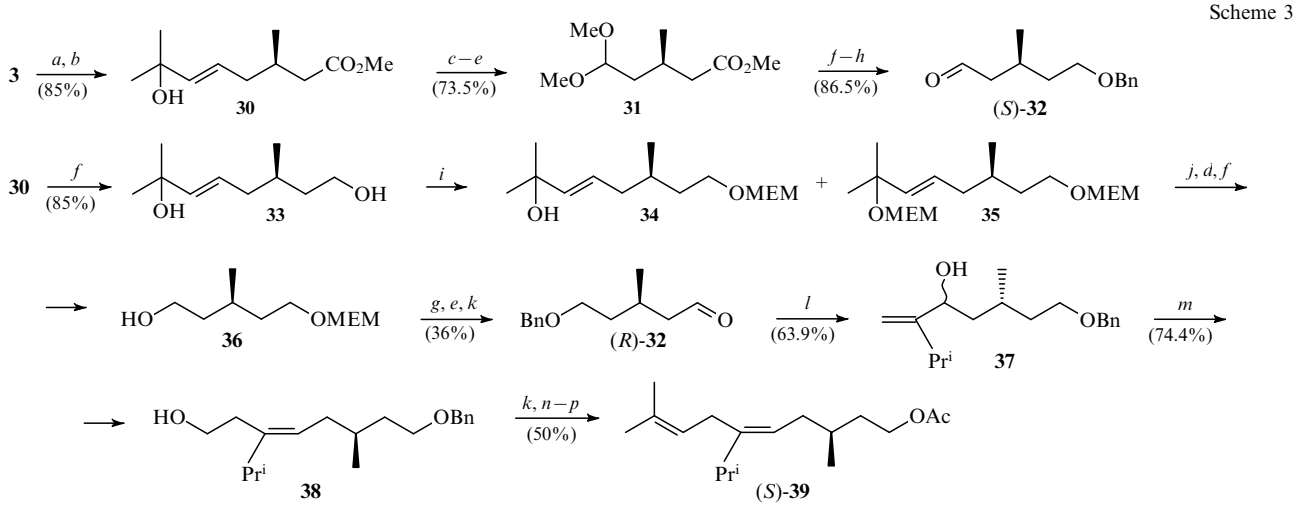
A scheme of synthesis of α-multistriatine **49**, the aggregation pheromone of the elm bark beetle (*Scolytus multistriatus*), on the basis of citronellol **4** has been developed. Thus, pyrolysis of the xanthate **41** gave the diene (*R*)-**42**, which was further converted into the diol **43** by chemospecific epoxidation of the trisubstituted double bond with subsequent hydrolysis of the intermediate epoxide. The oxidative cleavage of **43** gave the aldehyde (*R*)-**44**. Its α-methylation was carried out *via* the intermediate Schiff's base **45**. The resulting aldehyde **46** was converted *via* the ketone **47** into the epoxide **48**; its treatment with $SnCl_4$ gave a mixture of four stereoisomers from which **49** was isolated chromatographically (Scheme 4).[10]

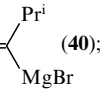
The tetrahydroxypyranylic ether of (*R*)-citronellol **2**, (*R*)-**50**, has proved to be a convenient starting material in the synthesis of (*R*)-(+)-2,3-dihydrofarnesol (*R*)-**52**, the antipode of terrestrol, the marker pheromone of the male bumblebee *Bombus terrestris*. To this end, (*R*)-**50** was converted into a mixture of the diastereo-



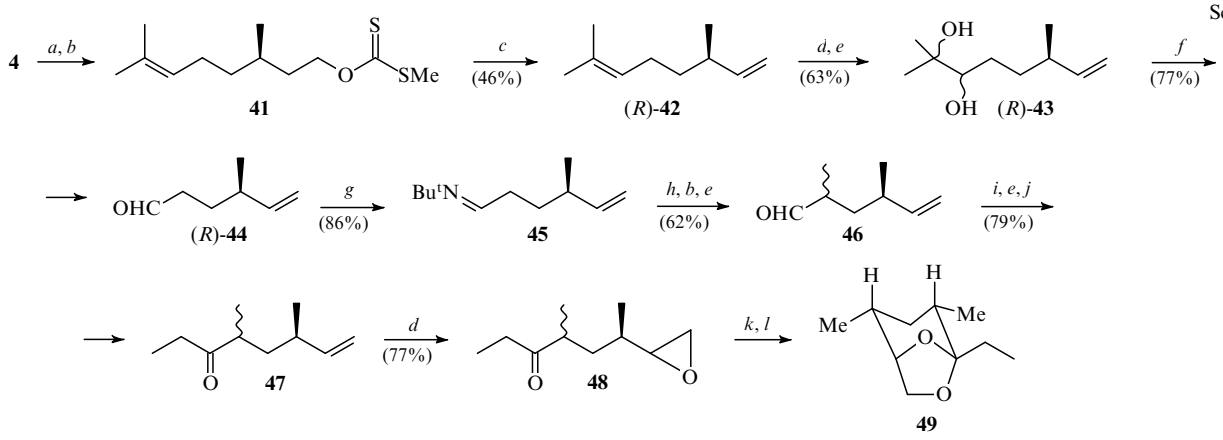
Reagents: (*a*) MCPBA; (*b*) LDA; (*c*) $\diagup\!\!=\!\!\diagdown$OEt/$Hg^{2+}$; (*d*) 180 °C; (*e*) $Ph_3P=CMe_2$; (*f*) H_3O^+.

Scheme 3



Reagents: (*a*) Ph_2Se_2/H_2O_2; (*b*) Bu^tOOH; (*c*) O_3/MeOH; (*d*) Me_2S; (*e*) MeOH/TsOH; (*f*) $LiAlH_4$; (*g*) $PhCH_2Br$/NaH; (*h*) $HClO_4$; (*i*) MEM – Cl/NaH [MEM = $CH_2O(CH_2)_2OMe$]; (*j*) O_3/MeOH – CH_2Cl_2/$NaHCO_3$; (*k*) Py · CrO_3; (*l*)  (**40**); (*m*) (1) $Bu^i_3SnCH_2I$/KH; (2) Bu^nLi; (*n*) $Me_2C=PPh_3$; (*o*) Li/NH_3; (*p*) Ac_2O/Py.

Scheme 4

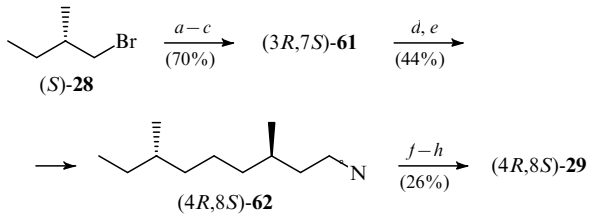


Reagents: (*a*) CS_2/NaH; (*b*) MeI; (*c*) 240 °C; (*d*) *m*-ClC_6H_4COOOH (MCPBA); (*e*) H_3O^+; (*f*) $Pb(OAc)_4$; (*g*) Bu^tNH_2; (*h*) LDA; (*i*) EtMgBr; (*j*) H_2CrO_4; (*k*) $SnCl_4$; (*l*) HPLC.

meric allyl vinyl ethers **51**. The subsequent Claisen rearrangement and the Wittig alkenation of the intermediate aldehyde gave (*R*)-**52**.[11]

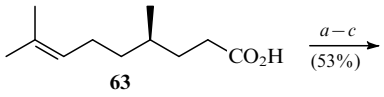
The derivatives of citronellol **4** have been used to obtain all the stereoisomeric 4,8-dimethyldecanals **29**.[12] In the synthesis of (4*R*,8*R*)-**29** and (4*R*,8*S*)-**29,** the original benzyl ether **53** underwent the Sharpless oxidation [8] into the allylic alcohol **54**. Ozonolysis of the latter and reduction gave the monoprotected diol **55**. Its derivatives, the tosylate **56** and the iodide **57**, have found application in the formation of the (4*R*)-chiral centre of **29**. The sulfone **60,** which has been prepared in several steps including the ozonolysis of the compound **30** into the aldehydo ester **58** and Huang–Minlon reduction of the latter into the acid **59**, was used for the formation of the (8*R*)-centre. The reaction of **60** with the iodide **57** and subsequent desulfonation of the condensation product yielded the alcohol (3*R*,7*R*)-**61**; its homologisation into the target aldehyde (*R,R*)-**29** was performed *via* the corresponding cyanide (Scheme 5).

For the formation of the (8*S*)-centre in the stereoisomer (4*R*,8*S*)-**29,** (2*S*)-methylbutyl bromide **28** has been used. Its reaction with the tosylate **56** gave the alcohol (3*R*,7*S*)-**61**, which was converted into the target product *via* the nitrile (4*R*,8*S*)-**62**.

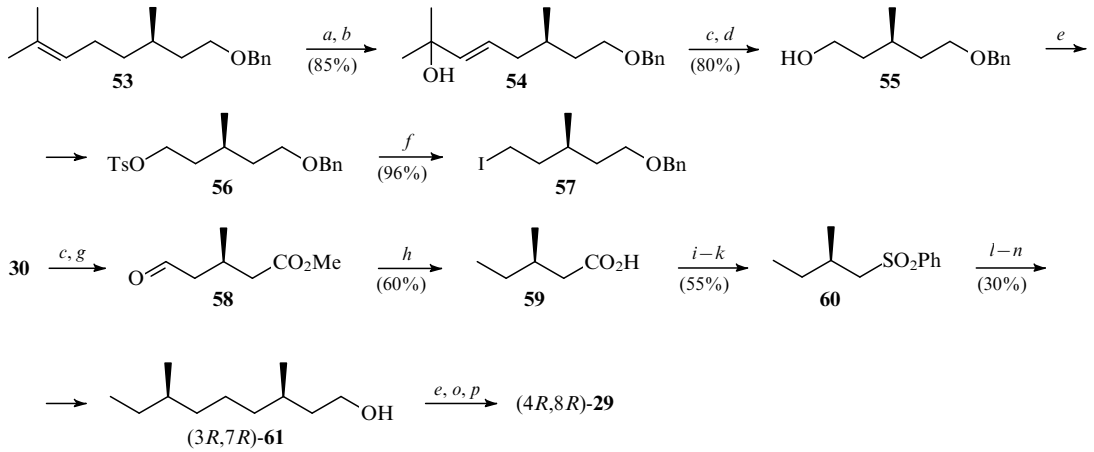


Reagents: (*a*) Mg; (*b*) **56**/Li_2CuCl_4; (*c*) H_2/Pd/C; (*d*) TsCl/Py; (*e*) NaCN; (*f*) NaOH; (*g*) $LiAlH_4$; (*h*) PCC.

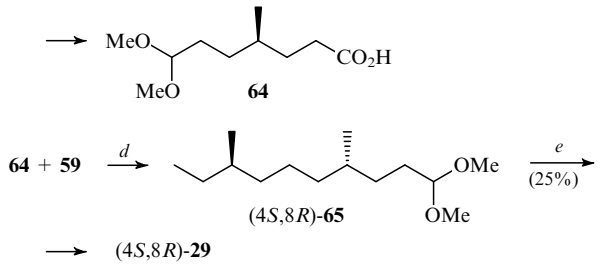
Electrolysis of a mixture of the acids **59** and **64** (obtained by ozonolysis of homocitronellic acid **63**) in MeONa/MeOH gave a mixture of the corresponding hydrocarbon, bisacetal, and (4*S*,8*R*)-**65**; the latter was isolated chromatographically. Compound (4*S*,8*R*)-**29** was obtained by treatment of (4*S*,8*R*)-**65** with $HClO_4$.



Scheme 5

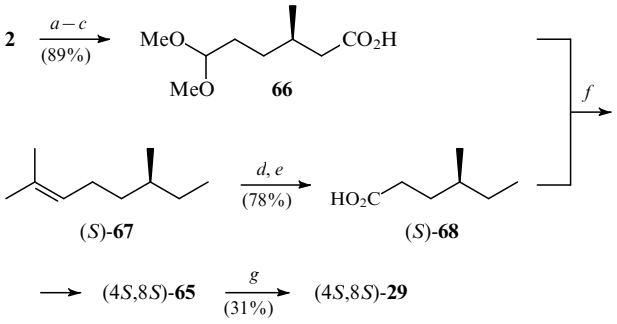


Reagents: (*a*) Ph_2Se_2/H_2O_2; (*b*) Bu^tOOH; (*c*) O_3/CH_2Cl_2–MeOH/$NaHCO_3$; (*d*) $NaBH_4$; (*e*) TsCl/Py; (*f*) NaI; (*g*) Me_2S; (*h*) $N_2H_4 \cdot H_2O$/KOH; (*i*) $Pb(OAc)_4/I_2$; (*j*) PhSNa; (*k*) MCPBA; (*l*) Bu^nLi; (*m*) **57**; (*n*) Li/$EtNH_2$; (*o*) NaCN; (*p*) Bu^i_2AlH.



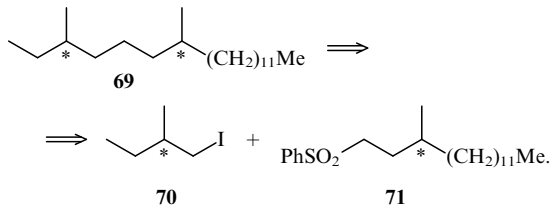
Reagents: (*a*) O_3/MeOH; (*b*) Me_2S; (*c*) MeOH/TsOH; (*d*) e^-, NaOMe/MeOH; (*e*) $HClO_4$.

The synthesis of the (*S,S*)-enantiomer **29** is based on the same principle. In this case, the role of chiral building blocks was played by the acids **66** and (*S*)-**68** synthesised from the products of ozonolysis of the acid **2** and tetrahydromyrcene (*S*)-**67**, respectively. The acetal (4*S*,8*S*)-**65** obtained in the electrolysis of an equimolar mixture of the acids **66** and (*S*)-**68** was further converted into the target product, (4*S*,8*S*)-**29**.

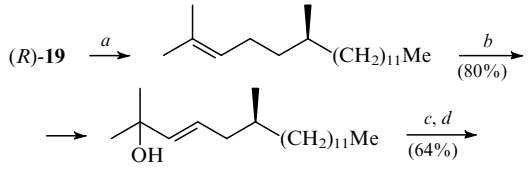


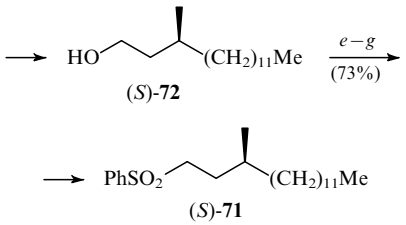
Reagents: (*a*) O_3/MeOH; (*b*) Me_2S; (*c*) MeOH/TsOH; (*d*) O_3/Me_2CO; (*e*) H_2CrO_4; (*f*) e^-, NaOMe/MeOH; (*g*) $HClO_4$.

All the four stereoisomers of 3,7-dimethylnonadecane **69**, the sex pheromone of the alfalfa leaf mining beetle (*Agromyza frontella*), have been synthesised on the basis of derivatives of citronellol **6** and **19**.[13] The key stage in this synthesis was the condensation of the chiral iodide **70** and sulfone **71**.



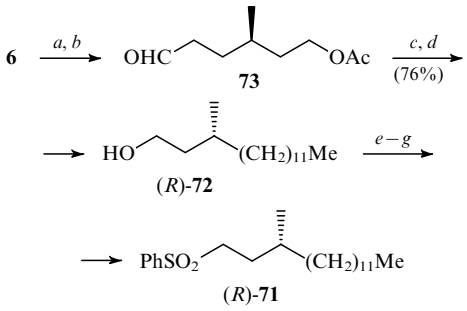
To obtain sulfone (*S*)-**71**, the alkylation product of the tosylate (*R*)-**19** was successively subjected to the Sharpless oxidation,[8] ozonolysis, and reduction; the resulting alcohol (*S*)-**72** was converted into (*S*)-**71** by conventional procedures.





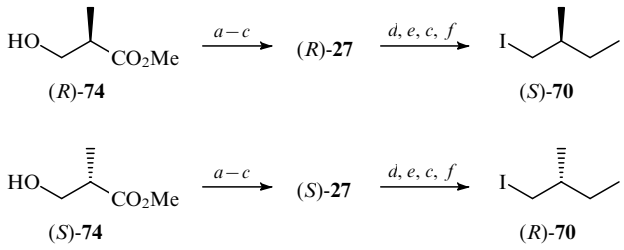
Reagents: (*a*) $Me(CH_2)_9MgBr/Li_2CuCl_4$; (*b*) $Ph_2Se_2/H_2O_2/Bu^tOOH$; (*c*) $O_3/CHCl_3$; (*d*) $NaBH_4$; (*e*) TsCl/Py; (*f*) PhSNa/MeOH; (*g*) MCPBA.

The (*R*)-enantiomer of the sulfone **71** was synthesised from the acetoxy aldehyde **73** derived from the compound **6** by ozonolysis and reduction. The Wittig alkenation of **73** and the subsequent hydrogenation of the intermediate alkene gave the alcohol (*R*)-**72**, which was converted into the sulfone (*R*)-**71** in a way analogous to that for the (*S*)-enantiomer.



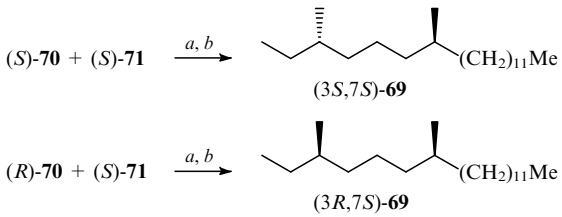
Reagents: (*a*) O_3/MeOH; (*b*) Me_2S; (*c*) $Ph_3P=CH(CH_2)_7Me$; (*d*) $LiAlH_4/CoCl_2$; (*e*) TsCl/Py; (*f*) PhSNa/MeOH; (*g*) MCPBA.

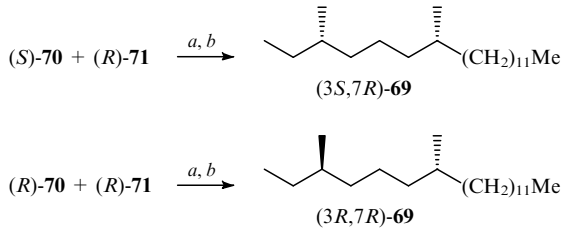
The synthesis of the chiral iodides **70** was carried out on the basis of the hydroxy esters **74** *via* the intermediate, selectively protected diols **27**.



Reagents: (*a*) DHP/TsOH; (*b*) $LiAlH_4$; (*c*) TsCl/Py; (*d*) $MeMgBr/Li_2CuCl_4$; (*e*) H_3O^+; (*f*) NaI/Me_2CO.

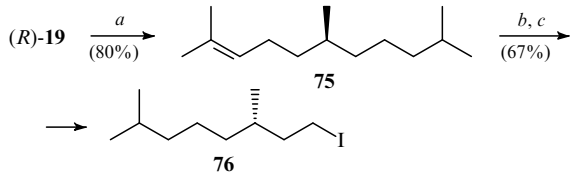
Reactions of the chiral sulfones **71** and iodides **70** in various combinations and subsequent desulfonation of the reaction products gave all four stereoisomers of the pheromone **69**.





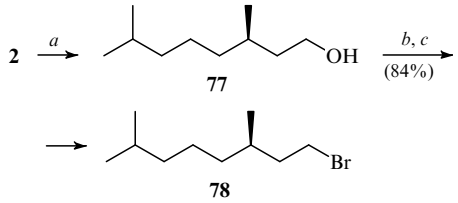
Reagents: (*a*) Bu^{n}Li; (*b*) Na – Hg.

The tosylate (*R*)-**19** has also found application in the synthesis of (2*R*,6*R*,10*R*)-6,10,14-trimethylpentadecan-2-ol **83**, the sex pheromone of the rice moth (*Corcyra cephalonica*) and its analogues having the (2*S*,6*R*,10*R*)-, (2*S*,6*S*,10*S*)-, or (2*R*,6*R*,10*S*)-configuration.[14] The building block **76** obtained from **19** *via* the alkene **75,** which was subjected to periodate scission in the presence of catalytic amounts of $RuCl_3$, was used for the formation of the (10*S*)-chiral centre of the two latter compounds.



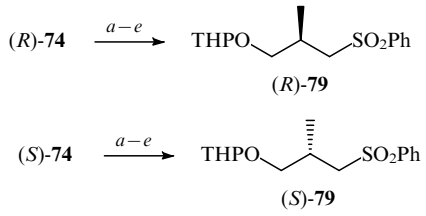
Reagents: (*a*) Bu^{i}MgBr/Li_2CuCl_4; (*b*) $NaIO_4$/$RuCl_3$;
(*c*) I_2/$Pd(OAc)_4$/*hv*/CCl_4 .

The formation of the (10*R*)-centre of the stereoisomers (2*R*,6*R*,10*R*)- and (2*S*,6*R*,10*R*)-**83** was carried out with the use of the bromide **78** obtained in high yield from dihydrocitronellol **77**, the reduction product of citronellic acid **2**.



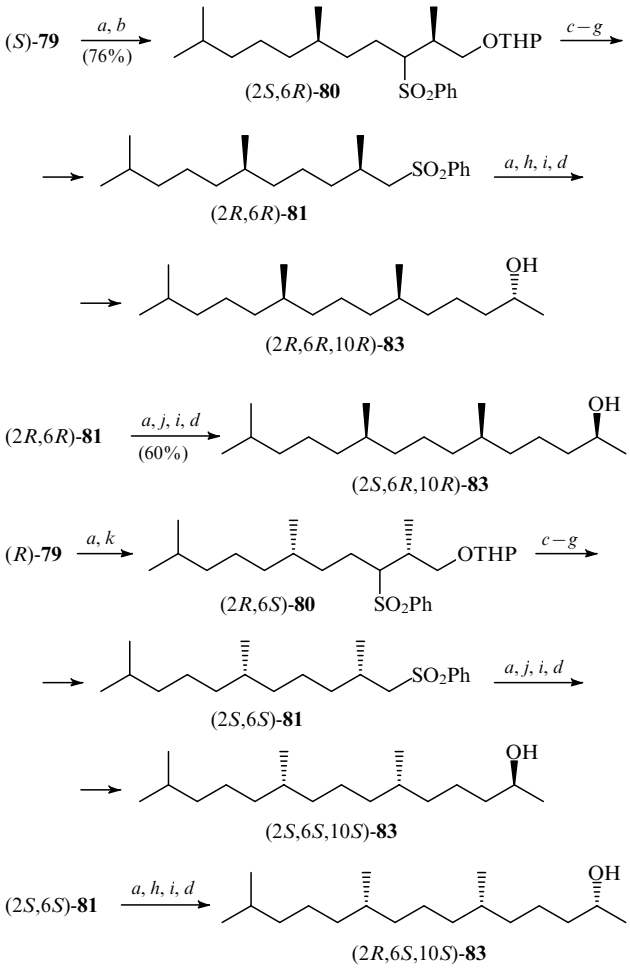
Reagents: (*a*) $LiAlH_4$/$CoCl_2$; (*b*) TsCl/Py; (*c*) NaBr/DMF.

The (*R*)- and (*S*)-sulfones **79** derived from (*R*)- and (*S*)-hydroxy acids **74** were used in the formation of (6*R*)- and (6*S*)-chiral centres of the corresponding stereoisomers **83**.

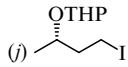


Reagents: (*a*) DHP/TsOH; (*b*) $LiAlH_4$; (*c*) TsCl/Py;
(*d*) NaSPh; (*e*) MCPBA.

Different versions of alkylation of the chiral sulfones **79** with the iodide **76** or the bromide **78** with subsequent desulfonation of the corresponding condensation products **80**, their conversion into the sulfones **81** and analogous sequences of reactions of the stereoisomers **81** and enantiomeric iodohydrins **82** resulted in the four stereoisomers of the target compounds **83**.

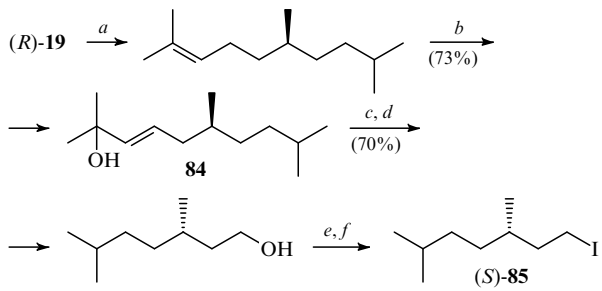


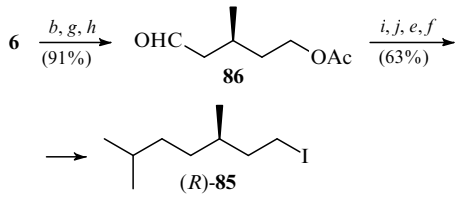
Reagents: (*a*) Bu^{n}Li; (*b*) **78**; (*c*) Na – Hg; (*d*) H_3O^+; (*e*) TsCl/Py;
(*f*) NaSPh; (*g*) MCPBA; (*h*) 

[(*R*)-**82**]; (*i*) Li/$EtNH_2$;
(*j*) 

[(*S*)-**82**]; (*k*) **76**.

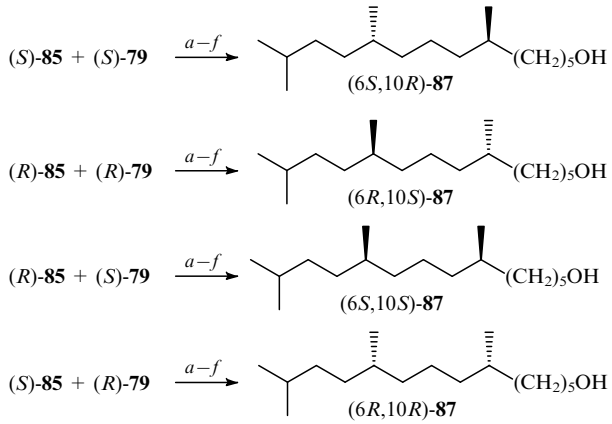
The obvious structural identity of the portion of 6,10,13-trimethyltetradecan-1-ol **87**, the aggregation pheromone of the predacious beetle (*Stiretrus anchgorago*), with that of the above-described pheromone **83** has encouraged their application in the synthesis of its four optical isomers.[15] The chiral building blocks **85** required for this purpose were prepared from citronellyl acetate (*S*)-**6** (following its ozonolysis) and the disubstituted alkene **84** synthesised from (*R*)-**19** by a two-step procedure.





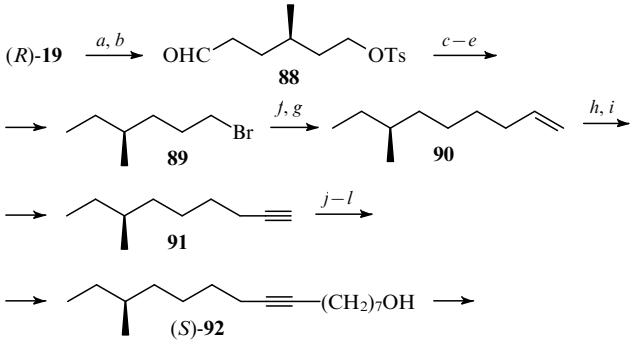
Reagents: (*a*) Pr^iMgBr/Li_2CuCl_4; (*b*) $Ph_2Se_2/H_2O_2/Bu^tOOH$;
(*c*) $O_3/CHCl_3$; (*d*) $NaBH_4$; (*e*) TsCl/Py; (*f*) NaI;
(*g*) O_3/MeOH; (*h*) Me_2S; (*i*) $Me_2C{=}PPh_3$; (*j*) $LiAlH_4/CoCl_2$.

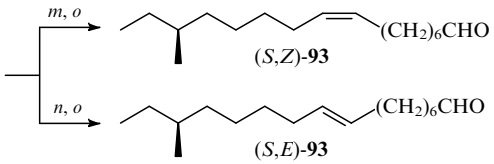
Reaction of the chiral iodides **85** with the sulfones (*R*)- and (*S*)-**79** (in different combinations) has made it possible to obtain all the stereoisomeric alcohols **87**.



Reagents: (*a*) Bu^nLi; (*b*) Na – Hg; (*c*) H_3O^+; (*d*) TsCl/Py;
(*e*) $ClMg(CH_2)_4OTHP/Li_2CuCl_4$; (*f*) H_3O^+.

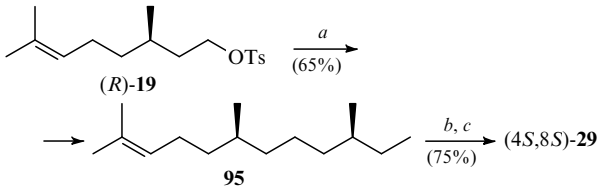
Citronellyl tosylate (*R*)-**19** was also used in the synthesis of (14*S*)-methylhexadec-(8*E*)- and -(8*Z*)-enals **93**, the optical antipodes of components of the pheromone of skin beetles of the *Trogoderma* genus.[16] The synthetic scheme involves oxidative cleavage of the double bond in (*R*)-**19**, subsequent reduction of both aldehyde and tosyl groups of compound **88,** and transformations of the alkene **90** into the corresponding acetylene **91**. The alkylation of the Li-derivative of compound **91** with the bromide **94** and selective hydrogenation of the resulting alcohol (*S*)-**92** completes the synthesis of **93**.





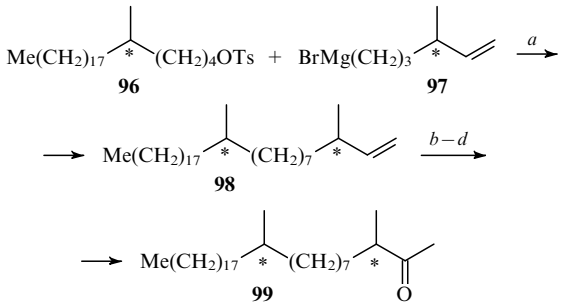
Reagents: (*a*)MCPBA; (*b*) HIO_4; (*c*) $LiAlH_4$; (*d*) TsCl/Py; (*e*) LiBr; (*f*) Mg;
(*g*) ; (*h*) Br_2/CCl_4; (*i*) $NaNH_2$; (*j*) Bu^nLi;
(*k*) $Br(CH_2)_7OTHP$ (**94**); (*l*) H_3O^+;
(*m*) $H_2/Pd/BaSO_4$/quinoline; (*n*) Na/NH_3; (*o*) PCC.

A short route to the synthesis of an enantiomerically pure (4*S*,8*S*)-dimethyldecanal **29** from the tosylate (*R*)-**19** and the accessible bromide (*S*)-**28** has been proposed;[17, 18] cross-coupling of these molecules gives the branched alkene (6*S*,10*S*)-**95,** which is converted into the target compound (4*S*,8*S*)-**29** by ozonolysis.



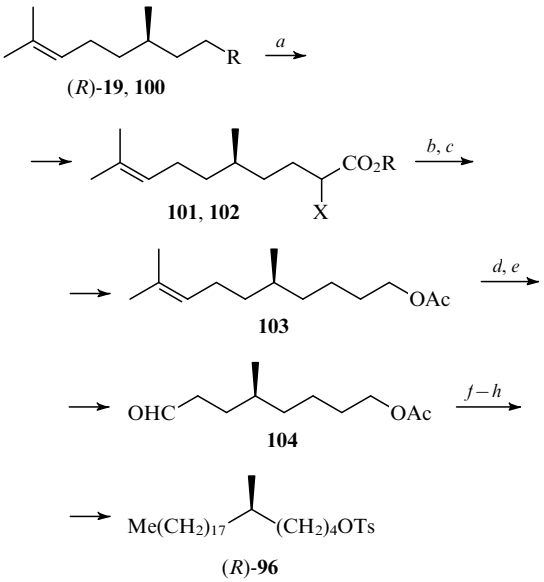
Reagents: (*a*) Br, [(*S*)-**28**]/Mg/Li_2CuCl_4; (*b*) O_3/CH_2Cl_2;
(*c*) Me_2S.

The tosylate (*R*)-**19** has also proved to be a convenient starting material in the synthesis of all the stereoisomers of 3,11-dimethylnonacosan-2-one **99**, the sex hormone of the German cockroach (*Blattella germanica*).[19] The key stage in this synthesis is the cross-coupling of the chiral tosylate **96** and the chiral Grignard reagent **97** to give the alkene **98**.



Reagents: (*a*) Li_2CuCl_4; (*b*) $Hg(OAc)_2$; (*c*) $NaBH_4$ – NaOH; (*d*) CrO_3.

The first step in the synthesis of the tosylate (*R*)-**96** was the conversion of (*R*)-**19** into the iodide **100**, which was then condensed with diethyl malonate. Saponification of the intermediate diester **101** and decarboxylation gave the acid **102**. It was converted into the acetate **103** and then into the acetoxyaldehyde **104** by oxidative cleavage of the double bond. The alkenation of compound **104** with C_{15}-triphenylphosphorane, the hydrogenation of the resulting alkene, and its subsequent tosylation completed the synthesis of (*R*)-**96**.

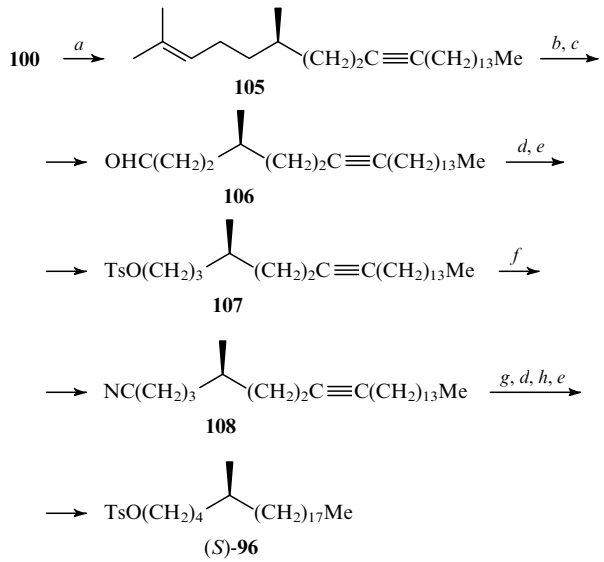


R = OTs [(*R*)-**19**], I (**100**);

X = CO_2Et, R = Et (**101**); X = R = H (**102**).

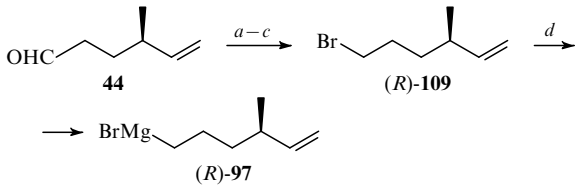
Reagents: (*a*) $CH_2(CO_2Et)_2/Bu^nLi$; (*b*) $LiAlH_4$; (*c*) Ac_2O/Py;
(*d*) MCPBA; (*e*) HIO_4; (*f*) $[Me(CH_2)_{14}PPh_3]Br/Bu^nLi$;
(*g*) H_2/Pd; (*h*) TsCl/Py.

The tosylate (*S*)-**96** was obtained from the product of alkylation of the iodide **100** with hexadec-1-ynyllithium. The enyne **105** was oxidised to the aldehyde **106** by cleavage of the double bond. The latter was further converted into the tosylate **107**; its homologisation *via* the nitrile **108** completed the synthesis of the tosylate (*S*)-**96**.



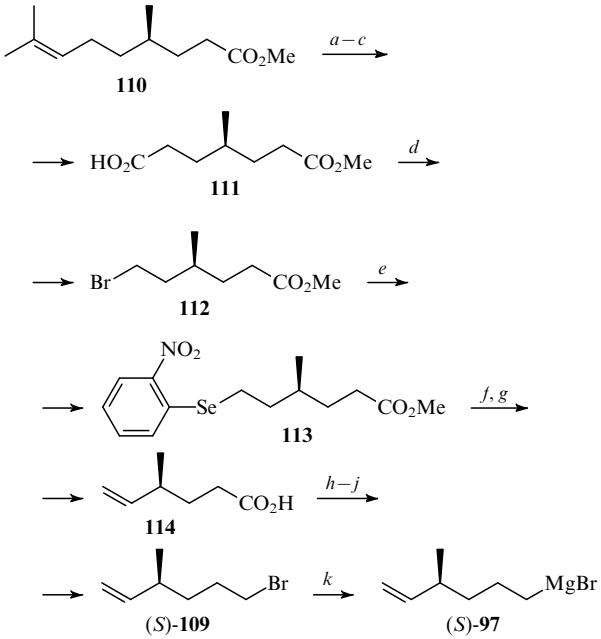
Reagents: (*a*) $HC\equiv C(CH_2)_{13}Me/Bu^nLi$; (*b*) MCPBA; (*c*) HIO_4;
(*d*) $LiAlH_4$; (*e*) TsCl/Py; (*f*) NaCN; (*g*) NaOH; (*h*) H_2/Pd.

The bromide (*R*)-**109** required for the synthesis of the Grignard reagent **97** was obtained from the aldehyde **44** by routine reactions.



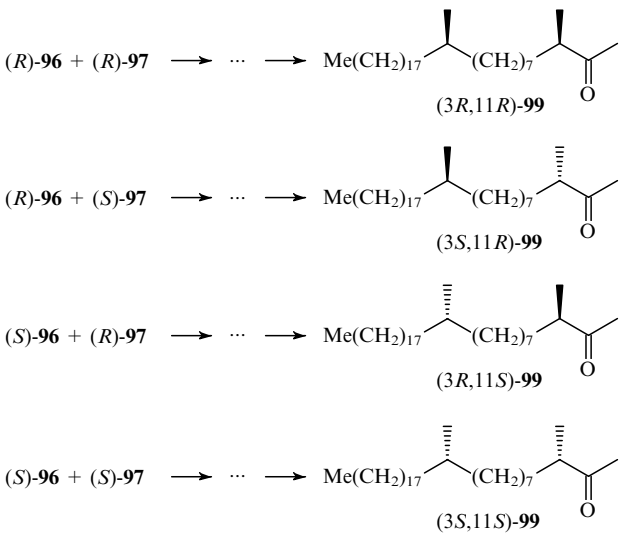
Reagents:(*a*) $LiAlH_4$; (*b*) TsCl/Py; (*c*) LiBr; (*d*) Mg.

The bromide (*S*)-**109** was prepared from methyl homocitronellate **110**. Its ozonolysis and subsequent oxidation gave the acid **111**. The methyl bromoalkanoate **112** obtained by the Hunsdiecker reaction was converted into the unsaturated acid **114** *via* the selenide **113**. The bromide (*S*)-**109** was synthesised from the acid **114** by standard procedures.

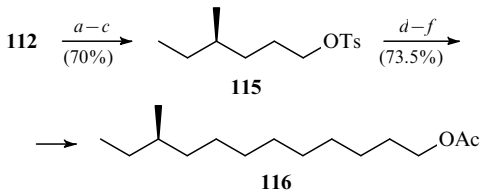


Reagents: (*a*) O_3/MeOH; (*b*) Me_2S; (*c*) CrO_3; (*d*) Ag_2O-Br_2;
(*e*) $2\text{-}NO_2C_6H_4SeCN/NaBH_4$; (*f*) NaOH; (*g*) H_2O_2;
(*h*) $LiAlH_4$; (*i*) TsCl/Py; (*j*) LiBr; (*k*) Mg.

Reactions of tosylates **96** with the Grignard reagents **97** followed by Markovnikov hydration of the corresponding alkenes and the oxidation of the resulting alcohols gave all the four stereoisomers of the pheromone **99**.[19]

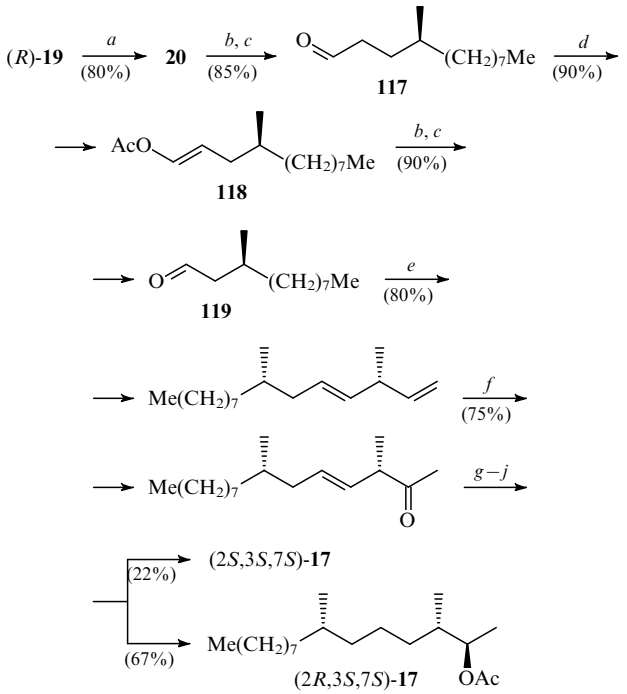


The methyl bromoalkanoate **112**, one of intermediate products in the scheme presented above, has also been employed in the synthesis of (10*R*)-methyldodecyl acetate **116**, the minor component of the sex pheromone of the tea leaf rolling moth (*Adoxophyes fasciata*). The formation of the hydrocarbon chain of **116** was carried out by cross-coupling of the tosylate **115** obtained from the bromide **112** and the Grignard reagent **117**.[20]



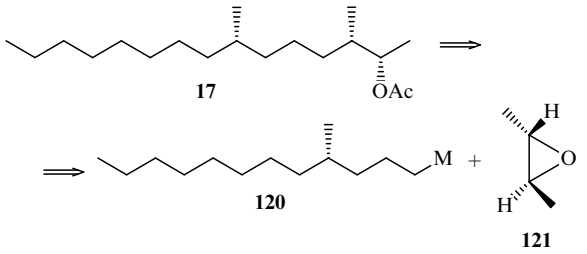
Reagents: (*a*) NaI; (*b*) $LiAlH_4$; (*c*) TsCl/Py;
(*d*) $BrMg(CH_2)_6OTHP$/(**117**)/Li_2CuCl_4; (*e*) MeOH/TsOH;
(*f*) Ac_2O/Py.

A formally two-step synthesis of *erythro*-(2*S*,3*S*,7*S*)- and *threo*-(2*R*,3*S*,7*S*)-diprionyl acetates **17** from the tosylate (*R*)-**19** has been carried out.[21] The aim of the first step was the formation of the structure of the chiral aldehyde **119**; this was accomplished by ozonolysis of the alkene **20** to the aldehyde **117** followed by ozonolysis of the derived enol acetate **118**. The reactions used at the second step of the synthesis of the target acetates (2*S*,3*S*,7*S*)-**17** and (2*R*,3*S*,7*S*)-**17** did not differ from those depicted in Scheme 1 for the enantiomers having the (*R*)-configuration of the C(7) atom.[4,5]

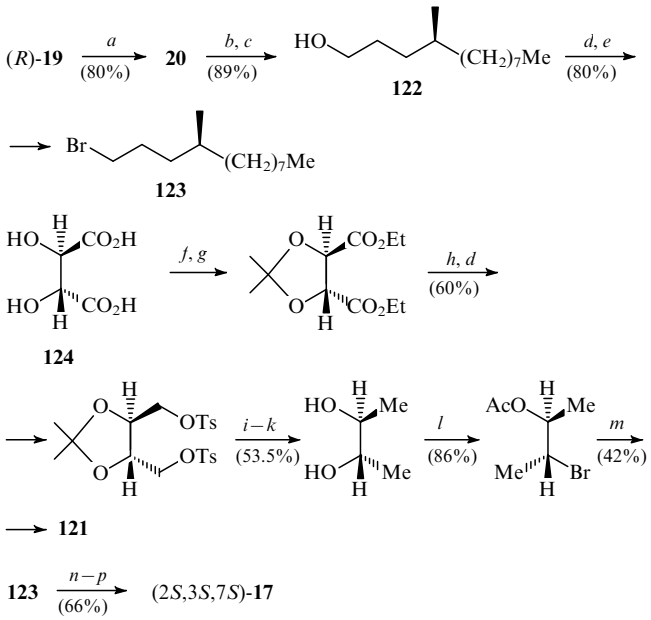


Reagents: (*a*) $Me(CH_2)_5MgCl$/CuI; (*b*) O_3/CH_2Cl_2 – MeOH;
(*c*) Me_2S; (*d*) Ac_2O/AcOK/Et_3N; (*e*) **12**/Bu^nLi;
(*f*) $O_2/PdCl_2$ – CuCl; (*g*) $NaBH_4$; (*h*) H_2/Pt; (*i*) HPLC;
(*j*) Ac_2O/Et_3N/DMAP.

The retrosynthetic analysis of (2*S*,3*S*,7*S*)-diprionyl acetate **17** suggests that this compound can be obtained by the reaction of the organometallic nucleophile **120** with (*S,S*)-2,3-epoxybutane **121**.

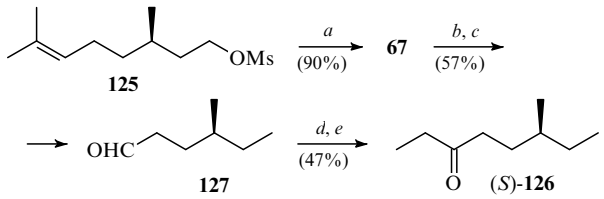


Mori *et al.*[22,23] have performed the synthesis of the bromide **123**, the chiral building block corresponding to the synthon **120**, by the following scheme. The coupling of the tosylate (*R*)-**19** with lithium dihexyl cuprate and subsequent ozonolysis of the alkene **20** gave the alcohol **122**, which was converted into the bromide by conventional methods. The complementary epoxide **121** was synthesised from the natural L-(+)-tartaric acid **124** in nine steps. The reaction of lithium dialkyl cuprate derived from the bromide **123** with the epoxide **121**, which occurred with high stereoselectivity with respect to all the three chiral centres, gave the target product, diprionyl acetate (2*S*,3*S*,7*S*)-**17**.



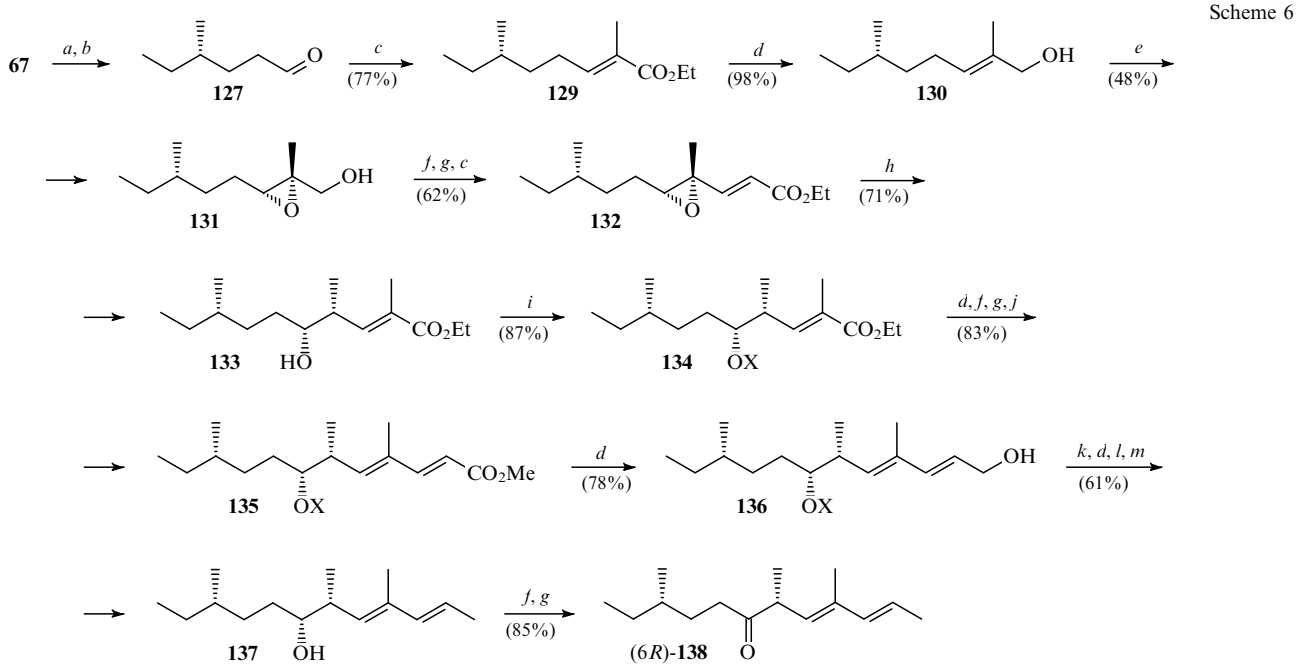
Reagents: (*a*) $[Me(CH_2)_5]_2CuLi$; (*b*) $O_3/CHCl_3$; (*c*) $NaBH_4$; (*d*) TsCl/Py;
(*e*) LiBr; (*f*) $EtOH/H^+$; (*g*) Me_2CO/H^+; (*h*) $LiAlH_4$; (*i*) NaI;
(*j*) H_2/Pd/C; (*k*) HCl; (*l*) HBr/AcOH; (*m*) KOH; (*n*) Li/CuI;
(*o*) **121**; (*p*) AcCl/Py.

Tetrahydromyrcene **67** obtained by reduction of citronellyl mesylate **125** was used in the synthesis of (6*S*)-methyloctan-3-one, (*S*)-**126**, the component of the alarm pheromone of ants of the *Crematogaster* genus.[24]



Reagents: (*a*) $LiAlH_4$; (*b*) MCPBA; (*c*) HIO_4; (*d*) EtMgBr; (*e*) $K_2Cr_2O_7$.

Scheme 6



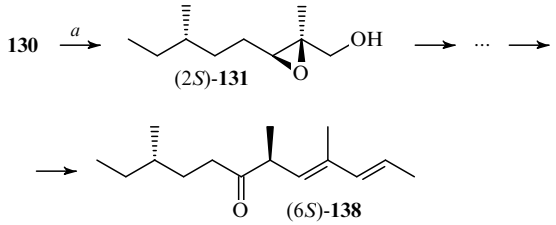
X = $SiMe_2Bu^t$.

Reagents: (*a*) $O_3/NaHCO_3$; (*b*) Me_2S; (*c*) $Ph_3P{=}C(Me)CO_2Et$ (**128**); (*d*) $LiAlH_4$; (*e*) D-(−)-diethyl tartrate [D-(−)-DET)]/$Ti(OPr^i)_4/Bu^tOOH$; (*f*) $(COCl)_2$ – DMSO; (*g*) Et_3N; (*h*) $[Pd_2(dba)_3 \cdot CHCl_3]/PPh_3$ (dba is dibenzoylacetone); (*i*) Bu^tMe_3SiCl/imidazole; (*j*) $(MeO)_2P(O)CH_2COOMe/Bu^nLi$; (*k*) SO_3/Py; (*l*) Bu_4NF; (*m*) HPLC.

(2*E*,4*E*,6*R*,10*S*)-4,6,10-Trimethyl-2,4-dodecadien-7-one, (6*R*)-**138,** and its (6*S*,10*S*)-isomer, (6*S*)-**138**, the major components of the sex pheromone of the cluster pine scale (*Matsucoccus feytaudi*), have been synthesised using the same building block **67**.[25] This synthesis is based on enantioselective epoxidation of the trisubstituted allylic alcohol **130** obtained by a series of transformations from the alkene **67**. The reaction sequence includes ozonolysis and reduction, the Wittig condensation of the resulting aldehyde **127** with the phosphorane **128**, and subsequent reduction of the ester **129** with $LiAlH_4$. The conversion of the hydroxy group of compound (2*R*)-**131** into the aldehyde group and Wittig alkenation gave the compound **132**; the opening of its epoxide ring resulted in the inversion of the C(4) chiral centre. All subsequent conversions of the compound **133** into the compound (6*R*)-**138** occurred with the retention of the configurations of the carbon atoms. The Horner reaction was used to complete the carbon chain of the compound **133** (Scheme 6).

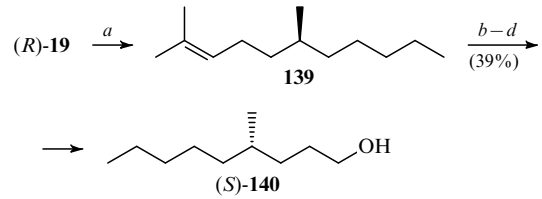
The use of L-(+)-diethyl tartrate in an analogous scheme at the epoxidation stage gave the (6*S*,10*S*) isomer of **138** *via* the compound (2*S*)-**131** (Scheme 7).

Scheme 7



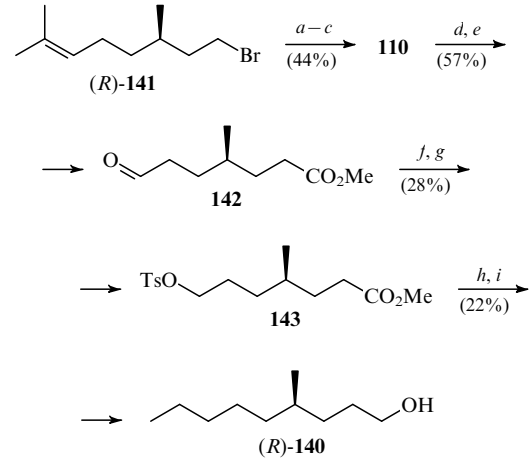
Reagents: (*a*) L-(−)-DET/$Ti(OPr^i)_4/Bu^tOOH$.

Both stereoisomers of 4-methylnonan-1-ol **140** the (*R*)-enantiomer of which is the sex pheromone of the mealworm (*Tenebrio molitor* L.), have been synthesised from citronellyl tosylate (*R*)-**19** and citronellyl bromide **141**.[26] The isomer (*S*)-**140** was obtained through oxidative scission of the double bond in the compound **139**, the condensation product of the tosylate (*R*)-**19** with Pr^nMgBr.



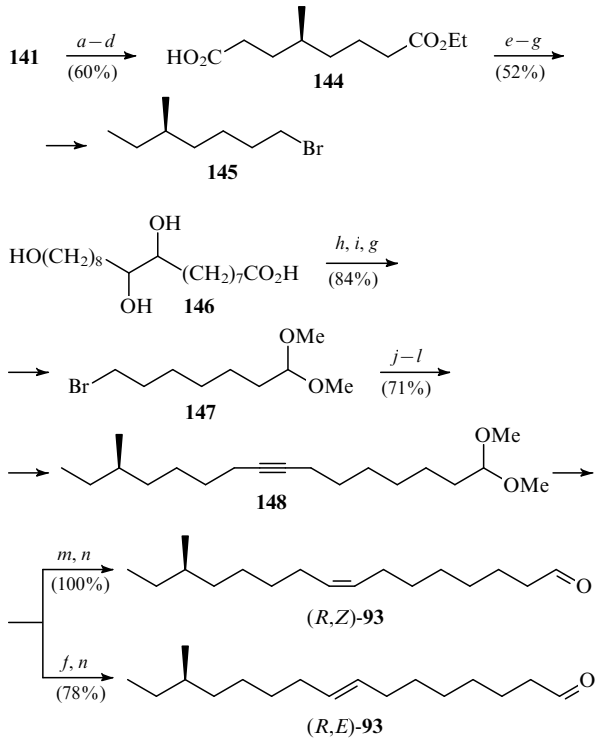
Reagents: (*a*) Pr^nMgBr/Li_2CuCl_4; (*b*) MCPBA; (*c*) HIO_4; (*d*) $LiAlH_4$.

The synthesis of the enantiomer (*R*)-**140** was carried out according to the scheme that involved the conversion of (*R*)-**141** into methyl homocitronellate **110** and oxidative scission of the double bond to give the aldehyde **142**, which was made to react with Et_2CuLi after conversion into the tosylate **143**. The reduction of the carboxyl group yields the target product.



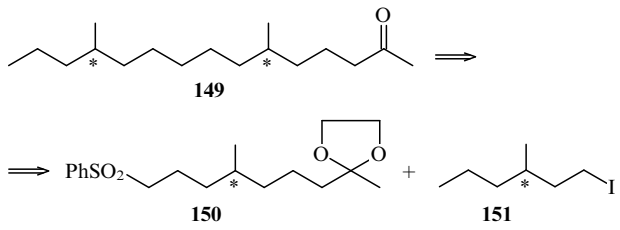
Reagents: (*a*) Mg; (*b*) CO_2; (*c*) $MeOH/H_2SO_4$; (*d*) MCPBA; (*e*) HIO_4; (*f*) $NaBH_4$; (*g*) TsCl/Py; (*h*) Et_2CuLi; (*i*) $LiAlH_4$.

The bromide **141** has proved to be a convenient starting material in the synthesis of the *Z*- and *E*-isomers of (*R*)-trogodermal **93**.[27] The conversion of **141** into the chiral synthon **145** involved the 'malonate' synthesis and ozonolysis with subsequent oxidation leading to the monoester of the dicarboxylic acid **144**. The achiral block **147** was obtained by oxidative scission of aleuritic acid **146**. Successive alkylation of sodium acetylenide with the bromide **147** and of the reaction product, with the chiral bromide **145** yielded the alkyne **148**, the precursor of the target pheromones, which were obtained by stereoselective hydrogenation.



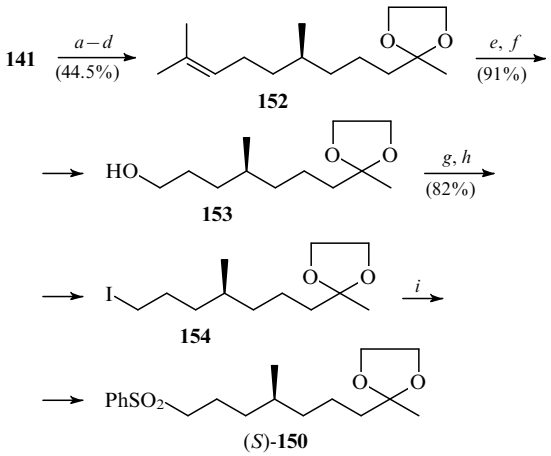
Reagents: (*a*) $NaCH(CO_2Et)_2$; (*b*) $LiCl/H_2O$; (*c*) O_3/MeOH; (*d*) H_2CrO_4; (*e*) $AgNO_3/K_2S_2O_8$; (*f*) $LiAlH_4$; (*g*) $Br_2 \cdot PPh_3$; (*h*) $NaIO_4$; (*i*) MeOH/HCl; (*j*) HC≡CNa; (*k*) Bu^nLi; (*l*) **145**; (*m*) H_2/Ni P-2; (*n*) pyridinium *p*-toluenesulfonate (PPTs)/H_2O.

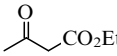
The same bromide (*R*)-**141** has been used in the synthesis of all the stereoisomers of 6,12-dimethylpentadecan-2-one **149**, the sex pheromone of the cucumber flea beetle (*Diabrotica balteata LeConta*). The key stage in this synthesis was the alkylation of the sulfone **150** with the iodide **151**.[28]



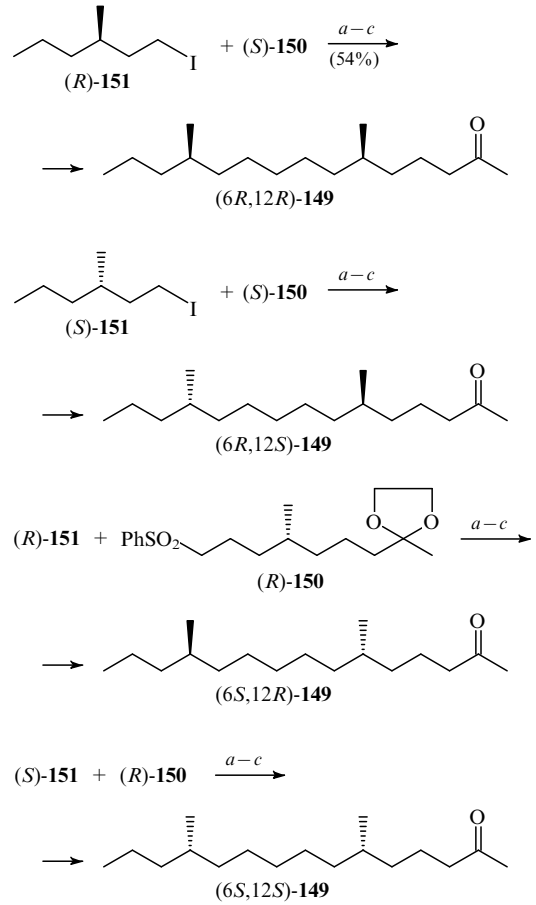
The (*R*)- and (*S*)-enantiomers of the iodide **151** were prepared as described.[29]

In the synthesis of the sulfone (*S*)-**150**, the bromide (*R*)-**141** was first converted into the ketal **152**; its ozonolysis and reduction gave the alcohol **153**. The latter was converted into (*S*)-**150** *via* the iodide **154**. The (*R*)-sulfone **150** was synthesised from citronellyl bromide (*S*)-**141** by an analogous scheme.



Reagents: (*a*)  (*b*) KOH; (*c*) HCl; (*d*) ; (*e*) O_3; (*f*) $NaBH_4$; (*g*) TsCl/Py; (*h*) NaI/$NaHCO_3$; (*i*) $NaSO_2Ph$.

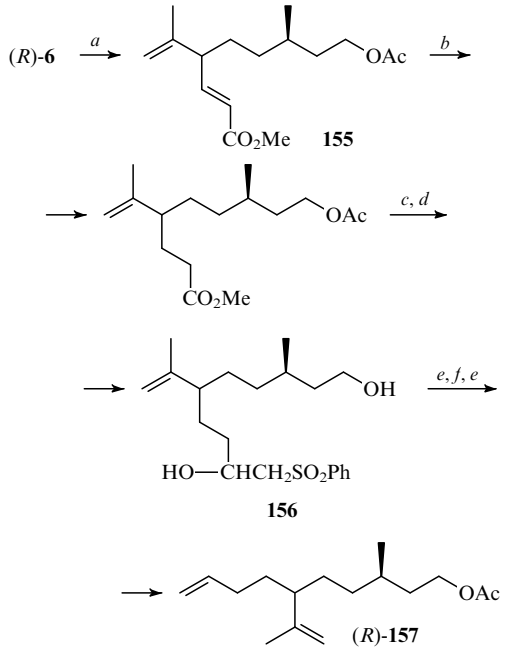
Different variants of the coupling of the sulfones (*R*)- and (*S*)-**150** with the iodides (*R*)- and (*S*)-**151** gave, after desulfonation of the condensation products, all the four optical isomers of **149**.



Reagents: (*a*) Bu^nLi; (*b*) Na–Hg; (*c*) HCl–H_2O.

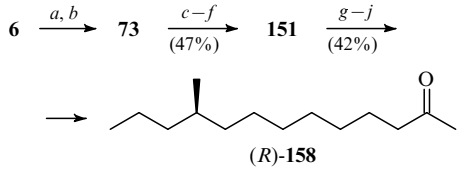
The synthesis of 6-isopropenyl-(3*R*)-methyldec-9-enyl acetate, (*R*)-**157**, the sex pheromone of the California red scale (*Aonidiella aurantii*), from (*R*)-citronellyl acetate **6** has been carried out.[30] The key stage in this synthesis was the $AlCl_3$-catalysed reaction of methyl propiate with the acetate **6,** which occurred with double bond migration to the terminal position to give the diester **155** (a 1 : 1 diastereoisomeric mixture). The

selective reduction of the conjugated double bond in **155** and the subsequent building of the butenyl fragment *via* the intermediate hydroxysulfone **156** yielded the target product, (*R*)-**157**. An analogous synthesis from (*S*)-citronellyl acetate **6** gives (*S*)-**157**.



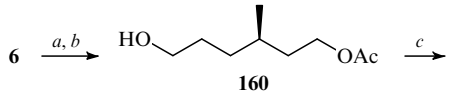
Reagents: (*a*) $HC{\equiv}CCO_2Me/AlCl_3$; (*b*) $Fe(CO)_5/NaOH$; (*c*) $PhSO_2CH_2Li$; (*d*) $NaBH_4$; (*e*) Ac_2O/Py; (*f*) Na – Hg.

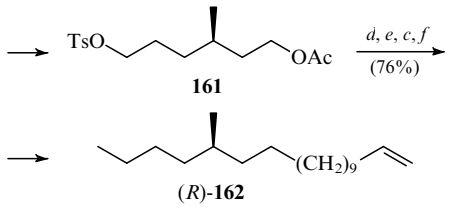
Ozonolysis of the acetate **6** and reduction give the acetoxy aldehyde **73,** which was used in the synthesis of (10*R*)-methyltridecan-2-one **158**, the pheromone of the Western spotted cucumber beetle (*Diabrotica undecimpunctata howardi*). After Wolff–Kishner reduction, the acetoxy aldehyde **73** was converted into the iodide **151**; its coupling with the complementary synthon **159** and conventional procedures gave the target ketone (*R*)-**158**.[29, 31]



Reagents: (*a*) O_3/MeOH; (*b*) Me_2S; (*c*) $NH_2NH_2 \cdot H_2O$; (*d*) KOH; (*e*) TsCl/Py; (*f*) NaI; (*g*) LiC≡C–(OTHP) (**159**); (*h*) H_3O^+; (*i*) H_2/Pd/C; (*j*) H_2CrO_4.

Yet another product of ozonolysis and reduction of the compound (*R*)-**6**, the hydroxyacetate **160,** was converted into the tosylate **161** and used in the synthesis of (14*R*)-methyloctadec-1-ene **162**, the antipode of the sex pheromone of the peach leaf mining beetle (*Lyonetia clerkella*).[32] Successive alkylation with lithium dimethyl and di(undec-10-enyl) cuprates completed the synthesis of the enantiomer (*R*)-**162**.

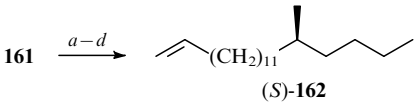




Reagents: (*a*) O_3/MeOH; (*b*) $NaBH_4$; (*c*) TsCl/Py; (*d*) Me_2CuLi; (*e*) NaOH/MeOH; (*f*) $[H_2C{=}CH(CH_2)_9]_2CuLi$.

In the synthesis of the pheromone (*S*)-**162**, the tosylate **161** was alkylated in the reverse order: at first, the alkene fragment of the molecule was built (Scheme 8) and then the reaction with lithium diethyl cuprate was carried out after the conversion of the acetyl group into the tosyl group.[32]

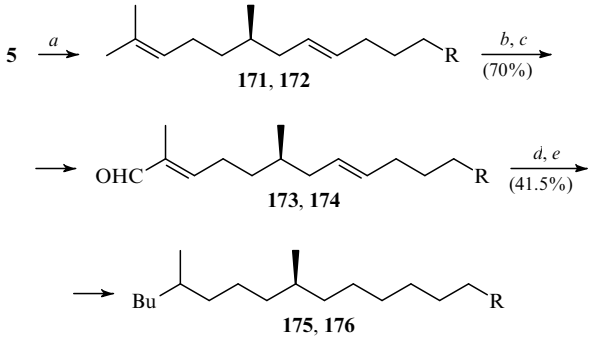
Scheme 8



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

The allylic alcohol **163** formed by the Sharpless oxidation [8] of the acetate **6** was used in the synthesis of (2*R*,8*R*)- and (2*S*,8*R*)-stereoisomers of 8-methyldec-2-yl propionate **170**, the pheromone of the Western flea beetle (*Diabrotica virgifera virgifera*), for the introduction of the (8*R*)-chiral centre.[33] To this end, compound **163** was converted into the bromide **164**. The hydroxy ester (*R*)-**166** prepared by hydrolysis of the (*R*)-poly-β-hydroxybutyrate **165** was used as the key compound in the synthesis of the second chiral fragment. Its antipode, (*S*)-**166**, was obtained by enzymic reduction of the oxo ester **167**. Successive alkylation of the dithiane **168**, first with the bromide **164** and then with the (*R*)- or (*S*)-iodides **82** and subsequent desulfonation of the compounds **169a** and **169b** gave the esters (2*R*,8*R*)- and (2*S*,8*R*)-**170**, respectively (Scheme 9).

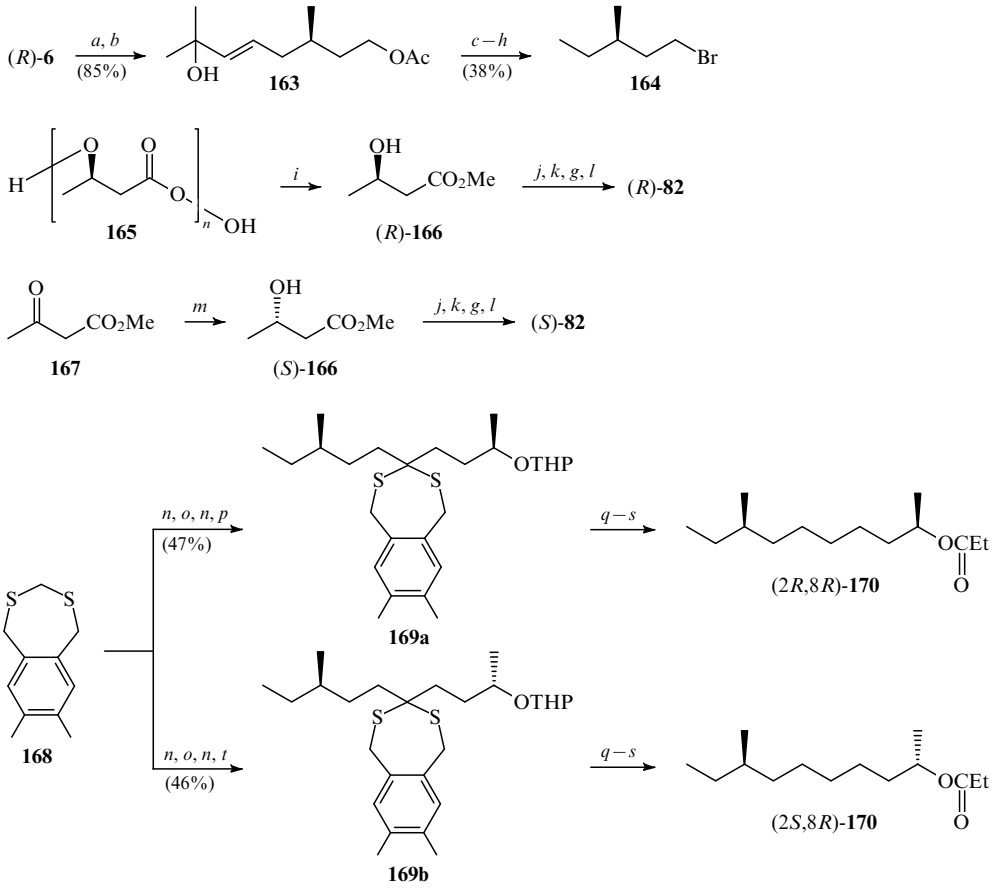
(5*S*/*R*,9*S*)-Dimethylheptadecane **175** and (5*S*/*R*,9*S*)-dimethylpentadecane **176**, the sex pheromones of *Leucoptera scitella* and *Perileucoptera coffeella*, respectively, have been synthesised from the citronellal **5**. The synthetic schemes involved the Wittig alkenation of the aldehyde **5**, selective allylic oxidation of the reaction products **171** and **172,** and repeated alkenation of the resulting aldehydes **173** and **174**.[34]



R = H (**172**, **174**, **176**, **178**), Et (**171**, **173**, **175**, **177**).

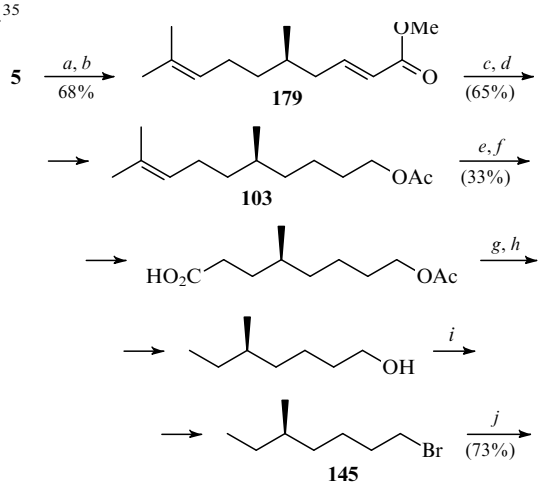
Reagents: (*a*) $[R(CH_2)_4PPh_3]Br$ (**177**, **178**)/NaOMe; (*b*) SeO_2; (*c*) PCC; (*d*) $[Pr^nPPh_3]Br$/NaOMe; (*e*) H_2/Pd/C.

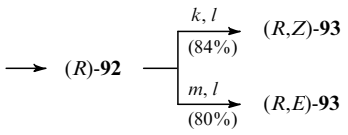
Scheme 9



Reagents: (*a*) Ph_2Se_2/H_2O_2; (*b*) Bu^tOOH; (*c*) O_3/MeOH; (*d*) Me_2S; (*e*) $NH_2NH_2 \cdot H_2O$; (*f*) KOH/H_2O; (*g*) TsCl/Py; (*h*) LiBr; (*i*) *hv*/H_3O^+; (*j*) DHP/TsOH; (*k*) $LiAlH_4$; (*l*) NaI; (*m*) baker's yeast; (*n*) Bu^nLi; (*o*) **164**; (*p*) (*R*)-**82**; (*q*) Raney Ni (Ni–Ra)/EtOH; (*r*) H_3O^+; (*s*) EtCOCl/Py; (*t*) (*S*)-**82**.

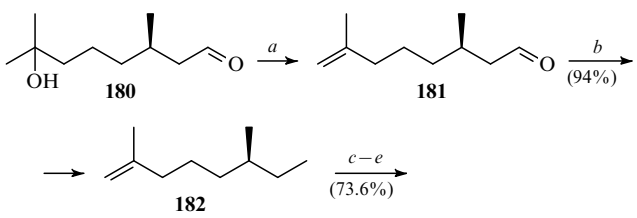
The citronellal (*R*)-**5** has also been employed in the synthesis of *Z*- and *E*-isomers of trogodermal (*R*)-**93**. The aldehyde **5** was condensed with malonic acid according to Doebner and then the dienic ester **179** was converted into the *Z*- or *E*-alkenes **93** by a reaction sequence that included the reduction of the double bond conjugated with the ester group, ozonolysis, and oxidation of the acetate **103** as well as stereoselective hydrogenation of the alkyne **92**.[35]

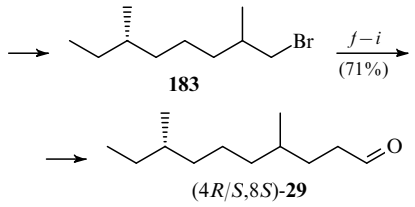




Reagents: (*a*) $CH_2(CO_2H)_2$; (*b*) MeOH/TsOH; (*c*) Li/NH_3/EtOH; (*d*) Ac_2O/Py; (*e*) O_3; (*f*) CrO_3; (*g*) $K_2S_2O_8/AgNO_3$; (*h*) KOH; (*i*) $Br_2 \cdot PPh_3$; (*j*) $LiC{\equiv}C(CH_2)_7OTHP$; (*k*) H_2/Ni–Ra; (*l*) PCC; (*m*) Na/NH_3/EtOH.

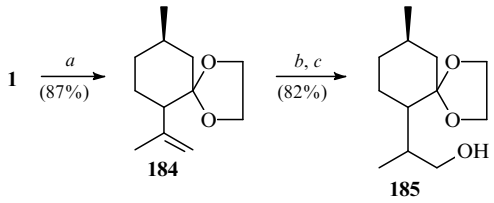
The citronellal derivative (*R*)-**180** served as the starting material in the synthesis of 4,8-dimethyldecanal **29**, configurationally homogeneous with respect to the C(8) atom.[36] The dehydration of the hydroxy aldehyde **180** gave the rodinal **181**, which was converted by the Wolff–Kishner reaction into the alkene **182**. Homologisation of the bromide **183** derived from the compound **182** by a two-step procedure has opened the way to the target product, (4*R*/*S*,8*S*)-**29**.





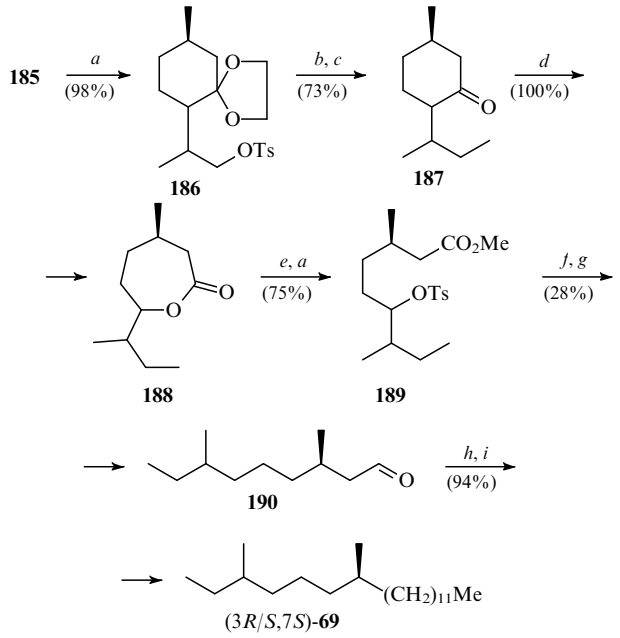
Reagents: (*a*) Al_2O_3, 350 °C; (*b*) $NH_2NH_2 \cdot H_2O/KOH$; (*c*) B_2H_6; (*d*) $H_2O_2/NaOH$; (*e*) $Br_2 \cdot PPh_3$; (*f*) $CH_2(CO_2Et)_2/NaH$; (*g*) AcOK; (*h*) $LiAlH_4$; (*i*) PCC.

The transformation of pulegone **1** involving the Baeyer–Williger reaction was used in the synthesis of two stereoisomeric 3,7-dimethylnonadecanes, (3*R*,7*R*/*S*)- and (3*R*/*S*,7*S*)-**69**.[37] The introduction of the protective ketal group under conditions of acid catalysis was accompanied by a migration of the double bond in the compound **1** to the terminal position. Hydroboration of the resulting α-alkene **184** and subsequent oxidation gave the alcohol **185**, the starting compound for both syntheses.



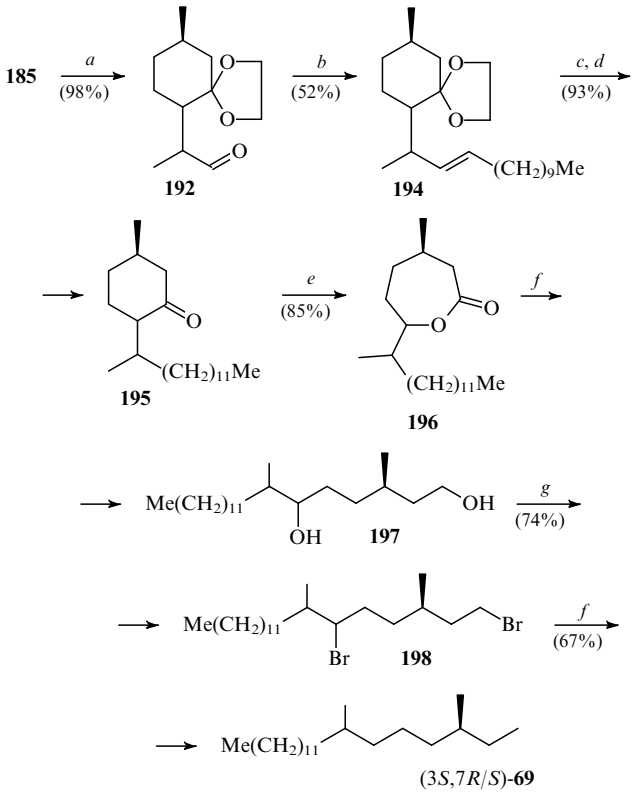
Reagents: (*a*) $(CH_2OH)_2/TsOH$; (*b*) B_2H_6 or 9-BBN; (*c*) $H_2O_2/NaOH$.

To obtain the stereoisomer (3*R*/*S*,7*S*)-**69**, the hydroxy acetal **185** was converted into the ketone **187** *via* the tosylate **186**. The lactone **188**, prepared from the ketone by a regiospecific Baeyer–Williger reaction, was converted into (3*R*/*S*,7*S*)-**69** by a sequence of reactions that involved acid cleavage of **188**, simultaneous reduction of the ester and tosyloxy groups in the compound **189**, and the Wittig reaction between the aldehyde **190** and the phosphorane **191**.[37]



Reagents: (*a*) TsCl/Py; (*b*) Me_2CuLi; (*c*) $HCl-H_2O$; (*d*) MCPBA; (*e*) $MeOH/H_2SO_4$; (*f*) $LiAlH_4$; (*g*) PCC; (*h*) $Me(CH_2)_8CH=PPh_3$ (**191**); (*i*) $H_2/Pd/C$.

In the synthesis of the isomer (3*S*,7*R*/*S*)-**69**, the aldehyde **192** obtained from the alcohol **185** was alkenated with the ylide **193**. The reaction product **194** was converted into the ketone **195**, which was then oxidised by the Baeyer–Williger reaction. The resulting lactone **196** was converted into the diol **197** and further into the dibromide **198**; its hydride reduction gave (3*S*,7*R*/*S*)-**69**.[37]



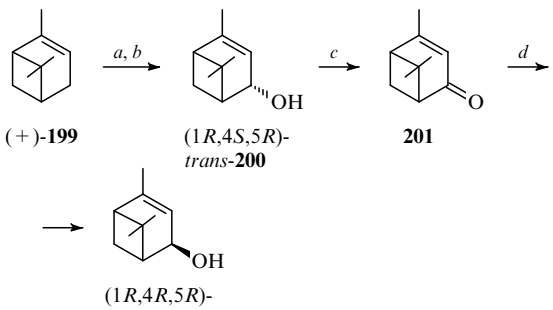
Reagents: (*a*) PCC; (*b*) $Me(CH_2)_9CH=PPh_3$ (**193**); (*c*) H_2/PtO_2; (*d*) $HCl-H_2O$; (*e*) MCPBA; (*f*) $LiAlH_4$; (*g*) $Br_2 \cdot PPh_3$.

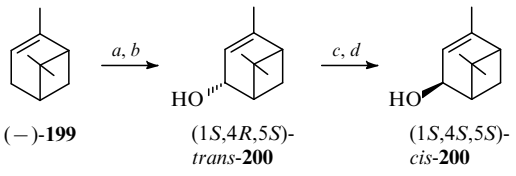
III. Syntheses on the basis of α- and β-pinenes

In the syntheses of pheromones, α- and β-pinenes have also been empoyed. The methods of their functionalisation can be divided into three groups: (1) reactions without scission of the rings; (2) reactions with the retention of the small (four-membered) ring, and (3) reactions with the opening of both rings.

1. Reactions without scission of the rings

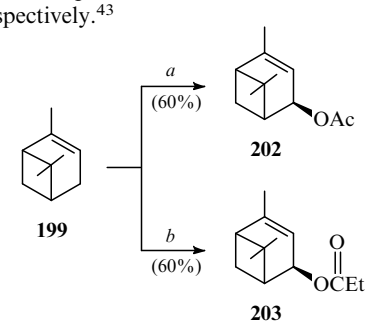
An example of the first type of conversions is the synthesis of *cis*- and *trans*-verbenols **200** constituting the aggregation pheromones of many species of bark beetles of *Ips* and *Dendroctonus* genera. Chiral *trans*-**200** were obtained by allylic oxidation of the corresponding enantiomers of α-pinene **199**,[38,39] whereas *cis*-**200**, by the Jones oxidation of *trans*-verbenol **200** into verbenones **201** with subsequent reduction with $NaBH_4$ [40,41] or $LiAlH_4$.[42]





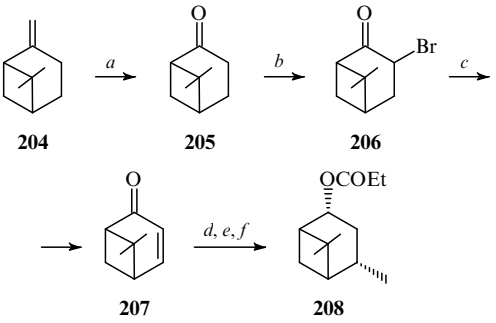
Reagents: (*a*) $Pb(OAc)_4$; (*b*) OH^-; (*c*) $H_2Cr_2O_7$; (*d*) $NaBH_4$ or $LiAlH_4$.

The effective cockroach attractants, *cis*-verbenyl acetate **202** and *cis*-verbenyl propionate **203**, have been synthesised by oxidation of α-pinene **199** with lead tetraacetate or tetrapropionate, respectively.[43]



Reagents: (*a*) $Pb(OAc)_4$; (*b*) $Pb(OCOEt)_4$.

Nopinone **205**, the product of ozonolysis of β-pinene **204**, has found wide application in the synthesis of insect pheromones.[44–46] For example, the bicyclic propionate **208** possessing the activity of the sex pheromone of cockroaches, was prepared by transformation of the ketone **205** into apoverbenone **207** *via* the corresponding monobromide **206**.[44]



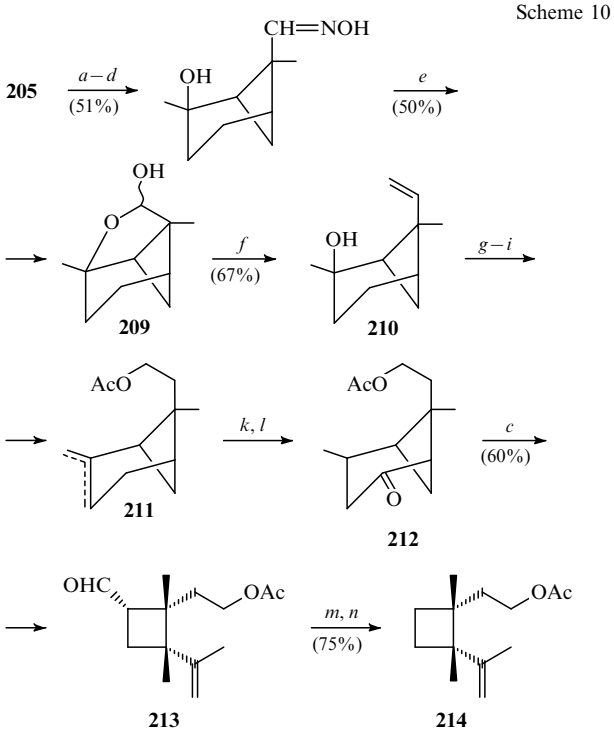
Reagents: (*a*) O_3/MeOH; (*b*) Br_2; (*c*) 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU); (*d*) Me_2CuLi; (*e*) $(Pr^iO)_3Al/Pr^iOH$; (*f*) $(EtCO)_2O$.

2. Reactions with the retention of the four-membered ring

The ketone **205** has also served as the starting material in the synthesis of (+)-grandisol **214**, the aggregation-sex pheromone of the boll weevil (*Anthonomus grandis*).[47,48] The lactol **209** prepared from the ketone **205** by a five-step procedure was converted by the Wittig reaction into the alkene **210** and then, by a series of simple reactions, into a mixture of alkenes **211**; their allylic oxidation and subsequent hydrogenation gave the ketone **212**. The Norrish photocleavage of this compound followed by deformylation of the resulting aldehyde **213** with the Wilkinson complex and the removal of acetate protection eventually resulted in the target pheromone, (1*R*,2*S*)-**214** (Scheme 10).

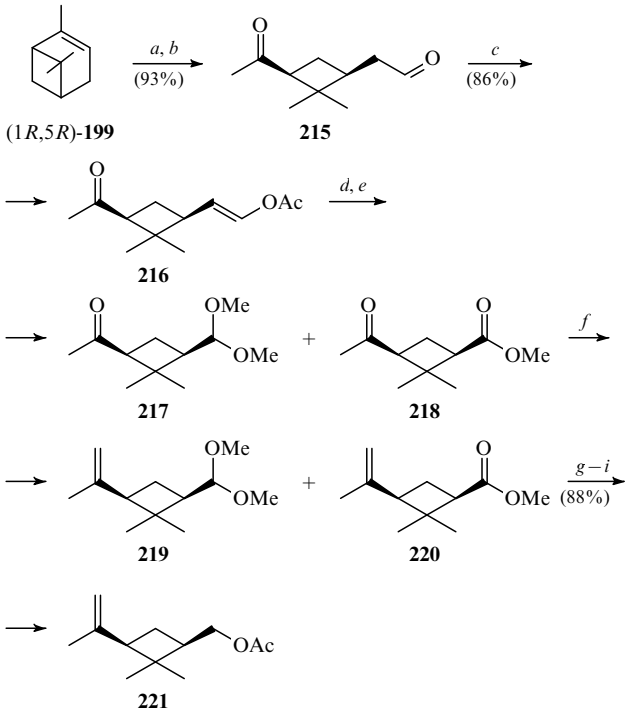
The scission of α-pinene **199** with the retention of the small ring was employed in the synthesis of (+)-(1*R*,3*R*)-1-acetoxymethyl-3-isopropenyl-2,2-dimethylcyclobutane **221**, the sex pheromone of the citrus mealybug (*Planococcus citri*).[49,50] This involved the ozonolysis of **199** to yield the oxo aldehyde **215** with the configuration of the chiral centres identical with that of the natural pheromone. The necessary shortening of the side chain was carried out *via* the enol acetate **216**; its ozonolysis gave a

Scheme 10



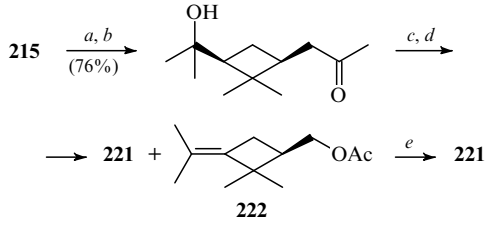
Reagents: (*a*) MeMgBr; (*b*) NOCl; (*c*) *hv*; (*d*) Δ; (*e*) H_3O^+; (*f*) $H_2C=PPh_3$; (*g*) R_2BH; (*h*) H_2O_2/NaOH; (*i*) Ac_2O/Py; (*j*) $POCl_3$/Py; (*k*) $CrO_3 \cdot Py$; (*l*) H_2/Pd/C; (*m*) $(PPh_3)_3RhCl$; (*n*) $LiAlH_4$.

mixture of the acetal **217** and the ester **218**. Treatment of this mixture with methylenephosphorane yielded a mixture of **219** and **220** further converted into the acetate **221** by a three-step procedure. Compound (−)-**221** was synthesised from α-(−)-pinene according to the same scheme.[51]



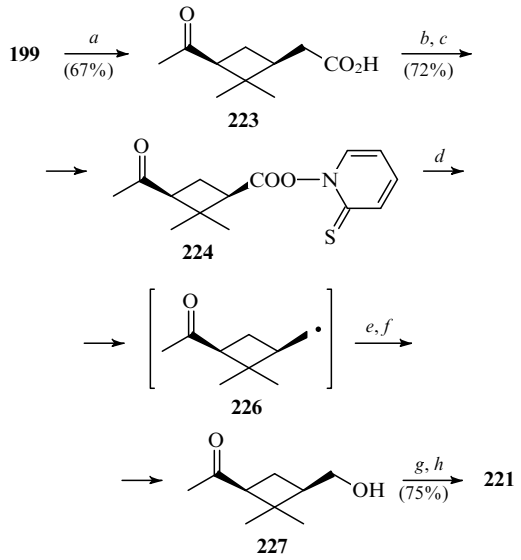
Reagents: (*a*) O_3/MeOH; (*b*) H_2/Pd/$CaCO_3$/PbO; (*c*) Ac_2O/NEt_3; (*d*) O_3/SiO_2; (*e*) MeOH/TsOH; (*f*) $H_2C=PPh_3$; (*g*) PPTs/H_2O; (*h*) Bu^i_2AlH; *i*) Ac_2O/Py.

The oxo aldehyde **215** is the key compound in yet another scheme of the synthesis of the compound **221** in which the final stage produced a mixture of acetates **221** and **222** separated chromatographically.[52]



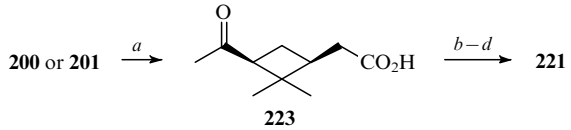
Reagents: (*a*) MeMgI; (*b*) CrO_3; (*c*) $PhCO_3H$; (*d*) $POCl_3$/Py; (*e*) $SiO_2/AgNO_3$.

The pheromone **221** has also been synthesised from the oxo acid **223**, another oxidation product of α-pinene **199**. Irradiation of the product of its reaction with *N*-hydroxy-2-thiopyridine with a tungsten-lamp light gave the intermediate radical **226**; its catalytic oxidation with oxygen and subsequent hydrolysis yielded the alcohol **227**. It was then converted into the target compound **221** by standard procedures.[53]



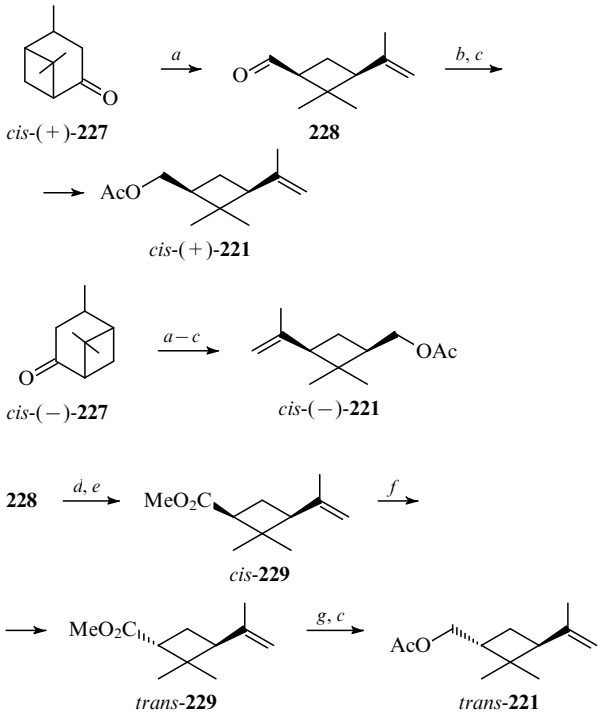
Reagents: (*a*) $KMnO_4/(NH_4)_2SO_4/H_2O$; (*b*) SO_2Cl_2; (*c*) HO–N(S) (**225**); (*d*) *hv*/CH_2Cl_2; (*e*) $O_2/Ph_2SbS(2\text{-}MeOC_6H_4)$; (*f*) H_2O; (*g*) Ac_2O/Py; (*h*) $H_2C=PPh_3$.

Yet another synthesis of **221** is based on the use of the oxo acid **223**, the product of the oxidative cleavage of (+)-verbenone **201** or *cis*- and *trans*-verbenols **200** with ruthenium chloride in combination with sodium periodate.[54]



Reagents: (*a*) $RuCl_3 \cdot 3H_2O/NaIO_4$; (*b*) $H_2C=PPh_3$; (*c*) $LiAlH_4$; (*d*) Ac_2O/Et_3N.

The cyclic aldehyde **228**, the photolysis product of *cis*-(+)-verbanone **227**, has also found application in the synthesis of *cis*-(+)-**221**. The *cis*-(−)-isomer **221** was obtained from *cis*-(−)-verbanone **227** in an analogous way. The *trans*-isomer **221** was synthesised by conversion of **228** into the *cis*-ester **229** with its subsequent epimerisation into the *trans*-isomer **229**.[55]

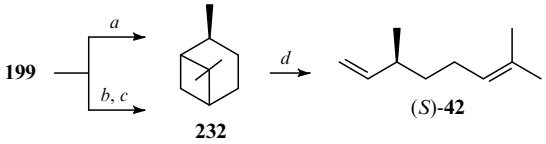


Reagents: (*a*) *hv*; (*b*) $NaBH_4$; (*c*) Ac_2O/Py; (*d*) CrO_3; (*e*) $MeOH/H^+$; (*f*) MeONa/MeOH; (*g*) $LiAlH_4$.

3. Reactions with the opening of both rings

An elegant method for the synthesis of both enantiomers of 2-methyl-6-methyleneocta-2,7-dien-4-ol (ipsdienol) **231**, the aggregation-sex pheromone of many *Ips* species, is based on a four-step transformation of the optically active verbenones **201**. β-Verbenols **230a**–**230d** obtained by the reduction of the corresponding non-conjugated ketones were subjected to flash pyrolysis to give the target alcohols **231** with the retention of the absolute configuration of the chiral centre of C(4) in the corresponding alcohols **230** (Scheme 11).[56]

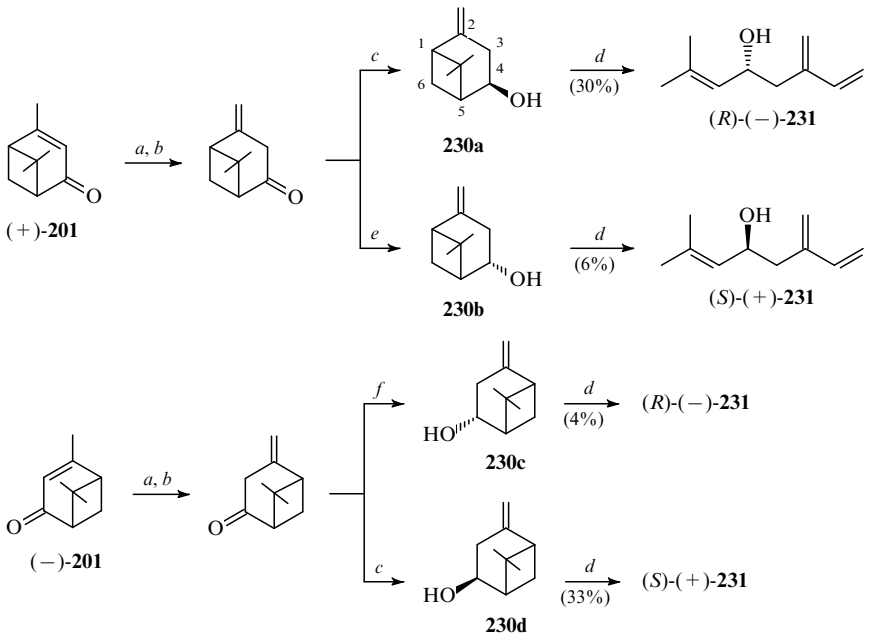
Catalytic hydrogenation of α-(+)-pinene **199** followed by hydroboration and hydrolysis give predominantly *cis*-(+)-pinane **232**.[57] Its thermolysis yields a mixture of products the main component of which is (*S*)-(+)-dihydromyrcene (*S*)-**42**.[58]



Reagents: (*a*) H_2/PtO_2 or Ni; (*b*) B_2H_6; (*c*) H_2O; (*d*) 550 °C.

The ketone **233**, the product of the Walker–Tsuji oxidation of the diene (*S*)-**42**, has proved to be a convenient starting material in the synthesis of diprionyl acetate **17** as an equimolar mixture of two diastereomeric pairs having (2*S*,3*S*,7*S*/*R*)- and (2*R*,3*S*,7*S*/*R*)-configurations.[59] Hydride reduction of the ketone **233** gave a mixture (~ 1 : 1) of the *erythro*-(2*S*,3*S*)- and *threo*-(2*R*,3*S*)-alcohols **234** converted into a mixture of diastereomeric diacetoxy alkenes **236** *via* the corresponding acetates **235**. The latter were obtained in higher yields from the products of allylic oxidation of the ketone **233**. The allylic acetoxy group in **236** was efficiently substituted by alkyl by treatment with the organocuprate reagent. The hydrogenation of the double bond in the thus obtained alkenyl acetate **237** resulting in the formation of the third chiral

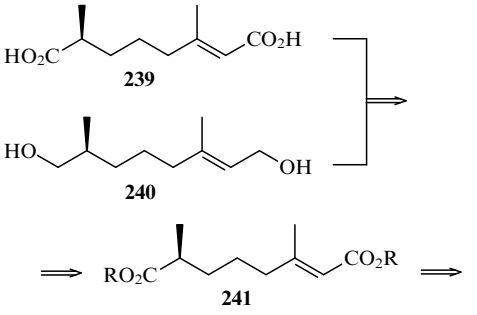
Scheme 11

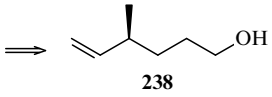


Reagents: (*a*) NaH; (*b*) H_3BO_3; (*c*) $LiAlH_4$; (*d*) 550 °C; (*e*) $(Pr^iO)_3Al/Pr^iOH$; (*f*) Li/NH_3.

centre at C(7) occurs in a fully nonstereoselective manner (Scheme 12).[59]

The unsaturated alcohol **238**, the product of selective ozonolysis of the diene (*S*)-**42** at the trisubstituted double bond, has been successfully employed in the synthesis of (3,7*S*)-dimethyloct-(2*E*)-enedioic acid **239** and (3,7*S*)-dimethyloct-(2*E*)-ene-1,8-diol **240**, the components of the sex pheromones of the Chinese bean weevil (*Callosobruchus chinensis*) and the African monarch (*Danaus chrysippus*), respectively. A retrosynthetic analysis of **239** and **240** revealed the efficiency of their syntheses *via* the intermediate diester **241**.[60]

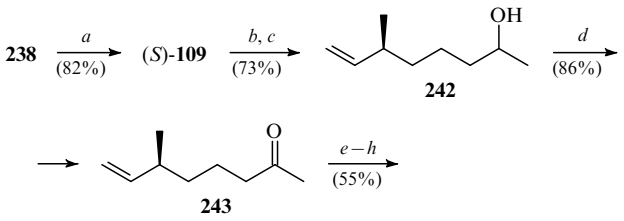




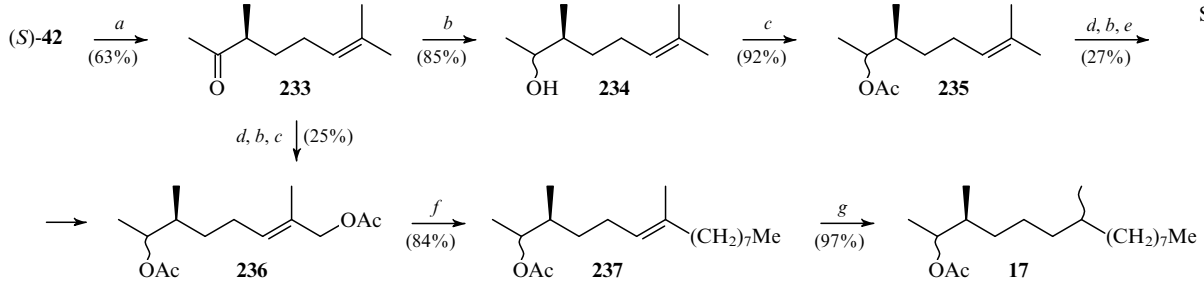
(*S*)-**42** $\xrightarrow[(81.4\%)]{a, b}$ **238**

Reagents: (*a*) $O_3/CH_2Cl_2/MeOH$; (*b*) $NaBH_4$.

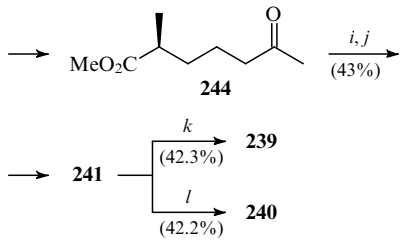
To this end, the bromide (*S*)-**109** derived from **238** was introduced into the Grignard reaction with the acetaldehyde; the resulting alcohol **242** was converted into the unsaturated ketone **243** which was further subjected to ozonolysis. The subsequent Horner alkenation of the oxo ester **244** resulted in the diester **241** the hydrolysis or the hydride reduction of which gave the target compounds, **239** and **240**.



Scheme 12

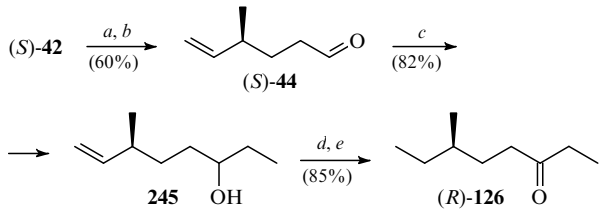


Reagents: (*a*) $O_2/PdCl_2-CuCl$; (*b*) $NaBH_4$; (*c*) $Ac_2O/NEt_3/DMAP$; (*d*) SeO_2; (*e*) Ac_2O/Py; (*f*) $Me(CH_2)_6Br/Mg/CuI$; (*g*) $H_2/Pd/C$.



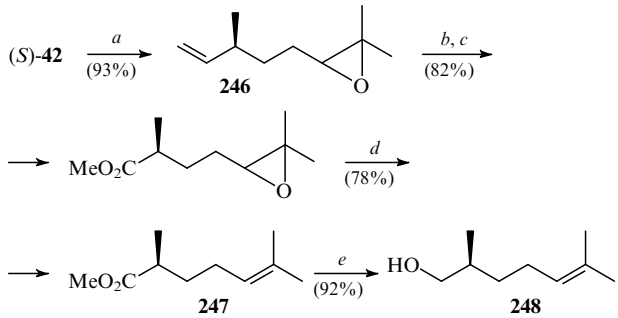
Reagents: (*a*) PBr_3/Py; (*b*) Mg; (*c*) MeCHO; (*d*) PCC; (*e*) O_3/CH_2Cl_2/MeOH; (*f*) H_2/Pd/$CaCO_3$–PbO; (*g*) Ag_2O; (*h*) CH_2N_2; (*i*) $(MeO)_2P(O)CH_2CO_2Et$/EtONa; (*j*) $SiO_2/AgNO_3$; (*k*) NaOH/MeOH; (*l*) Bu^i_2AlH.

The aldehyde (*S*)-**44**, another product of the ozonolytic cleavage of the diene (*S*)-**42**, was used in the synthesis of (6*R*)-methyloctan-3-one (*R*)-**126**, the component of the alarm pheromone of ants of the C*rematogaster* genus.[61] The interaction of the aldehyde (*S*)-**44** with EtMgBr, the catalytic hydrogenation of the double bond in the resulting alcohol **245**, and the subsequent oxidation gave the target ketone (*R*)-**126**.



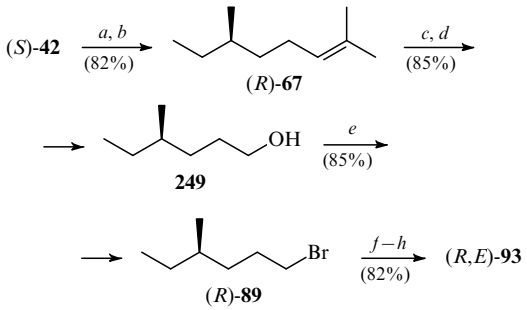
Reagents: (*a*) O_3/CH_2Cl_2/MeOH/$NaHCO_3$; (*b*) H_2/Pd/$CaCO_3$–PbO; (*c*) EtMgBr; (*d*) H_2/Pd/C; (*e*) PCC.

The synthesis of (2*S*),6-dimethylhept-5-en-1-ol **248**, the alarm pheromone of ants of the *Acanthomyops claviger* genus,[61] required the scission of the vinyl group in the diene (*S*)-**42**. For this purpose, the isopropylidene group, which is more sensitive to electrophilic reagents, was protected by conversion into the epoxide **246**. Its ozonolysis followed by regeneration of the double bond with AlI_3 resulted in the ester **247**, which was converted into the alcohol **248** by standard procedures.

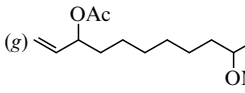


Reagents: (*a*) $Bu^tOOH/Mo(CO)_6$; (*b*) O_3/CH_2Cl_2–MeOH; (*c*) Ac_2O/Et_3N; (*d*) AlI_3/MeCN; (*e*) Bu^i_2AlH.

Catalytic hydroalumination of the diene (*S*)-**42** and subsequent hydrolysis gave the alkene (*R*)-**67**, which was converted by ozonolysis and reduction into the alcohol **249**. The corresponding bromide (*R*)-**89** was used in the synthesis of (*R*,*E*)-trogodermal **93**.[62] The regio- and stereo-selective coupling of the magnesium–cuprate reagent derived from (*R*)-**89** with the allylic acetate **250**, which occurs as the S_N2' process, and deprotection gave the target product, (*R*,*E*)-**93**.

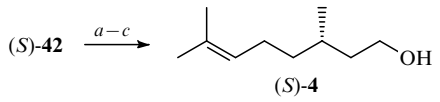


Reagents: (*a*) $Bu^i_2AlH/ZrCl_4$; (*b*) H_2O; (*c*) O_3/THF/MeOH; (*d*) $NaBH_4$; (*e*) PBr_3/Py; (*f*) Mg/CuI;



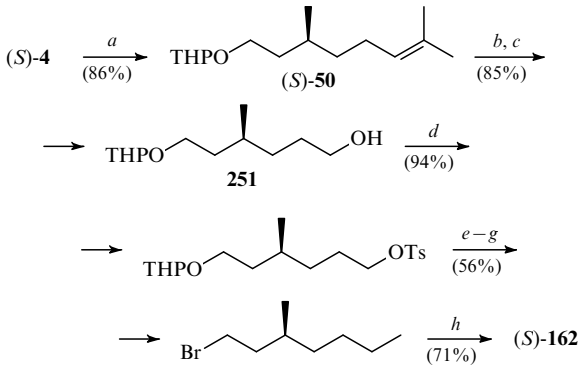
(*g*); (*h*) PPTs/H_2O.

(*S*)-Citronellol, (S)-**4**, is the only oxidation product of the organoaluminium adduct of dihydromyrcene (*S*)-**42**.[63] This compound and some of its derivatives were used in pheromone syntheses



Reagents: (*a*) Bu^i_3Al or $Bu^i_2AlH/ZrCl_4$; (*b*) O_2; (*c*) H_2O.

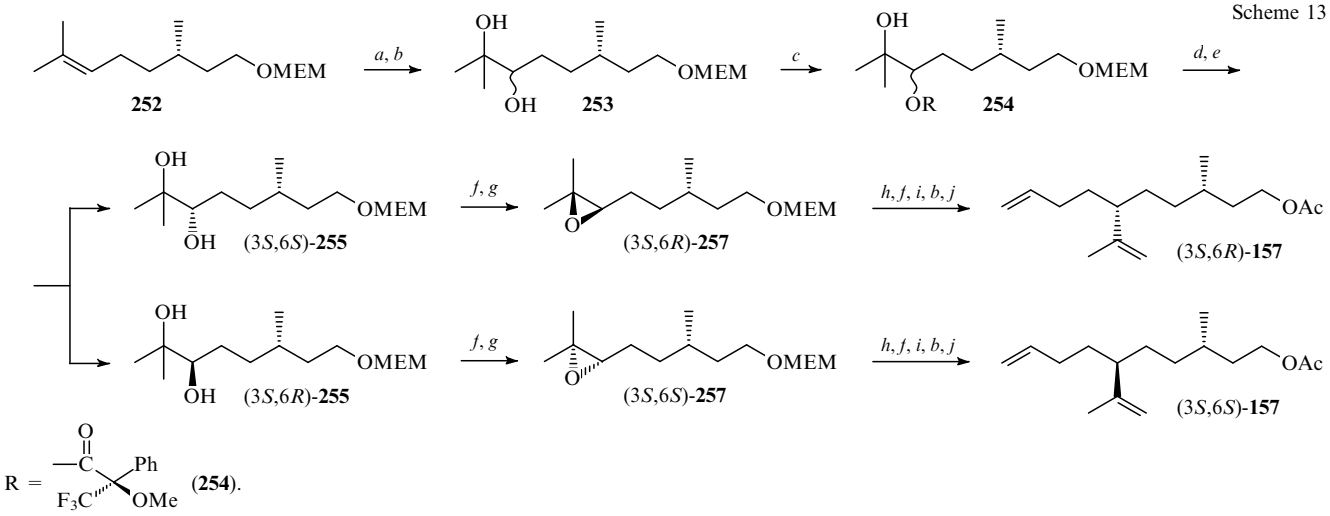
Thus the tetrahydropyranyl ether of (*S*)-citronellol, (*S*)-(**50**), has found application in the synthesis of (14*S*)-methyloctadec-1-ene, (*S*)-**162**, after its ozonolytic conversion into the monosubstituted diol **251**. Alkylation of the derived tosylate with MeMgI and the subsequent interaction of the bromo-derivative with undec-10-enylmagnesium bromide completed the synthesis of the pheromone (*S*)-**162**.[63]



Reagents: (*a*) DHP/TsOH; (*b*) O_3/MeOH; (*c*) $NaBH_4$; (*d*) TsCl/Py; (*e*) $MeMgI/Li_2CuCl_4$; (*f*) HCl–H_2O; (*g*) PBr_3/Py; (*h*) $H_2C{=}CH(CH_2)_9MgBr/CuI$–2,2′-bipyridyl (bipy).

The methoxyethylmethyl ether of citronellol **252** was used in the synthesis of (3*S*,6*R*)-**157**, the pheromone of the California red scale, and its (3*S*,6*S*)-enantiomer. For this purpose, compound **252** was converted into the glycol **253** by epoxidation and subsequent hydrolysis; the glycol was treated with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride **256** to give the diester **254** as a mixture of diastereomers readily separable chromatographically. Each of these was reduced to the corresponding diol **255**; selective mesylation of the secondary hydroxy group and treatment of the mesylates with an alkali gave epoxides **257** with inversion of the chiral centre at the C(6) atom. The

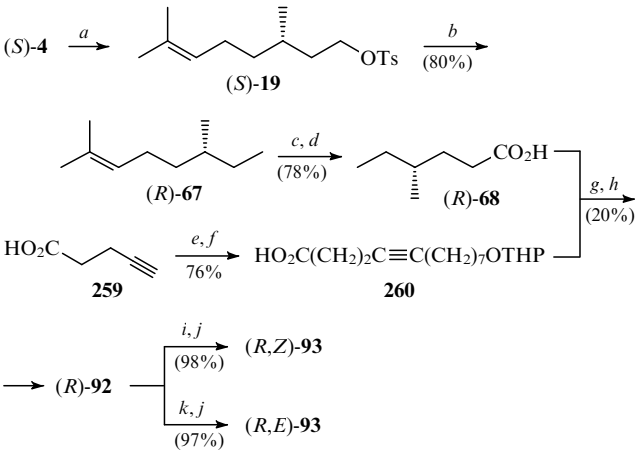
Scheme 13



Reagents: (*a*) MCPBA; (*b*) H_3O^+; (*c*) RCl (**256**); (*d*) HPLC; (*e*) $LiAlH_4$; (*f*) $MeSO_2Cl$; (*g*) KOH/MeOH; (*h*) $(H_2C=CHCH_2CH_2)_2CuLi$ (**258**); (*i*) Bu^nLi; (*j*) Ac_2O/Py.

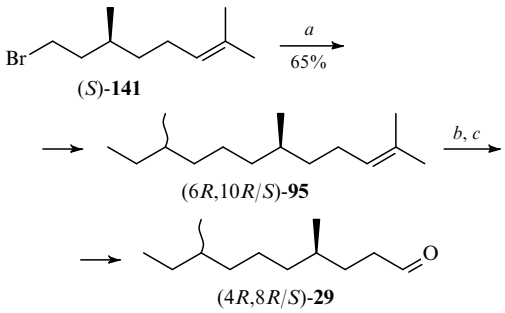
reaction of the epoxide with the cuprate reagent **258**, the dehydration of the intermediate alcohols, and the substitution of the methoxyethylmethyl group for the acetate group completed the synthesis of the pheromone **157** (Scheme 13).[64]

The isomeric trogodermals (*R*,*E*)- and (*R*,*Z*)-**93** were synthesised by electrolysis of a mixture of (−)-4*R*-methylhexanoic (*R*)-**68** and 12-(2-tetrahydropyranyloxy)dodec-4-ynoic **260** acids with subsequent stereoselective hydrogenation of the resulting acetylenic alcohol **92**.[65] The chiral acid (*R*)-**68** was synthesised by ozonolysis and oxidation of the alkene (*R*)-**67**, the product of hydride reduction of citronellyl tosylate (*S*)-**19**, whereas the achiral acid **260**, by alkylation of the pent-4-ynoic acid **259** acetylenide with the bromo ester **94**.



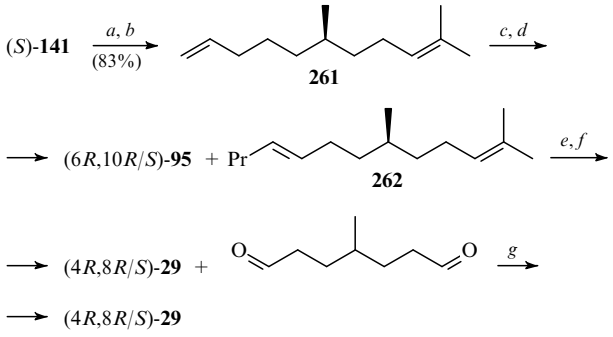
Reagents: (*a*) TsCl/Py; (*b*) $LiAlH_4$; (*c*) O_3; (*d*) H_2CrO_4; (*e*) Bu^nLi; (*f*) **94**; (*g*) e^-; (*h*) HCl; (*i*) H_2/Pd/$CaCO_3$ – PbO; (*j*) PCC; (*k*) Na/NH_3.

Citronellyl bromide (*S*)-**141** was used as the starting material in the synthesis of an equimolar mixture of the natural (4*R*,8*R*)- and the synergistic (4*R*,8*S*)-enantiomers of the mealworm attractants **29**.[66] The reaction of the bromide (*S*)-**141** with the Grignard reagent from racemic 1-bromo-2-methylbutane **28** gave the alkene **95**; its ozonolysis and the subsequent reduction of the peroxide completed the synthesis of the pheromone (4*R*,8*R*/*S*)-**29**.



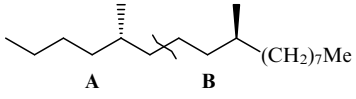
Reagents: (*a*) **28**/Mg/Li_2CuCl_4; (*b*) O_3/MeOH/CH_2Cl_2; (*c*) Me_2S.

The mixture (4*R*,8*R*/*S*)-**29** was obtained in higher yield according to a scheme involving the interaction of the Grignard reagent prepared from the bromide (*S*)-**141** with allyl bromide and selective carbomagnesation of the resulting diene **261** at the terminal double bond.[66] The carbomagnesation product **95** contained no more than 5% of the diene **262,** which was converted by ozonolysis into the corresponding dialdehyde, which was readily separated from the target product by chromatography.

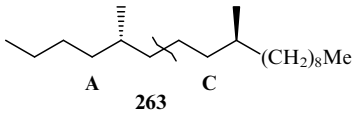


Reagents: (*a*) Mg; (*b*) $H_2C=CHCH_2Br/CuI$ – bipy; (*c*) Et_2Mg/Cp_2ZrCl_2; (*d*) H_3O^+; (*e*) O_3/MeOH – CH_2Cl_2; (*f*) Me_2S; (*g*) SiO_2.

The sex pheromone of *Leucoptera malifoliella* comprises two components: the major component, (5*S*,9*S*)-dimethylheptadecane **175**, and the minor component, (5*S*,9*S*)-dimethyloctadecane **263**. A retrosynthetic analysis of these compounds shows the expedience of their synthesis from the three chiral blocks: **A**, **B**, and **C**.[67]

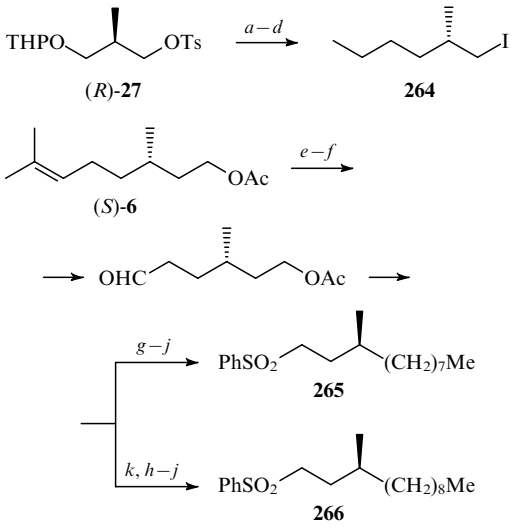


(5*S*,9*S*)-**175**



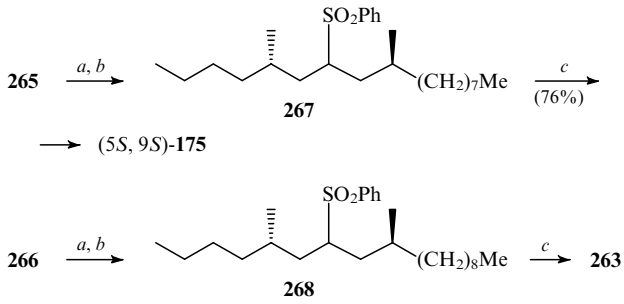
263

The iodide **264** corresponding to the fragment **A** was synthesised from the tosylate **27**, while the sulfones **265** and **266** corresponding to the blocks **B** and **C**, from (*S*)-citronellyl acetate, (*S*)-**6**.



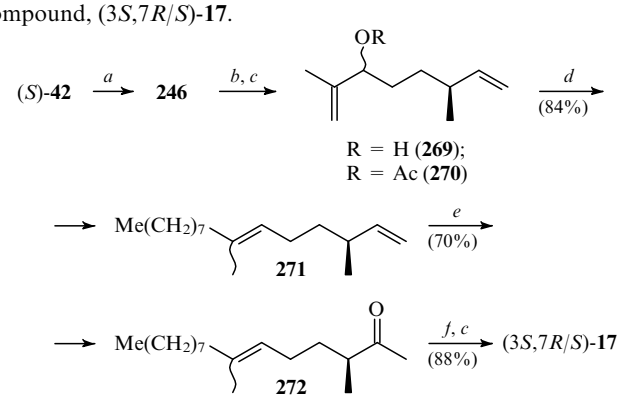
Reagents: (*a*) $PrMgBr/Li_2CuCl_4$; (*b*) H_3O^+; (*c*) TsCl/Py; (*d*) NaI; (*e*) O_3/MeOH; (*f*) Me_2S; (*g*) $Ph_3P=CHBu$; (*h*) $LiAlH_4/CoCl_2$; (*i*) PhSNa; (*j*) MCPBA; (*k*) $Ph_3P=CH(CH_2)_4Me$.

The alkylation of the sulfones **265** and **266** with the iodide **264** and subsequent desulfonation of the products **267** and **268** yielded the target structures, **175** and **263.**



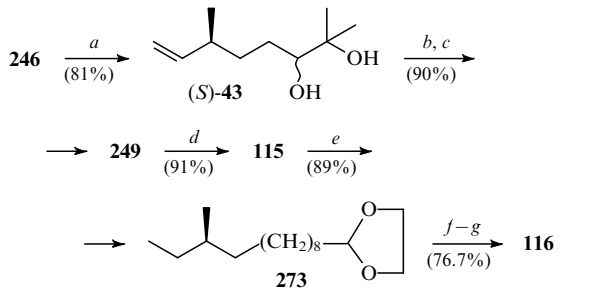
Reagents: (*a*) Bu^nLi; (*b*) **264**; (*c*) Na – Hg.

The oxidation of the diene (*S*)-**42** by peroxy acids occurs selectively with the formation of the monoepoxide **246**, which is smoothly isomerised into the allylic alcohol **269** employed in the synthesis of an equimolar mixture of *erythro*- and *threo*-diprionyl acetates **17**, which are configurationally homogeneous with respect to the (3*S*)-chiral centre.[68] The CuI-catalysed coupling of the acetate **270** with heptylmagnesium bromide, the conversion of the reaction product **271** into the enone **272** by Walker – Tsuji oxidation, and further simple conversions yielded the target compound, (3*S*,7*R*/*S*)-**17**.



Reagents: (*a*) MCPBA; (*b*) LDA; (*c*) Ac_2O/Et_3N/DMAP; (*d*) $Me(CH_2)_6MgBr$/CuI; (*e*) $O_2/PdCl_2 - CuCl$; (*f*) H_2/Ni.

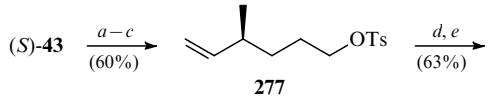
In the synthesis of (10*R*)-methyldodecyl acetate **116**, the monoepoxide **246** was converted into the saturated alcohol **249** *via* the diol (*S*)-**43**. Coupling of the derived tosylate **115** with the Grignard reagent **274** completed the synthesis of the pheromone **116**.[69]



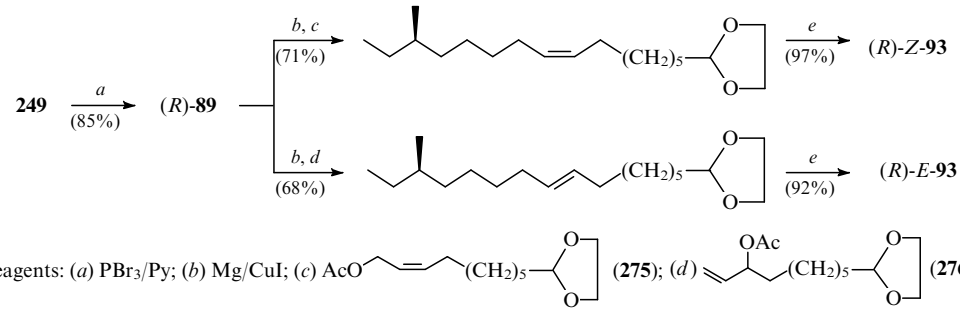
Reagents: (*a*) $HClO_4$; (*b*) HIO_4; (*c*) H_2/Ni; (*d*) TsCl/Py; (*e*) $BrMg(CH_2)_5$–(O,O) (**274**); (*f*) $HCl - H_2O$; (*g*) $NaBH_4$; (*h*) Ac_2O/Py.

The bromide (*R*)-**89**, another derivative of the alcohol **249**, was employed in the synthesis of *Z*- and *E*-trogodermals **93** having the (*R*)-configuration. The key stages in this synthesis are the CuI-catalysed cross-couplings of the corresponding Grignard reagent with the primary acetate **275**[70] and the secondary allylic acetate **276**[71] mediated by the S_N2 and S_N2' mechanisms, respectively (Scheme 14).

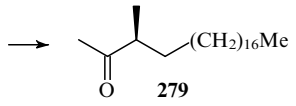
The acid **114** obtained by the Jones oxidation of the diol (*S*)-**43** was used in the synthesis of (+)-(3*S*)-methylheneicosan-2-one **279**, the analogue of the sex pheromone of the German cockroach (*Blattella germanica*). To this end, compound **114** was converted into the tosylate **277** by a two-step procedure; its coupling with the Grignard reagent **278** followed by the Walker – Tsuji oxidation of the intermediate alkene completed the synthesis of the target ketone **279**.[72]



Scheme 14



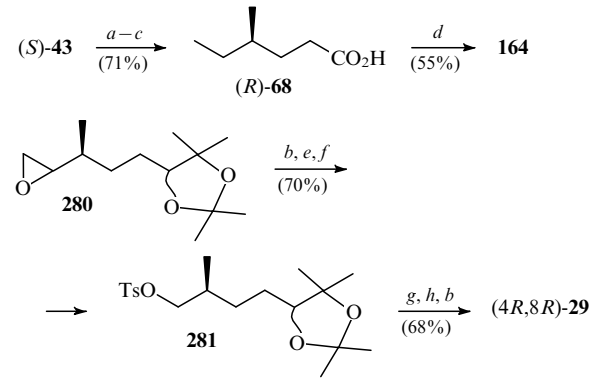
Reagents: (*a*) PBr_3/Py; (*b*) Mg/CuI; (*c*) AcO(CH$_2$)$_5$ (**275**); (*d*) OAc(CH$_2$)$_5$ (**276**); (*e*) H_3O^+.



Reagents: (*a*) H_2CrO_4; (*b*) $LiAlH_4$; (*c*) TsCl/Py;
(*d*) $Me(CH_2)_{14}MgBr$ (**278**)/Li_2CuCl_4; (*e*) $O_2/PdCl_2 - CuCl$.

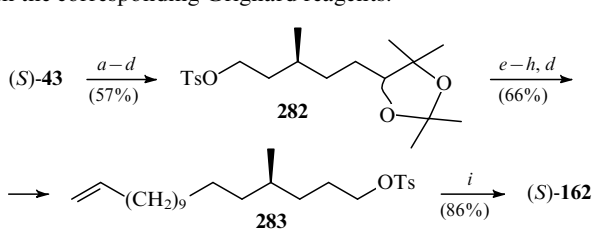
The diol (*S*)-**43** was used as the starting material in the synthesis of (4*R*,8*R*)-dimethyldecanal (4*R*,8*R*)-**29**, another isomer of the mealworm attractant.

The hydrogenation of the diol (*S*)-**43**, the periodate scission of the intermediate saturated analogue, and the oxidation of the resulting aldehyde with Ag_2O gave the saturated acid (*R*)-**68** further converted into the (*R*)-bromide **164** by the Hunsdiecker reaction. The tosylate **281**, the second component required for the synthesis of (4*R*,8*R*)-**29**, was synthesised from the epoxide **280**. The Wurtz condensation of compound **281** with the bromide **164** resulted, after a series of simple conversions, in the target product, (4*R*,8*R*)-**29**.[73]



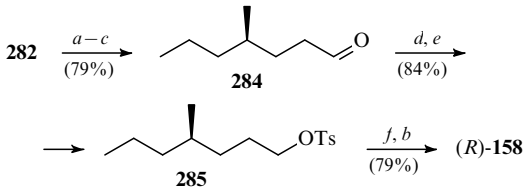
Reagents: (*a*) H_2/Pd/C; (*b*) HIO_4; (*c*) Ag_2O; (*d*) Br_2/HgO; (*e*) $NaBH_4$;
(*f*) TsCl/Py; (*g*) **164**/Mg/Li_2CuCl_4; (*h*) $AcOH - H_2O$.

The synthesis of the sex pheromone of the peach leaf mining beetle, (14*S*)-methyloctadec-1-ene (*S*)-**162**, from the diol (*S*)-**43** was based on the successive reactions of the tosylates **282** and **283** with the corresponding Grignard reagents.[74]



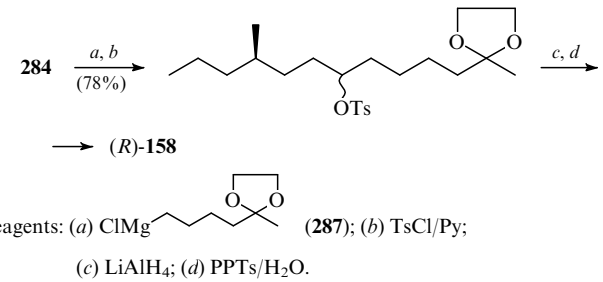
Reagents: (*a*) Me_2CO/TsOH; (*b*) B_2H_6; (*c*) H_2O_2/NaOH;
(*d*) TsCl/Py; (*e*) $H_2C=CH(CH_2)_9MgBr/Li_2CuCl_4$;
(*f*) $AcOH - H_2O$; (*g*) HIO_4; (*h*) $NaBH_4$; (*i*) MeMgI.

The tosyloxy acetonide **282** has also proved to be a convenient starting material for the synthesis of (10*R*)-methyltridecan-2-one, (*R*)-**158**, which involved the conversion of **282** into the aldehyde **284** and then into the tosylate **285**, which was then coupled with the Grignard reagent **286**.[75]



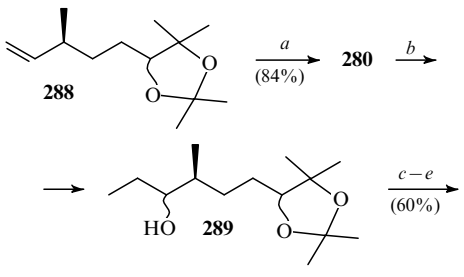
Reagents: (*a*) MeMgI/Li_2CuCl_4; (*b*) H_3O^+; (*c*) HIO_4; (*d*) $NaBH_4$;
(*e*) TsCl/Py; (*f*) BrMg (**286**).

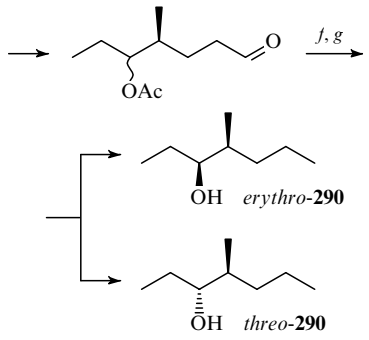
Yet another scheme of synthesis of the pheromone (*R*)-**158** is based on the interaction of the aldehyde **284** with the achiral organomagnesium compound **287**.[76]



Reagents: (*a*) ClMg (**287**); (*b*) TsCl/Py;
(*c*) $LiAlH_4$; (*d*) PPTs/H_2O.

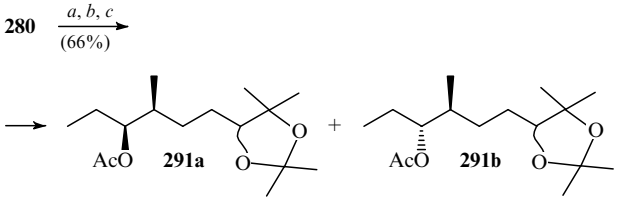
The unsaturated acetonide **288**, which is easily derived from (*S*)-**42**, can be oxidised by peroxy acids into the epoxide **280**, which has been used in the synthesis of 4-methylheptan-3-ol **290**; its (3*S*,4*S*)-isomer is the aggregation pheromone of the elm engraver (*Scolytus multistriatus*).[77] The interaction of compound **280** with MeMgI yields the secondary alcohol **289** with a 1 : 1 ratio of the *erythro*- and *threo*-isomers. Further conversions occur without the involvement of the chiral centres. Individual isomers were isolated by HPLC.





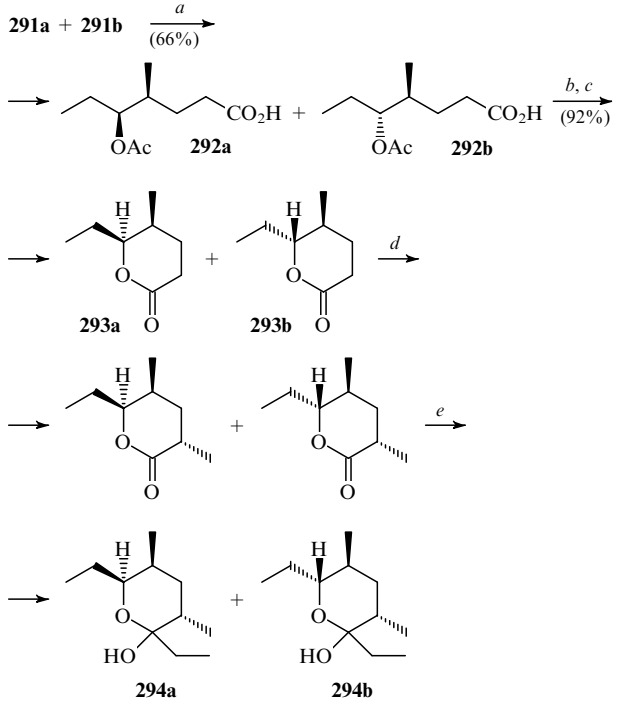
Reagents: (*a*) MCPBA; (*b*) MeMgI/CuI; (*c*) Ac_2O/Py; (*d*) AcOH – H_2O; (*e*) HIO_4; (*f*) $NH_2NH_2 \cdot H_2O$/KOH; (*g*) HPLC.

The stereoselectivity could be increased up to a ratio of 85 : 15 in favour of the *erythro*-isomer **291a** in the synthesis of (4*S*,6*S*,7*S*)-7-hydroxy-4,6-dimethylnonan-3-one (serricornin) **294a**, the sex pheromone of the tobacco beetle (*Lasioderma serricorne*).[78]



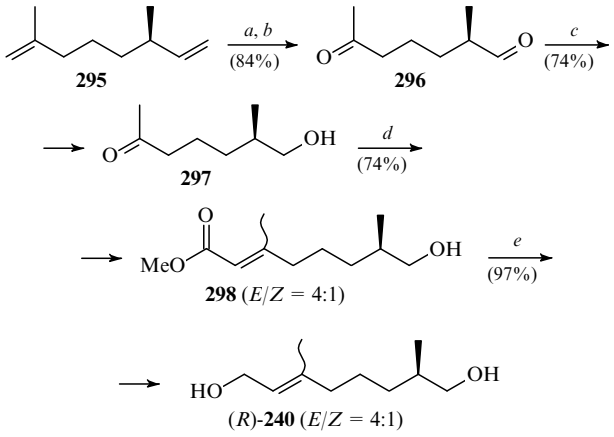
Reagents: (*a*) HIO_4 (*b*) $EtTi(OPr^i)_3$; (*c*) Ac_2O/Et_3N/DMAP.

Oxidative cleavage of the dioxolane ring of compounds **291a** and **291b** gave a mixture of *threo*- and *erythro*-acetoxy acids **292a** and **292b**; their alkaline hydrolysis yields a mixture of lactones **293a** and **293b**, which were converted into the target pheromone **294a** containing 15% of the *threo*-isomer **294b.**[79]



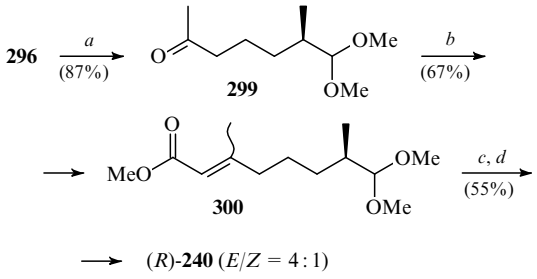
Reagents: (*a*) CrO_3/6N H_2SO_4; (*b*) KOH/MeOH; (*c*) HCl/H_2O; (*d*) MeI, $LiN(SiMe_3)_2$;[79] (*e*) EtMgBr.

The regioisomers of dihydromyrcene **42**, 2,6-dimethylocta-1,7-dienes **295** of (*R*)- or (*S*)-configuration are the starting chiral building blocks in the synthesis of (*R*)- and (*S*)-enantiomers of 3,7-dimethyloct-(2*E*)-ene-1,8-diol **240** and 3,7-dimethyloct-(2*E*)-ene-dioic acid **239**, the secretion product of the Monarch butterfly and, correspondingly, of the sex pheromone of *Callosobruchus chinensis*.[80] The ozonolysis of the diene (*R*)-**295**† results in the chiral oxoaldehyde **296**. Its aldehyde carbonyl group was protected either by selective hydride reduction to give the hydroxy ketone **297** or by conversion into the oxo acetal **299** for the subsequent selective alkenation. The Wittig – Horner reaction of the hydroxy ketone **297** with trimethyl phosphonoacetate gave a mixture of isomeric *E*- and *Z*-hydroxy esters **298**. Their reduction yielded a mixture of the corresponding *E*- and *Z*-diols **240** from which the individual *E*-isomer was isolated chromatographically.



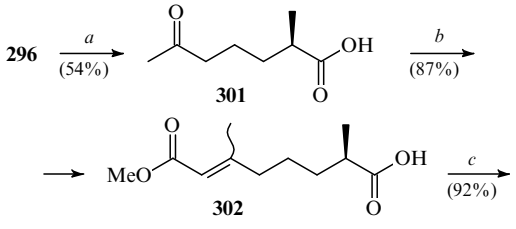
Reagents: (*a*) O_3; (*b*) Me_2S; (*c*) $NaBH_4$; (*d*) $(MeO)_2P(O)CH_2CO_2Me$/NaH; (*e*) $LiAlH_4$.

In the second version of this synthesis, the conversion of the oxo acetal **299** into the target diol (*R*)-**240** involved the Wittig – Horner reaction to give a mixture of *E*- and *Z*-esters **300**. Deprotection of the aldehyde function followed by hydride reduction yielded a 4 : 1 mixture of *E*- and *Z*-diols (*R*)-**240**.



Reagents: (*a*) MeOH/TsOH; (*b*) $(MeO)_2P(O)CH_2CO_2Me$/NaH; (*c*) NaOH/H_2O; (*d*) $LiAlH_4$.

Yet another method of synthesis of the pheromone (*R*)-**239** from the oxo aldehyde **296** has been proposed. This method involved the oxidation of the aldehyde function in the oxo aldehyde **296** and the Wittig – Horner coupling of the oxo acid **301** with trimethyl phosphonoacetate. The resulting mixture of monoesters of the dicarboxylic acids **302** ($E/Z \sim 4:1$) was hydrolysed and the *E*-isomer of (*R*)-**239** was isolated by HPLC.[80]



† The Schemes show the transformations for the (*R*)-enantiomers.



(*R*)-**239** ($E/Z \sim 4:1$)

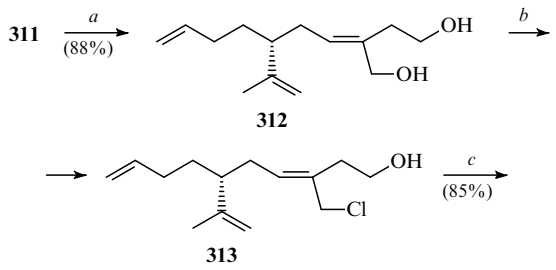
Reagents: (*a*) $AgNO_3/EtOH - H_2O$; (*b*) $(MeO)_2P(O)CH_2CO_2Me/NaH$; (*c*) HCO_2H/H_2O.

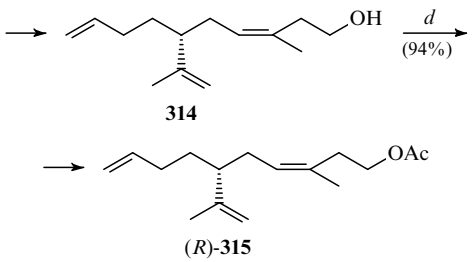
IV. Other syntheses

Other monoterpenoid compounds have been used in the synthesis of insect pheromones much more rarely so far. These include alkenes (limonene and dihydrolimonene), alcohols (menthol and linalool),[81] and ketones (menthone, carvone,[82–85] dihydrocarvone, and camphor).

Limonene **303** has proved to be a convenient starting material for the synthesis of pheromones with the isopropenyl group at the chiral centre. The enantiomer (*R*)-**303** was used to synthesise (6*R*)-isopropenyl-3-methyldeca-3,9-dien-1-yl acetate (*R*)-**315**, the sex hormone of the California red scale.[86] This goal was achieved by partial ozonolysis of (*R*)-**303** which occurred selectively at the endocyclic double bond. The resulting oxo acetal **304** was further converted into the intermediate diethyl phosphate **305**; its treatment with lithium in ammonia gave diene acetal **306**. Deprotection of the carbonyl group and the Peterson condensation of the resulting aldehyde **307** with the silylimine **308** gave the adduct **309**; its hydrolysis gave the conjugated aldehyde **310** further reduced to the allylic alcohol **311** (Scheme 15).

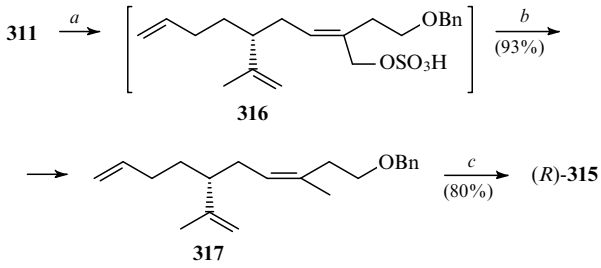
The conversion of the alcohol **311** into the target product, (*R*)-**315**, was carried out in two ways. The first of those involved mild debenzylation under conditions of the Birch reaction, subsequent conversion of the allylic alcohol group of the diol **312** into the allylic chloride, reduction of the chlorohydrin **313**, and acetylation of the alcohol **314**.





Reagents: (*a*) Li/NH3; (*b*) *N*-chlorosuccinimide (NCS)/Me_2S; (*c*) $LiAlH_4$; (*d*) Ac_2O/Py.

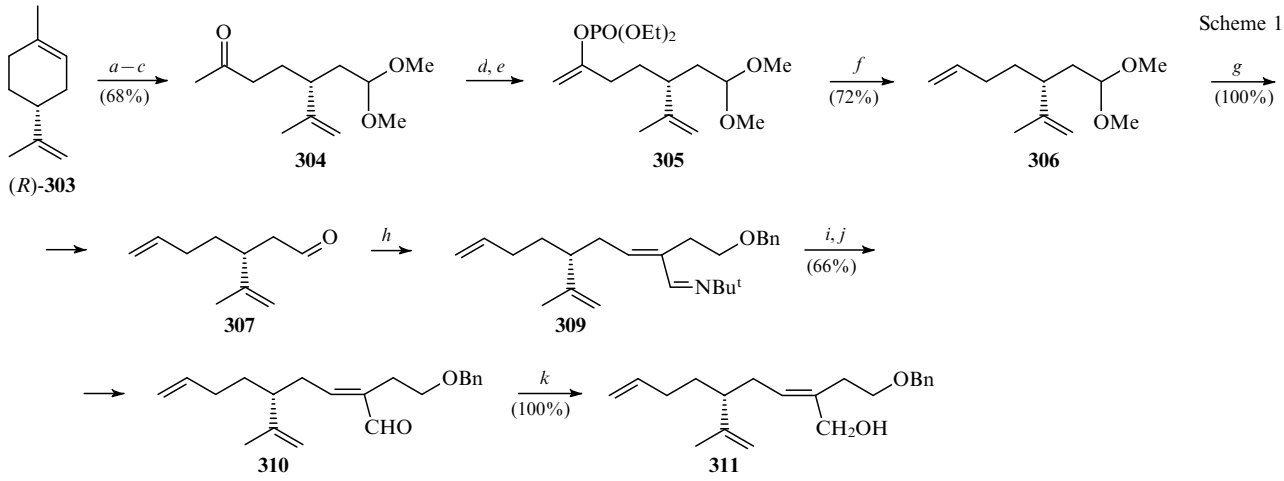
An alternative way of the transformation of the compound **311** into the acetate (*R*)-**315** involved the synthesis of the sulfonate **316** the reduction of which gave the benzyl ether (**317**). The substitution of the benzyl function in this ether for the acetate yielded the target product, (*R*)-**315**.



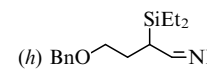
Reagents: (*a*) SO_3/Py; (*b*) $LiAlH_4$; (*c*) $Ac_2O/HClO_4$.

The bifunctional chiral synthon **304** was successfully used in the stereospecific synthesis of (6*R*)-isopropenyl-3,9-dimethyldeca-(3*Z*,9)- and -(3*E*,9)-dien-1-yl propionates **322** of which the *Z*-isomer is the sex pheromone of the white peach scale (*Pseudaulacaspis pentagona*).[87] In the synthesis of (*E*)-**322**, the dienal **318**, the product of methylenation and subsequent hydrolysis of the oxo acetal **304**, was converted into the trisubstituted intermediate alkene **320** (with the content of the *E*-isomer $\geqslant 97\%$) *via* the intermediate betaine **319** by using a Corey modification of the Wittig reaction. Deprotonation of the betaine formed from $MeCH=PPh_3$ and the chiral aldehyde **318** and subsequent treatment with ethylene oxide resulted in the *Z*-homoallylic alcohol **324** *via* the intermediate **323**; the compound **324** was then

Scheme 15

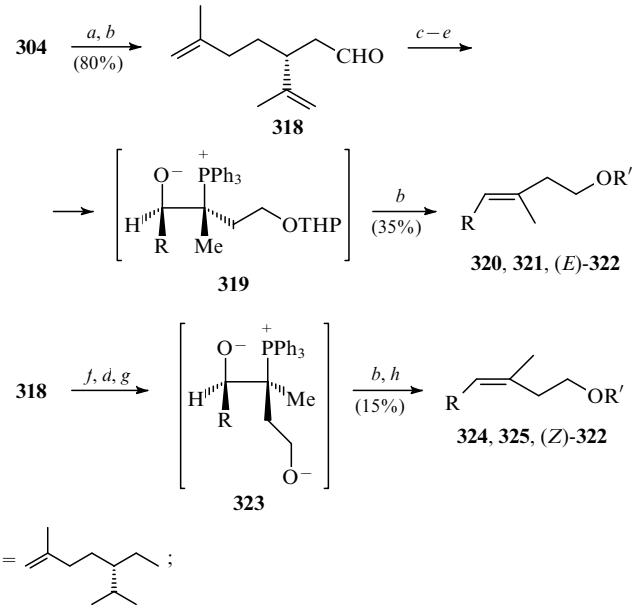


Reagents: (*a*) O_3/MeOH; (*b*) $(NH_2)_2CS$; (*c*) $HC(OMe)_3/CeCl_3 \cdot 6H_2O$; (*d*) LDA; (*e*) $ClPO(OEt)_2$; (*f*) Li/NH_3; (*g*) $HClO_4$;



(Bn = benzyl) (**308**)/Bu^nLi; (*i*) $(CO_2H)_2/H_2O$; (*j*) PCC; (*k*) $LiAlH_4$.

converted into the target component of the pheromone (*Z*)-**322** with the content of the major stereoisomer of ⩾ 98%.



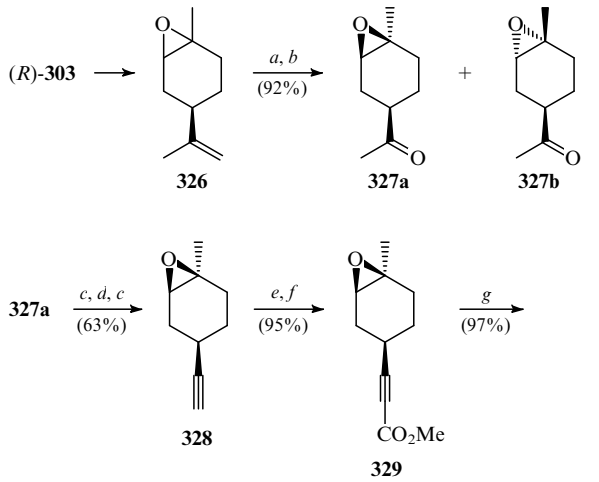
R′ = H (**321**, **325**); THP (**320**, **324**),EtCO [(*E*)-**322**, (*Z*)-**322**)].

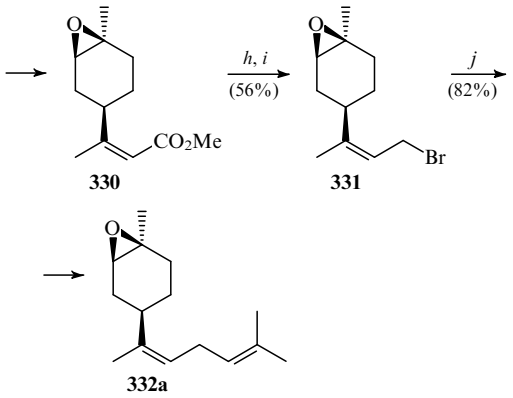
Reagents: (*a*) $Ph_3P=CH_2$; (*b*) H_3O^+; (*c*) $Ph_3P=CH(CH_2)_2OTHP$;

(*d*) Bu^nLi; (*e*) MeI; (*f*) $Ph_3P=CHMe$; (*g*) ;

(*h*) $EtCOCl/Et_3N$.

A synthetic procedure based on the ozonolysis of a 1 : 1 mixture of α- and β-limonene epoxides **326** has been proposed for the stereoisomers **332a** and **332b** of the sex pheromone of the green beetle (*Nezara viridula*).[88] The reduction of the corresponding ozonides yielded a mixture of the ketones **327a** and **327b**, which were separated chromatographically. To obtain the component **322**, the enantiomer **327a** was converted *via* the terminal alkyne **328** into the corresponding ester **329**. The regio- and stereospecific conjugated addition of Me_2CuLi gave the *Z*-alkene **330**, further converted into the bromide **331** *via* the corresponding alcohol. Its condensation with 1-lithio-2-methylpropene resulted in the target product, *endo*-epoxide **332a**.



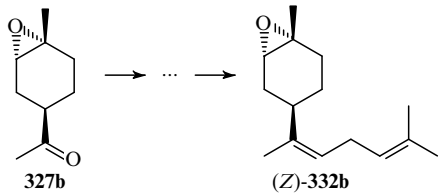


Reagents: (*a*) O_3; (*b*) PPh_3; (*c*) LDA; (*d*) $(EtO)_2P(O)Cl$; (*e*) Bu^nLi;

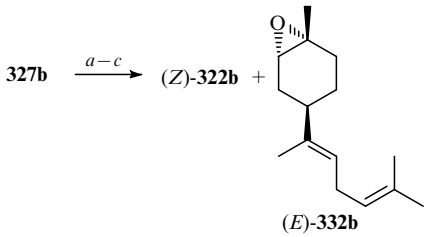
(*f*) $ClCO_2Me$; (*g*) Me_2CuLi; (*h*) Bu^i_2AlH; (*i*) $CBr_4 \cdot PPh_3$;

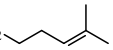
(*j*) Br/Bu^nLi.

The other component, **332b**, was obtained from the ketone **327b** in a similar way.[88]



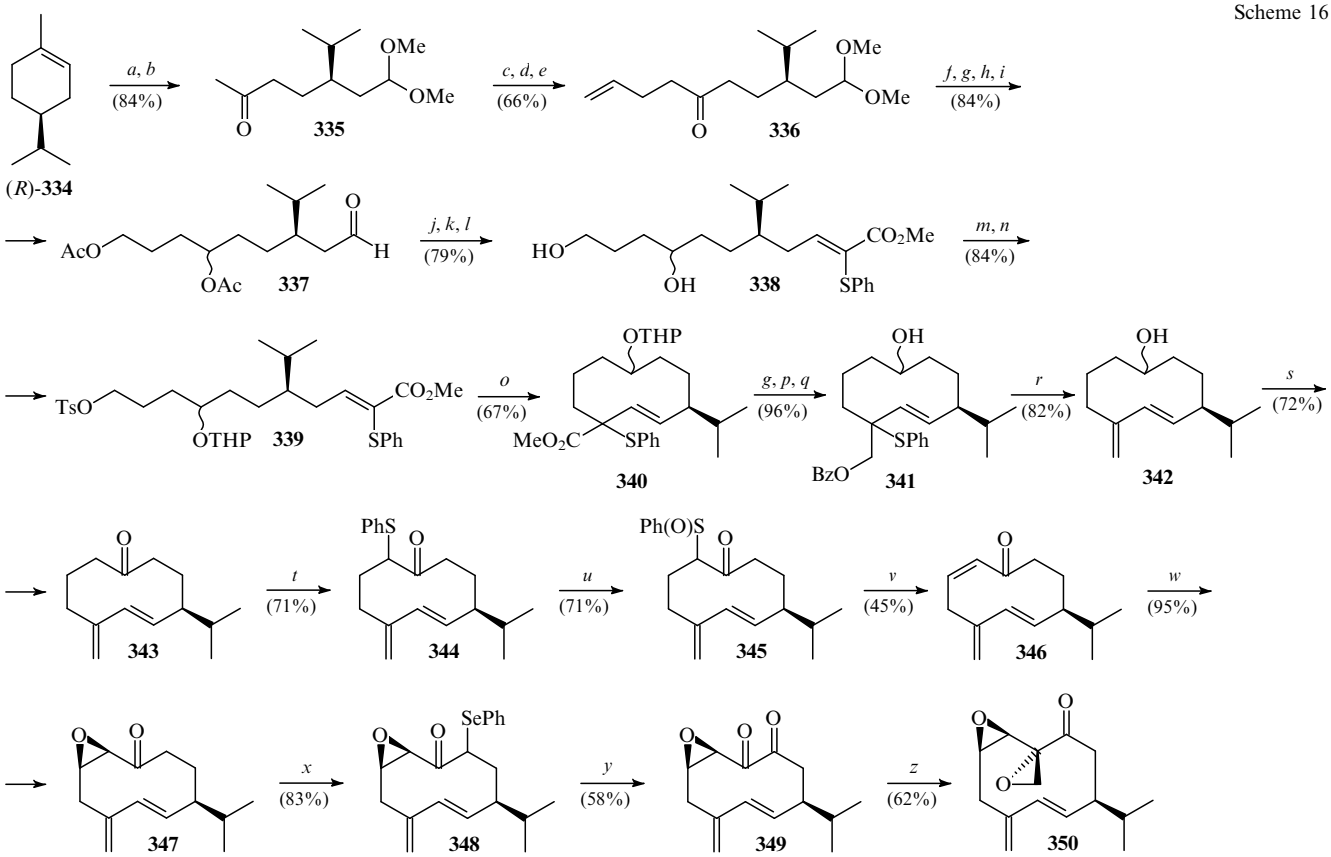
The epoxy ketone **327b** has found application as the starting material in an alternative synthesis of the pheromone **332b**. The coupling of **327b** with the sulfone **333** followed by desulfonation gave a mixture of *Z*- and *E*-isomers of the pheromone **332** from which (*Z*)-**332b** was isolated chromatographically.[89]



Reagents: (*a*) $PhSO_2$ (**333**)/Bu^nLi; (*b*) PhCOCl; (*c*) Na – Hg.

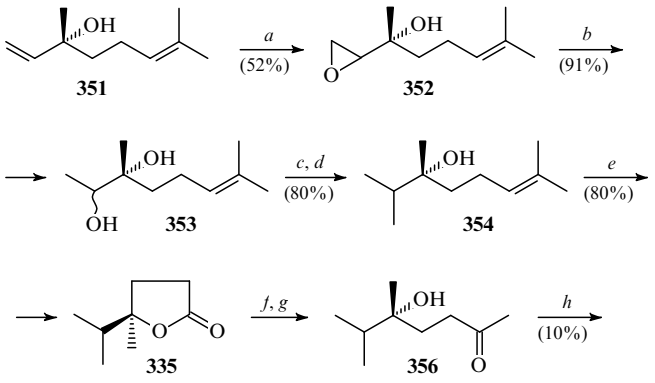
(+)-Dihydrolimonene (*R*)-**334** was used as the starting material in the synthesis of (−)-periplanone B (**350**), the sex pheromone of the American cockroach (*Periplaneta americana*).[90, 91] At the first stage of this synthesis, the terpene (*R*)-**334** was subjected to ozonolysis to give the dimethyl acetal **335**, which was further condensed with allyl bromide. The oxidative cleavage of the double bond in the alkene **336** and the reduction of the intermediate oxo aldehyde gave (after acetylation and deprotection) the aldehyde **337**, which was further converted into the unsaturated dihydroxy sulfide **338**. The tosylation of its primary alcohol group and the protection of the secondary hydroxy group gave compound **339**, which was cyclised upon deprotonation. The product **340** was converted into the sulfoxide by a series of simple reactions; its thermolysis yielded the α,β-unsaturated cyclic ketone **346**. The epoxidation of **346** proceeded regioselectively to give predominantly the epoxide **347**. The latter was converted into the diketone **349** *via* the phenyl selenide **348**; the interaction of **349** with ethylene dimethyl sulfide occurred selectively at one of the oxo groups and gave the target diepoxide **350** (Scheme 16).

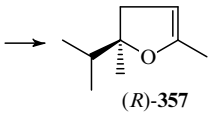
Scheme 16



Reagents: (*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/Et_3N/DMAP; (*n*) DHP/PPTs; (*o*) $NaN(SiMe_3)_2$; (*p*) BzCl/Py/DMAP; (*q*) Dowex 50W (H^+); (*r*) $Na-C_{10}H_8$; (*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*) $Me_2S=CH_2$.

(*R*)-(−)-Linalool (**351**) has found application in the synthesis of the cyclic enol ether, 2-isopropyl-(2*R*),5-dimethyl-2,3-dihydrofuran **357**, the sex pheromone of the female beetles *Hylecoetus dermestoides*. Thus hydroperoxide oxidation of **351** gave the epoxide **352** further reduced to the diol **353**. The selective tosylation of its secondary hydroxy group and the subsequent methylation of the tosylate yielded the alcohol **354**; its oxidation with $RuCl_3-NaIO_4$ gave the lactone **355** after spontaneous cyclisation of the intermediate hydroxy acid. The latter was converted into the hydroxy ketone **356**; its cyclisation by distillation over $CaSO_4$ completed the synthesis of the pheromone **357**.[92]



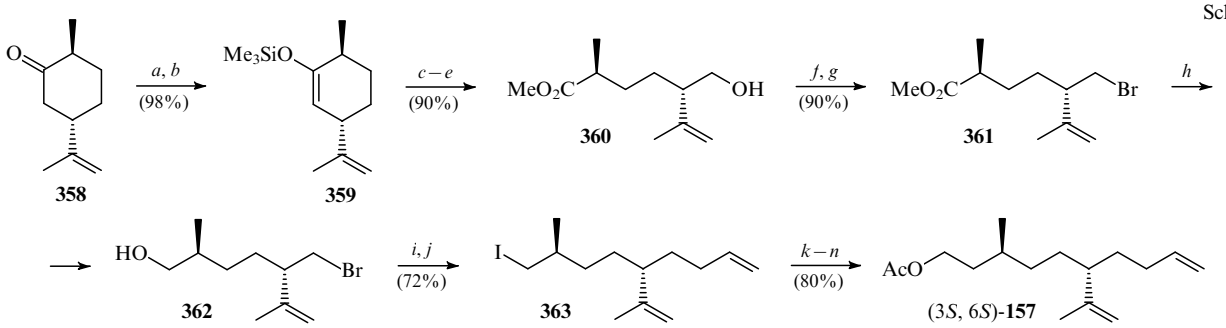


Reagents: (*a*) $Bu^tOOH/VO(acac)_2$; (*b*) $LiAlH_4$; (*c*) TsCl/Py; (*d*) $Me_2Cu(CN)Li_2$; (*e*) $RuCl_3/NaIO_4$; (*f*) LiOH; (*g*) LiMe; (*h*) distillation over $CaSO_4$.

(−)-Dihydrocarvone **358** was used in the synthesis of (3*S*,6*S*)-**157**, the component of the sex pheromone of the California red scale.[93] To this end, the ketone **358** was converted into the enol silyl ether **359**; its ozonolysis gave the hydroxy ester **360**. The latter was converted into the target product, (3*S*,6*S*)-**157** *via* the bromo ester **361**, bromohydrin **362**, iodide **363**, and the corresponding nitrile (Scheme 17).

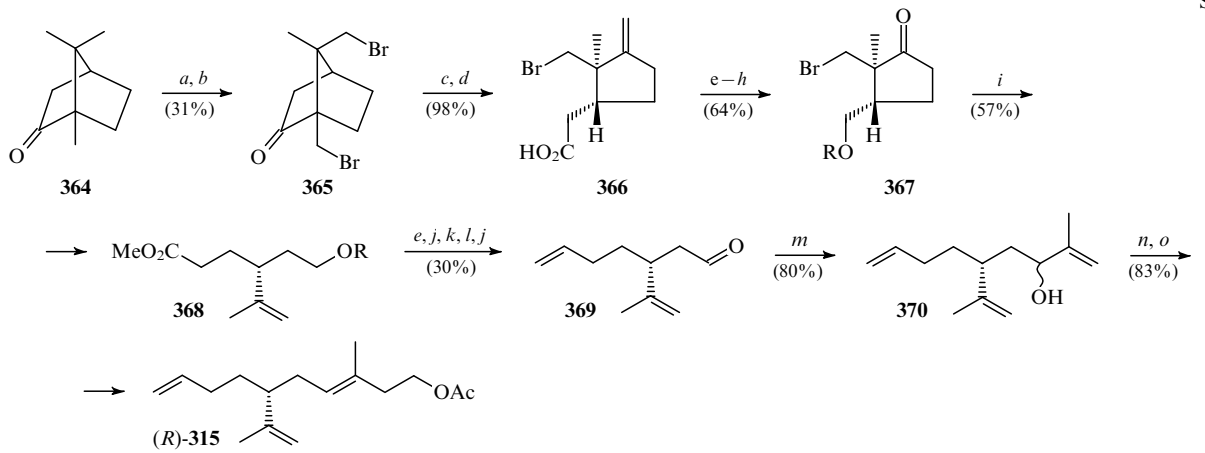
Another component of the sex pheromone of the California red scale, (*R*)-**315**, has been synthesised from (+)-camphor **364** taking advantage of possible cleavage of its 9,10-dibromo-derivative **365** under alkaline conditions to give the unsaturated bromo acid **366** which was converted into the β-bromo-ketone **367** by a series of simple reactions. Its treatment with NaOMe gave the acyclic hydroxy ester derivative **368**. The latter was transformed into the aldehyde **369** the condensation of which with 2-propenylmagnesium bromide gave the allylic alcohol **370**. Its stannyl derivative underwent a highly stereoselective 2,3-sigmatropic rearrangement into the corresponding homoallylic alcohol (Scheme 18).[94]

Scheme 17



Reagents: (*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*) Bu^i_2AlH; (*i*) $H_2C=CHCH_2MgCl/CuI$; (*j*) $I_2 \cdot PPh_3$; (*k*) NaCN; (*l*) NaOH; (*m*) $LiAlH_4$; (*n*) Ac_2O/Py.

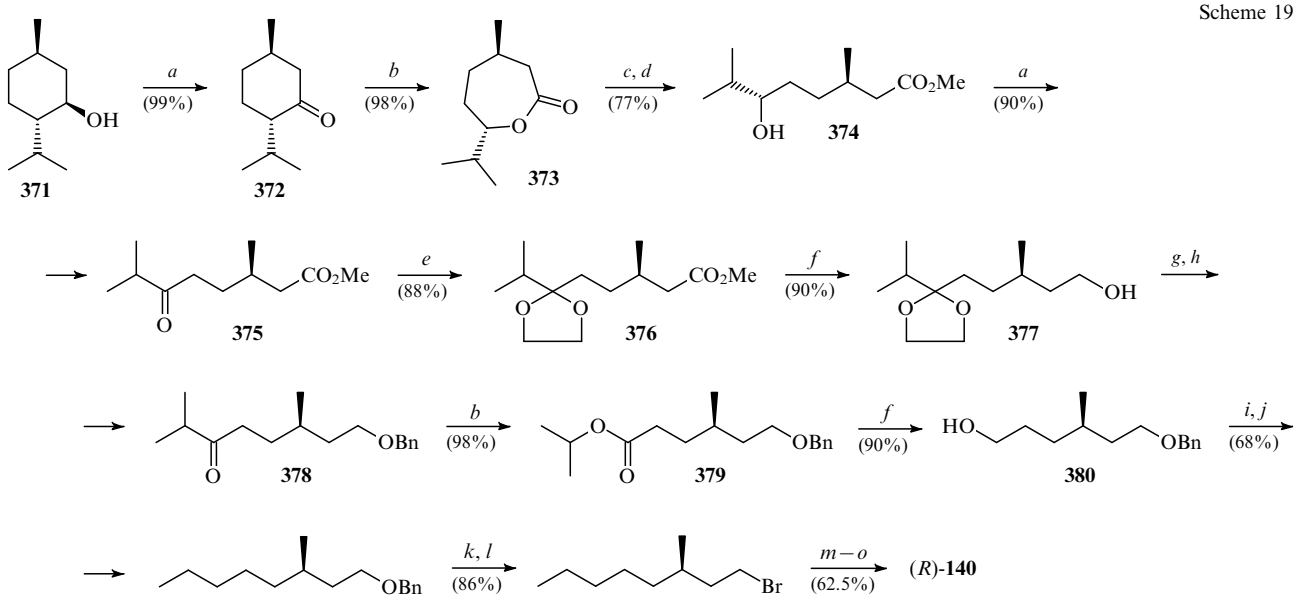
Scheme 18



R = Bu^tMe_2Si.

Reagents: (*a*) $Br_2/ClSO_3H$; (*b*) Zn/NaOH; (*c*) KOH/DMSO; (*d*) HCl; (*e*) $LiAlH_4$; (*f*) O_3/MeOH; (*g*) Me_2S; (*h*) Bu^tMe_2SiCl/DMAP; (*i*) NaOMe; (*j*) PCC; (*k*) $H_2C=PPh_3$; (*l*) Bu_4NF; (*m*) $CH_2=C(Me)MgBr$; (*n*) Bu_3SnCH_2I/Bu^nLi; (*o*) Ac_2O/Py.

Scheme 19

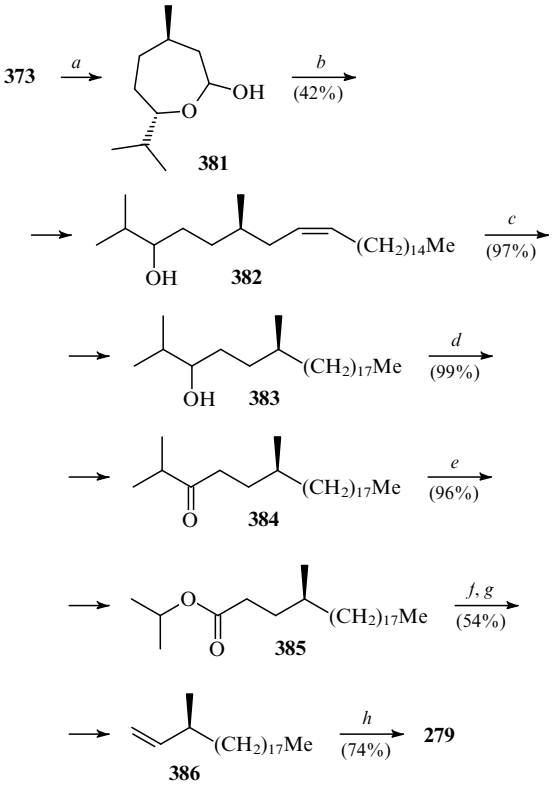


Reagents: (*a*) PCC; (*b*) $C_{10}H_{21}SO_3OH$; (*c*) KOH/MeOH; (*d*) MeOH/TsOH; (*e*) $(CH_2OH)_2$/TsOH; (*f*) Bu^i_2AlH; (*g*) BnCl/KOH; (*h*) HCl; (*i*) TsCl/Py; (*j*) Et_2CuLi; (*k*) $H_2/PdCl_2$; (*l*) PBr_3/Py; (*m*) Mg; (*n*) CO_2; (*o*) $LiAlH_4$.

(3*R*,7)-Dimethyloctan-(6*S*)-olide **373**, the product of regio- and stereo-specific Baeyer–Williger oxidation of (−)-menthone **372** derived from L-(−)-menthol **371** is especially promising in the synthesis of the enantiomerically pure insect pheromones.

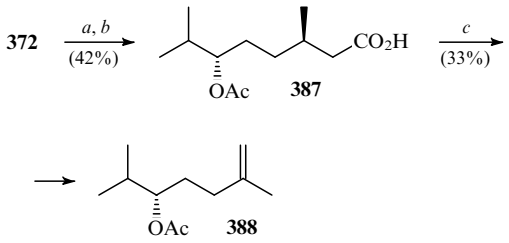
The synthesis of the pheromone of the mealworm, (*R*)-**140**, from the key lactone **373** involved the preparation of benzyloxy ketone **378** after a series of simple unambiguous transformations of the compound **374** into the compound **377**; its conversion into the target product involved the formation of the isopropyl ester **379** and the monobenzyl derivative of the diol **380** (Scheme 19).[95,96]

To obtain the optically pure analogue of the sex pheromone of the German cockroach **279**, the lactone **373** was reduced into the corresponding lactol **381**; its alkenation and hydrogenation of the resulting *Z*-alkene **382** gave the alcohol **383**. The further modification of its hydrocarbon skeleton to that of the target compound, α-methyl ketone **279,** involved the sequence of conversions which did not affect the chiral centre at C(6): *viz*., the oxidation of **383** to the ketone **384**, which underwent regiospecific Baeyer–Williger oxidation into the isopropyl ester **385** and the oxidative decarboxylation of the corresponding acid and Walker–Tsuji oxidation of the resulting alkene **386**.[97,98]



Reagents: (*a*) Bu^i_2AlH, −75 °C: (*b*) $[Me(CH_2)_{14}P^+Ph_3]Br^-/Bu^nLi$; (*c*) H_2/Ni; (*d*) PCC; (*e*) MCPBA; (*f*) KOH/MeOH; (*g*) $Pb(OAc)_4/Cu(OAc)_2 \cdot H_2O$; (*h*) $O_2/PdCl_2$–CuCl.

The synthesis of (3*S*)-acetoxy-2,6-dimethylhept-6-ene **388**, the analogue of the Comstock's scale (*Pseudococus comstocki*) pheromone, is also based on the Baeyer–Willig oxidation of the original ketone **372** and subsequent oxidative decarboxylation of the intermediate acetoxy acid **387**.[99]



Reagents: (*a*) $AcOOH/H_2SO_4$; (*b*) Ac_2O/Py; (*c*) $Pb(OAc)_4/Cu(OAc)_2$.

The present review clearly demonstrates the efficiency of application of optically active monoterpenoids in the syntheses of chiral insect pheromones.

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[d] — *Russ. Chem. Bull. (Engl. Transl.)*