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INSECT PHEROMONES SYNTHESIZED BY OXIDATIVE TRANSFORMATIONS OF NATURAL MONOTERPENOIDS

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The literature on oxidative transformations of natural monoterpenoids to synthesize insect pheromones was reviewed.

Key words: monoterpenoids, oxidation, insect pheromones.

The literature on pheromone chemistry is broad and reflects the consistent interest in this area over the last 20 years in the form of monographs [1-7] and reviews [8-15].

Insect pheromones known today are rather simple molecules (less than four asymmetric centers and four functional groups). Therefore, the "ideal" substrate (chiral or achiral) for most such structures is a moderately functionalized molecule, in particular, hydroxy- and amino-acids in addition to monoterpenoids. The last class of compounds is the most accessible for this series and is especially convenient for the synthesis of molecules with a branched C skeleton, primarily isoprenoid pheromones.

Oxidative methods of transforming monoterpenoids are the most convenient and widely used methods for carrying out various transformations of starting molecules and introducing most known functional groups. Considering this aspect, articles on the synthesis of insect pheromones that for one reason or another did not appear in previous reviews are reviewed herein.

ALLYLIC OXIDATION BY SELENIUM DIOXIDE

One of the most common methods for functionalizing the C skeleton of unsaturated monoterpenoids containing an isopropylidene group is regio- and stereoselective oxidation at the allylic position, for example, by SeO_2, of geraniol (**1**) and its derivatives or similar compounds. This method enables introduction into molecules of hydroxy- or oxo- functions that can be used in further transformations.

For example, treatment of geranylacetate (**2**) with a stoichiometric or catalytic (with *t*-BuOOH) amount of SeO_2 followed by hydride reduction gives unsaturated hydroxyacetate **3**, which is widely used to synthesize insect pheromones [16-19].

In particular, **3** was oxidized to aldehyde **4**, which was then converted to the olefin by *n*-propylidenephosphorane [16], to prepare racemic 5,9-dimethylheptadecane (**7**), the sex pheromone of the pear leaf blister moth (*Leucoptera scitella* Zeller). Organocuprate coupling of the resulting allylic acetate **5** with *n*-hexylmagnesium bromide led to 5,9-dimethyl-3,5,9-heptadecatriene (**6**), exhaustive hydrogenation of which gave the desired pheromone **7**.

Condensation of bromoacetate **8** wth sodium malonic ester was used [17] to synthesize 10-hydroxy-4,8-dimethyl-4*E*,8*E*-decadienoic acid (**11**), an acyclic precursor of ferrulactone I (**12**), which is the principal component of the aggregation pheromone of the rusty grain beetle (*Cryptolestes ferrugineus* Stephen). Decarboxylation of the resulting triester **9** and subsequent saponification gave the key hydroxyacid **11**, lactonization of which by *bis*-(4-*t*-butyl-N-isopropylimidazol-2-yl)disulfide gave the desired **12**.

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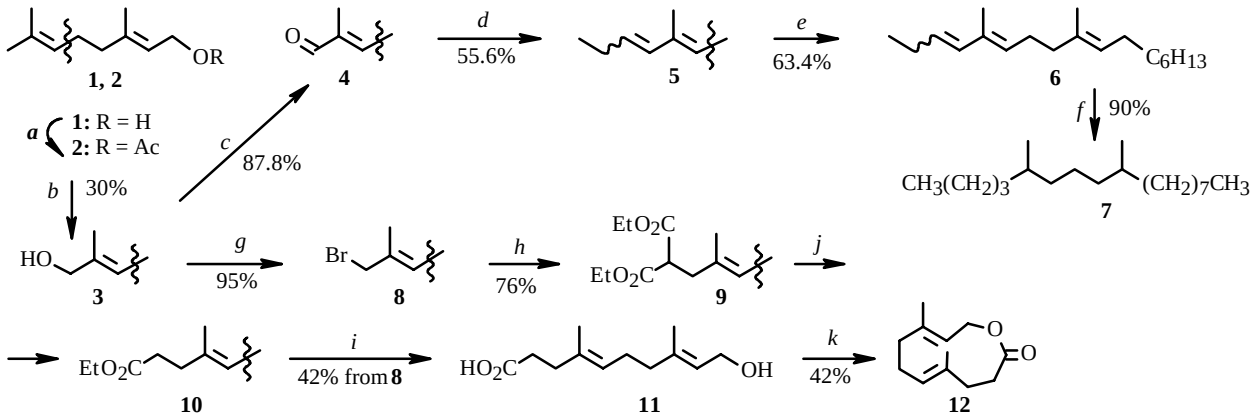
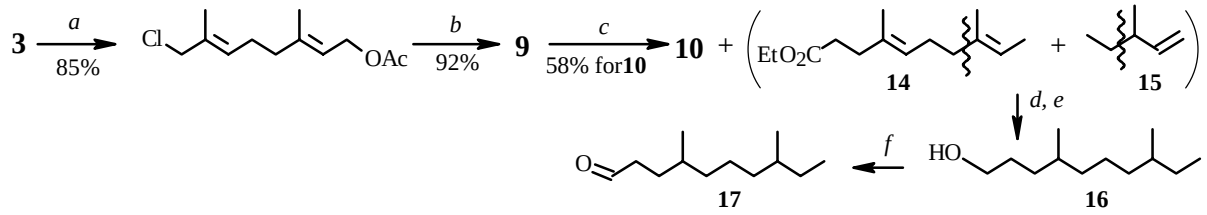


a. Ac_2O, Py; *b.* SeO_2, *t*-BuOOH; *c.* PCC; *d.* $C_3H_7P^+Ph_3Br^-$, *t*-BuOK; *e.* *n*-$C_6H_{13}MgBr$, CuI; *f.* H_2, Pd-C; *g.* CBr_4, PPh_3; *h.* $NaCH(CO_2Et)_2$; *j.* NaCl, DMF, H_2O, 160°C; *i.* NaOH, dihlim; *k.* BID, PPh_3

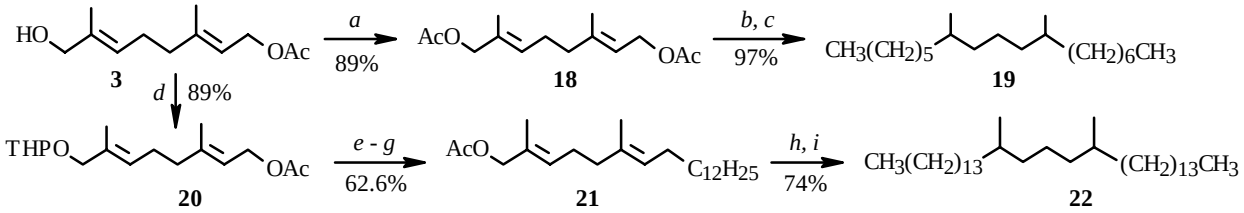
Odinokov et al. [18] changed the condensation and decarboxylation conditions in the synthesis of **11** from **3**. In the former instance, they used chloride **13** instead of bromide **8** and carried out the reaction in the presence of $Pd(OAc)_2$–PPh_3. This increased the yield of **9** to 90%. They used LiCl in aqueous DMF for the decarboxylation of triester **9** whereas NaCl was used previously [17]. They isolated from the reaction mixture the expected **10** in addition to its acetoxy hydrogenolysis products as a mixture (7:3) of esters of regioisomeric $\Delta^{8,9}$-**14** and $\Delta^{9,10}$-**15** 4,8-dimethyldecandienoic acids. Alkaline hydrolysis of **10** isolated by column chromatography gave the key hydroxyacid **11**.



a. $COCl_2$, DMF, Py; *b.* $NaCH(CO_2Et)_2$, $Pd(OAc)_2$-PPh_3, THF; *c.* DMF, LiCl, H_2O, 173°C; *d.* H_2, Pd-C; *e.* DIBAH; *f.* PCC (91%)

The resulting mixture of **14** and **15** was used to synthesize 4,8-dimethyldecanal (**17**), a racemic analog of the red flour beetle (*Tribolium castaneum* and *T. confusum*) aggregation pheromone, for which they were reduced to saturated alcohol **16**, oxidation of which gave the desired aldehyde **17**.

Use of hydroxyacetate **3** is very convenient for preparation of 1,5-dimethyl-branched pheromones [19].

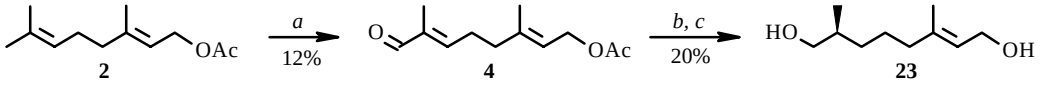


a. Ac_2O, Py; *b.* *n*-$C_5H_{11}MgBr$, CuI; *c.* H_2, Pd-C; *d.* DHP, TsOH; *e.* *n*-$C_{12}H_{25}MgBr$, CuI; *f.* TsOH, MeOH; *g.* Ac_2O, Py; *h.* *n*-$C_{13}H_{27}MgBr$, CuI; *i.* H_2, Pd-C

The C skeleton of **3** was extended by a one-step dialkylation of diacetate **18** with *n*-pentylmagnesium bromide in the synthesis of 7,11-dimethyloctadecane (**19**), a pheromone of the yellow fever mosquito (*Aedes aegypti*).

The same hydroxyacetate (**3**) was used by these same researchers to approach 15,19-dimethyltriacontane (**22**), a pheromone of the stable fly (*Stomoxys calcitrans*), for which a selective two-step lengthening of the chain of diether **20** was achieved.

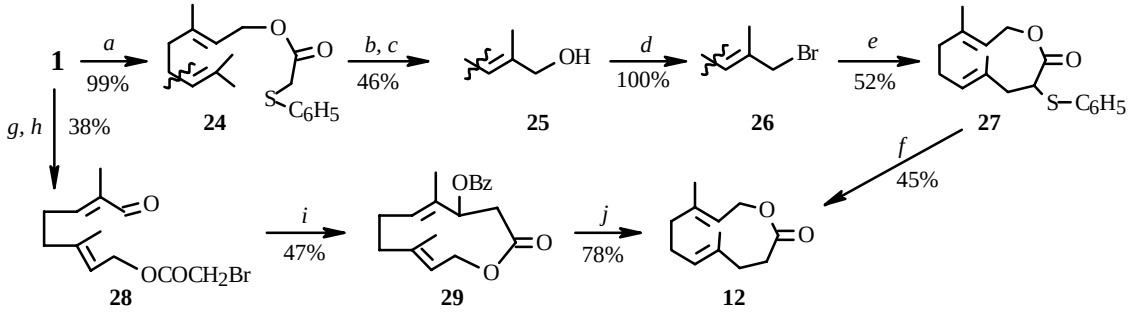
Allylic oxidation of **2** by SeO_2 gives **3** and a side product of acetoxyaldehyde **4**, which was used in a three-step synthesis of (*S*)-3,7-dimethyl-2*E*-octen-1,8-diol (**23**), a secretion of the plain tiger butterfly (*Danaus chrysippus*) [20]. Reduction of **4** by Baker's yeast, which transformed only the (*S*)-isomer, and subsequent alkaline hydrolysis gave diol **23** in 97% optical purity.



2 **4** **23**

a. SeO_2; *b.* BY, H_2O, 25°C; *c.* KOH

A (phenylthio)acetate of geraniol (**24**) was used to synthesize lactone **12** [17]. Allylic oxidation of **24** by SeO_2 followed by mild hydride reduction led to unsaturated monosubstituted diol **25**. Halogenation and further cyclization of bromide **26** gave in high yield S-containing macrolide **27**, desulfurization of which gave the desired pheromone **12**.

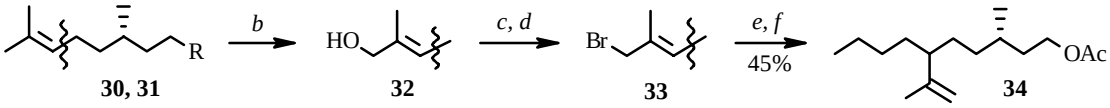


24 **25** **26** **27** **28** **29** **12**

a. $PhSCH_2COCl$, Py; *b.* SeO_2; *c.* $Na(CN)BH_3$; *d.* CBr_4, PPh_3; *e.* NaH, HMPA; *f.* Ni-Ra, EtOH; *g.* $BrCH_2COBr$, Et_3N; *h.* SeO_2 on SiO_2, *t*-BuOOH; *i.* SmI_2, THF, BzCl, DMAP; *j.* SmI_2, THF, HMPA, pivalic acid

In another synthesis [21] of lactone **12**, aldehyde **28**, the product of allylic oxidation of geraniol bromoacetic ester by *t*-BuOOH in the presence of a catalytic amount of SeO_2 on silica gel, underwent lactonization in the presence of SmI_2 to cyclic benzoate lactone **29**, further deacyloxylation of which by SmI_2 and pivalic acid gave the desired compound **12**.

A key step in the approach to a diastereomeric mixture of (3*S*,6*R*/*S*)-(-)-methyl-6-isopropenyldecanol acetate (**34**), a component of the sex pheromone of the California red scale (*Aonidiella aurantii*) [22], was the cross coupling of *n*-butyllithium with unsaturated bromoacetate **33**, which was prepared by allylic oxidation of the double bond of citronellylacetate (**31**) with subsequent two-step substitution of the hydroxyl by bromine. The coupling with *n*-butyllithium proceeds by an S_N2^1 mechanism and produces an isopropenyl substituent.

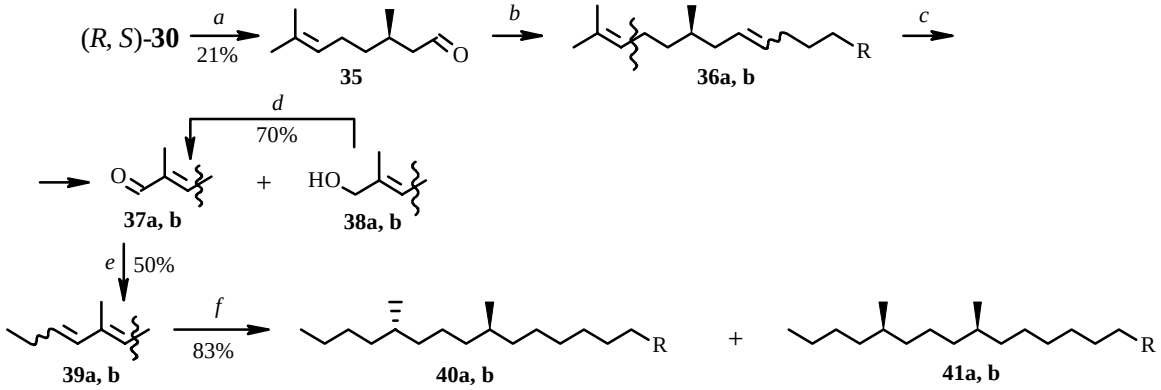


30, 31 **32** **33** **34**

a **30:** R = OH
31: R = OAc

a. Ac_2O, Py; *b.* SeO_2, *t*-BuOOH; *c.* TsCl, Py; *d.* LiBr, Me_2CO; *e.* *n*-BuLi, CuI; *f.* $BF_3 \cdot Et_2O$

Poppe et al. [23] proposed an interesting approach using allylic oxidation by SeO_2 for the synthesis of (5*S*,9*S*)-5,9-dimethylheptadecane (**40a**), the principal component of the sex pheromone of the pear leaf blister moth (*Leucoptera scitella*). Its (5*R*,9*S*)-isomer (**41a**) and (5*SR*,9*S*)-**40b** and (5*R*,9*S*)-dimethylpentadecanes (**41b**) are possible sex attractants of the coffee leaf miner moth (*Perileucoptera coffeella*).



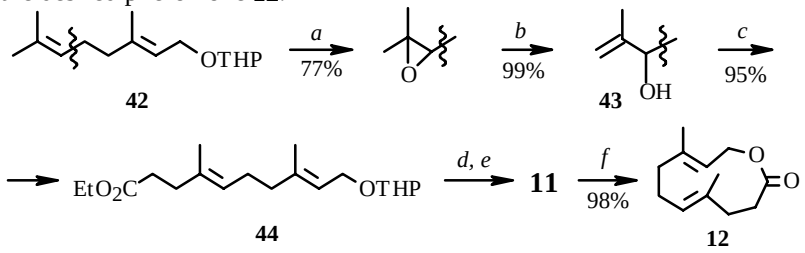
a. BY; *b.* $R(CH_2)_4P^+Ph_3Br^-$, NaOEt; *c.* SeO_2; *d.* PDC; *e.* *n*-$PrP^+Ph_3Br^-$, NaOEt; *f.* H_2, Pd-C

(*R*)-Citronellal (**35**), which was prepared by incubation of racemic citronellol (**30**) with Baker's yeast, was coupled with *n*-hexyliden or *n*-butylidenylides to produce the corresponding dienes **36a** and **b**, allylic oxidation of which gave a mixture of aldehydes **37a** and **b** and the accompanying alcohols **38a** and **b**, which were converted to the required aldehydes **37a** and **b** by the standard method. Then lengthening of the C chain by Wittig olefination with *n*-propylidenphosphorane and exhaustive hydrogenation of the resulting trienes **39a** and **b** completed the synthesis of the target pheromones **40a** and **b** and **41a** and **b**.

MONOTERPENOIDS FUNCTIONALIZED BY EPOXIDATION

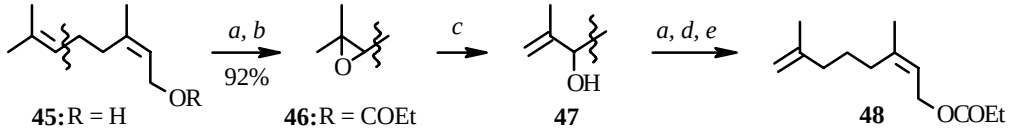
Selective epoxidation of the isopropylidene group of geraniol derivatives and similar structures is often used in synthetic approaches to insect pheromones from monoterpenoids. *m*-Chloroperbenzoic acid (MCPBA) is used most often for this.

Thus, epoxidation of the double bond of geraniol tetrahydropyranyl ether (**42**) was used to isomerize it into the terminal position using aluminum isopropylate in the synthesis of ferrulactone (**12**) [24]. Claisen rearrangement of the resulting allylic alcohol **43** gave the trisnorfarnesane structure in **44**. Its hydrolysis gave the key hydroxyacid **11**, which was cyclized under standard conditions into the desired pheromone **12**.



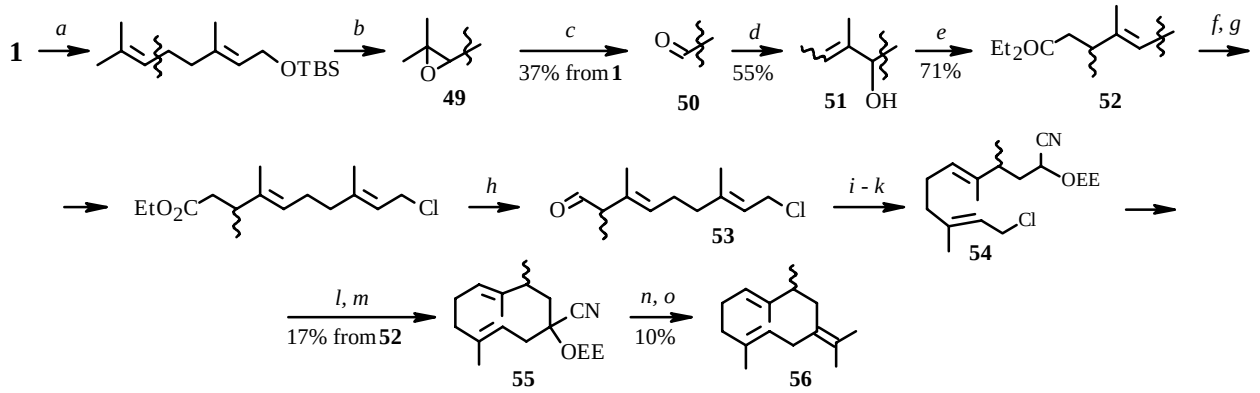
a. MCPBA, AcONa; *b.* $(i\text{-PrO})_3Al$; *c.* $MeC(OEt)_3$, $EtCO_2H$, 135°C; *d.* PPTS; *e.* KOH; *f.* BID, PPh_3, PhMe

An analogous approach with isomerization of the double bond of another monoterpenoid, nerol (**45**), was used to prepare of 3,7-dimethyl-2*Z*,7-octadien-1-ol propionate (**48**), a component of the California red scale (*A. aurantii*) pheromone [25, 26]. Here the double bond in the terminal position was substituted by treatment of epoxyester **46** with *t*-butylhypochlorite, which produced allyl alcohol **47**, deoxygenation of which gave the required **48**.



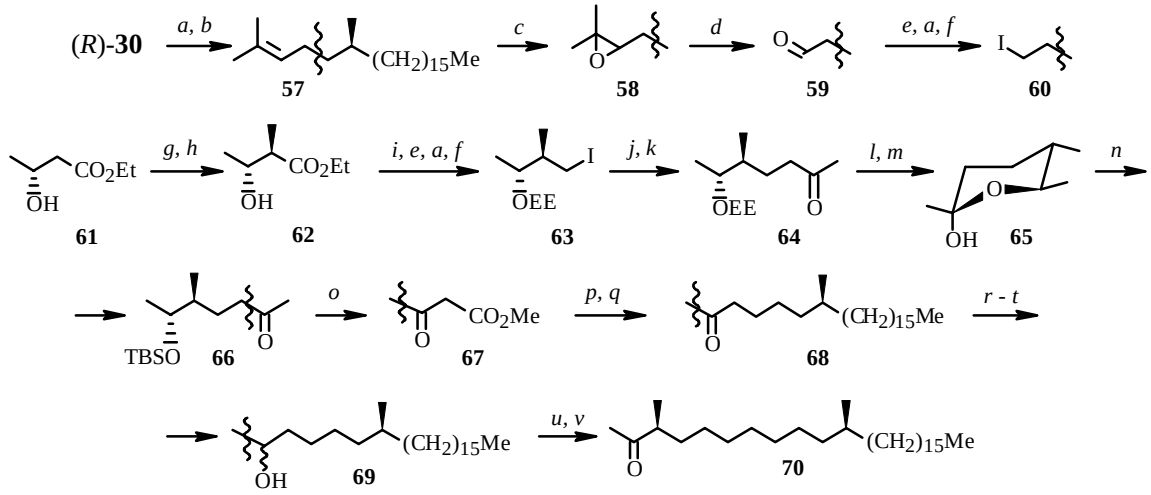
a. EtCOCl, Et_3N; *b.* MCPBA; *c.* *t*-BuOCl; *d.* MsCl, Et_3N; *e.* $LiAlH_4$

Epoxidation of the $\Delta^{6,7}$-bond of geraniol was used to shorten the C chain in the synthesis of racemic 9-methylgermacrene-B (**56**), a pheromone produced by male sand flies (*Lutzomyia longipalpis*) [27]. Compound **1** was fragmented through intermediate epoxide **49** of the corresponding TBS ether using periodic acid. The resulting aldehyde **50** was alkylated by a Grignard reagent to allyl alcohol **51**, Claisen rearrangement of which gave the trimethyl-branched diene α,ω-difunctionalized **52**. Then **52** was converted by known methods to aldehyde **53**, which was transformed successively through cyano derivatives **54** and **55** into the required pheromone **56**.



a. TBSCl, DMF; *b.* MCPBA; *c.* HIO_4; *d.* MeC=CMeMgBr, THF; *e.* $MeC(OEt)_3$, $EtCO_2H$, Δ; *f.* PPTS, MeOH; *g.* PPh_3, CCl_4; *h.* DIBAH, -78°C; *i.* TMSCN, KCN, 18-crown-6; *j.* $BnMe_3NF$, THF, H_2O; *k.* CH_2=CHOEt, PhH; *l.* NaHMDS; *m.* PPTS; *n.* NaOH, Et_2O; *o.* Me_2CBr_2, Sm, $CrCl_3$, SmI_2, THF

An analogous method for shortening the C chain was used in a convergent synthesis of (3*S*,11*S*)-3,11-dimethyl-2-heptacosane (**70**), a component of the sex pheromone of male German cockroaches (*Blattella germanica*), using (*R*)-citronellol (**30**) and ethyl-(*R*)-3-hydroxybutyrate (**61**) as starting materials [28].



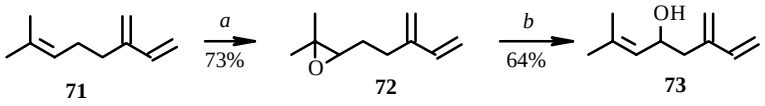
a. TsCl, Py; *b.* $Me(CH_2)_{13}MgBr$, Li_2CuCl_4; *c.* MCPBA; *d.* HIO_4; *e.* $LiAlH_4$, Et_2O; *f.* NaI, Me_2CO; *g.* LDA, THF, HMPA; *h.* MeI, -60°C; *i.* CH_2=CHOEt, TsOH; *j.* $MeCOCH_2CO_2Me$, K_2CO_3; *k.* NaOH, *l.* AcOH, THF, H_2O; *m.* recristallization from hexane; *n.* TBSCl; *o.* $CO(OMe)_2$, NaH, dioxane; *p.* **60**, K_2CO_3, MeCOEt; *q.* NaOH, *n*-Bu_4NOH, THF, H_2O; *r.* $NaBH_4$; *s.* MsCl, Py, DMAP; *t.* $LiBEt_3H$; *u.* HF, DME, H_2O; *v.* PCC

Epoxidation of alkene **57**, which was produced by extension of the C chain of starting (*R*)-**30** by a Schlosser—Grignard reaction, followed by periodate cleavage of epoxide **58** led to methyl-branched aldehyde **59**. Then **59** in three standard steps was converted to the first chiral synthon, iodide **60**.

The second chiral synthon was constructed starting with hydroxyester **61**. Its stereoselective methylation in the presence of two equivalents of lithium diisopropylamide gave a mixture of the *syn*- and *anti*-isomers of methyl-branched **62** in

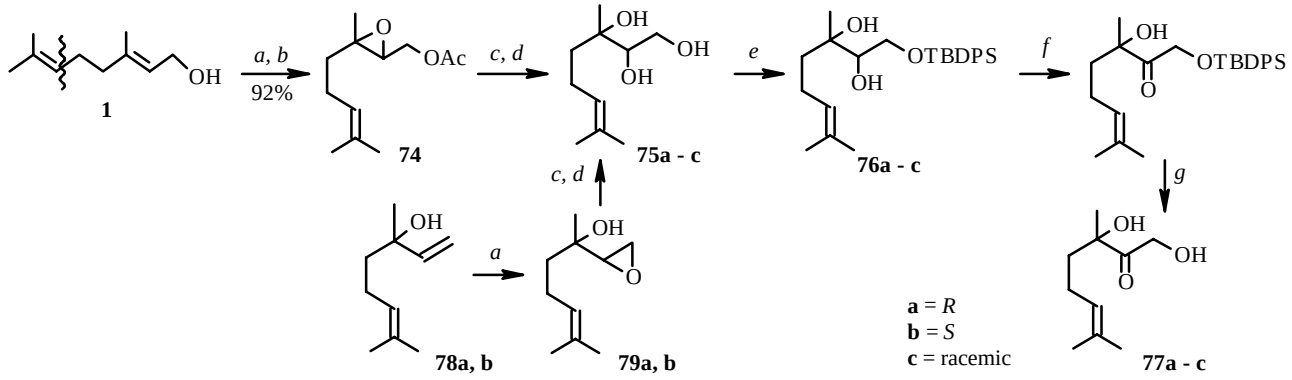
a 4:96 ratio. After protection of the hydroxyl, the ester was transformed in three steps into an iodomethylene group. Lengthening of the C chain in the resulting **63** by alkylation with acetoacetic ester gave ketoether **64**. Removal of the protecting group gave hemiacetal **65**, recrystallization of which enabled the *syn*-isomer to be completely removed. Treatment of **65** with *t*-butyldimethylsilylchloride and methoxycarbonylation of the intermediate ketoether **66** gave the β-ketodifunctionalized **67**. Alkylation of **67** through the sodium derivative by iodide **60** followed by deoxygenation gave silyl ether **69**, deprotection of which produced the desired pheromone **70**.

An original approach to the synthesis of ipsdienol (**73**), an aggregation pheromone of *Ips* bark beetles, was based on myrcene (**71**) [29]. Regioselective epoxidation of triene (**71**) at the $\Delta^{6,7}$-bond formed the epoxide **72**, in which the oxirane ring was opened by MeMgI at room temperature after 1 d to give the target pheromone **73**.



a. MCPBA; *b.* MeMgI

Epoxidation of geraniol and similar monoterpenoids can also be carried out selectively at the $\Delta^{2,3}$ bond by treatment with *t*-BuOOH in the presence of catalytic amounts of $VO(acac)_2$. Such an approach was used to prepare racemic 3,7-dimethyl-2-oxo-6-octen-1,3-diol (**77c**), which may be active as an aggregation pheromone of the Colorado beetle (*Leptinotarsa decemlineata*) [30].



a. t-BuOOH, $VO(acac)_2$; *b.* Ac_2O, Py; *c.* $HClO_4$, DMF; *d.* K_2CO_3, MeOH; *e.* TBDPSCl; *f.* DMSO, $(COCl)_2$, Et_3N; *g.* *n*-Bu_4NF

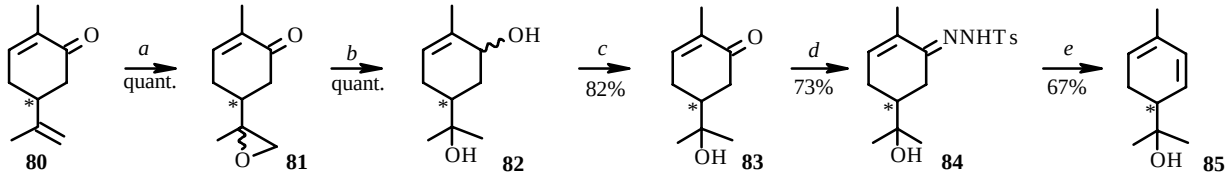
Regioselective epoxidation followed by acylation converted **1** into epoxyacetate **74**, opening of the oxirane ring of which and hydrolysis of the acetate gave triol **75c**. After selective protection of the primary hydroxyl, Swern oxidation of the secondary hydroxyl in **76c** followed by deprotection produced **77c** as a racemic mixture. Separation of the racemate **77c** by chiral GC gave two compounds, one of which was identical to the natural pheromone.

The isomers (*R*)-**77a** and (*S*)-**77b** were obtained from the linalool enantiomers (*R*)-**78a** and (*S*)-**78b**, respectively, to establish the absolute configuration of the natural pheromone. In particular, epoxidation of the terminal double bond of the (*R*)-isomer and then opening of the oxirane ring in (*R*)-**79a** gave triol (*R*)-**75a**. By analogy for the racemic species, the desired (*R*)-**77a** was obtained from (*R*)-**75a**.

The isomer (*S*)-**77b** was synthesized by the same synthetic pathway from (*S*)-**78b**. Biological tests showed that unsaturated oxodiol (*S*)-**77b** corresponded completely with the natural aggregation pheromone produced by male Colorado beetles whereas its (*R*)-isomer, i.e., **77a**, was inactive.

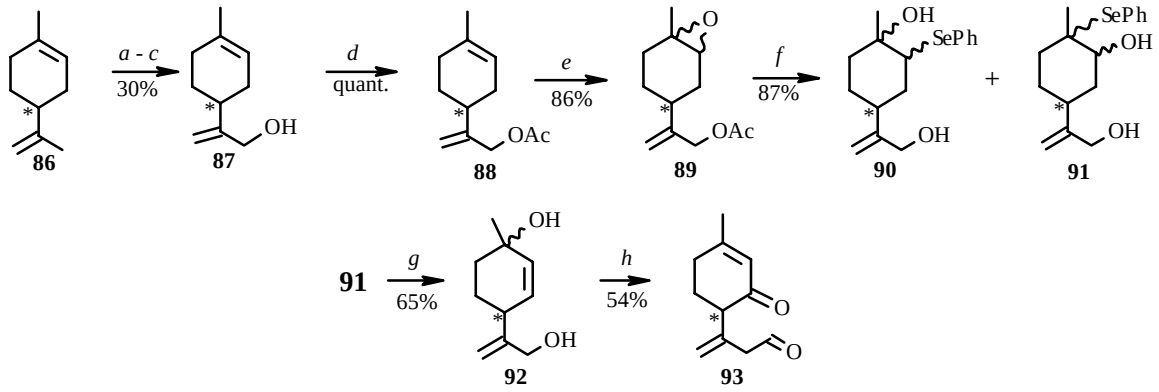
Regioselective epoxidation of the exocyclic double bond of carvone (**80**) by MCPBA was used to introduce a hydroxyl in establishing the absolute configuration of natural α-phellandren-8-ol (*p*-mentha-1,5-dien-8-ol) (**85**), a monoterpene isolated from bark and pine beetles (*Ips sexdentatus* Born, *I. acuminatus* Gyl, *Dendroctonus ponderosae* Hopkins) [31]. Both

enantiomers of **85** were synthesized from (*R*)- and (*S*)-carvone (**80**), respectively. Reduction of epoxide **81** involved the oxo group also, which was regenerated from the resulting diol **82** by selective oxidation with MnO_2 to ketoalcohol **83**. Deoxygenation occurring with deprotonation of the ketone by the Bamford—Stevens method [32] led through tosylhydrazone **84** to the desired dienol (*S*)-**85**. (*R*)-**85** was prepared analogously from (*R*)-carvone (**80**).



a. MCPBA; *b.* $LiAlH_4$; *c.* MnO_2; *d.* $TsNHNH_2$, HCl, MS 4 A°, THF; *e.* MeLi

The longhorn beetle (*Vesprus xatarti*) is a dangerous grape pest. Both enantiomers of 10-oxoisopiperitenone (vesperal) (**93**), a component of its sex pheromone, were synthesized in high optical purity and with a prepared C^{10}-template starting from (*S*)- and (*R*)-limonenes (**86**) [33] in order to determine its absolute configuration.



a. n-BuLi, TMEDA; *b.* O_2; *c.* Na_2SO_3; *d.* Ac_2O, Py; *e.* MCPBA; *f.* Ph_2Se_2, $NaBH_4$; *g.* H_2O_2, THF, H_2O; *h.* PCC, NaOAc

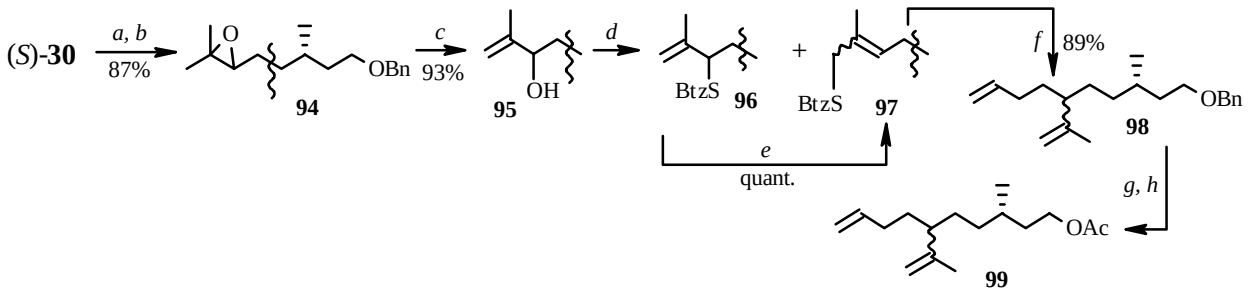
The hydroxyl was introduced on C-10 of diene (*R*)-**86** using the classical method of Crawford et al. [34] involving lithiation and oxidation of the organometallic intermediate, which gave unsaturated alcohol **87** in 30% yield without racemization at C-4.

The second oxygen function was introduced at C-3 via organoselenium intermediate **91**. For this, a mixture of diastereomers of **89**, prepared from **88** using MCPBA, was treated with phenylselenide anion as before [35]. In parallel with hydrolysis of the acetate, this gave a mixture of diols **90** and **91**, which were separated by chromatography. Then **91** was oxidatively cleaved by hydrogen peroxide to give bisallyl alcohol **92**, oxidation of which using Corey reagent gave the target (*S*)-vesperal (**93**).

The (*R*)-isomer of **93** was synthesized from (*S*)-limonene by an analogous scheme. According to tests, the (*R*)-isomer was completely identical to the natural pheromone.

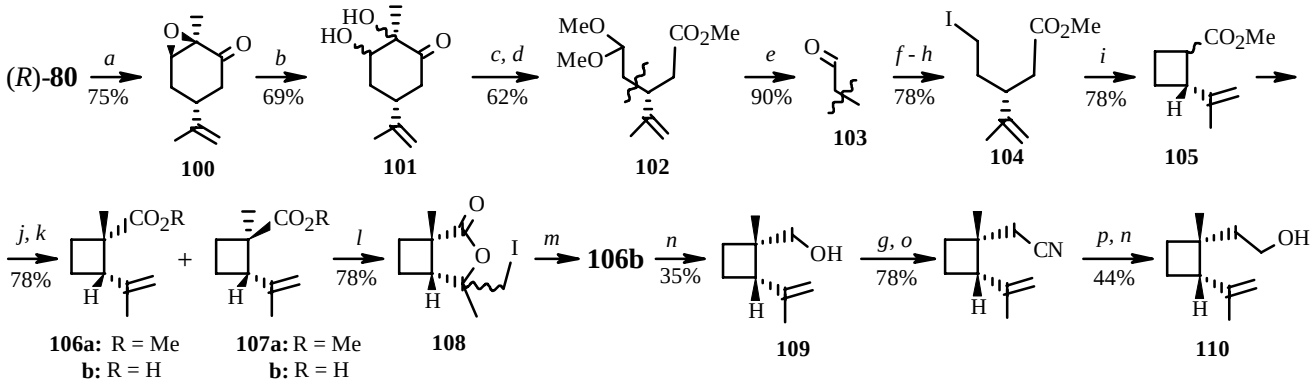
The examples given above [16-23] involve allylic oxidation of an isopropylidene group by SeO_2. Italian chemists [36] proposed a scheme in which the first step was epoxidation of (*S*)-citronellol (**30**) after protection of the hydroxyl in a simple and effective synthesis of (3*S*,6*R*/*S*)-3-methyl-6-isopropenyl-9-decen-1-ylacetates (**99**), components of the sex pheromone of California red scale (*A. aurantii*). Subsequent isomerization of oxirane **94** by aluminum isopropylate gave unsaturated allyl hydroxyether **95**. The butenyl radical was introduced into the molecule using a Grignard reaction and benzothiazolesulfide as the leaving group, which was added to substrate **95** by treatment with benzothiazole disulfide in toluene in the presence of triphenylphosphine. The resulting mixture of isomeric sulfides **96** and **97** was converted completely by irradiation into **97**. Alkylation of **97** by 3-buten-1-ylmagnesium bromide in the presence of Cu(I) bromide proceeded through an S_N2^1 mechanism exclusively to unsaturated ether **98**, from which the required acetate **99** was produced as a mixture of two diastereomers. It

should be noted that conditions for removing the benzyl protecting group by hydrogenolysis while not affecting the double bonds in the molecule were successfully found.



a. BnBr, NaH; *b.* MCPBA; *c.* $(i\text{-PrO})_3Al$; *d.* $BtzS_2$, PPh_3; *e. hv*; *f.* $CH_2{=}CH(CH_2)_2MgBr$, CuBr; *g.* H_2, Pd-C; *h.* AcCl, Py

Alkaline epoxidation of the conjugated double bond of (*R*)-carvone (**80**) was used to contract the ring in a synthesis of (+)-grandisol (**110**), a component of the boll weevil sex pheromone (*Anthonomus grandis*) [37].



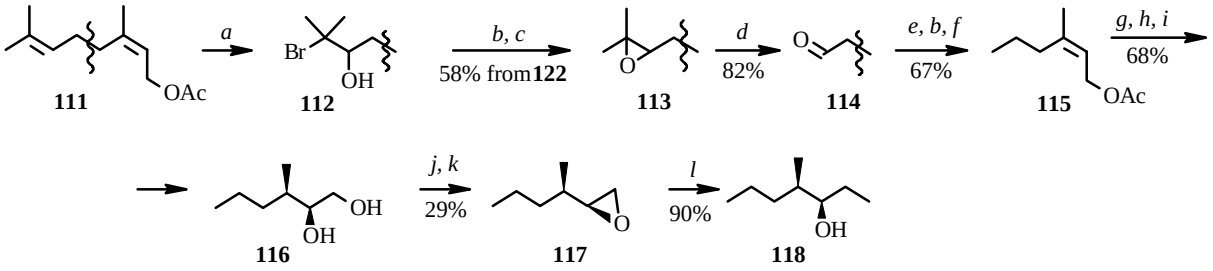
a. H_2O_2, NaOH, MeOH; *b.* $HClO_4$, THF; *c.* $NaIO_4$, MeOH; *d.* $HC(OMe)_3$, MeOH, TsOH; *e.* AcOH, H_2O; *f.* $NaBH_4$; *g.* TsCl, Py; *h.* NaI, Me_2CO; *i.* LDA, HMPA, THF; *j.* LDA, then MeI, THF; *k.* NaOH, MeOH; *l.* KI, I_2, $NaHCO_3$, CH_2Cl_2; *m.* Zn, NH_4Cl, EtOH; *n.* $LiAlH_4$; *o.* NaCN, HMPA, H_2O; *p.* DIBAH

Opening of epoxide **100** by acid gave ketodiol **101**. Periodate cleavage of **101** gave acetalester **102**, simple transformations of which produced haloester **104**. Enolization of **104** with subsequent intramolecular alkylation provided a path to the required cyclobutane **105**.

A methyl group of the required configuration was introduced by low-temperature methylation of the corresponding lithium derivative of ester **105**, which led to a diastereomeric mixture of **106a**,**b** and **107a**,**b**. Subsequent iodolactonization of this mixture cyclized only the *cis*-isomer of **106b** to form iodolactone **108**, which after reduction by zinc dust was regenerated into the single acid **106b**. Reduction of **106b** gave the alcohol (**109**), which was converted to the desired pheromone **110** through the cyanide homolog.

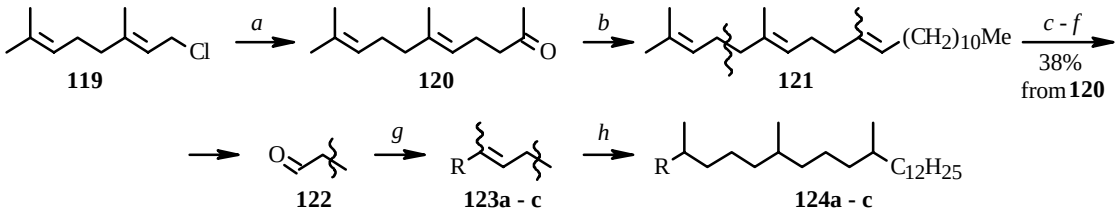
An isopropylidene group in linear monoterpenoids can be epoxidized both directly by peracids and by dehydrohalogenation of vicinal bromohydrins prepared, for example, using N-bromosuccinimide [38-39].

Thus, whereas Novak et al. [26] proposed using MCPBA to epoxidize the $\Delta^{5,6}$ double bond of nerol propionate (**48**), Mori [38] used hydroxybromination of nerylacetate (**111**) followed by dehydrobromination of the resulting bromohydrin **112** under alkaline conditions to give epoxide **113** in the synthesis of threo-(+)-4-methylheptan-3-ol (**118**), a pheromone of the elm bark beetle (*Scolytus multistratus*). Periodate cleavage of **113** gave ω-acetoxyaldehyde **114**, which was converted by a Huang—Minlon modification into unsaturated acetate **115**. The hydroxyl was added regioselectively to C-2 using an organoboron intermediate. Subsequent methylation of C-1 with dimethyllithiumcuprate of epoxide **117** corresponding to diol **116** completed the synthesis of the desired **118**.



a. NBS, DMF, H_2O; *b.* KOH; *c.* Ac_2O, Py; *d.* HIO_4; *e.* $N_2H_4 \cdot H_2O$, $(CH_2OH)_2$; f. DHF, TsOH; *g.* B_2H_6; *h.* 30% H_2O_2, NaOH; *i.* H_3O^+; *j.* HBr, AcOH; *k.* KOH, $(CH_2OH)_2$; *l.* Me_2CuLi

Double bonds are also fragmented via cleavage of the corresponding epoxide through an intermediate vicinal alcohol. This approach was used in the synthesis of 13,17,21-trimethyltri-(**124a**)-, -penta-(**124b**), and -hepta-(**124c**)-triacontanes, components of the sex pheromone of the tobacco hornworm (*Manduca sexta* L.) [39].

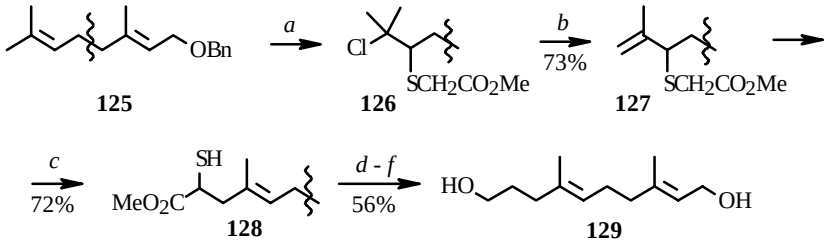


R = *n*-$C_{12}H_{25}$ (**a**); *n*-$C_{14}H_{29}$ (**b**); *n*-$C_{16}H_{33}$ (**c**)

a. $AcOCH_2CO_2Et$, base; *b.* $Me(CH_2)_{10}CH{=}PPh_3$; *c.* NBS, DME, H_2O; *d. i*-PrONa; *e.* $HClO_4$; *f.* $Pb(OAc)_4$; *g.* R-C(Me)=PPh_3; *h.* H_2, Pd-C

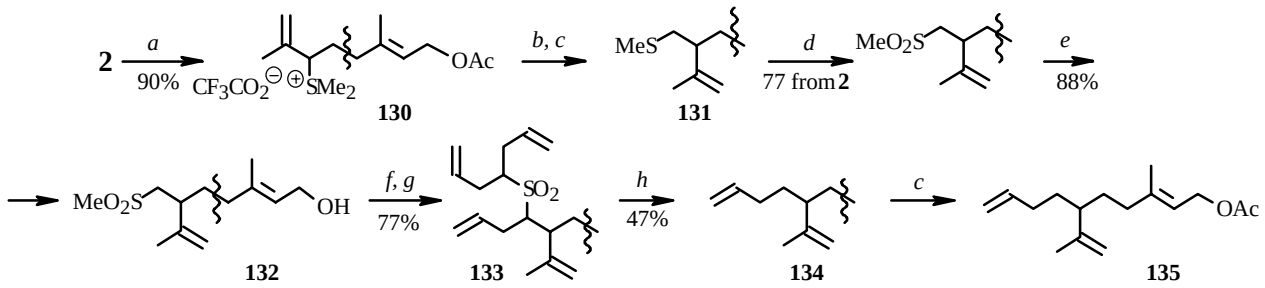
Triene **121**, the product of Wittig olefination of geranylacetone (**120**) by *n*-dodecylidenephosphorane, which was prepared in turn from geranylchloride (**119**), was used as a substrate for hydroxybromination. It was cleaved by a sequence of hydroxybromination, cyclization—decyclization, and fragmentation reactions using lead tetraacetate to aldehyde **122**. Olefination by the appropriate phosphoranes and exhaustive hydrogenation of the resulting trienes **123a**,**b**,**c** led to the required pheromones **124a**,**b**,**c**.

The methyl ester of acetic acid α-sulfochloride, like NBS, reacts regioselectively with acylic terpenoids. For example, its reaction with geraniol benzyl ether (**125**) was used to synthesize 3,7-dimethyl-2*E*,6*E*-decadien-1,10-diol (**129**), a component of the sex pheromone of the plain tiger butterfly (*D. chrysippus*) [40]. Dehydrohalogenation of the resulting α-chlorosulfide **126** led to an allylsulfide (**127**) with a terminal double bond. An intramolecular rearrangement of **127** in the presence of base gave α-mercaptoester **128** in good yield, desulfurization of which with further hydride reduction of the ester and deprotection led to the desired diol **129**.



a. MeO_2CCH_2SCl; *b.* DMF, 60°C; *c. t*-BuOK, THF, DMSO; *d.* Ni-Ra; *e.* $LiAlH_4$; *f.* H_2, Pd-C

An analogous rearrangement was used to prepare the racemic acetate of 2*E*,3-methyl-6-isopropenyl-9-decadien-1-ol (**135**), a component of the sex pheromone of the California red scale (*A. aurantii*) [41, 42]. Geranylacetate (**2**) was transformed by a Stevens rearrangement into sulfide **131** through an intermediate trifluoroacetate dimethylsufonium salt **130**. Subsequent conversions of sulfide **131**, culminating in its oxidation and alkylation of the resulting hydroxysulfone **132** by allylbromide, gave sulfone **133**, reductive desulfonylation of which gave alcohol **134**, which was easily converted to the target natural product **135**.

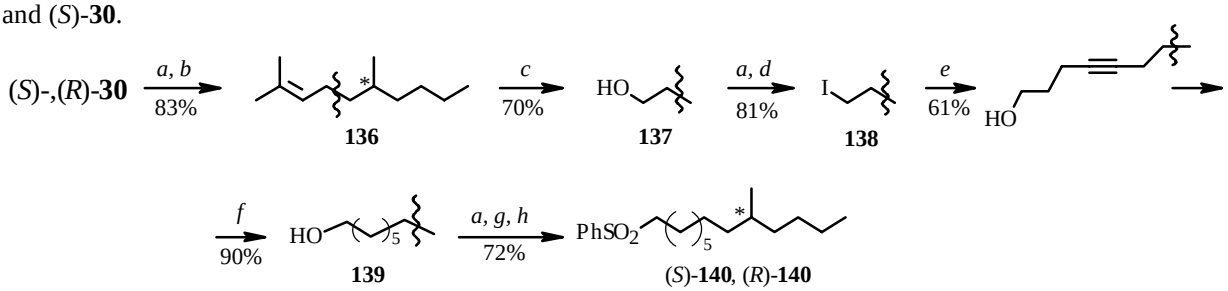


a. $(CF_3CO)_2O$, DMSO; *b.* MeONa; c. Ac_2O, Py; *d.* MCPBA; *e.* $LiAlH_4$; *f. n*-BuLi; *g.* CH_2=$CHCH_2Br$, THF, HMPA; *h.* Na, NH_3

OZONOLYSIS

Yet another oxidative method is ozonolytic cleavage of double bonds. It has also been widely used to synthesize insect pheromones [43-54] and is a convenient and practical method for preparing O-containing compounds.

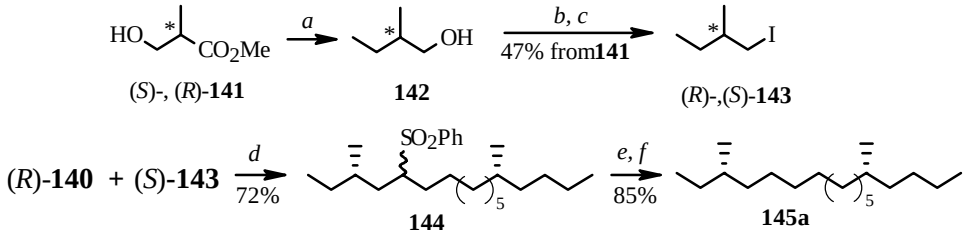
An example is the synthesis of all stereoisomers of 3,13-dimethylheptadecane (**145a-d**), the principal component of the western false hemlock looper (*Nepytia freemani*) sex pheromone [43]. The key step in this scheme was alkylation of phenylsulfones (*R*)- and (*S*)-**140** with a reactive α-methylene that were prepared from the corresponding enantiomers citronellol, (*R*)- and (*S*)-**30**.



a. TsCl, Py; *b.* EtMgBr, Li_2CuCl_4, THF; *c.* O_3, then $NaBH_4$; *d.* NaI, Me_2CO; *e. n*-BuLi, HC≡$CH(CH_2)_3OH$, THF, HMPA; *f.* H_2, PtO_2, EtOH; *g.* PhSH, NaOH, MeOH; *h.* MCPBA

The aforementioned organosulfur compounds were synthesized starting with alkylation of intermediate citronellyltosylate with ethylmagnesium bromide. Ozonolytic cleavage of the double bond of dimethyl-branched alkene **136** followed by hydride reduction of the peroxide ozonolysis products led to alcohol **137**, which was transformed into iodide **138**. Then, **138** was used to alkylate the lithium derivative of 4-pentyn-1-ol. Exhaustive hydrogenation, phenylthiylation of **139**, and oxidation by MCPBA gave the corresponding synthons (*R*)- and (*S*)-**140**.

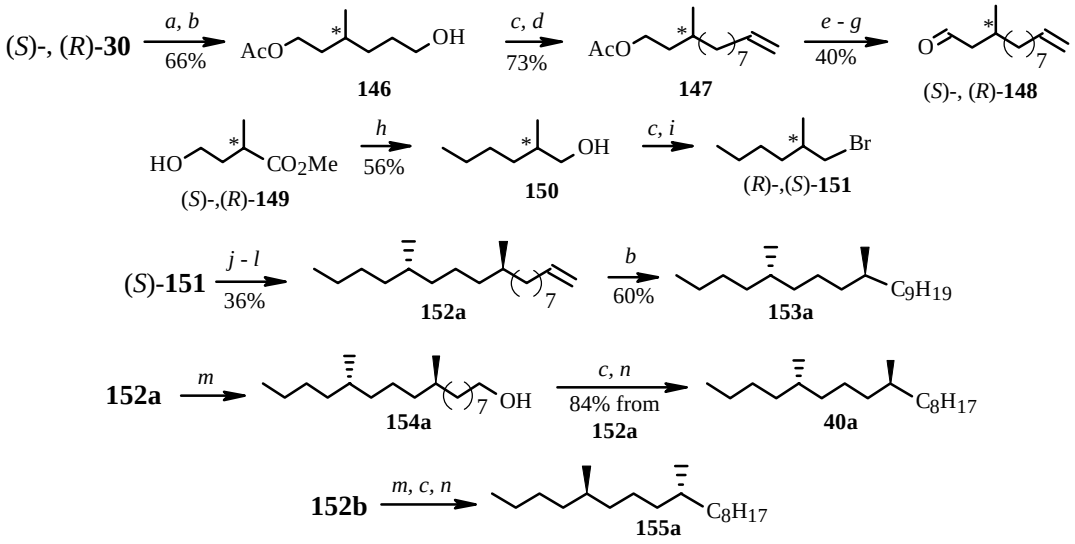
The second building block was synthesized using the required enantiomer of methyl 2-methyl-3-hydroxypropionate (**141**) as the substrate. Through a series of known transformations [44], including preparation of optically active 2-methylbutanol (**142**), it was converted to iodide **143**.



a. Ref. [44]; *b.* TsCl, Py; *c.* NaI, Me_2CO; *d. n*-BuLi, THF, HMPA; *e.* Na, Hg, Na_2HPO_4, EtOH; *f.* H_2, PtO_2

Combination of the lithium derivatives of sulfone **140** and iodide **143** through a cross-coupling reaction gave sulfone **144** with two optically pure chiral centers. Desulfurization and hydrogenation completed the synthesis of the desired pheromones **145a-d**.

A synthesis of all stereoisomers of 10,14-dimethyloctadec-1-ene (**152a-d**), 5,9-dimethyloctadecane (**153a-d**), and 5,9-dimethylheptadecane (**40a**, **41a**, and **155a**,**b**), components of the apple leafminer (*Lyonetia prunifoliella*) sex pheromone, was proposed starting with citronellol enantiomers (**30**) and methyl 2-methyl-3-hydroxybutanoate (**149**) [45].



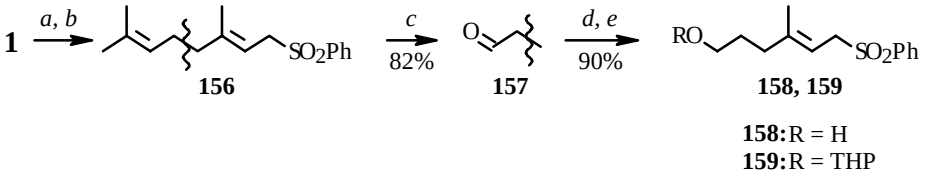
a. Ac_2O, Py; *b.* O_3, then $NaBH_4$; *c.* TsCl, Py; *d.* $H_2C{=}CH(CH_2)_4MgBr$, Li_2CuBr_2 ·Me_2S ·PhS, THF, HMPA; *e.* KOH; *f.* SiO_2 $AgNO_3$; *g.* PCC; *h.* ref. [47]; *i.* LiBr; *j.* Mg, then **148**; *k.* MsCl, Py; *l.* $LiBEt_3H$, THF; *m.* H_2, PtO_2; *n.* $LiAlH_4$, THF

Required isomers of **148** were prepared from (*R*)- and (*S*)-citronellol (**30**), which was first converted to acetoxyalcohol **146** [46] and then alkylated through the corresponding tosylate [47]. Hydrolysis of the resulting unsaturated acetate **147** with subsequent oxidation led to (*S*)- and (*R*)-aldehydes **148**, respectively.

Synthon **151** was prepared by a known method from the corresponding enantiomers of methyl 2-methyl-3-hydroxybutanoate (**149**) [47] through optically active 2-methylhexanol (**150**) [47]. Combinations of possible cross-couplings of (*S*)- and (*R*)-isomers of synthons **148** and **151** with subsequent simple transformations that did not affect the chiral centers led to all stereoisomers of the olefinic components of pheromone, **152a-d**. Catalytic hydrogenation of olefins **152a-d** produced the alkane components of the pheromone, **153a-d**.

The remaining stereosiomers of the pheromone **40a**, **41a**, and **155a**,**b** were synthesized from **152a-d** by ozonization followed by hydride reduction and deoxygenation of the intermediate alcohols **154a-d**.

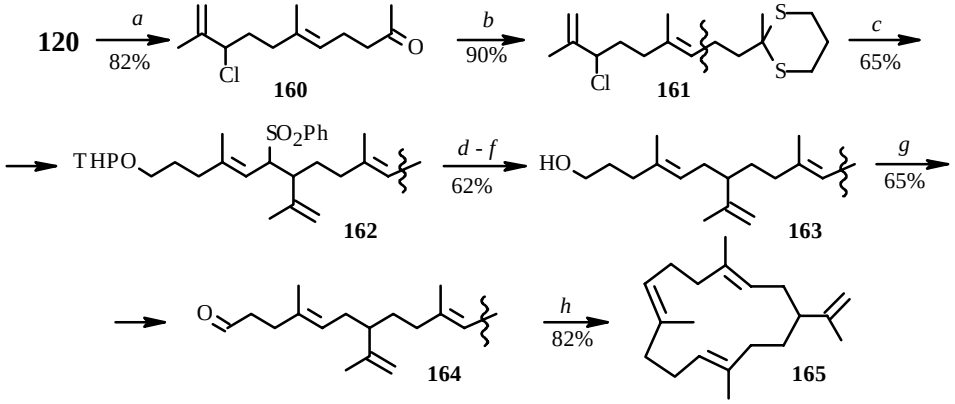
Two oxidative methods were used to prepare key blocks for a convergent synthesis of (+)-cembrene A (**165**), a highly effective tracking pheromone of termites (*Nastitermes exitiosus*) [48].



a. PBr_3; *b.* $NaSO_2Ph$, DMF; *c.* O_3, CH_2Cl_2, then Me_2S; *d.* $NaBH_4$, MeOH; *e.* DHP, TsOH

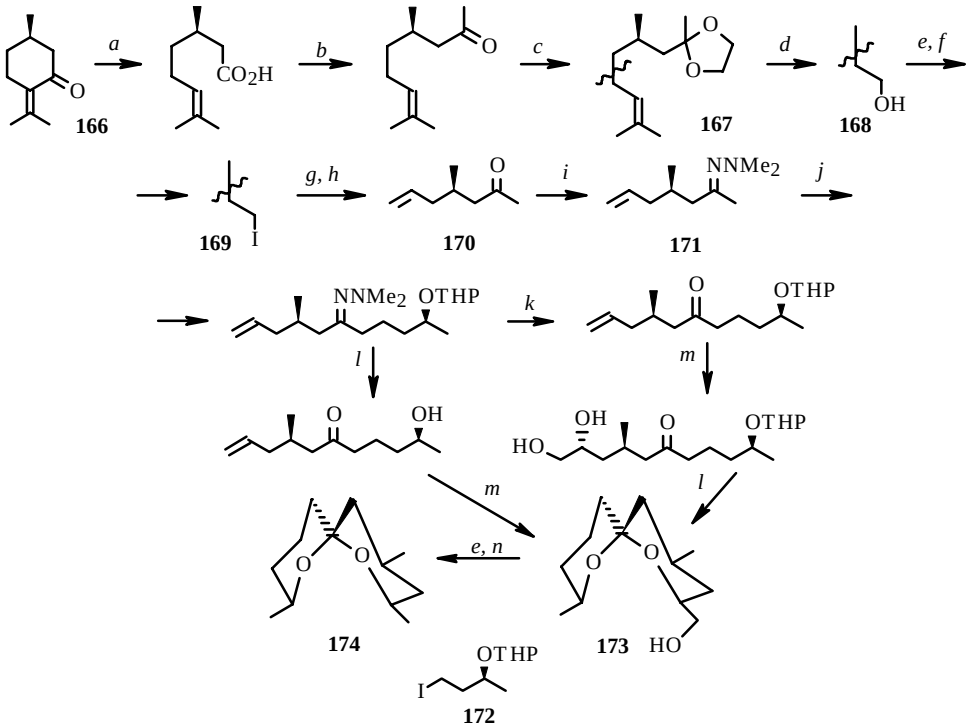
A key step in the synthesis of the first synthon **159** was ozonolytic fragmentation of geranylphenylsulfone **156**. For some reason the peroxide ozonolysis products of **156** were reduced in two steps, first to the aldehyde and then to the alcohol. However, in this instance it would have been simpler to convert immediately the peroxide ozonolysis products into the required alcohol **158** using $NaBH_4$.

To prepare the second synthon **161**, oxidation of geranylacetone **120** using sulfuryl chloride proceeded with allyl rearrangement to give secondary chloroketone **160**, which contained the isopropenyl group. By introducing dithiane protection of the oxo group, this block was prepared for cross-coupling with the first synthon, which was carried out successfully in aqueous base in the presence of an interphase-transfer catalyst. Further standard transformations of the resulting sulfone **162** led to the acyclic precursor oxodithiane **164**, intramolecular cyclization of which gave the required sesquiterpene **165**.



a. SO_2Cl_2, Na_2CO_3, CH_2Cl_2; *b*. $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$; *c*. NaOH, **159**, *n*-Bu_4NBr; *d*. PPTS; *e*. Na, Hg, NaH_2PO_4; *f*. $HgCl_2$, $CaCO_3$; *g*. PCC; *h*. $TiCl_3$-$AlCl_3$ (3:1), Zn-Cu, DME

The principal component of the abdominal gland secretion of the aposematic shield bug (*Cantao parentum* White) [Hemiptera: Scutelleridae] was established as (2*S*,4*R*,6*R*,8*S*)-trimethyl-1,7-dioxaspiro[5.5]undecane (**174**). This was the first example of a branched spiroacetal in the insect kingdom [49].



a. Ref. [52]; *b*. MeLi, -78°C; *c*. $HO(CH_2)_2OH$, TsOH; *d*. O_3, -78°C, then $NaBH_4$; *e*. TsCl; Py; *f*. NaI; *g*. *t*-BuOK; h. AcOH, 80°C; *i*. H_2NNMe_2, AcOH; *j*. LDA, -78°C, then **172**; *k*. SiO_2; *l*. HCl; *m*. AD-mix β, 0°C; *n*. $LiAlH_4$

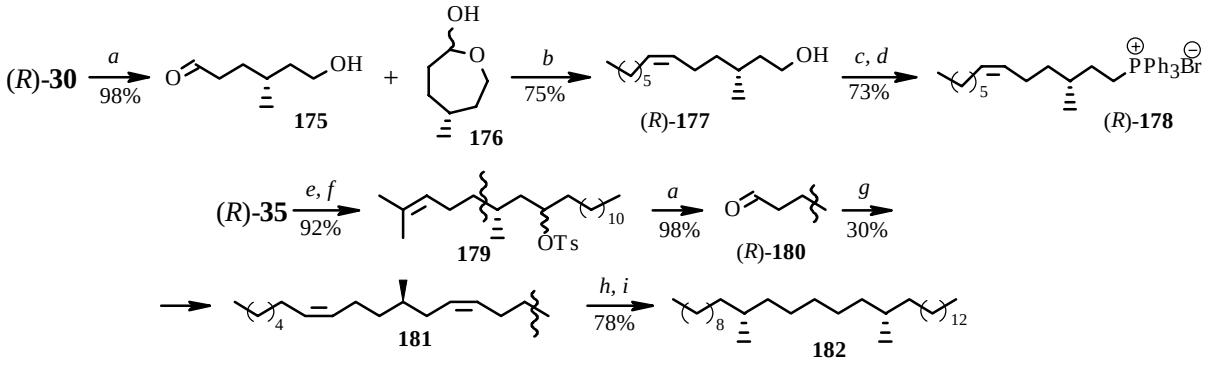
The enantioselective synthesis of this unique spiroacetal was carried out [50] starting with (*R*)-(+)-pulegone (**166**) through an intermediate acetonide of unsaturated ketone **167**. Successive ozonolysis of the double bond in **167** and reduction

of the peroxide products gave hydroxyketal **168**, dehydrogenation of which through the corresponding iodide **169** gave after acid hydrolysis ketoolefin **170**.

The required C chain was constructed by alkylation of the lithium derivative of the corresponding tosylhydrazone **171** by optically active substituted iodohydrin **172** [51].

The hydroxyl was introduced by oxidation of the double bond using the chiral osmium reagent AD-mix β. Simultaneous incorporation into the precursor of alcohols at the δ and δ′ positions relative to the oxo group caused ketal formation, which led to hydroxyketal **173**. Deoxygenation of **173** gave the target spiroketal **174**.

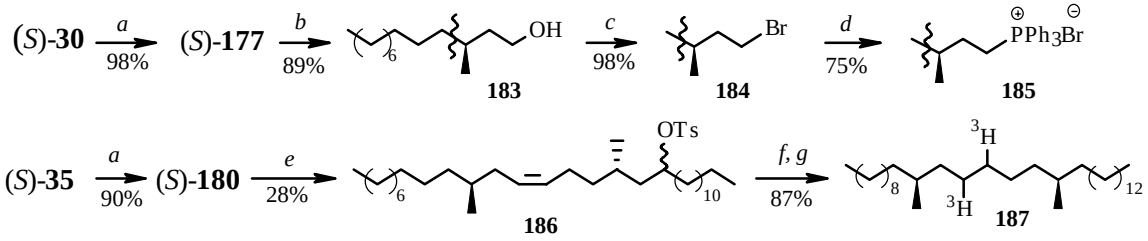
Ozonolysis was used as a functionalization method in the preparation of both synthons in a convergent synthesis of (11*R*,17*S*)-dimethylhentriacontane (**182**), a communication pheromone of ants *Camponotus vagus* [53]. Thus, phosphonium salt **178** was synthesized starting from (*R*)-citronellol (**30**), ozonolysis of which with subsequent reduction gave a mixture of hydroxyaldehyde **175** and hemiacetal **176**. Wittig olefination of this mixture gave (*Z*)-unsaturated alcohol **177**, which was converted further through the bromide to salt **178**.



a. O_3, -78°C, then Me_2S; *b.* *n*-$C_7H_{15}PPh_3Br$, *n*-BuLi, THF; *c.* CBr_4, PPh_3; *d.* PPh_3, MeCN;
e. Mg, $Me(CH_2)_{11}Br$, 10% $(CH_2Br)_2$, THF; *f.* TsCl, Py; *g.* (*R*)-**178**, *n*-BuLi, THF; *h.* $LiAlH_4$, NaH; *i.* H_2, Pd-C

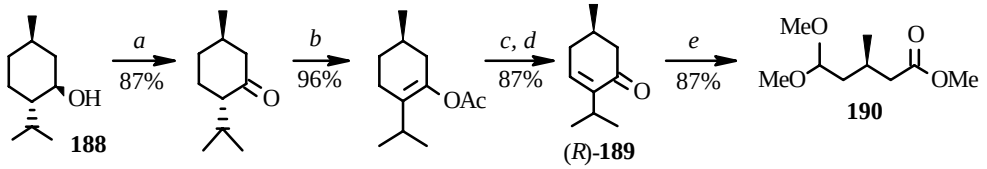
The second synthon was synthesized by ozonolytic cleavage of intermediate tosylate **179**, the esterification product of (*R*)-citronellal (**35**) alkylated with *n*-dodecylmagnesium bromide. The resulting aldehyde (*R*)-**180** underwent Wittig olefination by the phosphorane from phosphonium salt **178**. Reduction of tosyloxydiene **181** completed the synthesis of the desired pheromone **182**.

This same group [54] proposed a convergent synthesis of [$^3H_2$]-(11*S*,17*R*)-dimethylhentriacontane (**187**), a tritiated derivative of the *C. vagus* ant communication pheromone. Like in the scheme given above, the synthesis was performed from the two synthons tosyloxyaldehyde (*S*)-**180** and a transformation product of aldehyde (*S*)-**35** prepared by a previously described method [53]. Saturated bromide **184**, prepared from (*S*)-citronellol (*S*)-**30**, was used for phosphonium salt (*S*)-**185**. Wittig olefination of (*S*)-**180** gave tosyloxyolefin **186**, into which tritium was introduced using Wilkinson rhodium catalyst after deoxygenation. These transformations produced the target compound **187** in 22% overall yield calculated for starting (*S*)-**35**.



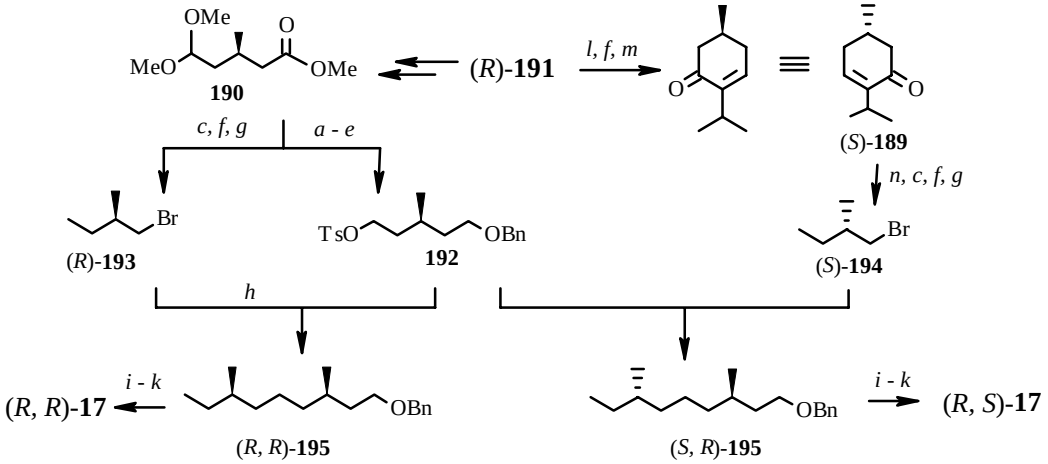
a. Ref. [54]; *b.* H_2, $(PPh_3)_3RhCl$, THF; *c.* CBr_4, PPh_3; *d.* PPh_3, MeCN; *e.* **206**, *n*-BuLi, THF; *f.* $LiAlH_4$;
g. Tr_2, $Rh(PPh_3)_3Cl$, THF

(*R*)-4-Menthenone, (*R*)-**189**, which is accessible from *l*-menthol (**188**), presents excellent synthetic possibilities for synthesizing optically pure methyl-substituted natural compounds [55-60]. We developed ozonolytic fragmentation of enone (*R*)-**189** to prepare the versatile optically pure bifunctional synthon (*R*)-**190**, methyl (*R*)-5,5-dimethoxy-3-methylpentanoic acid [61].



a. PCC; *b.* Ac_2O, TsOH; *c.* Br_2, CCl_4; *d.* MeOH; *e.* O_3, *c*-C_6H_{12} (or CCl_4)-MeOH then MeOH, TsOH

As an example of the use of this compound, we proposed convenient approaches to the synthesis of (*R*,*R*)-**17**- and (*R*,*S*)-**17**-4,8-dimethyldecanal, components of the aggregation pheromone of *Tribolium* flour beetles.



a. DIBAH; *b.* BnCl, KOH; *c.* PPTS, H_2O; *d.* $NaBH_4$; *e.* TsCl, Py; *f.* $N_2H_4 \cdot H_2SO_4$, KOH; *g.* Ag_2O, then Br_2;
h. Mg, Li_2CuCl_4; *i.* H_2/PtO_2; *j.* PBr_3/Py; *k.* Mg, then DMF; *l.* H_2O_2, NaOH, MeOH;
m. PCC; *n.* O_3, *c*-C_6H_{12} (or CCl_4)-MeOH then MeOH, TsOH

It was noted in a convergent synthesis of (*R*,*R*)-**17** that both optically active key synthons, toslyate **192** and bromide (*R*)-**193**, were synthesized from the aforementioned optically pure substrate (*R*)-**189**.

Synthon **192** was prepared using chemically selective hydride reduction of the ester in acetalester **190** to the alcohol, benzylation of which enabled the other end of the molecule to be transformed into the tosylate.

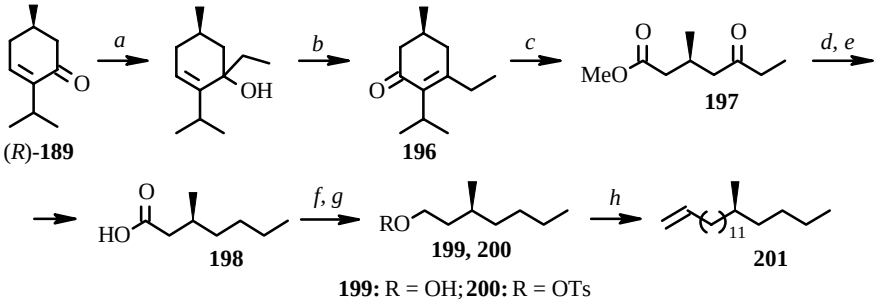
The second building block **193** was synthesized starting with conversion of the deprotected carbonyl in acetalester **190**. Subsequent Huang—Minlon reduction of the aldehyde and simultaneous hydrolysis of the ester produced the required bromide (*R*)-**193** after Hunsdiecker decarboxylation.

The key step included catalyzed alkylation of the tosyl group in **192** by the Grignard reagent from bromide (*R*)-**193**, which gave dimethyl-branched hydroxybenzyl ether **195**, subsequent simple transformations of which produced the desired aldehyde (*R*,*R*)-**17**.

The (*R*,*S*)-**17** isomer was synthesized analogously. Instead of bromide (*R*)-**193**, its (*S*)-**192** isomer prepared from (*S*)-4-methen-3-one, (*S*)-**189**, was used. (*S*)-**189**, in turn, was the configuration inversion product of (*R*)-**189**. (*R*)-**189** was transformed into (*S*)-**189** using Warton reduction of epoxyketones [62], which occurs with allyl rearrangement and forms allyl alcohols, oxidation of which gives unsaturated conjugated enones. Thus, carrying out these reactions caused inversion of the configuration of the asymmetric center in the starting chiral enone (*R*)-**189**.

Furthermore, using the synthesis of (14*S*)-methyloctadec-1-ene (**201**) [63], the sex pheromone of the apple leaf miner (*Lyonetia clerkella*), as an example, the novel synthetic possibilities of optically pure (*R*)-**189** were demonstrated. These were based on the susceptibility of conjugated enones for selective 1,2-addition of organometallic reagents with subsequent oxidative rearrangement of the resulting tertiary allyl alcohols by Cr(VI) [64, 65]. Ozonolytic decyclization of the resulting

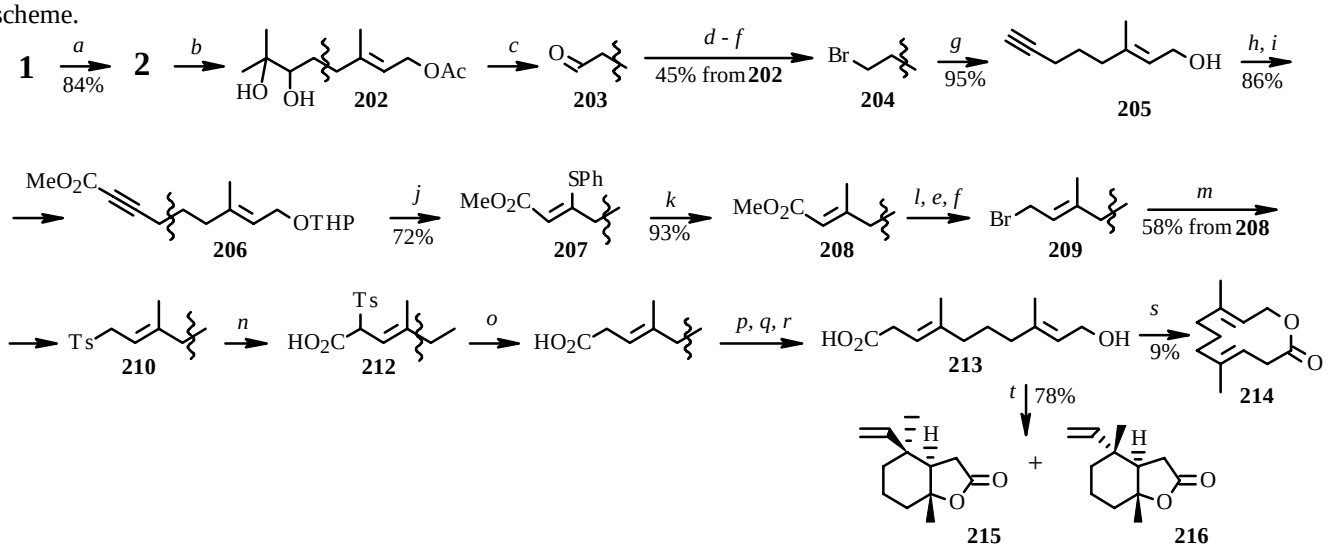
(*S*)-ethylmenthenone (**196**) and subsequent methanolysis gave ketoester **197**, Huang—Minlon deoxygenation of which accompanied by saponification of the ester gave (3*S*)-methylheptanoic acid (**198**), which was converted by standard methods through alcohol **199** and tosylate **200** into the target pheromone **201**.



a. EtLi; *b.* PCC; *c.* O_3, *c*-C_6H_{12}-MeOH then MeOH, TsOH; *d.* $N_2H_4 \cdot H_2SO_4$, KOH; *e.* KOH; *f.* $LiAlH_4$; *g.* TsCl, Py; *h.* $H_2C{=}CH(CH_2)_9MgBr$, Li_2CuCl

All aforementioned methods are used "classically" in organic synthesis. However, rather specific reagents, for example oxidizers based on Os(VIII) oxide [66-68] or singlet oxygen [69], are used just as often in constructing molecules.

The use of OsO_4 was proposed for preparing vicinal diol **202** from geraniol acetate (**2**) in the syntheses of suspensolide (**214**), anastrephin (**215**), and epianastrephin (**216**), components of the pheromone of the Caribbean fruit fly (*Anastrepha suspensa* Loew), a very dangerous pest of citrus in Central and North America [66]. The C skeleton of the key synthon hydroxyacid **213**, which contains two trisubstituted double bonds, was constructed using the transformations shown in the scheme.



a. Ac_2O, Py; *b.* OsO_4, N-methylmorpholine-N-oxide; *c.* $NaIO_4$; *d.* Li(*t*-BuO)$_2$AlH; *e.* TsCl, Py; *f.* LiBr, Me_2CO; *g.* LiC≡CH, NH_3, DMSO; *h.* TsOH, DHP; *i. n*-BuLi, THF, then MeOCOCl; *j.* PhSH, NaOH, MeOH; *k.* MeMgBr, CuI, THF; *l.* $LiAlH_4$; *m.* TsNa, DMF; *n. n*-BuLi, THF, then CO_2; *o.* Na-Hg, MeOH; *p.* CH_2N_2; *q.* TsOH; *r.* K_2CO_3, MeOH; *s.* $EtCO_2N{=}NCO_2Et$, PPh_3, PhH; *t.* $BF_3 \cdot Et_2O$

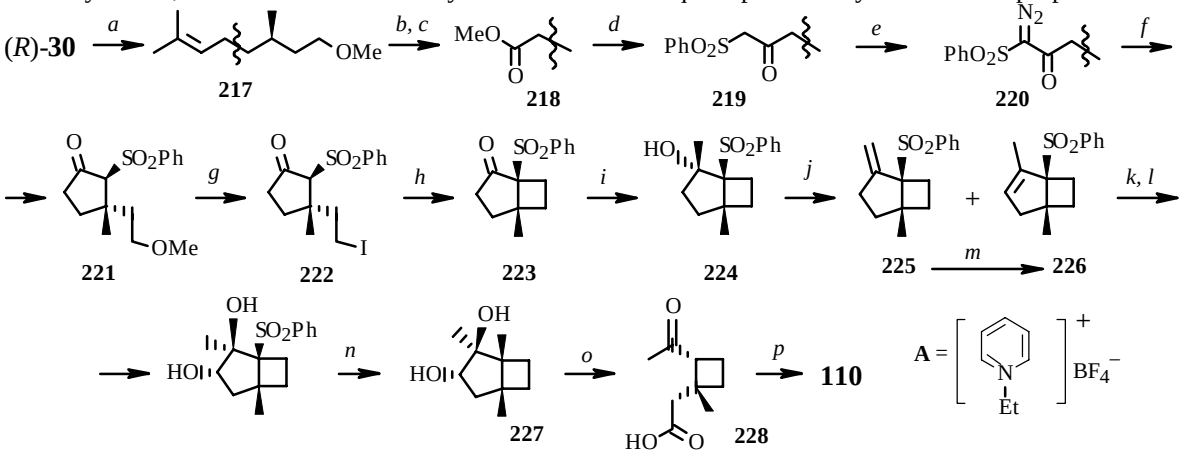
Geranylacetate (**2**) was oxidized by OsO_4 in the presence of co-oxidant *N*-methylmorpholine-*N*-oxide followed by periodate cleavage of diol **202** to aldehyde **203**, which was converted by standard methods to bromide **204**. Subsequent acetylenation of **204** in a mixture of liquid NH_3 and DMSO gave enyne alcohol **205**.

The second trisubstituted double bond was introduced using a literature method [70]. Michael addition of phenylthiol to unsaturated ester **206**, prepared by treatment of **205** with methylchloroformate, led to sulfide **207**, methylation of which gave (2*E*)-unsaturated ester **208**. Then **208** was converted by standard transformations to sulfone **210**. The C chain was lengthened by addition of CO_2 to the lithium derivative of **210** with subsequent desulfurization of **211**, which gave the THP ester of **212**,

which was converted to key hydroxyacid **213**. Lactonization of **213** by the method of Mitsunobu et al. [71] gave the target suspensolide **214**.

The previously described [72] acid-catalyzed cyclization of **214** gave racemic mixtures of (±)-**215** and (±)-**216**. The resulting compounds were purified by chromatography and separated using diastereomeric amides.

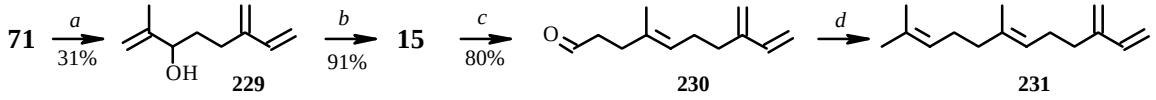
The use of chromic anhydride as a co-oxidant enabled Monteiro and Schpector [67] to fragment (*R*)-citronellol (**30**) protected as the methyl ether (**217**) at the double bond to give *ω*-methoxyacid **218**, which was used to synthesize (+)-grandisol (**110**). In this synthesis, the use of successive bicyclization with subsequent partial decyclization was proposed.



a. NaH, then MeI, DME; *b.* OsO_4, CrO_3, Me_2CO; *c.* H^+, MeOH, CH_2Cl_2; *d.* BnONa, THF, DMSO;
e. A, NaN_3, NaOAc, MeOH; *f.* $Rh_2(OAc)_4$, PhH; *g.* NaI, TMSCl, MeCN; *h.* NaH, THF; *i.* MeMgI, THF, Et_2O;
j. $SOCl_2$·Py; *k.* H_2O_2, HCO_2H, 100°C; *l.* NaOH, MeOH; *m.* *t*-BuOK, DMSO; *n.* Na-Hg; *o.* $NaIO_4$, $RuCl_3$, H_2O; *p.* Ref. [68]

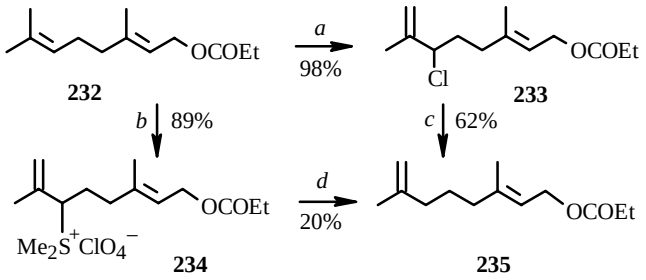
Disubstituted **218** was transformed into ketosulfone **219** and then into diazo derivative **220** in order to introduce the tertiary and quaternary C atoms of the required configuration. Carbenoid cyclization of **220** proceeded stereoselectively and was catalyzed by rhodium acetate to give cyclopentane sulfone **221**. Substitution of the methoxy by halide followed by another cyclization with asymmetry generation gave the key cyclobutane fragment of the target molecule. 1,2-Addition of methylmagnesium iodide to the ketone of **223** produced tertiary alcohol **224**, which was transformed into unsaturated sulfone **226**. The cyclopentane ring was opened by treatment of **227** with a mixture of ruthenium chloride and sodium periodate. The resulting ketoacid **228** was converted by a known method [68] into the desired pheromone **110**.

Oxidation by singlet oxygen of myrcene (**71**), which occurred with allyl rearrangement of the trisubstituted double bond, was used in a three-step synthesis of farnesene (**231**), a component of the fire ant (*Solenopsis invicta*) tracking pheromone [69]. Claisen rearrangement of the resulting triene alcohol **229** gave ester **15**, low-temperature hydride reduction of which with subsequent Wittig olefination of aldehyde **230** by isopropylidenetriphenylphosphorane led to the desired sesquiterpene **231**.



a. O_2, *hv*, *n*-Bu_4NBr; *b.* $CH(OEt)_3$, H^+, 139°C; *c.* DIBAH, -78°C; *d.* *i*-$PrPh_3P^+I^-$, *n*-BuLi

The synthetic pathway for *α*-geranylpropionate (**235**), a component of the sex pheromone of the San Jose scale (*Quadraspidiotus perniciosus*), that is based on isomerization of the isopropylidene groups of geraniol into an isopropenyl group is interesting [72, 73]. Two approaches were used for this. The first went through allyl chloride **233**, which was prepared by low-temperature chlorination of geranylpropionate **232** and subsequent dehalogenation; the second, through the dimethylsulfonium salt of geranylpropionate **234** with subsequent electrolytic reduction.



a. SO_2Cl_2, CH_2Cl_2, -60°C; *b.* DMSO, $(CF_3CO)_2O$, $LiClO_4$;
c. Zn, $NiCl_2$, PPh_3, NaI, DMF, H_2O; *d.* e^-

Thus, the literature indicates that oxidative methods are used in a wide range of transformations of monoterpenoids. Chiral substrates can be functionalized with retention of the absolute configuration of the asymmetric centers. This is one of the fundamental aspects of insect-pheromone synthesis.

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