

# Synthesis of Pheromones: Highlights from 2005-2007

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**Abstract:** The synthesis of insect pheromones published in the period 2005-2007 is reviewed. A total of 66 compounds from different insect orders and belonging to different structural classes were included.

## 1. INTRODUCTION

Pheromones are naturally occurring chemicals which are produced and released by an organism in order to transmit information to another individual of the same specie. So far, the use of pheromones has been documented for many species belonging to different taxa, with the insects clearly standing out in terms of number of species studied. This is probably due to several factors, including the relatively simple behavior of insects (facilitating the design of bioassays), their occurrence in great numbers (easy access to material), and their importance as pests in agriculture.

The study of insect pheromones is a fascinating research field. The prospect of unraveling the molecular basis of chemical communication as well as the possibility of developing environmentally benign methods of pest control is driving many research activities. In this context, pheromones need to be synthesized for two reasons. First, to provide authentic reference material needed for unambiguous identification of the natural compound by comparing their analytical data. Second, to provide the material necessary for the evaluation of their effect on insect behavior in laboratory bioassays or under natural conditions in the field. In many cases, insect pheromones were found to occur as pure or as defined mixtures of stereoisomers, so synthetic routes have to be developed, which lead with high selectivity to the desired geometric and/or absolute configuration. The synthesis of insect pheromones has been reviewed in a number of articles. Mori provided comprehensive overviews in 1981 and 1992 [1, 2] with a partial update in 2004 [3] and also published articles relating pheromone synthesis to specific topics [4-6]. The application of biocatalysis to pheromone synthesis has also been reviewed recently [7].

The present article is a follow-up of our summary of pheromone syntheses published from 2002-2004 [8]. Here, we review the most recent advances in the synthesis of pheromones published in the triennium 2005-2007.

## 2. SYNTHESIS OF ALKANES AS PHEROMONES

### 2.1. *meso*-7,11-Dimethylheptadecane (1)

The branched alkanes *meso*-7,11-dimethylheptadecane (1) and (*S*)-7-methylheptadecane constitute the female sex pheromones of the spring hemlock looper *Lambdina athasaria* and of the pitch pine looper *L. pellucidaria* [9, 10].

Nagano *et al.* [11] presented a stereoselective synthesis of 1. Starting from ethyl bromomethacrylate (A), they prepared diethyl 4-benzyloxy-2,6-dimethyleneheptanedioate (B), which was used in a diastereoselective chelation-controlled radical reaction with pentyl iodide in the key step (Scheme 1). Use of 6 equivalents of the Lewis acid MgBr<sub>2</sub>·OEt<sub>2</sub> and low temperatures turned out to be crucial for the high diastereoselectivity of the reaction.

### 2.2. 5,9-Dimethylpentadecane (2) and 5,9-dimethylhexadecane (3)

5,9-Dimethylpentadecane (2) and 5,9-dimethylhexadecane (3) are components of the sex pheromone of the coffee leaf miner *Leucoptera coffeella* [12].

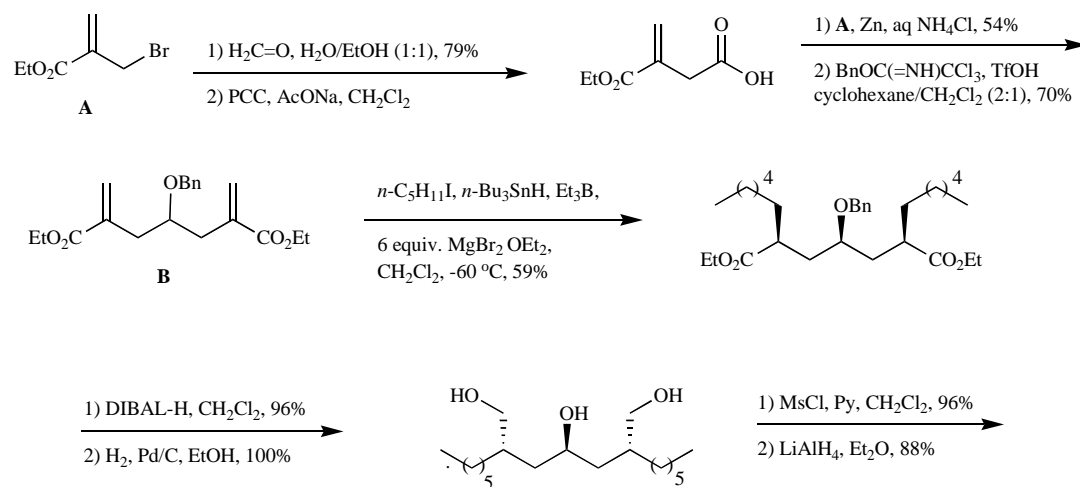
Racemic mixtures of both compounds were synthesized starting from citronellol by Doan *et al.* [13], using a sequence of ultrasound-assisted tosylation and alkylation reactions (Scheme 2). The overall yield was above 50 % over six steps in both cases, and the use of ultrasound shortened considerably the reaction times as compared to conventional procedures.

## 3. SYNTHESIS OF ALKENES AS PHEROMONES

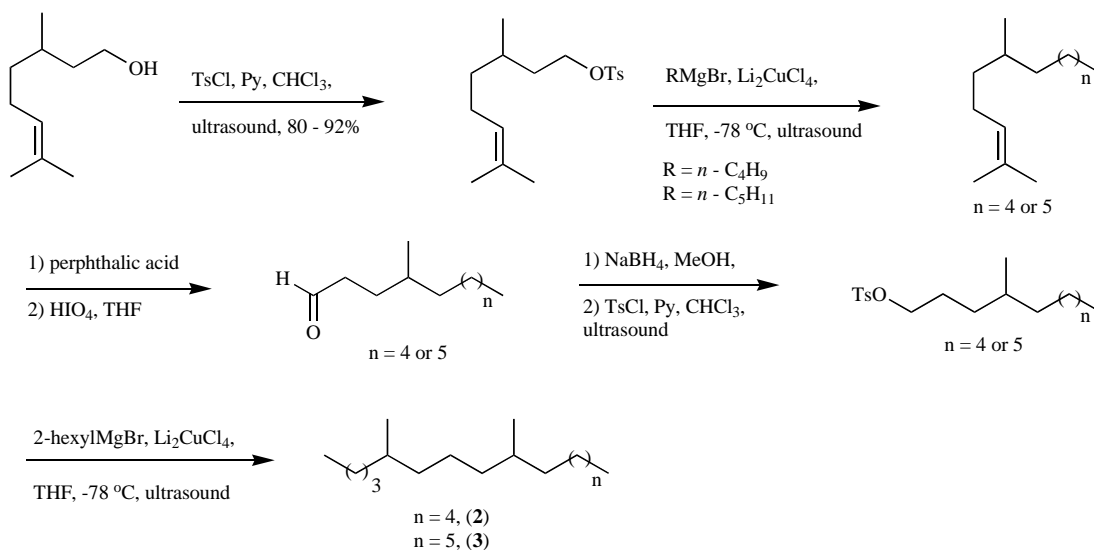
### 3.1. (*Z,Z*)-5,25-Hentriacontadiene (4) and (*Z,Z*)-5,27-tritriacontadiene (5)

(*Z,Z*)-5,25-Hentriacontadiene (4) and (*Z,Z*)-5,27-tritriacontadiene (5), have been identified as the major sex pheromone components from female cuticular extracts of *Drosophila ananassae* and *D. pallidosa*, respectively. The authors indicate that the major sex pheromone compounds are key factors in male recognition between *D. ananassae* and *D. pallidosa*, and that morphological differences are less important [14, 15].

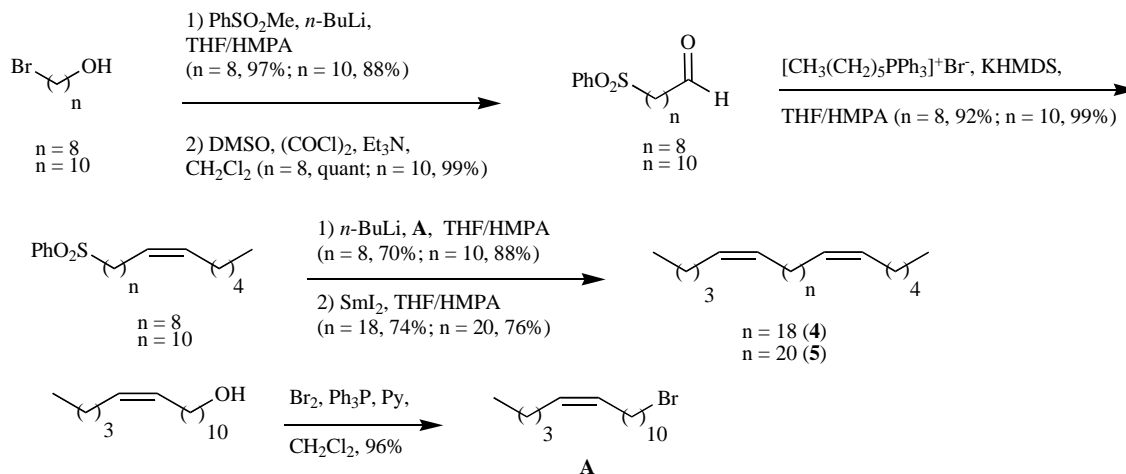
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Scheme 1.



Scheme 2.

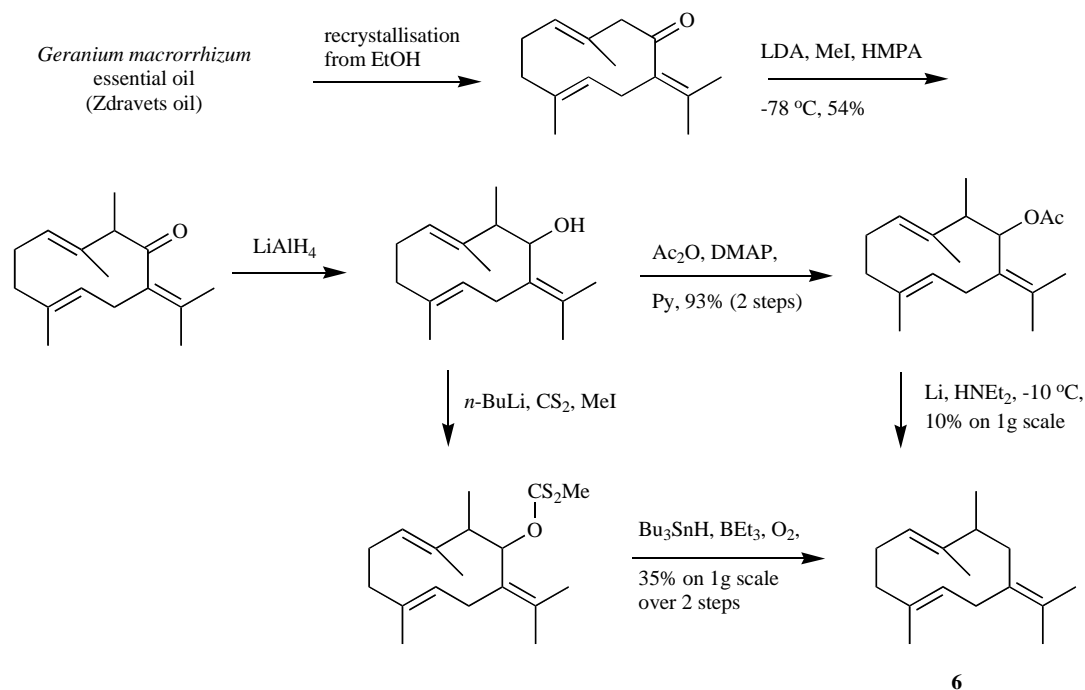


Scheme 3.

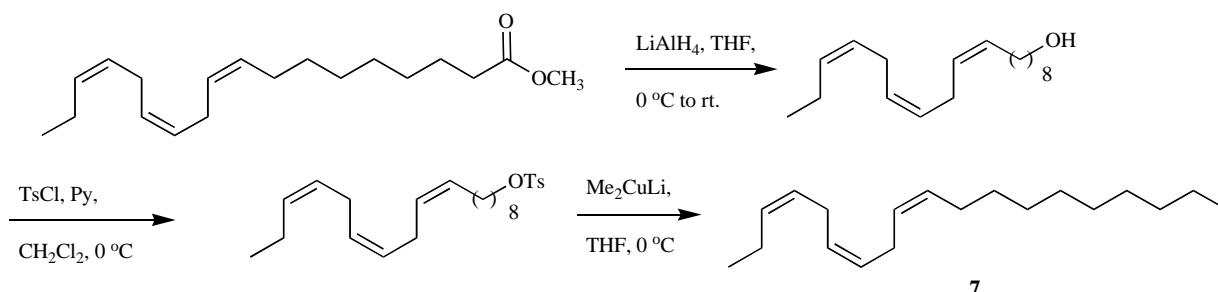
Morita *et al.* [16] described a synthesis of these two compounds employing Wittig olefination followed by a sulfone coupling (Scheme 3).

### 3.2. 9-Methylgermacrene-B (6)

The structure of the sex pheromone produced by the males of the sandfly *Lutzomyia longipalpis*, from the Lap-



Scheme 4.



Scheme 5.

inha Cave (Minas Gerais State) region of Brazil, has been proposed as the novel homosesquiterpene 9-methylgermacrene-B [17]. The structure and absolute configuration was defined as (*S*) by comparing analytical data and biological activity of the synthetic enantiomers with the natural product [18].

Hooper *et al.* [19] described a synthesis of **6** starting from germacrene, which is the main component of the essential oil of the cranesbill *Geranium macrorrhizum* (Zdravets oil) and was obtained in pure form by recrystallization. Subsequent methylation and deoxygenation afforded the racemic pheromone over 4 steps (Scheme 4).

### 3.3. (3Z,6Z,9Z)-3,6,9-Nonadecatriene (7)

(3Z,6Z,9Z)-3,6,9-Nonadecatriene is the pheromone of a number of geometrid and noctuid moths, for example it has been identified in the autumn gum moth *Mnesampela privata* [20].

The use of butylated hydroxytoluene as an antioxidant to prevent loss of product was the key factor in the short synthesis presented by Davies *et al.* [21]. Methyl linoleate (either enriched from linseed oil or pure) was reduced to the alcohol, which was converted to the tosylate. Reaction with lithium dimethyl cuprate afforded **7** without C19 contami-

nants in 65 % (starting from enriched methyl linoleate) and 85 % (starting from pure methyl linoleate) yield, respectively (Scheme 5). All steps were carried out in the presence of 1 % the antioxidant, which was carried through the synthesis and assured an improved yield as compared to previous methods.

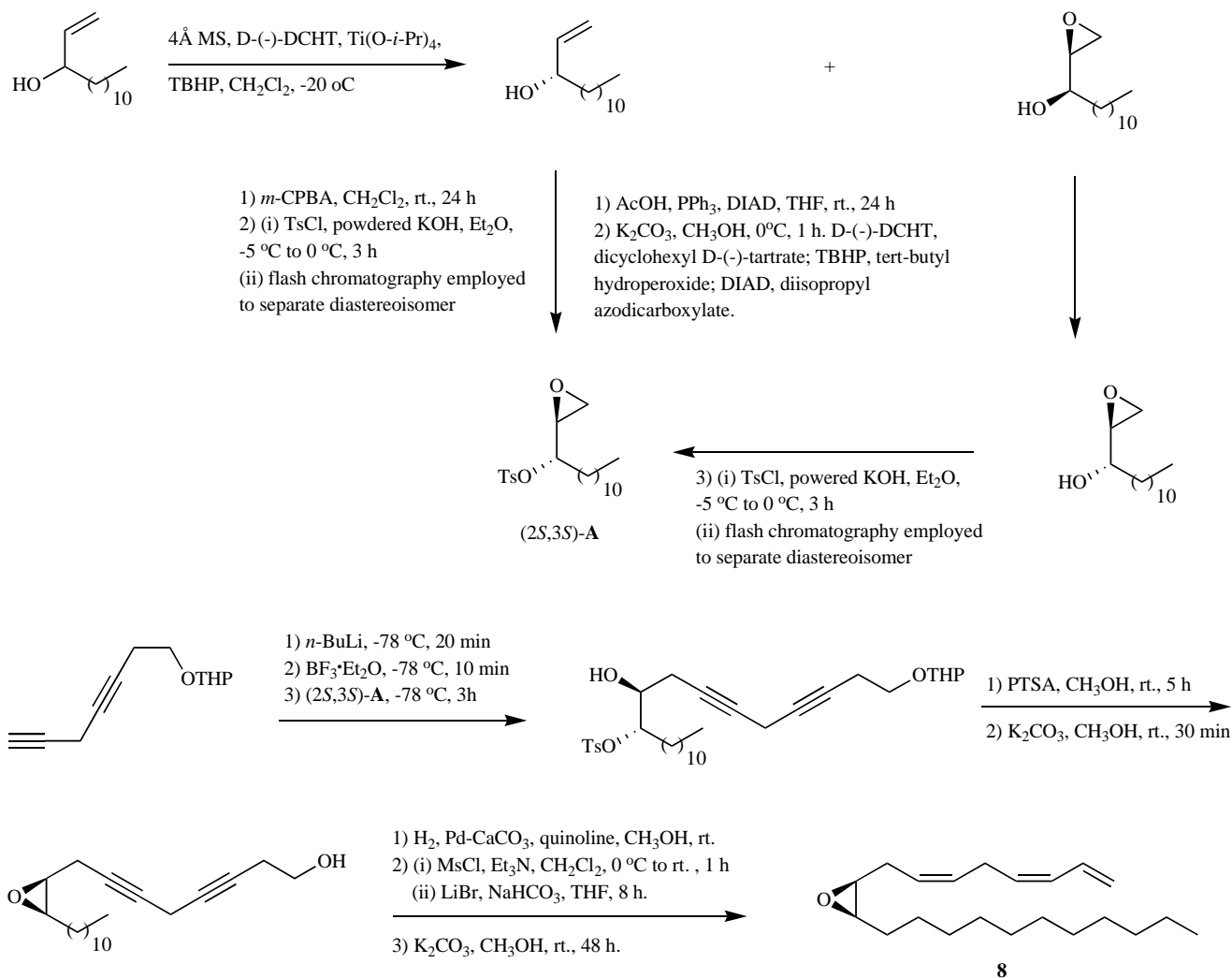
## 4. SYNTHESIS OF EPOXY PHEROMONES

### 4.1. (3Z,6Z,9S,10R)-9,10-Epoxy-1,3,6-heneicosatriene (8) and (3Z,6Z,9S,10R)-9,10-epoxy-3,6-heneicosadiene (9)

(3Z,6Z)-9,10-Epoxy-1,3,6-heneicosatriene (**8**) and (3Z,6Z)-9,10-epoxy-3,6-heneicosadiene (**9**) were identified in the sex pheromone gland of the arctiid moth, *Hyphantria cunea*. Of the synthesized enantiomers, the (9S,10R) alkenes were biologically active, while the (9R,10S) forms were inactive [22].

*Diacrisia obliqua* is a polyphagous insect attacking many crops, particularly oil seed crops in India and Bangladesh [23]. Persoons *et al.* showed that the pheromone of *D. obliqua* is a five component blend consisting of **8**, **9**, (9Z,12Z)-octadecadienal, (9Z,12Z,15Z)-octadecatrienal and (3Z,6Z,9Z)-heneicosatriene [24].

Che and Zhang [25] described an enantioselective synthesis of **8** utilizing a coupling reaction between a 1,4-diene and the chiral epoxy tosylate **A** (Scheme 6).



Scheme 6.

Nakanishi and Mori [26] described a new and more practical synthesis of **8** and **9** to furnish these compounds in a suitable quantity (Scheme 7). The synthesis of both pheromones was performed employing the chiral epoxide **A** obtained in 84–87% e.e. from lipase-catalyzed asymmetric acetylation of the racemic epoxide in the key step. (2*S*,3*R*)-**A** was converted to the triflate and alkylated with diynes **D** (synthesis of **8**) and **E** (synthesis of **9**), respectively. The resulting epoxy diynes were further transformed to **8** and **9**, respectively, including Lindlar semihydrogenation and a final alkylation step.

#### 4.2. (7*R*,8*S*)-(+)-7,8-Epoxy-2-methyloctadecane (**10**) (disparlure)

Disparlure (2-methyl-7,8-epoxyoctadecane, **10**) is the single sex attractant pheromone emitted by the female gypsy moth, *Lymantria (Porthetria) dispar* [27]. Iwaki *et al.* [28] established the configuration of natural **10** to be (7*R*,8*S*) by synthesis, and also observed that this isomer is attractive while the enantiomer results in an inhibitory response.

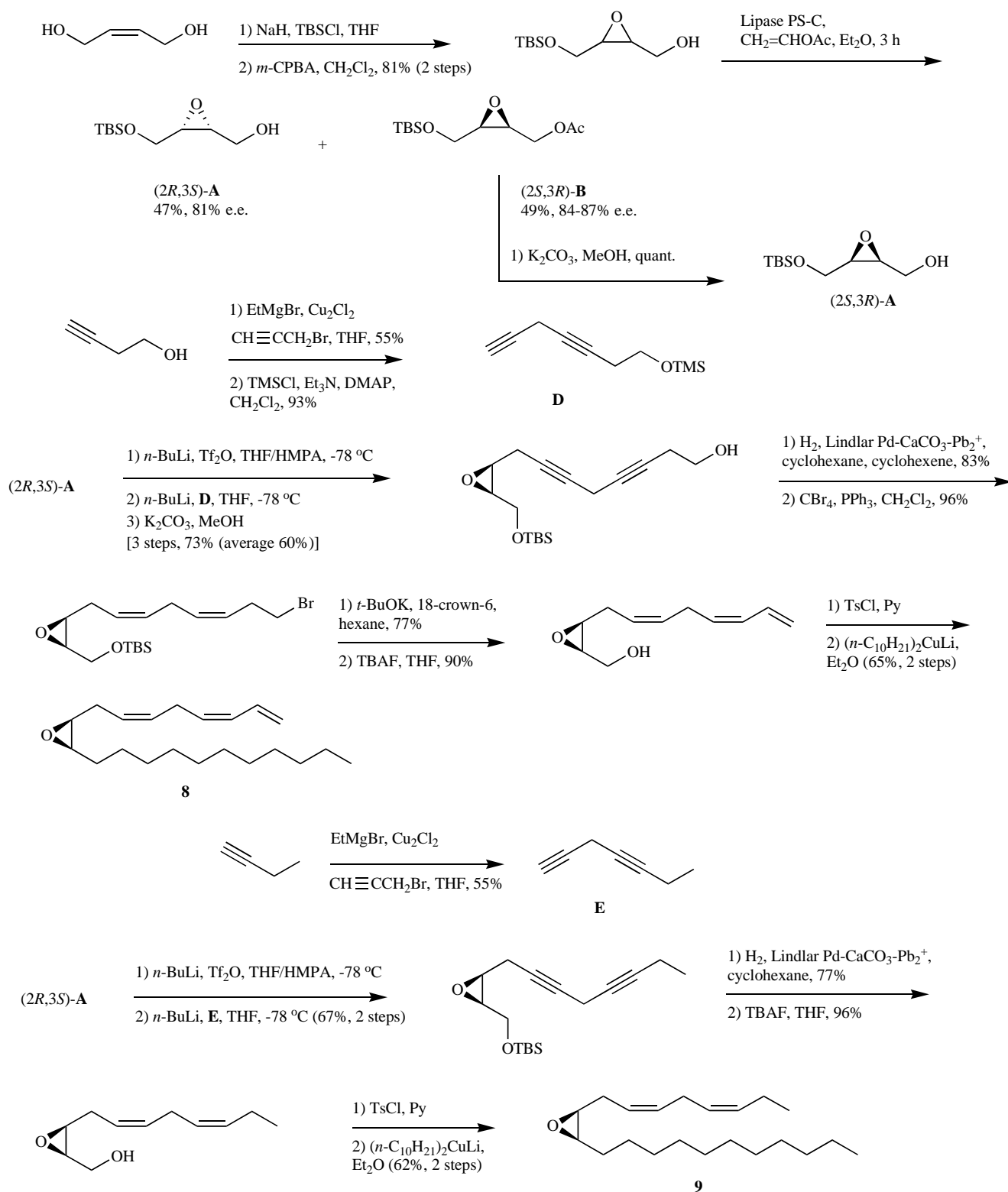
Koumbis and Chronopoulos [29] described a short route to obtain both enantiomers of disparlure, starting from isopropylidene D- and L-erythrose (both available in multigram quantities from D- and L-arabinose), respectively, which

were subjected to two Wittig olefinations. The saturated acetonide obtained after hydrogenation with Raney-Ni was transformed to the epoxide via the diol (Scheme 8).

An enantiodivergent route to both enantiomers of disparlure was developed by Prasad and Anbarasan [30]. The common precursor for both enantiomers was the homoallylic alcohol **A**, obtained in 5 steps from the bis-Weinreb amide of L-tartaric acid. The hydroxy group of **A** was either protected as tosylate (synthesis of (-)-**10**) or as *tert*-butyldimethylsilyl ether (synthesis of (+)-**10**). Building up of the carbon skeleton by cross metathesis reactions and subsequent partial deprotection and cyclization furnished the enantiomers in a high overall yield (Scheme 9).

#### 4.3. (6*Z*,9*Z*,11*S*,12*S*)-*trans*-11,12-Epoxy-6,9-heneicosadiene (**11**) (posticlure)

Posticlure [(6*Z*,9*Z*,11*S*,12*S*)-*trans*-11,12-epoxy-6,9-heneicosadiene (**11**)] is the pheromone of the tussock moth *Orgyia postica*, a pest of mango and litchi trees in Japan [31]. A multigram synthesis of the *trans*-epoxide pheromone, starting from diethyl L-tartrate was carried out by Fernandes [32], employing Wittig olefinations and the stereoselective conversion of an intermediate diol to the epoxide (Scheme 10).



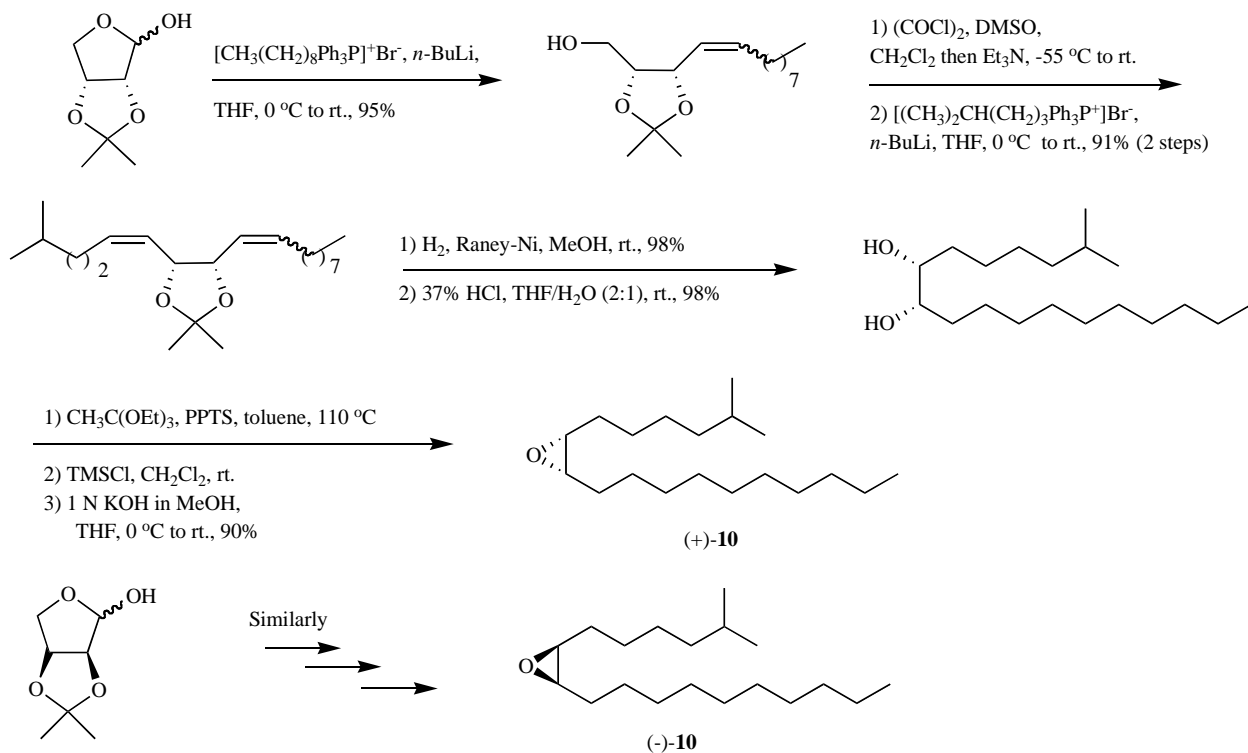
Scheme 7.

## 5. SYNTHESIS OF NON-ISOPRENOIDAL PHEROMONE ALCOHOLS AND THEIR ESTERS

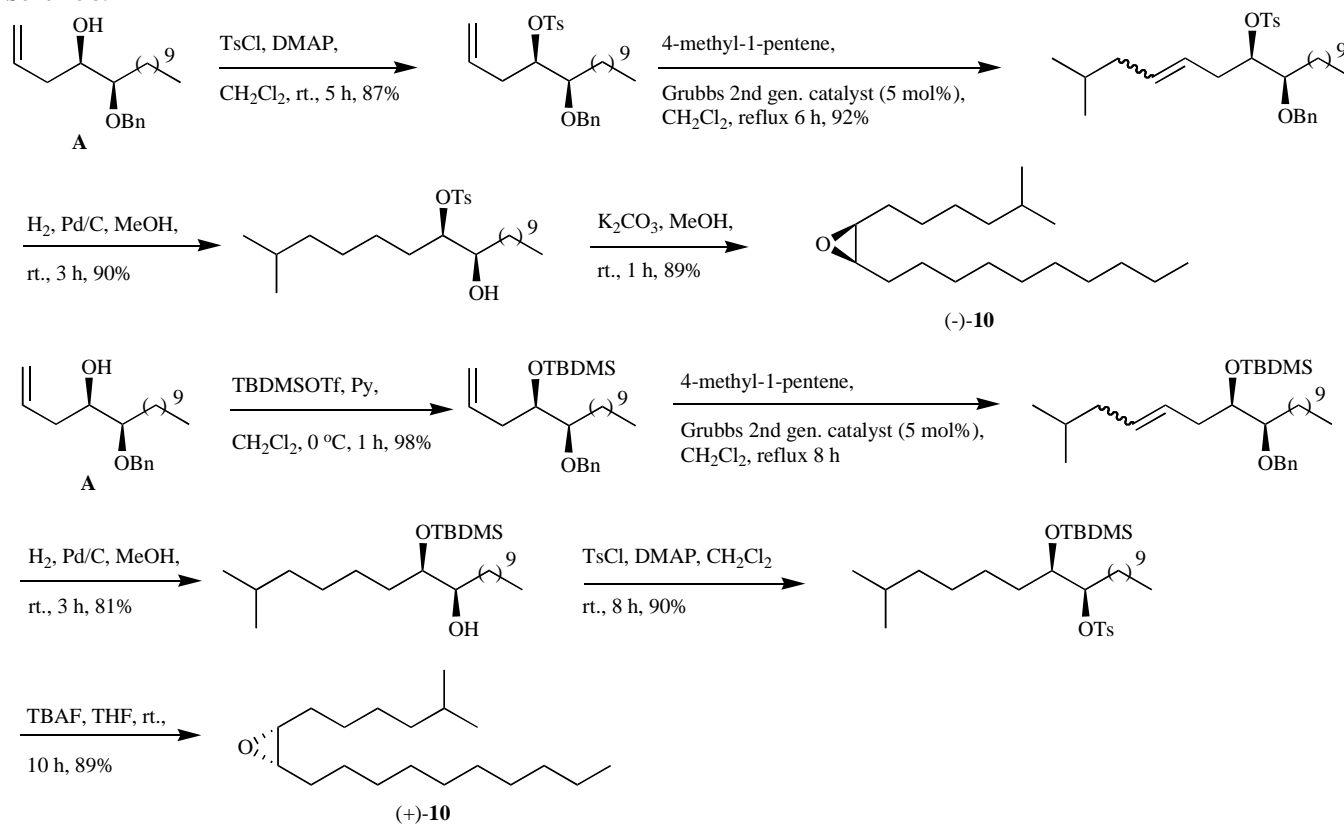
### 5.1. (2*S*,3*S*,7*S*)-3,7-Dimethylpentadecan-2-ol (**12**) and (2*S*,3*S*,7*S*)-3,7-dimethylpentadec-2-yl acetate (**13**)

Since the pioneering work of Coppel, Jewett and co-workers [33, 34], it is known that the sex pheromones of

several species of pine sawflies are esters that share a common alcohol moiety, namely 3,7-dimethylpentadecan-2-ol (**12**). *Neodiprion lecontei* and *N. sertifer* produce the acetate **13** as the major component of their pheromones, whereas *Diprion similis* uses the propionate [33]. Later studies revealed that the (2*S*,3*S*,7*S*) stereoisomers showed the highest activity for all *Neodiprion* species [35, 36].



Scheme 8.

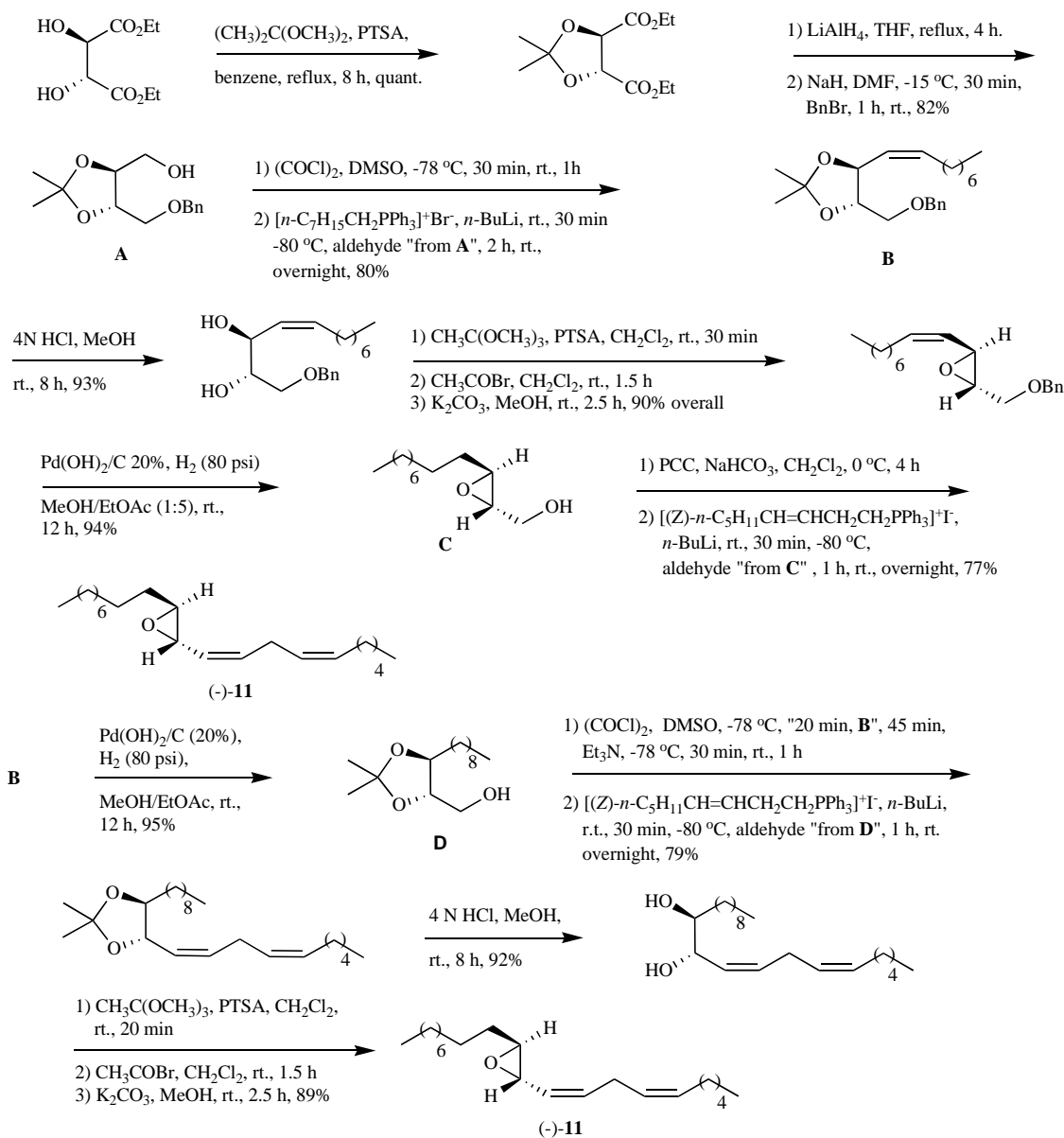


Scheme 9.

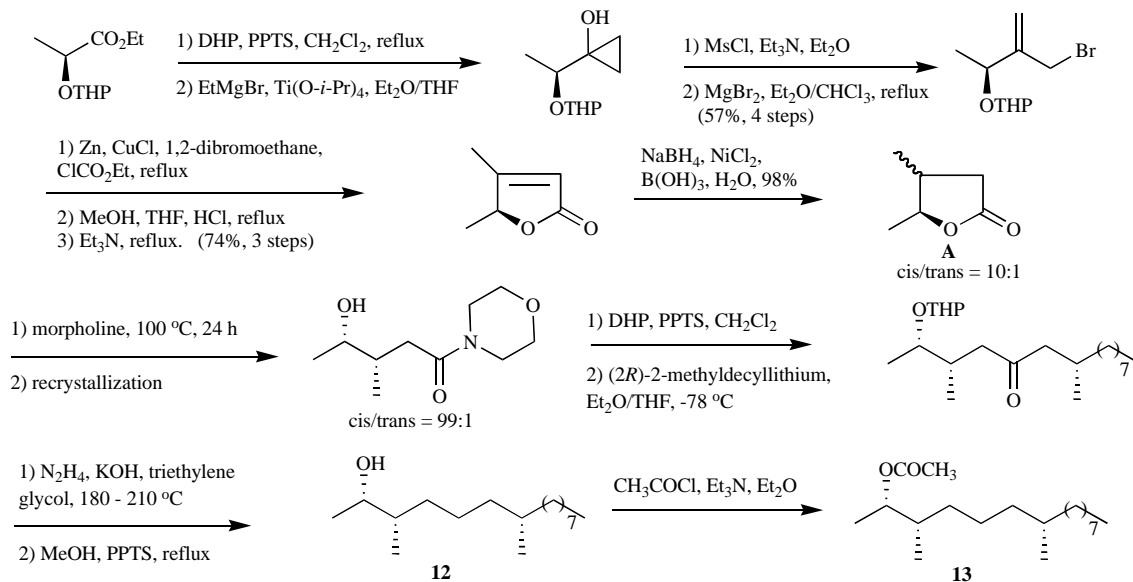
Bekish *et al.* [37] reported a stereoselective synthesis of alcohol **12** and acetate **13** based on the creation of methyl branches in the carbon chain using the transformation of carboxylic esters into 2-substituted allyl halides via sulfonates of tertiary cyclopropanols (Scheme 11).

## 5.2. 7-Methyloctyl 5-methylhexanoate (**14**), 7-methyloctyl octanoate (**15**), 7-methyloctyl 7-methyloctanoate (**16**), and 7-methyloctyl (*Z*)-4-decenoate (**17**)

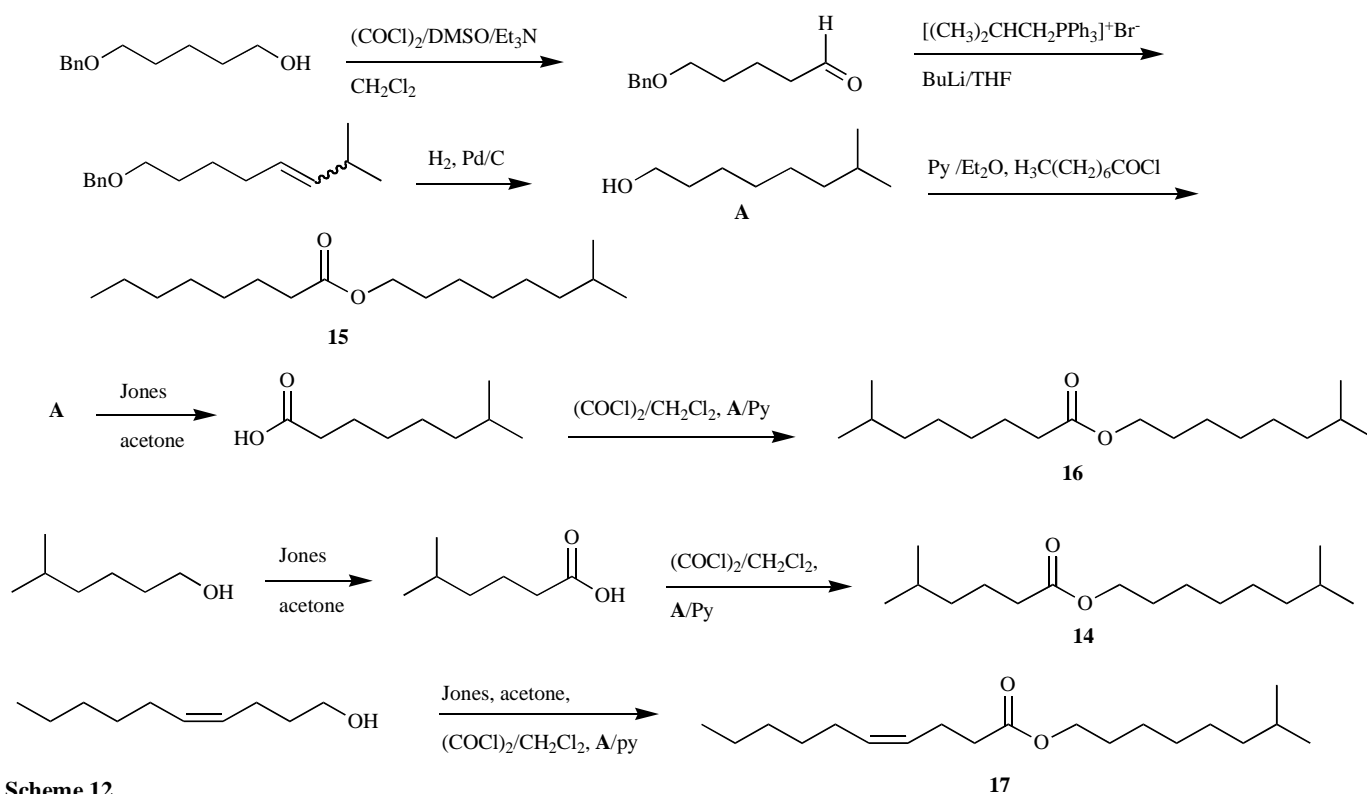
7-Methyloctyl 5-methylhexanoate (**14**), 7-methyloctyl octanoate (**15**), 7-methyloctyl 7-methyloctanoate (**16**), 7-



Scheme 10.



Scheme 11.



Scheme 12.

methyloctyl (*Z*)-4-decenoate (**17**) were identified by Tolasch *et al.* as components of the sex pheromone produced by females of the click beetle *Elatер ferrugineus* [38]. The same authors described a simple synthesis to obtain all four compounds. The alcohol moiety **A** common to all esters was obtained in four steps from 1,5-pentanediol, involving mono-protection, partial oxidation, Wittig olefination and hydrogenation reactions. The acid moieties were either commercially available or synthesized from the corresponding alcohols by Jones oxidation (Scheme 12).

### 5.3. (2*S*,10*S*)-2,10-Diacetoxyundecane (**18**)

(2*S*,10*S*)-2,10-Diacetoxyundecane (**18**) constitutes, together with (2*S*,9*S*)-2,9-diacetoxyundecane and (*S*)-2-acetoxyundecane, the sex pheromone of the swede midge *Contarinia nasturtii* [39].

A novel approach for a remote asymmetric induction to obtain 1,9-*anti* diols was presented by Cahill *et al.* [40]. The diastereoselective synthesis of the furanyl spiroacetal **A** allowed the preparation of spiroacetal fruit fly pheromones **B** and **C**, which were used in the synthesis of the diastereomerically pure mixture of (*R,R*) and (*S,S*) isomers of 1,9-*anti* diol **D** by transacetalisation. Kinetic resolution of ( $\pm$ )-**D** using *Candida antarctica* lipase B afforded the (*R,R*)-diacetate and the (*S,S*)-diol, which was converted to **18** with acetic anhydride (Scheme 13).

### 5.4. (2*S*,7*S*)-2,7-Dibutyroxynonane (**19**)

The orange wheat blossom midge *Sitodiplosis mosellana* is a worldwide pest of wheat crops. The sex pheromone has been identified as (2*S*,7*S*)-2,7-dibutyroxynonane (**19**) [41], and a mixture of isomers is effective in monitoring the pest.

The stereoselective synthesis of (2*S*,7*S*)-**19** was achieved by Hooper *et al.* [42] using a diastereoselective ring closure metathesis reaction of the mixed silaketal **A** in the key step (Scheme 14). The other stereogenic center had been defined by the use of (*S*)-5-hexen-2-ol during preparation of **A**.

### 5.5. (4*E*,7*Z*)-4,7-Tridecadienyl acetate (**20**)

(4*E*,7*Z*)-4,7-Tridecadienyl acetate (**20**) is a component of the pheromone of the potato moth *Phthorimaea operculella* [43].

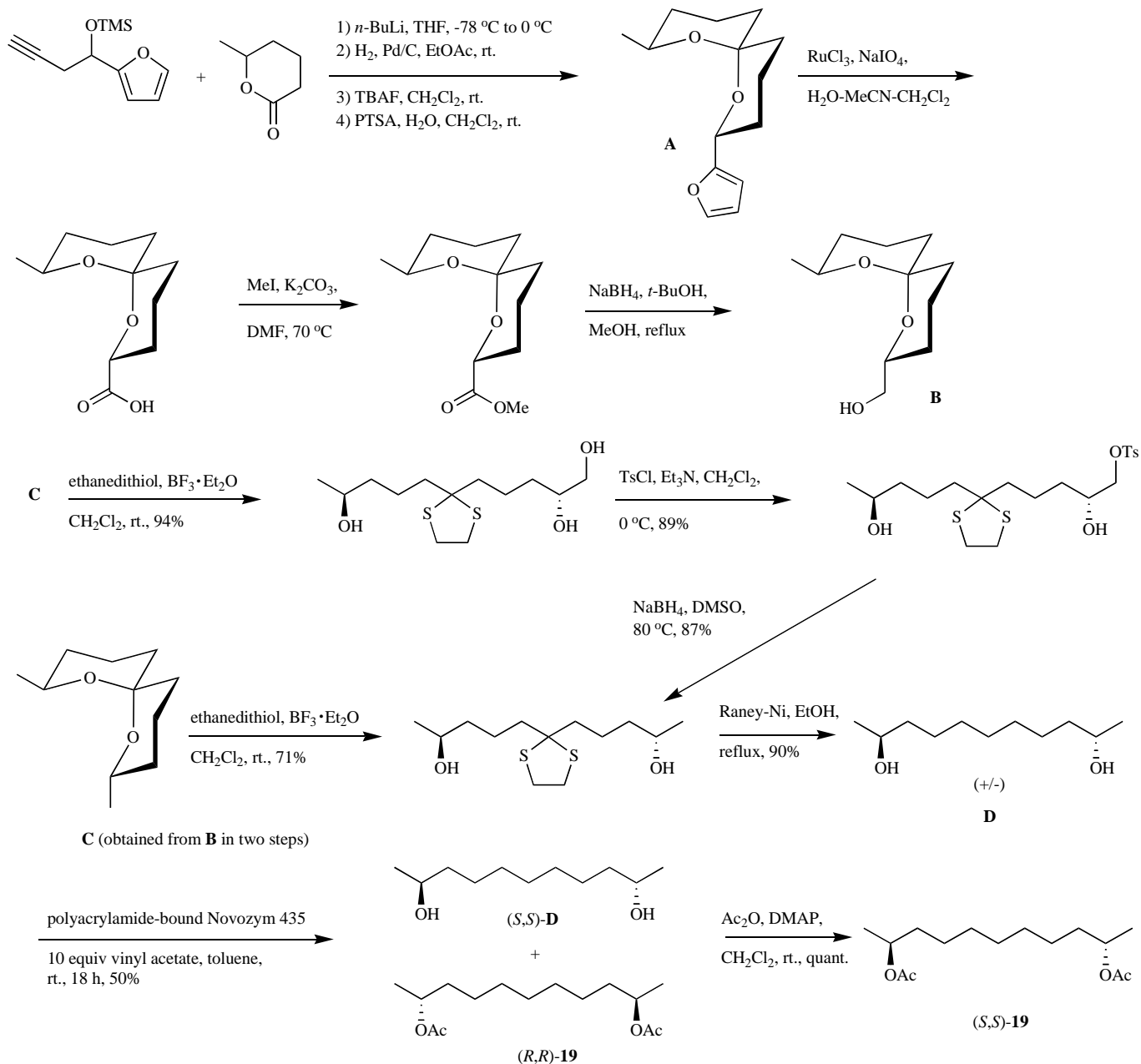
Starting from acrolein, Vakhidov and Musina [44] obtained the allylic alcohol **A** by Grignard reaction. The key step was a stereoselective Claisen rearrangement of **A** with triethylorthoacetate in the presence of propanoic acid. Oxidation of the resulting hydroxy ester and stereoselective Wittig reaction completed the carbon chain and was followed by reduction and acetylation to obtain **20** in high purity (Scheme 15).

### 5.6. (4*E*,6*Z*,10*Z*)-4,6,10-Hexadecatrien-1-ol (**21**)

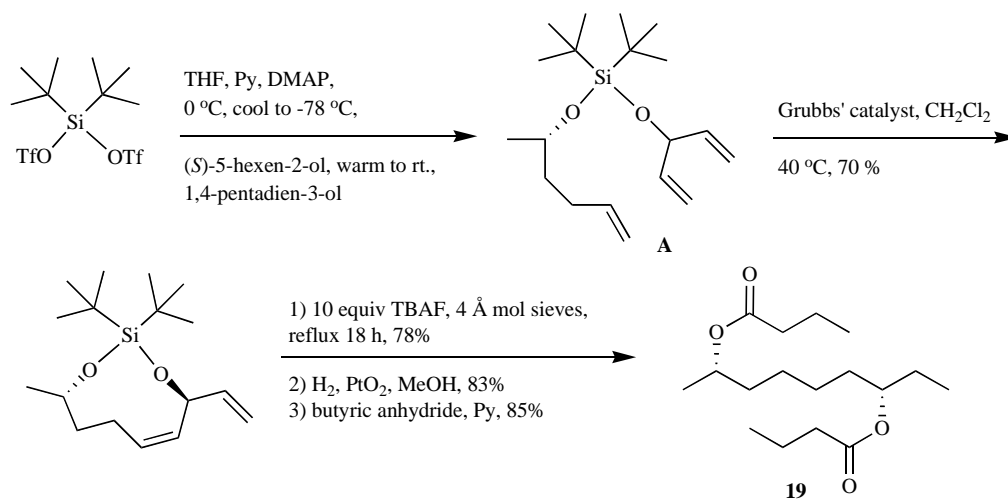
(4*E*,6*Z*,10*Z*)-4,6,10-Hexadecatrien-1-ol (**21**) is the one of five components of the pheromone bouquet of the cocoa pod borer *Conopomorpha cramerella* [45].

Pereira and Cabezas [46] described a new method of preparation of 1,5-diyne, by reaction of 1,3-dilithiopropyne and propargylic chlorides. Two methodologies were used for the synthesis of endiynes **C**. In the first, the authors coupled the lithiated 1,5-dialkyne **A** with the vinylic iodide obtained from alkyne **B** by hydroboration and reaction with iodine. Alternatively, the vinylic bromide obtained from **B** by hydrosilylation and reaction with NBS, was coupled to **A** using Sonogashira's palladium cross coupling reaction (Scheme 16).

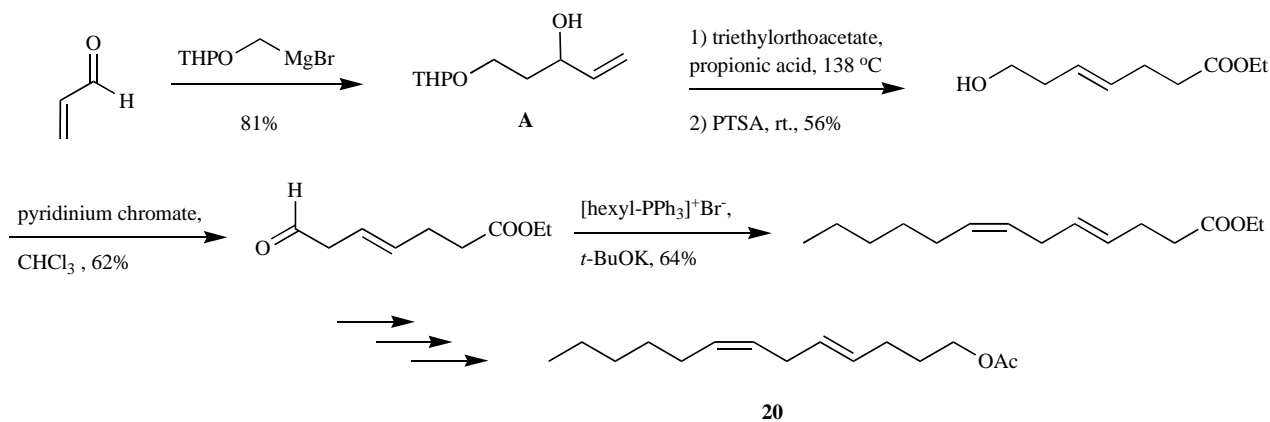




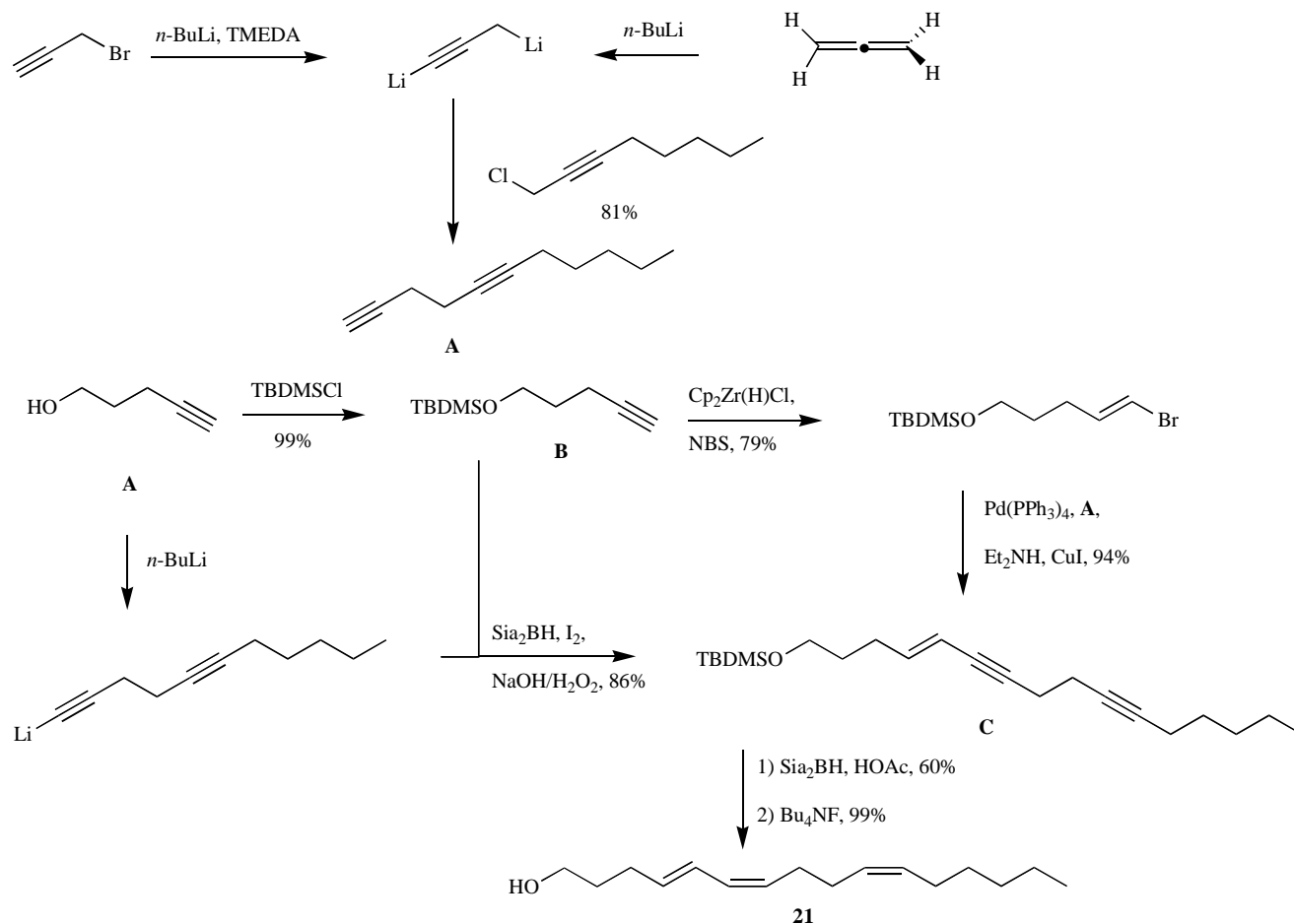
Scheme 13.



Scheme 14.



Scheme 15.



Scheme 16.

## 6. SYNTHESIS OF NON-ISOPRENOIDAL ALDEHYDES, KETONES, ACIDS, AND ESTERS AS PHEROMONES

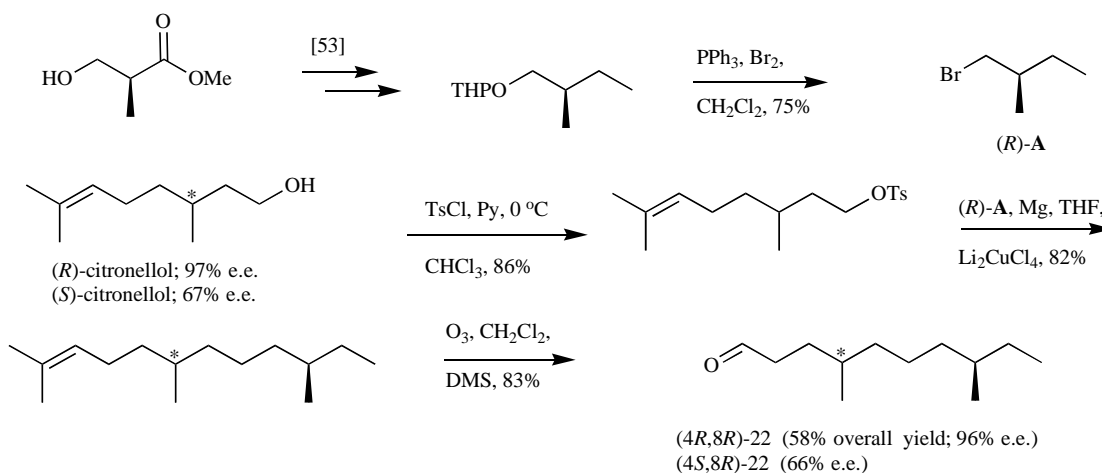
### 6.1. 4,8-Dimethyldecanal (**22**)

The aggregation pheromone of the stored foodstuffs pests *Tribolium castaneum* and *T. confusum* was isolated and identified by Suzuki as 4,8-dimethyldecanal (**22**) [47, 48]. Mori and co-workers [49] developed the first total synthesis of all of the four possible isomers of **22**, establishing the absolute configuration of the natural pheromone as (4*R*,8*R*)-**22**. Later, bioassays showed that a 8:2 mixture of the isomers (4*R*,8*R*)

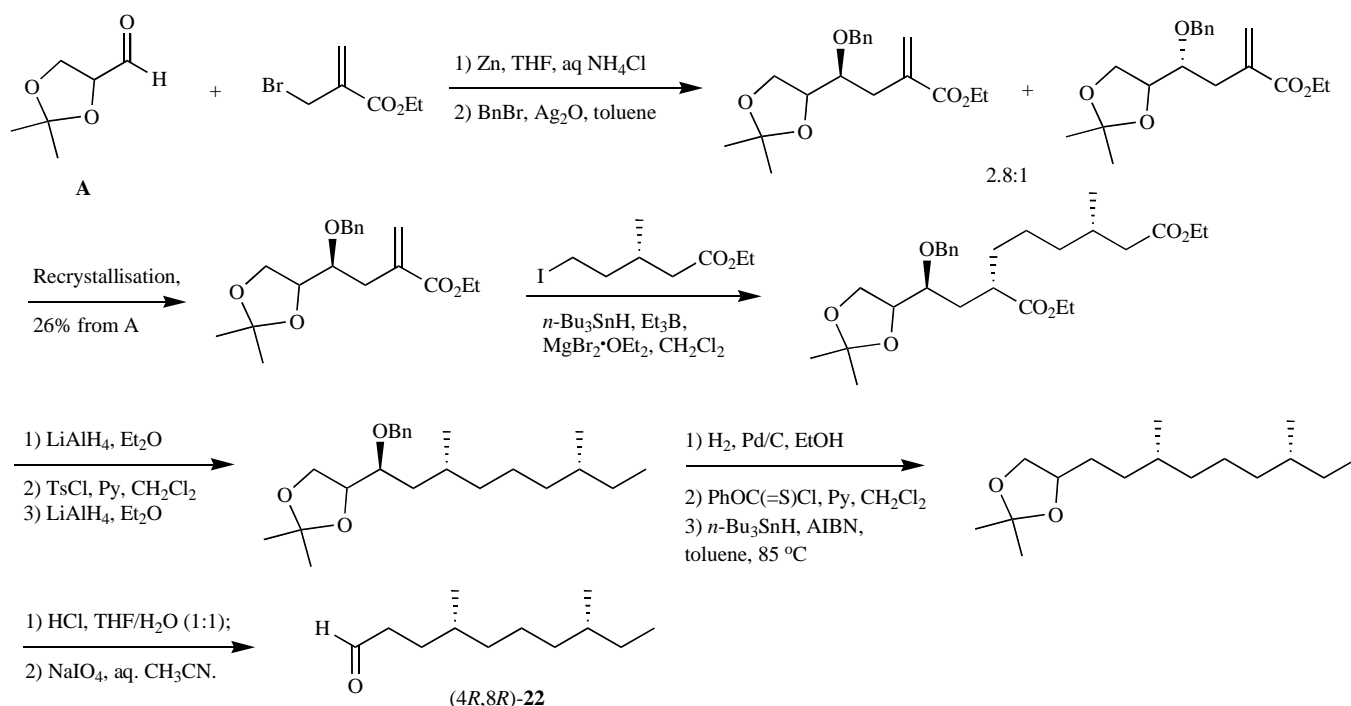
and (4*R*,8*S*) was about 10 times more active than (4*R*,8*R*) alone [50].

Zarbin *et al.* [51] described a synthesis of (4*R*,8*R*)- and (4*S*,8*R*)-**22**, coupling the Grignard reagent obtained from (*R*)-2-methyl-1-bromobutane **A** and the tosylate of (*R*)- and (*S*)-citronellol, respectively (Scheme 17), followed by ozonolysis of the double bond of the resulting alkene. The key intermediate **A** was obtained optically pure in five steps from methyl (*S*)-3-hydroxy-2-methylpropionate [52, 53].

Another methodology was described by Kameda and Naganano [54]. Starting from (*R*)-2,3-*O*-isopropylidene-glycerol-aldehyde, they obtained **22** in 11 steps and 7% overall yield



Scheme 17.



Scheme 18.

(Scheme 18). The key step in the synthesis was the highly diastereoselective chelation-controlled radical reaction of ethyl (4*S*,5*R*)-4-benzyloxy-5,6-(isopropylidenedioxy)-2-methylenehexanoate with ethyl (*R*)-5-iodo-3-methylpentanoate performed in the presence of 7 equivalents of MgBr<sub>2</sub>·OEt<sub>2</sub>.

## 6.2. (*E*)-4-Oxo-2-hexenal (23), (*E*)-4-oxo-2-octenal (24), and (*E*)-4-oxo-2-decenal (25)

Defensive secretions of stink bugs (Heteroptera: Pentatomidae) are characterized by the presence of (*E*)-4-oxo-2-alkenals with chain lengths of 6, 8, and 10 carbon atoms [55, 56]. More recently, these compounds also have been identified as pheromone components of nymphal [57] and adult bugs [56, 58].

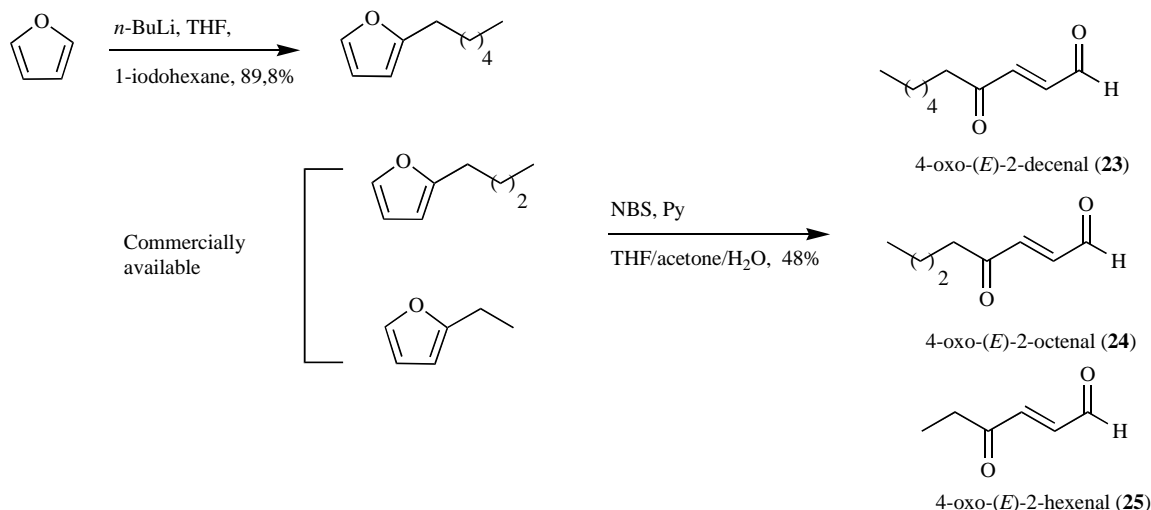
Moreira and Millar [59] described a simple one step syntheses of (*E*)-4-oxo-2-hexenal (23) and (*E*)-4-oxo-2-octenal

(24) from commercially available 2-ethyl- and 2-butylfurans respectively, and a two step synthesis of (*E*)-4-oxo-2-decenal (25) (Scheme 19).

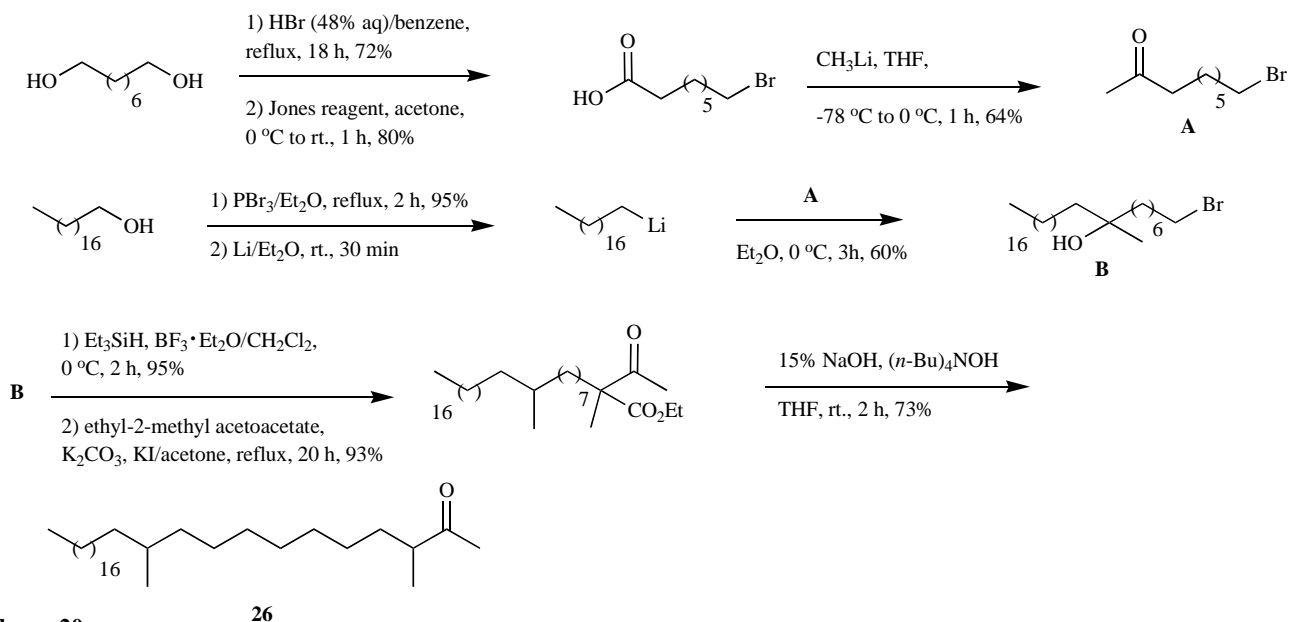
## 6.3. 3,11-Dimethylnonacosan-2-one (26)

In 1974, Nishida *et al.* [60] isolated and identified 3,11-dimethyl-2-nonacosanone (26) as the major component of the female-produced contact sex pheromone of the German cockroach, *Blattella germanica*.

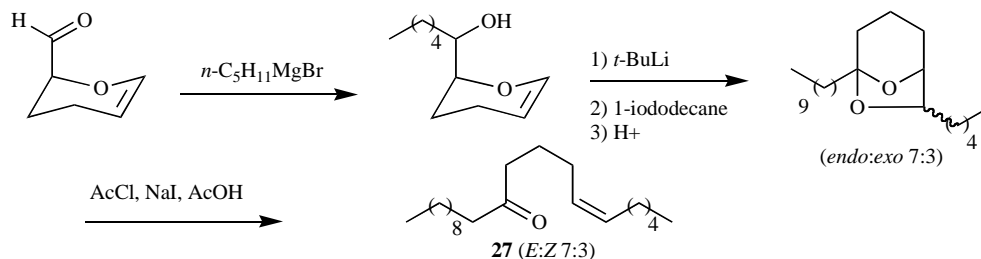
Ahn *et al.* [61] described a simple synthesis of 26, starting from 1,8-octanediol. The key steps are the alkylation of the methyl ketone **A** (obtained from methylation of 8-bromooctanoic acid) to yield bromoalcohol **B**, and coupling of **B** with the anion of the commercially available ethyl 2-methylacetoacetate. The final decarboxylation step yielded 26 (Scheme 20).



Scheme 19.



Scheme 20.



Scheme 21.

#### 6.4. (*Z*)-6-Heneicosen-11-one (**27**)

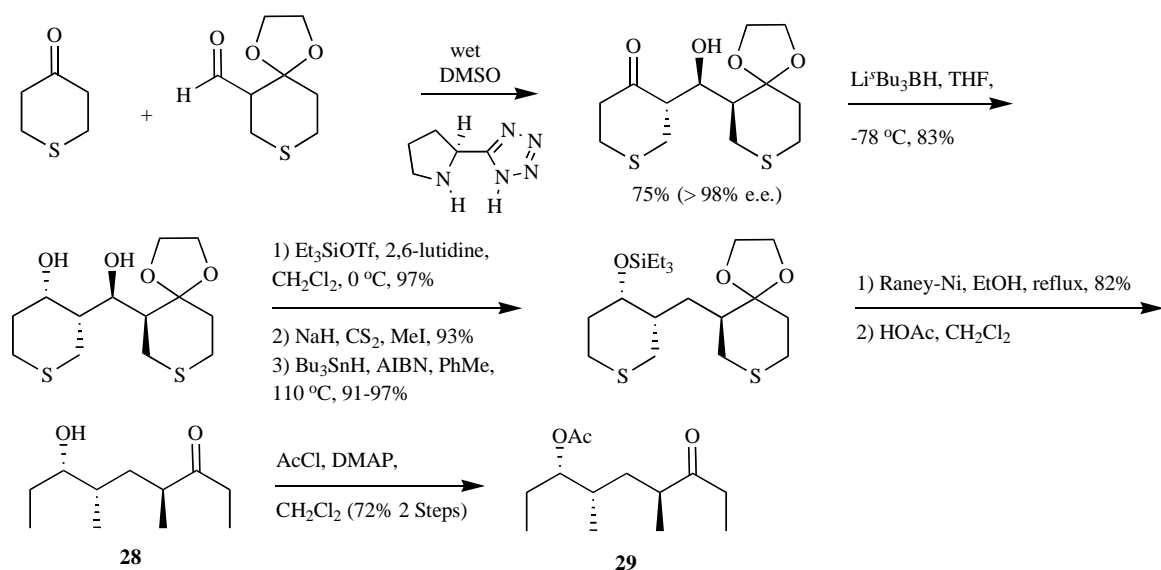
(*Z*)-6-Heneicosen-11-one (**27**) was first reported in 1975 as the pheromone of the Douglas-fir tussock moth *Orgyia pseudotsugata* [62]. It has also been found that a 60:40 (*E/Z*) mixture of **27** was considerably more active than pure (*Z*)-**27** [63].

Shin *et al.* [64] developed a selective method for the transformation of 6,8-dioxabicyclo[3.2.1]octanes to  $\delta,\epsilon$ -enones by Lewis acid-induced C–O bond cleavage. The use of AcCl–NaI was crucial for the selectivity of the reaction.

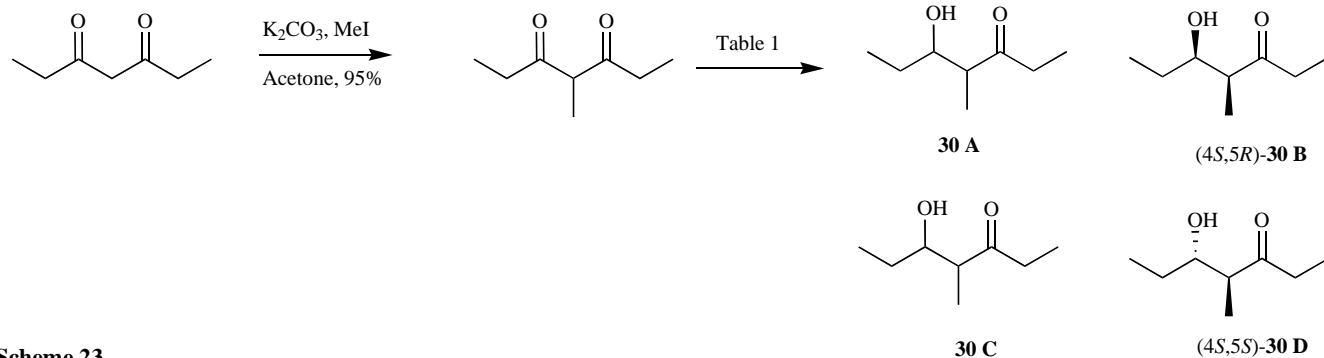
The method was applied to the synthesis of **27**, employing 5-decyl-7-pentyl-6,8-dioxabicyclo[3.2.1]octane, which was prepared by the reaction of the dimer of acrolein with *n*-pentylmagnesium bromide, with subsequent alkylation and cyclization steps (Scheme 21).

#### 6.5. (4*S*,6*S*,7*S*)-7-Hydroxy-4,6-dimethyl-3-nonanone (**28**) (serricornin)

Serricornin [(4*S*,6*S*,7*S*)-7-hydroxy-4,6-dimethyl-3-nonanone, (4*S*,6*S*,7*S*)-**28**] is the sex pheromone produced by females of the cigarette beetle, *Lasioderma serricorne* [65-69].



Scheme 22.



Scheme 23.

Ward *et al.* [70] described a synthesis of serricornin in 7 steps and 31% overall yield, employing an enantioselective direct aldol reaction with a chiral tetrazole catalyst derived from L-proline in the key step. The keto group of the aldol adduct was stereoselectively reduced using Li(*sec*-Bu)<sub>3</sub>BH, and the resulting diol **A** was monosilylated and submitted to Barton-McCombie deoxygenation followed by desulfurization and deprotection to afford **28**, which was isolated and characterized as the acetate **29** (Scheme 22).

### 6.6. 5-Hydroxy-4-methyl-3-heptanone (**30**) (sitophilure)

Sitophilure (5-hydroxy-4-methyl-3-heptanone, **30**) was identified in 1984 by Phillips *et al.* [71, 72] as the male-produced aggregation pheromone of the rice weevil, *Sitophilus oryzae* and of the maize weevil, *Sitophilus zeamais*. The synthesis of the four possible stereoisomers of **30** followed by indoor bioassays, revealed the (4*S*,5*R*) isomer to be the active form of the pheromone [73, 74].

Kalaitzakis *et al.* [75] described a chemoenzymatic synthesis of sitophilure in two steps and an overall yield of 81%, starting from commercially available 3,5-heptanedione (Scheme 23). The key step of this synthesis relies on the stereoselective reduction of the chemically synthesized precursor of (+)-sitophilure, 4-methyl-3,5-heptanedione, by isolated NADPH-dependent ketoreductases (KRED) (Table 1).

The absolute stereochemistry of products **30 B** and **30 D** was determined by the use of chiral derivatizing agents.

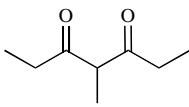
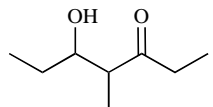
### 6.7. 1-Ethylpropyl 3-hydroxy-2-methylpentanoate (**31**) (sitophilate)

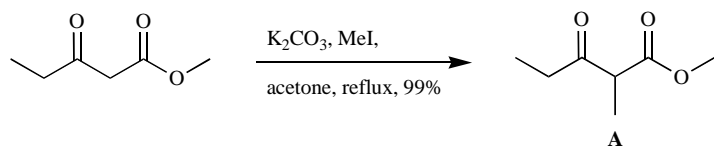
Sitophilate (1-ethylpropyl 2-methyl-3-hydroxypentanoate, **31**) was identified by Phillips *et al.* [76] as the male-produced aggregation pheromone of the granary weevil *Sitophilus granarius*. Bioassays employing all of the synthetic isomers revealed (2*S*,3*R*)-**31** to be the natural pheromone [77].

Kalaitzakis *et al.* [78] worked out a chemoenzymatic synthesis using a ketoreductase (KRED) for the selective reduction of β-ketoester **A**. Of over 100 enzymes tested, the KRED-A1B gave the best selectivity towards the desired (2*S*,3*R*) configuration. The diastereomeric purity of sitophilate was improved either by chromatographic separation after transesterification (Scheme 24, pathway 1) or by use of an enzymatic hydrolysis of the resulting β-hydroxyester **B** (pathway 2) and subsequent esterification with 3-bromopentane.

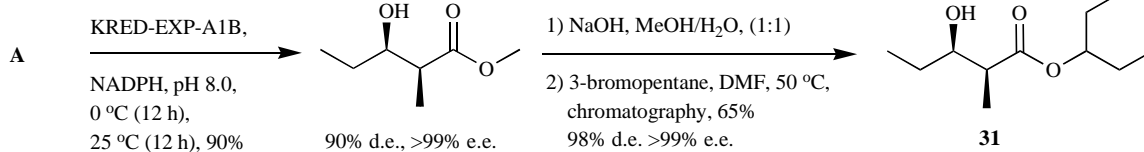
Gil *et al.* [79] described a two-step synthesis of **31** employing the condensation of the dianion of propanoic acid and propanal, and subsequent esterification with 3-pentanol (Scheme 25). Different bases, reaction conditions and chiral

Table 1.

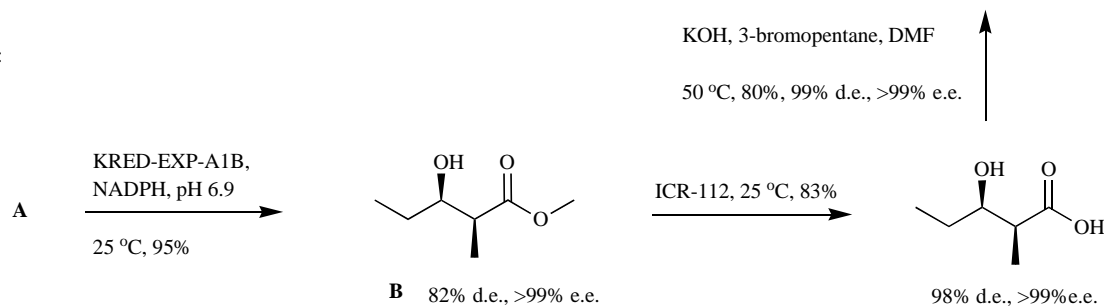
Substrate	KRED	Diastereomeric Ratio % (30)				Conversion (time)	U/mg	Product
		A	B	C	D			
	101	3	-	6	91	100% (6h)	0.042	
	114	8	4	-	88	90% (24h)	0.042	
	115	4	-	4	92	100% (6h)	0.016	
	118	4	-	-	96	93% (24h)	0.069	
	119	<1	-	-	>99	100% (12h)	0.204	
	123	20	-	-	80	100% (6h)	0.032	
	128	3	-	1	96	100% (3h)	0.180	
	130	6	-	-	94	100% (16h)	0.046	
	A1A	<2	-	-	>98	20% (24h)	0.058	
	A1B	-	97	3	-	100% (40min)	0.184	
	A1C	-	98	2	-	100% (1h)	0.168	
	A1D	-	97	3	-	100% (1h)	0.131	



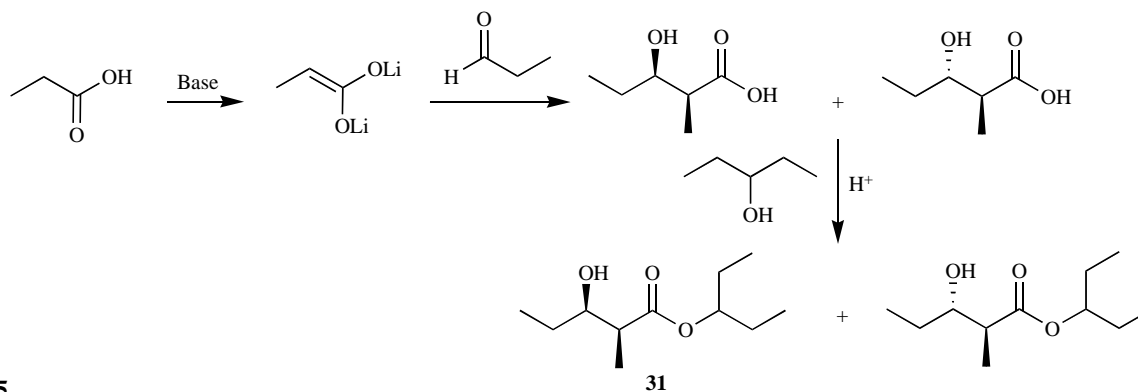
pathway 1:



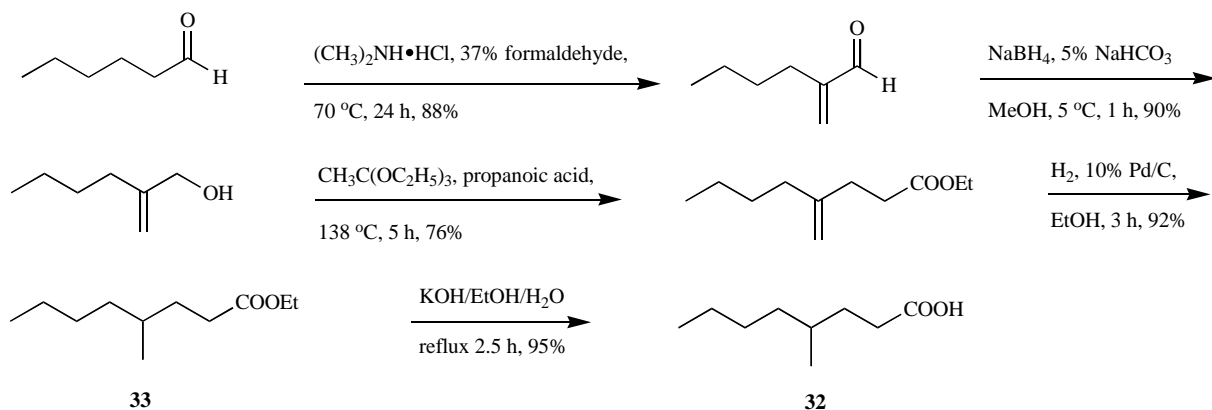
pathway 2:



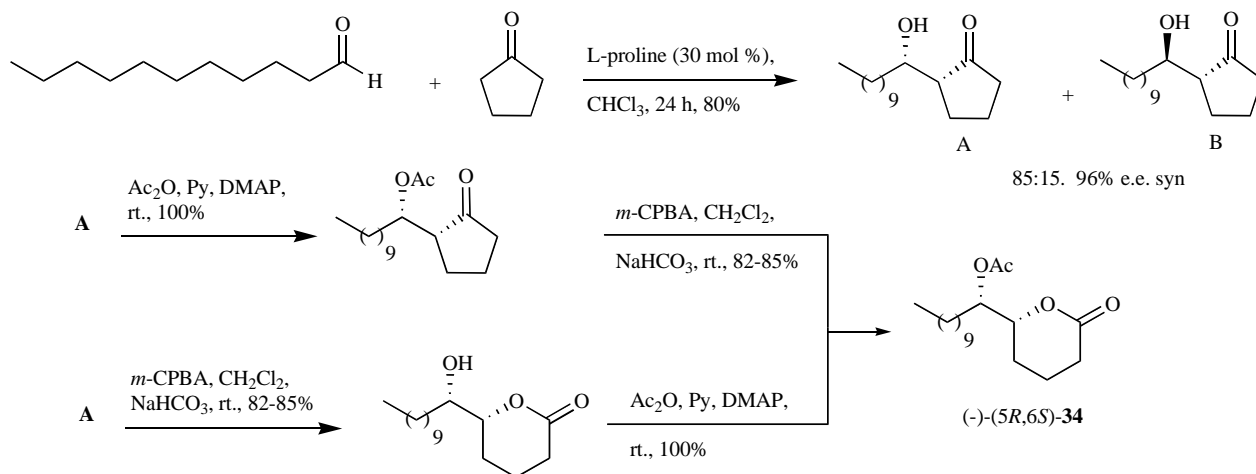
Scheme 24.



Scheme 25.



Scheme 26.



Scheme 27.

amines as bases were tested, but only a modest diastereoselectivity and a modest degree of asymmetric induction was obtained.

### 6.8. 4-Methyloctanoic acid (32)

4-Methyloctanoic acid (**32**) and its ethyl ester (**33**) are aggregation pheromones of *Oryctes rhinoceros* beetles, pests of coconut and date palm crops in Southeast Asia and North Africa [80-82].

A five-step synthesis with high overall yield was developed by Ragoussis *et al.* [83]. The key step is a Claisen orthoester rearrangement of the intermediate formed by reaction of 2-methylene-1-hexanol and triethylorthoacetate, resulting in chain elongation and completion of the carbon skeleton (Scheme 26).

## 7. SYNTHESIS OF LACTONES AS PHEROMONES

### 7.1. (5R,6S)-6-Acetoxyhexadecan-5-olide (34)

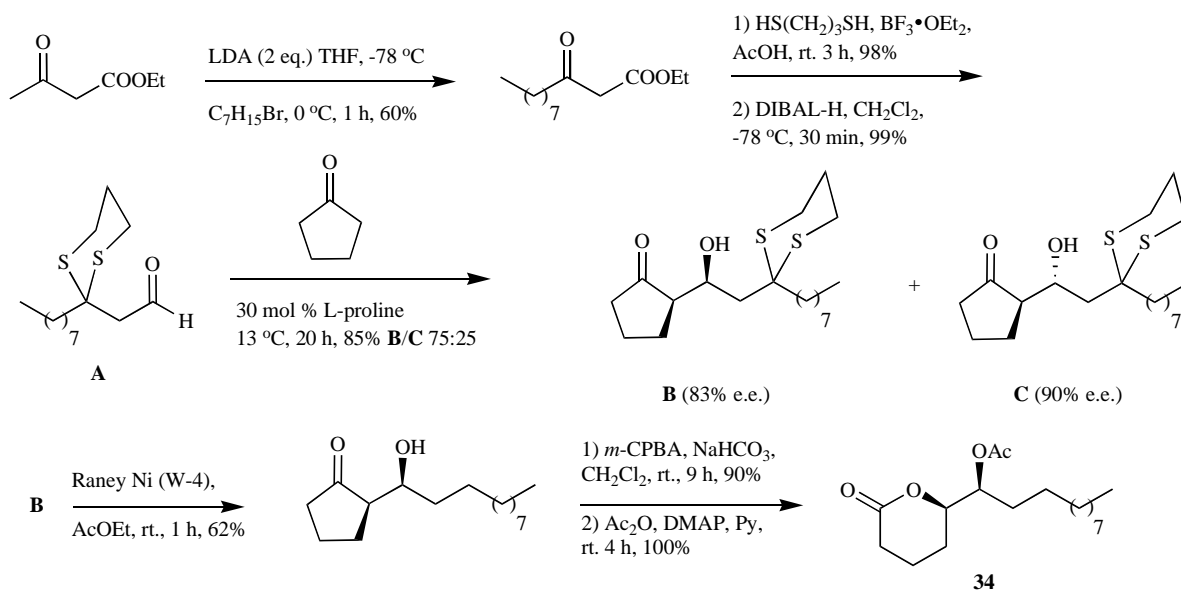
The major component of the oviposition attractant pheromone of the mosquito *Culex pipiens fatigans* was identified by Laurence and Pickett [84] in 1982 as *erythro*-6-acetoxy-5-hexadecanolide (**34**). The absolute configuration was established as (-)-(5R,6S) by comparative chromatography of the 6-trifluoroacetoxy derivatives of the natural pheromone and of the synthetic (-)-(5R,6S) and (+)-(5S,6R) enantiomers [85].

Sun *et al.* [86] described a synthesis of (5R,6S)-**34** employing a L-proline-catalyzed asymmetric aldol reaction in the key step, giving diastereomeric intermediates **A** and **B** in a 85:15 ratio. **A** was obtained in 96% e.e., but it was not stated if or how the diastereomers were separated. Transformation of **A** by Baeyer-Villiger oxidation followed by acetylation (or the inverse sequence) yielded **34** (Scheme 27).

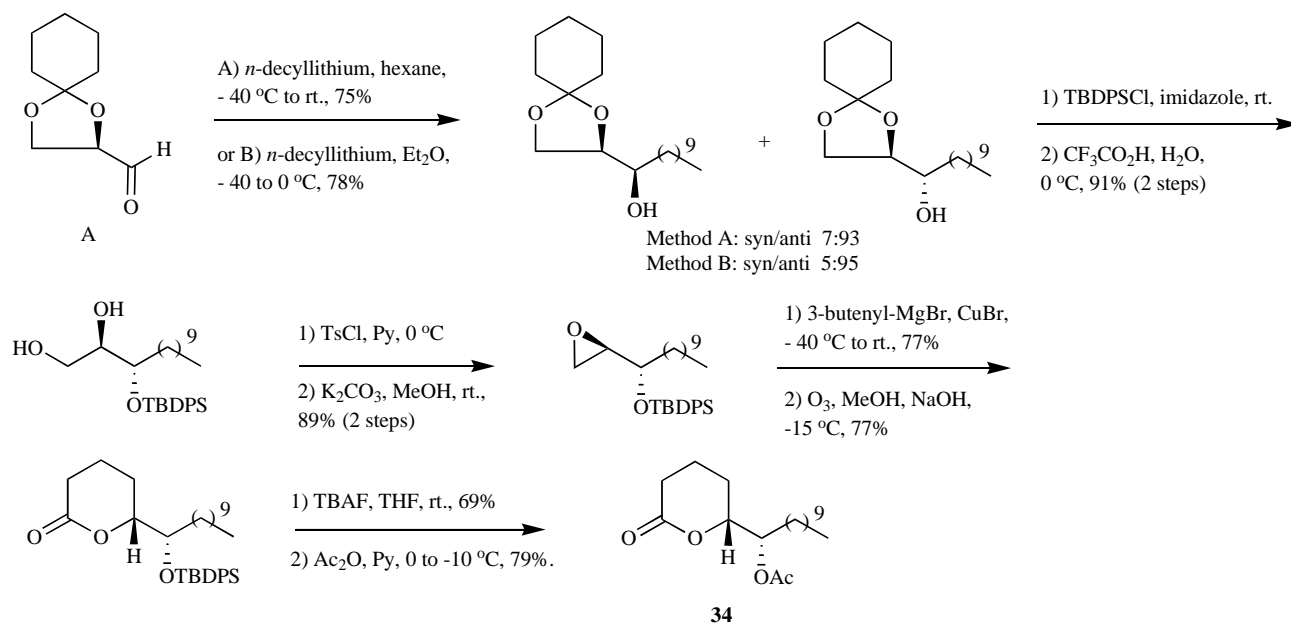
In a similar approach, Ikishima *et al.* [87] obtained the aldol adducts **B** and **C** (75:25) by L-proline-catalyzed aldol condensation between 1,3-dithiane **A** and cyclopentanone. Adduct **B** was obtained in 83% e.e. and separated from **C** by chromatography. Desulfurization of **B** followed by Baeyer-Villiger oxidation and acetylation yielded **34** (Scheme 28).

Dhotare *et al.* [88] reported the synthesis of (5R,6S)-**34** by a stereoselective addition of *n*-decyllithium to (*R*)-2,3-cyclohexylidene-glyceraldehyde **A** in the key step. The adduct was straightforwardly converted to **34** in 8 steps (Scheme 29).

The stereoselective synthesis developed by Prasad and Anbarasan [89] started from the bis-Weinreb amide of L-tartaric acid which was converted to the benzyloxy aldehyde **A**. Allylation of **A** and acetalisation of the resulting homoallylic alcohol with acrolein diethyl acetal afforded key intermediate **B**, which was subjected to a ring closure metathesis reaction. Mitsunobu inversion and a final lactol oxidation are further key steps in this synthesis (Scheme 30).



Scheme 28.



Scheme 29.

## 7.2. (4*R*,9*Z*)-Octadec-9-en-4-olide (35)

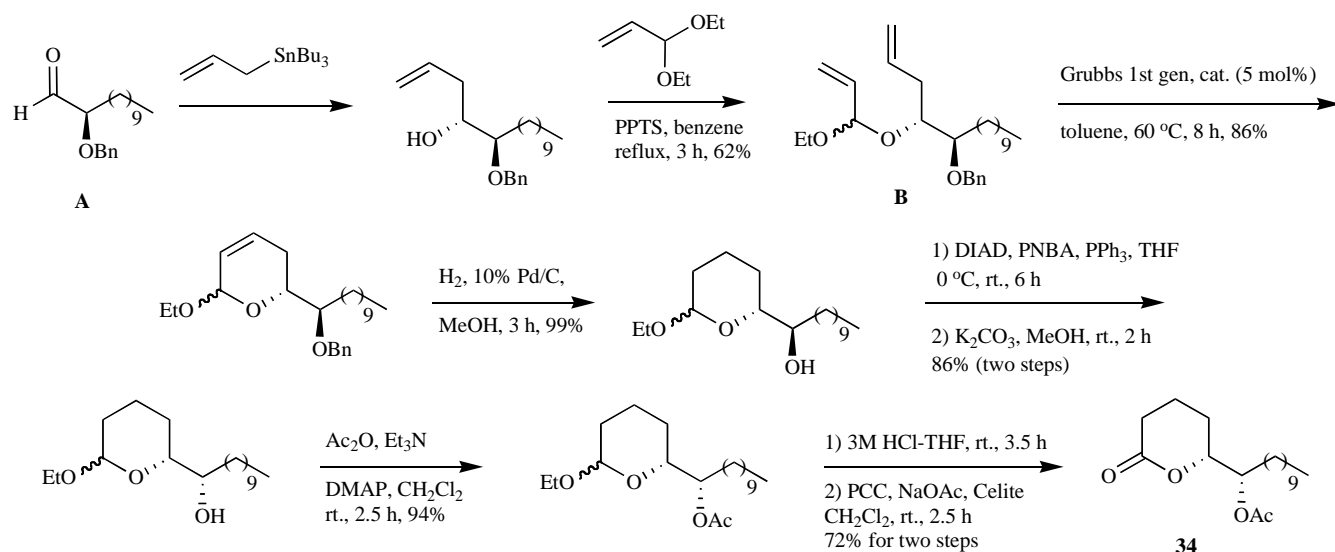
In 2001 Cossé *et al.* [90] isolated and identified (*Z*)-octadec-9-en-4-olide (**35**) as a female-specific and antennally active compound from the female currant stem girdler, *Janus integer*, a pest of red currant in North America. The absolute configuration has been established as (*R*) by synthesis [91] and bioassays [92].

Mori [93] described a synthesis of **35** in a gram quantities using a Sharpless asymmetric dihydroxylation obtaining the chiral diol **A**, which was converted to epoxide **B** presenting 87% e.e. Jacobsen hydrolytic kinetic resolution improved the optical purity to 96% e.e. Meyer's oxazoline alkylation method [94, 95] was adopted to convert (*R*)-**B** to (*R*)-octadec-9-yn-4-olide, which was partially hydrogenated to yield **35** (Scheme 31).

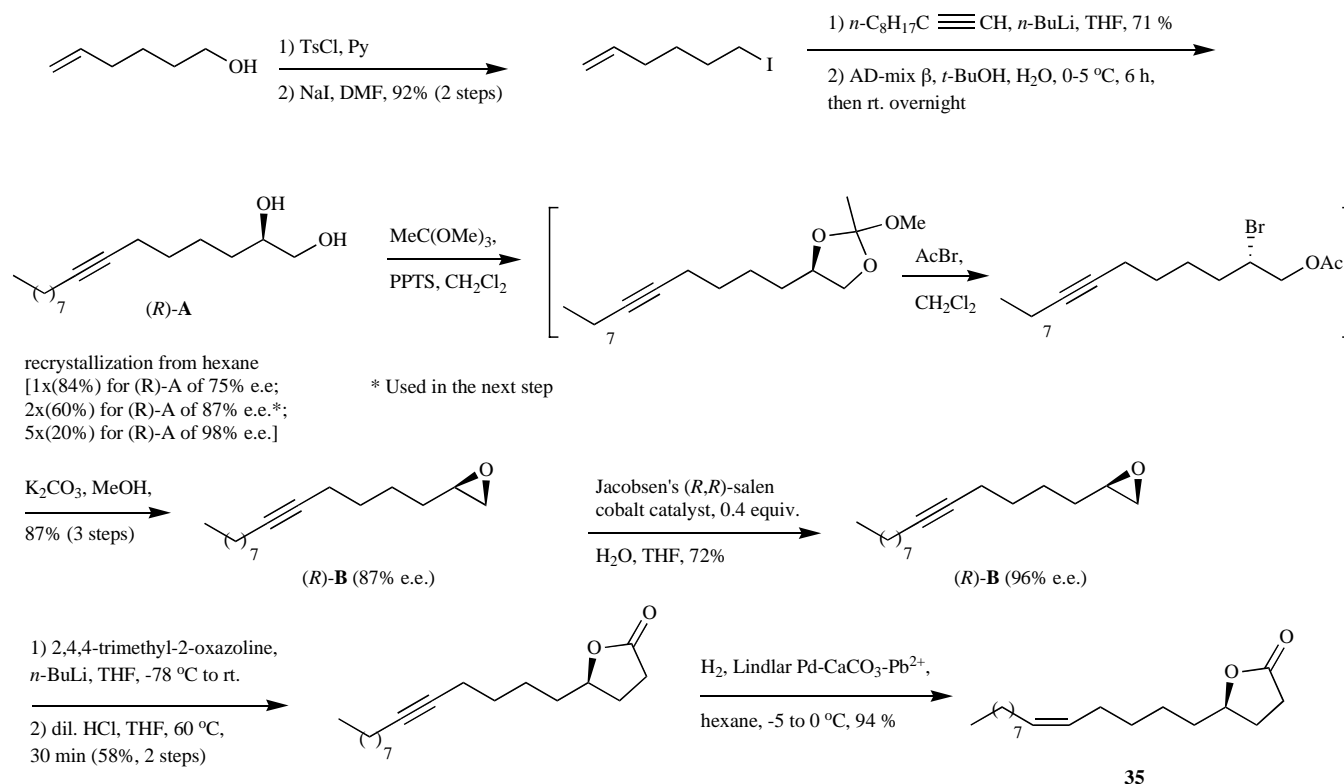
A stereoselective synthesis of **35** was presented by Sabitha *et al.* [96]. Base-induced ring opening of the chiral epoxy chloride **A** and subsequent treatment with butyl bromide, gave the acetylenic diol **B**, which was subjected to a zipper isomerization by treatment with 1,3-diaminopropane and sodium amide in the key step (Scheme 32). The resulting terminal alkyne was chain elongated and transformed to **35** in 4 further steps.

Another sequence, using similar intermediates, was presented by the same author [97] (Scheme 33). The chiral epoxy chloride **A** was prepared in several steps, including a Sharpless asymmetric epoxidation. The resulting alkyne **B** was methoxycarbonylated at the triple bond after protection of the hydroxyl group, while the other extreme was subjected to deprotection, oxidation, and stereoselective Wittig reaction resulting in chain-elongation; followed by the final deprotection and cyclization steps.





Scheme 30.



Scheme 31.

### 7.3. (S)-5-Hexadecanolide (36)

(S)-5-Hexadecanolide (**36**) was isolated from mandibular glands of the queens of the oriental hornet, *Vespa orientalis* [98] where it functions as a pheromone to stimulate the workers to construct queen cells.

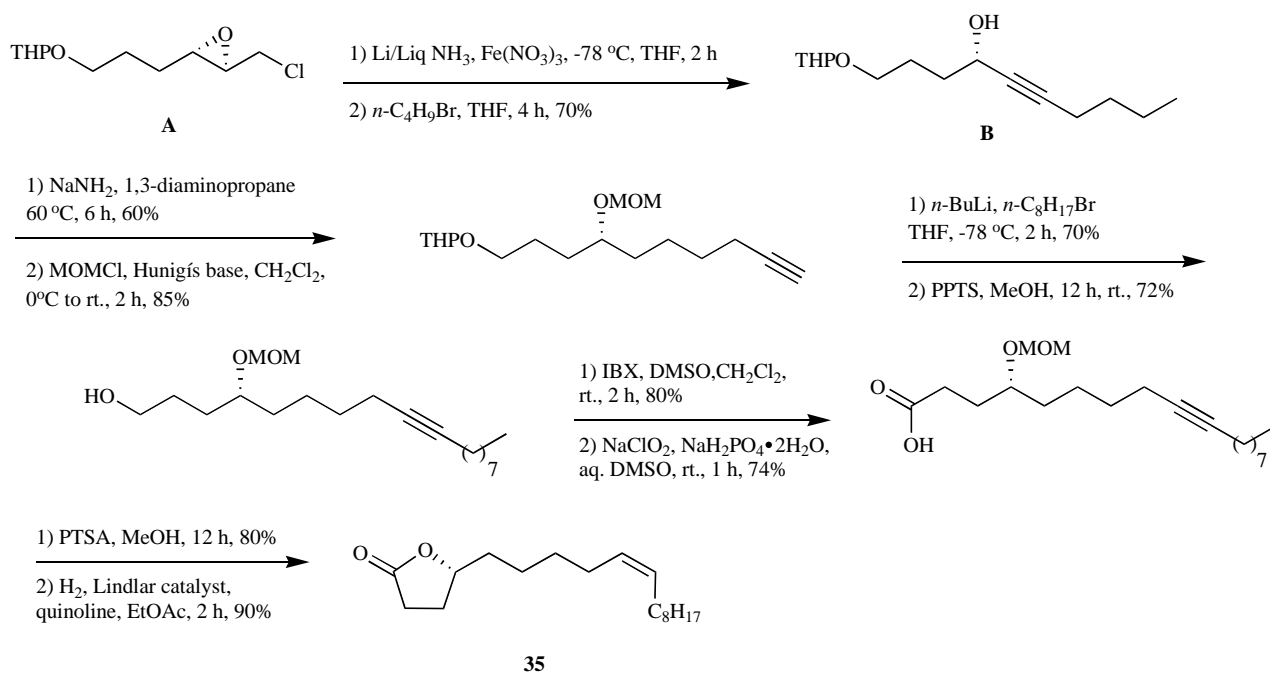
Sabitha *et al.* [99, 100] described two similar approaches to the synthesis of this pheromone. In both syntheses the key step was the base-induced opening of a chiral epoxide by lithium amide in liquid ammonia at  $-78^\circ\text{C}$ , and subsequent

treatment with 1-bromononane to give the chiral alkynols **A** and **B**, which finally were converted to **36** (Scheme 34).

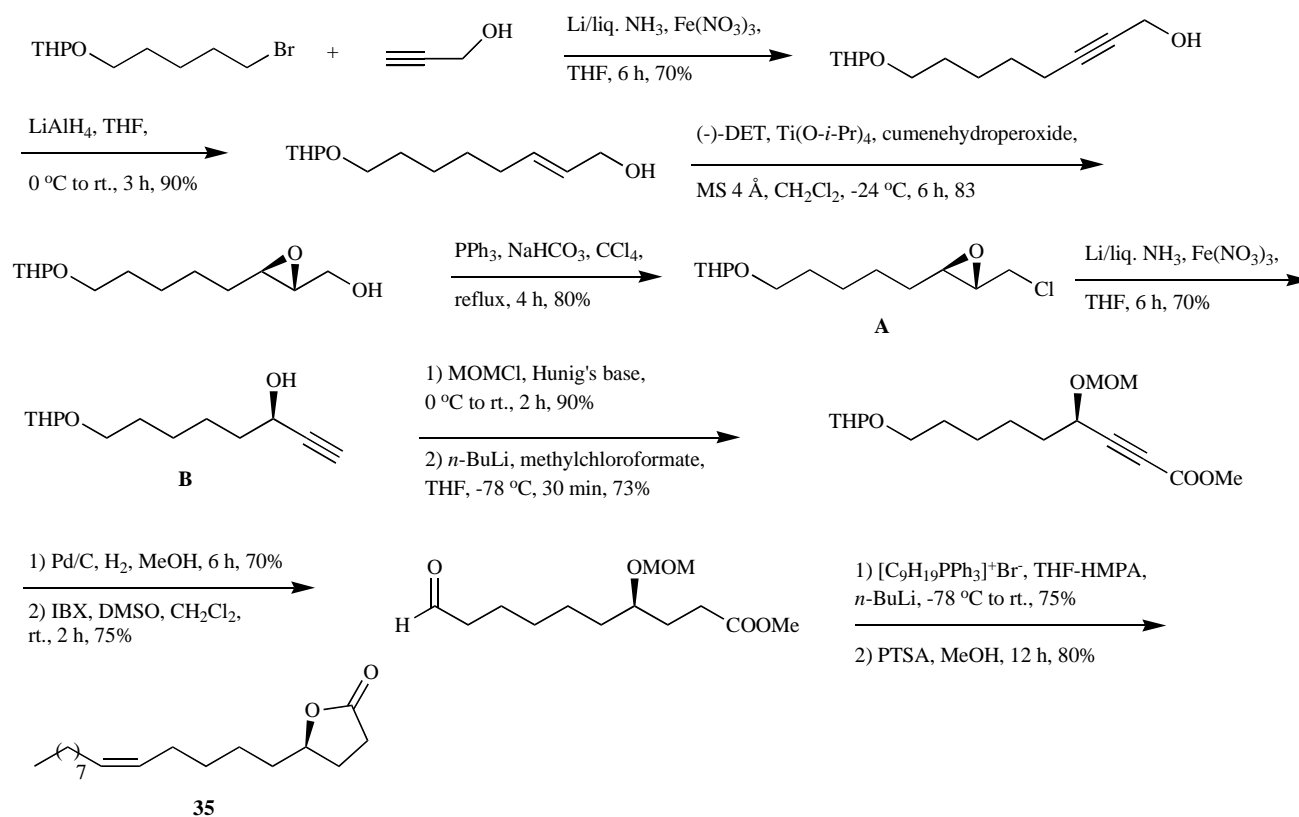
### 7.4. (R)-4-Dodecanolide (37)

(R)-4-Dodecanolide (**37**) is a defensive secretion isolated from the pygidial glands of rove beetles, *Bledius mandibularis* and *Bledius spectabilis* [101].

The synthesis of Sabitha *et al.* [99] started with the chiral propargylic alcohol **A** [102], which was methoxycarbo-



Scheme 32.



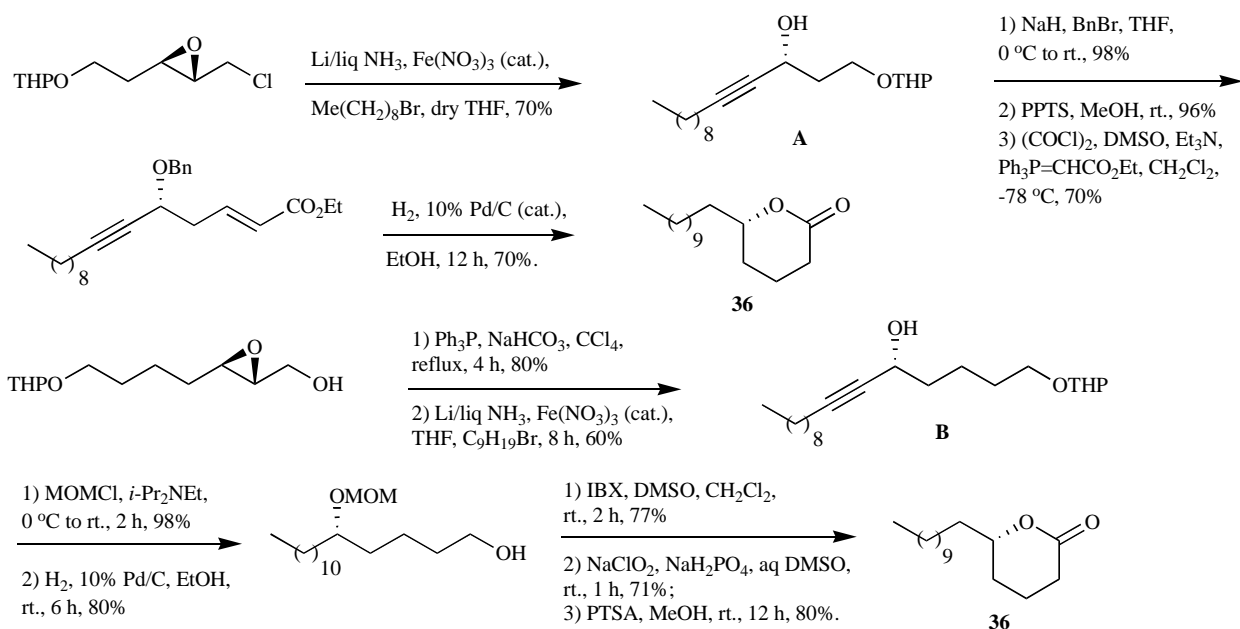
Scheme 33.

lated after protection. Hydrogenation and deprotection gave directly **37** (Scheme 35).

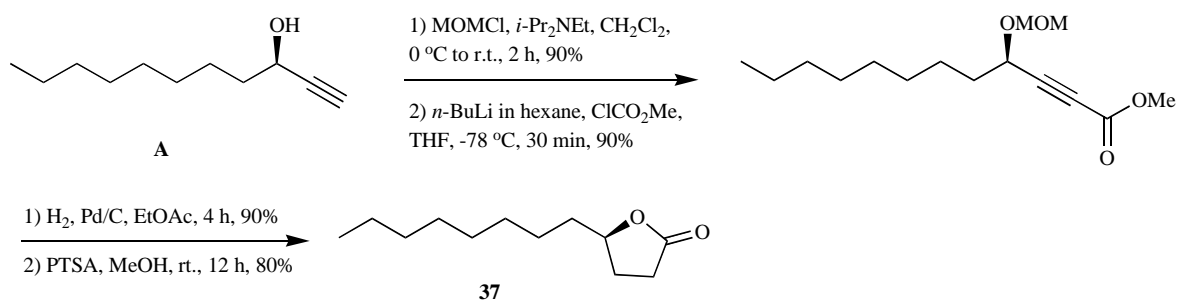
### 7.5. (4*R*,5*Z*)-5-Tetradecen-4-olide (**38**) (japonilure)

(*R*)-Japonilure [(4*R*,5*Z*)-5-tetradecen-4-olide, (**38**)] is the female-produced pheromone of the Japanese beetle *Popillia japonica* [103].

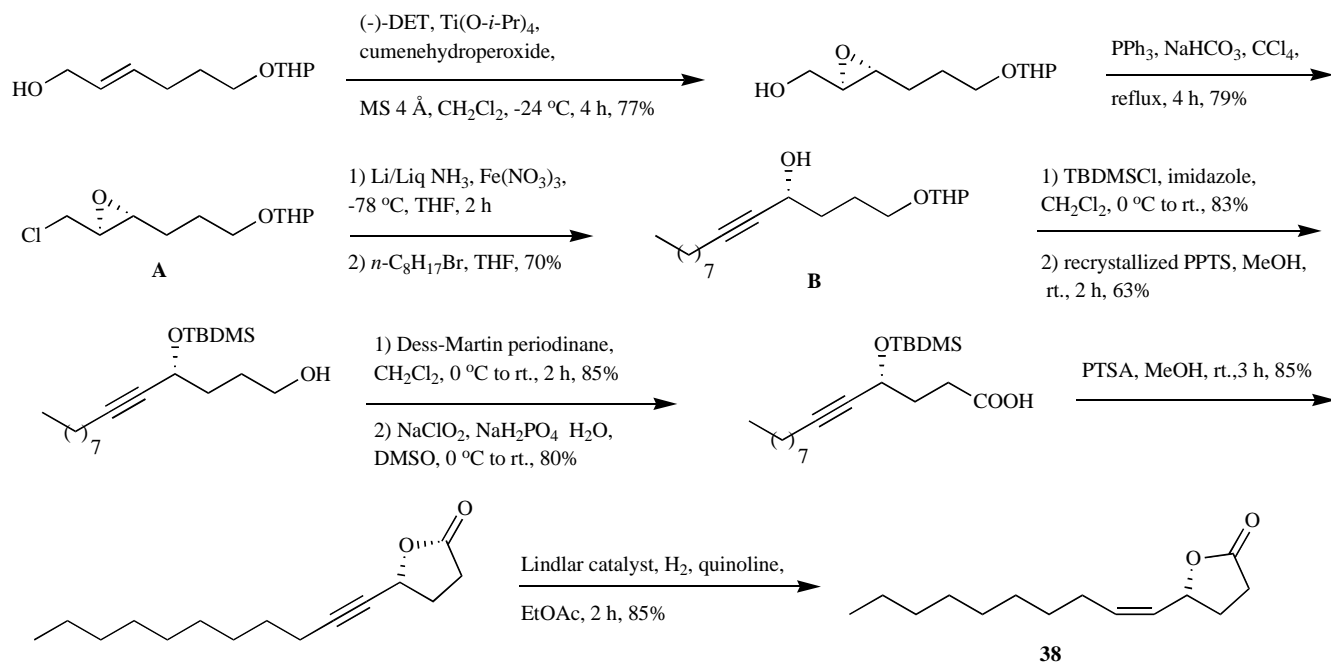
The synthesis of **38** presented by Sabitha *et al.* [97] involved the preparation of the chiral epoxy chloride **A** (by stereoselective reduction of a triple bond and asymmetric Sharpless epoxidation), which was subjected to a base-induced ring opening followed by treatment with 1-bromooctane in a one-pot reaction to give alkyne **B** with the carbon skeleton already established. **B** was further transformed to **38** in five steps (Scheme 36).



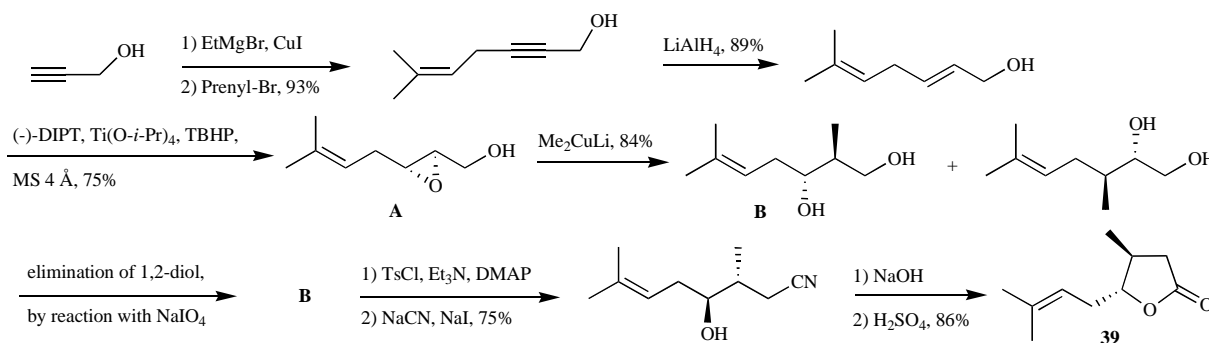
Scheme 34.



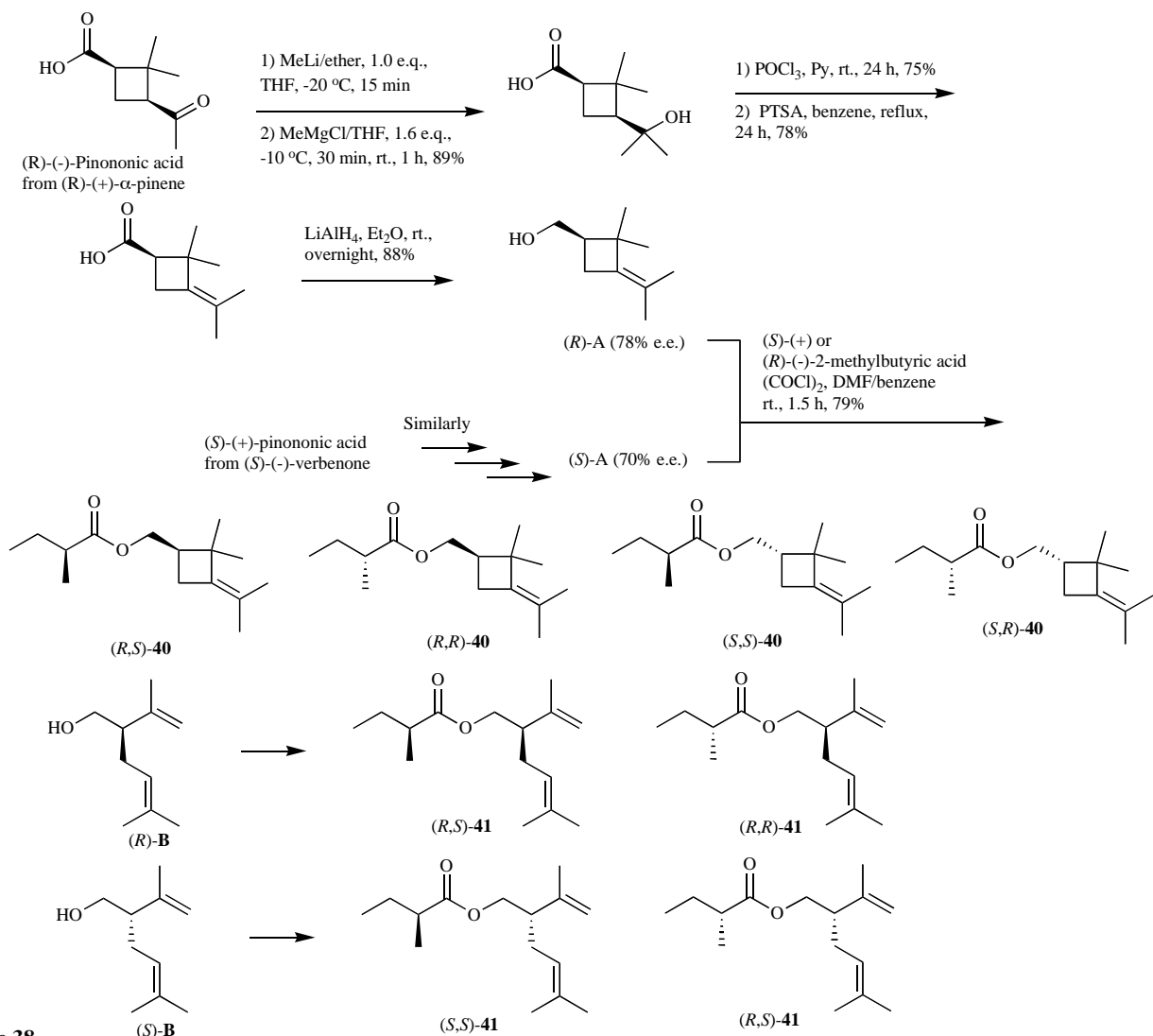
Scheme 35.



Scheme 36.



Scheme 37.



Scheme 38.

### 7.6. (3*S*,4*R*)-3,7-Dimethyl-6-octen-4-olide (**39**) (eldanolide)

Eldanolide [(3*S*,4*R*)-3,7-dimethyl-6-octen-4-olide, (**39**)] is a male-produced monoterpene sex attractant for the African sugarcane stem borer *Eldana sacharina* [104].

The synthesis of **39** presented by Kong *et al.* [105] involved the preparation of the chiral epoxy alcohol **A** (93.4% e.e.) in 4 steps from propargyl alcohol, including a Sharpless epoxidation (Scheme 37). Methylation of the epoxide provided a mixture of a 1,2- and a 1,3-diol **B**, which was resolved by cleavage of the 1,2-diol by reaction with NaIO<sub>4</sub>

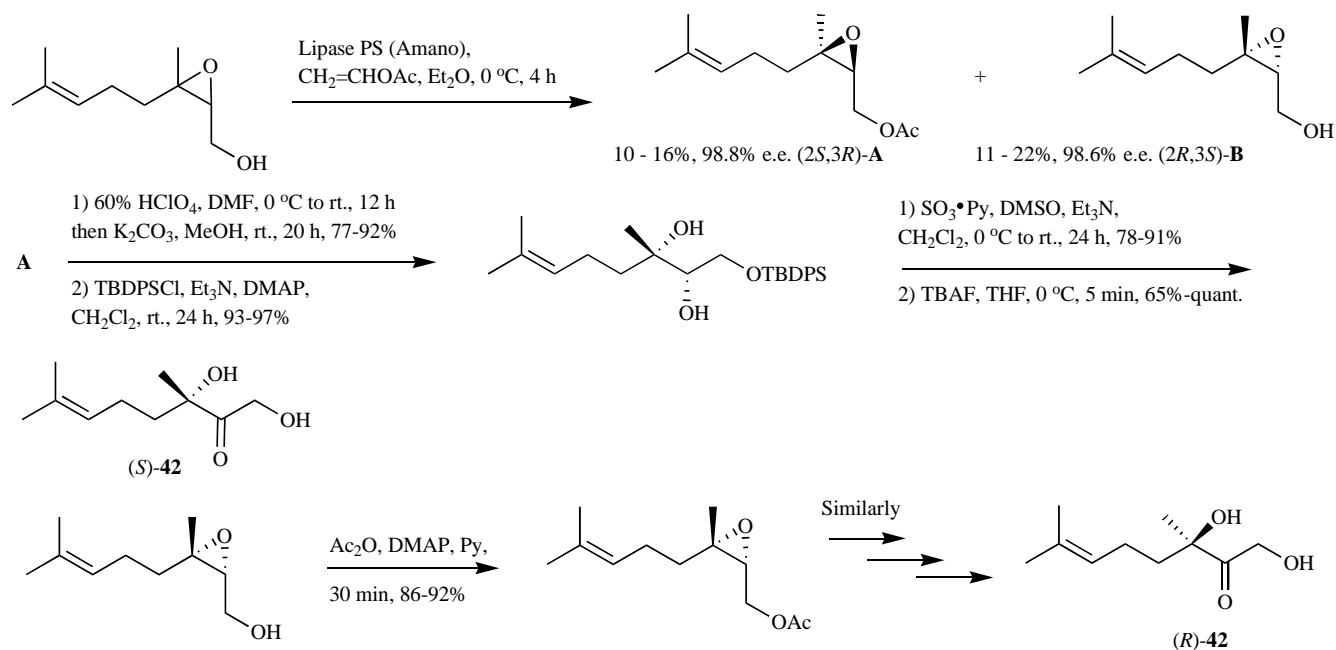
and subsequent chromatography, providing pure **B**. Chain elongation by reaction with cyanide, hydrolysis and lactonization finally provided **39** in 22% overall yield.

## 8. SYNTHESIS OF ISOPRENOIDS AS PHEROMONES

### 8.1. Synthesis of Isoprenoidal Pheromone Alcohols and their Esters as Pheromones

#### 8.1.1. Maconelliyl 2-methylbutanoate (**40**) and lavandulyl 2-methylbutanoate (**41**)

Maconelliyl 2-methylbutanoate (**40**) and lavandulyl 2-methylbutanoate (**41**) have been identified as constituents of



Scheme 39.

the female-produced pheromone of the pink hibiscus mealybug, *Maconellicoccus hirsutus*, which is an exotic insect pest in Southern California and Florida [106].

Zhang and Nie [107] described an enantioselective synthesis of all stereoisomers of these two compounds, starting from (*R*)- and (*S*)-pinonic acids, which are easily prepared from (*R*)- $\alpha$ -pinene and (*S*)-verbenone, respectively. Methylation, elimination of water, and reduction of the carboxyl group afforded (*R*)- and (*S*)-maconelliol (**A**), respectively. Esterification of **A** was carried out with commercially available (*S*)-2-methylbutyric acid and previously prepared (*R*)-2-methylbutyric acid [108] to afford all four stereoisomers of **40**. For the synthesis of all isomers of **41**, (*R*)- and (*S*)-lavandulol (**B**), prepared according to the method described by Cardillo *et al.* [108], were esterified with (*S*)- and (*R*)-2-methylbutyric acids (Scheme 38).

#### 8.1.2. 3,7-Dimethyl-2-oxo-6-octene-1,3-diol (**42**)

Dickens *et al.* [109] identified 3,7-dimethyl-2-oxo-6-octene-1,3-diol (**42**) as the male-produced aggregation pheromone from the Colorado potato beetle (*Leptinotarsa decemlineata*). The absolute configuration of natural **42** was determined by Oliver *et al.* [110] to be (*S*) by synthesis of the racemate and both enantiomers from geraniol and (*R*)- and (*S*)-linalool, respectively.

Tashiro and Mori [111] described the synthesis of pure enantiomers of **42** employing the lipase-catalysed enantioselective acetylation of ( $\pm$ )-2,3-epoxynerol in the key step, yielding acetate (2*S*,3*R*)-**A** (98.8% e.e.) and alcohol (2*R*,3*S*)-**B** (98.6% e.e.). Ring opening under inversion of the configuration at carbon 3 of **A** by treatment with  $\text{HClO}_4$  in DMF at  $0^\circ\text{C}$  and subsequent protection of the primary hydroxyl group was followed by selective oxidation and deprotection to give (*S*)-**42**. The enantiomer was obtained similarly starting with alcohol **B** (Scheme 39).

#### 8.1.3. (1*S*,4*R*)-4-Isopropyl-1-methyl-2-cyclohexen-1-ol (**43**)

(1*S*,4*R*)-4-Isopropyl-1-methyl-2-cyclohexen-1-ol (**43**) is the aggregation pheromone of the ambrosia beetle *Platypus quercivorus*, and the absolute configuration of the pheromone was established as (1*S*,4*R*) [112, 113].

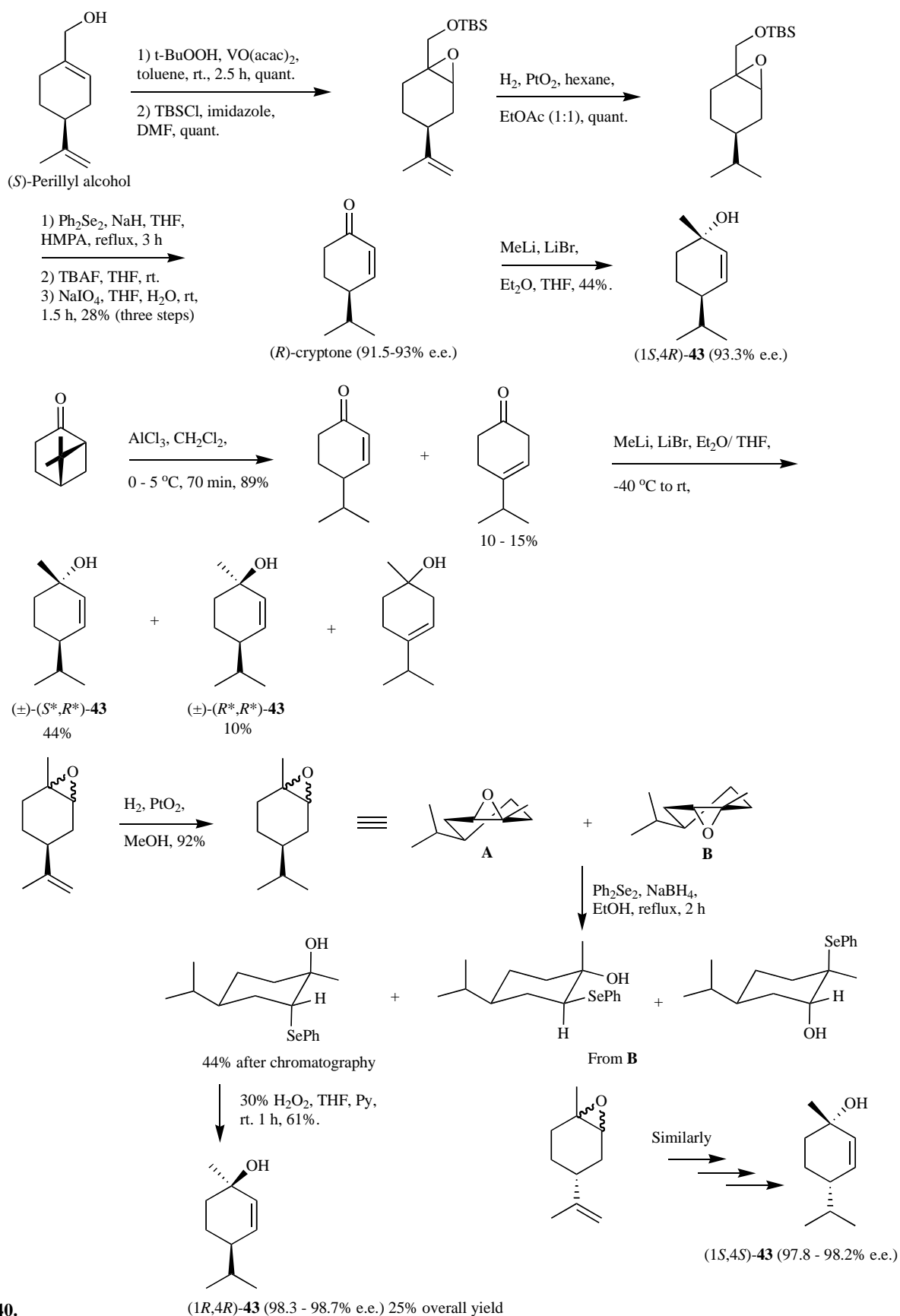
Mori [114] described a synthesis of the (1*S*,4*R*), (1*R*,4*R*), and (1*S*,4*S*) isomers and of a racemic mixture of **43**. In this paper Mori mentioned that (1*R*\*,4*R*\*)-4-isopropyl-1-methyl-2-cyclohexen-1-ol was detected as a minor component of the frass volatiles of *P. quercivorus*. Synthesis of (1*S*,4*R*)-**43** was performed by addition of methyl lithium to (*R*)-cryptone (91.5–93% e.e.) obtained in six steps from (*S*)-perillyl alcohol. The racemic pheromone was also prepared by methylation of ( $\pm$ )-cryptone, prepared from (+)-nopinone. Both (1*R*,4*R*)- and (1*S*,4*S*)-isomers (98% e.e.) of the pheromone were synthesized from the enantiomers of dihydrolimonene oxide (Scheme 40).

#### 8.1.4. *cis*-2-(2-Isopropenyl-1-methylcyclobutyl)ethanol (**44**) (grandisol)

Grandisol [*cis*-2-(2-isopropenyl-1-methylcyclobutyl)ethanol, **44**] has first been identified as a male-produced pheromone from the boll weevil *Anthonomus grandis* [115], and has since been found in other insect species [116-118].

Racemic grandisol, contaminated with 10% of the *trans* diastereomer fragranol (**45**) was prepared by Bernard *et al.* [119] via an efficient route starting from 2-(1-methyl-2-phenylthioethyl)cyclobutanone (**A**), involving the 1,4-addition of lithium dimethylcuprate to the cyclobutylidene aldehyde **B** in the key step (Scheme 41).

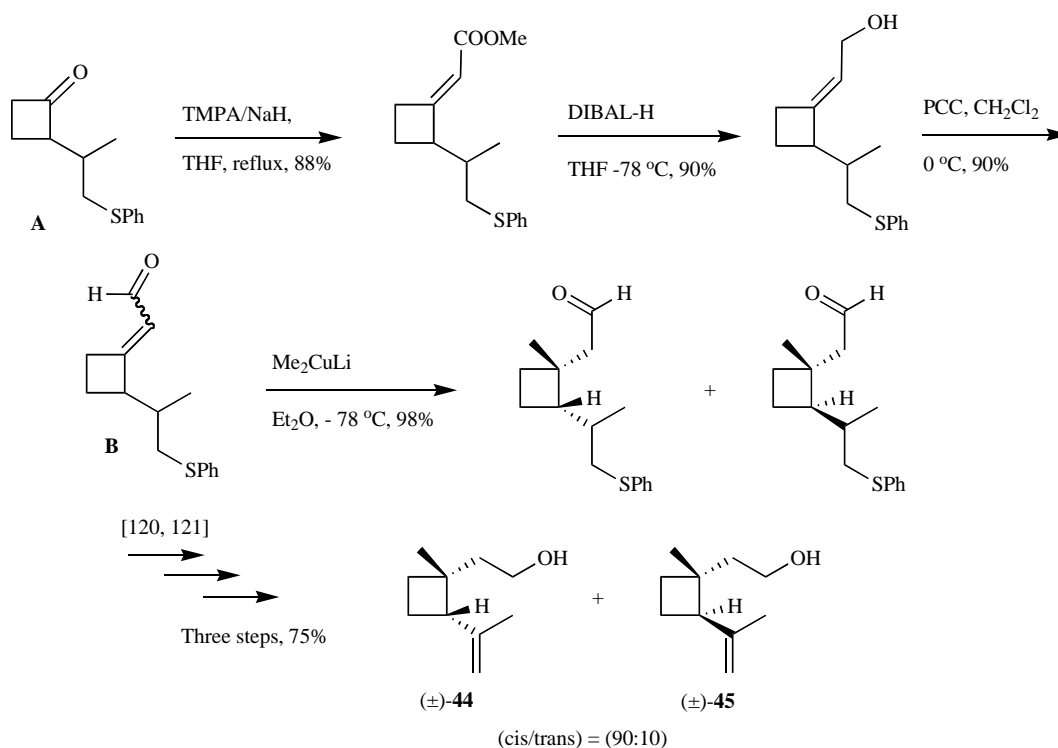
Pure (1*R*,2*S*)-(-)-grandisol was prepared following a similar sequence (Scheme 42). A more bulky substituent at position 2 of the enantiopure cyclobutylidene aldehyde **B** improved the diastereoselectivity of the copper-catalyzed



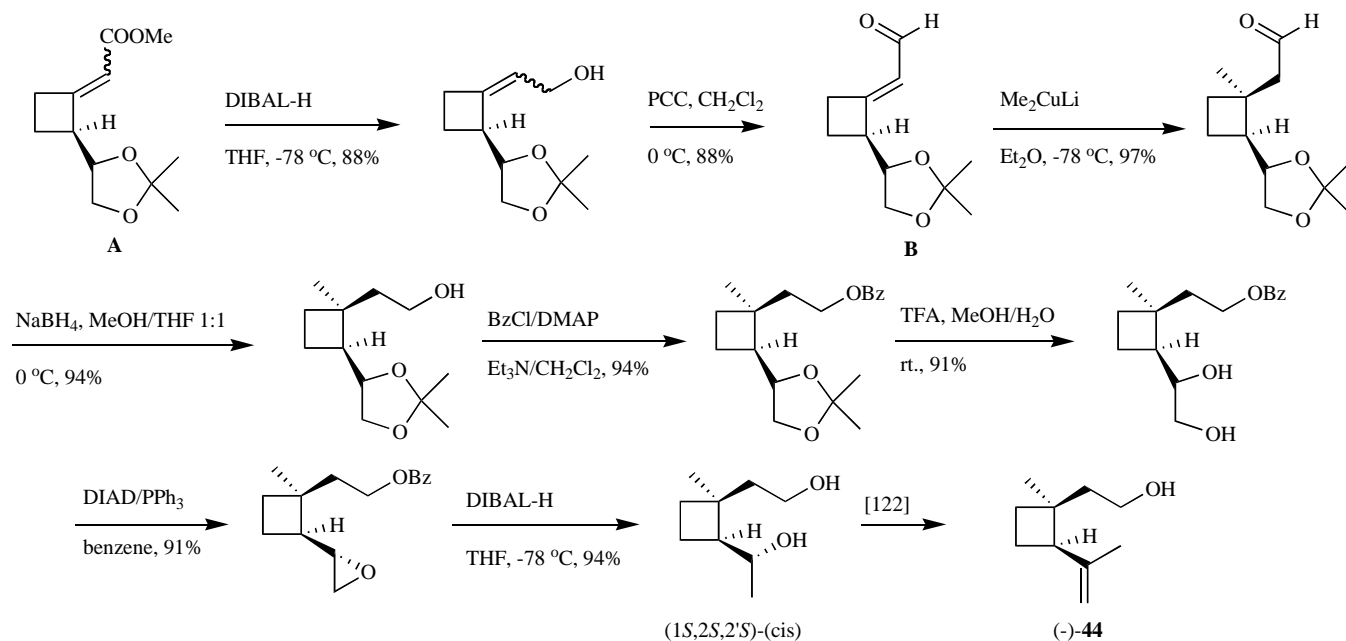
Scheme 40.

methylation key step. **B** (obtained from **A** by reduction and partial oxidation) was used as the substrate, because direct

methylation of TBDMSOTf-activated **A** with  $\text{Me}_2\text{CuLi}$  resulted in lower diastereoselectivity.



Scheme 41.



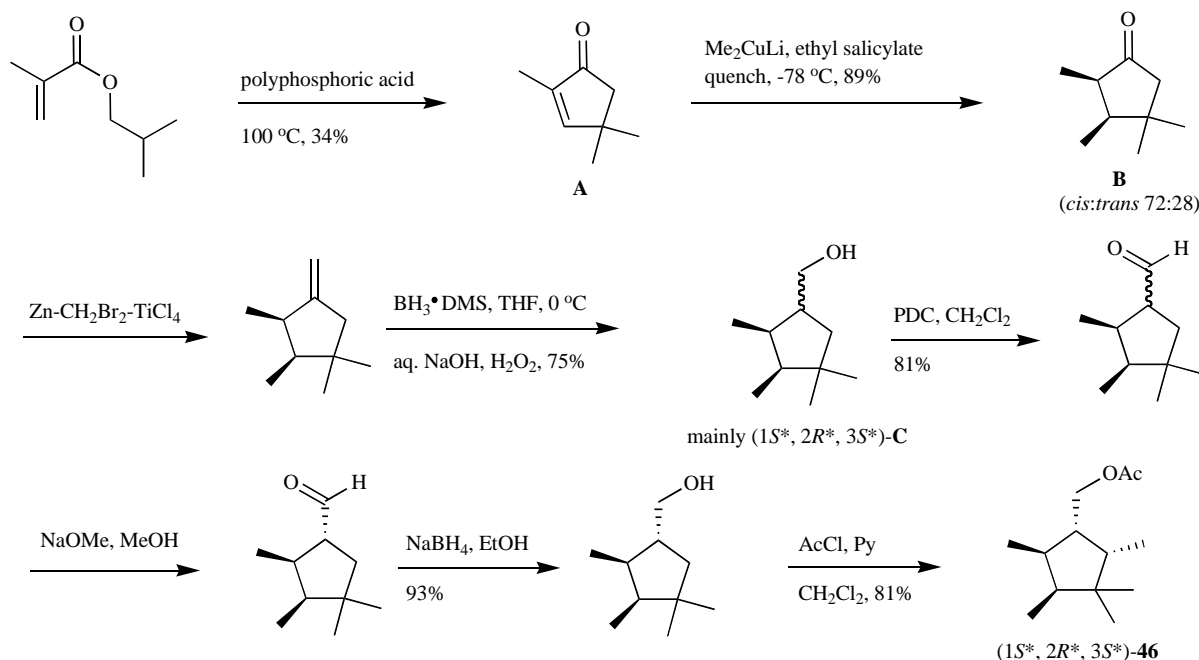
Scheme 42.

### 8.1.5. 1-Acetoxyethyl-2,3,4,4-tetramethylcyclopentane (46)

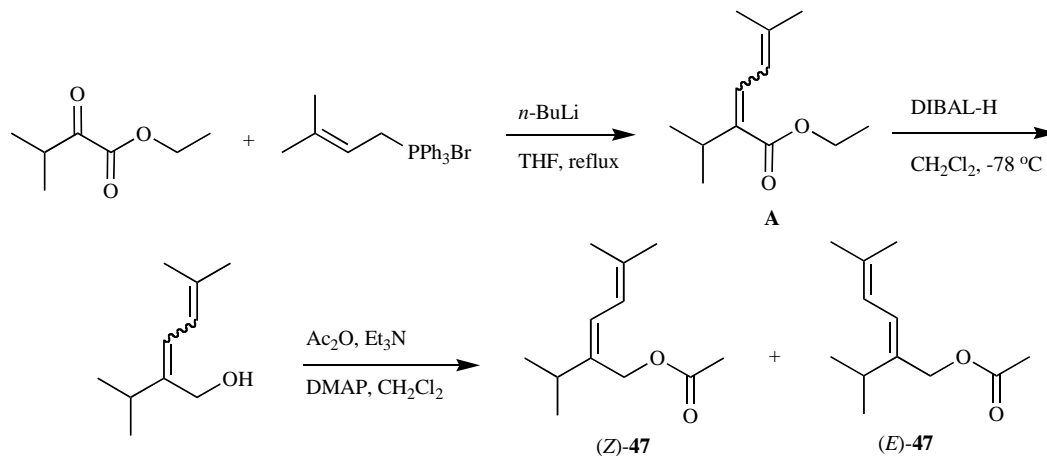
(1*R*\*,2*R*\*,3*S*\*)-1-Acetoxyethyl-2,3,4,4-tetramethylcyclopentane (**46**) is the female-produced sex pheromone of the obscure mealybug *Pseudococcus viburni* [123].

The synthesis developed by Millar and Midland [124] started with a polyphosphoric acid-catalyzed cyclization of isobutyl methacrylate to obtain the  $\alpha,\beta$ -unsaturated cyclopentenone **A**. 1,4-Addition of lithium dimethylcuprate to

**A** usually affords the trans isomer, but careful selection of the reaction conditions (reaction at -40 °C and quenching with ethyl salicylate at -78 °C) resulted in a 72:28 cis:trans mixture of intermediate **B**. Conversion of the carbonyl group to a methylene group and subsequent hydroboration yielded alcohol **C** as a mixture of isomers, from which (1*S*\*,2*R*\*,3*S*\*)-**C** was isolated by column chromatography and Kugelrohr distillation. Inversion of the stereogenic center at carbon 1 and acetylation gave (1*R*\*,2*R*\*,3*S*\*)-**46**, showing 90% isomeric purity (Scheme 43).



Scheme 43.



Scheme 44.

#### 8.1.6. 2-Isopropyl-5-methyl-2,4-hexadienyl acetate (**47**)

Ho *et al.* identified 2-isopropyl-5-methyl-2,4-hexadienyl acetate (**47**) as the sex pheromone produced by females of the passionvine mealybug *Planococcus minor*, and presented a non-stereoselective synthesis of the compound [125].

Wittig reaction between ethyl 3-methyl-2-oxobutanoate and the ylide of 3-methylbut-2-enyltriphenylphosphonium bromide yielded a mixture of the esters (*E*)- and (*Z*)-**A**, which was transformed to a mixture of (*E*)- and (*Z*)-**47** by reduction and acetylation (Scheme 44). The stereoisomers were separated by HPLC for assignment of the geometry of the natural product, which turned out to be (*E*).

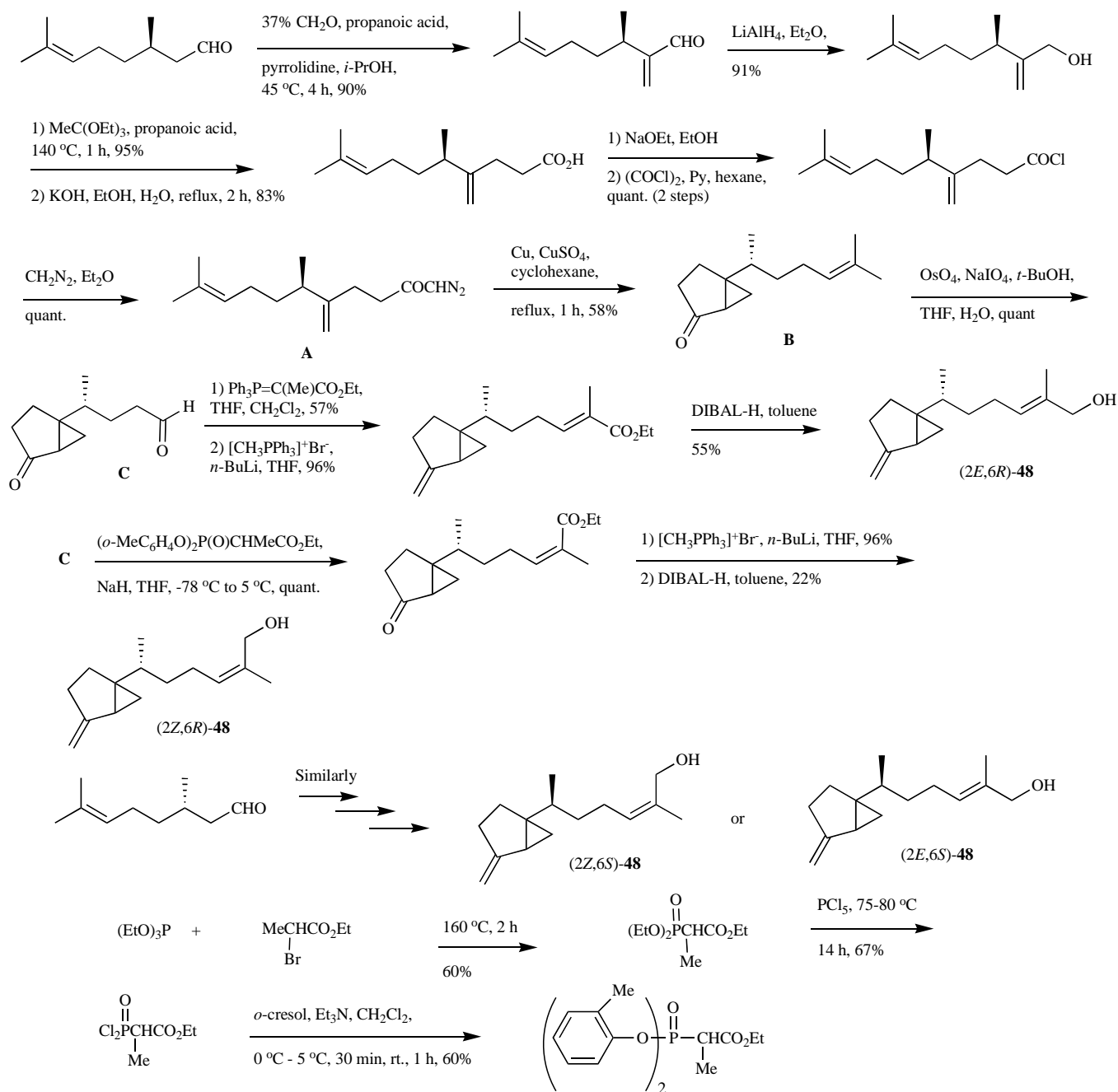
#### 8.1.7. 2-Methyl-6-(4'-methylenebicyclo[3.1.0]hexyl)hept-2-en-1-ol (**48**)

The aggregation pheromone of the stink bug *Erysarcoris lewisi* has been proposed to be (*E*)-2-methyl-6-(4'-methylenebicyclo[3.1.0]hexyl)hept-2-en-1-ol (**48**) [126].

Mori synthesized the (*2E,6R*)-, (*2E,6S*)-, (*2Z,6R*)-, and (*2Z,6S*)-isomers of **48**, starting from citronellal [127]. The

absolute configuration at carbon 6 was defined by the use of (*R*)- or (*S*)-citronellal, respectively, while the geometry of the double bond was established by stereoselective olefination reactions. Citronellal was converted to diazoketone **A** in 7 steps, including methylenation and a Claisen orthoester rearrangement as the key steps of this part of the synthesis (Scheme 45). The  $\alpha$ -ketocarbene generated from **A** added intramolecularly to the exo methylene double bond, establishing the bicyclic structure in intermediate **B**. This reaction cannot be controlled stereochemically and a mixture of two diastereomers of **B** was obtained in each case. The double bond of **B** was cleaved oxidatively to give aldehyde **C**, which was converted to (*E*)-**48** in 3 further steps with the (*E*)-selective olefination of the formyl group with (carbethoxymethylidene)triphenylphosphorane as the key step. To obtain (*Z*)-**48**, the olefination of aldehyde **C** was carried out employing Ando's reagent ethyl 2-(di-*o*-tolylphosphono)propanoate, which in turn was prepared in three steps from triethyl orthophosphite and ethyl 2-bromopropanoate (Scheme 45). Bioassays with the synthetic isomers suggested the natural pheromone to show (*2Z,6R*) configuration.





Scheme 45.

## 8.2 Synthesis of Isoprenoidal Aldehydes, Ketones and Acids as Pheromones

### 8.2.1. (*R*)-1,1,5,8-Tetramethyl-1,2,3,4,5-pentahydrobenzo[a][7]annulene (49) [(*R*)-*ar*-himachalene]

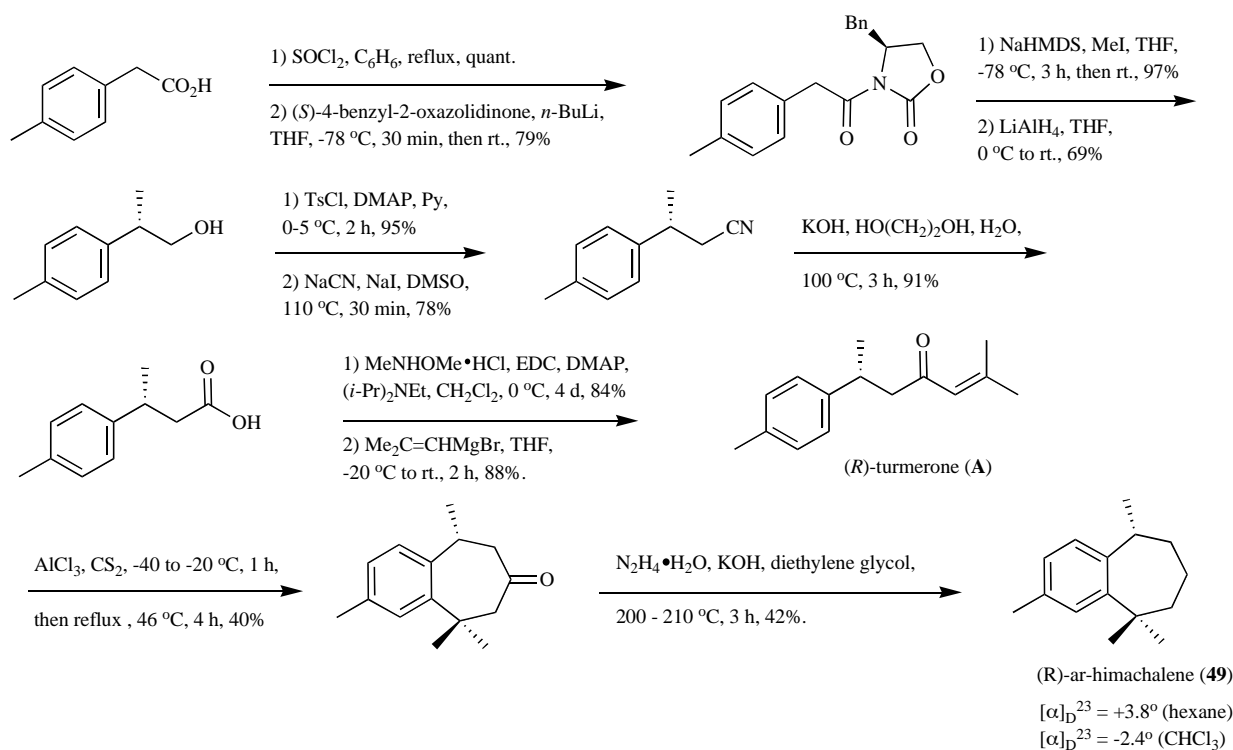
In 2001 Bartelt *et al.* [128] isolated and identified the male-produced pheromone of the flea beetle *Aphthona flava* as (*S*)-*ar*-himachalene (49). Mori [129] proposed the opposite absolute configuration for the natural compound.

Mori [130, 131] described a synthesis of (*R*)-turmerone A from (4-methylphenyl)acetic acid employing Evans' asymmetric alkylation in the key step. (*R*)-Turmerone was converted to (*R*)-*ar*-himachalene according to Pandey and Dev's

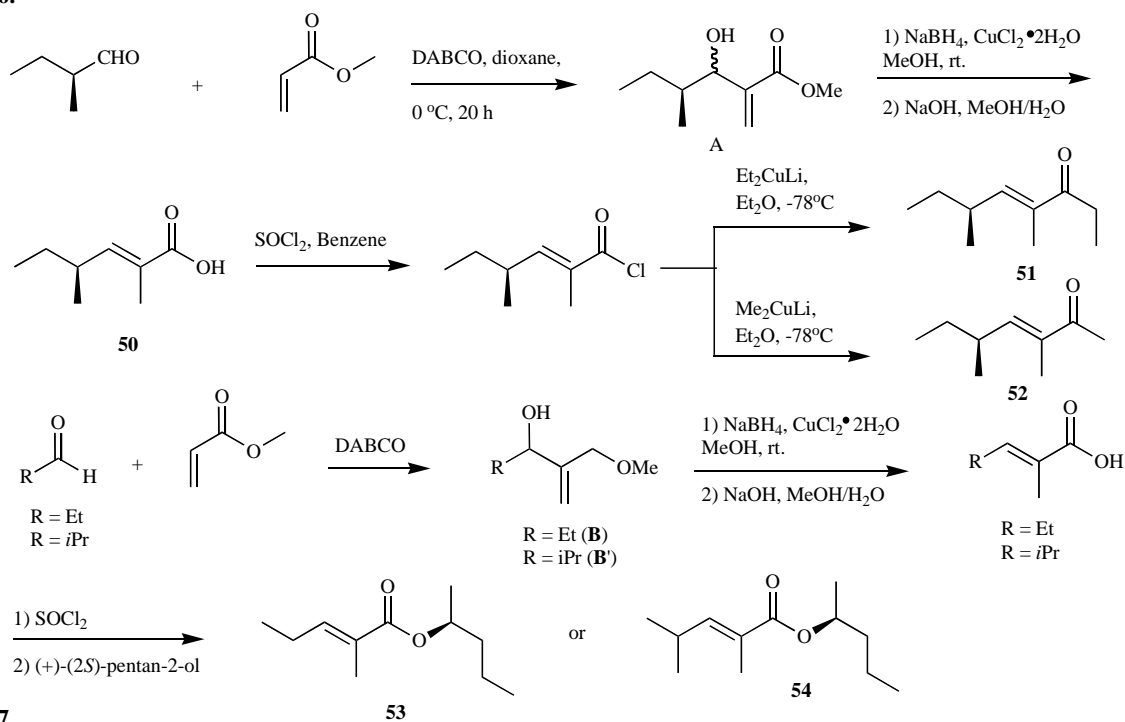
procedure [132] (Scheme 46). Interestingly, (*R*)-49 was dextrorotatory in hexane, while levorotatory in chloroform.

### 8.2.2. (2*E*,4*S*)-2,4-Dimethylhex-2-enoic acid (50), 4,6-dimethylnon-4-en-3-one [(*S*)-manicone, 51], 3,5-dimethyl-oct-3-en-2-one [(*S*)-normanicone], 52, (1*S*)-1-methylbutyl-(2*E*)-2-methylpent-2-enoate (dominicalure-I, 53) and (1*S*)-1-methylbutyl (2*E*)-2,4-dimethylpent-2-enoate (dominicalure-II, 54)

(2*E*,4*S*)-2,4-Dimethylhex-2-enoic acid (50) is a caste-specific substance present in the mandibular glands of the male carpenter ants in the genus *Camponotus* [133]. (*S*)-Manicone (4,6-dimethylnon-4-en-3-one, 51) and (*S*)-



Scheme 46.

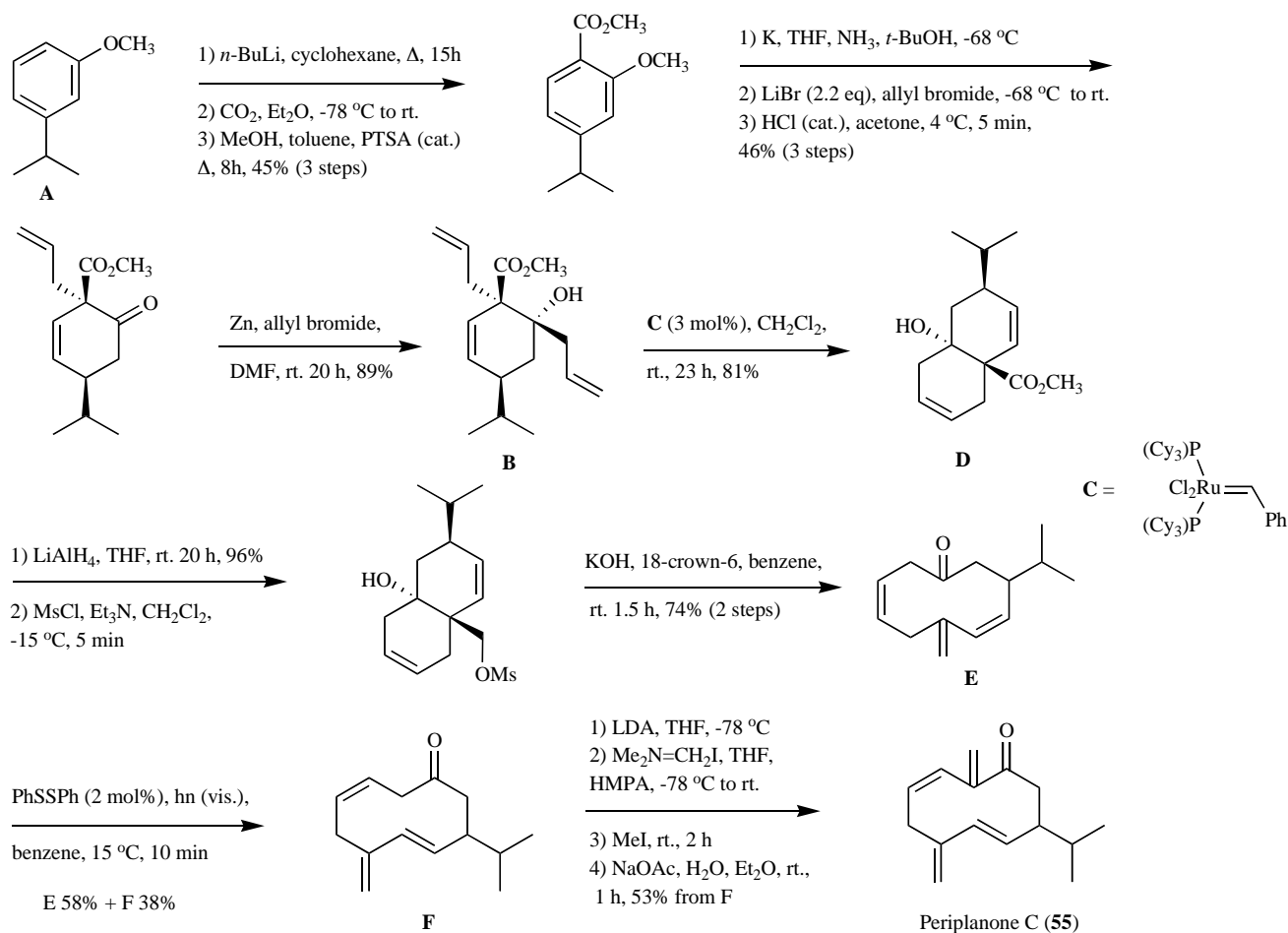


Scheme 47.

normanicone (3,5-dimethyl-oct-3-en-2-one, **52**) are the mandibular-gland alarm pheromone components of the ants in the genus *Manica* [134, 135]. Dominicalure-I [(1*S*)-1-Methylbutyl (2*E*)-2-methylpent-2-enoate, **53**] and dominicalure-II [(1*S*)-1-methylbutyl (2*E*)-2,4-dimethylpent-2-enoate, **54**] are the aggregation pheromones of the lesser grain borer *Rhyzopertha dominica* [136].

Das *et al.* [137] described a synthesis of these pheromone compounds employing Baylis–Hillman adducts. Compounds

**50**, **51** and **52** were obtained from Baylis–Hillman adduct **A**, which was treated with sodium borohydride in the presence of  $\text{CuCl}_2\cdot 2\text{H}_2\text{O}$  in MeOH to give the corresponding (*E*)-2-methyl-2-alkenoate, which was hydrolyzed yielding acid **50**. Transformation of **50** to the acid chloride and alkylation with lithium diethylcuprate and lithium dimethylcuprate yielded **51** and **52**, respectively. For the synthesis of **53** and **54**, the Baylis–Hillman adducts **B** and **B'** were subjected to a similar reaction sequence (Scheme 47).



Scheme 48.

### 8.2.3. (3*Z*,7*E*)-9-Isopropyl-2,6-dimethylene-3,7-cyclodecadien-1-one (periplanone C, 55)

Periplanone C [(3*Z*,7*E*)-9-isopropyl-2,6-dimethylene-3,7-cyclodecadien-1-one, **55**] is one of at least four biologically active components of the sex pheromone of the American cockroach, *Periplaneta americana* [138-143].

The key steps of the synthesis of racemic **55** presented by Matovic *et al.* [144] are a ring closure metathesis (RCM) reaction, assuring the *Z* configuration of the newly formed double bond in the bicyclic intermediate **D**, and subsequent rupture of the central bond yielding **E**. The monocyclic precursor **B** was obtained from the anisole derivative **A** and submitted to RCM using Grubbs first generation catalyst (**C**) to yield the bicyclic intermediate **D**. The rupture of the central bond was achieved by Grob fragmentation under ionic conditions and yielded the (*Z,Z*)-cyclodecadienone **E**, which could be isomerized photochemically under radical conditions to the (*Z,E*)-cyclodecadienone **F**. The lithium enolate of **F** was aminomethylated with Eschenmoser's reagent and **55** was obtained after spontaneous elimination of dimethylamine (Scheme 48).

### 8.2.4. (*E*)- and (*Z*)-3-Methyl-4-heptenoic acid (56), and 3-methyleneheptanoic acid (57)

The volatile sex pheromone released by females of the cowpea weevil *Callosobruchus maculatus* has been identi-

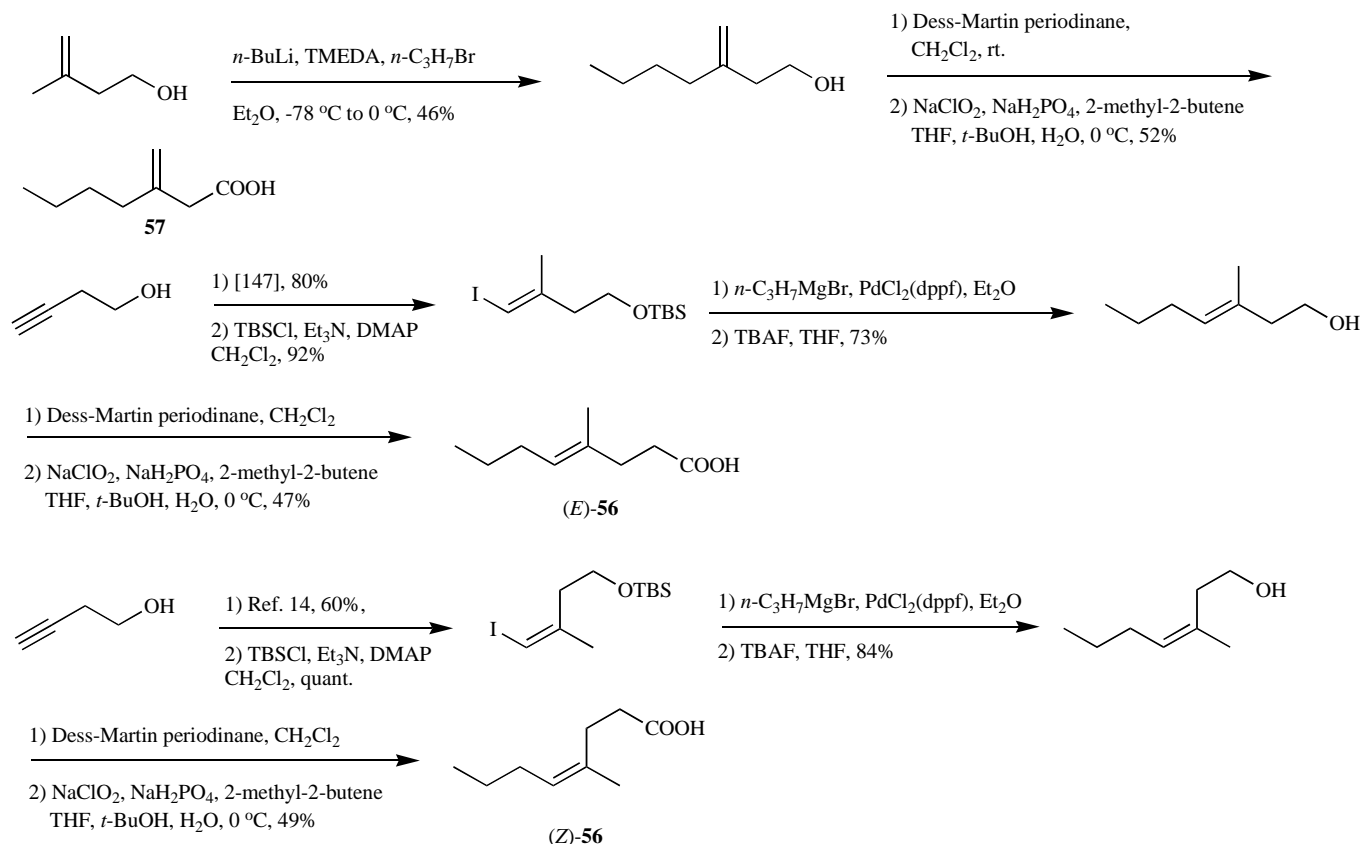
fied to be a mixture of (*E*)- and (*Z*)-3-methyl-2-heptenoic acid, (*E*)- and (*Z*)-3-methyl-4-heptenoic acid (**56**), and 3-methyleneheptanoic acid (**57**) [145].

The three latter compounds have been synthesized by Yajima *et al.* [146]. **57** was prepared using Chong's procedure of alkylation of the dianion of 3-methyl-3-buten-1-ol, followed by sequential Dess-Martin and Pinnick oxidations to give the target molecule in a moderate yield but without isomerization of the somewhat sensitive 3-*exo* methylene double bond. For the synthesis of **56**, the (*E*) and (*Z*) isomers of the vinylic iodide 4-iodo-3-methyl-3-buten-1-ol were prepared from 3-butyne-1-ol, respectively, and further transformed via alkylation and oxidation to the desired products (Scheme 49) [147, 148].

## 9. SYNTHESIS OF ACETALS AS PHEROMONES

### 9.1. (1*S*,3*R*,5*R*,7*S*)-1-Ethyl-3,5,7-trimethyl-2,8-dioxabicyclo[3.2.1]octane [(+)-sordidin, 58] and (1*S*,3*R*,5*R*,7*R*)-1-ethyl-3,5,7-trimethyl-2,8-dioxabicyclo[3.2.1]octane [(−)-7-*epi*-sordidin, 59]

The banana weevil *Cosmopolites sordidus* is the most devastating insect pest on banana plants worldwide [149]. The major compound of the male-produced aggregation pheromone has been identified as (1*S*,3*R*,5*R*,7*S*)-1-ethyl-3,5,7-trimethyl-2,8-dioxabicyclo[3.2.1]octane (**58**), which was given the common name sordidin [150-152]. A minor component of the volatile bouquet released by the weevil is

**Scheme 49.**

(1*S*,3*R*,5*R*,7*R*)-7-*epi*-sordidin (**59**) [153]. Interestingly, the enantiomer of the latter has been found in caddisflies [154].

An asymmetric synthesis of (1*S*,3*R*,5*R*,7*S*)-**58** and (1*S*,3*R*,5*R*,7*R*)-**59** was performed by Enders *et al.* [155]. The first two stereogenic centers were formed by three  $\alpha$ -alkylations of the RAMP-hydrazone of 2,2-dimethyl-1,3-dioxan-5-one **A**. The third stereogenic center was formed by diastereoselective epoxide opening employing the azanolate of 3-pentanone SAEP-hydrazone in the key step (Scheme 50). The mixture of the diastereomers was separated by preparative gas chromatography, furnishing the pure enantiomers with e.e. > 98%.

## 9.2. 1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octane (**60**) (frontalin)

Frontalin (1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane, **60**) was first isolated and identified as a component of the aggregation pheromones of the southern pine beetle (*Dendroctonus frontalis*) and of the western pine beetle (*Dendroctonus brevicomis*) by Kinzer *et al.* [158]. By means of bioassays with pure synthetic enantiomers, Mori [159, 160] showed the absolute configuration of natural **60** to be (1*S*,5*R*) in both species.

Prasad *et al.* [161] described an enantioselective formal synthesis of frontalin employing the addition of Grignard reagents to the bis-Weinreb amide **A** derived from L-(+)-tartaric acid and to **B** as the key steps (Scheme 51).

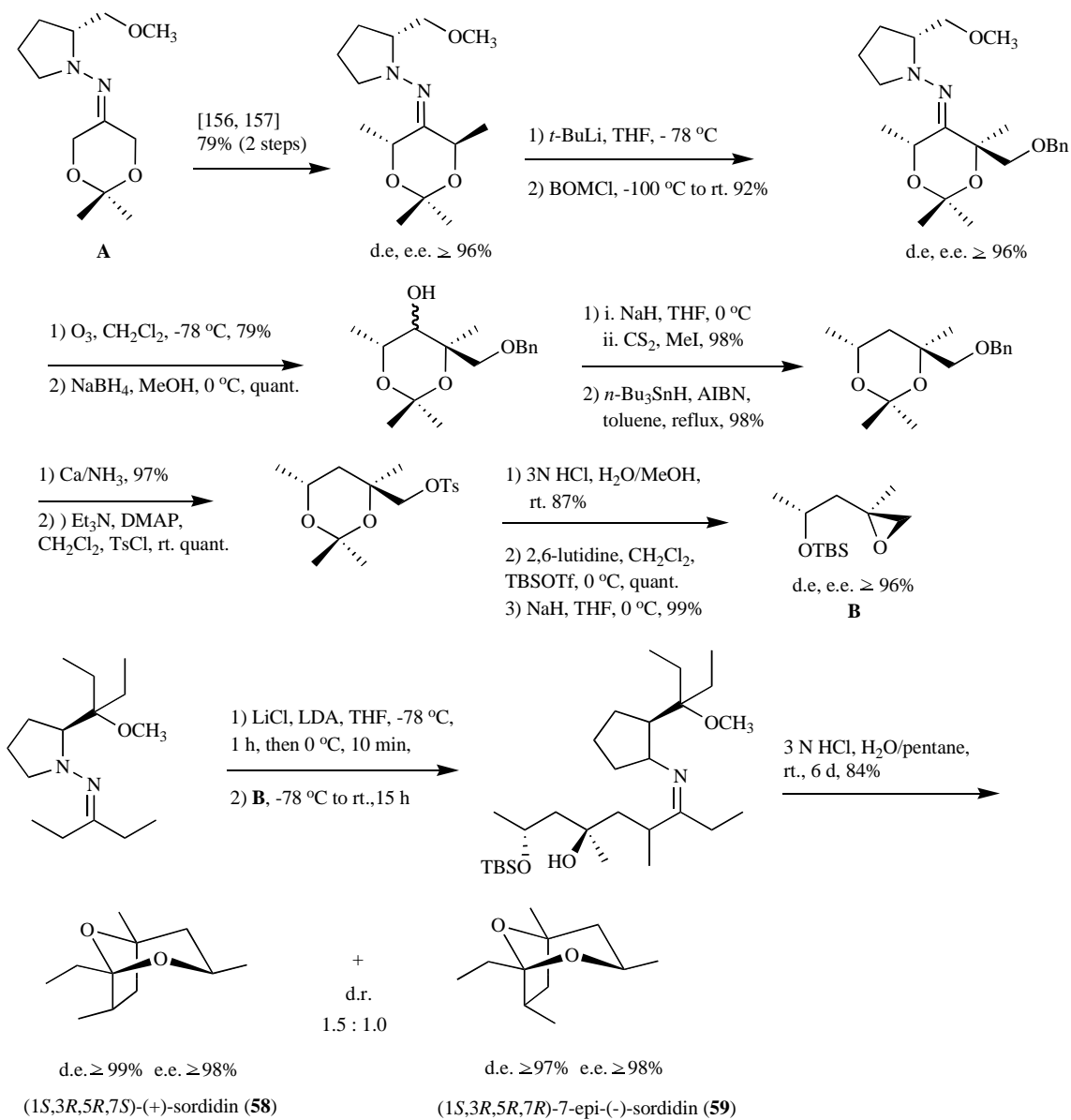
Schuster *et al.* [163] described a stereoselective synthesis of **60** by addition of an organo zinc reagent to an  $\alpha$ -keto ester

coupled to a chiral auxiliary. The synthesis was performed either in solution (98 % e.e. for (+)-**60**) or with the  $\alpha$ -keto ester-chiral auxiliary complex immobilized (86 % e.e.) (Scheme 52).

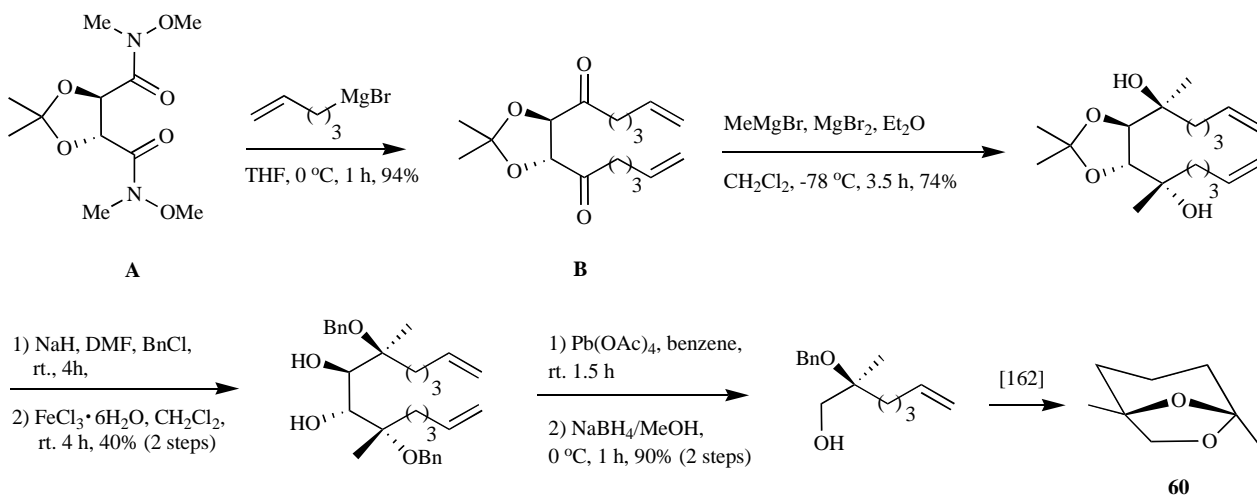
## 9.3. *exo*-Brevicomine (**61**), 1'-hydroxy-*exo*-brevicomine (**62**) and 2-hydroxy-*exo*-brevicomine (**63**)

*exo*-Brevicomine (**61**) and *endo*-brevicomine (*exo*- and *endo*-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane) are common components of the aggregation pheromone system of several bark beetle species of the genera *Dendroctonus* and *Dryocoetes* [160, 164-166]. Francke *et al.* [167] have identified 1'-hydroxy-*exo*-brevicomine (**62**) and 2-hydroxy-*exo*-brevicomine (**63**) from the pine beetle *Dendroctonus ponderosae*.

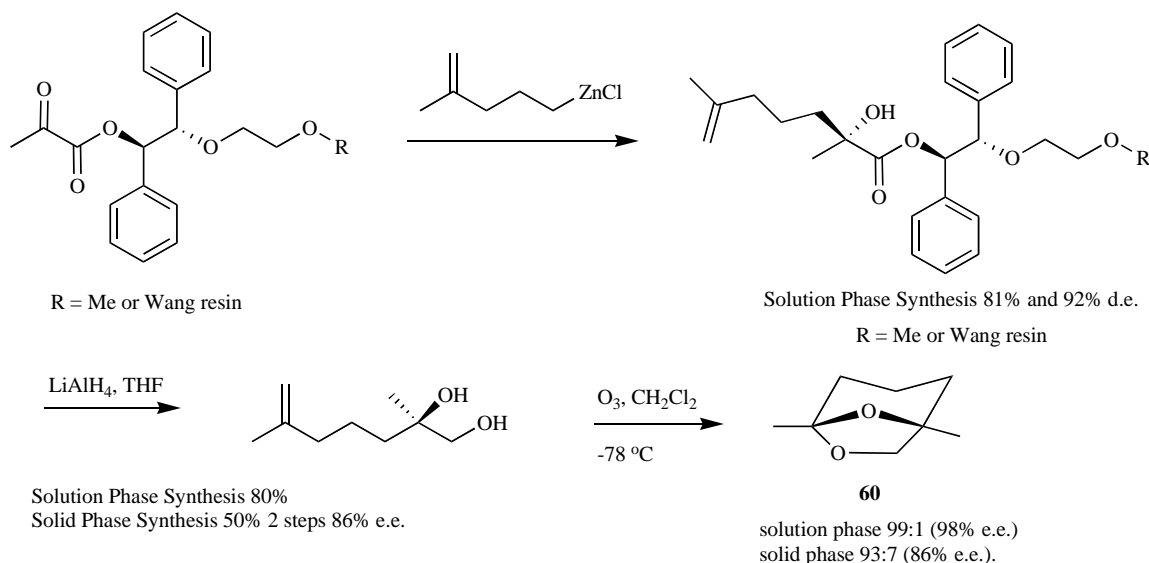
Prasad *et al.* [168-170] described a synthesis of **61**, **62**, and **63** employing addition of Grignard reagents to the bis-Weinreb amide **A** derived from L-(+)-tartaric acid and subsequent stereoselective reduction of the keto function with L-selectride or K-selectride as common steps (Schemes 53 – 55). **61** was synthesized from diol **B** by oxidative cleavage with lead tetraacetate in benzene and subsequent stereoselective alkylation of the resulting aldehyde to yield the corresponding *threo* alcohol **C** as a single diastereomer. Wacker oxidation of terminal olefin and simultaneous debenzoylation and intramolecular acetalization with Pd/C in MeOH and a trace of 3 M HCl gave the compound **61** (Scheme 53). For the synthesis of **62**, TBDMS protected amide **D** was reduced with sodium borohydride, tosylated, and reduced with super hydride to obtain acetonide **E**. Wacker oxidation and cycliza-



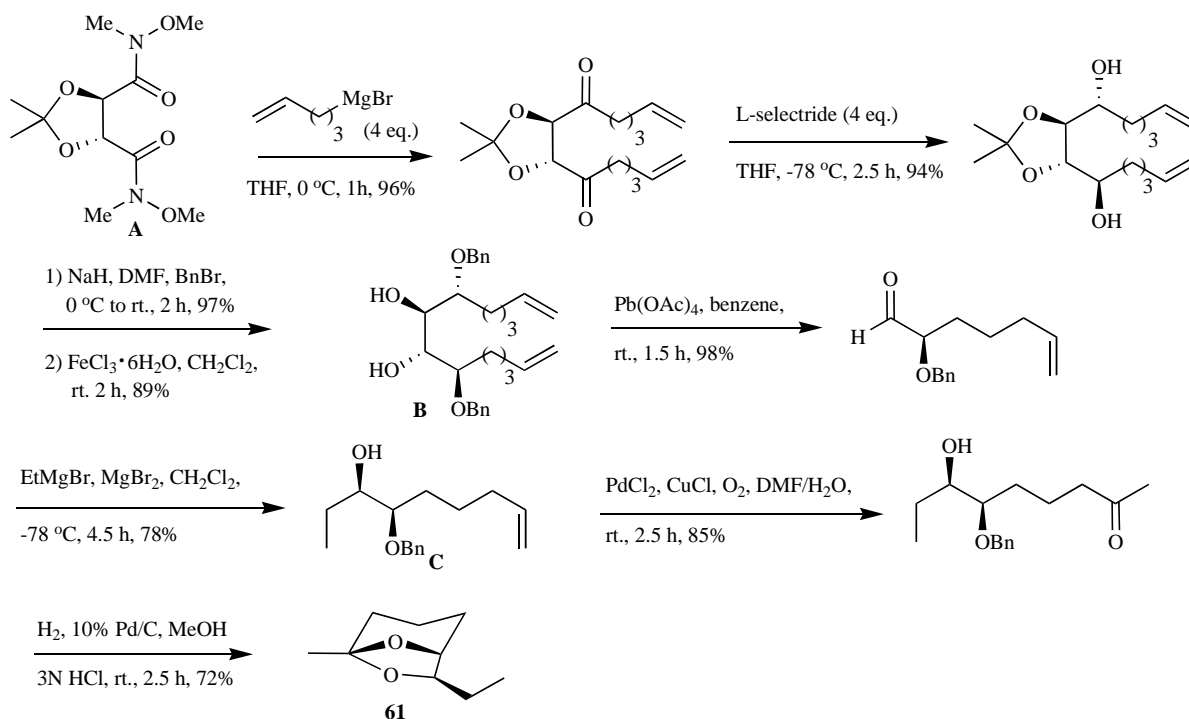
Scheme 50.



Scheme 51.



Scheme 52.



Scheme 53.

tion yielded **62** (Scheme 54). For the synthesis of **63**, TBDMS protected amide **F** was reduced with DIBAL-H and treated with phosphorus ylide to give the  $\alpha,\beta$ -unsaturated ketone **G**. Hydrogenation over Pd/C and simultaneous deprotection of the silyl ether and acetonide afford triol **H**, which instantly ketalized to **63** (Scheme 55).

#### 9.4. ( $\pm$ )-1,7-Dioxaspiro[5.5]undecane (**64**) and (2R\*,6S\*)-2-methyl-1,7-dioxaspiro[5.5]undecane (**65**)

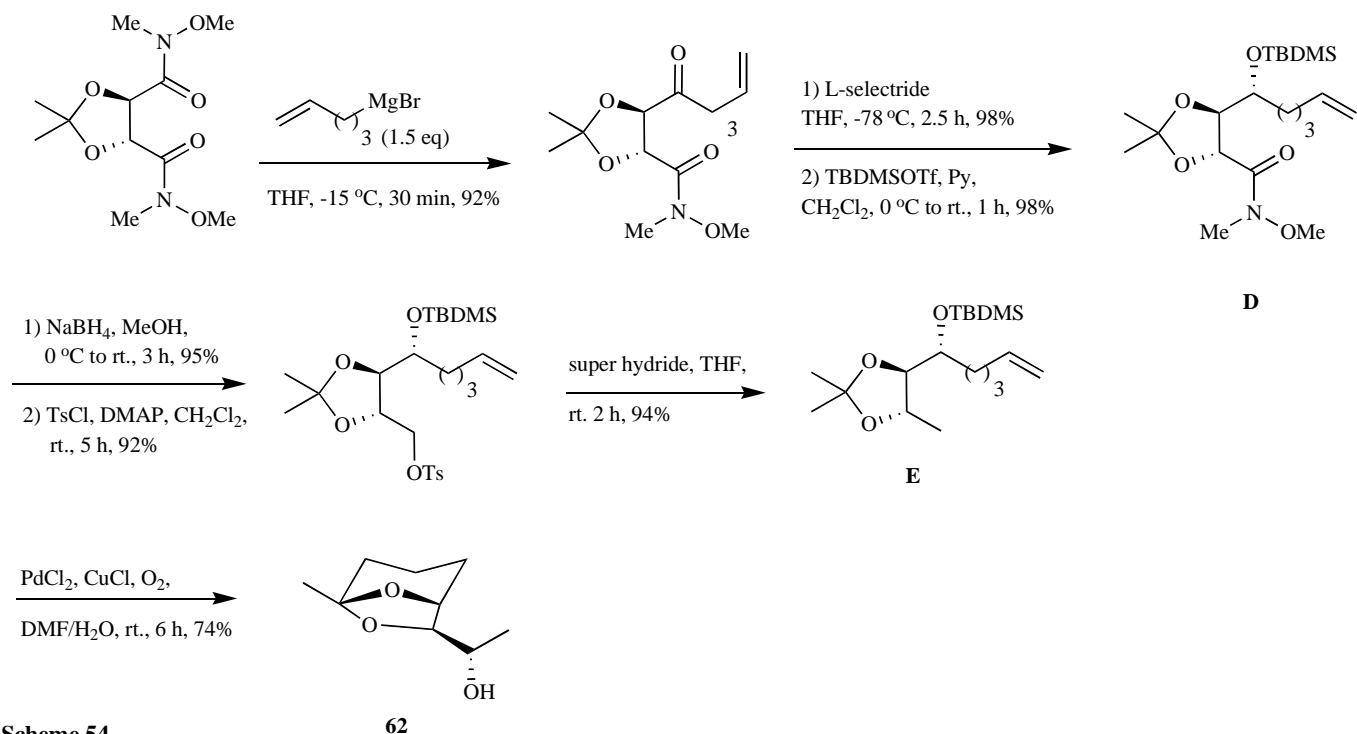
1,7-Dioxaspiro[5.5]undecane (**64**) has been identified as the major component of the sex pheromone released by females of the olive fruit fly *Dacus oleae* [171]. In bioassays, (*R*)-**64** was shown to be active against the males, whereas (*S*)-**64** was active against females [172]. 2-Methyl-1,7-

dioxaspiro[5.5]undecane (**65**) was identified as volatile component of the cleptoparasite bee *Epeolus cruciger* [173]. Conway *et al.* [174] described a synthesis of these two spiroketal compounds employing stereospecific Stille coupling reactions of 2-metallo-dihydropyrans with suitable (*Z*)-1-iodoalkenols and subsequent cyclisation (Scheme 56).

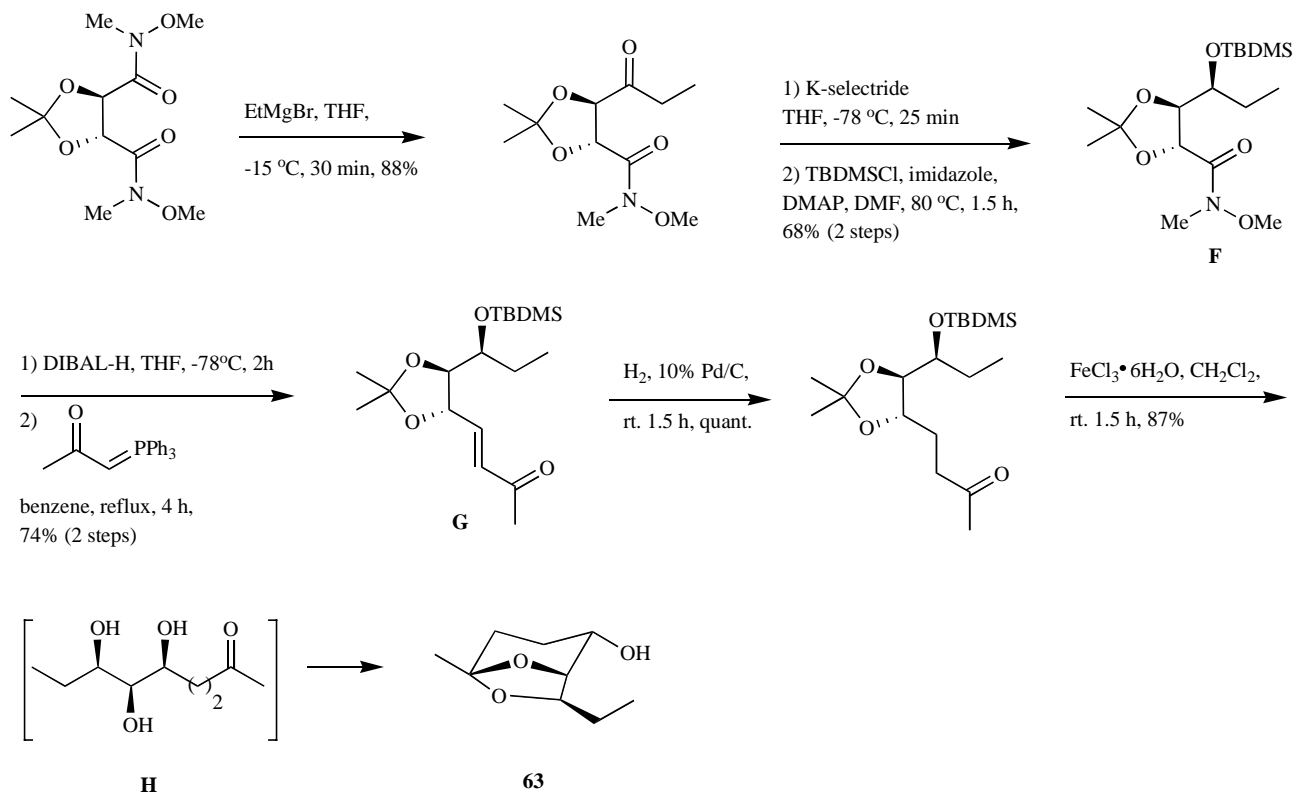
## 10. SYNTHESIS OF ALLENES AS PHEROMONES

### 10.1. Methyl (*R,E*)-tetradeca-2,4,5-trienoate (**66**)

Methyl (*R,E*)-(-)-tetradeca-2,4,5-trienoate (**66**) has been of synthetic interest since Horler determined it to be a sex attractant produced by the male bean weevil, *Acanthoscelides obtectus* [175].



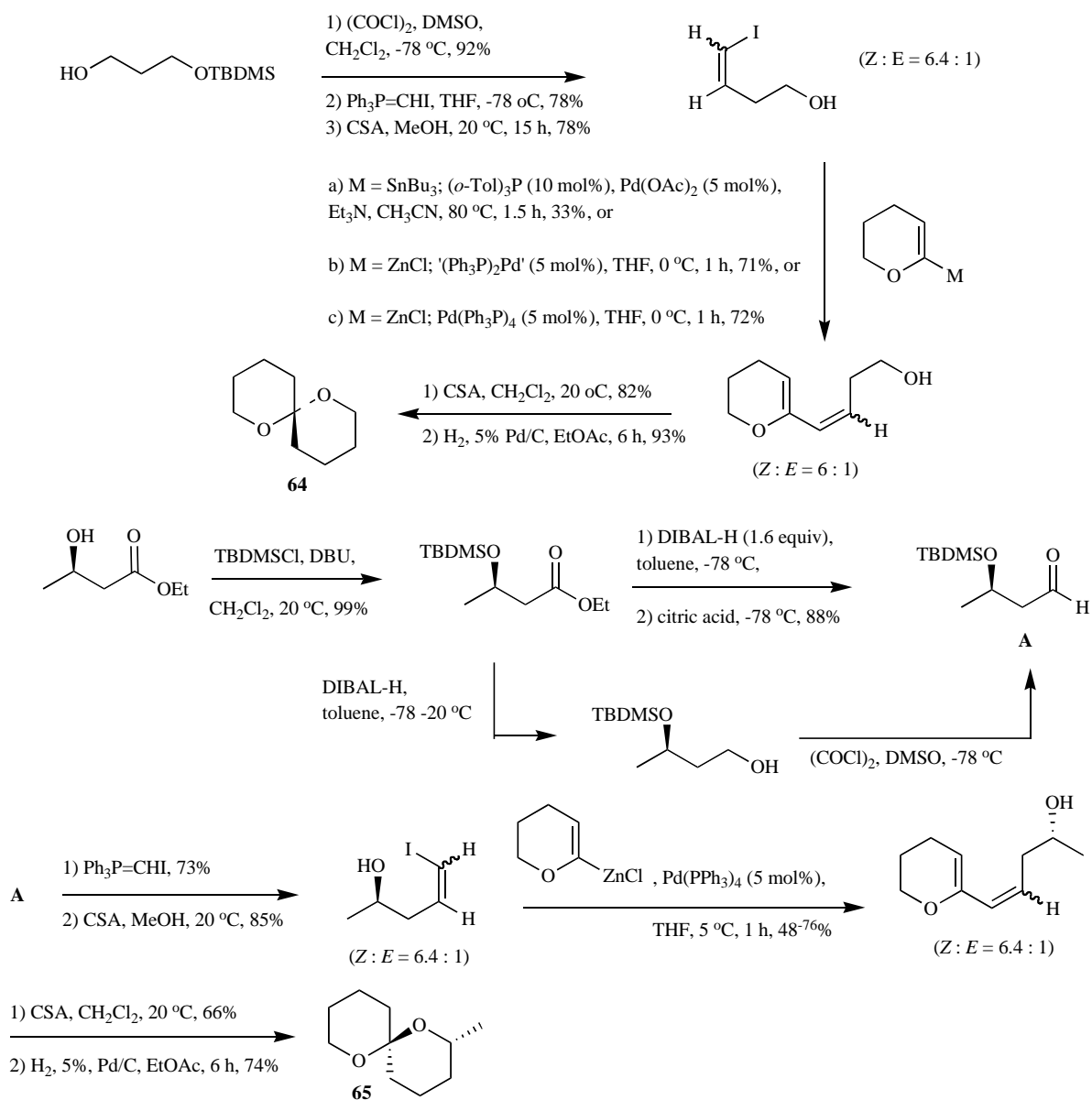
Scheme 54.



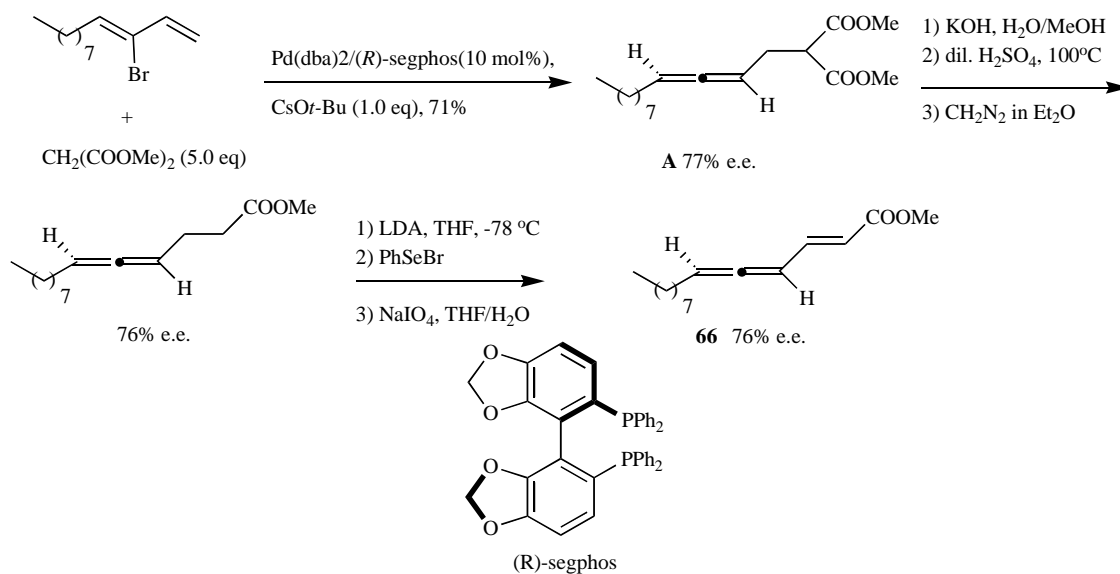
Scheme 55.

Ogasawara *et al.* [176] described an enantioselective synthesis of this chiral allene using a palladium-catalyzed reaction for the synthesis of the allene moiety in the key step. Allene intermediate **A** was prepared by reaction of 3-bromo-1,3-dodecadiene and dimethyl malonate. The use of  $\text{Pd}(\text{dba})_2/(R)\text{-segphos}$  catalyst and 5 equivalents of malonate

were the best conditions in terms of both yield and asymmetric induction (71% yield, 77% e.e.). Methanolic hydrolysis, acidic decarboxylation and treatment with diazomethane resulted in decarboxylation of **A** nearly without racemization. A final desaturation step gave **66** in 76% e.e. (Scheme 57).



Scheme 56.



Scheme 57.



## ABBREVIATIONS

Ac	=	acetyl
AIBN	=	azobisisobutyronitrile
BnBr	=	benzyl bromide
BOMCl	=	benzyloxymethyl chloride
<i>m</i> -CPBA	=	<i>m</i> -chloroperbenzoic acid
CSA	=	camphorsulfonic acid
DABCO	=	1,4-diazabicyclo[2.2.2]octane
DBU	=	diazabicyclo[5.4.0]undecene
DCHT	=	dicyclohexyl tartrate
DET	=	diethyl tartrate
DHP	=	3,4-dihydro-2 <i>H</i> -pyran
DIAD	=	diisopropyl azodicarboxylate
DIBAL-H	=	diisobutylaluminium hydride
DIPT	=	diisopropyl tartrate
DMAP	=	4-dimethylaminopyridine
DMF	=	<i>N,N</i> -dimethylformamide
DMS	=	dimethylsulfide
DMSO	=	dimethylsulfoxide
EDC	=	1-ethyl-3-(3-dimethyl aminopropyl)carbodiimide
HMPA	=	hexamethylphosphoramide
IBX	=	2-iodoxybenzoic acid
KHMDS	=	potassium hexamethyldisilazide
LDA	=	lithium diisopropylamide
MOMCl	=	methoxymethyl chloride
MsCl	=	methanesulfonyl chloride (mesyl chloride)
NaHMDS	=	sodium hexamethyldisilazide
PCC	=	pyridinium chlorochromate
PDC	=	pyridinium dichromate
PNBA	=	<i>p</i> -nitrobenzoic acid
PPh <sub>3</sub>	=	triphenyl phosphine
PPTS	=	pyridinium <i>p</i> -toluenesulfonate
PTSA	=	<i>p</i> -toluenesulfonic acid
Py	=	pyridine
TBAF	=	tetra- <i>n</i> -butylammonium fluoride
TBDMSCl	=	<i>tert</i> -butyldimethylsilyl chloride
TBDPSCI	=	<i>tert</i> -butyldiphenylchlorosilane
TBHP	=	<i>tert</i> -butyl hydroperoxide
TBSCl	=	<i>tert</i> -butyldimethylsilyl chloride
TBSOTf	=	<i>tert</i> -butyldimethylsilyl triflate
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
THP	=	tetrahydropyranyl
TMEDA	=	tetramethylethylenediamine
TMSCl	=	trimethylsilyl chloride
TsCl	=	<i>p</i> -toluenesulfonyl chloride (tosyl chloride)

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