

Insect Pheromone Synthesis in Brazil: an Overview[#]

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Nesta revisão estão descritas as sínteses de feromônios de insetos desenvolvidas e publicadas por grupos de pesquisa brasileiros, e tem por objetivo apresentar o estado da arte desta área de pesquisa no país e fornecer uma informação rápida sobre as moléculas já sintetizadas e metodologias empregadas. As sínteses estão apresentadas em ordem cronológica, exceto quando se trata de diferentes metodologias para a mesma molécula.

This review describes the syntheses of insect pheromones developed and published by Brazilian research groups and aims to present the state of the art of this area in the country, and also to serve as a quick view of the already synthesized molecules and employed methodology. The syntheses are presented in chronological order, except when they refer to different approaches for the same molecule.

Keywords. Brazil, chemical ecology, insect pheromone, organic synthesis

1. Introduction

The ever-increasing use of conventional pesticides leads to resistant pests, severely alters natural ecology, damages the environment and, ultimately, affects the economy adversely. The number of insect and other species developing resistance to pesticides is growing steadily, forcing chemical companies to develop novel pesticide formulas. In response to the problems caused by the increased use of conventional pesticides, the concept of integrated pest management (IPM) was developed. IPM combines chemical, biological and agrotechnical approaches to achieve pest control at a reasonable cost while minimizing damage to the environment. The first step in IPM is effective monitoring by the use of pheromones.¹

Pheromones are substances which occur in Nature and are used for chemical communication between animals. The term pheromone (from the Greek *pherein* = to transfer and *hormon* = to excite), coined by Karlson and Luscher,² is a substance which is secreted by an individual and received by a second individual of the same species, in which it releases a specific reaction, for example, a specific behaviour or a

development process. The main ways of exploiting pheromones in pest control are: monitoring, mating disruption and mass trapping.³ Such pheromone applications provide significant cost reduction and environmental benefits to the farmer, to the consumer and to the society.

The first chemical identification of a pheromone took place in the late 1950s, after almost two decades of work by a team led by Butenandt.⁴ The team chose to study the domesticated silk moth, *Bombyx mori*, which could be reared in the enormous numbers needed. The silk moth pheromone was identified as (10*E*,12*Z*)-hexadecadien-1-ol (**1**), bombykol. This first sex pheromone identified was achiral, but in the late 1960s a number of chiral pheromones were discovered such as (+)-*exo*-brevicomine **2**, the pheromone of the western pine beetle, *Dendroctonus brevicomis*⁵ and (*Z*)-(-)-14-methylhexadec-8-en-1-ol (**3**), the sex attractant of female dermestid beetle, *Trogoderma inclusum*⁶ (Figure 1).

An understanding of the relationship between structure and biological effect requires that the absolute

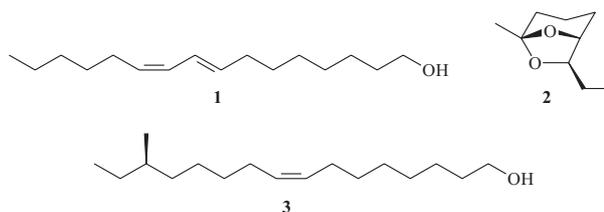


Figure 1. Structures of insect pheromones

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[#]This paper is dedicated to Prof. J. Tércio B. Ferreira, on the occasion of the 10th year of his decease.

configurations of the naturally occurring chiral pheromones are determined. It is now well established that pheromones are not always enantiomerically pure. Therefore, their enantiomeric composition must be determined in detail.⁷

Difficulties are often encountered in stereochemical studies of pheromones, because they are usually obtained in small quantities. Thus, organic synthesis plays an essential role on the pheromone chemistry, as it provides material for rigorous determination of the (absolute) configuration of the molecules and for carrying out extensive biological tests. The synthesis of compound **3** described in 1973 by Mori was the first successful identification of the absolute configuration of an insect pheromone by its enantioselective synthesis.^{8,9} Several reviews have been described focusing on many aspects of pheromone science.¹⁰⁻¹⁷

Rapid progress has been made in research on insect pheromones in Brazil during the last decade, including the identification, synthesis, biosynthesis and field evaluation of the bioactive compounds and continuing attempts are expected in the coming years.¹⁸ The growth of the field in Brazil naturally led to the organization of national meetings in the area. In December, 1999 the first Brazilian Meeting on Chemical Ecology (I EBEQ) was held at the Chemistry Department of Universidade Federal do Paraná and nowadays the community looks forward the fifth issue of the meeting, scheduled for October, 2007. As a consequence of the large diffusion of research results presented at I EBEQ, a special issue of the *Journal of the Brazilian Chemical Society* (2000,11(6)) was dedicated to Chemical Ecology. This issue features contributions from research groups from Brazil and abroad and provides an overview of the area in the late 1990s.

In this review, we summarize insect pheromone synthesis research in Brazil. The aim is to present the state of the art of this area in the country, and also to serve as an overview of the already synthesized molecules and employed methodology. The syntheses are presented

in chronological order, except when they refer to different approaches for the same molecule.

2. Synthesis of the pheromones

2.1. (*E*)- and (*Z*)-3,3-Dimethyl- $\Delta^{1,\beta}$ -cyclohexaneethanal (**4**) and (*Z*)-3,3-dimethyl- $\Delta^{1,\beta}$ -cyclohexaneethanol (**5**)

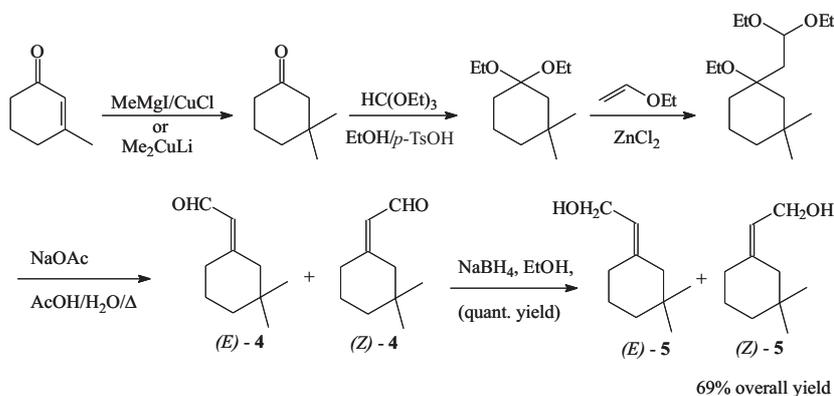
Compounds *Z*- and *E*-**4** and **5** are components of the pheromone produced by male boll weevil, *Anthonomus grandis*, and were identified and first synthesized by Tumlinson *et al.*¹⁹ In 1978, Souza and Gonçalves described the syntheses of these components, being the first pheromone synthesis developed in Brazil.²⁰ The *Z*- and *E*-aldehydes **4** were prepared from commercially available 3-methyl-2-cyclohexen-1-one, in 69% overall yield. The third component, the *Z* alcohol **5** was prepared by reduction of a mixture of aldehydes **4** with NaBH₄, in quantitative yield (Scheme 1).

2.2. 7-Hydroxy-4,6-dimethyl-3-nonanone (**6**) (*Serricornin*)

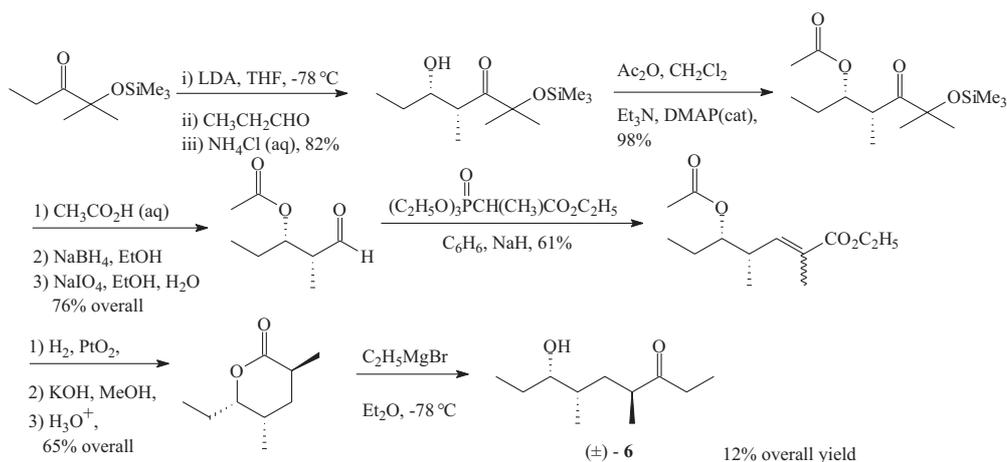
Serricornin is the sex pheromone produced by female cigarette beetle, *Lasioderma serricorne*.²¹⁻²⁴ Its absolute configuration was definitively established by Mori and co-workers^{25,26} as (4*S*, 6*S*, 7*S*)-**6**. Pilli and Murta^{27,28} described an efficient 12 step diastereoselective synthesis of (\pm)-**6**, in 12% overall yield (Scheme 2).

Ferreira *et al.* described a formal and enantioselective synthesis of (4*S*,6*S*,7*S*)-(-)-*serricornin* (**6**).²⁹ The (4*S*,5*S*)-4-methyl-5-ethyl- δ -valerolactone was synthesized with a high degree of enantioselectivity (> 99% *e.e.*), starting from (*R*)-(+)-(*E*)-1-propenyl-*p*-tolylsulfoxide, having the enantioselective Marino's lactonization as the key step (Scheme 3).

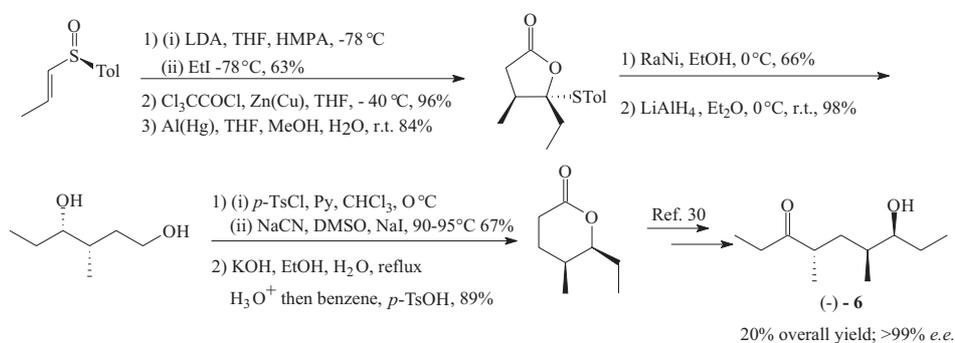
Two other approaches to the synthesis of (-)-**6** were also reported by Pilli and co-workers. In the first³¹ the oxazolidinone **A** was straightforwardly converted to the



Scheme 1.



Scheme 2.



Scheme 3.

homochiral lactone **B** in 6 steps, a known³² precursor of (-)-**6** (Scheme 4). In the second method,³³ a short preparation of enantiomerically enriched (80% *e.e.*) (-)-**6** was developed in 8 steps and 13% overall yield, from methyl (*R*)-3-hydroxypentanoate readily prepared by baker's yeast reduction of methyl 3-oxopentanoate in the presence of allyl alcohol as enzyme inhibitor (Scheme 5).

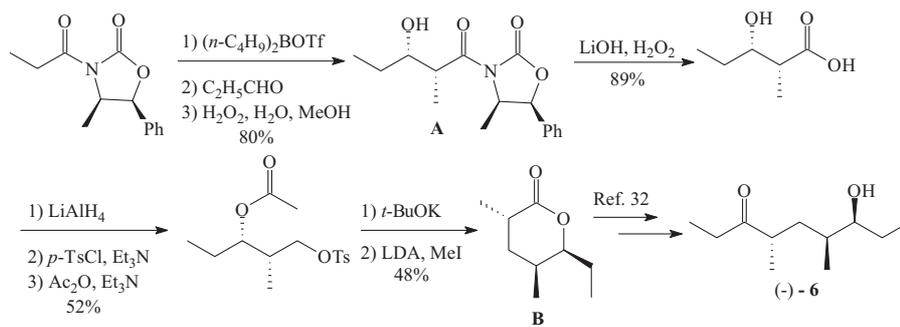
2.3. 1,7-Dimethylnonyl propanoate (**7**)

The sex pheromone emitted by female western corn rootworms, *Diabrotica virgifera virgifera*, was isolated and identified as 1,7-dimethylnonyl propanoate (**7**).³⁴ This compound is also attractive to several *Diabrotica* species.^{35,36}

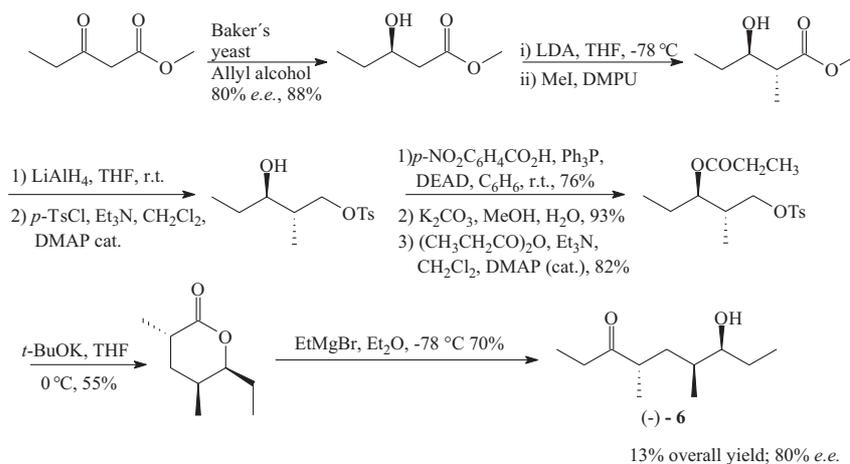
Males of *D. virgifera virgifera* and *D. virgifera zea* responded to (2*R*,8*R*)- and (2*S*,8*R*)-**7**, while *D. porracea* responded exclusively to (2*S*,8*R*)-**7**. Only the (2*R*,8*R*)-**7** was attractive to the northern corn rootworm, *D. barberi*. The synthesis of (2*S*,8*S*)- and (2*S*,8*R*)-**7** was described by Ferreira and Simonelli,³⁷ employing (*S*)-4-iodo-2-butanol **A** as a key intermediate. The synthesis was accomplished using remote stereochemical relationships between carbons 3 and 9 of the 3,9-dimethyl decanolides **B** and **C** (Scheme 6).

2.4. 5-Hydroxy-4-methyl-3-heptanone (**8**) (*Sitophilure*)

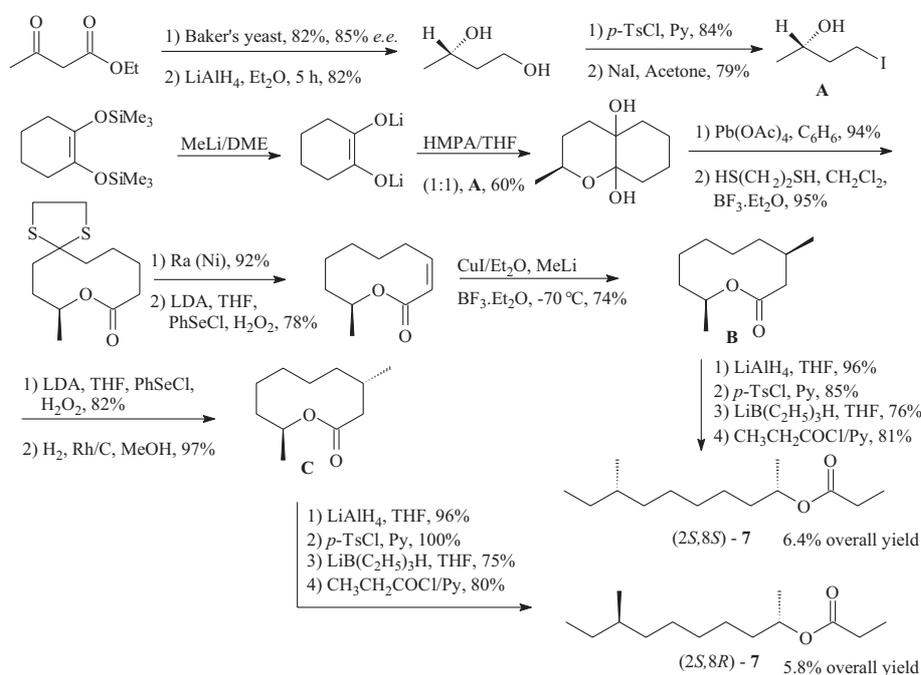
In 1984, Phillips and co-workers^{38,39} identified the male-produced aggregation pheromone of the rice weevil,



Scheme 4.



Scheme 5.



Scheme 6.

Sitophilus oryzae, and of the maize weevil, *Sitophilus zeamais*, as 5-hydroxy-4-methyl-3-heptanone (**8**) and named this new compound as sitophilure. The syntheses of the four possible stereoisomers of **8**, followed by laboratory bioassays, revealed the (4*S*,5*R*)-**8** as the active isomer.^{40,41}

Pilli *et al.*⁴² described the synthesis of racemic **8** employing the addition of the lithium enolate of 2-methyl-2-trimethylsilyloxy-3-pentanone to propionaldehyde, followed by ethyllithium addition and oxidative cleavage with periodic acid (16.5% overall yield). In the same work, the addition of the boron enolate of 3-pentanone to propionaldehyde, followed by oxidative treatment, afforded a 9:1 mixture of (4*SR*, 5*RS*)- and (4*SR*, 5*SR*)-**8**, in 43% overall yield (Scheme 7).

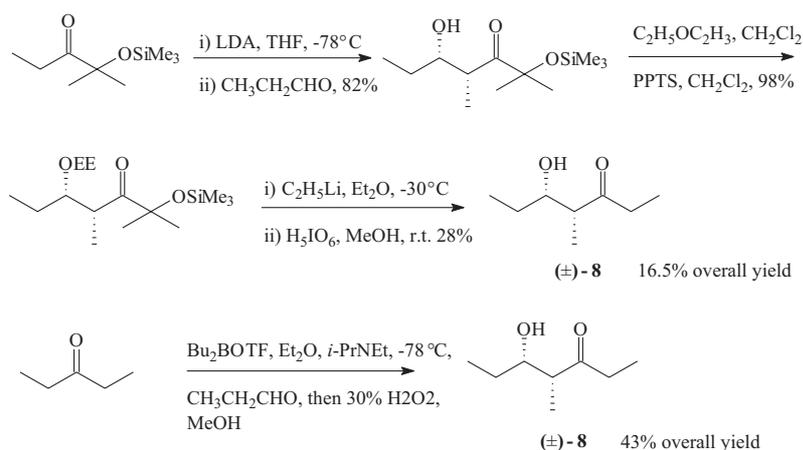
Pilli and Riatto⁴³ described later an asymmetric synthesis of (+)-sitophilure (**8**). The synthesis was carried

out in 12 steps, in 18% overall yield and 82% enantiomeric excess, with the enzymatic reduction of methyl 3-oxopentanoate with *S. cerevisiae* in the presence of ethyl chloroacetate being used to generate the key chiral synthon (Scheme 8).

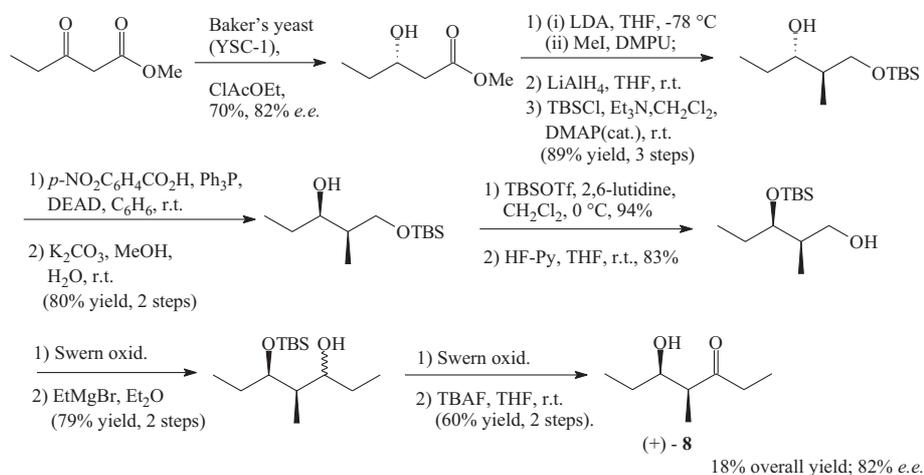
2.5. 3,5-Dimethyl-6-(1'-methylbutyl)-tetrahydro-2H-pyran-2-one (**9**) (Invictolide)

Invictolide is a component of the queen recognition pheromone of the fire ant *Solenopsis invicta*^{44,45} The absolute configuration of the natural product was established as (3*R*,5*R*,6*S*,1'*R*)-**9**, after the development of the synthesis by Mori and Nakazono.⁴⁶

A stereoselective total synthesis of (±)-invictolide (**9**) was described by Pilli and Murta.⁴⁷ The TiCl₄-



Scheme 7.



Scheme 8.

mediated addition of silyl ketene thioacetal to (±)-3-(benzyloxy)-2-methylpropionaldehyde afforded exclusively a thioester, which was straightforwardly converted to diol **A** (ca. 31% yield). The same diol was also prepared after LiAlH_4 reduction of the major aldol formed in the condensation between the lithium enolate of 2,6-di-*tert*-butyl-4-methylphenyl propanoate and (±)-2-methylvaleraldehyde. Intramolecular alkylation (*t*-BuOK, THF) of **B** or **C** gave a 40:60 mixture of (±)-**9** and its C(3) epimer (10 steps, 8% overall yield). Catalytic hydrogenation of unsaturated lactone **D** afforded (±)-**9** in 80% yield (8 steps, 14% overall yield). (Scheme 9).

2.6. (*E*)-6-Nonen-1-ol (**10**) and methyl (*E*)-6-nonenolate (**11**)

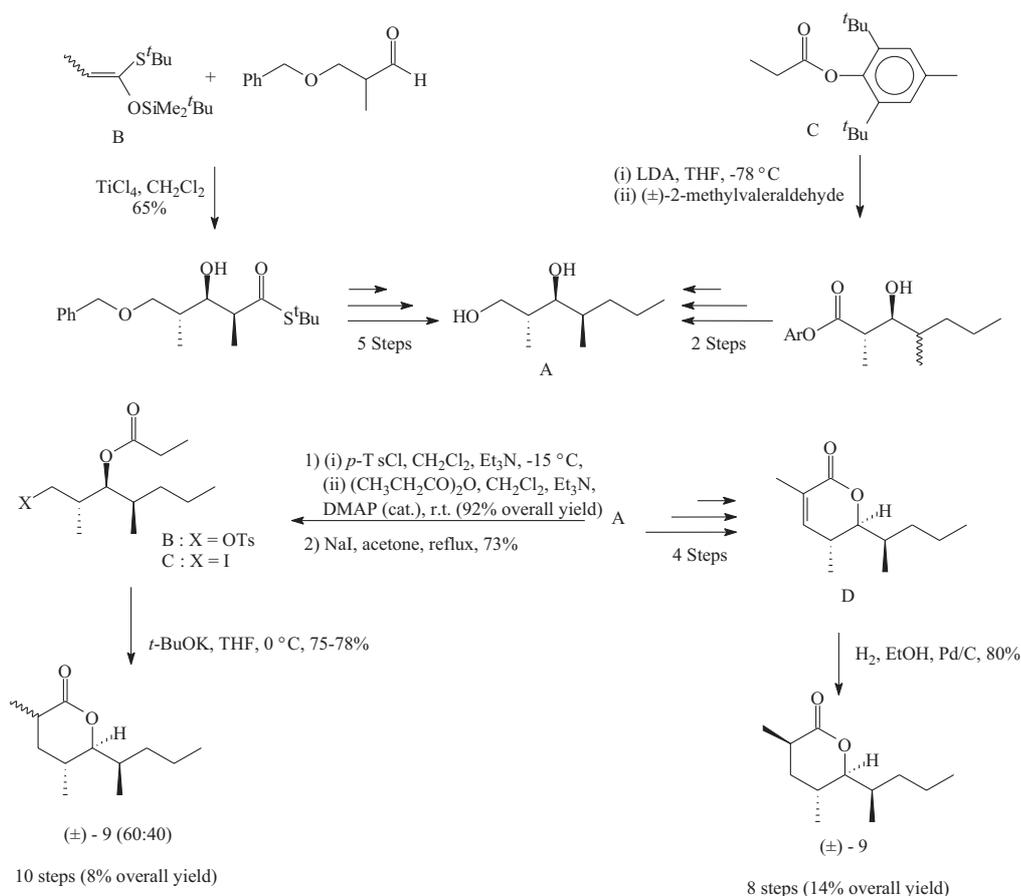
Mahajan and Tresvenzol⁴⁸ have prepared (*E*)-6-nonen-1-ol (**10**) and methyl (*E*)-6-nonenolate (**11**), two components of the sex pheromone of the Mediterranean fruit fly, *Ceratitis capitata*⁵⁰, starting from cyclohexanone (Scheme 10).

2.7. (*Z*)-4-(1', 5'-dimethyl 1', 4'-hexadienyl)-1, 2-epoxy-1-methylcyclohexane (**12**)

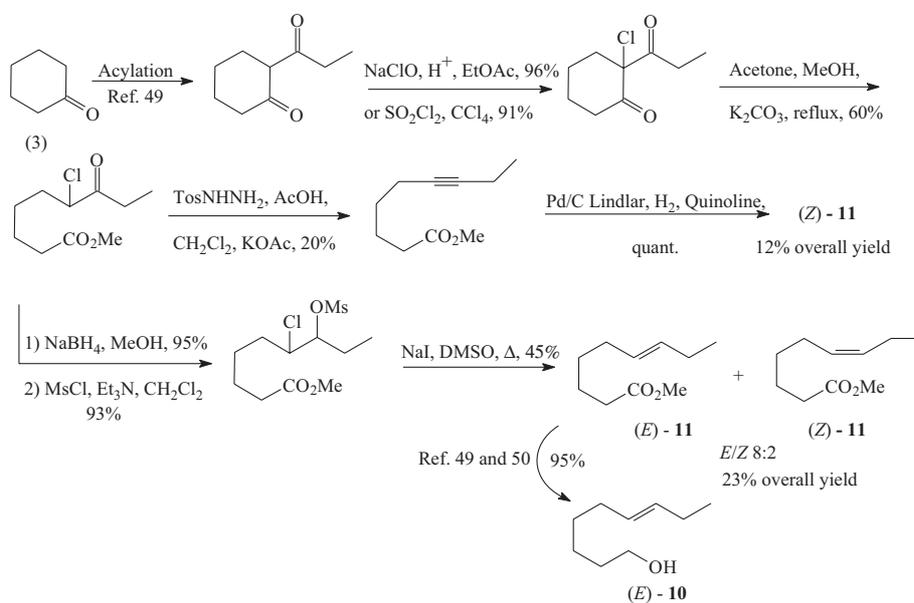
Compound **12** is the male-produced sex pheromone of the green stink bug, *Nezara viridula*,⁵¹ an important pest of several agricultural crops that is distributed throughout many parts of the world.⁵² The Brazilian population of *N. viridula* employs (*Z*)-(1*S*,2*R*,4*S*)-**12** as its pheromone.⁵³ Baptistella and Aleixo⁵⁴ described the synthesis of pheromone **12** by a convergent stereocontrolled sequence, using (*S*)-(-)-perillyl alcohol as starting material (18% overall yield, 99% *e.e.*) (Scheme 11).

2.8. (*Z*)-9-Tricosene (**13**)

Carlson and co-workers described the identification of the sex pheromone produced by female house fly, *Musca domestica* as (*Z*)-9-tricosene (**13**).⁵⁵ Marques *et al.* reported the synthesis of **13** employing a Kolbe electrolysis of the oleic and heptanoic acids, in MeOH/MeONa in 28% overall yield (Scheme 12).⁵⁶



Scheme 9.

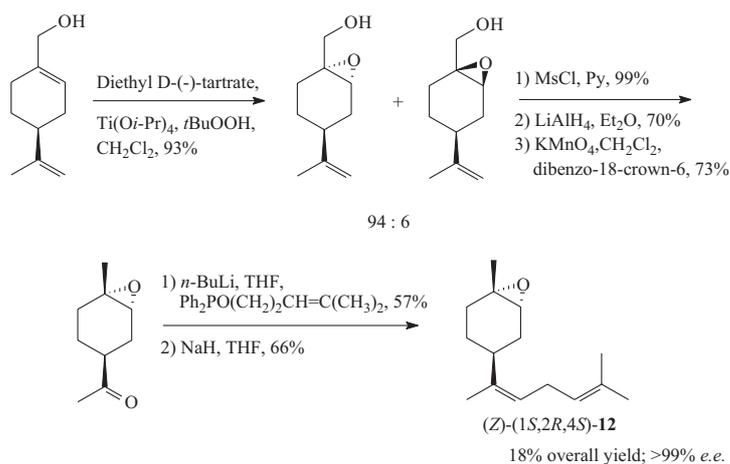


Scheme 10.

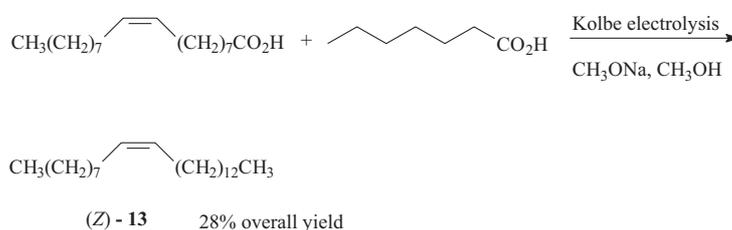
2.9. *cis*-2-Isopropenyl-1-methylcyclobutaneethanol (**14**) (*Grandisol*)

Grandisol (14) is the major component of the male-produced pheromone of the cotton boll weevil,

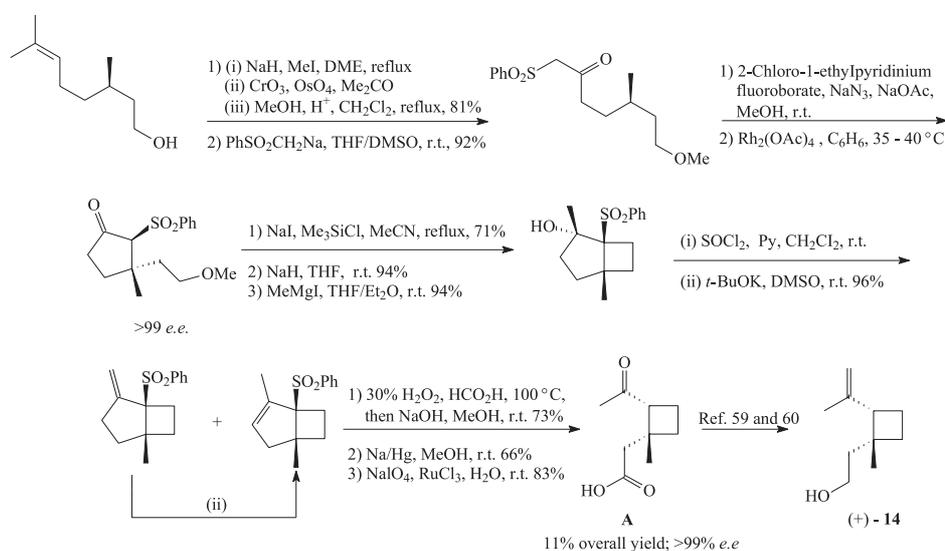
Anthonomus grandis.¹⁹ The alcohol and its corresponding aldehyde, grandisal, were also found in the pheromonal secretion of several other beetles.⁵⁷ The potential use of this pheromone in traps for monitoring crop infestation in integrated pest management prompted research groups



Scheme 11.



Scheme 12.



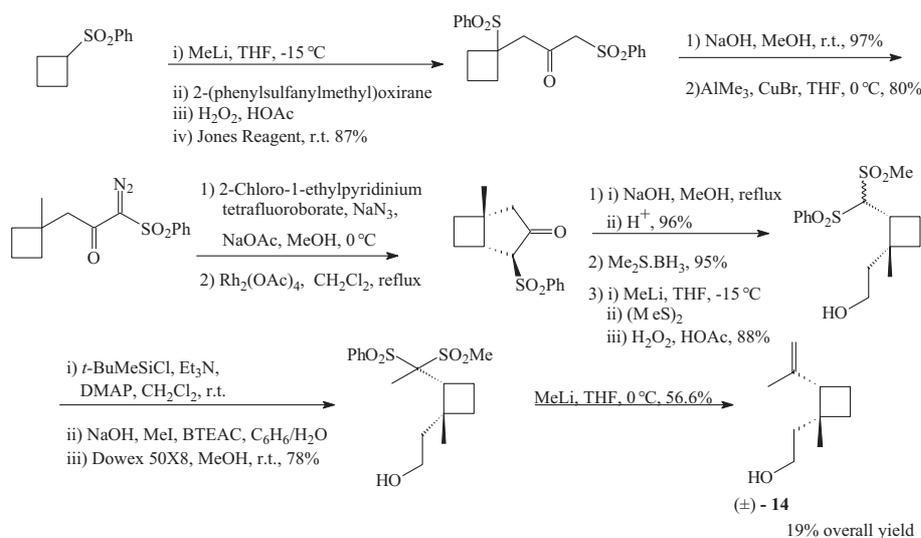
Scheme 13.

world wide to search for an efficient preparation of the more active (+)-enantiomer.

Monteiro and Zukerman-Schpector⁵⁸ reported a 10 steps synthesis of (1*S*,2*R*)-2-acetyl-1-methylcyclobutaneacetic acid **A** (11% overall yield, > 99% e.e.), in which the key step was a rhodium catalyzed intramolecular carbenoid cyclization of an α -diazo- β -ketosulfone, readily available from (+)-citronellol. Because **A** has already been converted into

(+)-grandisol (**14**),^{59,60} the described preparation constitutes a formal synthesis of the optically active pheromone (Scheme 13).

Monteiro and Stefani⁶¹ described a stereoselective synthesis of (\pm)-grandisol (**14**) in 19% overall yield, starting with a simple cyclobutyl derivative to which the methyl group and the 1,2-*cis* disposed side chains were appended through a remote alkylation protocol (Scheme 14).



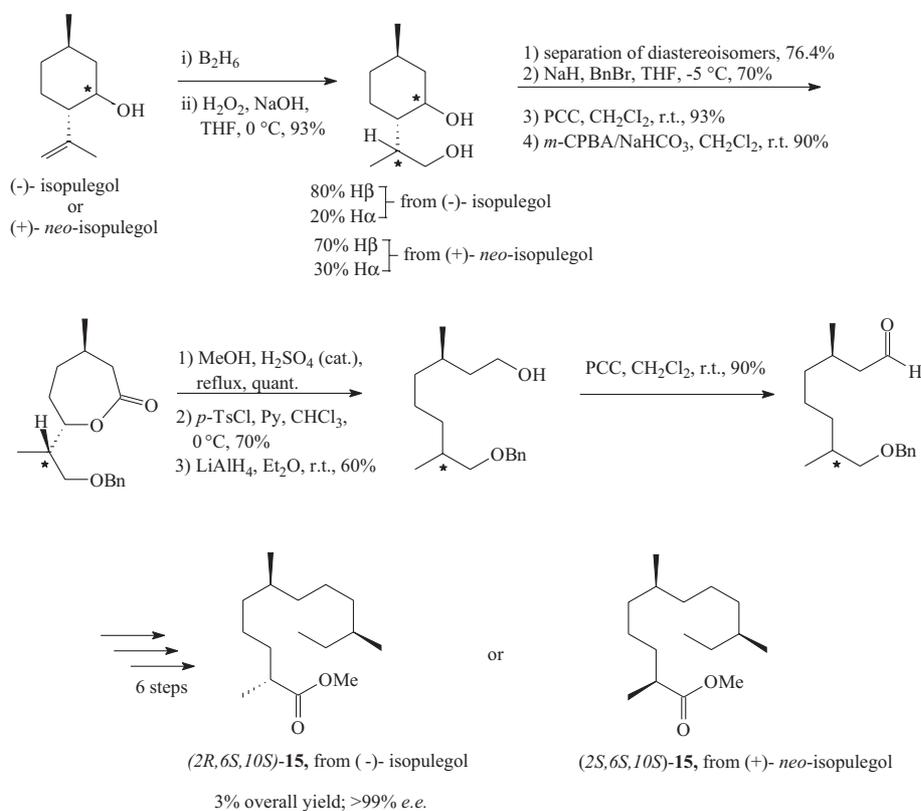
Scheme 14.

2.10. Methyl 2,6,10-trimethyldodecanoate (**15**) and methyl 2,6,10-trimethyltridecanoate (**16**)

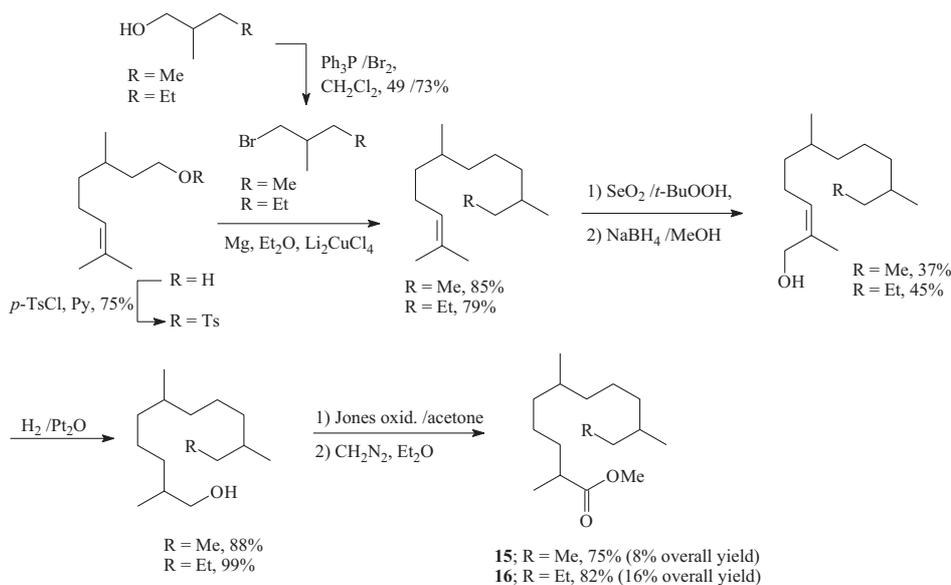
In 1994, Aldrich and co-workers identified methyl 2,6,10-trimethyldodecanoate (**15**) and methyl 2,6,10-trimethyltridecanoate (**16**) as components of the male-produced sex pheromones of the stink bugs, *Euschistus heros* and *Euschistus obscurus*.^{62,63} The same compounds were later found in headspace volatiles from Brazilian

male bug, *Piezodorus guildinii*, but the biological roles of these compounds in the species have not been delineated.^{64,65} A stereospecific synthesis of the eight stereoisomers of **16** was developed by Mori and Murata,⁶⁶ but the absolute configuration of this insect-produced compound was never reported.

Ferreira and Zarbin⁶⁷ described enantioselective syntheses of the stereoisomers (2*R*,6*S*,10*S*)- and (2*S*,6*S*,10*S*)-**15**, out of eight possible, employing the



Scheme 15.



Scheme 16.

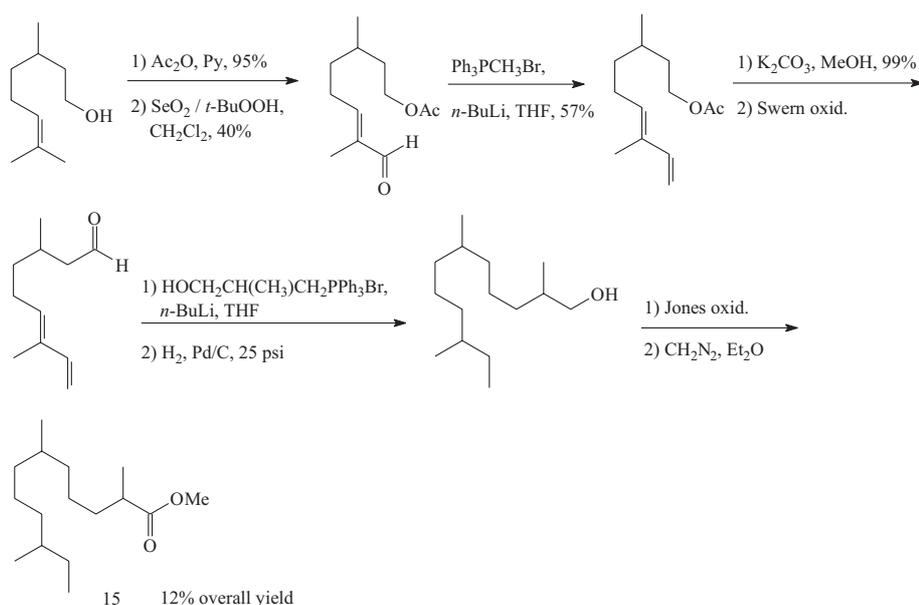
stereoselective hydroboration of (-)-isopulegol and (+)-*neo*-isopulegol as the key reaction, and incorporating a third chiral synthon, (*S*)-(+)-1-bromo-2-methylbutane (3% overall yield, >99% *e.e.*) (Scheme 15). In theory, this synthesis can be modified to produce any of the other isomers by an appropriate combination of the other enantiomers of these three synthons.⁶⁸

A nonselective synthesis of **15** and **16** described by Zarbin *et al.*⁶⁹ involved chain extension of the tosylate of (\pm)-citronellol with 2-methylpentyl or 2-methylbutyl magnesium bromide to give the appropriate carbon skeleton. Allylic oxidation with SeO_2 , hydrogenation and adjustment of functional groups completed the synthesis

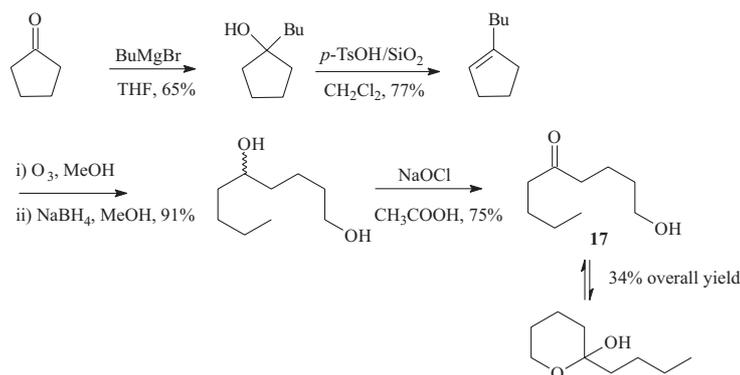
(8 and 16% overall yield, respectively) (Scheme 16). Zarbin *et al.*⁷⁰ published another synthesis based on citronellol, reversing the modification of the ends of the chain. After an allylic oxidation and two Wittig reactions, the pheromone **15** (12% overall yield) was obtained in good yields (Scheme 17).

2.11. 1-Hydroxy-5-nonanone (**17**)

The hydroxy-ketone **17** was identified as a minor component of the rectal glandular extract and volatile emission of males of the fruit fly *Bactrocera cacuminatus*.⁷¹ Ferreira and Zarbin⁷² described an expeditious synthesis of



Scheme 17.



Scheme 18.

17 in four steps and 34% overall yield, starting from cyclopentanone. The final product was obtained in equilibrium with the respective hemiacetal (Scheme 18).

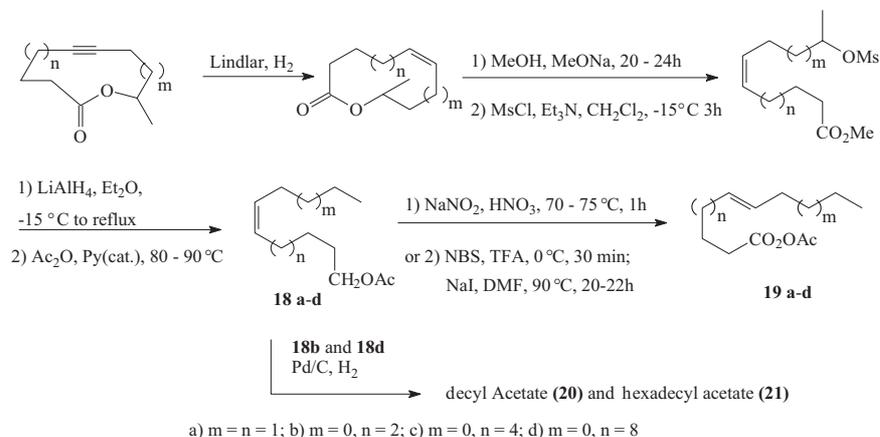
2.12. (*Z*)-5-Decenyl acetate (**18a**), (*Z*)-8-dodecyl acetate (**18c**), (*E*)-8-dodecyl acetate (**19c**), decyl acetate (**20**), and hexadecyl acetate (**21**)

Mahajan and Resck⁷³ described the synthesis of several acyclic insect pheromones, along with their geometric and/or positional isomers, starting from *Z*-lactones, which are easily available from the corresponding acetylenic lactones, prepared from cycloalkanones. The *Z* to *E*

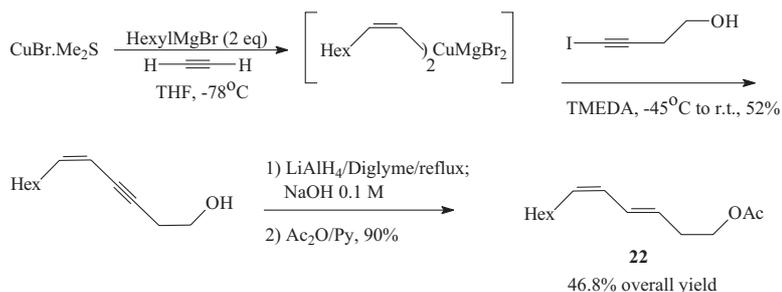
isomerization of alkenyl acetates **18a-d** to **19a-d** was carried out both by a catalytic technique (NaNO_2 , HNO_3 , Δ) and chemical inversion procedure (NBS, TFA; NaI, DMF, Δ). Decyl acetate (**20**) and hexadecyl acetate (**21**), pheromone components of the turnip moth *Agrotis segetum* and the male butterfly *Lycorea ceres ceres*, respectively, were obtained by the catalytic hydrogenation of the corresponding *Z*-alkenyl acetates (Scheme 19).

2.13. (*3E,5Z*)-3,5-Dodecadienyl acetate (**22**)

(*3E,5Z*)-3,5-Dodecadienyl acetate (**22**) was identified by Unelius *et al.* as the sex pheromone of the leafroller



Scheme 19.



Scheme 20.

moth *Bonagota cranaodes*, an economically important insect pest of apples in Southern Brazil.⁷⁴ Simonelli *et al.*⁷⁵ described a stereoselective synthesis of this compound using methodology based on the coupling of a *Z*-alkenyl cuprate with 1-iodo-2-butyn-4-ol (46.8% overall yield)(Scheme 20).

2.14. 4,8-Dimethyldecanal (**23**)

In 1980, Suzuki identified 4,8-dimethyldecanal (**23**) as the aggregation pheromone of the red flour beetle, *Tribolium castaneum*, and of the confused beetle, *Tribolium confusum*, notorious pests of various stored foodstuffs.^{76,77} Mori and co-workers^{78,79} established the absolute configuration of the pheromone as (4*R*,8*R*)-**23**. Suzuki *et al.*⁸⁰ later found that a mixture of the isomers (4*R*,8*R*)- and (4*R*,8*S*)-, in a ratio of 8:2, was about 10 times more active than (4*R*,8*R*)-**23** alone.

Zarbin *et al.*^{81,82} developed a stereospecific synthesis of all four possible isomers of **23**. The synthesis was achieved by connecting the chiral building blocks (*R*)-2-methyl-1-bromobutane, (*R*)-**A**, (derived from methyl (*S*)-3-hydroxy-2-methylpropionate),^{83,84} and (*S*)-2-methyl-1-bromobutane, (*S*)-**A**, commercially available, with (*R*)- and/or (*S*)-citronellol derivatives **B** (Scheme 21).

2.15. 3,5,6-Trimethyltetrahydropyran-2*H*-one (**24**)

Brown and Moore⁸⁵ reported the identification of δ -lactone **24** in the extract of male heads of *Calomyrmex* *sp.* ants, that was presumed to function as a sex pheromone. Pilli *et al.*⁸⁶ described the synthesis of four racemates of lactone **24**. The *anti*-hydroxy ester **A** was

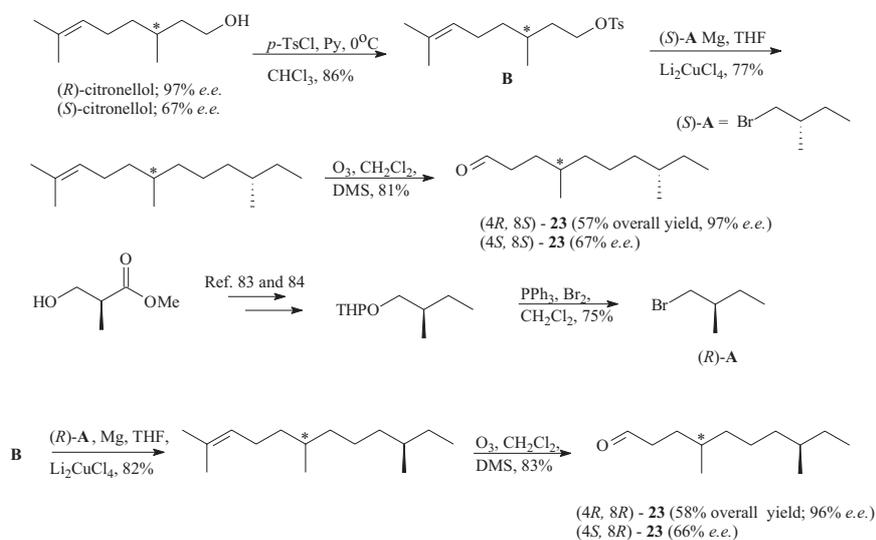
produced through the stereoselective aldol condensation of the *E*-lithium enolate derived from 2,6-di-*tert*-butyl-4-methylphenyl propionate and acetaldehyde. Compound **A** was converted into tosylate **B**, which was employed as common intermediate in two different routes of the synthesis of δ -lactones **24a** and **24b** (Scheme 22). Similarly, a mixture of δ -lactones **24c** and **24d** was prepared starting with the stereoselective aldol condensation of acetaldehyde and the lithium enolate of the *syn*-selective silyloxyketone **C** (Scheme 23). Based on the comparison of mass spectra and gas chromatographic properties of lactones **24a-24d** with those reported in the literature for the natural product,⁸⁵ the relative configuration was assigned as (3*SR*,5*RS*,6*SR*)-**24**.

2.16. (*E*)-4-Oxo-2-hexenal (**25**)

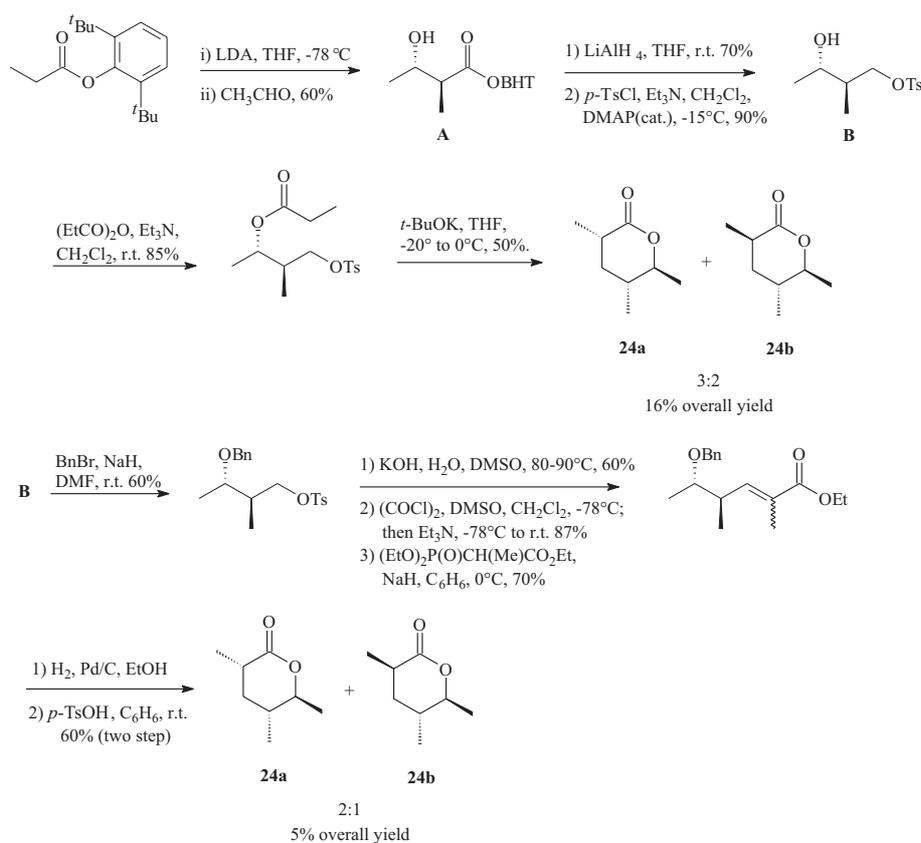
In 2000, Zarbin *et al.*⁸⁷ described the identification of (*E*)-4-oxo-2-hexenal (**25**) as component of the alarm pheromone system of *Piezodorus guildinii*, a member of the stinkbug complex in soybeans that is an economically important pest in Brazil.⁸⁸ The same compound has been found in secretions from many other bug species.⁸⁹ To confirm this identification, the authors synthesized (*E*)-**25** in five steps and 22% overall yield, starting from (*E*)-1,4-butanediol⁸⁷ (Scheme 24).

2.17. (2*R*,3*R*,7*S*)-3,7 -Dimethylpentadecan-2-ol (**26**) (Diprionol)

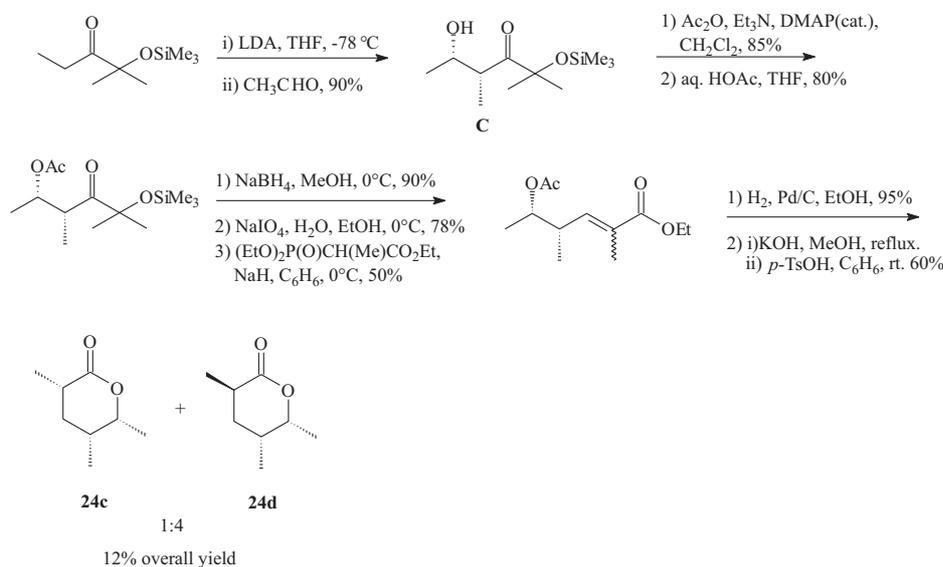
The pine sawfly, *Neodiprion sertifer*, is a widespread and economically important forest insect in North



Scheme 21.



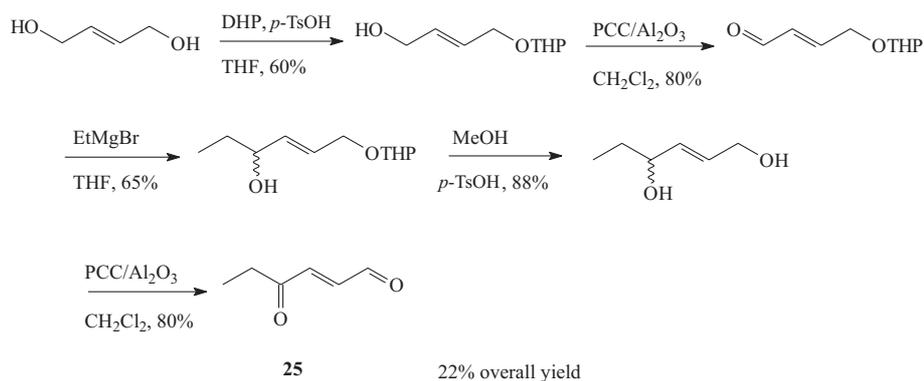
Scheme 22.



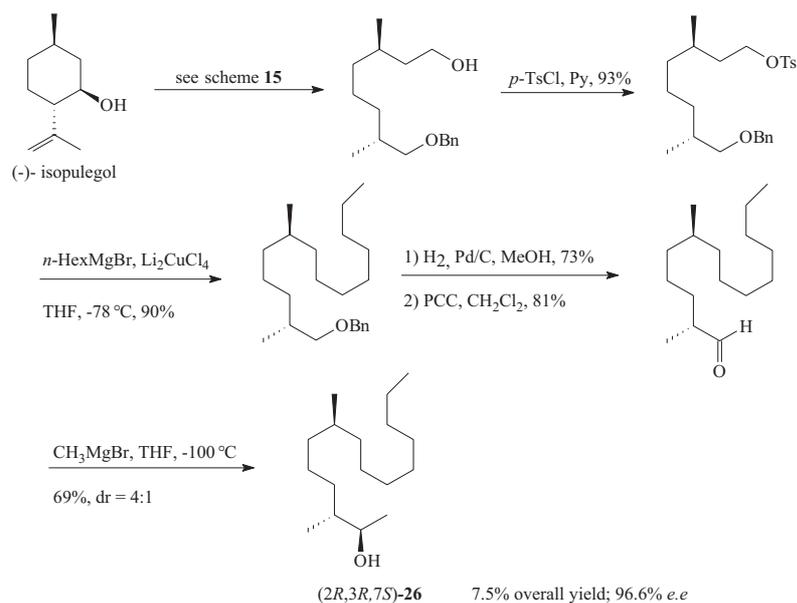
Scheme 23.

America, Japan, and Europe.⁹⁰ Anderbrandt *et al.*⁹¹ have investigated the geographic pattern of male sawfly responses at eight field sites ranging from Japan in the east to Canada in the west. It has been demonstrated that the main sex pheromone components of this species are

the acetate or propionate of 3,7-dimethylpentadecan-2-ol (diprionol). Moreira and Corrêa⁹² described an enantioselective synthesis (96.6% *e.e.*) of (2*R*,3*R*,7*S*)-diprionol (**26**) in 12 steps and 7.5% overall yield, starting from commercial (-)-isopulegol⁶⁷ (Scheme 25).



Scheme 24.



Scheme 25.

2.18. 1-Ethylpropyl 2-methyl-3-hydroxypentanoate (**27**) (*Sitophilate*)

The male-produced aggregation pheromone of the granary weevil, *Sitophilus granarius*, was identified by Phillips *et al.*⁹³ as 1-ethylpropyl 2-methyl-3-hydroxypentanoate (**27**), *sitophilate*. Bioassays employing all of the synthetic isomers revealed (*2S,3R*)-**27** to be the natural pheromone.⁹⁴

Mateus *et al.*⁹⁵ described a diastereoselective synthesis of racemic **27**, with a key step being a diastereoselective heterogeneous catalytic hydrogenation reaction of Baylis-Hillman adducts originating from aliphatic aldehydes (Scheme 26).

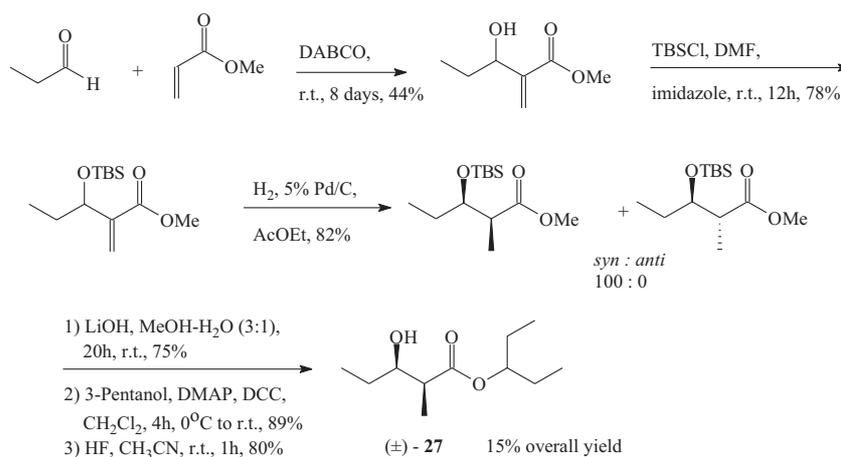
2.19. *N*-2'-Methylbutyl-2-methylbutylamide (**28**)

The four stereoisomers of *N*-2'-methylbutyl-2-methylbutylamide (**28**), the sex pheromone of the longhorn

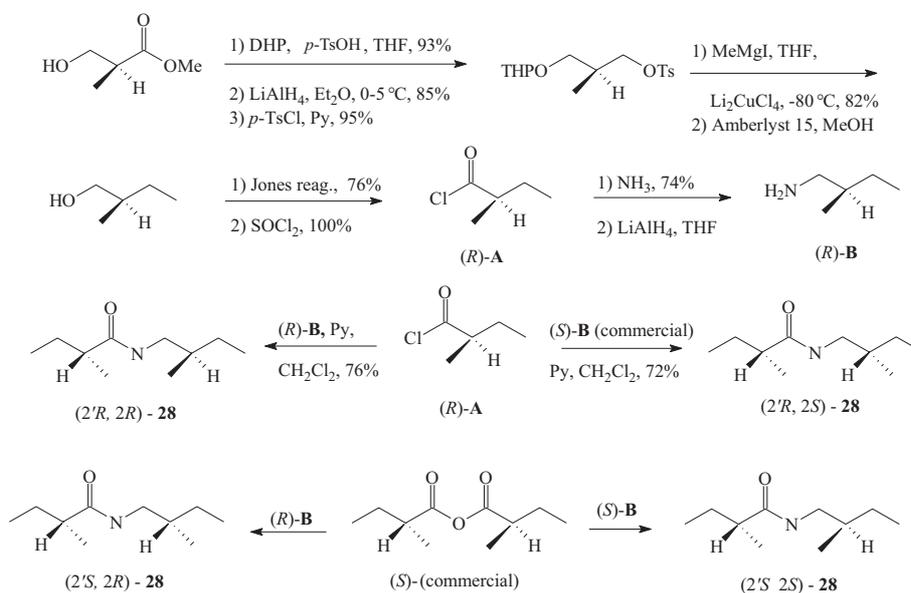
beetle *Migdolus fryanus*, an economically important pest of sugarcane in South America,⁹⁶ were synthesized by Santangelo *et al.*⁸⁴ The key intermediate 2-methylbutan-1-ol is commercially available only in its (*S*)-(-) form. The (*R*)-(+)-enantiomer was obtained optically pure from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate, in five steps (Scheme 27).

2.20. (1*S*,5*R*,7*S*)-5-Ethyl-7-methyl-6,8-dioxabicyclo[3.2.1]octane (**29**) (*exo*-Isobrevicomin) and (1*R*,5*S*,7*R*)-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane (**2**) (*exo*-Brevicomin)

(-)-*exo*-Isobrevicomin (**29**) and (+)-*exo*-brevicomin (**2**) are volatile substances produced by males of the beetles *Dendroctonus* spp., which infest pine trees found in the northern hemisphere, frequently causing the death of their host.⁹⁷⁻⁹⁹ The isolation and the first synthesis of (-)-**29**, and the respective hydroxylated derivatives, were reported in 1996 by Francke and co-workers.¹⁰⁰



Scheme 26.



Scheme 27.

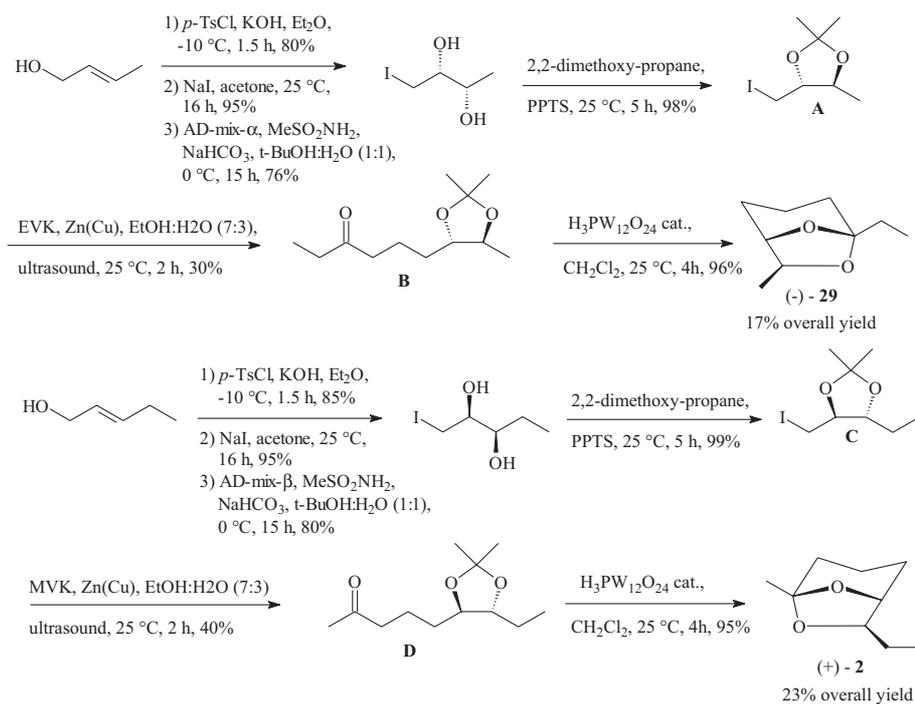
In order to obtain these aggregation pheromones, which present the 6,8-dioxabicyclo[3.2.1]octane structure, the synthetic strategies utilized by Resck and Sousa¹⁰¹ had as key steps the Sharpless asymmetric dihydroxylation and a conjugate addition reaction, promoted by Zn(Cu) couple in aqueous medium and accelerated by ultrasound. The conjugate addition of acetonides **A** and **C** to the unsaturated ketones, methyl vinyl ketone and ethyl vinyl ketone, respectively, furnished adducts **B** and **D**. The intramolecular catalyzed cyclization of compounds **B** and **D** with phosphotungstic acid (H₃PW₁₂O₄₀) produced *exo*-isobrevicomin **29** (17% overall yield) and *exo*-brevicomin **2** (23% overall yield) (Scheme 28).

2.21. 2-Methyl-4-octanol (**30**)

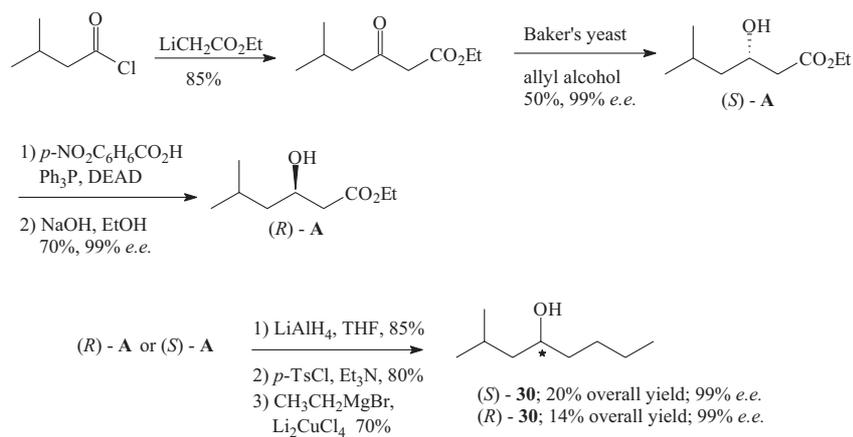
2-Methyl-4-octanol (**30**) has been identified as a component of the aggregation pheromones of several

curculionid species.¹⁰²⁻¹⁰⁴ Baraldi *et al.*¹⁰⁵ reported an enantioselective synthesis of (*R*)- and (*S*)-**30**. The (*S*)-isomer was efficiently prepared in five steps and 20% overall yield (99% *e.e.*), and its (*R*)-enantiomer in six steps and 14% overall yield (99% *e.e.*), both from commercial isovaleryl chloride. The key step of this synthetic route was the asymmetric reduction of ethyl 5-methyl-3-oxohexanoate with *Saccharomyces cerevisiae* to its corresponding (*S*)-alcohol **A** in high enantiomeric excess (Scheme 29).

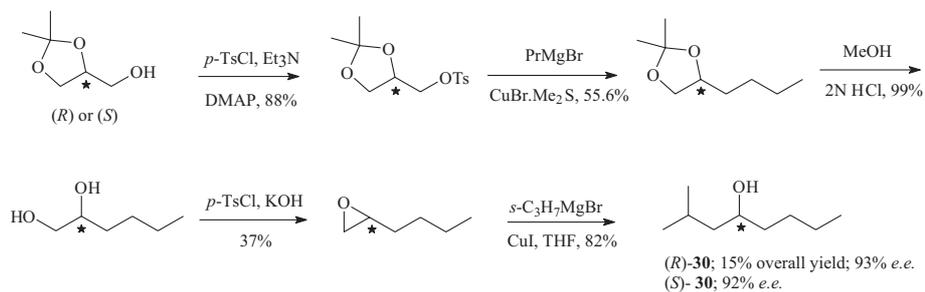
Recently, Zarbin *et al.*¹⁰⁶ identified alcohol **30** as a male-produced aggregation pheromone of the sugarcane weevil, *Sphenophorus levis*. The authors synthesized both enantiomers in five steps (15% overall yield) and 92% *e.e.* from commercially available (*R*)- and (*S*)-2,2-dimethyl-1,3-dioxolane-4-methanol as starting material. Enantiomeric resolution by gas chromatography with a chiral column demonstrated that the



Scheme 28.



Scheme 29.

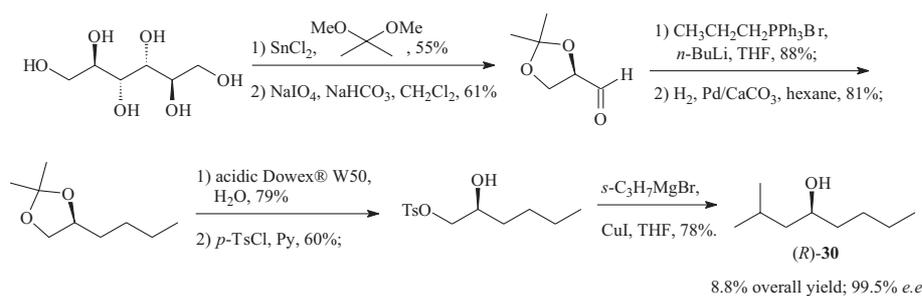


Scheme 30.

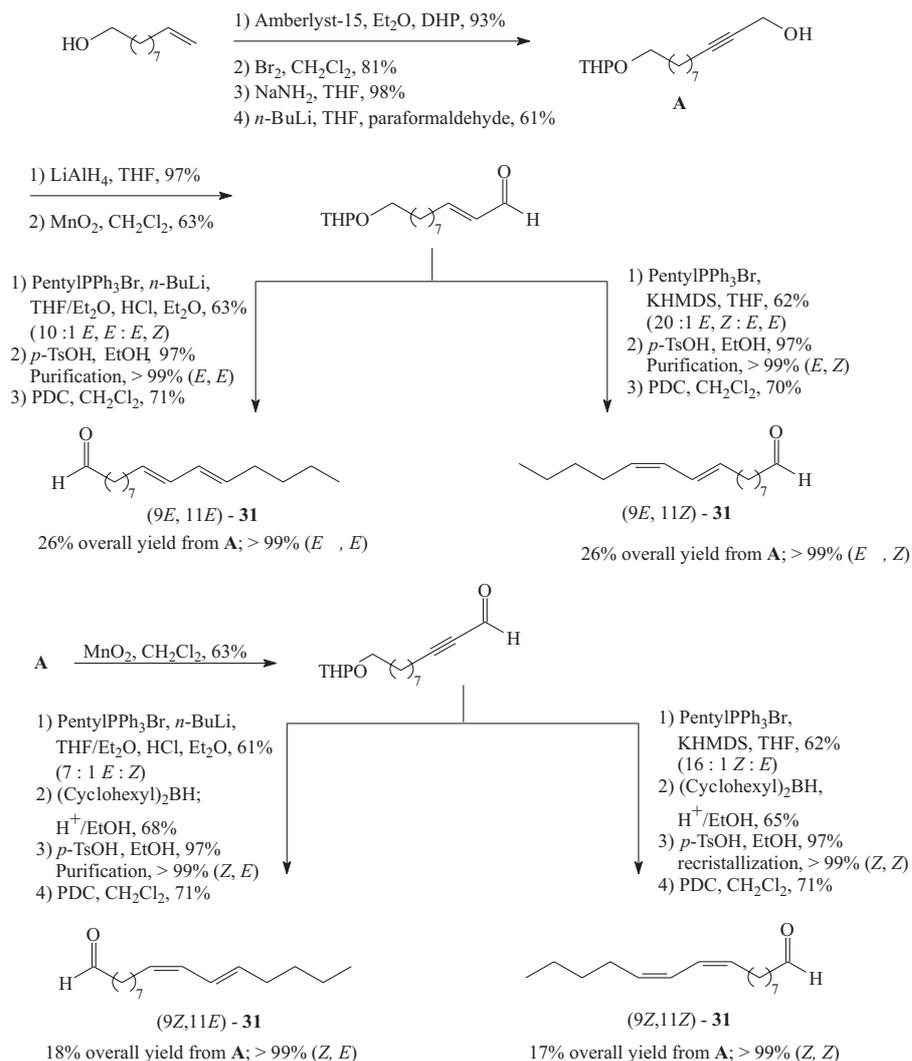
natural alcohol possessed the (*S*)-configuration (Scheme 30).

In order to establish the importance of the stereochemistry on the biological activity of this compound, Zarbin *et al.*¹⁰⁷ described a new and highly enantioselective approach to the synthesis of natural

(*S*)-30, starting from the easily available *D*-mannitol, in a route that employed the known (*R*)-glyceraldehyde acetone as key intermediate. The GC analysis of an acetyl derivative of the final product, using a chiral stationary phase column, revealed an enantiomeric excess higher than 99.5% (Scheme 31).



Scheme 31.



Scheme 32.

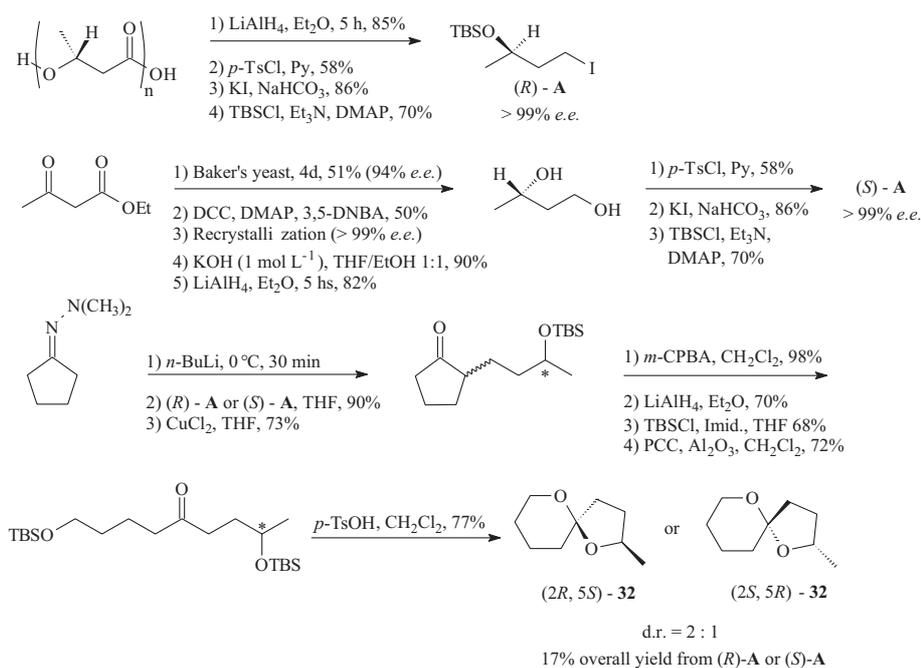
2.22. (*9Z*, *11E*)-9,11-Hexadecadienal (**31**)

(*9Z*, *11E*)-9,11-Hexadecadienal (**31**) is a component of the sex pheromone of the sugar cane borer, *Diatraea saccharalis*, an economically important pest distributed from Argentina to Cuba.¹⁰⁸⁻¹¹⁰ Santangelo *et al.*¹¹¹ reported the syntheses of all four possible isomers of **31** employing one starting material, 9-decen-1-ol, via

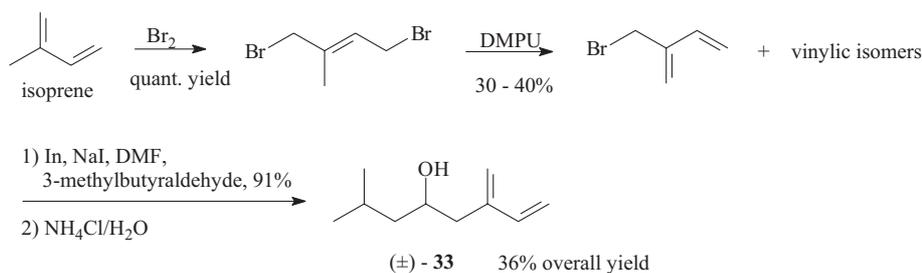
divergent synthetic routes (17-26% overall yield) (Scheme 32).

2.23. 2-Methyl-1,6-dioxaspiro[4.5]decane (**32**)

The spiroketal 2-methyl-1,6-dioxaspiro[4.5]decane (**32**) was identified by Francke *et al.*^{112,113} as a minor pheromone component of the common wasp, *Paravespula*



Scheme 33.



Scheme 34.

vulgaris. Zarbin *et al.*¹¹⁴ described a diastereoselective approach to (*2R*,*5S*)- and (*2S*,*5R*)-**32**. The route employed an alkylation reaction between the cyclopentanone *N,N*-dimethylhydrazone and the chiral iodides (*R*)- or (*S*)-**A**, controlling the stereocenter at C-2 of the molecules. The alkylated products were transformed into the 1,8-*O*-TBS-1,8-dihydroxy-5-nonanones in four steps, and a subsequent stereoselective spiroketalization in acidic media, afforded a diastereoisomeric mixture (1:2) of both isomers of **32** (Scheme 33).

2.24. 2-Methyl-6-methylene-7-octen-4-ol (**33**) (*Ipsenol*)

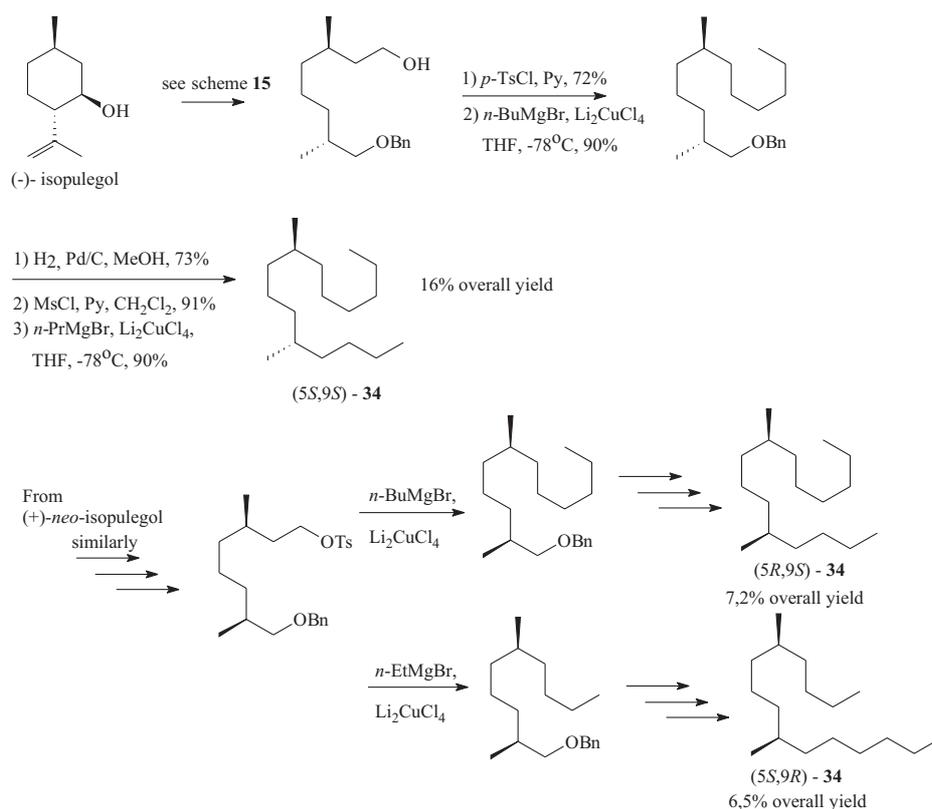
Ipsenol **33** was identified as an aggregation pheromone component of the bark beetle, *Ips paraconfusus*.¹¹⁵ Ceschi *et al.*¹¹⁶ described a short synthesis of (\pm)-*ipsenol* **33** employing a selective indium insertion on a mixture of 2-bromomethyl-1,3-butadiene and its vinylic isomers, in 36% overall yield (Scheme 33).

2.25. 5,9-Dimethylpentadecane (**34**)

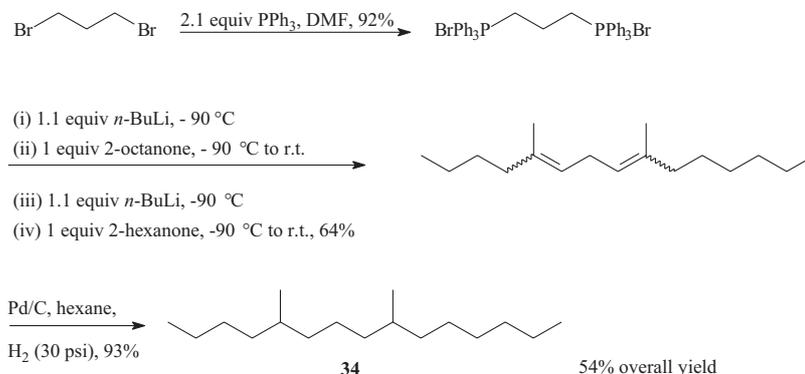
The coffee leaf miner, *Leucoptera coffeella*, is an economically important pest of coffee trees in Brazil. It has been demonstrated by Francke and co-workers¹¹⁷ that the main component of the female-produced sex pheromone of this species is 5,9-dimethylpentadecane (**34**), however, the stereochemistry of the natural pheromone remains unknown.

Moreira and Corrêa¹¹⁸ described an enantioselective synthesis of three stereoisomers of **34**, from commercial isopulegol and synthetic *neo*-isopulegol^{67,92} (Scheme 35).

Zarbin *et al.*¹¹⁹ described a direct synthesis of racemic **34** employing an unsymmetrical double Wittig olefination to build the carbon skeleton of the molecule as the key reaction. The bis-phosphonium salt, derived from 1,3-dibromopropane, was reacted sequentially in one pot with the ketones 2-octanone and 2-hexanone, affording the unsymmetrical diene. This was readily hydrogenated over Pd/C, furnishing a



Scheme 35.



Scheme 36.

mixture of all possible stereoisomers of pheromone **34** in 54% overall yield. (Scheme 36). Synthetic racemic **34** showed high biological activity when tested in field experiments.

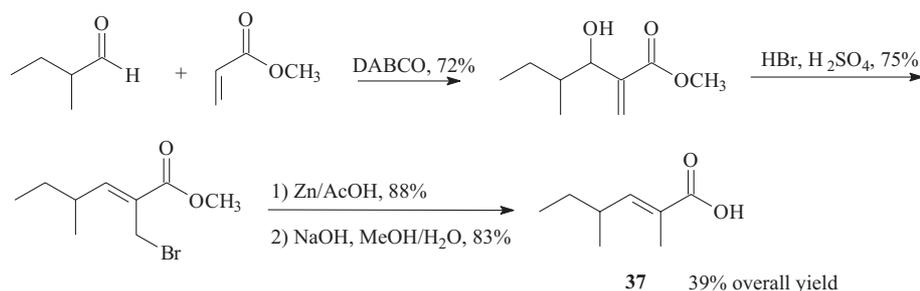
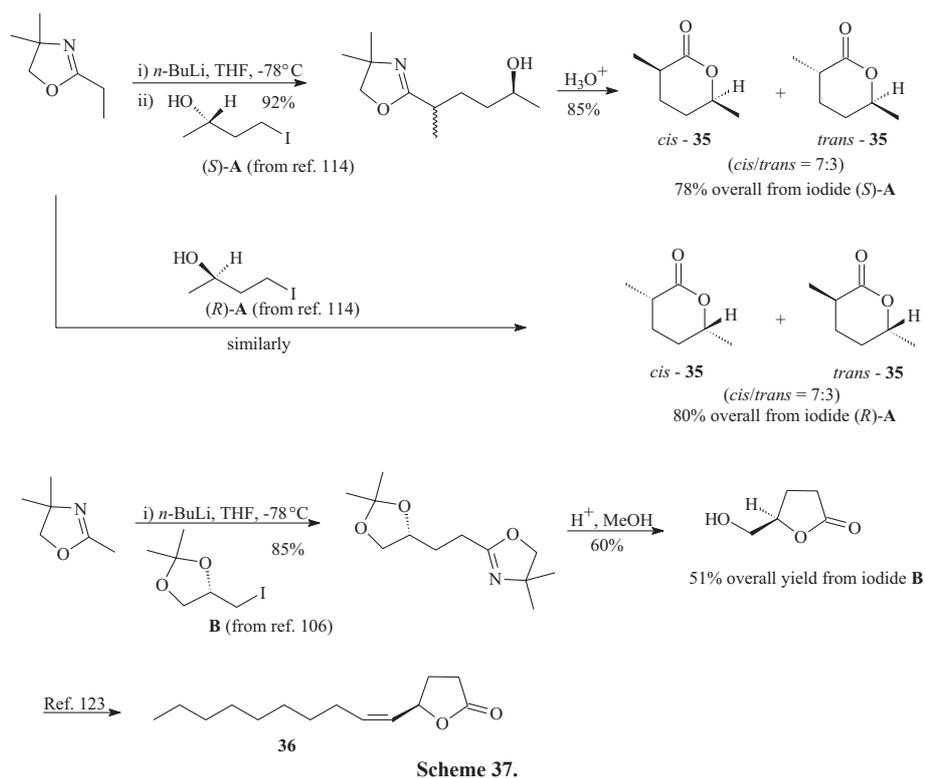
2.26. *cis*- and *trans*-2-Methyl-5-hexanolide (**35**) and (4*R*,5*Z*)-5-tetradecen-4-olide (**36**)

cis-2-Methyl-5-hexanolide (**35**) is a component of the pheromone blend of the carpenter bee, *Xylocopa hirtissima*,¹²⁰ while (4*R*,5*Z*)-5-tetradecen-4-olide (**36**) is the sex pheromone of the Japanese beetle, *Popillia japonica*.¹²¹ Zarbin *et al.*¹²² proposed a general approach to the synthesis of chiral pheromone lactones from readily available starting

materials derived from 2-oxazolines. As an application, the diastereoselective synthesis of *cis*- and *trans*-**35** and a formal synthesis of (4*R*,5*Z*)-**36** were described (Scheme 37).

2.27. (*E*)-2,4-Dimethyl-2-hexenoic acid (**37**)

(*E*)-2,4-Dimethyl-2-hexenoic acid (**37**) is a caste-specific substance present in the mandibular glands of male ants in the genus *Camponotus*.¹²⁴ Fernandes *et al.*¹²⁵ described a synthesis of **37** in 39% overall yield and high stereoselectivity by zinc-promoted reduction of 2-(bromomethyl) alkenoates derived from Baylis–Hillman adducts (Scheme 38).



2.28. (*Z*)-7,15-Hexadecadien-4-olide (**38**)

(*Z*)-7,15-Hexadecadien-4-olide (**38**) was described by Leal *et al.*¹²⁶ as the female sex pheromone of the yellowish elongate chafer, *Heptophylla picea*. Clososki *et al.*¹²⁷ described an enzymatic synthesis of (*R*)- and (*S*)-**38**. A known lipase-catalysed enantioselective lactonization in the key step afforded a common precursor for both enantiomers of the pheromone, in 92% *e.e.* [overall yield: 27% for (*S*)- and 18% for (*R*)-isomer] (Scheme 39).

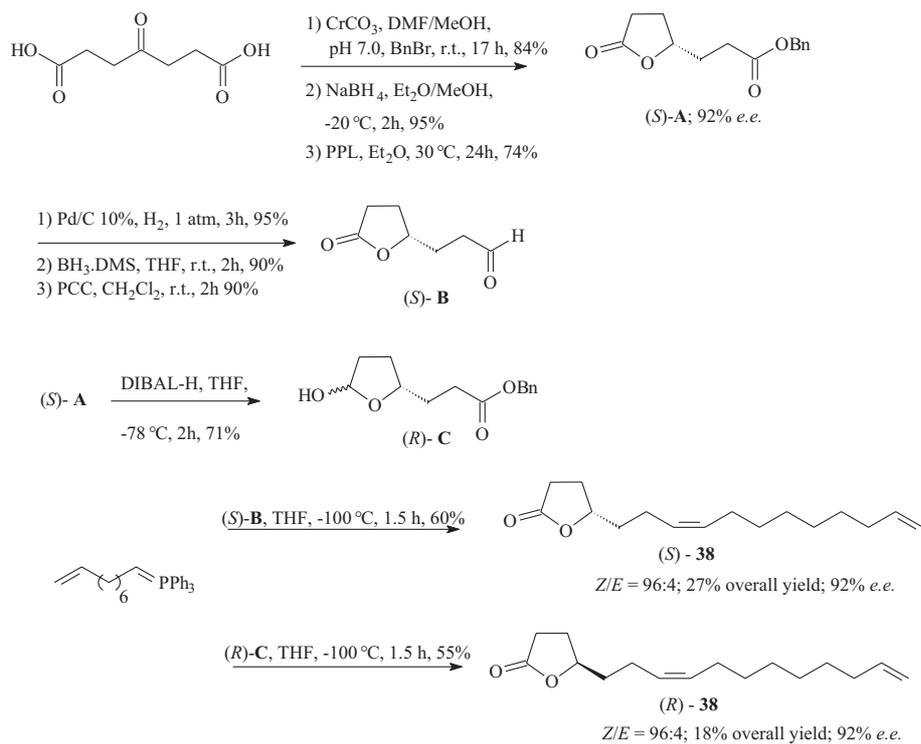
2.29. (3*Z*, 6*Z*, 8*E*)-Dodecatrien-1-ol (**39**)

The subterranean termite, *Heterotermes tenuis*, is a pest of great importance for the Brazilian economy as it causes serious damages in commercial plantations of *Eucalyptus* spp. and sugarcane.¹²⁸ (3*Z*,6*Z*,8*E*)-Dodecatrien-1-ol (**39**) has been identified as a pheromone of several species of

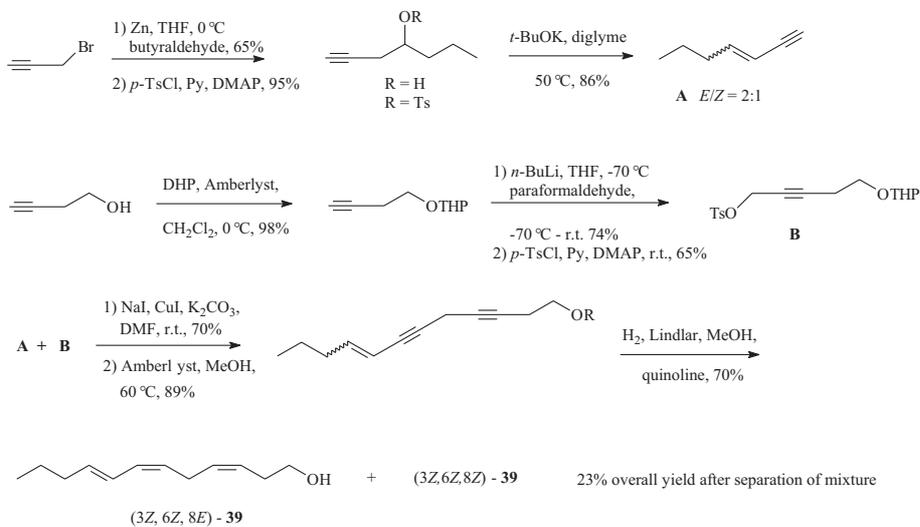
subterranean termites.^{129,130} Batista-Pereira *et al.*¹³¹ described the synthesis and electroantennographic (EAG) bioassays of **39** with *H. tenuis* antennae (Scheme 40).

2.30. 1,5-dimethyl-6,8-dioxabicyclo [3.2.1]octane (**40**) (*frontalin*)

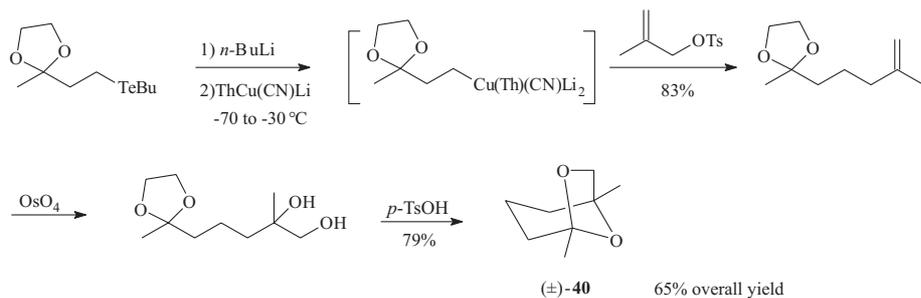
Frontalin (**40**), first isolated by Kinzer,¹³² is a component of the aggregation pheromone of the southern pine beetle, *Dendroctonus frontalis* Zimmerman, and western pine beetle, *Dendroctonus brevicomis* Le Conte. Through unambiguous syntheses of both enantiomers and biological testing, Mori^{133,134} has shown that the absolute configuration of the biologically active compound is (1*S*,5*R*)-**40**. dos Santos *et al.*¹³⁵ described the synthesis of (±)-frontalin (**40**) in 65% overall yield, employing an organocuprate generated by tellurium/lithium exchange in the key step (Scheme 41).



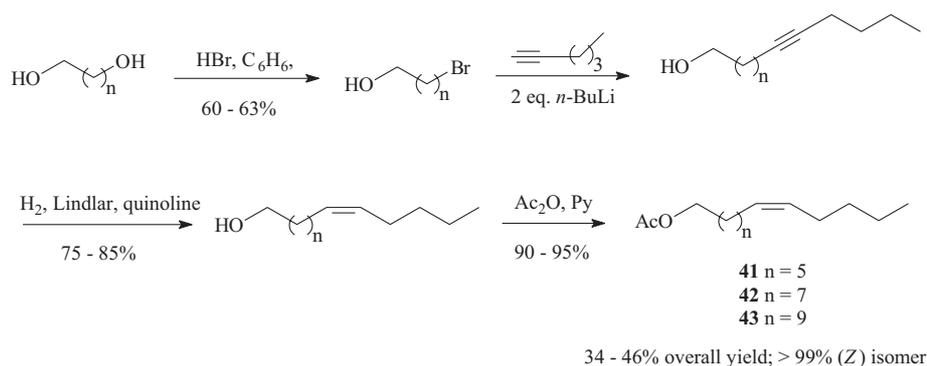
Scheme 39.



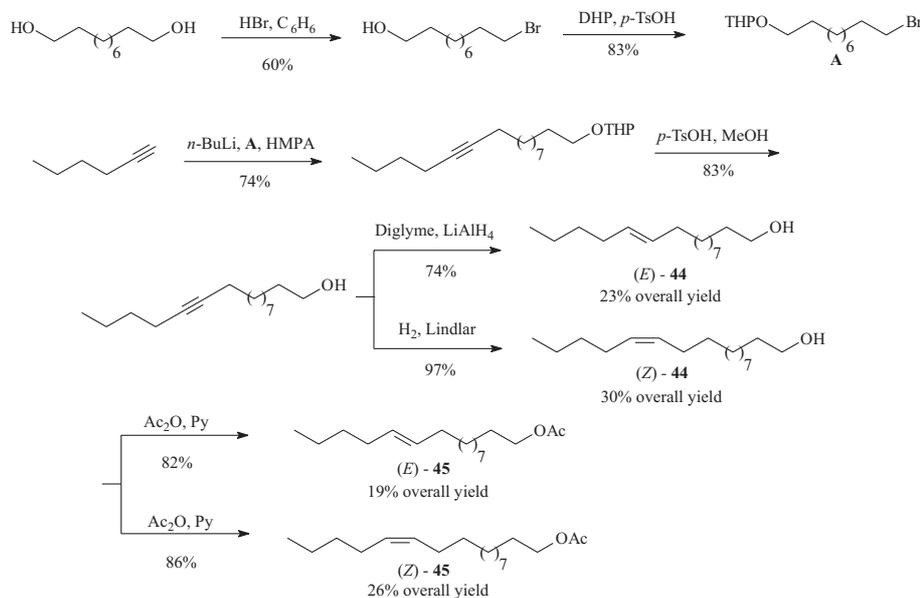
Scheme 40.



Scheme 41.



Scheme 42.



Scheme 43.

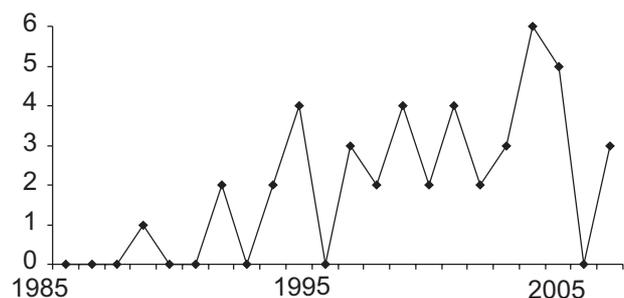


Figure 2. Number of syntheses of insect pheromones developed and published by Brazilian research groups in the last two decades

2.31. (Z)-7-Dodecenyl acetate (**41**), (Z)-9-tetradecenyl acetate (**42**), (Z)-11-hexadecenyl acetate (**43**), (E)-11-hexadecenyl acetate (**44**), and (E)-11-hexadecen-1-ol (**45**)

Acetates **41-43** have been described as components of the sex pheromone of the fall armyworm, *Spodoptera frugiperda*, an important economic pest of maize and other grass crops in North, Central, and parts of South

America.¹³⁶ Batista-Pereira *et al.*¹³⁷ examined the pheromone blend of a Brazilian population of females *S. frugiperda* and reported the synthesis of pheromone components through alkylation of alkynes with bromoalcohols (34-46 % overall yield) (Scheme 42).

(E)-11-Hexadecen-1-ol (**44**) and (E)-11-hexadecenyl acetate (**45**) have been recently described by Zarbin *et al.*¹³⁸ as components of the sex pheromone of *Lonomia obliqua*, one of the most important urban insects in Brazil due to the urticating spines in the larval stage. This moth has become of great importance in medicine because of the danger it represents.¹³⁹ Compounds **44** and **45** were synthesized employing alkyne chemistry (23 – 30% overall yield) (Scheme 43).

3. Conclusions and Perspectives

In conclusion, in the last 20 years projects involving Chemical Ecology and more specifically synthesis of insect pheromones have considerably grown in Brazil

(Figure 2). Several research groups are also working in isolation and identification of pheromones of Brazilian insect pests, which will certainly contribute for the development of the area in the near future.

Control of insects using pheromones is a multidisciplinary approach and requires efforts on many facets. Nowadays, there is a greater demand to produce environmentally sound and chemical residue-free agricultural products, and the initial doubt and obstacles against using pheromones for pest management have been overcome in recent decades.¹⁴⁰

In Brazil, the research and the development of this area is still concentrating in the Academia. The challenge today for the accurate monitoring and/or control of insects using pheromone is the production in large scale of the pheromone components and the development of proper dispenser system, which would decrease the price of the blends and stimulate their use in the field. This would be a prerequisite to be able to defeat the army of insects in the next decade.



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Zarbin in the Chemical Ecology course of the graduate program in Chemistry at UFPR.



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Carlos, with part of his thesis developed at the National Institute of Sericultural and Entomological Science, in Tsukuba, Japan. He is presently head of the Laboratory of Semiochemicals at UFPR and member of the Brazilian Chemical Society, Entomological Society of Brazil, and International Society of Chemical Ecology, where acts as councilor. His main research interest is focused on the identification, synthesis, biosynthesis and field evaluation of insect pheromones and other semiochemicals.

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