CHEMICAL ECOLOGY OF *RHYNCHOPHORUS* PALM WEEVILS AND *ORYCTES* COCONUT BEETLES

by

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Abstract

Production of methyl branched, secondary alcohols as aggregation pheromones in the African palm weevil, *Rhynchophorus phoenicis* (F.) (3-methyl-4-octanol, phoenicol), the palmetto weevil, *R. cruentatus* (F.) (5-methyl-4-octanol, cruentol), and the Asian palm weevil *R. bilineatus* (Montr.) (4-methyl-5-nonanol, ferrugineol) was established. Stereoisomeric mixtures of aggregation pheromones (cruentol, phoenicol and ferrugineol) in combination with host material strongly attracted weevils in field experiments.

Sharpless asymmetric epoxidation of the appropriate allylic alcohol followed by diastereoselective epoxide opening with trimethylaluminum; selective monotosylation and alkylation provided the syntheses of all stereoisomers, of phoenicol, cruentol, ferrugineol and ferrugineone, from common and inexpensive reagents. The stereoselective production of these pheromones, as well as their antennal and field response, was demonstrated in *R. cruentatus, R. phoenicis, R. bilineatus, R. ferrugineus* and *R. vulneratus.*

Coupled gas chromatographic-electroantennographic detection analyses and coupled GC-mass spectrometry of the volatiles produced by male and female West Indian sugarcane weevils (WISW), *Metamasius hemipterus sericeus* (Oliv.), revealed eight male specific, EAD-active compounds: 4-methyl-5-nonanol, 2-methyl-4-heptanol, 2-methyl-4-octanol, 3-pentanol, and the corresponding ketones. Field experiments in Florida demonstrated that the alcohols, in combination with sugarcane were most attractive, whereas addition of the ketones or replacement of alcohols with ketones significantly reduced attraction. Field experiments in Costa Rica examined this attraction to alcohols singly and in all binary, ternary and quaternary combinations. 4-Methyl-5-nonanol was the major aggregation pheromone, equally attracting both male and female WISW. Stereoisomeric mixture of the nonanol and the (4*S*,5*S*)-isomer were equally

attractive. Addition of (*S*)-, (*R*)- or (±)-2-methyl-4-heptanol to (4*S*,5*S*)-4-methyl-5-nonanol slightly enhanced attraction. 2-Methyl-4-heptanol was also found to be the male-produced aggregation pheromone of the sympatric weevil *Paramasius distortus*.

Male coconut rhinoceros beetles, *Oryctes monoceros* (Oliv.) and *O. rhinoceros* (L.), produce three sex-specific compounds, ethyl 4-methyloctanoate, ethyl 4-methylheptanoate, and 4-methyloctanoic acid, the first of which was demonstrated to be an aggregation pheromone in each species. The racemic pheromones were prepared by conjugate addition of organocuprates to ethyl acrylate while chiral isomers were prepared from enantiomerically enriched citronellol. Field experiments demonstrated that racemic and ethyl (4*S*)-methyloctanoate were equally attractive to *O. rhinoceros*.

The EAD-active compounds from the mango fruit fly, *Anastrepha obliqua* (Macq.) volatiles were identified as *Z,E*-farnesene, *E,E*-farnesene and (3*Z*,6*Z*)-3,6-nonadien-1-ol. The compounds occurred at approximate 40, 8 and 52 %, respectively. Efforts towards the regioselective syntheses of these farnesenes are presented.

Exposure of mountain pine beetles males, *Dendroctonus ponderosae* (Hopkins), spruce beetles, *D. rufipennis* (Kirby), pine engravers, *Ips pini* (Say), and *I. tridens* (Mannerheim), and West Indian sugarcane weevils, *Metamasius hemipterus sericeus* (Olivier) to 4,4-$^2H_2$- or protio-6-methyl-6-hepten-2-one resulted in production of deuterio- or protio-frontalin, respectively. Similarly, exposure of spruce beetles, *M. hemipterus* and *I. tridens* to (*Z*)-6-nonen-2-one resulted in the production of *exo*-brevicomin. Production of enantiomerically enriched frontalin and *exo*-brevicomin by all beetles exposed to these precursors demonstrated widespread occurrence of non-specific polysubstrate monooxidases in these Coleoptera.

Dedication

To my family for their belief in me and

to "The Stranger" for being always there when I needed it.

"...There are two ways of walking through a wood. The first is to try one or several routes (so as to get out of the wood as fast as possible, say or to reach the house of grandmother, Tom Thumb, or Hansel and Gretel); the second is to walk so as to discover what the wood is like and find out why some paths are accessible and others are not..."

Umberto Eco in *Six walks in the fictional woods*, 1994.

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Finally, thanks to "the stranger" for pulling me out of trouble and giving me advice and support (chemical, computational and moral!) when I needed it and to all my family for their belief in me.

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List of Schemes

List of Abbreviations

anhyd.	anhydrous
ANOVA	analysis of variance
APW	American palm weevil
br	broad (^{1}H NMR)
CI	chemical ionization (mass spectroscopy)
COSY	correlated spectroscopy (H NMR)
Cp	cyclopentadienyl
Cp_2ZrCl_2	dichlorobis(η5-cyclopentadienyl) zirconium
cruentol	5-methyl-4-octanol
δ	chemical shift in ppm downfield from tetramethyl silane
d	doublet (^{1}H NMR)
(+)-DET	(+)-diethyl tartrate
(-)-DET	(-)-diethyl tartrate
DEAD	diethyl azocarboxylate
DIAD	diisopropyl azocarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	4-*N*,*N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dt	double triplet (^{1}H NMR)
DTAMP	diethyl aluminum 2,2,6,6-tetramethylpiperidide
EA	ethyl acetate
EAD	electroantennogram detection

EB	ethyl butyrate
EC	ethyl chysanthemumate, rhinolure
ee	enantiomeric excess
EI	electron impact (mass spectroscopy)
EIB	ethyl isobutyrate
EP	ethyl propionate
equiv.	equivalent
Eschenmoser's salt	*N,N*-dimethylmethyleneammonium iodide
Et_2O	diethyl ether
Exp.	experiment
ferrugineol	4-methyl-5-nonanol
ferrugineone	4-methyl-5-nonanone
FID	flame ionization detector
FTIR	Fourier transformation infrared
g	grams
GC	gas chromatography
HETCOSY	hetero correlated spectroscopy (NMR)
HMPA	hexamethyl phosphoric triamide
Hz	Hertz
i-Pr_2MgBr	bromomagnesium diisopropylamide
ID	internal diameter
J	coupling constant (NMR)
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMD	lithium hexamethyldisilazide
LTMP	lithium tetramethylpiperidide
M	mol L^{-1}

m	multiplet (^{1}H NMR), meter (distance)
m/z	mass to charge ratio (mass spectroscopy)
MBA	α-methyl benzyl amine
Me	methyl
mL	milliliter
3A/4A MS	3A or 4A molecular sieves
MS	Mass spectrometry
MVK	methyl vinyl ketone
n-Bu_4NF	tetrabutylammonium fluoride
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect (^{1}H NMR)
NOESY	nuclear Overhauser and exchange spectroscopy
p-TsOH	*para*-toluenesulfonic acid
phoenicol	3-methyl-4-octanol
Py	pyridine
q	quartet (^{1}H NMR)
R_f	retention factor (thin layer chromatography)
RI	retention indices (gas chromatography)
s	singlet (^{1}H NMR)
SAMP	(*S*)-1-amino-2-methoxymethyl-pyrrolidine
SE	standard error
SEM	standard error of mean
SIM	selected ion monitoring
SO_3•Py	pyridine-sulfur trioxide complex
t	triplet
$(Ph_3P)_4Pd$	tetrakis(triphenylphosphine)palladium
TBSCl	*tert*-butyldimethylsilyl chloride

Tf	triflate, trifluoromethanosulfonate
Tf_2NPh	*N,N*-bis(trifluoromethylsulfonyl)anilide
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethyl silyl
TMSCl	trimethyl silyl chloride
TMP•HBr	2,2,6,6-tetramethylpiperidinium bromide
TS	transition state
Ts	tosylate
TsCl	*p*-toluenesulfonyl chloride
$VO(acac)_2$	vanadium acetylacetonate
WISW	West Indian sugarcane weevil

Chapter 1

General Introduction

1.1. Chemical Ecology and Interactions Between Organisms.

Chemical ecology is defined as "the study of structure, function, and biosynthesis of natural products; their importance at all levels of ecological organizations; their evolutionary origin, and their applications to social needs".[1] The subject of chemical communication is considered as part of chemical ecology. Chemical communication is a mode of information transfer among members of the class Insecta, and it is arguably the primary communication mechanism in the insect world. Semiochemicals are employed for both intra- and interspecific communication and are divided in two major groups: pheromones and allelochemics. Many types of interactions mediated by semiochemicals have been identified. In this thesis, special attention is focused on two of them.

1.1.1. Plant-Insect Interactions.

Many plants produce secondary metabolites that are attractive, distasteful or toxic to insects. The majority of these compounds are not essential for the normal growth and reproductive functions of the plant. Compounds that mediate interspecific interactions are classified as allelochemics. These are divided in two main groups: allomones and kairomones.[1,2] Allomones are those chemicals that favour their producers and kairomones are the ones that benefit their receivers. However, is worth to mention that these roles are not mutually exclusive.

In this work, only the effects of plant kairomones in the chemical ecology of palm weevils and beetles will be discussed.

Chemical structures of kairomones are diverse. Many terpenoids, alcohols, aldehydes, esters and sulfur compounds have been reported as plant kairomones. The majority are volatile (boiling points lower than 340°C), with molecular weights less than 250; and are believed to be readily released by diffusion, leaching, exudation, plant damage or decay. They are often active at nanogram to microgram levels. The ability of insects to respond is considered an adaptative process. It has been suggested that kairomones first gave benefit to the emitter but later in the evolutionary process became beneficial to the receiver.[1,2c]

1.1.2. Insect-Insect Interactions.

Compounds which convey information between members of the same species are known as pheromones. They are secreted by one individual and perceived by a second individual of the same species producing specific reactions in the latter, for example, a definitive behavior or developmental process.[3]

Evidence for the presence of pheromones dates from the 17th century.[4a] In 1875, Jean Henri Fabre, a French naturalist, placed a newly emerged female moth (the Great Peacock, Europe's biggest moth), inside a wire-gauze cage.[4b] That night, his home was visited by about forty male moths seeking the female. The first isolation and identification of an insect pheromone was published in 1959, from the silkworm moth, *Bombyx mori* (L.).[4c,d] The pheromone was named bombykol and was identified as (*E,Z*)-10,12-hexadecadien-1-ol. Since then pheromones have been identified for ~1000 insects species.[1,2]

Pheromones are classified according to the response they elicit. If the chemical stimulus trigger an inmediate and reversible change in the behaviour of the recipient is called "releaser", and if this stimulus cause delay, last response is

refered to as "primer".[4e] Pheromones are known which elicit the following responses: a) sexual; b) aggregation; c) dispersal; d) oviposition; e) alarm, and f) trail-marking. Some pheromones appear to have more than one function.

The most widespread and widely documented types of pheromone are those which are used to increase the probability of mating. Sex pheromones may be produced by females or males. In some cases, both sexes contribute to the chemical communication involved in mating. In many cases, different pheromone components are responsible for the principal behavioural phases of mate location and courtship. Sex pheromones are primarily used by the Lepidoptera. Usually, a virgin female moth will announce her availability through release of sex pheromone ("calling" behaviour) and this will cause flight response and approach by perceiving males. Most female moths call at dusk or at night. This behaviour is in fine tune with their circadiam rhythm. Their photoperiod and environmental temperature play important roles in defining this behaviour.[4g-i] The pheromonal blend is produced in specialized glands on the terminal segment of the female abdomen and are perceived by chemosensory sensilla of male antennae. Male moths respond to the pheromone by flying upwind in a zig-zag pattern (anemotaxis). This movement allow them to progress upwind in an odour plume. Flight manoeuvres are dictated by the interaction of the male with individual odour pulses.[4j-l] Baker and coworkers,[4m] demonstrated the operation of at least two changes in receptor output that may be responsible for cessation of upwind flight in moths which correspond to an adaptation and attenuattion of the antenna to pheromone concentration in the plume. After landing, males are further induced to initiate courtship behaviour which terminates in mating.[2]

Aggregation pheromones have been reported for members of the Coleoptera, Dictyoptera, Hemiptera, Homoptera and Orthoptera. These

pheromones can be released by either sex and serve to attract both sexes. In bark and ambrosia beetles, the pheromones are usually released from the hind-gut and are synergized by tree-produced kairomones. The reasons for aggregation are numerous and include reproduction, defence against predators, shelter, colonization and overcoming host resistance by mass attack. Aggregation usually occurs by chemotaxis in which the insect detects a gradient of pheromone to which it orients by anemotaxis.[4n,o] Dispersive or spacing pheromones elicit behavior resulting in increased spacing between conspecifics and a reduction in intraspecific competition.[1,2,4p] Oviposition pheromones are compounds that stimulate oviposition. Alarm pheromones are characteristic of social insects such as termites, ants, wasps and honeybees.[1,2,4p] These compounds stimulate escape and other defensive behaviours. They are generally highly volatile, low molecular weight compounds that can be spread rapidly through a colony, acting quickly and over short time periods.

Trail pheromones induce recruitment or emigration and are commonly use by many foraging ants and termites. They are used to recruit insects in a colony to new food sources or to facilitate migration of a colony to a new site. These compounds are more persistent than many other types of pheromones.[4q]

1.2. Stereobiology.

The olfactory character of an organic compound is a function of both structure and stereochemistry. These two factors lead to yes/no responses in olfactation, making the task of structure determination, stereochemistry and synthesis (geometry and chirality) important.[5] The chemical and stereochemical purities of synthetic pheromones are often import determinants of biological activity. The problems associated with the presence of the "wrong" stereoisomer that may result in antagonistic responses require, in general, that the synthetic

pheromones have high chemical and geometrical/optical purity. Often precise mixtures of geometrical isomers are essential for effective field response. Optical purity is rarely important in determination of pheromonal activity.

Silverstein[6] has defined nine possible response categories for chiral insect pheromones (Table 1.1).

Table 1.1. Silverstein's response categories.

Category	Enantiomer produced	Activity	Occurrence*
1	Single	Natural enantiomer more active than the other	+
2	Single	Both enantiomers equally active	-
3	Single	Unnatural enantiomer more active than natural	-
4	Single	Unnatural synergized response of natural enantiomer	-
5	Single	Unnatural blocks response to natural enantiomer	+
6	Both	Strongest response to natural ratio	+
7	Both	Strongest response to one rather than other or natural ratio	+
8	Both	Equal response to both enantiomers in all ratios	-
9	Both	One inhibits response to other	-

(*) (+) = Present in nature. (-) = Never reported in nature.

Recently, Mori[5f] extended this table to include the effect of responses to diastereoisomers and combination of enantiospecific and geometric specific responses.

1.3. Insect Olfaction.[7,5g]

The receptor sites for pheromones are located in insect antennae. When pheromone molecules are received by and excite a suitable insect chemoreceptor, the behavioural message is transmitted. Antennae occur in pairs and are located on the head and fortified by the deutocerebrum of the brain. These organs have movement in all directions, possess nerve channels directly connected to the midbrain and have a great variety of hairs, sensilla (each sensillum contains two or more olfactory receptor neurons) and pore plates (these pores allow odour molecules to interact with the neuron receptors) that typically cover the flagellum (distal portion of the antenna). The sensilla are responsible for the response to chemical stimuli. They exist as hair-like (*sensilla trichodea*), cone-like (*sensilla basiconica*), sensory pits (*sensilla coeloconica*), and as pore-plates (*sensilla placodea*).[1,5b,7a,b] The degree of sensitivity is determined by two main aspects: the sensory information (data transfer from the olfactory environment to the central neural system) and the sensory transduction (all biophysical processes which transform the chemical stimulus into a nervous exitation) which is given by the threshold of the bioactive molecule.[7b-d] The specificity of a receptor cell is determined by the stimulus-response curves of all effective substances together with the threshold concentrations which would provid a semilog plot (response curve).[7b]

The mechanism of action of insect chemoreceptors is still under investigation. It is believed that membrane-bound macromolecules act as receptors which are complementary in size, shape and stereochemical configuration to the bioactive molecules.[7e,f] This complementarity causes a conformational change in the receptor when it is associated with the bioactive molecule, opening ion channels that induce changes in conductance across the membrane. A resultant electrical current is transmitted to the brain. Such

potential changes can be measured and are the fundamental phenomenon on which the electrophysiological technique known as electroantennogram (EAG) is based. EAG recordings correspond to a summation of the receptor potentials from several olfactory cells. If the EAG is coupled to a gas chromatograph, a powerful analytical tool is obtained (gas chromatographic electroantennographic detection: GC-EAD) that allows continuous examination of candidate bioactive compounds that have been resolved in time by GC techniques. In this system, antennae of the insect are used as GC detector. Comparison of retention times of antennally active insect volatiles with those detected by flame ionization facilitates identification of candidate pheromones.

1.4. Objectives of This Thesis.

Rhynchophorus palm weevils and *Oryctes* palm/coconut beetles are destructive pests of commercial and ornamental palms in the tropics. At the commencement of this work very little was known about the chemical communication systems of these insects. In view of the agronomical importance of their hosts, the structure, stereochemistry and field testing of the insect-produced pheromone(s) and the identification of host volatiles were the main objectives of this work. Preliminary work on the identification and synthesis of the male-produced pheromones of the mango fruit fly *Anastrepha obliqua* (Macq.) was also carried out. Finally, hypotheses concerning the biosynthetic origin of frontalin in *Dendroctonus rufipennis* (K.) were tested.

This thesis is divided into six chapters. Chapter 2 describes the identification, synthesis, configurational assignment and field testing of the aggregation pheromones of *Rhynchophorus phoenicis, R. cruentatus, R. bilineatus, R. ferrugineus and R. vulneratus.* Synthetic methodologies including Sharpless asymmetric epoxidation, stereoselective epoxide opening by $AlMe_3$

and Mitsunobu reactions have been applied to achieve the synthetic goals. Use of coupled gas chromatography-electroantennographic detection (GC-EAD) and chiral chromatography among other techniques, allowed the determination of the absolute configuration of the weevil-produced compounds. Chapter 3 describes the identification, synthesis, configurational assignment and field testing of the aggregation pheromones of the sugarcane weevil *Metamasius hemipterus sericeus* and the sympatric *Paramasius distortus*. Synthetic and analytical methodologies similar to those describe in Chapter 2 were employed. Chapter 4 outlines the identification, synthesis, configurational assignment and field testing of the aggregation pheromones of the coconut beetles *Oryctes monoceros* and *O. rhinoceros*. The pheromones were synthesized through conjugate addition of organocuprates to ethyl acrylate, which provided a shorter route to racemic 4-alkyl substituted ethyl esters than those previously reported. Use of readily available enantiomers of citronellol allowed synthesis of both enantiomers of ethyl 4-methyloctanoate. Chapter 5 describes the identification and attempts to synthesize the male-specific EAD active volatiles of the mango fruit fly *Anastrepha obliqua*. Synthetic strategies such as zirconium-catalyzed carboalumination, DIBAL-H reduction of propargylic alcohols and selective enolization of α,β-unsaturated ketones were used in this endeavor. Protocols toward the regioselective preparation of *E*- and *Z*-enolphosphates of α,β-unsaturated ketones are presented. Chapter 6 describes the transformation of presumptive precursors to frontalin and *exo*-brevicomin by bark beetles and the sugarcane weevil. Production of enantiomerically enriched frontalin and exo-brevicomin by all beetles exposed to respective precursors represent non-specific and non-selective biotransformations, and demonstrate widespread occurrence of non-specific polysubstrate monooxidases in these Coleoptera.

Chapter 2

Aggregation Pheromones of the African Palm Weevil, *Rhynchophorus phoenicis* (Fabricius), the Palmetto Weevil, *R. cruentatus* (Fabricius) and the Asian Palm Weevils *R. bilineatus* (Montr.), *R. ferrugineus* (Olivier), and *R. vulneratus* (Panzer). (Coleoptera: Curculionidae).

2.1. Description of the Oil Palm.

The oil palm, *Elaeis guineensis* (Jacq.) a native of West Africa, is an established plantation crop in West Africa, Southeast Asia, Mexico, Central America, and the northern half of South America. A typical palm stem can reach 15 m at maturity, and is terminated with a crown of large, dark green, pinnate fronds. Fruit-bearing starts in the fourth year and reaches full yield within a few years. The economically productive life of oil palm is about twenty five years. Palms are typically planted at a density of 143 *per* hectare; each of which yields 12 fruit bunches annually. Bunches weigh about 20 kg of palm 20 % is oil. In the New World, there are 350,000 hectares of cultivated oil palm, with a 1990 oil production estimated to be valued at more than $ 400,000,000.[8]

2.2. The African Palm Weevil, *Rhynchophorus phoenicis* (F.): Its Habitat.

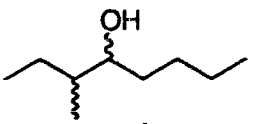
The African palm weevil, *R. phoenicis*, is confined to tropical Africa, and has been reported in Côte d'Ivoire, Sierra Leone, Nigeria, Angola, Ghana, Zaire and East Africa.[8b] It inflicts damage on oil palms when larvae bore into the meristem.[9] The cycle from egg to adult covers about 2-4 months. The adult is a large (40-55 mm), reddish-brown insect, with two reddish bands on the thorax.

Although palm weevils are known to be attracted to volatiles of palm, the presence of a pheromone in *R. phoenicis* was not demonstrated before this work.

2.3. Aggregation Pheromone of the African Palm Weevil.

R. phoenicis were collected[i] in oil palm plantations 40-50 km northeast of Abidjan, Côte d'Ivoire. Ten male and fifteen female *R. phoenicis* were placed in separate Nalgene desiccators containing sugarcane. Volatiles were collected on Porapak Q traps for four days.[10] Collected volatiles were eluted with pentane from the Porapak trap and concentrated by distillation (for details see experimental section). Gas chromatographic analysis of the extracts with FID and EAD revealed a male-specific, strongly EAD-active compound (Figure 2.1) with a GC-mass spectrum suggesting a methyl-branched secondary alcohol.

Treatment of the Porapak Q extract with Jones' reagent and subsequent mass spectrometry of the oxidized candidate extract yielded a ketone with a *m/z* = 142. Analysis of the mass spectrum, [*m/z* (relative intensity) = 41 (M^+-$C_6H_{11}O$, 37), 57 (M^+-C_5H_9O, 100), 72 (12), 85 (M^+-C_4H_8, 71), 142 (15)] indicated a carbonyl group at C-4. Based on the mass spectrum of this ketone and retention index comparison of the parent alcohol with authentic methyl-branched secondary octanols and nonanols, the EAD active alcohol was proposed to be 3-methyl-4-octanol, (**1**) which was named phoenicol. Antennal activity, identical retention time and mass spectrometric comparisons of synthetic **1** and the male-produced compound confirmed the structural assignment.



1

[i] Collection by Dr. A. Cam Oehlschlager and Ms. Lilliana M. Gonzalez.

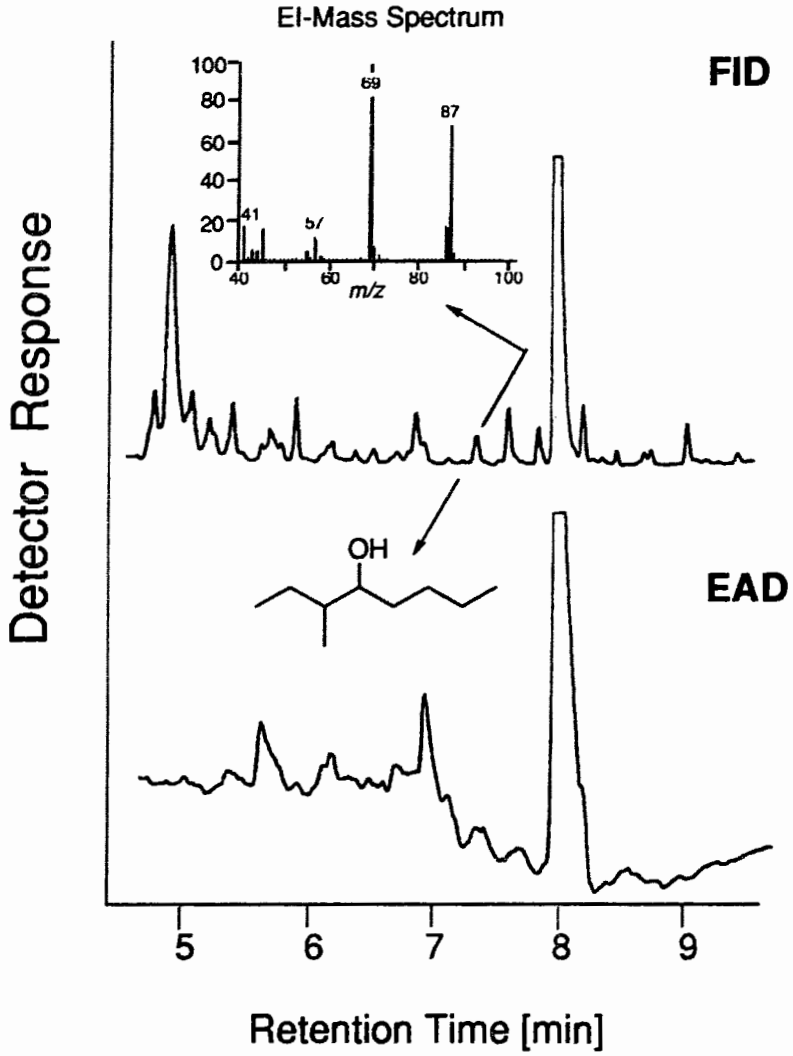


Figure 2.1. FID and EAD responses to volatiles obtained from male *Rhynchophorus phoenicis* feeding on sugarcane. The antennal recording was carried out with an antenna of a female weevil. Gas chromatographic conditions : linear flow velocity: 35 cm s^{-1}, injector and detector temperatures: 220°C, temperature programming: 70°C (1 min), 10°C *per* min to 180°C; SP-1000 column (30 m X 0.25 mm ID). The molecular ion of **1** was not observed.

Two field experiments (13-20 August 1992[ii]) were conducted in a ten-year old stand of oil palms in the La Me Research Station, Côte d'Ivoire.[11] Thirty 15-L bucket traps[12] were attached at chest height to mature oil palms in complete randomized blocks with traps at 27 m intervals and blocks 81 m apart.[12] The first 3-treatment, 10-replicate experiment tested the attraction of fresh palm stem pieces alone or in combination with synthetic **1** released at 0.4 and 4 mg *per* day, respectively (Figure 2.2, Experiment 1). The second 3-treatment, 10-replicate experiment tested the attraction of fresh palm stem pieces, **1** released at 4 mg *per* day, and combination thereof (Figure 2.2, Experiment 2). While traps baited with palm pieces or pheromone **1** alone captured few *R. phoenicis*, palm pieces and pheromone combined were significantly more attractive. Attraction to oil palm stem pieces peaked 2-3 days after cutting (Figure 2.3), as was found for the American palm weevil, *R. palmarum*,[12] the palmetto weevil, *R. cruentatus* (see next section), the Asian palm weevils *R. bilineatus* (see section 2.8 of this chapter), *R. ferrugineus* and *R. vulneratus*, and the West Indian sugarcane weevil, *Metamasius hemipterus sericeus* (Olivier) (see Chapter 3).

[ii] Tests conducted by Dr. Gerhard Gries and Ms. Regine Gries, Department of Biological Science, Simon Fraser University

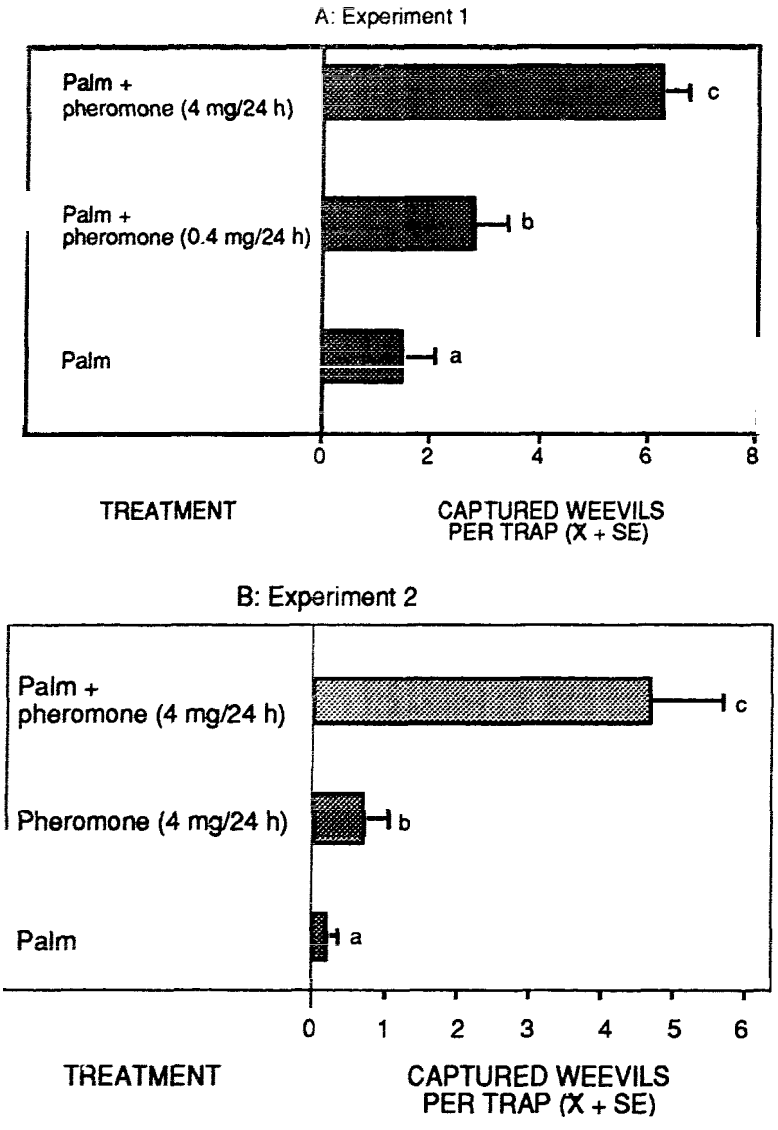


Figure 2.2. Captures of male and female *Rhynchophorus phoenicis*, La Me Research Station, Côte d'Ivoire. A) Experiment 1: traps baited with fresh palm pieces alone or in combination with 3-methyl-4-octanol (**1**) at two release rates; 13-17 August 1992, N = 10. B) Experiment 2: Traps were baited with fresh palm pieces, **1**, and the combination thereof; 18-20 August 1992, N = 10. For each experiment, bars with the same letter are not significantly different: ANOVA on data transformed by log (x+1), followed by Tukey's test, $p < 0.05$.

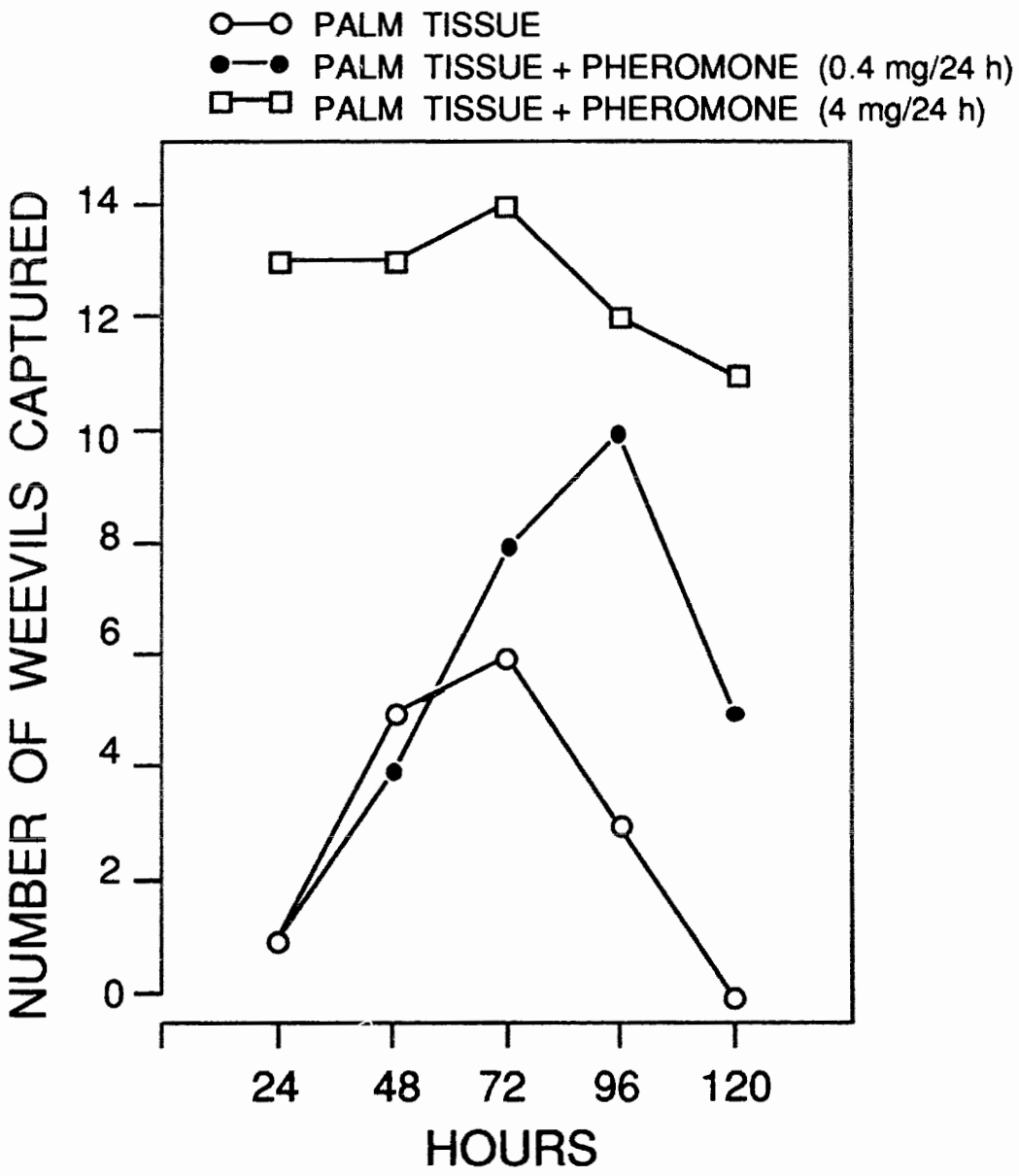


Figure 2.3. Age-dependent attraction to oil palm stem tissue alone and in combination with 3-methyl-4-octanol (**1**).

2.4. The Sabal Palm Weevil, *Rhynchophorus cruentatus* (F.): Its Habitat and Current Control.

Rhynchophorus cruentatus (F.), the palmetto weevil, is the only species of palm weevil found in the continental United States.[13] The range of this large (24-33 mm) beetle is from the coastal regions of South Carolina through the Florida Keys and Texas coast. Preferred hosts for *R. cruentatus* include the cabbage palmetto, *Sabal palmetto* (Walter), coconut palm, *Cocos nucifera* (Linnaeus), date palm, Canary Island date palms, *Phoenix canariensis* (Ortorum ex Chabaud) and the saw palmetto, *Serrenoa repens* (Bartram).[14a] The weevil usually attacks only transplanted or otherwise stressed palms.[14,15] Females lay eggs in leaf bases or directly in wounds of host palms, and immature stages develop in the crown and stem. Damage is due to larval tunneling which can be lethal if the terminal bud is killed. Weevil presence is not usually detectable until fatal damage and its associated rot have occurred. Prophylactic insecticide treatment applied to palms before planting, and removal and destruction of infested palms are the current control methods for *R. cruentatus.* Economic loss for Canary Island date palm can be important since the wholesale price is between $ 1,000 and 4,000 *per* palm compared with ~ $ 50 for a mature sabal palm.[14a]

Volatiles emanating from wounded and moribund *S. palmetto* are attractive to palmetto weevils and freshly chopped crown and stem tissue are used to trap *R. cruentatus.*[14b] Olfactometer bioassay and field tests of male volatiles, female volatiles and caged adults *plus* palm tissue, demonstrated the presence of a male-produced aggregation pheromone.[16]

2.5. Aggregation Pheromone of the Palmetto Weevil.

Thirty to forty male and female weevils (collected[iii] in a native *S. palmetto* stand 12 km south of La Belle, Florida or laboratory-reared[17]) were aerated separately in a modified Nalgene desiccator with and without sugarcane for seven days. Volatiles were eluted from Porapak Q with distilled pentane and concentrated by distillation (for details see experimental section).[10]

GC and GC-EAD analysis of volatiles from fed and unfed male weevils revealed a strongly EAD-active compound (Figure 2.4). Mass spectra (EI and CI mode) of the candidate pheromone (Figure 2.5) suggested a methyl-branched, secondary alcohol with a *m/z* = 143 (M^+-1) and a strong *m/z* = 127 (M^++H^+-H_2O) in the CI MS spectrum. High resolution mass spectra of the weevil-produced, EAD active compound, indicated a molecular formula of $C_9H_{20}O$. Fragmentation leading to *m/z* = 73 (M^+-C_5H_{11}) suggested that the hydroxyl group was bonded to C-2, C-3 or C-4. Based on mass spectrometric data and retention index (DB-210 and DB-23 columns) comparison with authentic methyl-branched secondary alcohols (Table 2.1), it was hypothesized that EAD active compound was 5-methyl-4-octanol, which was named cruentol, (**2**). Although only a few examples are presented, it was possible to correlate the methyl and hydroxyl group position with retention time. Moving the methyl toward the middle of the molecule decreased elution time.

Identical mass spectra and Kovats retention indices on two columns with different retention characteristics (DB-5: 1060, DB-23: 1489/1492) and similar

[iii] Collected by Dr. Robin M. Giblin-Davis, IFAS, University of Florida, Fort Lauderdale, Florida.

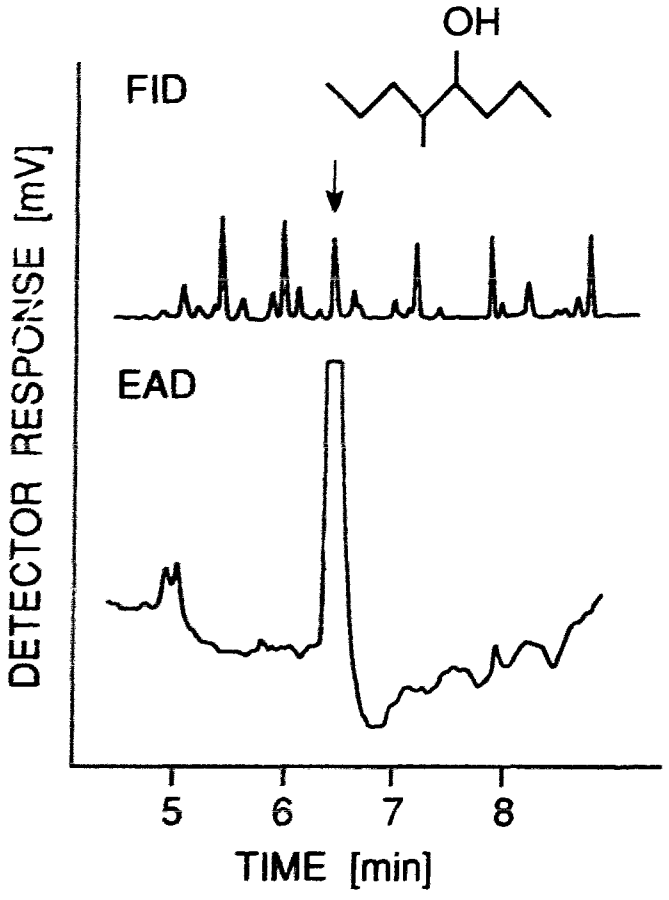


Figure 2.4. Flame ionization detector (FID) and electroantennographic detector (EAD) responses to volatiles collected for seven days from unfed *Rhynchophorus cruentatus* males. Antennal recordings (EAD) were carried out with a *R. cruentatus* male antenna. Gas chromatographic conditions : linear flow velocity: 35 cm s^{-1}, injector and detector temperatures: 220°C, temperature programming: 70°C (1 min), 10°C *per* min to 240°C; DB-5 column (30 m X 0.25 mm ID).

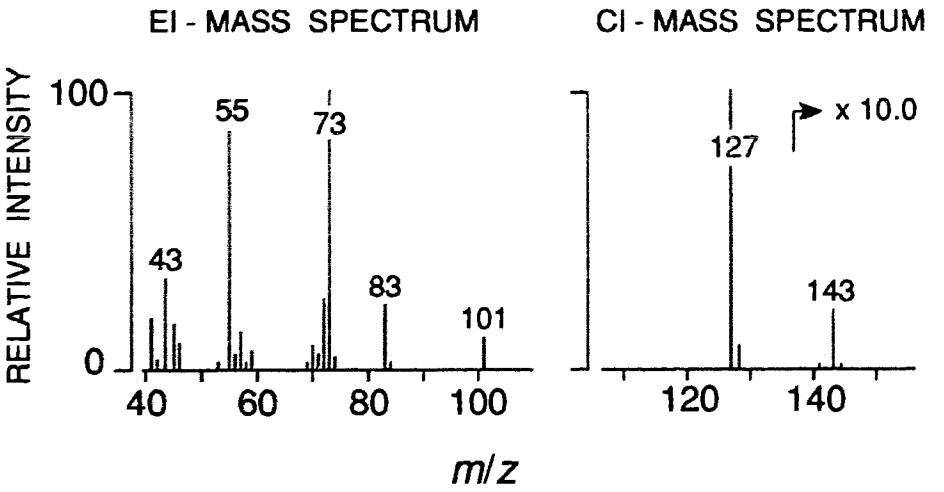
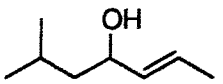
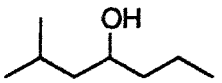
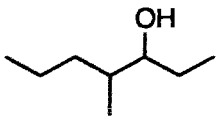
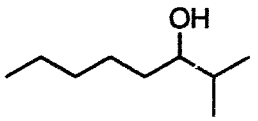
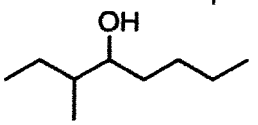
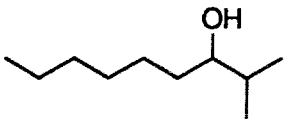
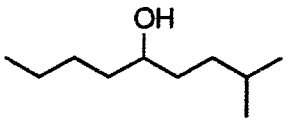
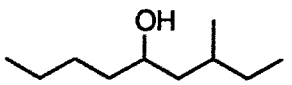
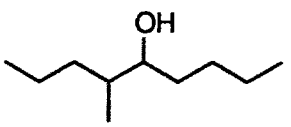


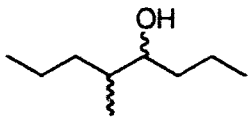
Figure 2.5. Mass spectra of weevil-produced 5-methyl-4-octanol.

Table 2.1. Retention indices of standard alcohols on DB-210 and DB-23 fused silica columns.

Compound	Retention index	
	DB-210	DB-23
	1098	1285
	1000	1280
	1016/1020[a]	1301/1302[a]
	1117	1395
	1216/1220[a]	1494
	1221	1504
	1215	1498
	1216/1220[a]	1494
	1210/1214[a]	1489/1492[a]
Weevil-produced compound	1208/1211[a]	1489/1492[a]

(a) Two values are presented due to separation of the diastereoisomers (*syn* and *anti*) on these stationary phases.

GC-EAD responses to equivalent amounts of synthetic **2** and the male-produced compound confirmed the structural assignment.



2

Field experiments[iv] conducted in a 300-ha pasture interspersed with *S. palmetto* and *S. repens* 12 km south of La Belle, Florida,[16] using a complete randomized block design with traps at 20 m intervals and blocks 300 m apart, tested attraction of **2** in combination with palm stem tissue (Figure 2.6). Traps employed for these tests allowed entering weevils to "smell" the volatiles emitted from the traps but not to see the food bait. Entering weevils were killed by drowning in soapy water. Low (0.4 mg *per* day) and high (4 mg *per* day) release of pheromone equally enhanced attraction of weevils to palm tissue. Ten to fifteen times more weevils were captured in traps baited with palm *plus* pheromone than any of the other treatments (Figure 2.6). The addition of live conspecific males to traps baited with palm tissue and pheromone did not enhance weevil capture over traps baited only with palm *plus* pheromone (Figure 2.7), suggesting that cruentol is the major male produced volatile essential for optimal attraction. While a stereoisomeric mixture of synthetic cruentol combined with palm tissue attracted large number of weevils, optimal attraction may require only one stereoisomer in combination with synergistic host volatiles. This issue will be discussed in the next sections.

[iv] Conducted by Dr. Robin Giblin-Davis, IFAS, University of Florida, Fort Lauderdale, Florida.

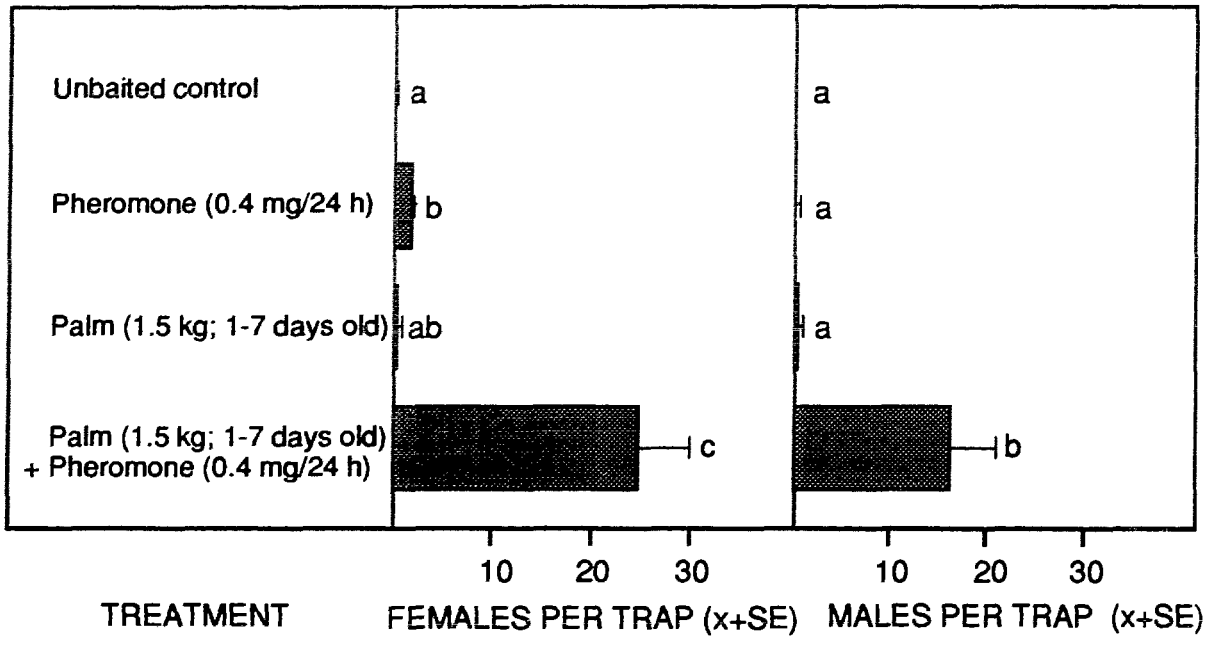


Figure 2.6. Mean (+SEM) capture of *Rhynchophorus cruentatus* in lethal traps baited with *S. palmetto* tissue, 5-methyl-4-octanol (**2**), or both combined, La Belle, Florida, June 5-19, 1992, N = 5. Means within a sex followed by the same letter are not significantly different ($p < 0.05$; least significant difference), treatment effects; males: F = 25.9; df = 3, 12; $p < 0.01$; females: F = 38.0; df = 3, 12; $p < 0.01$.

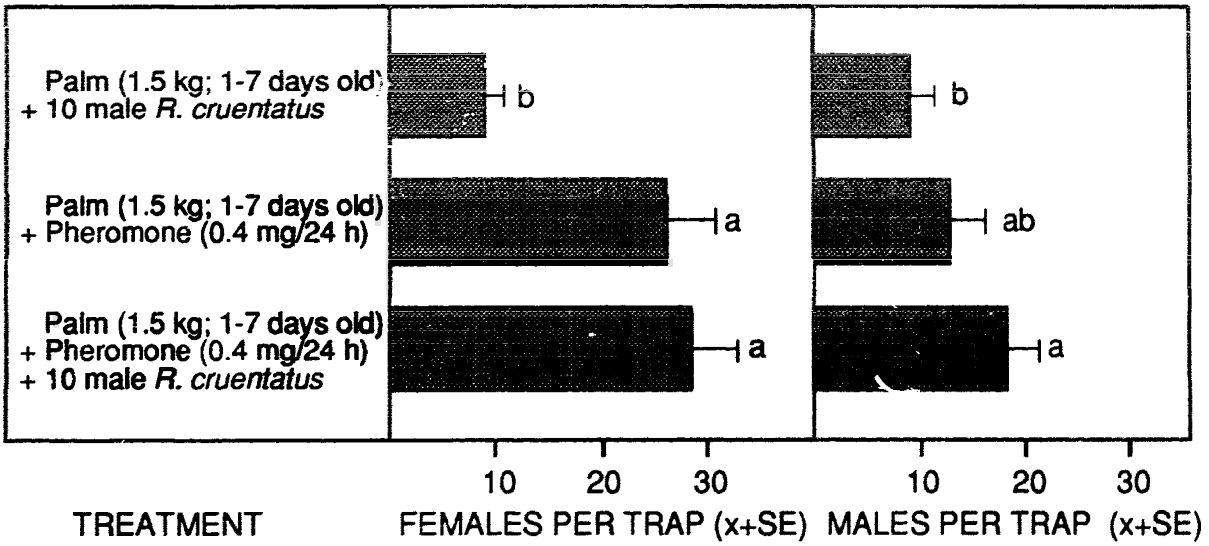


Figure 2.7. Mean (+SEM) capture of *Rhynchophorus cruentatus* in lethal traps baited with *S. palmetto* tissue, 5-methyl-4-octanol (**2**), ten *R. cruentatus* males, or both combined, La Belle, Florida, July 2-16, 1992, N = 4. Means within a sex followed by the same letter are not significantly different ($p < 0.05$; least significant difference), treatment effects; males: F = 6.0; df = 2, 6; $p < 0.04$; females: F = 6.9; df = 2, 6; $p < 0.03$.

2.6. Palm Volatiles: Synergistic Kairomones.

Selection of specific plants for feeding and reproduction has been well documented in the Coleoptera, particularly for scolytid and curculionid beetles.[1,18] Short-chain alcohols, ketones, esters, carboxylic acids, aldehydes, oleoresin, monoterpenes and sesquiterpenes alone or in combination have been associated with host selection behavior.[19] Ethanol, myrcene, α-pinene, β-phellandrene, and camphene enhance response to aggregation pheromones in bark and ambrosia beetles.[20] α-Cubebene, typically released from moribund elm trees, enhances attraction in the elm bark beetle, *Scolytus multistriatus* Marsham.[21] Propanoic and butanoic acids, methanol, 2-propanol, 1-heptanol, methyl butanoate and propanal synergize pheromone attraction of the dried fruit beetle, *Carpophilus hemipterus* Linnaeus.[22] In mimicking whole-wheat bread dough odour, a blend of acetaldehyde, ethyl acetate, ethanol, 1-propanol, 2-methyl-1-propanol, 2-methyl-1-butanol and 3-methyl-1-butanol attracted the nitidulids *Carpophilus lugubris* Murray, *Glischrochilus quadrisignatus* Say, and *G. fasciatus* Olivier[23] and synergistically enhanced attraction to *C. lugubris* pheromone.[24] As in the maize weevil, *Sitophilus zeamais* Motschulsky,[25] attraction of *Rhynchophorus* weevils to aggregation pheromones invariably requires the presence of synergistic plant tissue.[11,12,16b,26] Therefore, identification of attractive host volatiles is the next step in understanding the chemical ecology of these insects.

Four oil palm stem volatiles elicited good antennal responses in GC-EAD analyses (Figure 2.8).[27] EI and CI mass spectra of these compounds and authentic standards indicated that they were ethyl acetate (EA, **3**), ethyl propionate (EP, **4**), ethyl isobutyrate (EIB, **5**), and ethyl butyrate (EB, **6**). Field experiments in Côte d'Ivoire,[27a] disclosed that EA and EP but not all synthetic esters combined enhanced attraction to phoenicol (**1**). Ethyl propionate alone

enhanced pheromone attraction more than any other EAD active oil palm stem volatile, but was still less effective than freshly cut oil palm stem tissue (Figure 2.9). Increase, culmination, and decrease of attraction to palm tissue within three to five days after cutting[11,12,16b,26,27] indicate the semiochemical composition is probably critical for optimal attraction of weevils. Potato leaf volatiles, e.g., *cis*-3-hexen-1-ol, *cis*-3-hexenyl acetate, *trans*-2-hexanal, and *trans*-2-hexen-1-ol only induce positive anemotaxis in the Colorado beetle, *Leptinotarsa decemlineata* Say, when released in natural ratios.[28] Antennally active palm volatiles should therefore be field tested at ratios and release rates equivalent to those of palm tissue at peak attraction. Abundance and ratio of palm volatiles in extracts may not accurately reflect natural release rates of palm tissue and may depend on the volatile collection technique. This lack of knowledge of natural palm volatile composition, aside from the presence of unknown components, may explain the higher activity of palm tissue *versus* EP as a pheromone synergist (Figure 2.9). Absorbents, such as charcoal and glass-wool as well as cryogenic traps should be evaluated. Only if synthetic palm volatiles were chemically simple and required in small amounts would they be an economically feasible replacement for the currently used insecticide-treated sugarcane or palm stem tissue in commercial, semiochemical-based management of *Rhynchophorus* weevils in oil and date palm.

2.7. The Asian Palm Weevil, *Rhynchophorus bilineatus* (Montr.): Its Habitat.

Rhynchophorus bilineatus (Montr.), occurs in eastern Indonesia and Papua New Guinea, and is particularly associated with the indigenous sago palm, *Metroxylon sagu,* but also attacks coconut. In Papua New Guinea, this

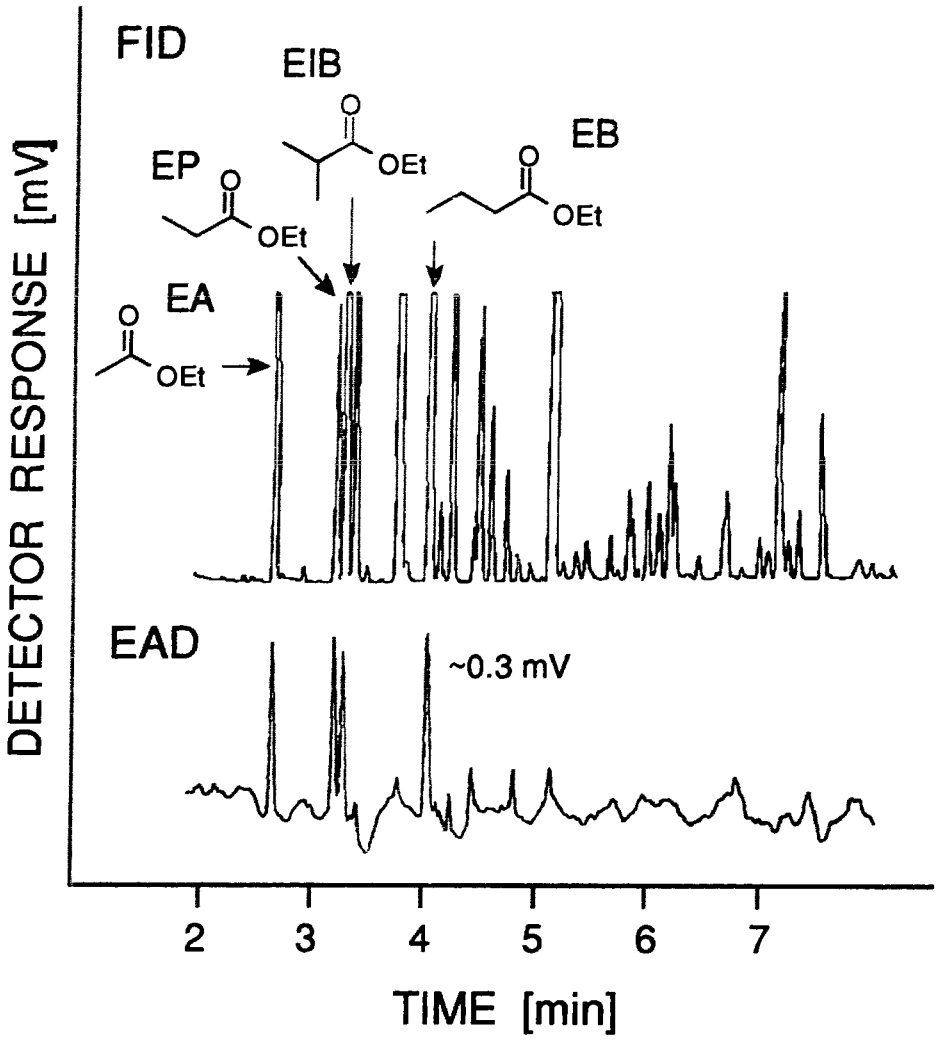


Figure 2.8. Flame ionization detector (FID) and male *Rhynchophorus phoenicis* antenna (EAD) responses to African oil palm volatiles chromatographed on a SP-1000-coated, fused silica column (30 m X 0.25 mm ID) (1 min at 50°C, 10°C *per* min to 180°C).

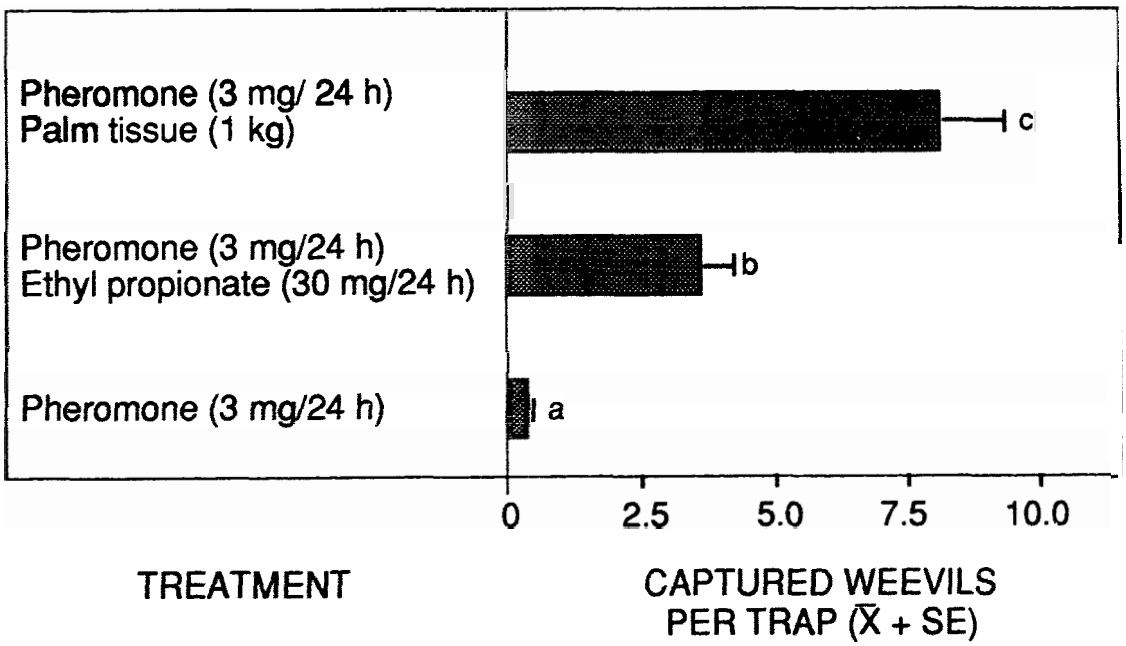


Figure 2.9. Mean (+SEM) capture of *Rhynchophorus phoenicis* in traps baited with pheromone alone or in combination with either ethyl propionate or 1 kg of one to three-day old palm tissue. La Me Research Station, Côte d'Ivoire, May 14-17, 1993, N = 10. Bars followed by the same letter are not significantly different; $p < 0.05$, ANOVA followed by Scheffé test. Traps and experimental design as for experiments in Figures 2.6 and 2.7.

palm weevil causes mortality of coconut palms used as shade trees in cocoa plantations. While the weevil may directly attack the palms, they are frequently attracted to and oviposit in feeding tunnels of the New Guinean rhinoceros beetle, *Scapanes australis* (Boisd.). As for the two previous described weevils, *R. bilineatus* larvae feeding often destroys the terminal bud contributing to death of the palm.[13]

2.8. Aggregation Pheromone of The Asian Palm Weevil, *R. bilineatus*.

Male and female *R. bilineatus* of mixed age and sex were collected in cocoa plantations interspersed with coconut palms near Rabaul, East New Britain Province, Papua New Guinea.[v] Twenty five male and twenty female *R. bilineatus* were aerated separately for 6-7 days in a modified Nalgene desiccator containing 0-4 day-old sectioned apples (apple was found to be a suitable food for *Rhynchophorus* spp. in the laboratory and has been successfully used as an additive to pheromone baited traps for *R. ferrugineus* in the United Arab Emirates[26d]). Insect- and host-produced volatiles were collected on Porapak Q traps. Volatiles were eluted from Porapak Q with pentane; the eluent was concentrated by distillation and subjected to gas chromatographic analysis which revealed several male-specific compounds (Figure 2.10). GC-EAD (Figure 2.11) disclosed only one male-specific compound that elicited strong antennal response from male and female weevils. GC-MS in both EI and CI mode (see experimental section for details), and retention characteristics were consistent with 4-methyl-5-nonanol (**7**), the recently identified aggregation pheromone of two other Asian palm weevils *R. ferrugineus* Olivier and *R. vulneratus* Panzer.[29]

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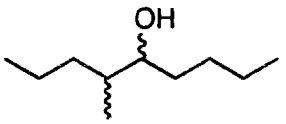
[v] Collections and field experiments were conducted by Dr. Robert N. Prior, Papua New Guinea Cocoa and Coconut Research Institute, Rabaul, Papua New Guinea.



7

Field experiments[v] were conducted in coconut palm-shaded cocoa plantations near Kervera and Vunabang, Papua New Guinea. Modified white 19-L plastic bucket traps were attached to palms at chest height in complete randomized blocks with traps at 27 m intervals and blocks 80 m apart.[12] Detergent-laced (0.3 %) water (2- 3 cm) in the bottom of each trap retained captured weevils. A wire mesh above the water held sugarcane stalks (4-5 pieces ~20 cm long). Every three to four days sugarcane was changed and weevils counted. The first 3-treatment experiment tested the attractiveness of **7** (3 mg *per* day), sugarcane stalk and both combined (Figure 2.12). The second 4-treatment experiment tested sugarcane alone and in combination with **7** released at 0.3, 3.0 or 30 mg *per* day (@ 25°C, Figure 2.13).

The first field experiment indicated that **7** or sugarcane alone were not very attractive but both in combination caught significant numbers of weevils (Figure 2.12). Synergistic attraction of *R. bilineatus* to traps containing both aggregation pheromone and sugarcane is consistent with findings in five other species of the Rhynchophorinae.

Sugarcane tested in combination with **7** released at 0.3, 3.0 or 30 mg *per* day resulted in dose-dependent attraction of weevils with optimal response at 3 mg *per* day (Figure 2.13). *R. palmarum* responded equally well to the same three release rates of its pheromone when combined with food but without food preferred the 30 mg *per* day dose.[12] In the presence of palm tissue, *R. ferrugineus* is more strongly attracted to traps from which 3 mg *per* day rather than 0.3 mg *per* day of **7** are released.[29a] Traps containing **7**, sugarcane and

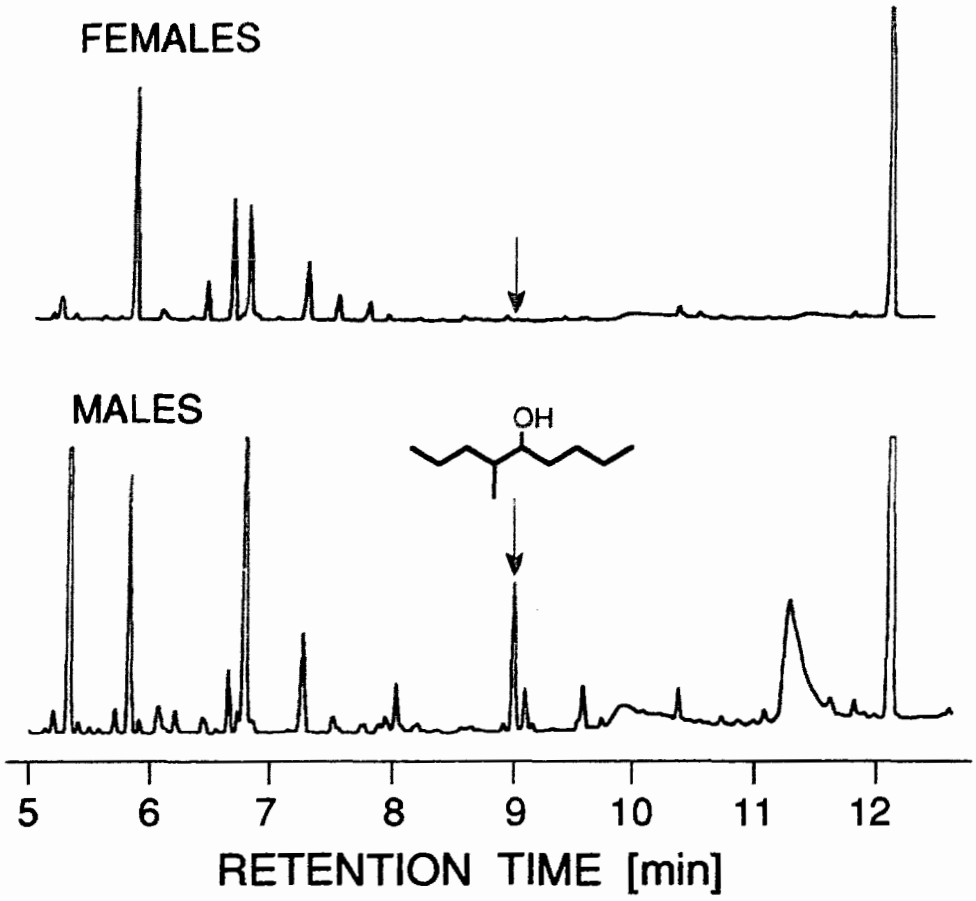


Figure 2.10. Gas chromatograms of volatiles obtained from female and male *Rhynchophorus bilineatus* feeding on apples. Chromatography: SP-1000 fused silica column (30 m X 0.5 mm ID); temperature program: 1 min at 50°C, 10°C *per* min to 180°C.

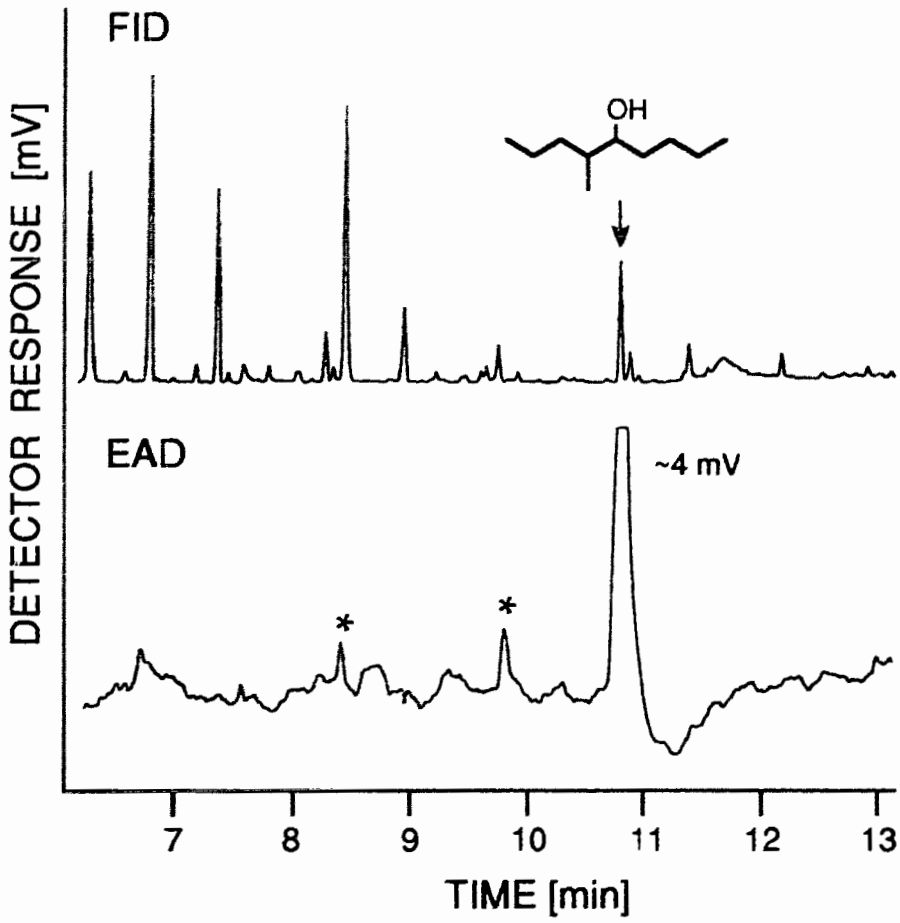


Figure 2.11. Flame ionization (FID) and electroantennographic detector (EAD: female *Rhynchophorus bilineatus* antenna) responses to volatiles obtained from male *R. bilineatus* feeding on apples (* = apple-derived components). Column: SP-1000 fused silica (30 m X 0.25 mm ID). Chromatography as in figure 2.10.

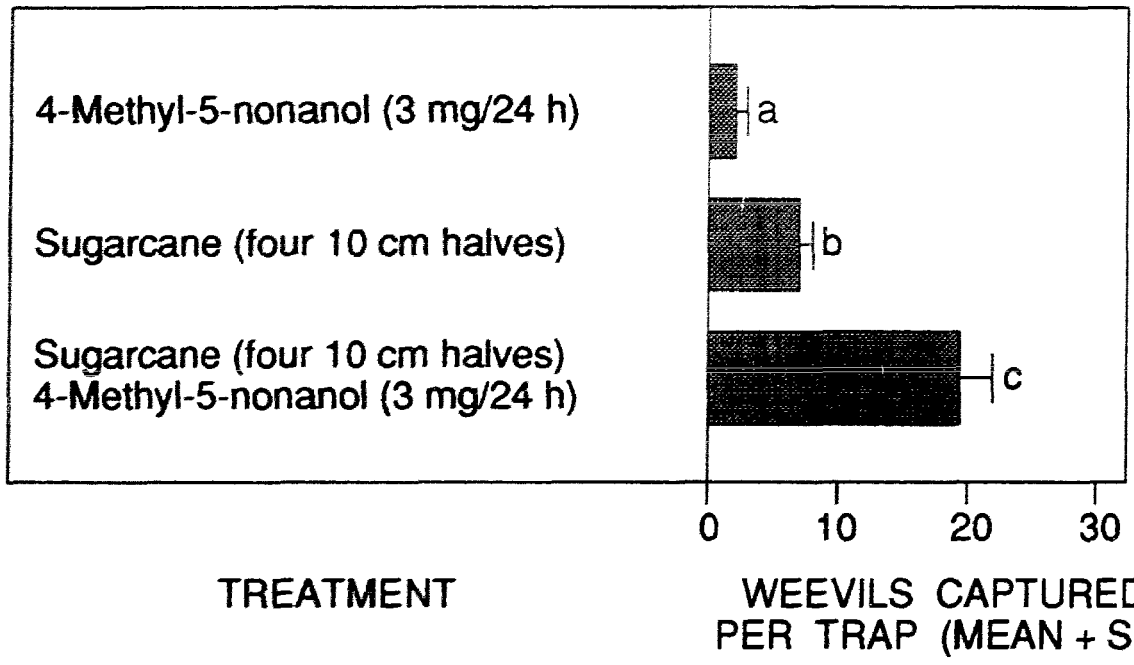


Figure 2.12. Mean (+SEM) captures of *Rhynchophorus bilineatus* in traps baited with sugarcane, 7 or both in combination. Experiment (N = 16) was conducted in Kervera plantation, 2 November to 4 December, 1992. Data transformed $[(X + 0.5)^{0.5}]$ to approximate homogeneity are presented untransformed. ANOVA, $F = 29.18$; df = 2,15; $p < 0.001$. Means followed by the same letter are not significantly different (Bonferroni's test, $p < 0.05$).

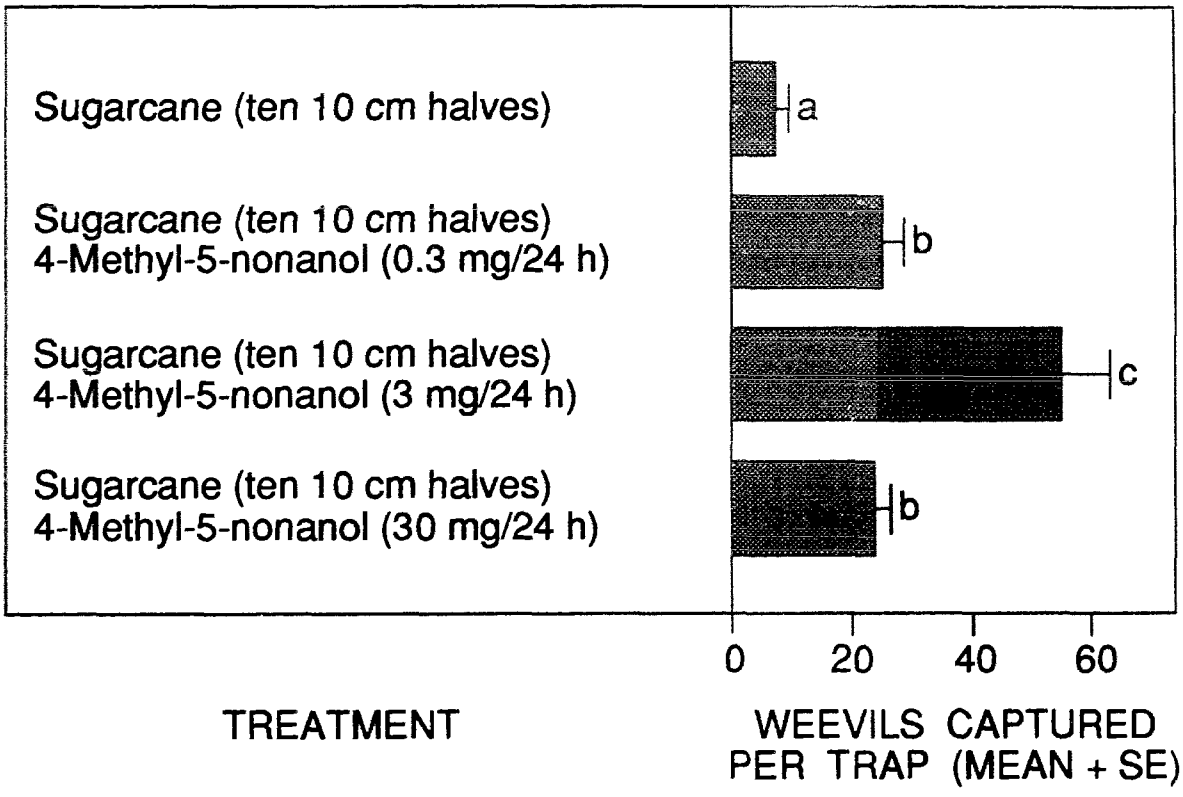


Figure 2.13. Mean (+SEM) captures of *Rhynchophorus bilineatus* in buckets traps baited with sugarcane alone or combined with **7** at three release rates. Experiment (N =15) conducted at Vunabang plantation, 25 November, 1992 to 5 January, 1993. Data transformed $[(X + 0.5)^{0.5}]$ to approximate homogeneity are presented untransformed. ANOVA, $F = 24.67$; $df = 3, 14$; $p < 0.001$. Means followed by the same letter are not significantly different (Bonferroni's test, $p < 0.05$).

detergent-laced water are presently used in Papua New Guinea to mass trap *R. bilineatus* (R. Prior and S. Laup, personal communication).

2.9. Chirality and Pheromone Perception.

Many coleopteran pheromones are optically active.[5a,30] Enantioselective production of and response to chiral isomers of pheromones contribute to the species specificity of semiochemical communication.[31] In some cases, the presence of non-natural enantiomers in synthetic pheromones has been demonstrated to alter response. For instance, the male-produced aggregation pheromone in the southern pine beetle, *Dendroctonus frontalis* Zimm., (1*R*,5*S*,7*S*)-(+)-*endo*-brevicomin, *endo*-7-ethyl-5-methyl-6,8-dioxa-[3.2.1]octane, markedly enhances the response by both sexes to female-produced frontalin (1,5-dimethyl-6,8-dioxa-[3.2.1]octane), whereas the presence of the antipode in racemic *endo*-brevicomin interferes with attraction.[32] In the Japanese beetle, *Popillia japonica* Newman, female-produced Japonilure, (*R,Z*)-(-)-5-(1-decenyl)oxacyclopentan-2-one, strongly attracts males, whereas the antipode inhibits response.[33] In the scarab beetle, *Anomala cuprea* Hope, only the (*R,Z*)-(-)-5-(1-octenyl)oxacyclopentan-2-one attracts conspecifics while the presence of the non-natural enantiomer reduces attraction.[30b]

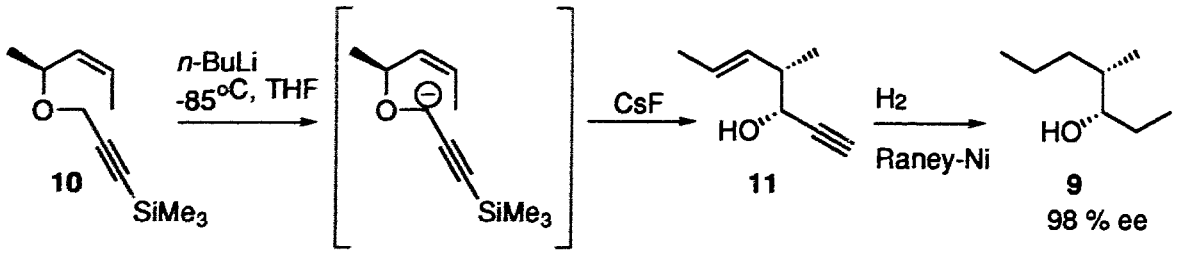
Pheromone specificity also contributes to habitat and resource partitioning among competing species in the Coleoptera. Only rarely has intraspecific attraction and interspecific interruption of response been attributed to enantiospecific production of more than one aggregation pheromone. (+)-Ipsdienol and (-)-ipsenol produced by *Ips paraconfusus* Lanier interrupt the aggregation of sympatric *I. pini* Say.[31d,34] *Trogoderma granarium* (Everts) uses the (*R*)-(-)-enantiomers of (*Z*)- and (*E*)-trogodermal in a 92: 8 ratio, while beetles in three other *Trogoderma* spp. respond to the (*R*)-(-)-enantiomers of either (*E*)- or

(*Z*)-trogodermal.[35] Ratios of both geometrical and optical isomers of brevicomin determine response and pheromonal specificity of sympatric *Dryocoetes confusus* (Swaine) and *D. affaber* (Mannerheim).[36] Determination of insect-produced pheromone stereoisomers is required to fully elucidate the chemical communication system for a target insect and to implement efficient pheromone-based monitoring and/or management. The aggregation pheromones of *R. cruentatus*, *R. phoenicis* and *R. bilineatus* identified above are chiral secondary alcohols, in addition, 4-methyl-5-nonanol (ferrugineol, **7**) has recently been shown to be a male-produced aggregation pheromone of the two Asian palm weevils, *R. ferrugineus* (Oliv.) and *R. vulneratus* (Panz.).[29] 4-Methyl-5-nonanone (ferrugineone, **8**) is also produced by male *R. ferrugineus* and *R. vulneratus* and elicits antennal responses by both palm weevils, but seemed to have behavioral activity only in *R. ferrugineus*.[29a] Lack of pronounced differences in response to isomeric **7** and **8** suggested that pheromone chirality may impart species specificity of semiochemical communication. Therefore, it was hypothesized that enantiospecific production of and response to **8** contributes to species isolation. In this study, optically active isomers of phoenicol,[37a] (**1**), cruentol,[37a] (**2**), ferrugineol,[37b,c] (**7**) and ferrugineone,[37b] (**8**), were prepared, the chirality of natural isomers determined and attraction to natural and non-natural stereoisomers examined in field tests.

2.10. Synthesis of α-Methyl Secondary Alcohols. Background.

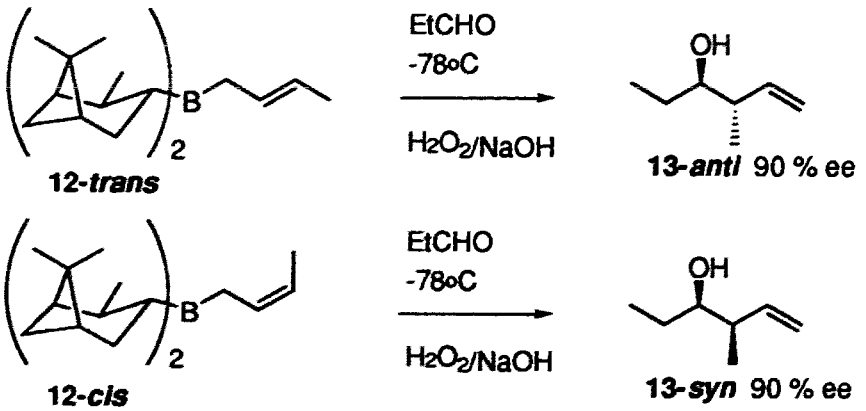
Optically active α-methyl secondary alcohols have been synthesized through diverse methods.[38] [2,3]-Sigmatropic rearrangements of allylic ethers provide access to *syn* stereoisomers in high optical purity. For example, 4-methyl-3-heptanol, **9**, one of the pheromone components of the elm bark beetle,

Scolytus multistriatus Marsham, was synthesized in 98 % enantiomeric excess (ee) from allylic ether **10** *via* **11** (Scheme 2.1).[39]



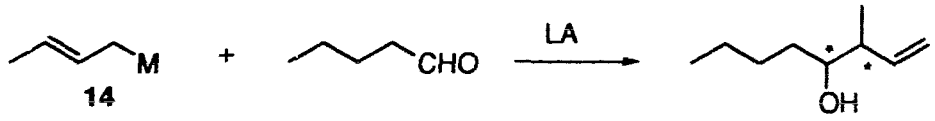
Scheme 2.1. [2,3]-Sigmatropic rearrangement of chiral allylic ethers to chiral α-methyl secondary alcohols.

Chiral allylboration, using diisopinocamphenylboranes,[40] also offers access to the target compounds in good optical purities (Scheme 2.2). The availability of *cis* and *trans* crotylboranes **12** provides entry to both *anti* and *syn* stereoisomers (e.g. **13-*anti*** and **13-*syn***).



Scheme 2.2. Allylboration of aldehydes with diisopinocamphenylboranes,

Lewis acid catalyzed coupling of allyl- or crotyl-organometallics, **14** (Scheme 2.3) and aldehydes has been used by several groups to prepare substituted secondary alcohols with excellent *syn/anti* and enantio-selectivities.[41]

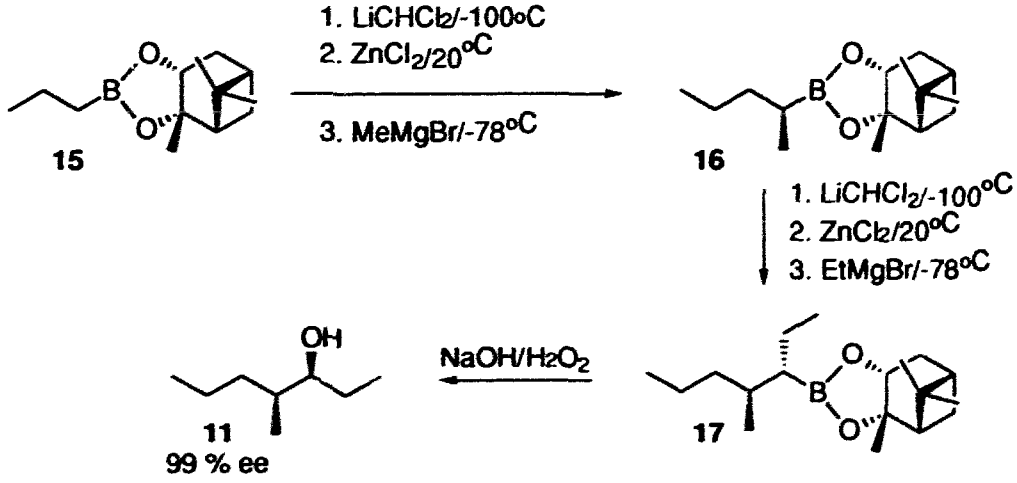


M = -$SnBu_3$, -$SiMe_3$

LA = BF_3•Et_2O, $ZnCl_2$, $AlCl_3$, $SnCl_4$, MgBr•Et_2O, $TiCl_4$, $InCl_3$

Scheme 2.3. Alkylation of aldehydes by crotyl organometallics catalyzed by Lewis Acids.

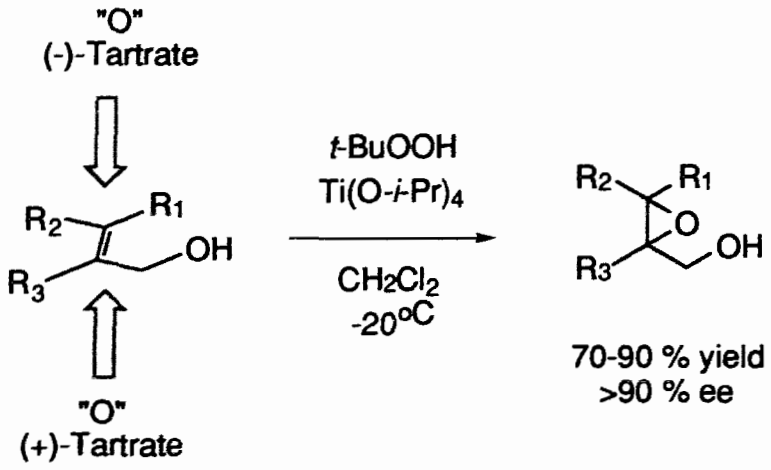
Matteson[42] has developed a one carbon homologation procedure, using (dichloromethyl)lithium and pinanediol boronic esters (e.g., **15**). The process generated chiral boronic esters **16** which can be further elaborated (**17**) before oxidative removal of the boron to give chiral substituted alcohols in >99 % enantiomeric excess. The utility of this methodology has been demonstrated in the syntheses of *exo*-brevicomin and 4-methyl-3-heptanol, **9** (Scheme 2.4).



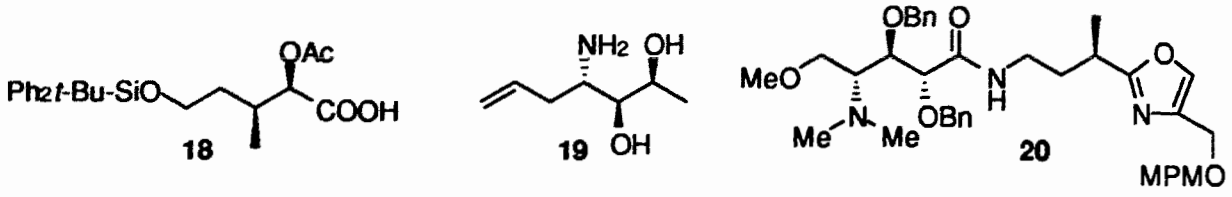
Scheme 2.4. Matteson one-carbon homologation using pinanediol boronic esters.

Sharpless asymmetric epoxidation (Scheme 2.5),[43] in its stoichiometric[44a] or catalytic[44b,c] version, combined with diastereoselective oxirane opening[45] has

been extensively used in the synthesis of chiral alcohols and amines. This methodology has been applied in the synthesis of verrucarinic acid (**18**),[46] amino alcohols e.g., **19**, (total synthesis of anti-cancer aminosugars)[47] and **20** [C(26)-C(37) fragment of the phosphatase inhibitor calyculin A].[45d]



Scheme 2.5. Sharpless asymmetric epoxidation.



Of all methods used to prepare chiral α-methyl secondary alcohols, the Sharpless asymmetric epoxidation combined with diastereoselective ring opening was the most appealing for preparation of chiral palm weevil pheromones. This strategy uses inexpensive reagents and allows synthesis of all four stereoisomers of each pheromone from common intermediates.

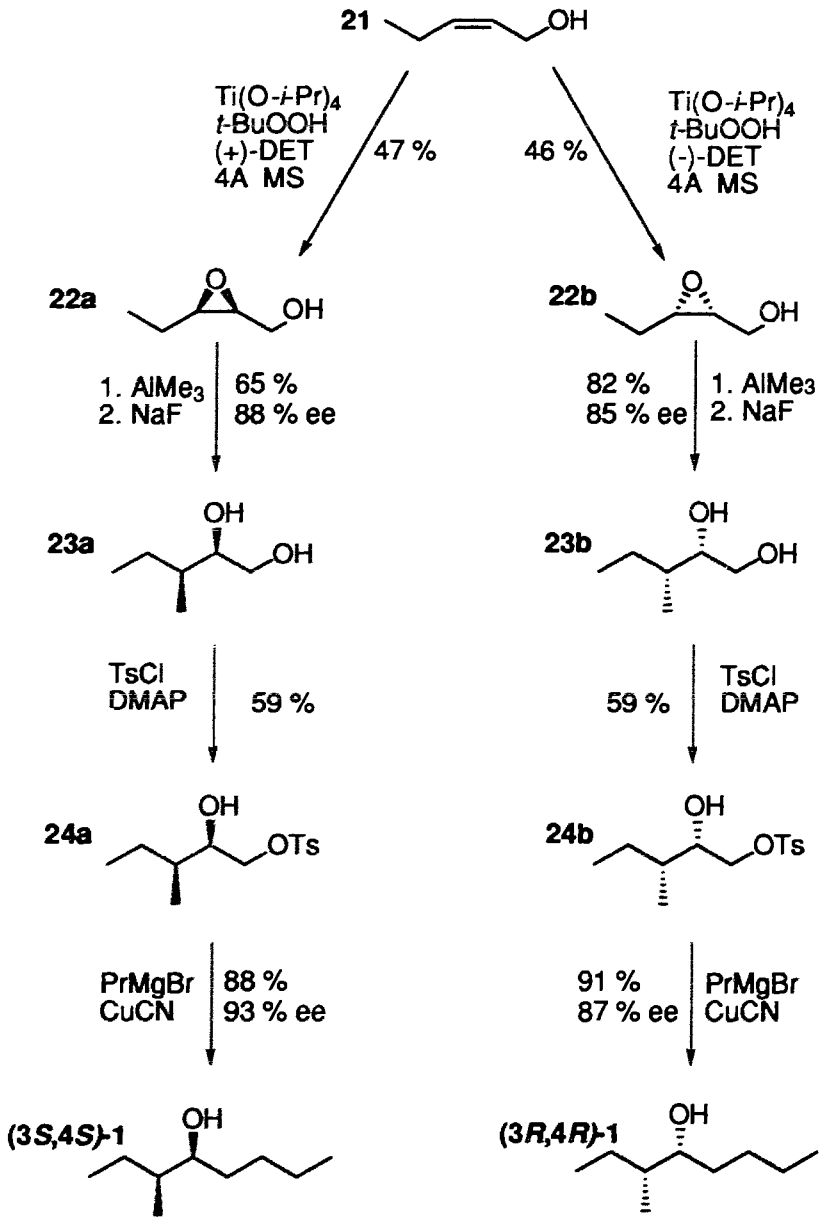
2.11. Stereoselective Synthesis of All Stereoisomers of Phoenicol (1), Cruentol (2), Ferrugineol (7) and Ferrugineone (8).

2.11.1. Synthesis of Phoenicol Stereoisomers.

(*3R, 4R*)-, (*3S, 4S*)-, (*3R, 4S*)-, and (*3S, 4R*)-3-methyl-4-octanol [(*R,R*)-, (*S,S*)-, (*R,S*)- and (*S,R*)-phoenicol)] were synthesized[37a] according to a method modified from Nakagawa and Mori[48] which involved: 1) asymmetric epoxidation of (*Z*-) or (*E*)-2-penten-1-ol;[44c,49] 2) regioselective epoxide opening with trimethylaluminum;[45a-d] 3) selective monotosylation, and 4) alkylation using an organomagnesium cuprate (Schemes 2.6 and 2.7).[50] This strategy has previously been used by Nakawaga and Mori to prepare two stereoisomers of the elm bark beetle pheromone, 4-methyl-3-heptanol (**9**).[48] By this protocol, (3*S*,4*S*)-4-methyl-3-heptanol was obtained in 11 % yield (over four steps) and 84 % ee, whereas its (3*S*,4*R*)-isomer was obtained in 12 % overall yield (four steps) and 92 % ee.

In the present work, the asymmetric epoxidation of commercially available (*Z*)-2-penten-1-ol (**21**) was initially optimized. The nature of the tartrate (diethyl *vs.* diisopropyl tartrate), temperature and ratio of Ti(O-*i*-Pr)$_4$ and *t*-BuOOH were varied to maximize the enantiomeric excess of the product (see Table 2.2, pp. 42 and later discussion).

Synthesis of the *syn*-isomers commenced with the asymmetric epoxidation of **21** to afford epoxides **22a** and **22b** in modest chemical and optical yields (Scheme 2.6). Diastereoselective oxirane opening using three equivalents of $AlMe_3$ in the presence of a catalytic amount of *n*-BuLi allowed introduction of the α-methyl group without stereochemical scrambling. Selective monotosylation and chain extension afforded (3*S*,4*S*)-**1** in 16 % overall yield and 93 % ee. Its antipode, (3*R*,4*R*)-**1** was obtained in 20 % overall yield and in 87 % ee.

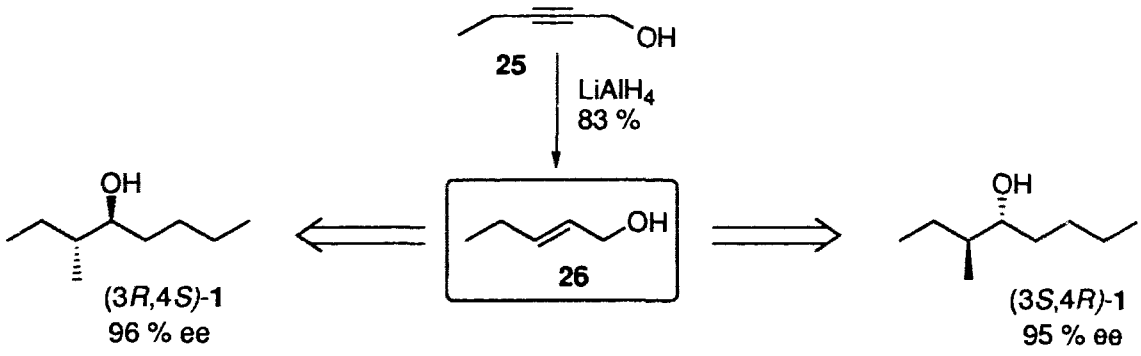


Scheme 2.6. Synthesis of *syn*-isomers of phoenicol.

Optical purities of epoxides were determined by GC analyses of the corresponding *O*-acetyllactyl esters[51] on a DB-23 fused silica column.

The analogous *anti*-isomers were synthesized according to the same synthetic scheme using (*E*-)-2-penten-1-ol, **26**, (Scheme 2.7). Alkenol **26** was prepared by hydride reduction of 3-pentynol (**25**) in 83 % yield.[52] (3*R*,4*S*)-**1** was

prepared in 13 % overall yield and 96 % ee and (3*S*,4*R*)-**1** was obtained in 14 % overall yield and 95 % ee.



Scheme 2.7. Synthesis of the *anti*-isomers of phoenicol.

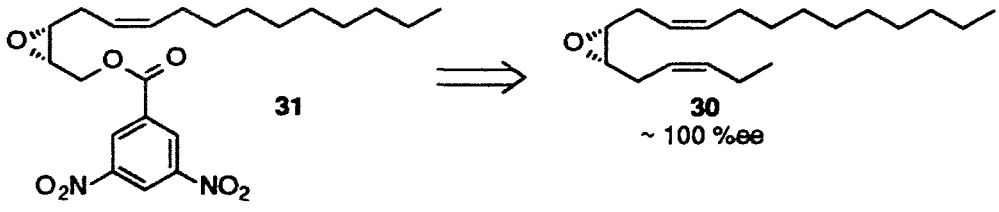
In contrast to the synthesis of Nakagawa and Mori,[48] which used stoichiometric amounts of tartrate, the present epoxidation used 0.5 equivalents of catalyst in the presence of 4A molecular sieves coupled with addition of the oxidizing agent at -78°C to increase optical purity of the epoxide (Table 2.2). Examination of the reaction conditions showed that higher enantioselectivities were achieved with diethyl tartrate compared to diisopropyl tartrate and when the oxidizing agent (*t*-BuOOH) was added at -78°C rather than at -20°C (Table 2.2). Epoxidations maintained at -20°C until 97-98 % conversion required two days for **22a** and **22b** and 3-4 h for **27a** and **27b**. Since the epoxides are slightly soluble in water, non aqueous work-up[44c] was used. This was followed by flash chromatography. Separation of tartrate from epoxides required two or more chromatographic cycles (non-aqueous work-up only removes titanium as the citrate complex) and may explain the modest isolated yields.

27a **27b**

Diastereoselective epoxide ring-opening was conducted with neat $AlMe_3$ rather than $AlMe_3$ in hexane solution. This modification accelerated the reaction to completion in less than one hour compared to 2-3 days reported by previous workers. Work-up *via* addition of saturated NaF[45b] at -40°C rather than the recommended aqueous HCl, improved isolated yields of 3-methyl-1,2-pentanediols (59-82 %). This is probably due to the high solubility of the diols in water. Products arising from breakage of the α-bond or retention of configuration during the cleavage of the β-epoxide bond were not detected by GC or ^1H NMR analysis.

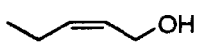
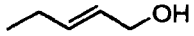
Syn isomers of **1** were obtained with moderate optical purities from asymmetric epoxidation of *Z*-alkenols. This is not surprising, since *Z*-alkenols are only slowly epoxidized (epoxidation takes 2-3 days for **22** *versus* 3-4 h for **27**) and give variable enantioselectivity.[43b]

In the synthesis of enantiomers of (3*Z*,9*Z*)-*cis*-6,7-epoxy-3,9-nonadecadiene, **30**, a pheromone component of the European moth, *Erannis defoliaria*, Mori and Brevet,[53] generated chirally pure epoxides through several recrystallizations of 3,5-dinitrobenzoate derivatives, a process that leads to yields in the range of 40 % for the pure dinitrobenzoates (e.g., **31**). In similar fashion, optically pure pine scale pheromones were synthesized.[54]



This strategy failed when applied to epoxides **22a** and **22b** since the *p*-nitrobenzoates and 3,5-dinitrobenzoates of both epoxides were oils between 0°C and 25°C.

Table 2.2. Effect of temperature, nature of the tartrate and epoxidation method on the optical purity of selected epoxides.

Substrate	Method*	Tartrate§	Temperature	Product	%ee¥
	A	(+)-DIPT	-78°C to -20°C[a]		88
	B	(+)-DIPT	-78°C to -20°C		86
	C	(+)-DIPT	-20°C[b]		80
	A	(+)-DET	-78°C to -20°C		90
	B	(+)-DET	-78°C to -20°C		90
	C	(+)-DET	-20°C		86
	A	(+)-DIPT	-78°C to -20°C		90
	B	(+)-DIPT	-78°C to -20°C		89
	C	(+)-DIPT	-20°C		81
	A	(+)-DET	-78°C to -20°C		97
	B	(+)-DET	-78°C to -20°C		96
	C	(+)-DET	-20°C		93
	A	(+)-DIPT	-78°C to -20°C		92
	B	(+)-DIPT	-78°C to -20°C		91
	C	(+)-DIPT	-20°C		86
	A	(+)-DET	-78°C to -20°C		95
	B	(+)-DET	-78°C to -20°C		96
	C	(+)-DET	-20°C		92

(a) Tartrate, Ti(*i*-OPr)$_4$ and alkenol mixed at -78°C and aged for 15 min before addition of *t*-BuOOH and warming to -20°C.

(b) Same as (a) but at -20°C.

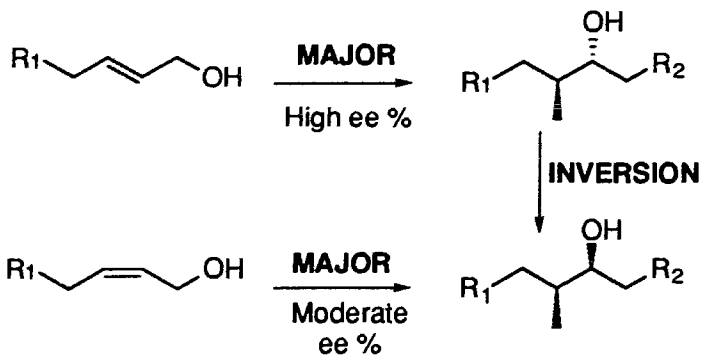
(*) Method A: stoichiometric, no molecular sieves added. Method B: 50 mol% tartrate, molecular sieves added. Method C: catalytic, 5 mol% tartrate molecular sieves added.

(§) (+)-DIPT: (+)-diisopropyl tartrate. (+)-DET: (+)-diethyl tartrate.

(¥) Determined by GC analyses of *O*-acetyllactyl esters on a DB-23 fused silica column. Similar results were obtained when (-)- tartrates were used.

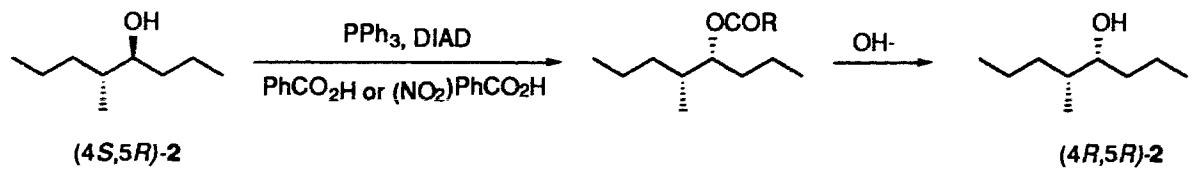
2.11.2. Synthesis of Cruentol Stereoisomers.

Anti-α-substituted alcohols of high optical purity are easily obtained from the corresponding epoxides (e.g., (3*R*,4*S*)-**1** from **27a** or (3*S*,4*R*)-**1** from **27b**). Sharpless asymmetric epoxidation of *E*-alkenols produces epoxides with high enantiomeric excess. It is possible to prepare to the *syn*-isomers through inversion of configuration of the hydroxyl group without perturbation of the adjacent stereogenic centre or reduction of the overall optical purity (Scheme 2.8).



Scheme 2.8. Proposed obtention of *syn*-stereoisomers through configurational inversion of hydroxyl bearing carbon.

The *syn* isomers of 5-methyl-4-octanol, [cruentol, (**2**)] were obtained in high enantiomeric excess through Mitsunobu[55] mediated inversion of configuration of the hydroxyl bearing carbon of (4*S*,5*R*)-**2** and (4*R*,5*S*)-**2** (Scheme 2.9).

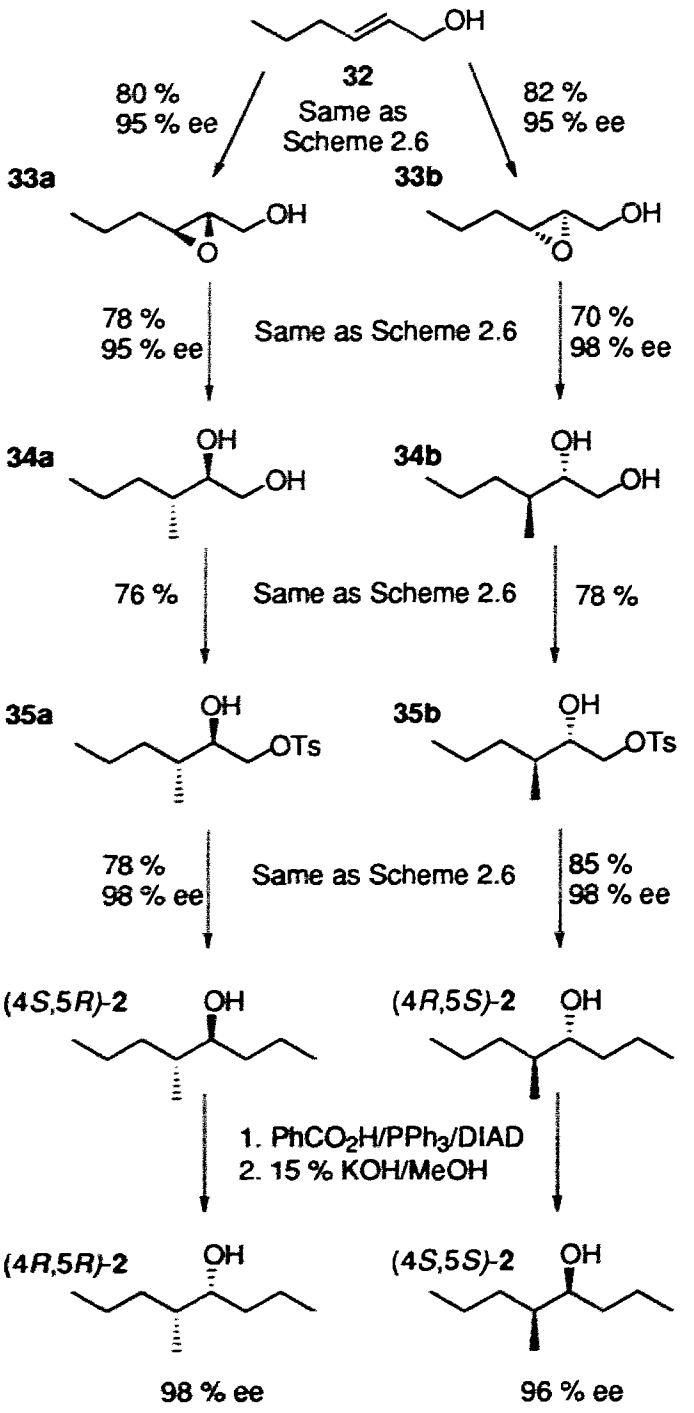


Scheme 2.9. Mitsunobu mediated inversion of (4*S*,5*R*)-cruentol .

Synthesis of the *anti* isomers of 5-methyl-4-octanol was achieved following the procedure used above for preparation of the *anti* isomers of 3-methyl-4-octanol (phoenicol) (Scheme 2.10). Thus, commercially available (*E*)-2-hexen-1-ol (**32**) was epoxidized using (2*R*,3*R*)- or (2*S*,3*S*)-diethyl tartrate to give epoxides **33a** and **33b**, respectively, in good chemical yield (80-82 %) and optical purity (95 % ee) (Scheme 2.10). Epoxidations were maintained at -20°C until 97-98 % conversion (3-4 h). Ferrous sulfate/tartaric acid work-up[44c] followed by chromatography (single cycle) cleanly gave the epoxides. Diastereoselective epoxide ring-opening with neat $AlMe_3$, followed by quenching with 3 M HCl, afforded the corresponding diols after flash chromatography (70-78 % yield, 95-98 % ee). As above, products arising from breakage of the α-bond or retention of configuration during cleavage of the epoxide were not detected by GC or ^1H NMR analysis. Tosylation and cuprate displacement afforded (4*S*,5*R*)-**2** (37 % yield over four steps) and (4*R*,5*S*)-**2** (38 % yield over four steps) in high optical purity (98 % ee).

Use of *p*-nitrobenzoic acid/PPh_3/diethyl azocarboxylate (DEAD) in THF (Mitsunobu reaction), yielded less than 25% of the corresponding *p*-nitrobenzoates. Successful Mitsunobu conditions (~51 % yields) employed benzoic acid/Ph_3P/diisopropyl azocarboxylate (DIAD) and benzene as a solvent.[47,56] No epimerization or retention of configuration was observed by ^1H NMR analysis of the reaction mixtures.

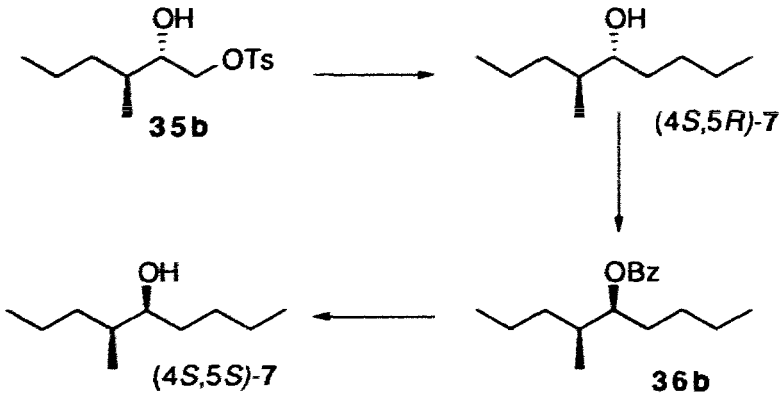
Syn stereoisomers of cruentol were obtained in 18-19 % yield (96-98 % ee) over six steps. Optical purities of the alcohols were determined by GC analyses on the Cyclodex-B column and by GC analyses of the *O*-acetyllactate esters. Optical purities of epoxides **33a** (95 %) and **33b** (95 %) were determined by GC analysis of corresponding *O*-acetyllactyl esters[51] on a DB-23 fused silica column.



Scheme 2.10. Synthesis of stereoisomers of 5-methyl-4-octanol.

2.11.3. Synthesis of Ferrugineol and Ferrugineone Stereoisomers.

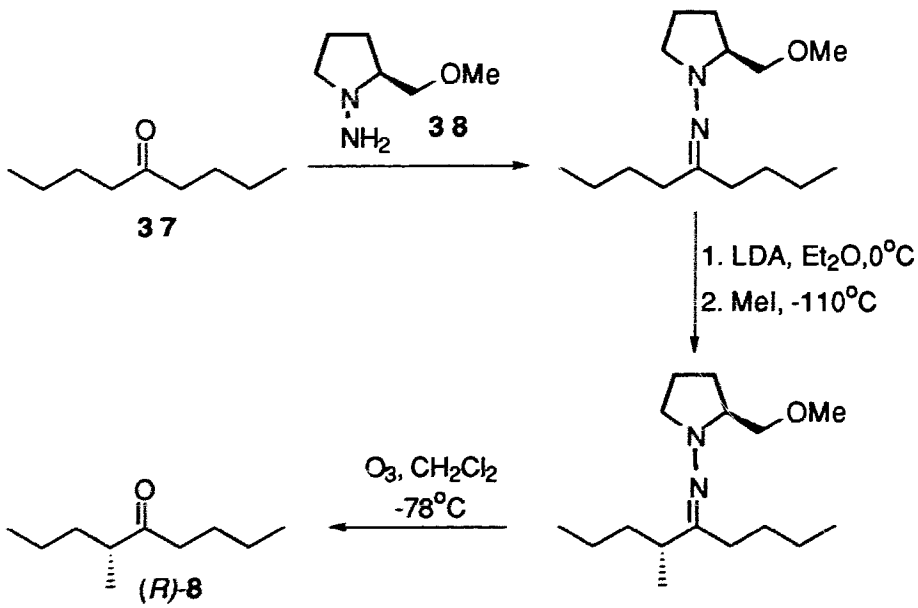
Stereoisomers of **7** were produced according to routes used for preparation of structurally related pheromones of *R. phoenicis* and *R. cruentatus*. (2*S*,3*S*)-3-Methyl-1-tosyloxyhexan 2-ol (**35b**) and its antipode were alkylated *via* cuprate (Grignard) displacement of (*4S,5R*)-**7** and its enantiomer. The hydroxyl bearing carbons of both stereoisomers were inverted through Mitsunobu chemistry (e.g., *via* **36b**) to produce (*4S,5S*)-**7** and its antipode in 95-98 % ee (Scheme 2.11).



Scheme 2.11. Synthesis of ferrugineol stereoisomers.

Ketone (*R*)-**8** has previously been prepared by Enders and coworkers in excellent optical purity (98 % ee) using (*S*)-1-amino-2-methoxymethyl-pyrrolidine (SAMP, **38**) as a chiral auxiliary (Scheme 2.12).[57]

Although both enantiomers of the chiral auxiliary are available, this method requires stoichiometric amounts of these expensive reagents. Since the stereoisomers of **7** were obtained with very high enantiomeric excess, the oxidation of these alcohols to the corresponding ketone was investigated. Brown and coworkers,[58] found that Jones' oxidation of alcohols possessing chiral α-



Scheme 2.12. Previous synthesis of (*R*)-**8** using SAMP-hydrazone method

carbons proceeds without loss of optical activity if conducted in a two-phase system (Et_2O:H_2O). Applying Brown's procedure, (*4S,5R*)-**7** and its antipode yielded (*S*)-**2** and (*R*)-**2**, respectively, in high chemical yield and optical purity. Synthesis of ketones (*S*)-**2** and (*R*)-**2** in 30-35 % yield over six steps (95 % ee) from (*E*)-2-hexen-1-ol is comparable to the 44% overall yield obtained in the previous three step synthesis of (*R*)-**2**.[57] Optical purities of (*4S,5R*)-**7** (96 %), (*4R,5S*)-**7** (95 %), (*4S,5S*)-**7** (98 %), (*4R,5R*)-**7** (98 %), (*S*)-**8** (95 %) and (*R*)-**8** (95 %) were determined by GC analyses on a Cyclodex-B fused silica column.

2.12. Determination of Configuration of Weevil-Produced Pheromones.

Individually, phoenicol, cruentol and ferrugineol each elute from a polar SP-1000-coated fused silica column as two resolved stereoisomers. The components eluting with the shorter retention times coincided with the male-produced pheromone of each weevil and were hypothesized to be the *syn*

diastereoisomers. This assignment was made by analogy with the chromatographic behaviour of the aggregation pheromone 4-methyl-3-heptanol of the smaller European elm bark beetle, *Scolytus multistriatus* (Marsham), which also has two stereogenic centres and exists as two diastereoisomeric forms which are separable by GC on a polar Carbowax 20M column and the naturally-produced pheromone was identified as (4*S*,3*S*)-4-methyl-3-heptanol.[48,59,60] Analysis of stereoselectively prepared *syn* and *anti* stereoisomers of phoenicol, cruentol and ferrugineol confirmed the assignments.

Synthetic (*R,R*)-, (*S,S*)-, (*R,S*)-, and (*S,R*)-isomers of each pheromone (phoenicol, cruentol and ferrugineol) were separated with baseline resolution on a Cyclodex-B fused silica column. GC-MS analyses under selected ion monitoring (GC-MS-SIM) on a Cyclodex-B column of weevil-produced pheromones revealed that males of *R. phoenicis* , *R. cruentatus*, *R. bilineatus*, *R. ferrugineus* and *R. vulneratus* produce the (*S,S*)-stereoisomers of their pheromones (Figures 2.14, 2.15, 2.16, 2.17). *S. multistriatus* also produces the *S,S*-stereoisomer of 4-methyl-3-heptanol,[59] whereas the large European elm bark beetle, *Scolytus scolytus* (F.), produces both (*3S,4S*)- and (*3R,4S*)-4-methyl-3-heptanol.[60]

Because (*4S,5S*)-**7** is an aggregation pheromone in both *R. ferrugineus* and *R. vulneratus* it was hypothesized that enantiospecific production of and response to **8** may impart species-specificity of pheromone communication. Lack of pronounced differences in response to **7** and **8** suggested that pheromone chirality may impart species specificity of semiochemical communication.[29a] However, GC-MS-SIM analyses on a Cyclodex-B column of weevil-produced **8**, synthetic **8** and each of the two enantiomers of **8** indicated that both *R. ferrugineus* and *R. vulneratus* produce (*S*)-**8** (Figure 2.17).[38b]

Production of and response solely to (4*S*,5*S*)-**7** by *R. bilineatus* (Figure 2.18), *R. ferrugineus* and *R. vulneratus* (Figure 2.19) suggest other (semiochemical) signals contributing to reproductive isolation of these weevils. Male-produced 4-methyl-5-nonanone in sympatric *R. ferrugineus* and *R. vulneratus* may impart specificity of pheromone communication, if its production were enantio- and species-specific. Geographically isolated *R. bilineatus*, in contrast, does not compete with other *Rhynchophorus* weevils for pheromone communication channels, and for that reason may only produce (4*S*,5*S*)-**7** but not the corresponding ketone. GC-EAD analysis on a Cyclodex-B column of weevil-produced **8**, synthetic **8** and each of the two enantiomers of **8** indicated that both *R. ferrugineus* and *R. vulneratus* antennally respond more strongly to (*S*)-**8** than to (*R*)-**8** (Figure 2.19).

Coupled gas chromatographic-electroantennographic detection (GC-EAD) of synthetic phoenicol (Figure 2.20), cruentol (Figure 2.21) and ferrugineol (Figure 2.18 and 2.19) revealed strong antennal responses to weevil-produced (*S,S*)-phoenicol (*S,S*)-cruentol and (*S,S*)-ferrugineol. Lack of or reduced response to later eluting stereoisomers cannot be explained by an antennal refractory period. In GC-EAD recordings with the same Cyclodex-B column, antennae of the Asian palm weevils *R. ferrugineus* and *R. vulneratus* distinctively respond to both, closely eluting (*S*)- and (*R*)-4-methyl-5-nonanone (Figure 2.19). Similarly, in GC-EAD analyses of oil palm stem volatiles antennae of male and female *R. phoenicis* responded within 2.5 minutes to four esters of which two were barely baseline separated (Figure 2.8). Strong antennal activity of the (*S,S*)-, and weak activity of (*S,R*)- and (*R,S*)-isomers of phoenicol and cruentol (Figures 2.20 and 2.21) suggest that sensory recognition of the natural (*S,S*)-stereoisomer is more dependent on the stereochemistry of the methyl than the

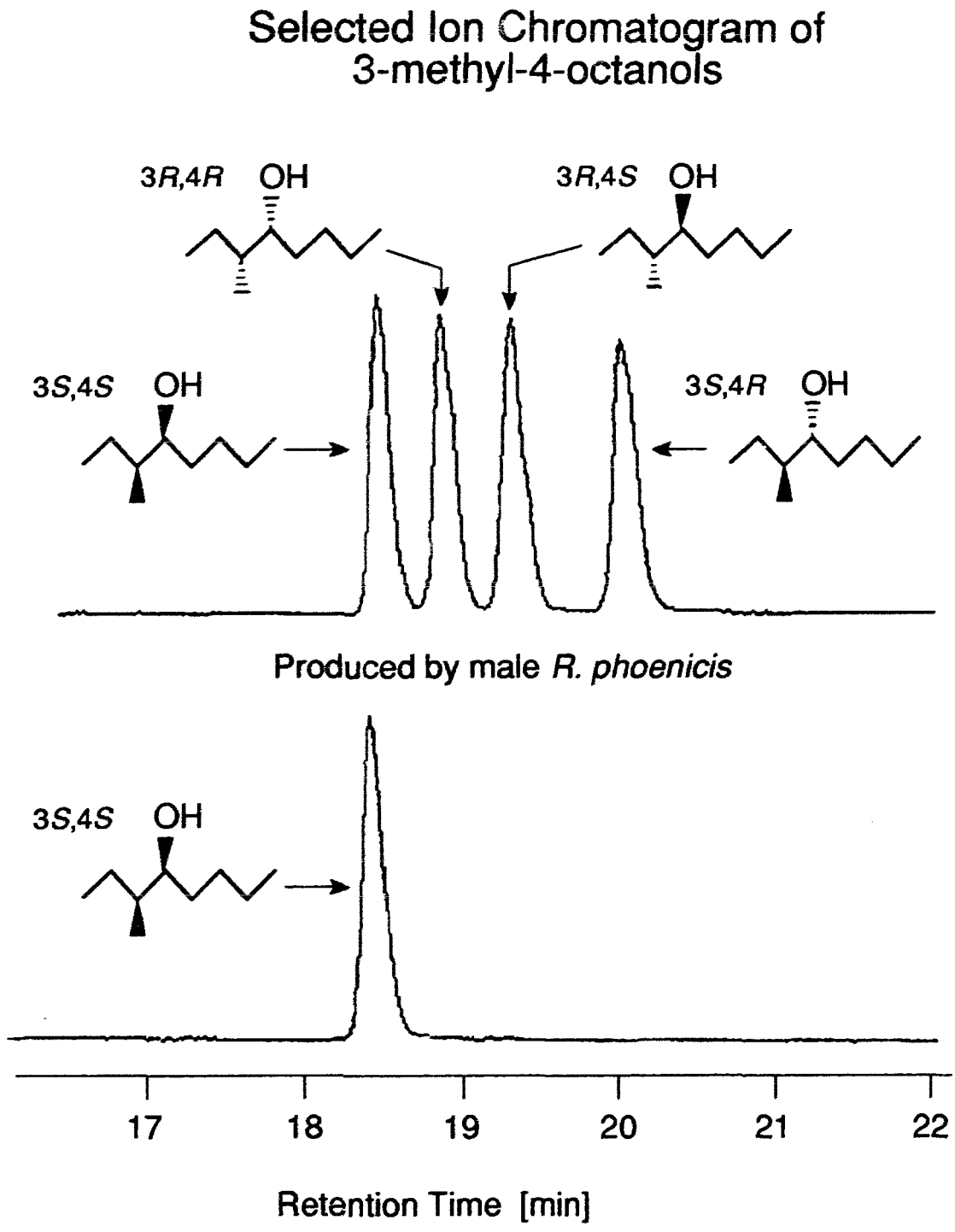


Figure 2.14. Selected ion chromatogram (*m/z* 127) of stereoisomeric and weevil-produced 3-methyl-4-octanol. Ion *m/z* 127 [$(M^+ + H^+ - H_2O)$] is the base ion of the full scan mass spectrum in CI mode (Cyclodex-B fused silica column (30 m X 0.25 mm ID); 90°C isothermal; linear flow velocity of carrier gas : 35 cm s^{-1}; injector temperature: 220°C).

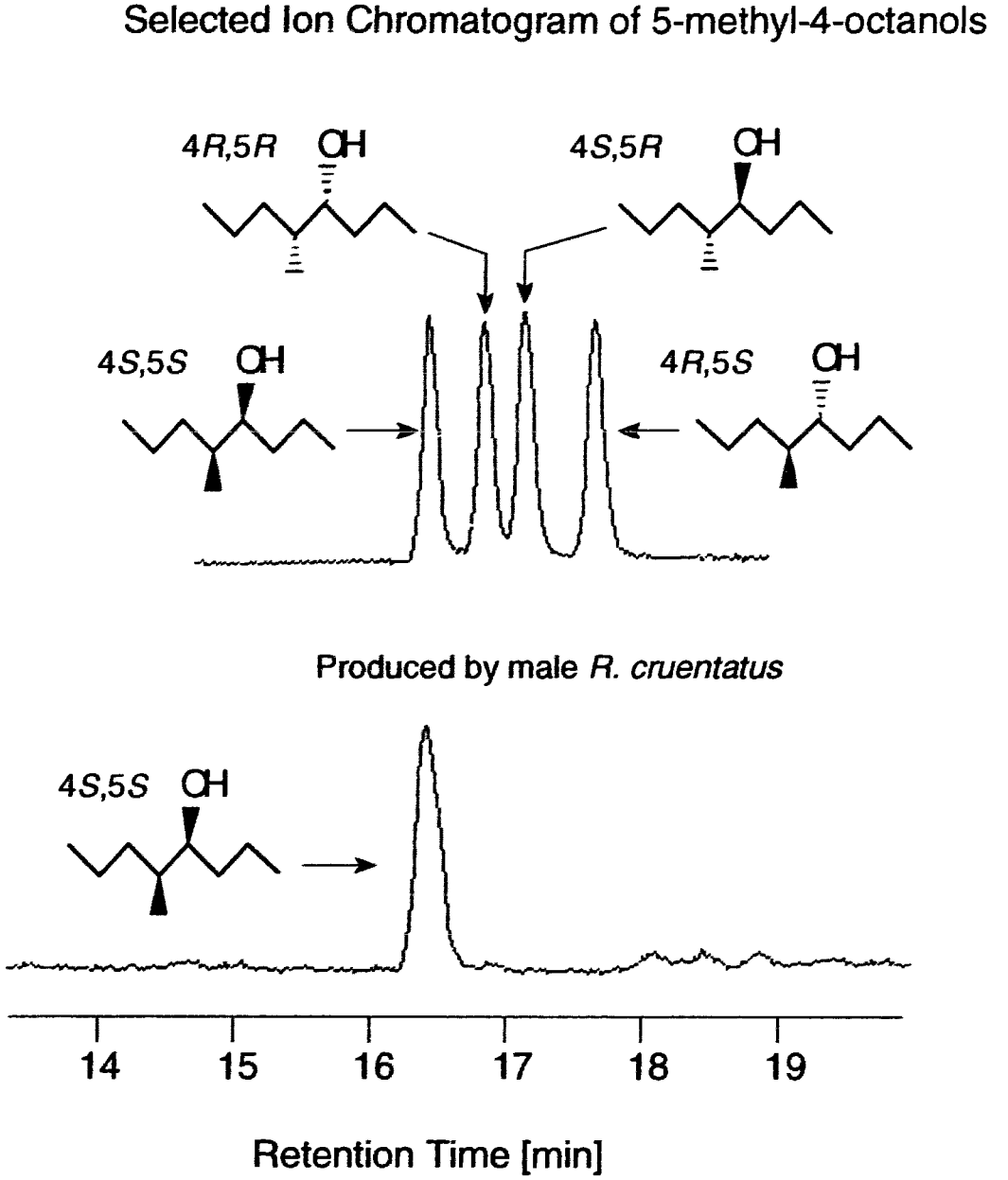


Figure 2.15. Selected ion chromatogram (*m/z* 127) of stereoisomeric and weevil-produced 5-methyl-4-octanol. Ion *m/z* 127 [$(M^+ + H^+ - H_2O)$] is the base ion of the full scan mass spectrum in CI mode (chromatographic conditions as in Figure 2.14).

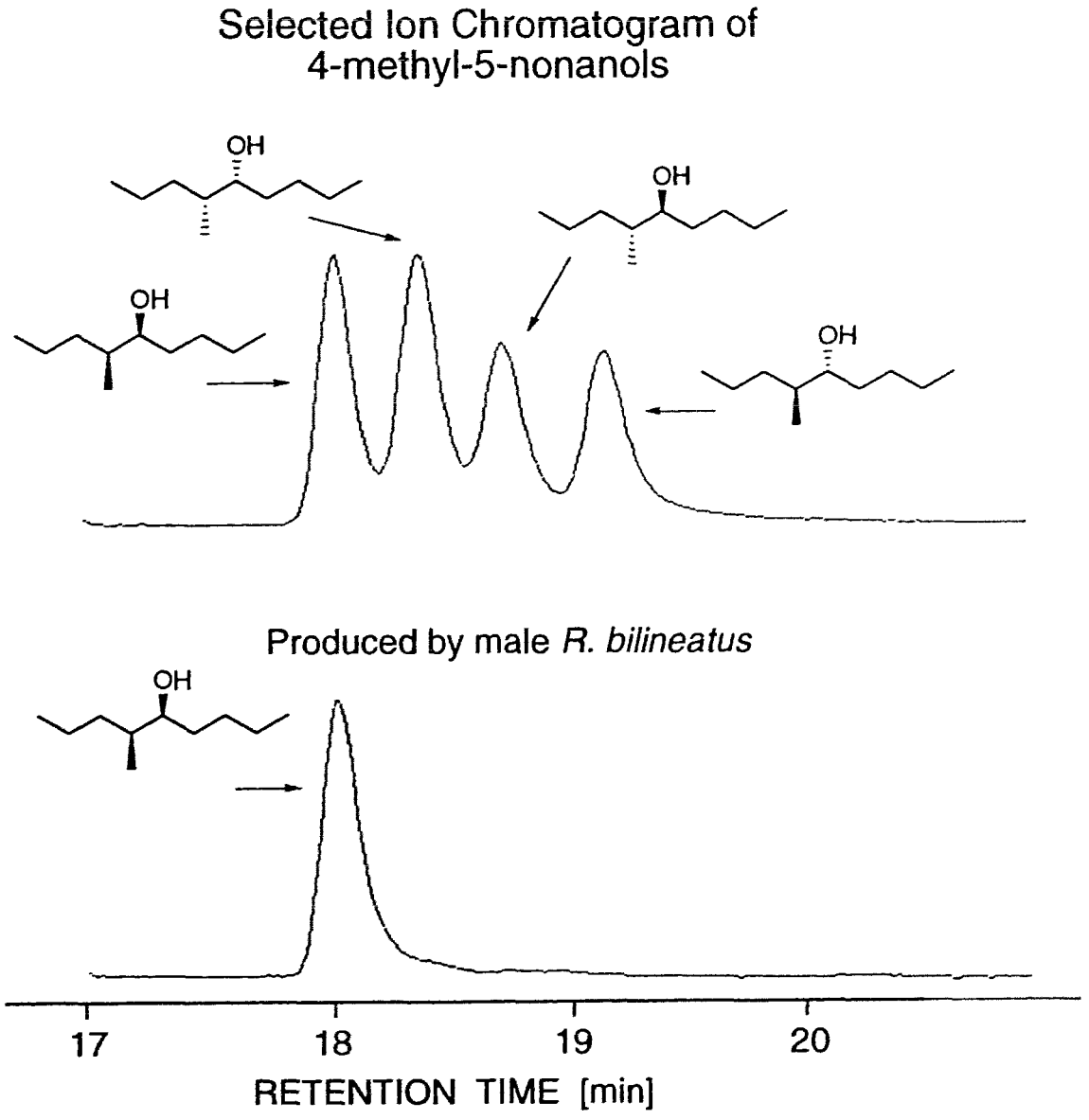


Figure 2.16. Selected ion chromatogram (*m/z* = 69, 87 and 101) of stereoisomeric and weevil produce **7**. Ion *m/z* 101 [(M^+-C_4H_9)] is the base ion of full scan in EI mass spectrum (Cyclodex-B fused silica column (30 m X 0.25 mm ID); 100°C isothermal; split injector; linear flow velocity of carrier gas: 35 cm s^{-1}; injector temperature: 220°C).

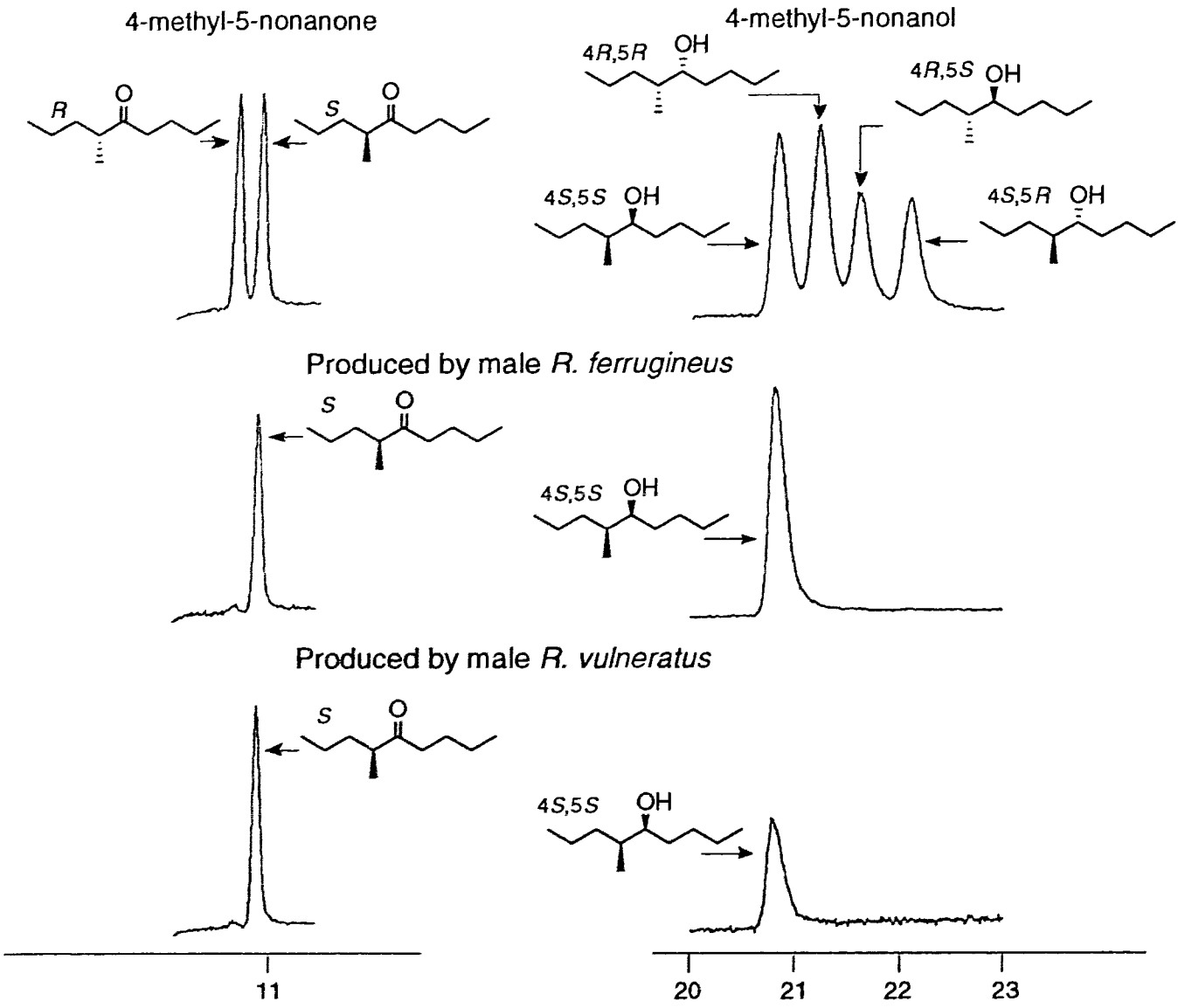


Figure 2.17. Selected ion chromatograms (*m/z* 157 and *m/z* 141) of stereoisomeric and weevil-produced 4-methyl-5-nonanone (**8**) and 4-methyl-5-nonanol (**7**). Ions *m/z* 157 [$(M^+ + H^+)$] and *m/z* 141 [$(M^+ + H^+ - H_2O)$] are respectively the parent ions of the full scan mass spectra in CI mode of **8** and **7**, column and chromatography as in Figure 2.16 but conditions were slightly different. Retention time variation primarily due to differential MS vacuum between runs.

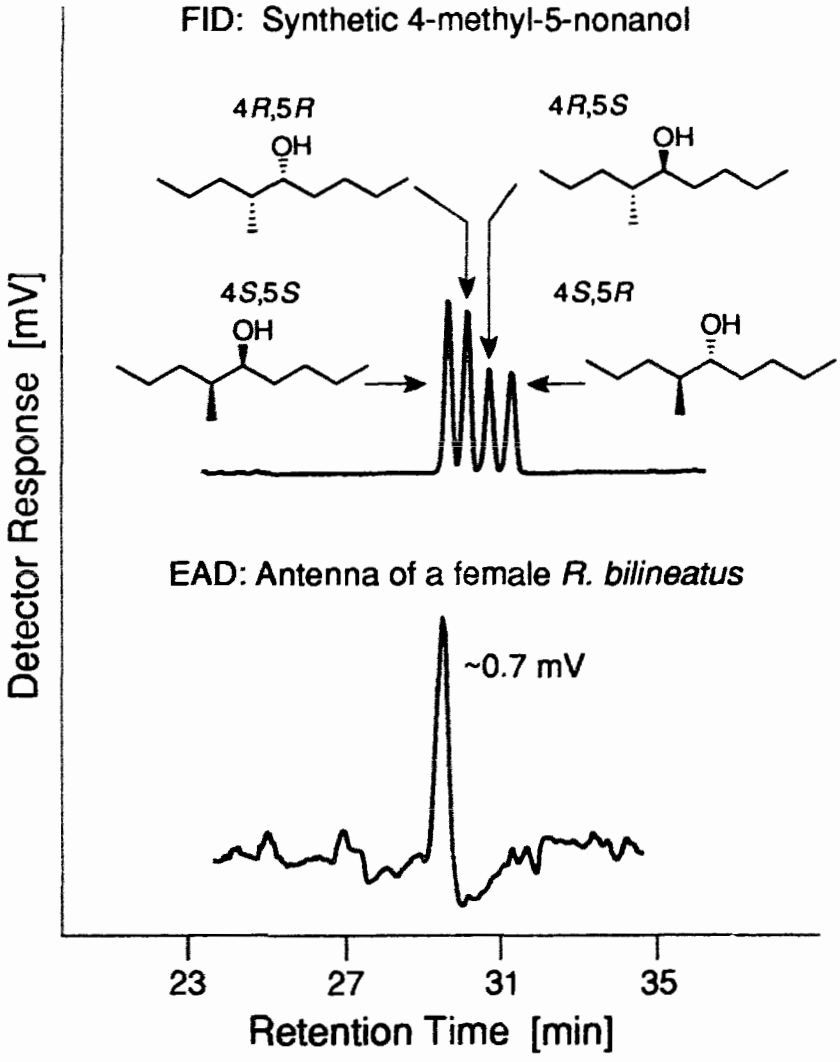


Figure 2.18. Representative GC-EAD recordings of female *R. bilineatus* antenna responding to stereoisomers of 4-methyl-5-nonanol (**7**). Column and chromatographic conditions as in Figure 2.16. Use of different gas chromatograph instrument in this determination accounts for the difference in retention times between Figure 2.16 and Figure 2.18.

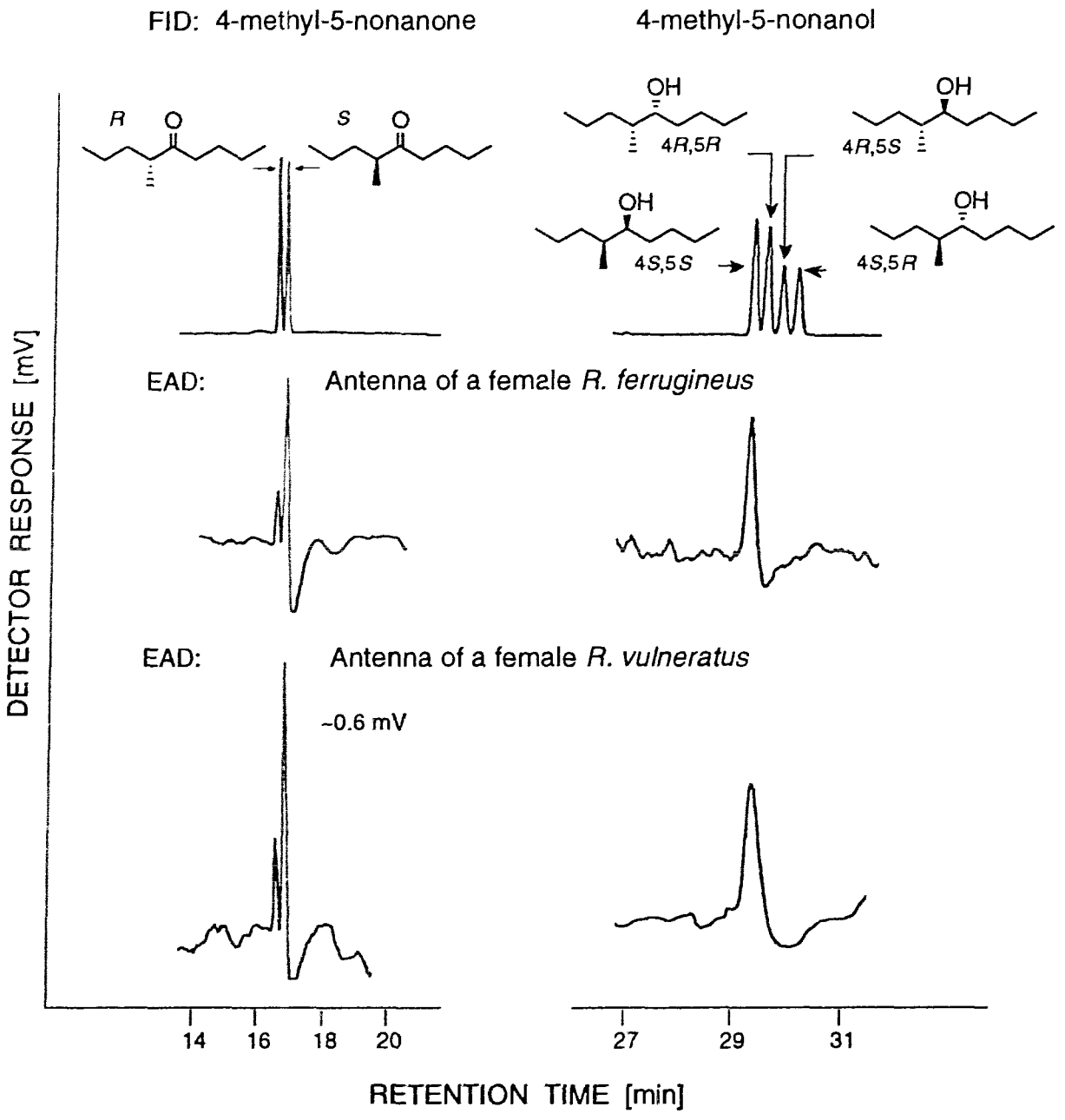


Figure 2.19. Representative GC-EAD recordings of female *R. ferrugineus* and *R. vulneratus* antenna responding to stereoisomers of 4-methyl-5-nonanone (**8**) and 4-methyl-5-nonanol (**7**). Different weevil antennae and chart speeds of 0.5 and 1.0 cm *per* min were used for the analyses of **8** and **7**, respectively. Column and chromatographic conditions as in Figure 2.16. Use of different gas chromatograph instrument in this determination accounts for difference in retention times between Figures 2.16 and 2.19.

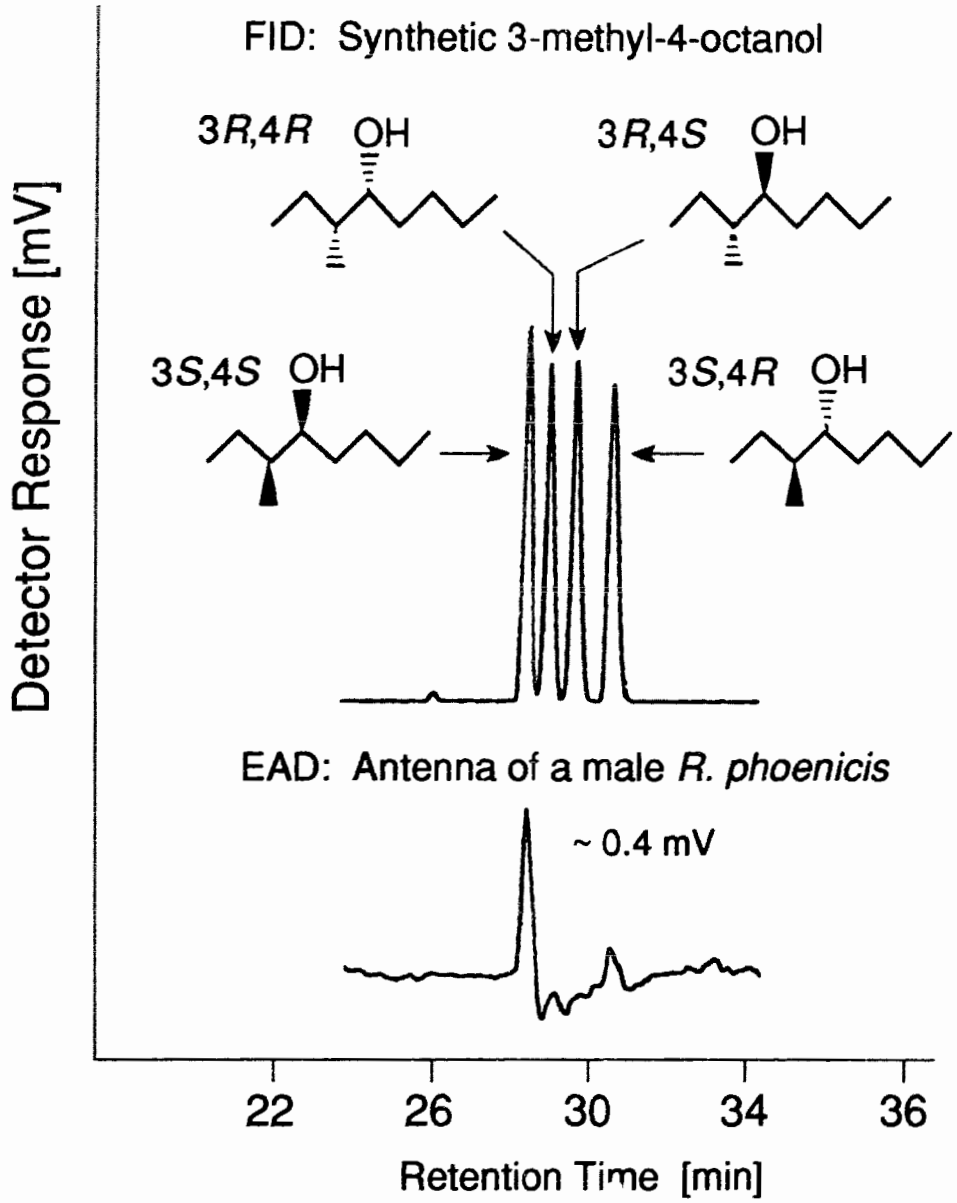


Figure 2.20. Representative GC-EAD recording of a female *Rhynchophorus phoenicis* antenna responding to stereoisomers of 3-methyl-4-octanol (**1**); split injection; column and chromatographic conditions as in Figure 2.14. Use of different gas chromatograph instrument in this determination accounts for the difference in retention times between Figures 2.14 and 2.20.

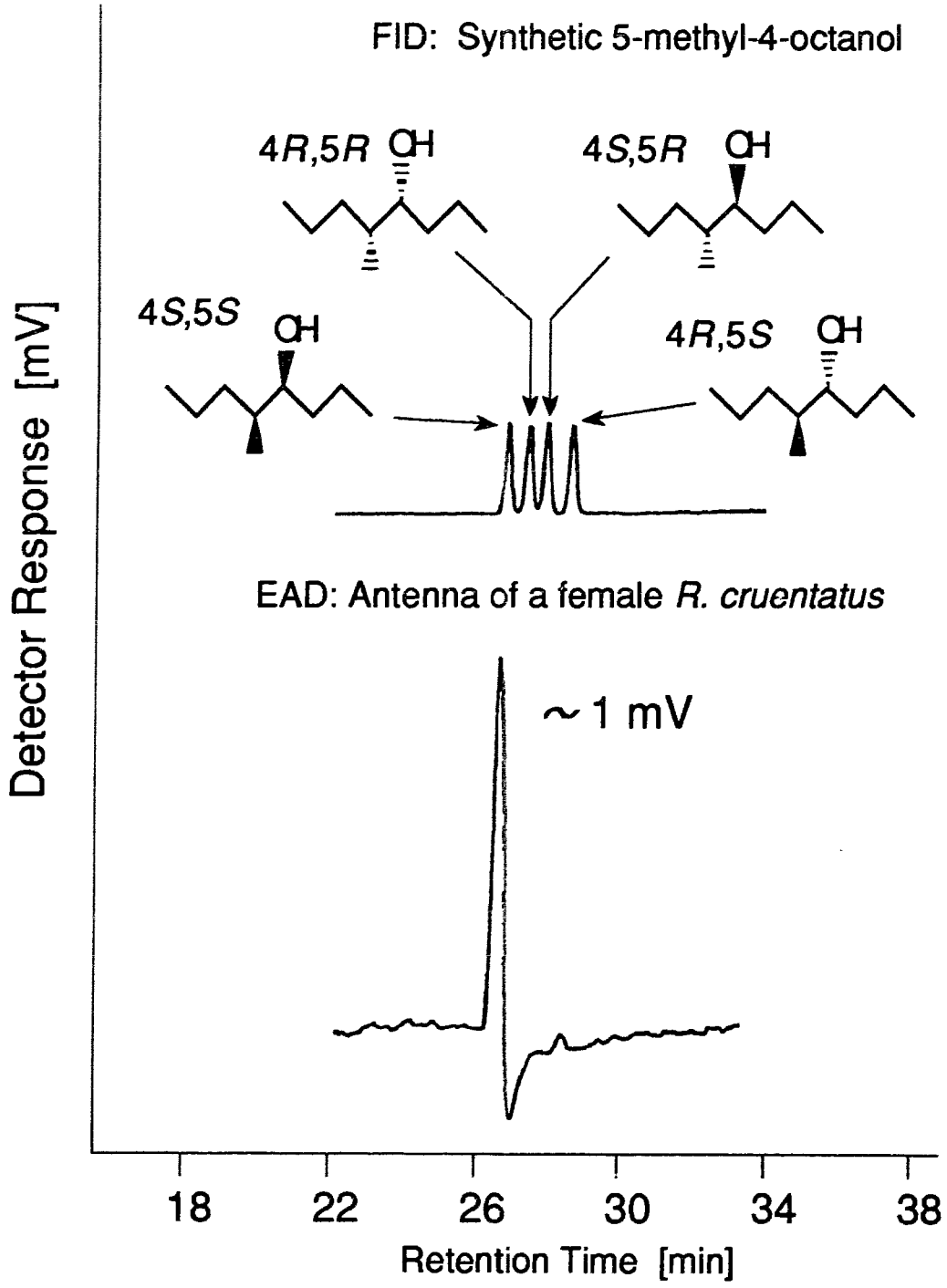


Figure 2.21. Representative GC-EAD recording of a female *Rhynchophorus cruentatus* antenna responding to stereoisomers of 5-methyl-4-octanol (**2**); split injection; column and chromatographic conditions as in Figure 2.16. Use of different gas chromatograph instrument in this determination accounts for difference in retention times between Figures 2.15 and 2.21.

hydroxyl group. Similar response was not observed in any of the Asian palm weevils.

2.13. Field Activity of Pheromone Stereoisomers.

2.13.1. *R. phoenicis.*[vi]

A 6-replicate, 5-treatment experiment in a 10-year-old oil palm stand (La Me Research Station, Côte d'Ivoire) tested attraction of oil palm stem tissue (250 g) alone or in combination with either stereoisomeric, (*S,S*)-, (*R,R*)- or (*S,S*)- plus (*R,R*)-phoenicol. Traps were attached at chest height to oil palms in randomized blocks with traps at 27 m intervals and blocks 81 m apart.[12] (*S,S*)- or (*R,R*)-phoenicol were released at 0.5 mg *per* day (@ 25°C) from single 1.0 mm ID capillary tubes cut 1.0 cm above pheromone meniscus and placed inside 1.5 mL capped polypropylene centrifuge tubes with two 2 mm holes below the top. Racemic phoenicol was dispensed at 2 mg *per* day (@ 25°C) from four capillary tubes inside a 400 µL capped polypropylene centrifuge tube. Fresh palm tissue in each trap was treated with the insecticide (biodegradable) Evisect "S" (0.3 % thiocyclam-hydrogenoxalate in water) to retain captured weevils. Trap catch data were subjected to analysis of variance followed by Scheffé test for comparisons of means.[61]

2.13.2. *R. cruentatus.*[vii]

A 12-replicate, 4-treatment experiment in the same location as for weevil collection tested attraction of *Sabal palmetto* tissue (1.5 kg) alone or in combination with either stereoisomeric, (*S,S*)-, or (*R,R*)-cruentol. Traps[16a] were

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[vi] Field test conducted by Dr. Gerhard Gries and Ms. Regine Gries, Department of Biological Sciences, Simon Fraser University.

[vii] Field tests conducted by Dr. Robin Giblin-Davis, IFAS, University of Florida, Fort Lauderdale, Florida.

secured on the ground in randomized complete blocks with traps at 20 m intervals and blocks at least 50 m apart. The test used a modification of Weissling's trap,[16a] which contained a tapered, inverted white plastic container (4.9 L) with a screened lid suspended screen side down in the mouth of the bucket by a capped PVC pipe (1.3 cm diameter) from which pheromone release devices were hung. (*S,S*)-, or (*R,R*)-cruentol were released at 0.06 mg *per* day (@ 25°C) from one and stereoisomeric cruentol from four bottom-sealed 1 mm ID capillary tubes cut 1.0 cm above pheromone liquid meniscus and placed in bottom-sealed microhematocrit tubes (length 75 mm, ID 1.1-1.2 mm). Hematocrit tubes were placed into 400 µL capped polypropylene centrifuge tubes (6 mm holes were drilled 1.8 cm from the top). Placement of the pheromone filled capillary tubes inside a second hematocrit tube slowed release of the pheromone by eight times compared to the experiment conducted with phoenicol. Trap catch date were subjected to square root (x + 0.5) transformation and ANOVA followed by Waller-Duncan k-ratio *t* test to test differences between means ($p \leq 0.05$).

2.13.3. *R. bilineatus.*[viii]

Field experiments were conducted in the Vimy plantation, Papua New Guinea, which is near the location used for testing of the diastereoisomeric mixture. Traps and experimental design were as described in section 2.8.

A 3-treatment, 10-replicate experiment tested sugarcane alone and in combination with **7** (0.4 mg per day), (4*S*,5*S*)-**7** or (4*R*,5*R*)-**7** (each stereoisomer at 0.1 mg per day). Compounds were released from one or four glass capillary tubes (1 mm ID), cut 1 cm above the liquid meniscus and placed inside 300 µL capped plastic centrifuge tubes with two 2 mm holes near the top. Assumptions of data normality and homogeneity of variance were tested by graphical

[viii] Field test conducted by Dr. Robert N. Prior, Papua New Guinea Cocoa and Coconut Research Institute, Rabaul, Papua New Guinea.

assessment of log (variance) versus log (means), and Bartlett's test respectively. Data were transformed by $(x + 0.5)^{0.5}$ to eliminate heteroscedasity[60] and were subjected to ANOVA with means compared by Bonferroni's *t*-test.

2.13.4. *R. ferrugineus and R. vulneratus.*[ix]

Traps and experimental design were as described in Section 2.13.1 for testing of chiral isomers of phoenicol. A 4-treatment, 20-replicate experiment (16-30 August 1993) tested attraction of both *R. ferrugineus* and *R. vulneratus* to coconut tissue alone or in combination with stereoisomeric **7** (0.4 mg per day @ 25°C), (4*S*,5*S*)-**7** or (4*R*,5*R*)-**7** (0.1 mg per day @ 25°C). A second 4-treatment, 20 replicate experiment (29 November-4 December, 7-15 December, 1993) tested attraction of both *R. ferrugineus* and *R. vulneratus* to coconut stem alone or in combination with racemic (0.4 mg *per* day @ 25°C), (*S*)- or (*R*)-**8** (0.2 mg *per* day @ 25°C). A final 4-treatment, 19-replicate experiment (9-21 July and 21 November-6 December 1994) tested attraction of both *R. ferrugineus* and *R. vulneratus* to (4*S*,5*S*)-**7** (1 mg per day @ 25°C) plus coconut stem alone or in combination with either racemic (0.2 mg per day @ 25 °C), (*S*)-, or (*R*)-**8** (0.1 mg per day @ 25°C), approximating the natural 10 : 1 ratio.[29a] Despite transformation by log(x + 1), data for all field experiments were not normally distributed and were therefore subjected to analysis by X^2 tests ($\alpha = 0.05$) for species and treatment differences.[61]

2.14. Field Activity Results.

2.14.1. *R. phoenicis* and *R. cruentatus.*

In field experiments (*S,S*)-phoenicol and (*S,S*)-cruentol strongly synergized attraction of weevils to palm stem tissue (Figures 2.22 and 2.23).

[ix] Field test conducted by Ms. Rebecca Hallett, Department of Biological Sciences, Simon Fraser University.

Stereoisomeric mixtures were as attractive as (*S,S*)-isomers and weakly EAD-active (*S,R*)-isomers (Figures 2.20 and 2.21) neither enhanced nor reduced behavioural activity of the stereoisomeric mixtures. Lack of strong antennal and any behavioural activity (Figures 2.22 and 2.23) of non-natural isomers suggests that each species utilizes only one stereoisomer as a pheromone. In practice, mixtures of all four stereoisomers of each pheromone are used in combination with host materials to mass trap *R. phoenicis* and *R. cruentatus*.

2.14.2. *R. bilineatus.*

In field experiments, **7** and (4*S*,5*S*)-**7**, but not (4*R*,5*R*)-**7**, enhanced attraction of weevils to sugarcane baited traps (Figure 2.24). Slightly higher attraction of **7** compared to (4*S*,5*S*)-**7** is not understood because only the latter stereoisomer was detected in male volatiles and elicits antennal responses.

The occurrence of (4*S*,5*S*)-**7** in the American[29a] and three Asian palm weevils supports the hypothesis that the American palm weevil speciated from Asian weevils. This would be consistent with the prevailing theory that palm trees evolved in Southeast Asia, spread through Africa and eventually arrived in the Americas.[62]

2.14.3. *R. ferrugineus* and *R. vulneratus.*

In field experiments, **7** or (*4S,5S*)-**7**, but not (*4R,5R*)-**7**, significantly enhanced attraction of both *R. ferrugineus* and *R. vulneratus* to traps baited with coconut stem tissue (Figure 2.27). No significant differences in attraction were found between the two species. As reported in other Rhynchophorinae, non-natural stereoisomers of the aggregation pheromone neither enhanced nor reduced attraction to the natural isomer.

Comparison of capture rates of traps baited with coconut stem tissue and (4*S*,5*S*)-**7** plus either **8**, (*S*)-**8** or (*R*)-**8** at the natural 10: 1 ratio of **7**: **8** did not reveal behavioral activity of **8** or its enantiomers (Figure 2.28). No significant differences were found between the two species or between the two time periods in which the experiment was conducted.

Although **8** is antennally active in both species the results of four experiments did not disclose behavioral activity for either species in Indonesia. Furthermore, in field experiments in Java, **8** did not have significant behavioral activity in either weevil and did not impart specificity of pheromone communication. Throughout their wide geographic distribution, populations of *R. ferrugineus* and/or *R. vulneratus* may exist that respond to **8**.

Although *R. ferrugineus* and *R. vulneratus* are distinguished primarily by differences in dorsal coloration,[13] there are color intermorphs between the two species.[29a] Moreover, they are sympatric with similar food preferences,[13] and in captivity exhibit interspecific copulation (Rebecca Hallett, personal communication). In the scolytid genus *Ips*, closely related species are cross attractive, but unlike *R. ferrugineus* and *R. vulneratus* maintain reproductive isolation through allopatric or parapatric distributions.[63] Failing the demonstration of other pre- or postzygotic reproductive isolating mechanisms, such as nonviability of progeny, *R. ferrugineus* and *R. vulneratus* has been recommended to be synonymized (Rebecca Hallett, personal communication).

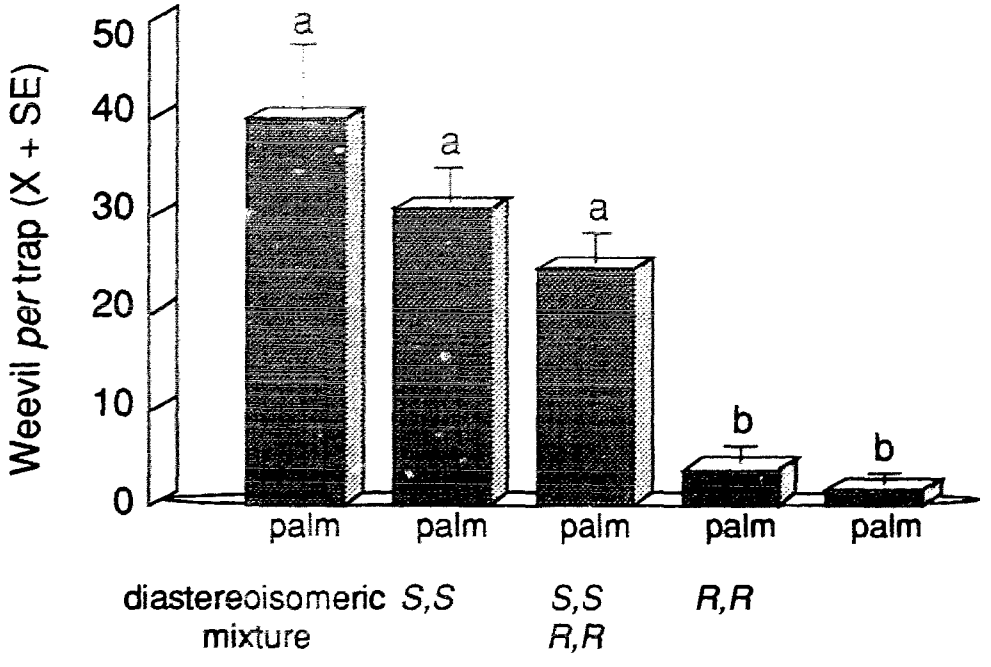


Figure 2.22. Means (+SEM) captures of male and female *Rhynchophorus phoenicis* in traps baited with 250 g of chopped oil palm tissue alone and in combination with either stereoisomeric, (3*S*,4*S*)-, (3*R*,4*R*)- or (*3S*,*4S*)- plus (*3R*,4*R*)-phoenicol. La Me Research Station, Côte d'Ivoire; 6-10 May, 1993; ANOVA (N = 6) followed by Scheffé test, $p < 0.05$. Bars superscripted by same letter are not significantly different.

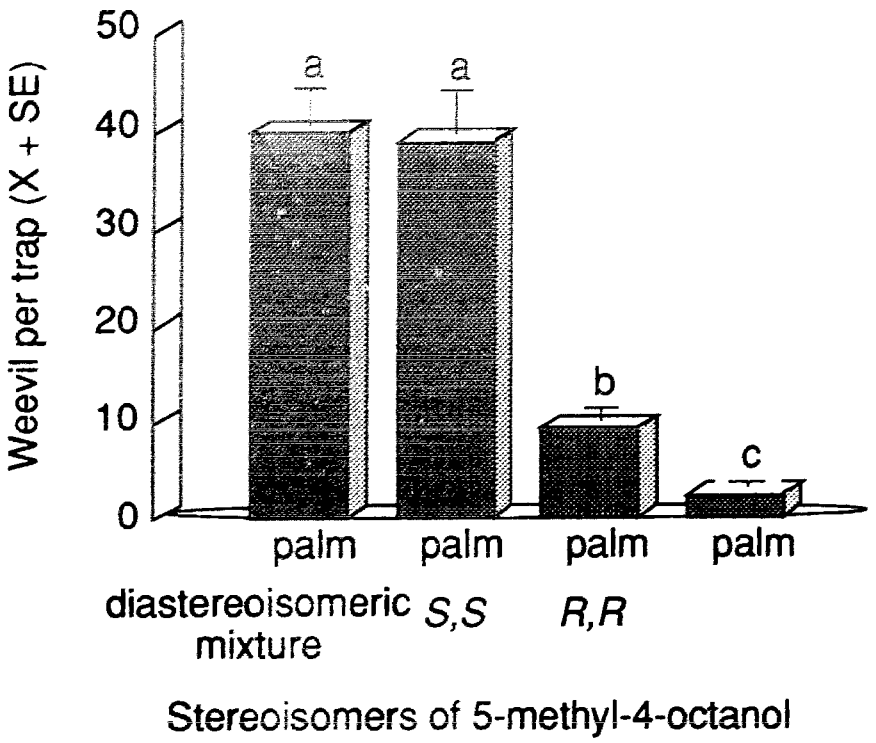


Figure 2.23. Means (+SEM)captures of male and female *Rhynchophorus cruentatus* in traps baited with 1.5 kg of chopped *Sabal palmetto* palm tissue alone and in combination with either stereoisomeric, (4*S*,5*S*)-, or (4*R*,5*R*)-cruentol. La Belle, Florida, USA, 9-16 June, 1993; ANOVA (N = 12) on transformed data $(X + 0.5)^{0.5}$ followed by Waller-Duncan *k*-ratio *t* test. Bars superscripted by the same letter are not significantly different.

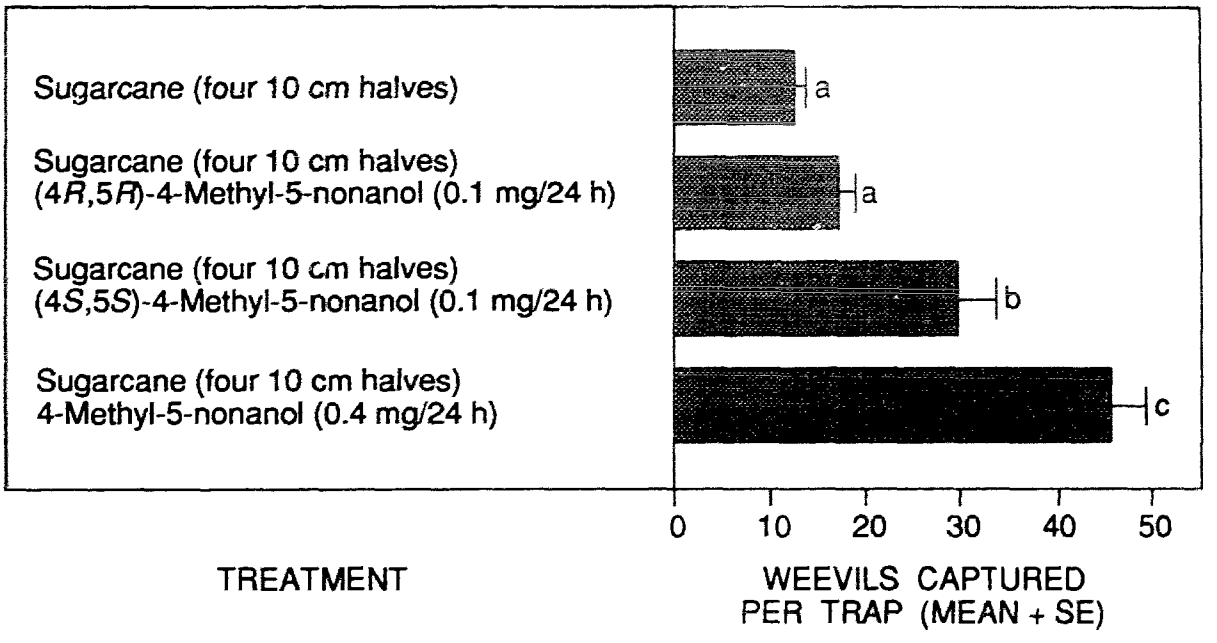


Figure 2.24. Mean (+SEM) captures of *Rhynchophorus bilineatus* in traps baited with sugarcane, pheromone or both in combination. Vimy plantation, Papua New Guinea; 21 January to 22 February, 1994; (N = 10). Analysis determined there was not date effect. ANOVA on pooled trap catches, F = 22.22; df = 3,36; $p < 0.005$). Means followed by the same letter are not significantly different (Bonferroni's test, $p < 0.05$).

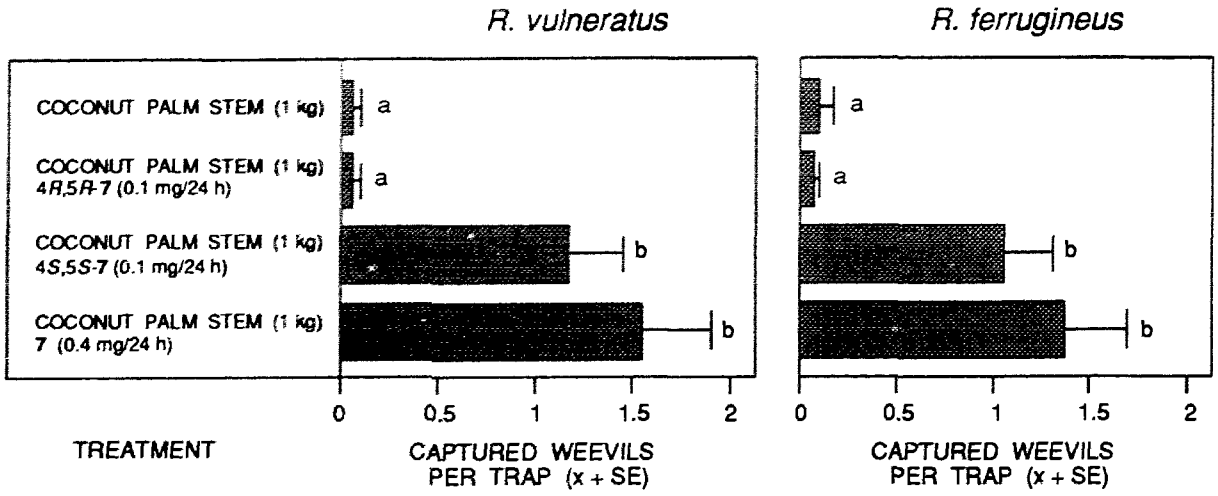


Figure 2.25. Mean (+SEM) captures of *Rhynchophorus ferrugineus* (X^2= 41.157, df = 3, p<0.01) and *R. vulneratus* (X^2= 36.987, df = 3, p<0.01) in bucket traps baited with stereoisomers of 4-methyl-5-nonanol (**7**) and coconut stem tissue (Coconut Research Station, Pakuwon, West Java) 16-30 August 1993; (N = 20). Means followed by the same letter are not significantly different (X^2 test, α<0.05).

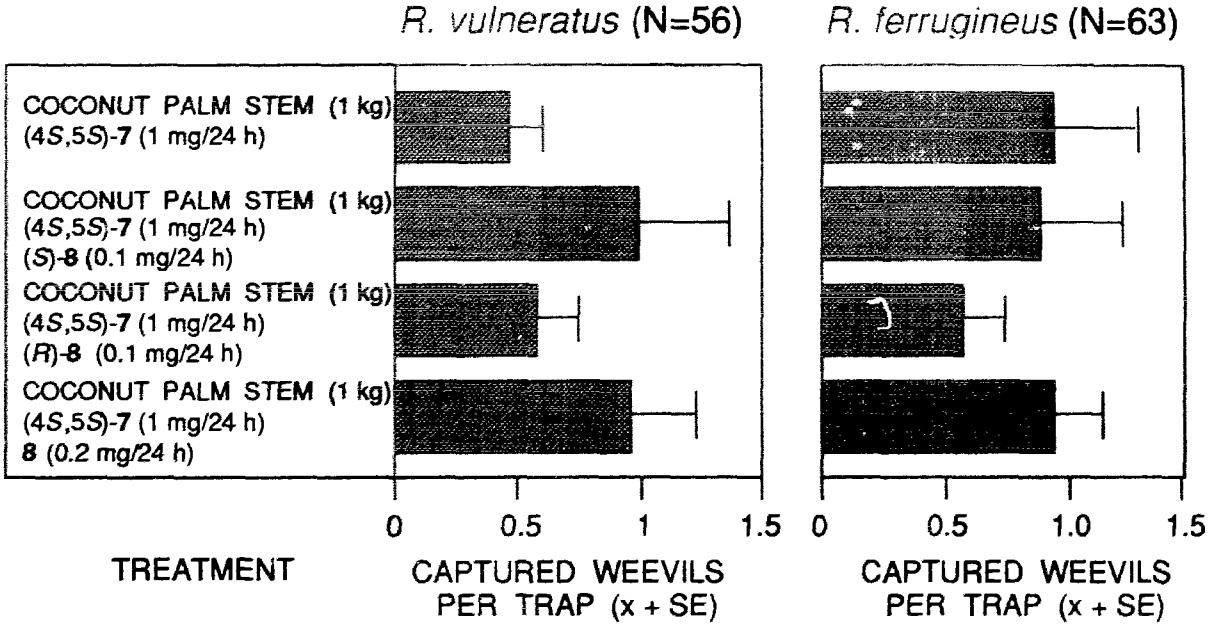
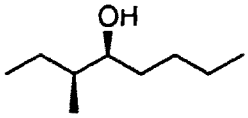


Figure 2.28. Mean (+SEM) captures of *Rhynchophorus ferrugineus* and *R. vulneratus* in bucket traps baited with coconut stem tissue, (*4S,5S*)-4-methyl-5-nonanol (**7**) and isomers of 4-methyl-5-nonanone (**8**) (Coconut Research Station, Pakuwon, West Java, 9-21 July and 21 November- 6 December, 1994; (N = 19). Data pooled for two time periods). Means are not significantly different (X^2 test, $\alpha = 0.05$).

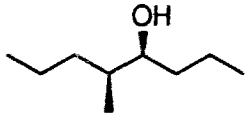
2.15. Summary.

Palm weevils in the Rhynchophorinae produce methyl branched, secondary alcohols as aggregation pheromones: (*E*)-6-methyl-2-hepten-4-ol (rhynchophorol) [American palm weevil, *Rhynchophorus palmarum* (L.)];[64] 3-methyl-4-octanol (phoenicol) [African palm weevil, *R. phoenicis* (F.)];[11] 5-methyl-4-octanol (cruentol) [Palmetto weevil, *R. cruentatus* (F.)][16] and 4-methyl-5-nonanol (ferrugineol) [Asian palm weevils, *R. bilineatus* (Montr.),[38c] *R. ferrugineus* (Oliv.), and *R. vulneratus* (Panz)].[29a] Stereoisomeric mixtures (phoenicol,[38a] cruentol,[38a] and ferrugineol[38b,c]) of synthetic aggregation pheromones in combination with host material strongly attracted weevils in field experiments. Stereoselective production of, and response to specific pheromones has been demonstrated.[38]



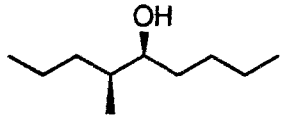
Phoenicol

Rhynchophorus phoenicis
African palm weevil



Cruentol

Rhynchophorus cruentatus
Palmetto weevil

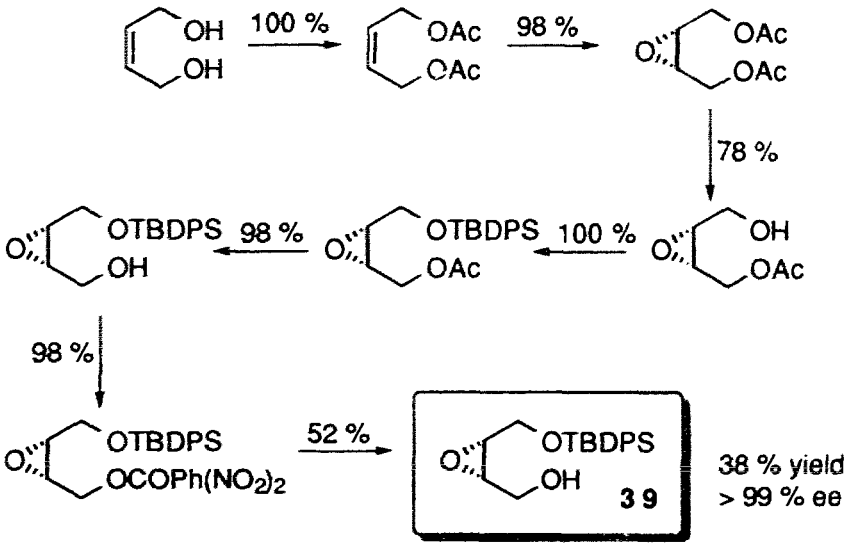


Ferrugineol

Rhynchophorus ferrugineus
Asian palm weevil
Rhynchophorus vulneratus
Red stripe palm weevil
Rhynchophorus bilineatus

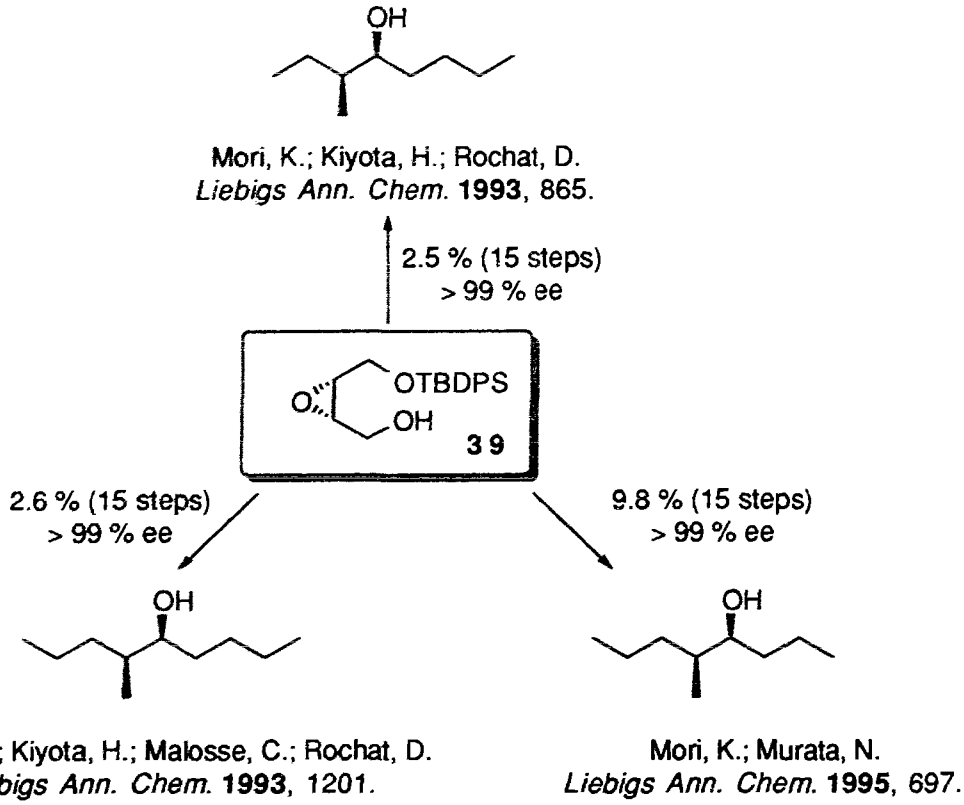
2.16. Note Added in Proof.

After the present work was published,[65] Mori recently accomplished syntheses of phoenicol,[66a] ferrugineol[66b] and cruentol[66c] *via* intermediate **39**. Thus, **39** was produced *via* a seven step procedure (Scheme 2.13) of which the key feature is the lipase (PPL)-catalyzed hydrolysis of 1,4-diacetoxy-*cis*-2,3-epoxybutane followed by recrystallization of the 3,5-dinitrobenzoate and hydrolysis .[67]



Scheme 2.13. Synthesis of chiral building block **39** by Mori.

Conversion of **39** to phoenicol,[66a] ferrugineol[66b] and cruentol[66c] was achieved by regioselective epoxide opening of **39** using $AlMe_3$ or Me_2CuLi, functional group protection and modification, and organocuprate mediated carbon chain extension (Scheme 2.14). Overall chemical yields were between 2.5 and 9.8 % and optical purities were > 99 % ee. In all cases EAD activity and stereospecific pheromone production were demonstrated. In no case was field attraction demonstrated.



Scheme 2.14. Syntheses of Rhynchophorinae pheromones by Mori *et al.*

2.17. Experimental Section.

2.17.1. Instrumentation for Spectroscopic Analyses.

Nuclear Magnetic Resonance (NMR) spectroscopy was conducted on a Bruker AMX-400 spectrometer at 400.13 and 100.62 MHz for ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra, respectively. ^{1}H and $^{13}C\{^{1}H\}$ chemical shifts are reported in parts per million (ppm, δ) and relative to $CHCl_3$ (7.26 ppm) and (77.0 ppm) respectively. Gas chromatographic analyses were performed on Hewlett-Packard 5880A and 5890 instruments equipped with a flame ionization detector and a fused silica, DB-1 coated column (15 m X 0.25 mm ID; 0.25 mm film) or on a fused silica, Cyclodex-B-coated column (30 m X 0.25 mm) (J & W Scientific). Mass spectra were obtained on a Hewlett-Packard 5985B GC/MS equipped with a DB-1 fused silica column (30 m x 0.25 mm ID; with 0.25 μm film) operating at 70 eV for electron impact (EI). Chemical ionization (CI) was performed using isobutane as the proton source. CI- or EI-MS was conducted in both full-scan and selected-ion monitoring mode (SIM). Full-scan mass spectra of synthetic pheromones were obtained to select diagnostic ions. For GC-MSCI- or GC-MSEI-SIM, synthetic compounds, hexane and concentrated weevil-produced volatiles were injected in split mode and analyzed by scanning for diagnostic ions. Elemental analyses were performed using a Carlo Erba Model-1106 Elemental Analyzer. IR spectra were recorded on a Perkin Elmer Model FT 1605 spectrophotometer.

2.17.2. General Chemical Procedures.

Diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), benzene and pentane were freshly distilled from sodium-benzophenone-ketyl, CaH_2, activated 4A molecular sieves and P_2O_5, respectively. Triphenylphosphine was dried over P_2O_5 under high vacuum overnight. *n*-Butyllithium was purchased from Aldrich

and titrated according to the method of Watson and Eastham.[68] Molecular sieves (3A and 4A) were freshly activated by heating at ~200°C overnight under high vacuum. Chemicals obtained from commercial sources were used without further purification unless otherwise indicated. All glassware and syringes were dried in an oven overnight at 140°C and flushed with argon immediately prior use. Transfers of reagents were performed with syringes equipped with stainless-steel needles. A nitrogen glovebag was used to weight all moisture-sensitive compounds. All moisture and air sensitive reactions were conducted under positive pressure of argon. Column chromatography refers to flash chromatography using Silica Gel 60 (230-400 mesh, E Merck, Darmstadt).[69] Thin layer chromatography (TLC) was conducted on aluminum backed plates precoated with Merck Silica Gel 60F-254 as the adsorbent, and visualized by treatment with an acidic solution (10 % H_2SO_4) of 1 % $Ce(SO_4)_2$ and 1.5 % molybdic acid followed by gentle heating.

2.17.3. Volatile Collection.[10]

Field collected or laboratory-reared insects (for numbers and sex, see respective sections in this Chapter) were placed in modified 9 L Nalgene™ desiccators with or without food (sugarcane or palm tissue, for details see text in this Chapter). An aspirator-driven, charcoal-filtered airstream (1.5 L *per* min) was maintained through the desiccator for a specific length of time (for details see text). Insect and/or plant volatiles were collected on 10 g of Porapak Q packed in Pyrex glass or metal tubing. Volatiles were eluted from the Porapak Q with distilled pentane and concentrated by distillation.

2.17.4. Electroantennographic Analyses.[7d]

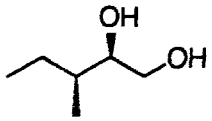
For GC-EAD recordings, an insect antenna was removed from the rostrum and suspended between two glass capillary electrodes (Ag-AgCl) with the antennal base being inserted into one electrode and the olfactory club impaled by the other. Antennal responses were amplified using a custom-built amplifier with a passive low-pass filter and a cut-off frequency of 10 kHz. All recordings were performed by Ms. Regine Gries, Department of Biological Sciences, Simon Fraser University.

3-Methyl-4-octanol (**1**, phoenicol), 5-methyl-4-octanol (**2**, cruentol), 4-methyl-5-nonanol (**7**, ferrugineol) were prepared from the corresponding Grignard reactions of suitable organomagnesium reagents and aldehydes, and purified by vacuum distillation. Further oxidation of **7** with Jones' reagent yielded 4-methyl-5-nonanone (**8**, ferrugineone).

***(2S,3R)*-2,3-Epoxy-1-pentanol (22a).** Titanium (IV) isopropoxide (11.4 mL, 10.87 g, 38 mmol) in dry CH_2Cl_2 (250 mL) was mixed under argon with 1 g of 4A powdered, activated molecular sieves. After cooling to -78°C, diethyl (*2R,3R*)-tartrate (L-(+)-DET, 7.8 mL, 9.9 g, 0.05 mol) was added *via* syringe followed by addition of (*Z*)-2-penten-1-ol (**21**) (8.21 mL, 7.0 g, 80 mmol). The mixture was stirred 15 min prior to dropwise addition of 5.7 M anhyd. *tert*-butyl hydroperoxide in CH_2Cl_2 (25 mL, 0.15 mol) (prepared as described in reference 43c) (precooled to -20°C). After the reaction had warmed to -20°C it was stirred at this temperature for 48 h. The reaction was monitored by TLC (2:8, pentane:ether; R_f = 0.39). Non-aqueous work-up[44c] followed by column chromatography (2:8, pentane:ether) gave **22a** (3.79 g, 46 % yield, 90 % *ee*) as a

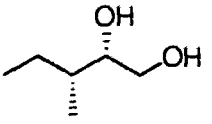
colourless liquid. ^{1}H NMR ($CDCl_3$, ppm): 1.02 (3 H, t, J = 8.6 Hz), 1.52 (2 H, m), 2.04 (1 H, brs, D_2O exchangeable), 2.41 (2 H, t, J = 10.0 Hz), 3.15 (1 H, dd, J = 5.0, 10 Hz), 3.68 (1 H, dd, J = 4, 10 Hz); ^{13}C NMR ($CDCl_3$, ppm) 61.82, 57.10, 56.98, 26.22, 13.91. Anal. Calcd. for $C_5H_{10}O_2$: C, 58.78; H, 9.87. Found: C, 58.80; H, 9.93.

(*2R,3S*)-2,3-Epoxy-1-pentanol (22b). (3.93 g, 47 % yield, 87 % ee. Anal. Calcd. for $C_5H_{10}O_2$: C, 58.78; H, 9.87. Found: C, 58.81; H, 9.91) was synthesized following the same procedure using diethyl (*2S,3S*)-tartrate (D-(-)-DET) as the epoxidation catalyst. The same spectroscopic characteristics were obtained as for **22a**.

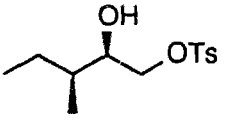


(2*R*,3*S*)-3-Methyl-1,2-pentanediol (23a). A pentane (200 mL) solution of **22a** (3.78 g, 37 mmol) was cooled to -50°C. Then neat $AlMe_3$ (10.5 mL, 0.11 mol) was added dropwise followed by 2.49 M *n*-butyllithium (8 mL, 20 mmol). After stirring at -50°C for 20 min., the cooling bath was removed and the flask allowed to warm to room temperature. Monitoring the reaction by GC and TLC (1:9, pentane:ether; R_f = 0.19) indicated reaction completion after 30 min. The reaction was quenched with NaF:H_2O (1:1)[45b] at 0°C. The white precipitate which formed was filtered and the obtained solid was washed with Et_2O. The ethereal layer was dried over anhyd. $MgSO_4$ and concentrated *in vacuo* to give a pale yellow liquid. Purification by column chromatography (1:9, pentane:Et_2O) afforded **23a** (2.93 g, 64.4 % yield, 88.5 % ee) as a colourless liquid. ^{1}H NMR ($CDCl_3$, ppm): 0.88 (3 H, t, J = 8.0 Hz), 0.90 (3 H, d, J = 8.0 Hz), 1.20 (1 H, m),

1.42 (2 H, m), 2.15 (2 H, brs, D_2O exchangeable), 3.45 (2 H, m), 3.62 (1 H, m); ^{13}C ($CDCl_3$, ppm): 75.52, 65.21, 37.40, 25.71, 14.11, 11.53. CI-MS *m/z* (isobutane, relative intensity): 119 (M^++1, 40). Anal. Calcd. for $C_6H_{14}O_2$: C, 60.97; H, 11.95. Found: C, 60.93; H, 11.94.

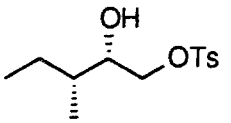


(2*S*,3*R*)-3-Methyl-1,2-pentanediol (23b). 3.59 g, 82 % yield, 85 % ee. Anal. Calcd. for $C_6H_{14}O_2$: C, 60.97; H, 11.95. Found: C, 60.98; H, 11.96. The same spectroscopic characteristics as the antipode were obtained.

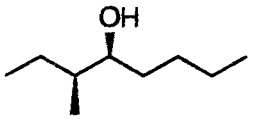


(2*R*,3*S*)-3-Methyl-1-tosyloxy-2-pentanol (24a). To a solution of **23a** (2.92 g, 25 mmol) in dry pyridine, dimethylaminopyridine (DMAP) (0.73 g, 6 mmol) was added. The flask was cooled to -20°C (ethylene glycol:water:dry ice) and *p*-toluenesulfonyl chloride (5.73 g, 0.03 mol) added in one portion. After stirring 7 h at -20 to -10°C and monitoring the reaction by GC and TLC (6:4, pentane:ether, R_f = 0.27), the mixture was poured into ice-cooled NaCl solution and extracted (2 X 30 mL) with Et_2O. The organic layer was washed with 3 M HCl, saturated $NaHCO_3$, saturated NaCl and dried over anhyd. $MgSO_4$. After concentration and column chromatography (6:4, pentane:ether), solvent residues were removed under vacuum to give **24a** (4.0 g, 59 %) as a pale yellow oil. ^1H NMR ($CDCl_3$, ppm): 0.85 (3 H, d, *J* = 8.0 Hz), 0.86 (3 H, t, *J* = 8.0 Hz), 1.20 (1 H, m), 1.45 (2 H, m), 1.90 (1 H, brs, D_2O exchangeable), 2.50 (3H, s), 3.72 (1 H, dt, *J* = 8, 4 Hz), 3.98 (1 H, dd, *J* = 8.0, 2.5 Hz), 4.04 (1 H, dd, *J* = 8.0, 1.5 Hz); 7.34 (2 H, d, *J* = 8.0 Hz); 7.80 (2 H, d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, ppm): 144.95, 133.0,

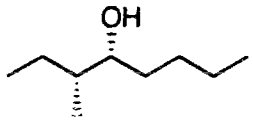
129.89, 127.90, 72.93, 72.75, 36.97, 25.62, 21.57, 13.57, 11.41; CI-MS *m/z* (relative intensity): 273 (M^+ + 1, 100).



(2*S*,3*R*)-3-Methyl-1-tosyloxy-2-pentanol (24b). 4.0 g, 59 % yield. The same spectroscopic characteristics as the antipode were obtained.



(3*S*,4*S*)-3-Methyl-4-octanol [(3*S*,4*S*)-1]. Propyl magnesium bromide (0.17 mol) in dry Et_2O [prepared by Grignard reaction between *n*-propyl bromide and magnesium turnings] was cooled to -40°C and CuCN (1.58 g, 17 mmol) was added in one portion. After stirring the mixture for 30 min, the flask was cooled to -78°C and **24a** (4.89 g, 17 mmol) in dry Et_2O (25 mL) added *via* cannula. After 30 min of stirring the cold bath was removed and the reaction allowed to warm to room temperature. The course of the reaction was followed by GC and TLC (9:1, pentane:ether, R_f = 0.58). Upon completion, the reaction was quenched with 3 M HCl at 0°C. The aqueous layer extracted with Et_2O (3 X 25 mL) which was washed with both saturated $NaHCO_3$ and NaCl, then dried over anhyd. $MgSO_4$. Column chromatography (9:1, pentane:ether) afforded 1.97 g (91 %) of (3*S*,4*S*)-**1** as a colourless liquid. $[\alpha]_D^{20}$ = -19.2° (c = 2.125, Et_2O); ^1H NMR ($CDCl_3$, ppm): 0.82 (3 H, d, *J* = 8.0 Hz), 0.85-0.98 (6 H, m), 1.19 (2 H, m), 1.2-1.58 (7 H, m), 1.68 (1 H, s. D_2O exchangeable), 3.41 (1 H, m); ^{13}C NMR ($CDCl_3$, ppm): 74.83, 39.94, 34.17, 28.42, 25.98, 22.76, 14.02, 13.11, 11.65. Anal. Calcd. for $C_9H_{20}O$: C, 74.92; H, 13.98. Found: C, 74.77; H, 13.88.



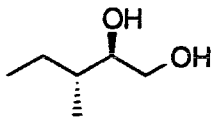
(3*R*,4*R*)-3-Methyl-4-octanol (3*R*,4*R*-1). ($[\alpha]_D^{20}$ = +17.8° (c = 2.320, Et_2O); 1.97 g, 91 % yield, 87 % ee. Anal. Calcd. for $C_9H_{20}O$: C, 74.92; H, 13.98. Found: C, 74.89; H, 13.75). The same spectroscopic characteristics as the antipode were obtained.

(*E*-)-2-penten-1-ol (26). 3-Pentyn-1-ol (**25**) was reduced with $LiAlH_4$ in 83 % yield, according to the procedure reported in reference 52. ^1H NMR ($CDCl_3$, ppm): 1.0 (3 H, t, J = 7.3 Hz), 1.8 (1 H, brs, D_2O exchangeable), 2.05 (2 H, m, J = 8.0, 1.2 Hz), 4.05 (2 H, d, J = 8.0 Hz), 5.60 (1 H, dt, J = 13.8, 1.3 Hz), 5.75 (1 H, dt, J = 13.8, 1.3 Hz); ^{13}C NMR ($CDCl_3$, ppm): 134.83, 127.94, 63.68, 25.14, 13.30.

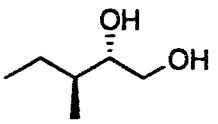
(*2S,3S*)-2,3-Epoxy-1-pentanol (27a). Powdered 4A activated molecular sieves (0.5 g) and titanium (IV) isopropoxide (5.7 mL, 5.42 g, 19 mmol) in dry CH_2Cl_2 (150 mL) were cooled to -78°C in a acetone-dry ice bath. To this was added *via* syringe diethyl (*2R,3R*)-tartrate (L-(+)-DET) (3.9 mL, 4.69 g, 23 mmol) and (*E*)-2-penten-1-ol (3.4 g, 39 mmol). After stirring the mixture 15 min., 5.7 M anhyd. *tert*-butyl hydroperoxide (12 mL, 68 mmol) in CH_2Cl_2 (precooled to -20°C) was added dropwise. After the reaction warmed to -20°C it was stirred at this temperature for 4 h and monitored by TLC (2:8, pentane:ether; R_f = 0.39). Non-aqueous work-up followed by column chromatography gave **27a** (1.70 g, 43 % yield, 96 % ee) as a colourless liquid. ^1H NMR ($CDCl_3$, ppm): 0.96 (3 H, t, J = 8 Hz), 1.52 (2 H, m), 2.80 (2 H, t, J = 8.0 Hz), 3.02 (1 H, brs, D_2O exchangeable),

3.45 (1 H, dd, J = 4.0, 8.0 Hz), 3.70 (1 H, dd, J = 8.0, 2 Hz); ^{13}C ($CDCl_3$, ppm): 62.05, 58.32, 57.10, 24.41, 13.91. Anal. Calcd. for $C_5H_{10}O_2$: C, 58.78; H, 9.87. Found: C, 58.79; H, 9.90.

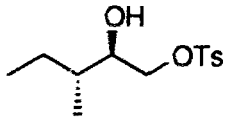
(*2R,3R*)-2,3-Epoxy-1-pentanol (27b). (1.64 g, 41 % yield, 96 % ee. Anal. Calcd. for $C_5H_{10}O_2$: C, 58.78; H, 9.87. Found: C, 58.75; H, 9.90) was prepared following the same procedure using diethyl (*2S,3S*)-tartrate [D-(-)-DET]. The same spectroscopic characteristics as the antipode were obtained.



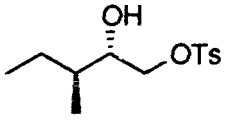
(2*R*,3*R*)-3-Methyl-1,2-pentanediol (28a). A procedure similar to that used for the preparation of **23** was employed. 1.18 g, 59 % yield, 96 % ee. ^1H NMR ($CDCl_3$, ppm): 0.86 (3 H, t, J = 8.0 Hz), 0.91 (3 H, d, J = 8.0 Hz), 1.18 (1 H, m), 1.40 (2 H, m), 3.12 (2 H, brs, D_2O exchangeable), 3.40 (2 H, m), 3.55 (1 H, m); CI-MS *m/z* (relative intensity): 119 (M^++1, 45). Anal. Calcd. for $C_6H_{14}O_2$: C, 60.97; H, 11.95. Found: C, 60.95; H, 11.97.



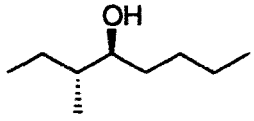
(2*S*,3*S*)-3-Methyl-1,2-pentanediol (28b). 1.28 g, 67 % yield, 95 % ee. Anal. Calcd. for $C_6H_{14}O_2$: C, 60.97; H, 11.95. Found: C, 60.96; H, 11.97. The same spectroscopic characteristics as the antipode were obtained.



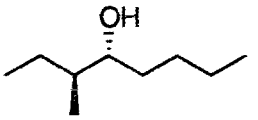
(2*R*,3*R*)-3-Methyl-1-tosyloxy-2-pentanol (29a). A procedure similar to that used in the synthesis of **24** was employed. 1.52 g, 60 % yield. ^{1}H NMR ($CDCl_3$, ppm): 0.84 (3 H, d, *J* = 8.0 Hz), 0.86 (3 H, *t*, *J* = 8.0 Hz), 1.22 (1 H, m), 1.45 (2 H, m), 2.0 (1 H, brs, D_2O exchangeable), 3.64 (1 H, dt, *J* = 8.0, 4.0 Hz), 3.94 (1 H, dd, *J* = 8, 2.5 Hz), 4.01 (1 H, dd, *J* = 8, 1.5 Hz); 7.30 (2 H, d, *J* = 8 Hz); 7.75 (2 H, d, *J* = 8 Hz); CI-MS *m/z* (relative intensity): 273 (M^+ + 1, 100)].



(2*S*,3*S*)-3-Methyl-1-tosyloxy-2-pentanol (29b). 1.71 g, 62 % yield. The same spectroscopic characteristics as the antipode were obtained.



(3*R*,4*S*)-3-Methyl-4-octanol [(3*R*,4*S*)-1]. The procedure used was that for the synthesis of (3*S*,4*S*)-**1** was employed. 0.68 g, 85 % yield, 96 % ee. ^{1}H NMR ($CDCl_3$, ppm): 0.81 (3H, d, *J* = 8.1 Hz), 0.84-1.0 (6H, m), 1.20 (2H, m), 1.22-1.60 (7H, m), 1.70 (1H, brs, D_2O exchangeable), 3.45 (1H, m); ^{13}C NMR ($CDCl_3$, ppm): 75.71, 40.50, 33.07, 28.25, 24.55, 22.76, 14.70, 13.11, 11.82. Anal. Calcd. for $C_9H_{20}O$: C, 74.92; H, 13.98. Found: C, 74.76; H, 14.07.

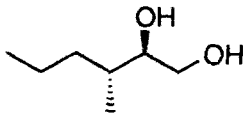


(3*S*,4*R*)-3-Methyl-4-octanol [(3*S*,4*R*)-1]. 0.76 g, 84 % yield, 95 % ee. Anal. Calcd. for $C_9H_{20}O$: C, 74.92, H; 13.98. Found: C, 75.06; H, 14.01. The same spectroscopic characteristics as the antipode were obtained.

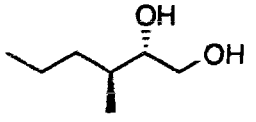
(*2S,3S*)-2,3-Epoxy-1-hexanol (33a). This compound was prepared according to the procedure employed for **22a**. Powdered, activated 4A molecular sieves (1g) and titanium (IV) isopropoxide (8.4 mL, 8.79 g, 31 mmol) in dry CH_2Cl_2 (250 mL) were cooled to -78°C in a acetone-dry ice bath. Diethyl (*2R,3R*)-tartrate (L-(+)-DET) (6.3 mL, 5.23 g, 25 mmol) and (*E*)-2-hexen-1-ol (**32**) (6.1 mL, 5.2 g, 52 mmol) were added *via* syringe. Stirring of the mixture was followed by dropwise addition of 6.2 M anhyd. *tert*-butyl hydroperoxide (18 mL, 0.11 mol) in CH_2Cl_2 (precooled to -20°C). The reaction was allowed to warm to -20°C with stirring and was stirred at this temperature for 3 h while it was monitored by TLC (4:6, hexane/ether; R_f = 0.19). Ferrous sulfate/tartaric acid work-up[44c] followed by column chromatography gave **33a** (4.82 g, 80 % yield, 95 % ee) as a colourless liquid, which crystallized as white needles at -20°C. ^{1}H NMR ($CDCl_3$, ppm): 0.96 (3 H, t, J = 7.6 Hz), 1.48 (2 H, m), 1.54 (2 H, m), 1.80 (1 H, brs, D_2O exchangeable), 2.92 (2 H, m), 3.60 (1 H, dd, J = 5, 10 Hz), 3.90 (1H, dd, J = 10, 2.5 Hz); ^{13}C NMR ($CDCl_3$, ppm): 61.76, 58.34, 55.81, 33.57, 19.23, 13.84.

(*2R,3R*)-2,3-Epoxy-1-hexanol (33b). This compound was prepared by the procedure used for **33a** but employing diethyl (*2S,3S*)-tartrate [D-(-)-DET]

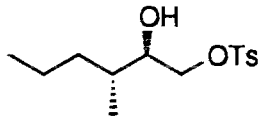
(4.94 g, 82 % yield, 95 % ee). The same spectroscopic characteristics as the antipode were obtained.



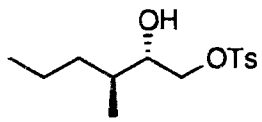
(*2R,3R*)-3-Methyl-1,3-hexanediol (34a). This compound was prepared according to the procedure employed for **23**. To a solution of **33a** (4.80 g, 0.04 mol) in dry pentane (250 mL) cooled to -50°C was added dropwise neat $AlMe_3$ (11.9 mL, 8.64, 0.11 mol). This was followed by addition of 2.49 M *n*-butyllithium (16 mL, 0.04 mol). After stirring 20 min, the cooling bath was removed and the flask allowed to warm to room temperature. The reaction was monitored by GC and TLC (2:8, hexane/ethyl acetate, R_f = 0.33) and was complete after 30 min. After quenching with 3 M HCl at 0°C and separation of the two phases, the aqueous layer was extracted with ether (3 X 40 mL) which was dried over anhyd. $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography afforded **34a** (4.26 g, 78 % yield, 95 % ee) as a colourless liquid which crystallized as a white solid at -20°C. ^1H NMR ($CDCl_3$, ppm): 0.88 (3 H, t, J = 10.1 Hz), 0.90 (3 H, d, J = 10.1 Hz), 1.14 (1 H, *m*), 1.25 (1 H, *m*), 1.46 (1 H, *m*), 1.60 (1 H, m), 2.10 (1 H, brs, D_2O exchangeable), 2.24 (1 H, brs, D_2O exchangeable), 3.50 (2 H, m), 3.70 (1 H, m); ^{13}C NMR ($CDCl_3$, ppm): 76.28, 64.66, 35.94, 34.68, 20.06, 15.14, 14.26; CI-MS *m/z* (relative intensity): 119 (M^++1, 40)].



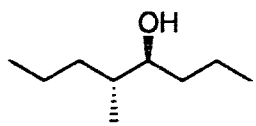
(*2R,3R*)-3-Methyl-1,3-hexanediol (34b). 3.91 g, 70 % yield, 98 % ee. The same spectroscopic characteristics as the antipode were obtained.



(2*R*,3*R*)-3-Methyl-1-tosyloxy-2-hexanol (35a). This compound was prepared by the procedure used for the synthesis of **24**. After purification by column chromatography (6:4, pentane:ether, R_f = 0.45) **35a** (6.54 g, 76 % yield) was obtained as a pale yellow oil. ^{1}H NMR ($CDCl_3$, ppm): 0.86 (6 H, m), 1.18 (2H, m), 1.40 (2H, m), 1.60 (1H, m), 1.90 (1H, brs D_2O exchangeable), 2.48 (3H, s), 3.64 (1H, m), 3.98 (1H, dd, J = 12.0, 8.0 Hz), 4.10 (1H, dd, J = 12.0, 4.0 Hz), 7.38 (2H, d, J = 8.0 Hz), 7.80 (2H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, ppm): 144.99, 132.5, 129.92, 127.93, 73.43, 72.66, 35.54, 34.15, 21.26, 19.96, 15.10, 14.16 ppm.

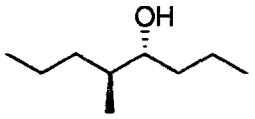


(2*S*,3*S*)-3-Methyl-1-tosyloxy-2-hexanol (13b). 6.09 g, 78 % yield. The same spectroscopic characteristics as the antipode were obtained.

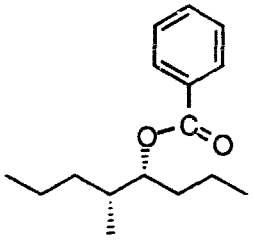


***(4S, 5R)*-5-Methyl-4-octanol [(4*S*,5*R*)-2].** This compound was prepared by the route used for (3*S*,4*S*)-**1** except that ethyl magnesium bromide (3 M solution in Et_2O) was used. After purification by column chromatography (9:1, pentane:ether, R_f = 0.08) (4*S*,5*R*)-**2** (2.74 g, 78 % yield, 98 % ee) was obtained as colourless liquid which crystallized as a white solid at -20°C. ^{1}H NMR ($CDCl_3$, ppm): 0.90 (3 H, t, J = 8.0 Hz), 0.92 (3 H, d, J = 8.0 Hz), 0.94 (3 H, t, J = 8.0 Hz), 1.10 (1 H, m), 1.24 (1 H, m), 1.32 (1H, m), 1.40 (4 H, m), 1.50 (1 H, m), 1.70 (1 H, brs, D_2O exchangeable), 3.48 (1 H, m); ^{13}C NMR ($CDCl_3$, ppm):

75.82, 38.61, 35.64, 34.17, 20.42, 19.28, 15.24, 14.34, 14.13; CI-MS *m/z* (relative intensity): 1 27 (100) (M^+- H_2O); Anal. Calcd. for $C_9H_{20}O$: C, 74.92; H, 13.98. Found: C, 75.16; H, 14.11.

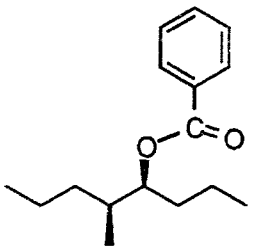


(*4R, 5S*)-5-Methyl-4-octanol [(4*R*,5*S*)-2]. 2.73 g, 85 % yield, 98 % ee; Anal. Calcd. for $C_9H_{20}O$: C, 74.92; H, 13.98. Found: C, 74.87; H, 14.08. Same spectroscopic characteristics as the antipode were obtained.

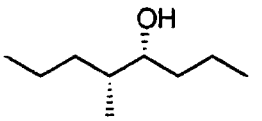


[(*4R, 5R*)-5-Methyl-4-octyl)] benzoate (35a). Triphenylphosphine (9.97 g, 38 mmol) and (4*S*,5*R*)-**2** (2.74 g, 19 mmol) in dry benzene (30 mL) were added *via* cannula to diisopropyl azodicarboxylate (7.68 g, 7.5 mL, 38 mmol) and benzoic acid (4.64 g, 38 mmol) in dry benzene (45 mL). After stirring overnight at room temperature, pentane was added at which point a white precipitate formed. The mixture was filtered through a Florisil pad and concentrated under vacuum. Purification by column chromatography (9:1, pentane:ether, R_f = 0.61) afforded **35a** (2.35 g, 50 % yield) as a pale yellow liquid and unreacted alcohol in separated fractions. ^{1}H NMR ($CDCl_3$, ppm): 0.88 (3 H, t, *J* = 9.0 Hz), 0.98 (3 H, t, *J* = 9.0 Hz), 1.00 (3 H, d, *J* = 9.0 Hz), 1.10 (1 H, m), 1.38, (5 H, m), 1.58 (1 H, m), 1.70 (1 H, m), 1.80 (1 H, m), 5.10 (1 H, m), 7.40 (2 H, dd, *J* = 9.0, 2.0 Hz), 7.54 (1 H, ddd, *J* = 9.0, 2.0 Hz), 8.04 (2 H, dd, *J* = 9.0, 2.0 Hz); ^{13}C NMR ($CDCl_3$, ppm): 166.37, 132.62, 130.98, 129.56, 128.29, 77.74, 36.27, 35.41, 33.77, 20.34, 19.07,

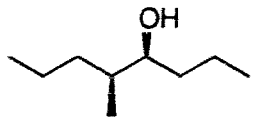
14.48, 14.22, 14.01; CI-MS *m/z* (relative intensity): 127 (M^+- C_6H_5-CO, 100)]. Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.36; H, 9.75. Found: C, 77.33; H, 9.77.



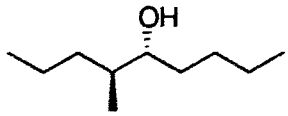
[(*4S, 5S*)-5-Methyl-4-octyl)] benzoate (35b). 2.70 g, 57.3 % yield. Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.36; H, 9.75. Found: C, 77.37; H, 9.79. The same spectroscopic characteristics as the antipode were obtained.



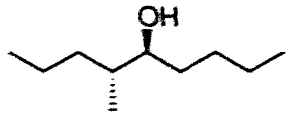
(*4R, 5R*)-5-Methyl-4-octanol [(4*R*,5*R*)-2]. To a 15 % KOH solution of methanol was added **35a** (1.30 g, 52 mmol). After stirring the mixture overnight the mixture was quenched with water and extracted with Et_2O (3 X 30 mL). The ether extracts were washed with dilute HCl and saturated NaCl and then dried over anhyd. $MgSO_4$. Concentration *in vacuo* and column chromatography (9:1, pentane:ether, R_f = 0.13) gave (4*R*,5*R*)-**2** (0.71 g, 95 % yield, 98 % ee) as a colourless liquid. $[\alpha]_D^{20}$ = +33.5° (c = 1.331, Et_2O); ^1H NMR ($CDCl_3$, ppm): 0.89 (3 H, d, *J* = 8.0 Hz), 0.92 (3 H, t, *J* = 8.0 Hz), 0.95 (3 H, t, *J* = 8.0 Hz), 1.12 (1 H, m), 1.24 (1 H, m), 1.33 (1H, m), 1.39 (5 H, m), 1.48 (1 H, m), 3.40 (1 H, m); ^{13}C NMR ($CDCl_3$, ppm): 75.04, 38.70, 36.73, 35.73, 20.51, 19.51, 15.33, 14.38, 13.65; Anal. Calcd. for $C_9H_{20}O$: C, 74.92; H, 13.98. Found: C, 74.74; H, 13.84.



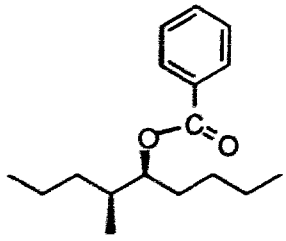
(*4S, 5S*)-5-Methyl-4-octanol [(*4S,5S*)-2]. $[\alpha]_D^{20}$ = -32.4° (c = 1.223, Et_2O); 0.75 g, 89 % yield, 96 % ee; Anal. Calcd. for $C_9H_{20}O$: C, 74.92; H, 13.98. Found: C, 74.69; H, 13.81. The same spectroscopic characteristics as the antipode were obtained.



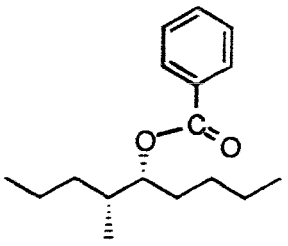
(*4S,5R*)-4-Methyl-5-nonanol [(*4S,5R*)-7]. Propyl magnesium bromide (0.20 mol) in dry Et_2O [prepared by Grignard reaction between *n*-propyl bromide and magnesium turnings] was cooled to -40°C, then CuCN (1.58 g, 20 mmol) was added. After stirring the mixture for 30 min, the flask was cooled to -78°C and **35b** (2*S*,3*S*)-3-methyl-1-tosyloxyhexan-2-ol (5.43 g, 19 mmol) in dry Et_2O (25 mL) added *via* cannula. After 30 min of stirring the cold bath was removed and the reaction allowed to warm to room temperature. The progress of the reaction was followed by analysis of aliquots by GC and TLC (9:1, pentane:ether, R_f = 0.13). Upon completion, the reaction was quenched with 3 M HCl at 0°C. The aqueous layer was extracted with Et_2O (3 X 25 mL), washed with saturated $NaHCO_3$ and NaCl, and dried over anhyd. $MgSO_4$. Column chromatography (9:1, pentane:ether) afforded 2.39 g (86 % yield, 96 % ee) of (*4S,5R*)-**7** as a colourless liquid. ^1H NMR ($CDCl_3$, ppm): 0.88 (3H, d, *J* = 8.0 Hz), 0.90 (6H, m), 1.34 (12H, m), 3.44 (1 H, m); ^{13}C NMR ($CDCl_3$, ppm): 76.07, 38.55, 34.12, 33.09, 28.32, 22.78, 20.40, 15.24, 14.33, 14.04; CI-MS *m/z* (relative intensity): 140 (100) (M^+- H_2O); Anal. Calcd. for $C_{10}H_{22}O$: C, 75.87; H, 14.02; Found: C, 76.10; H, 13.98.



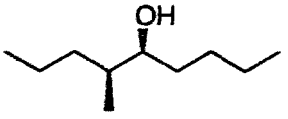
(*4R, 5S*)-4-Methyl-5-nonanol [(*4R,5S*)-7]. 2.62 g, 83 % yield, 95 % ee; Anal. Calcd. for $C_{10}H_{22}O$: C, 75.87; H, 14.02; Found: C, 75.62; H, 13.97. The same spectroscopic characteristics as the antipode were obtained.



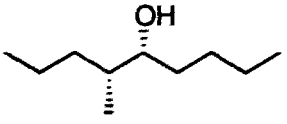
[(*4S, 5S*)-4-Methyl-5-nonyl)] benzoate (36b). Triphenylphosphine (7.87 g, 30 mmol), benzoic acid (3.66 g, 30 mmol) and (*4S,5R*)-**7** (2.39 g, 15 mmol) in dry benzene (100 mL) were stirred for 10 min at -10°C before diisopropyl azodicarboxylate (6.07 g, 5.9 mL, 30 mmol) was added *via* syringe. After stirring overnight at room temperature, pentane was added resulting in the formation of a white precipitate. The reaction mixture was filtered through a Florisil pad and concentrated *in vacuo*. Purification by column chromatography (9:1, pentane:ether, R_f = 0.61) afforded **36b** (2.46 g, 63 % yield) as a pale yellow liquid: ^{1}H NMR ($CDCl_3$, ppm): 0.90 (6H,m), 1.0 (3H, d, J = 8.9 Hz), 1.20 (2H, m), 1.36 (5H, m), 1.51 (1H, m), 1.60 (1H, m), 1,70 (1H, m), 1.98 (1H, m), 5.10 (1H. m), 7.48 (2H, ttt, J = 7.5, 1Hz), 7.55 (1H, ttt, J = 7.5, 1Hz), 7.56 (2H, dd, J = 7.5, 1Hz); ^{13}C NMR ($CDCl_3$, ppm): 166.33, 132.59, 130.97, 129.54, 128.27, 125.48, 77.94, 36.19, 35.41, 31.23, 27.95, 22.62, 20.31, 14.41, 14.02, 13.92; CI-MS *m/z* (relative intensity): 262 (2), 140 (M^+- C_6H_5-CO, 100). Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99; Found: C, 77.71; H, 10.17.



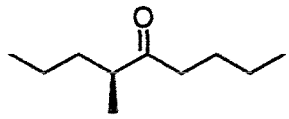
[(*4R, 5R*)-4-Methyl-5-nonyl)] benzoate (36a). 3.06 g, 73 % yield. Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99; Found: C, 77.76; H, 9.90. The same spectroscopic characteristics as the antipode were obtained.



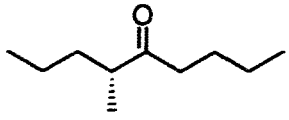
(*4S, 5S*)-4-Methyl-5-nonanol [(4*S,5S*)-7]. To a 15 % KOH solution of methanol was added **36b** (2.46 g, 9.4 mmol). After stirring the mixture overnight it was quenched with water and extracted with Et_2O (3 X 30 mL). The ether extracts were washed with dilute HCl and saturated NaCl and then dried over anhyd. $MgSO_4$. Concentration *in vacuo* and column chromatography (9:1, pentane:ether, R_f = 0.13) gave (*4S,5S*)-**7** (1.20 g, 81 % yield, 98 % ee) as a colourless liquid: $[\alpha]_D^{20}$ = -25.5° (c = 1.765, Et_2O); ^1H NMR ($CDCl_3$, ppm): 0.86 (2H, d, *J* = 8.0 Hz), 0.90 (6H, m), 1.18 (2H, m), 1.34, (10H, m), 3.48 (1H, m); ^{13}C ($CDCl_3$, ppm): 75.19, 37.91, 35.64, 34.19, 28.45, 22.75, 20.43, 14.27, 14.00, 13.50; Anal. Calcd. for $C_{10}H_{22}O$: C, 75.87; H, 14.02; Found: C, 76.01; H, 13.90.



(*4R, 5R*)-4-Methyl-5-nonanol [(*4R,5R*)-7]. 1.59 g, 85 % yield, 98 % ee; $[\alpha]_D^{20}$ = +26.6° (c = 1.895, Et_2O); Anal. Calcd. for $C_{10}H_{22}O$: C, 75.87; H, 14.02; Found: C, 76.00; H, 13.99. The same spectroscopic characteristics as the antipode were obtained.



(*S*)-4-methyl-5-nonanone [(*S*)-8]. To (*4S,5R*)-**7** (2.89 g, 18 mmol, 96 % ee) dissolved in Et_2O (50 mL) and cooled to -10°C was added 28 mL of a cold mixture of 11.38 g $Na_2Cr_2O_7 \cdot 2H_2O$, 16 mL H_2SO_4 and 30 mL H_2O. The dropwise addition was accompanied by vigorous stirring and maintenance of the temperature below 0°C. The progress of the reaction was monitored by analysis of aliquots which were periodically removed from the reaction [TLC (9:1, pentane:ether, R_f = 0.58)]. Upon completion, the mixture was washed with saturated oxalic acid solution. The ether layer was separated and the aqueous layer was extracted (2 X 10 mL) with Et_2O. The combined ether extracts were washed with saturated $NaHCO_3$ and NaCl and dried over anhyd. $MgSO_4$. Column chromatography (9:1, pentane: Et_2O) yielded (*S*)-**8**, 2.34 g (83 % yield, 95 % ee). $[\alpha]_D^{20}$ = +16.3° (c = 2.220, Et_2O); IR (neat) 2959, 2874, 1713, 1460, 1409, 1378, 1124, 1046, 989 cm^{-1}; ^1H NMR ($CDCl_3$, ppm): 0.90 (6H, m), 1.04 (3H, d, *J* = 8.1 Hz), 1.29 (5H, m), 1.55 (2H, m), 1.60 (1H, m), 2.42 (2H, ddd, *J* = 8.1, 4.0 Hz), 2.52 (1H, m); ^{13}C ($CDCl_3$, ppm): 214.94, 46.12, 40.84, 35.23, 25.86, 22.32, 20.49, 16.32, 14.09, 14.02; Anal. Calcd. for $C_{10}H_{20}O$: C, 76.85; H, 12.91; Found: C, 76.75; H, 12.86.



(*R*)-4-methyl-5-nonanone [(*R*)-8]. 2.40 g, 95 % yield, 95 % ee; $[\alpha]_D^{20}$ = -13.4° (c = 2.390, Et_2O); Anal. Calcd. for $C_{10}H_{22}O$: C, 76.85; H, 12.91; Found: C, 77.03; H, 13.11. The same spectroscopic characteristics as the antipode were obtained.

Chapter 3

Aggregation Pheromones and Host Kairomones of the West Indian Sugarcane Weevil, *Metamasius hemipterus sericeus* (Olivier) and *Paramasius distortus* (Gemminger & Harold) (=*Metamasius inaequalis* [Gyllenhal]) (Coleoptera. Curculionidae)

3.1. The West Indian Sugarcane weevil, *Metamasius hemipterus sericeus* (Oliv.). Its Habitat and Current Control.

3.1.1. *Metamasius hemipterus sericeus.*

The West Indian sugarcane weevil (WISW), *Metamasius hemipterus sericeus* is a pest of sugarcane, pineapple, palms and banana.[70] It is found in the Greater Antilles, Central America south of Nicaragua to western Colombia and Ecuador, and Africa.[71] In the mid 1980's WISW was introduced to Florida where it has become a significant pest of ornamental palms and sugarcane.[72] For example, in Florida the container and field-grown ornamental palm industry is valued at more than $ 50 million per year. Current Florida Department of Plant Industry regulations stipulate that palm nurseries with WISW must be quarantined and sprayed with insecticides until the weevils are no longer detectable in plants for sale or distribution.[72b]

Beetles are attracted to, and oviposit in, damaged or unhealthy plants and rotten fruits (e.g., pineapple, mango, papaya)[70] where the larvae develop in about seven weeks.[71]

Attraction of *Metamasius* to sugarcane[72,73] is used in Central America to infect field populations with entomopathogens.[74] Volatiles emitted by several host plants and by male WISW attract male and female weevils and has been used in insecticide-baited traps to capture them.[73] More recently, a "lethal pitfall

trap", which avoids the use of insecticide has been used to trap WISW in Florida.[72]

3.1.2. *Paramasius distortus.*

Little is known about this insect. It was classified first by Günther as *Metamasius inaequalis* (Gyllenhal), and recorded by Vaurie[70] under this name, and also as a junior homonym of what is now *Sphenophorus inaequalis.* Wibmer and O'Brien[75] later designated it as *P. distortus* which is the accepted name. Its range extends through most of Brazil, Peru and all northern South America, Panama, Costa Rica and Nicaragua in Central America. A smaller weevil (8.5-12 mm) than *M. hemipterus* (10-20 mm), it is considered a secondary pest, sharing the same host range as *Metamasius* and other Rhynchophorinae. It is commonly cross attracted to pheromone-baited traps of *R. palmarum* and *M. hemipterus.*[76] Its ecology is similar to *Metamasius.*

3.2. Male-produced Aggregation Pheromones of *M. hemipterus* and *P. distortus.*

3.2.1. *M. hemipterus.*

Thirty-eight male and female weevils collected[i] in a banana plantation 7 km west of Homestead, Dade County, Florida were placed into separate Nalgene desiccators containing water-moistened Kimwipes™[10] (for details, see Experimental Section, Chapter 2). Weevil-released volatiles were collected for four days on Porapak Q. Using another desiccator, cut sugarcane stalk (1 kg) was aerated for two days. Volatiles were eluted from Porapak Q with pentane and concentrated by distillation.

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[i] Collection by Dr. Robin Giblin-Davis, IFAS, University of Florida, Fort Lauderdale, Florida

Gas chromatographic (GC) analysis of volatiles with flame ionization detector (FID) and electroantennographic detector (EAD) revealed 8 male-specific compounds (Figure 3.1). Seven of these (**40-42**, **7**, **43-45**) elicited weak to moderate antennal responses (Figure 3.1). Hydrogenation and re-analysis of weevil volatiles by GC-EAD revealed the same antennal responses, indicating all EAD-active compounds were saturated. Coupled GC-mass spectrometric analysis of EAD-active volatiles in both EI and CI modes indicated they were methyl-branched ketones and secondary alcohols with molecular weights of 86, 88, 128, 130, 142, 144, 156 and 158. Structures of (**40**) and (**7**) (Figure 3.1) were hypothesized to be 3-pentanol (**40**) and 4-methyl-5-nonanol (**7**) based on similarities of their mass spectra with those previously reported.[29a,77] Retention indices (RI) of (**41**) (RI 1310) and (**42**) (RI 1410) on a SP-1000-coated fused silica column suggested they were saturated homologues of (*E*)-6-methyl-2-hepten-4-ol, the aggregation pheromone of the *R. palmarum*, the American palm weevil.[64] Hydrogenation of *R. palmarum* volatiles converted the unsaturated aggregation pheromone to 2-methyl-4-heptanol whose retention times coincided with those of *M. h. sericeus*-produced (**41**) on two GC-columns (SP-1000 and DB-5). Thus, it was hypothesized that **41** and **42** were 2-methyl-4-heptanol and 2-methyl-4-octanol. Identical retention and mass spectrometric characteristics of authentic alcohols (**40-42**, **7**) and ketones (**43-45**, **8**) with male-produced compounds confirmed structural assignments of all candidate pheromones.

GC-EAD analyses of sugarcane volatiles revealed four antennally active components (Figure 3.2). Through GC-MS analyses of authentic standards, the three most EAD-active compounds were identified as ethyl acetate (**3**), ethyl propionate (**4**) and ethyl butyrate (**6**).

3.2.2. *P. distortus.*

Forty male and female weevils collected[ii] in a oil palm plantation near Coto, Costa Rica were aerated separately in a modified Nalgene desiccators with and without sugarcane for four days (for details, see Experimental Section, Chapter 2). Volatiles were eluted from Porapak Q with distilled pentane and concentrated by distillation.[10]

GC and GC-EAD analysis of volatiles from fed and unfed male weevils revealed a strongly EAD-active compound (Figure 3.3). GC-MS in both EI and CI mode and retention characteristics were consistent with 2-methyl-4-heptanol (**41**), which was also identified as a candidate pheromone for WISW.

3.3. Field Experiments.

3.3.1. *M. hemipterus.*

Field tests[iii] of candidate semiochemicals were conducted in a two year old banana plantation near Homestead, Florida, and in commercial oil palm plantations near Coto, Costa Rica. Experiments with 7-10 replicates each employed pitfall traps[72] or Dipel™ traps[10] which were set up in complete randomized blocks with treatments and blocks 20 m apart. Pitfall traps used in pheromone experiments contained 2-3 cm of soapy (3 % by weight of Alkonox) or equally effective, insecticide-laced (3 g *per* liter of Sevin 80) water to retain captured weevils. Traps were buried in the shade with their openings 2-3 cm above the soil surface. Dipel™ traps used in kairomone experiments were hung at chest height from palms. Attractants were suspended from the lid, and insecticide-treated food or water covered the bottom. Candidate pheromones **40-45,7-8** were dispensed from membrane release devices[78] emitting 3 mg *per*

[ii] Collection by Dr. Allan C. Oehlschlager.

[iii] Conducted by Dr. Robin Giblin-Davis in Florida and by Drs. Allan C. Oehlschlager and Carlos Chinchilla of Palma Tica of Costa Rica.

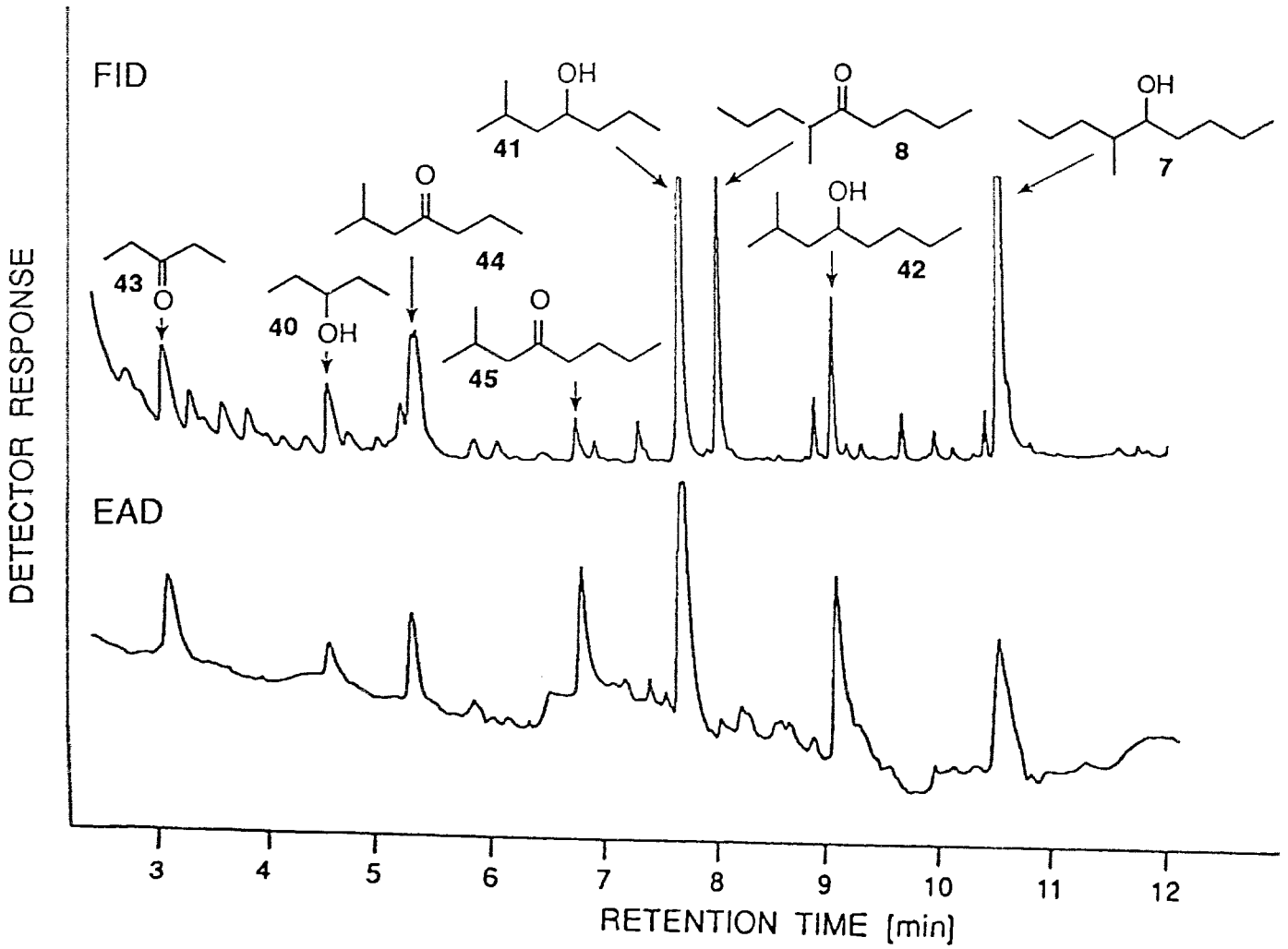


Figure 3.1. Flame ionization (FID) and electroantennographic detector (EAD: female *WISW* antenna) responses to volatiles obtained from unfed male *WISW*. Chromatography: SP-1000 coated fused silica column (30 m x 0.25 mm ID); temperature program: 1 min at 50°C, 10°C *per* minute to 180°C.

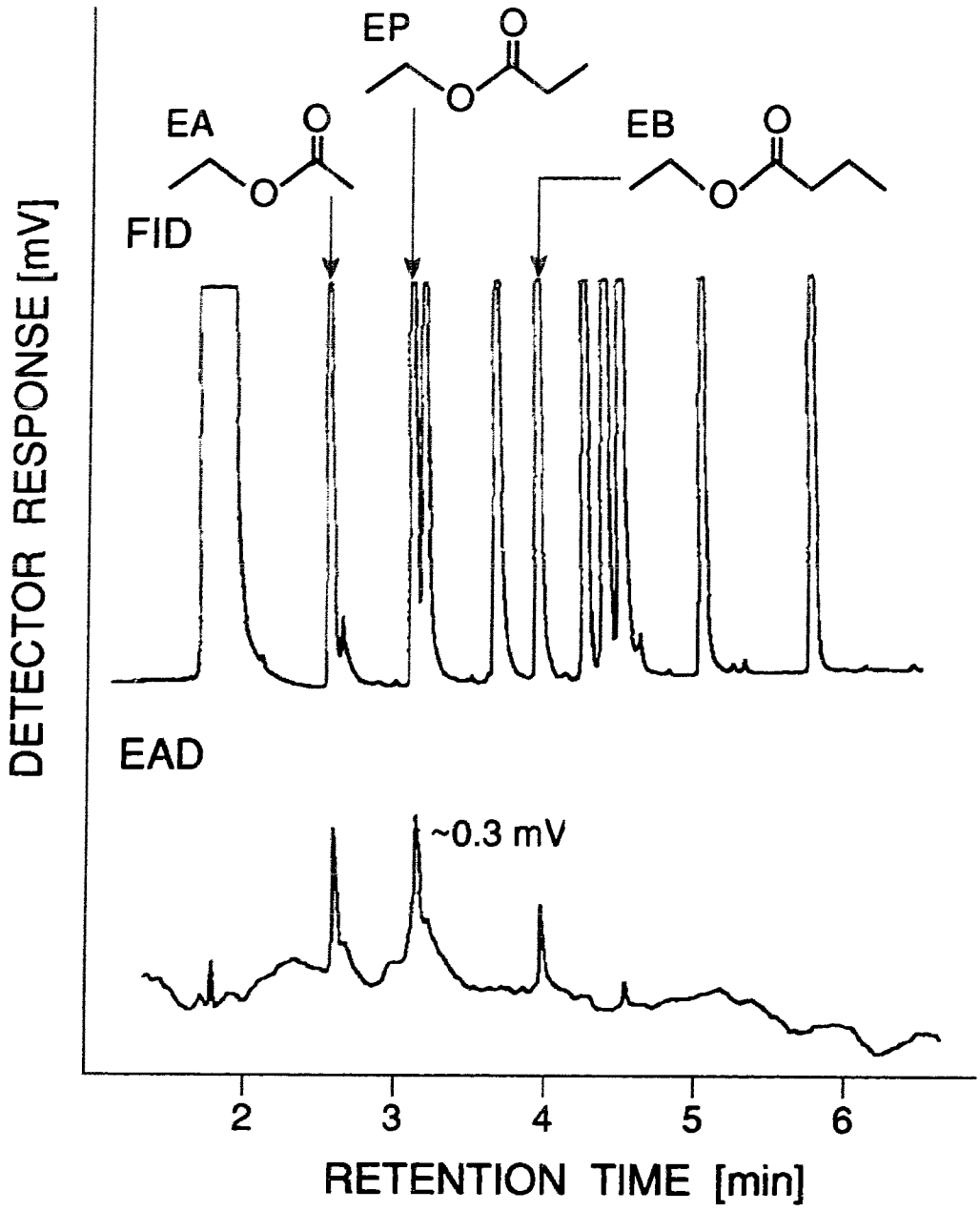


Figure 3.2. Flame ionization (FID) and electroantennographic detector (EAD: female *WISW* antenna) responses to volatiles obtained from sugarcane. Column and chromatographic conditions as in Figure 3.1.

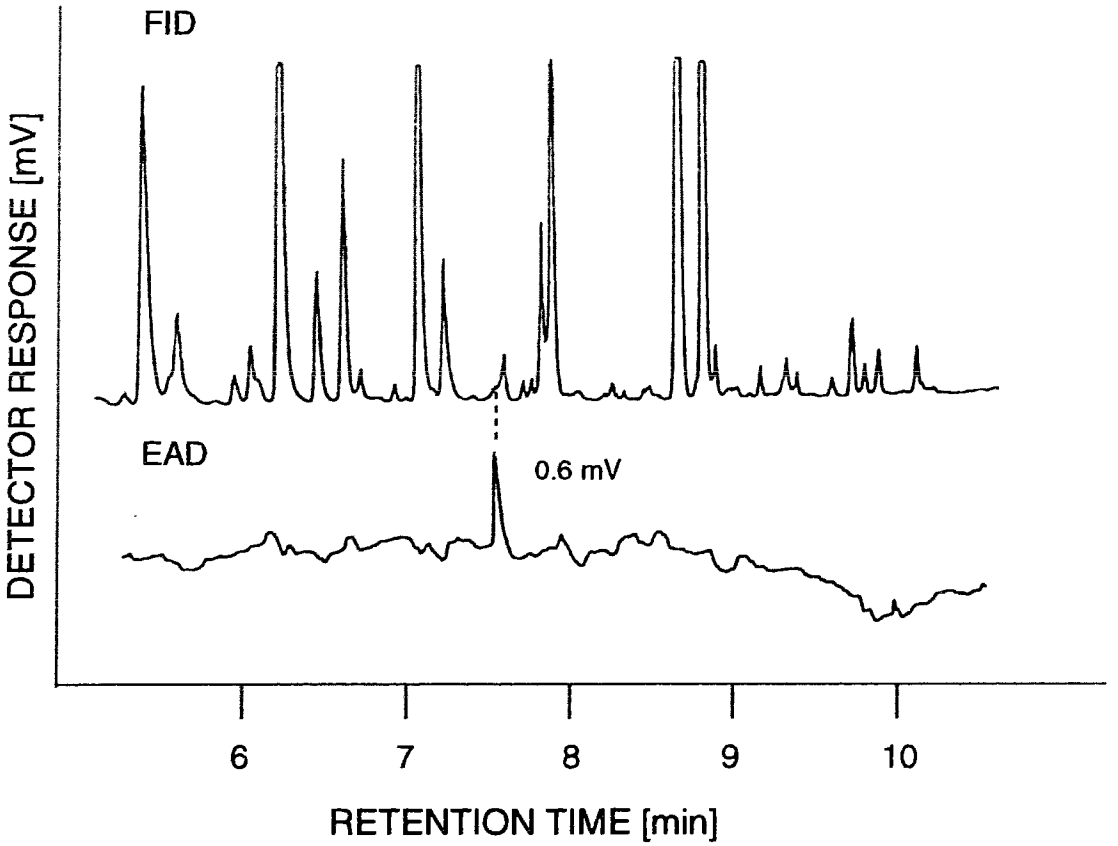


Figure 3.3. Flame ionization (FID) and electroantennographic detector (EAD: female *P. distortus* antenna) responses to volatiles obtained from fed male *P. distortus.* Column and chromatographic conditions similar to those in Figure 3.1.

day of each component at 25°C under laboratory conditions. Host volatiles were released at 20 mg *per* day (at 25°C under laboratory conditions) from 10 mL plastic vials. Sugarcane (250 g *per* trap) was prepared immediately before placement.

Assumptions of normality and homogeneity of variance were tested on all data by graphical assessment of log variance *vs.* log mean and Bartlett's test, respectively (SAS Institute, 1985 or Systat 5.2, 1992). Data that did not exhibit a normal distribution were transformed by $(x + 0.5)^{0.5}$ or log $(x + 1)$ and subjected to analysis of variance (ANOVA) (PROC GLM, SAS, 1985 or MGLH Fully Factorial, Systat 5.2, 1992) with means compared by Bonferroni's or Tukey's test at $p = 0.05$ (SAS Institute 1985 or Systat 5.2).[61] Means presented are untransformed. In some cases data were analyzed nonparametrically using the chi-square approximation method of a Kruskal-Wallis or Wilcoxon ranked sum test ($p = 0.05$) (SAS Institute 1985). Multiple comparisons were separated using the Q-test statistic ($p = 0.05$).

The first trapping experiment tested attraction of WISW to traps containing sugarcane alone and in combination with either alcohols, ketones or both (**40-42, 7** plus **43-45, 8**). Experiment 2 tested attraction of male and female weevils to sugarcane, alcohols or both combined. The third and fourth experiments tested alcohols in quaternary and all possible ternary (Exp. 3) or binary (Exp. 4) combinations with and without sugarcane. Experiment 5 tested attractiveness of sugarcane, alcohols (**40-42, 7**) singly or in quaternary combination. Experiments 6, 7 and 8 tested **7:41** (8:1) alone or in combination with sugarcane or with ethyl acetate, ethyl propionate or ethyl butyrate singly (Exp. 6) or in all binary (Exp. 7) and ternary combinations (Exp. 8).

The production of four EAD-active alcohols and corresponding ketones (Figure 3.1), suggested a complex chemical communication system of WISW.

In field trapping experiments, the alcohols but not the ketones enhanced weevil attraction to sugarcane (Exp. 1, Figure 3.4). Presence of the ketones reduced attraction to the alcohols (Figure 3.4). Addition of ketones to this binary combination or replacement of alcohols with ketones significantly reduced attraction. Sugarcane and alcohols were similarly effective (Exp. 2, Figure 3.5) and equally attracted male and female WISW. Testing the alcohols in all possible ternary mixtures with (Exp. 3, Figure 3.6A) or without sugarcane (Exp. 3, Figure 3.6B) and binary (Exp. 4, Figure 3.7A-3.7C) blends with or without sugarcane and singly with or without sugarcane (Exp. 5, Figure 3.8A-3.8B) indicated that any treatment that contained **7** was as attractive as the quaternary blend. This behavior is consistent with findings that *Rhynchophorus* weevils produce and respond to one aggregation pheromone (see Chapter 2). Only one compound, **7**, was essential for pheromonal attraction of WISW. In view of the strong attractiveness of **7**, superior EAD-activity of **41** was surprising (Figure 3.1). Experiments 3-5 were repeated several times, and in all cases it was apparent that **7** was essential in transmitting the semiochemical message to WISW males and females. Lack of clear role of the other EAD-active alcohols cannot be attributed to a low population of this insect (e.g., compare Figures 3.7A and 3.7C) or to the presence or absence of sugarcane (compare Figures 3.7A and 3.7B). However, due to the cross attractive behavior of conspecific *P. distortus* to *M. h. sericeus traps*, 2-methyl-4-heptanol (**41**) was chosen to examine the synergistic effect of EAD-active host volatiles and the field activity of the stereoisomers of **7** and **41**. Due to high capture rates when sugarcane is present and the fact that no statistical behavioral difference has been found between treatments with and without sugarcane, some of the following experiments were performed in the absence of sugarcane.

The semiochemical role of EAD-active ketones is not understood. Released together with EAD-active alcohols, they reduced attraction in field experiments, suggesting a role as intra- or inter specific "spacing" pheromones. Attraction to alcohol pheromones and "antiaggregative" characteristics of the corresponding ketones has been well documented in the Douglas fir beetle, *Dendroctonus pseudotsugae* (Hopkins)[79] and in the mountain pine beetle, *D. ponderosae* (Hopkins).[80] Production of antiaggregative ketones may have been artificially induced by aeration of many confined weevils. Alternatively, ketone release rates may have significantly differed from optimal, natural rates.

Although **7** was attractive by itself, attractiveness strongly increased when it was combined with sugarcane (e.g., Figure 3.7C). Antennally active sugarcane volatiles (Figure 3.2), ethyl acetate, ethyl propionate and ethyl butyrate exhibited kairomonal attraction in field experiments (Exp. 6, Figure 3.9). Attractiveness of alcohols **7** and **41** at a 8:1 ratio (assuming one stereoisomer of each is biologically active, this proportion is close to the natural ratio) increased upon addition of ethyl acetate, ethyl propionate or ethyl butyrate singly (Exp. 6, Figure 3.9) or in binary (Exp. 7, Figure 3.10) or ternary combinations (Exp. 8, Figure 3.11). However, none of these esters alone or in combination (Figures 3.10 and 3.11) exhibited synergistic attraction equivalent to sugarcane, suggesting the presence of additional, as yet unknown, sugarcane kairomones (synergy activity of sugarcane exceeded that of the above esters 10-100 times).

The same esters in fermenting tissues of African oil palm, *Elaeis guineensis* (Jacq.) coconut palm, *Cocos nucifera* L., and cabbage palmetto, *Sabal palmetto* (Walter), also elicited antennal responses by *Rhynchophorus* weevils (Dr. Gerhard Gries, personal communication). However, kairomonal attraction of ethyl butyrate in WISW, ethyl acetate in *R. cruentatus*,[27b] *R. palmarum*[27c] and WISW, and ethyl propionate in *R. phoenicis*[27a] and WISW did

not approximate synergy activity of host plant tissue. Antennal and behavioral activities of the same esters in *Metamasius* (WISW) and *Rhynchophorus* weevils indicates recognition of the same kairomones in different plant tissues. As yet unknown kairomones in palm and sugarcane may be cross generic attractants, whose identification may promote semiochemical-based management of *Rhynchophorus* and *Metamasius* weevils. It has been recently found[72b] that release of large amounts of ethyl acetate from traps containing an 8:1 mixture of **7**:**41** and sugarcane increases attractancy to WISW.

3.3.2. *P. distortus.*

Field tests[iv] of candidate semiochemicals were conducted in commercial oil palm plantations near Coto, Costa Rica using pitfall traps.[14b,16] Experiments were set up in complete randomized blocks with treatments and blocks 20 m apart. Trap placement and release rate was similar at those used for *M. hemipterus*.

This field experiment[iv] demonstrated attraction of *P. distortus* to traps containing sugarcane alone or in combination with alcohol **41** (data not shown). A second experiment tested attraction of **41** alone. Results of this experiment (Figure 3.12) confirmed biological activity of **41** alone.

[iv] Conducted by Dr. Carlos Chinchilla, Palma Tica of Costa Rica.

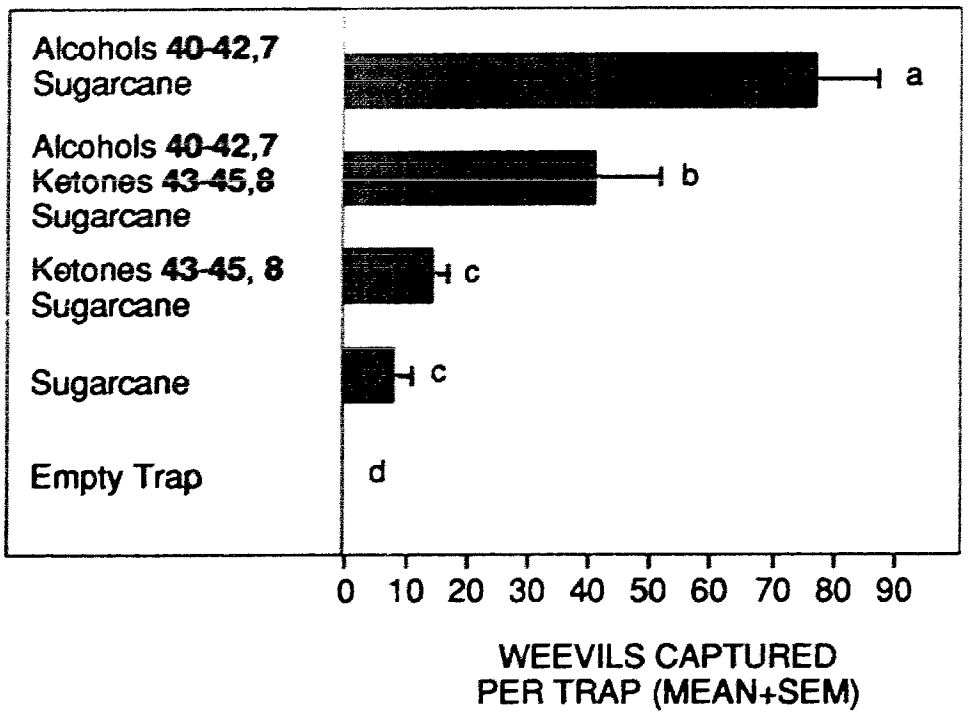


Figure 3.4. Mean (+SEM) captures of *WISW* in traps baited with sugarcane and alcohols **40-42** and **7**, sugarcane and alcohols **40-42**, **7** and ketones **43-45**, **8** and sugarcane and ketones **43-45**, **8**. The experiment (**N** = 10) was conducted in a banana plantation near Dade Co., Florida, 5-10 March 1993. Data transformed by $(X + 0.5)^{0.5}$ to approximate homogeneity are presented untransformed. Means followed by the same letter are not significantly different according to a Waller-Duncan k-ratio *t*-test ($k = 100$, $p_{1/4}$ 0.05).

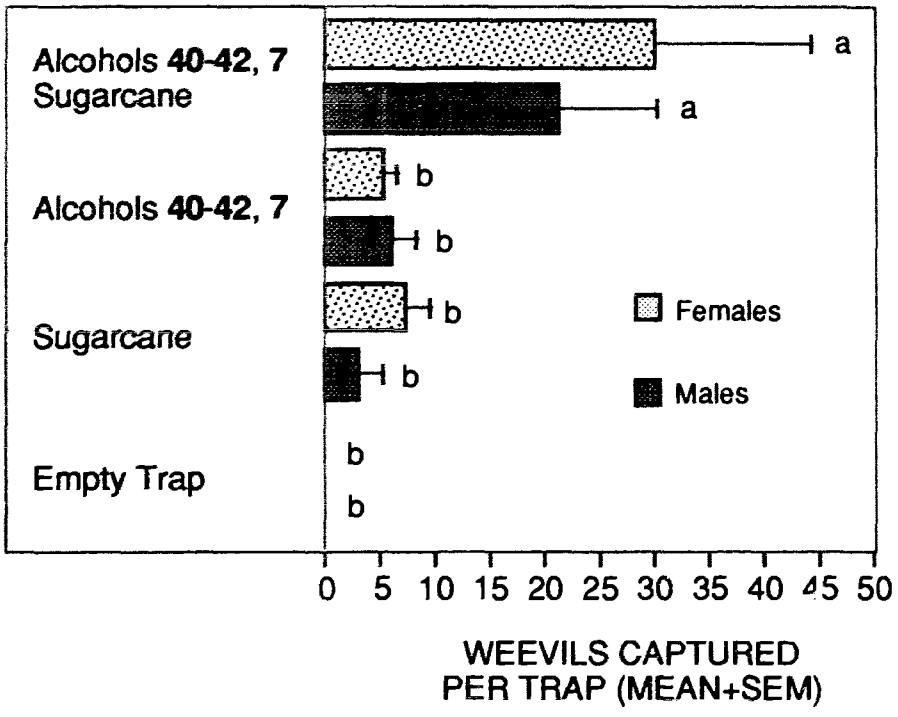


Figure 3.5. Mean (+SEM) captures of *WISW* in traps baited with sugarcane and alcohols **40-42** and **7** alone or in combination. The experiment (N = 10) was conducted in a banana plantation near Dade Co, Florida, 31 March-5 April 1993. Data transformed by $(X + 0.5)^{0.5}$ to approximate homogeneity are presented untransformed. Means followed by the same letter are not significantly different according to a Waller-Duncan k-ratio *t*-test on $(x+0.5)^{0.5}$ transformed data (k = 100; $p_{1/4}$ 0.05)

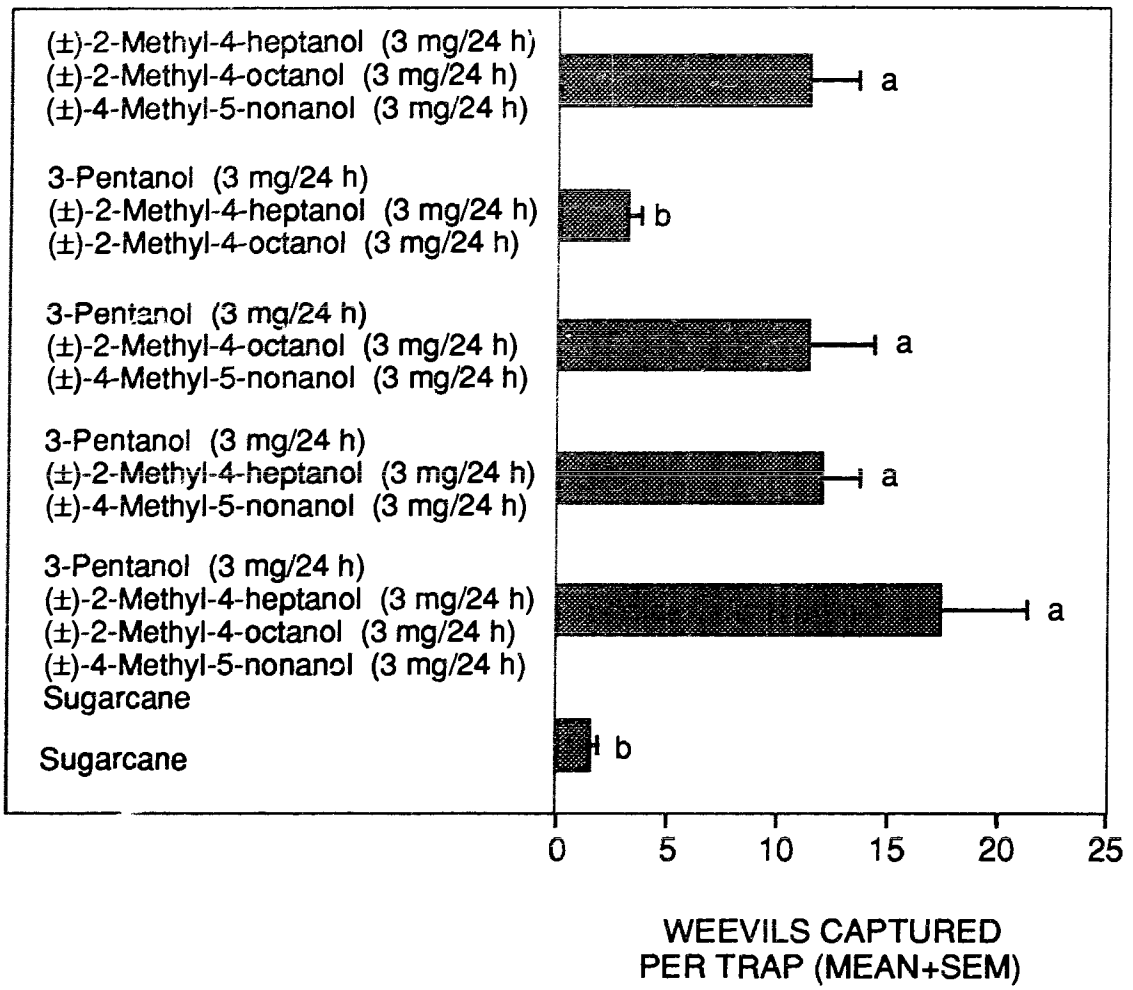


Figure 3.6A. Mean (+SEM) captures of *WISW* in traps baited with sugarcane in combination with all ternary combinations of alcohols **40-42** and **7**, sugarcane with **40-42** and **7**, and sugarcane alone. The experiment (N = 8) was conducted in a palm plantation near Coto, Costa Rica, 11-13 September 1993. Data transformed by $(X + 0.5)^{0.5}$ to approximate homogeneity are presented untransformed. ANOVA, $F = 12.38$, $df = 5, 42$, $p < 0.001$. Means followed by the same letter are not significantly different (Bonferroni's *t*-test, $p < 0.05$).

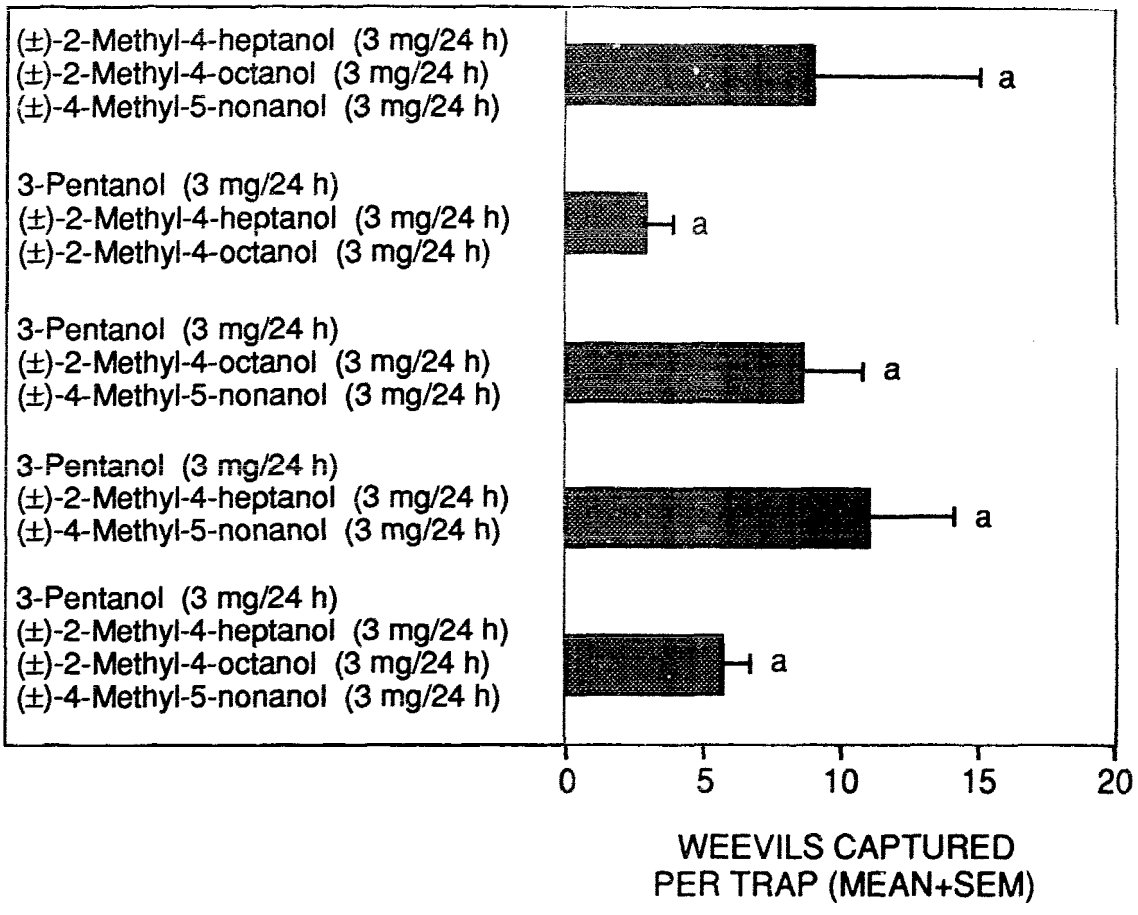


Figure 3.6B. Mean (+standard error) captures of *WISW* in traps baited with all ternary combinations of alcohols **40-42** and **7** or **40-42** and **7**. The experiment (N = 7) was conducted in a palm plantation near Coto, Costa Rica, 16-21 March 1994. Data transformed by $(X + 0.5)^{0.5}$ to approximate homogeneity are presented untransformed. ANOVA on transformed data followed by Bonferroni's test indicated no statistical difference between treatments at $p < 0.05$.

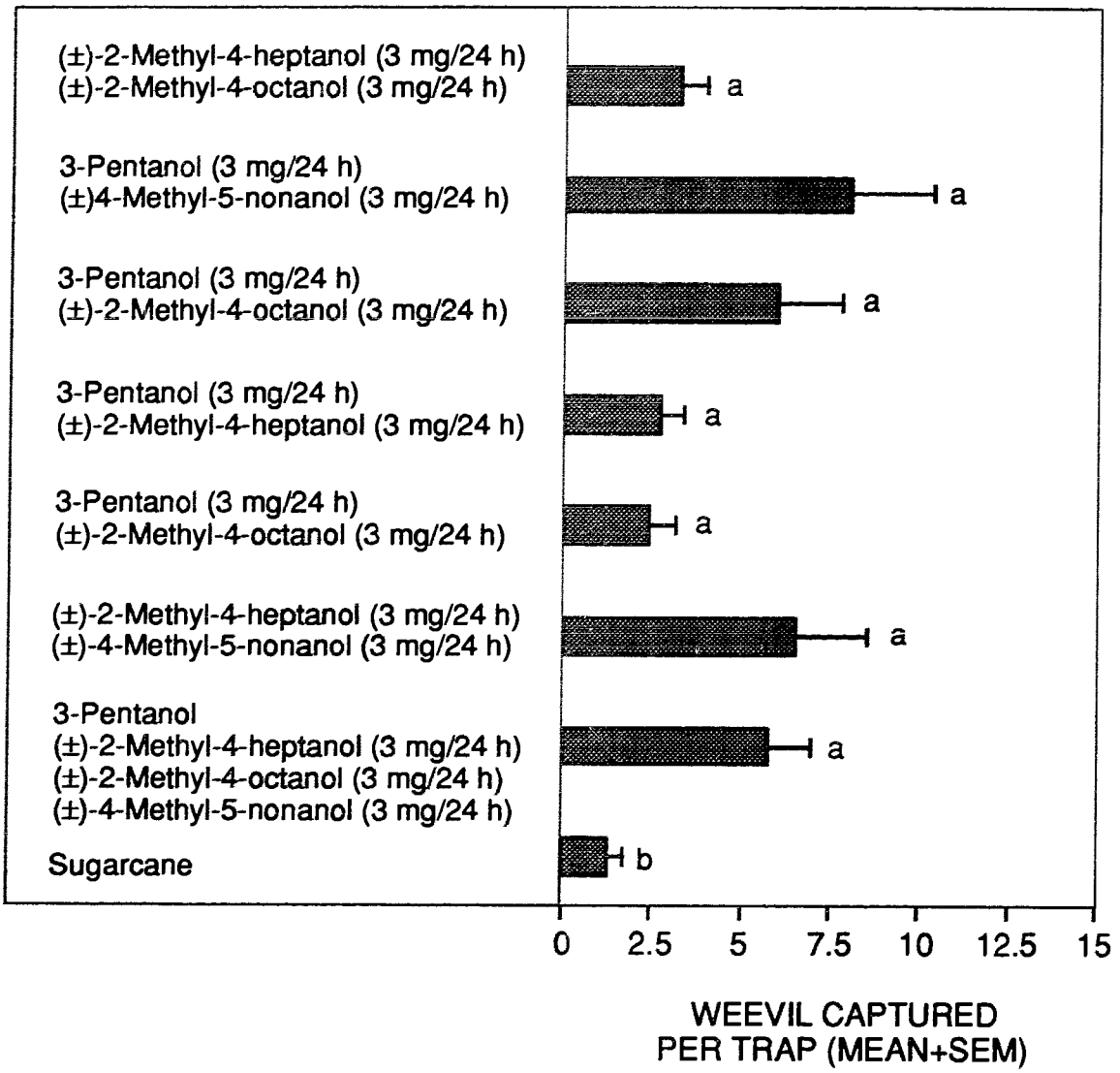


Figure 3.7A. Mean (+SEM) captures of *WISW* in traps baited with sugarcane in combination with all binary combinations of alcohols **40-42** and **7**, sugarcane with **40-42** and **7**, and sugarcane alone. The experiment (N = 10) was conducted in a palm plantation near Coto, Costa Rica, 18-23 August 1993. $\chi^2 = 19.9$, df = 7, $p < 0.0005$ (Kruskal-Wallis test). Means followed by same letter are not significantly different ($p = 0.05$).

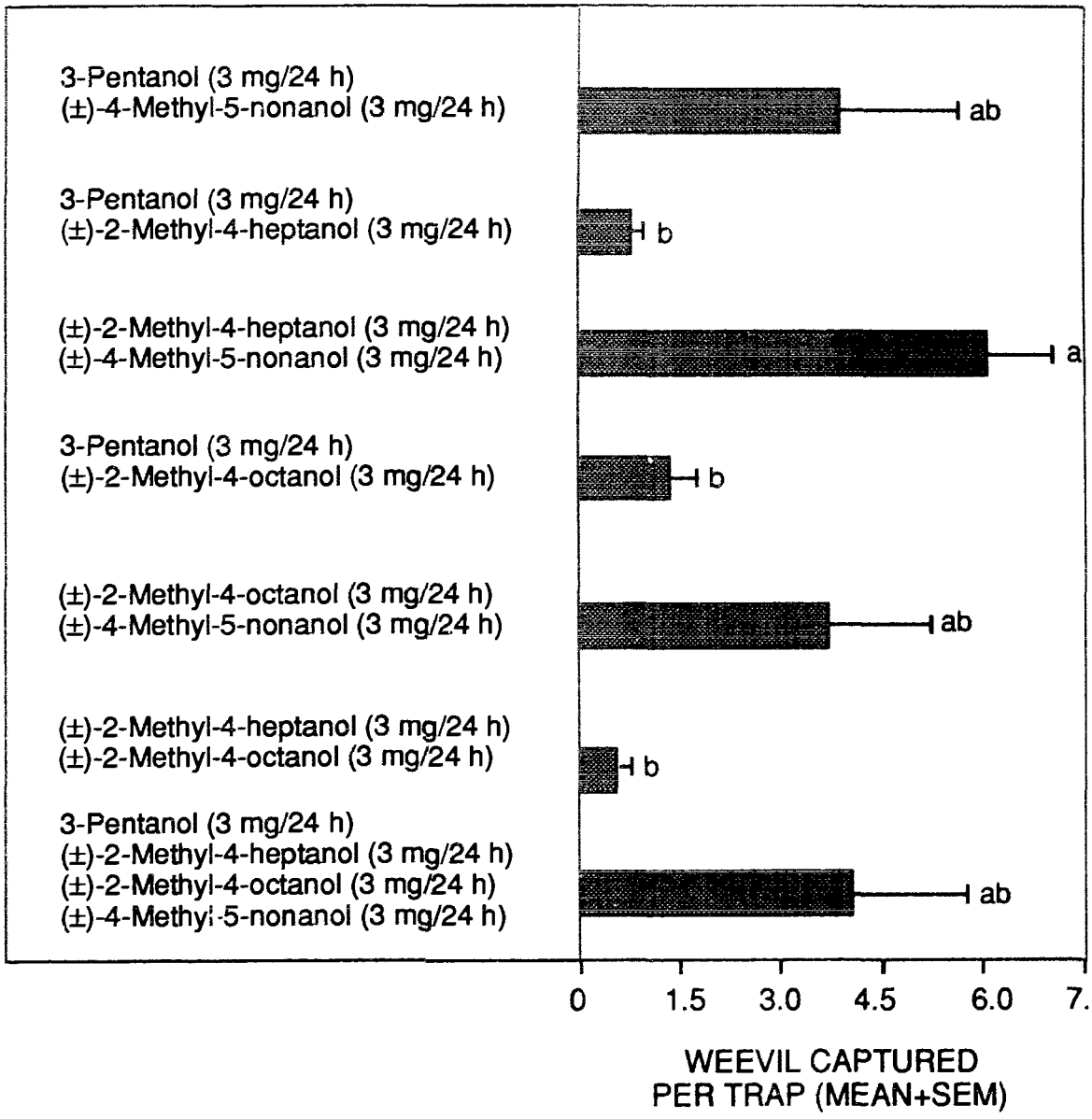


Figure 3.7B. Mean (+SEM) captures of *WISW* in traps baited with alcohols **40-42** and **7** in quaternary and all possible binary combinations. The experiment (N = 7) was conducted in an oil palm plantation surrounding Coto, Costa Rica, 12-15 November 1993. Data transformed by $(X + 0.5)^{0.5}$ to approximate homogeneity are presented untransformed. ANOVA, $F = 6.46$; $df = 6, 36$; $p < 0.0001$. Means followed by the same letter are not significantly different (Bonferroni's *t*-test, $p < 0.05$).

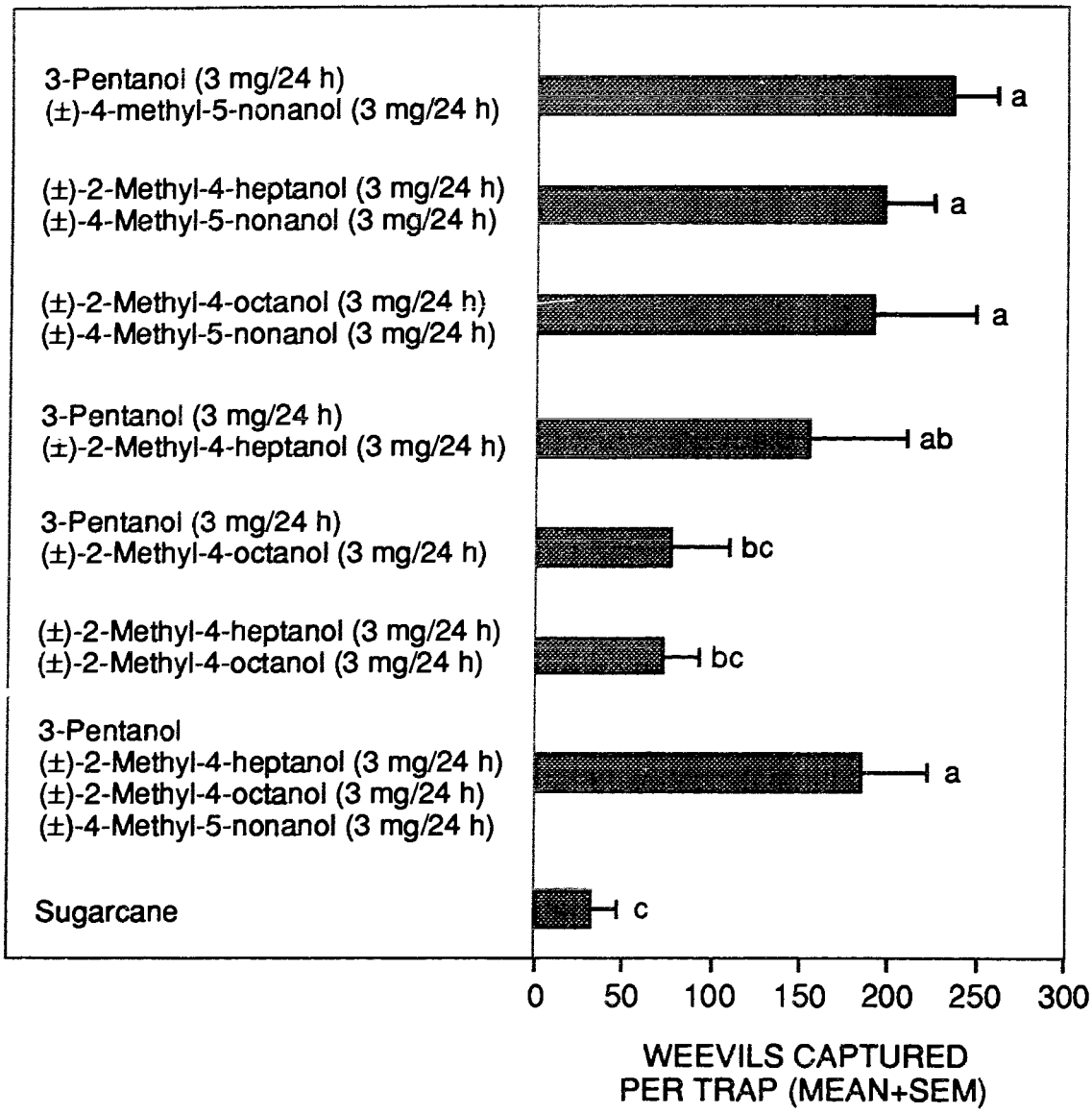


Figure 3.7C. Mean (+SEM) captures of *WISW* in traps baited with sugarcane in combination with all binary combinations of alcohols **40-42** and **7**, sugarcane with **40-42** and **7**, and sugarcane alone. The experiment (N = 6) was conducted in a palm plantation near Rio Claro, Costa Rica, 5-8 January 1994. Data transformed by $(X + 0.5)^{0.5}$ to approximate homogeneity are presented untransformed. ANOVA, F = 4.98, df = 7, 40, $p < 0.0004$. Means followed by the same letter are not significantly different (Bonferroni's t-test, $p < 0.05$).

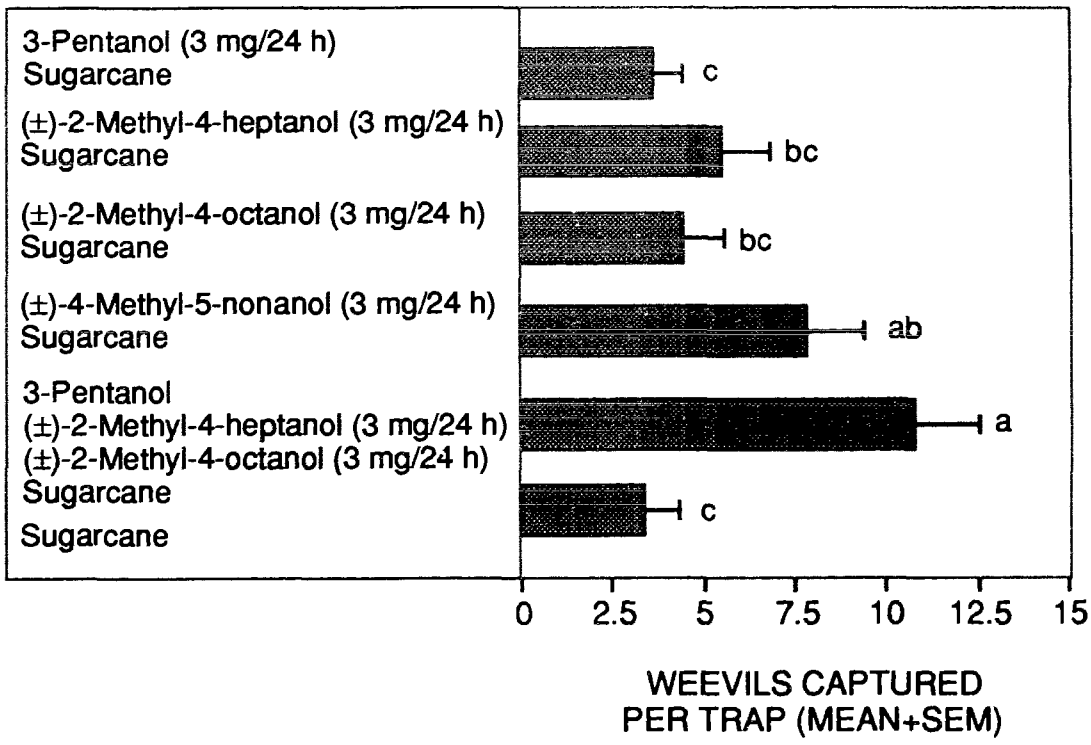


Figure 3.8A. Mean (+SEM) captures of *WISW* in traps baited with sugarcane in combination with individual alcohols **40-42** and **7**, sugarcane with **40-42** and **7**, and sugarcane alone. The experiment (N = 16) was conducted in a palm plantation near Coto, Costa Rica, 30 August-1 September 1993. $\chi^2 = 19.3$, df = 5, $p < 0.0023$ (Kruskal-Wallis test). Means followed by same letter are not significantly different ($p = 0.05$).

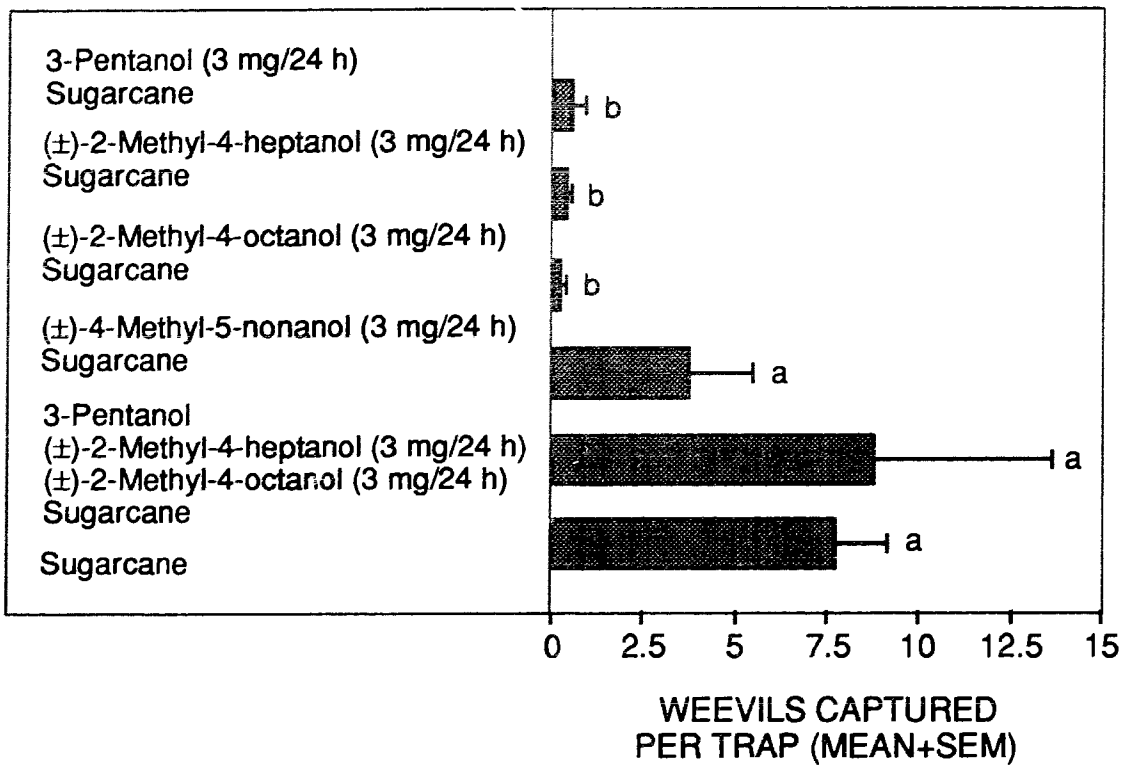


Figure 3.8B. Mean (+SEM) captures of *WISW* in traps baited with individual alcohols **40-42** and **7**, the combination of **40-42** and **7**, and sugarcane alone. The experiment (N = 8) was conducted in a palm plantation near Coto, Costa Rica, 3-7 December 1993. Data transformed by $(X + 0.5)^{0.5}$ to approximate homogeneity are presented untransformed. $F = 10.73$, $df = 5, 35$, $p < 0.0001$ (Friedman's test). Means followed by the same letter are not significantly different, $p < 0.05$.

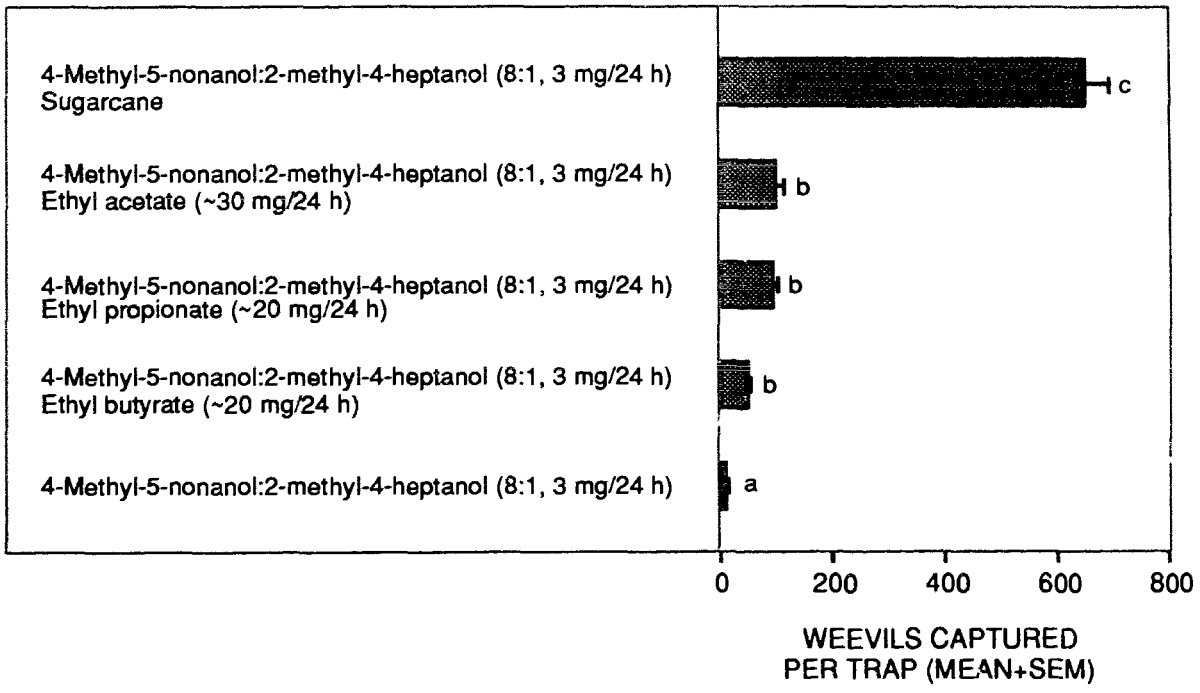


Figure 3.9. Mean (+SEM) captures of *WISW* in traps baited with a 8:1 mixture of **7:41** alone and combined with ethyl acetate, ethyl propionate, ethyl butyrate or sugarcane. The sugarcane was pre-soaked in Sevin 80. Other treatments used detergent-laced water as the killing agent. The experiment (N = 9) was conducted in an oil palm plantation surrounding Coto, Costa Rica, 11-21 October 1994. Data transformed by $(X + 1)^{0.5}$ to approximate homogeneity are presented untransformed. ANOVA, $F = 13.56$; $df = 4, 38$; $p < 0.0001$. Means followed by the same letter are not significantly different (Bonferroni's *t*-test, $p < 0.05$).

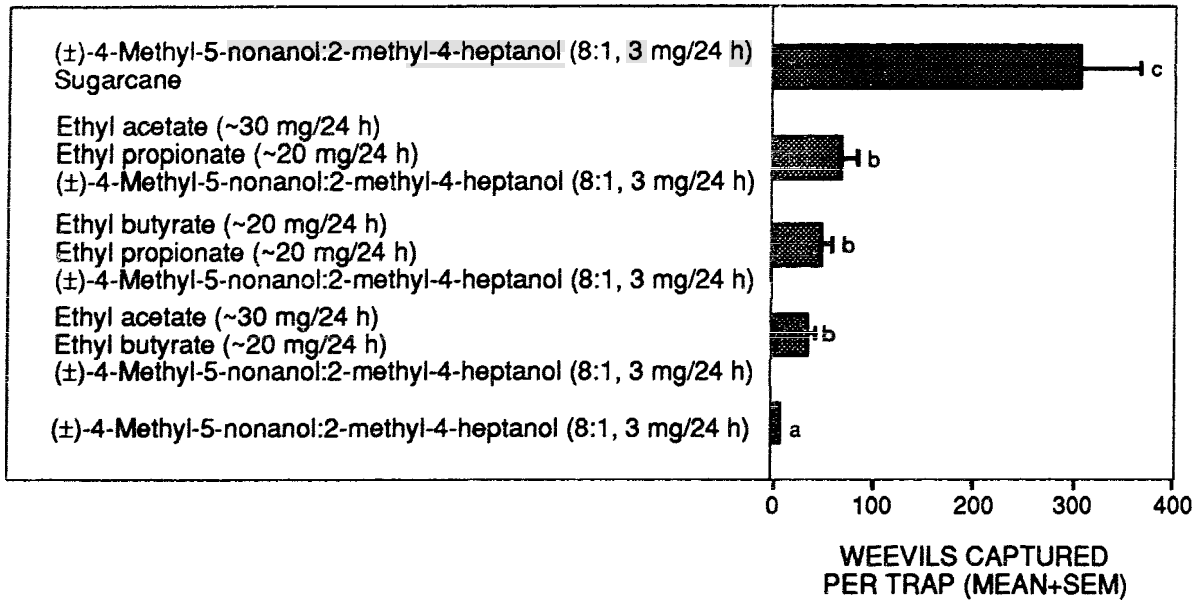


Figure 3.10. Mean (+SEM) captures of *WISW* in traps baited with a 8:1 mixture of **7:41** alone, 8:1 mixture of **7:41** and binary combinations of ethyl acetate, ethyl propionate, ethyl butyrate or sugarcane. The sugarcane was pre-soaked in Sevin 80. Other treatments used detergent-laced water as the killing agent. The experiment (N = 9) was conducted in an oil palm plantation surrounding Coto, Costa Rica, 21-28 October 1994. Data transformed by log (x + 1) to approximate homogeneity are presented untransformed. ANOVA, $F = 49.66$; $df = 4, 39$; $p < 0.0001$. Means followed by the same letter are not significantly different (Bonferroni's *t*-test, $p < 0.05$).

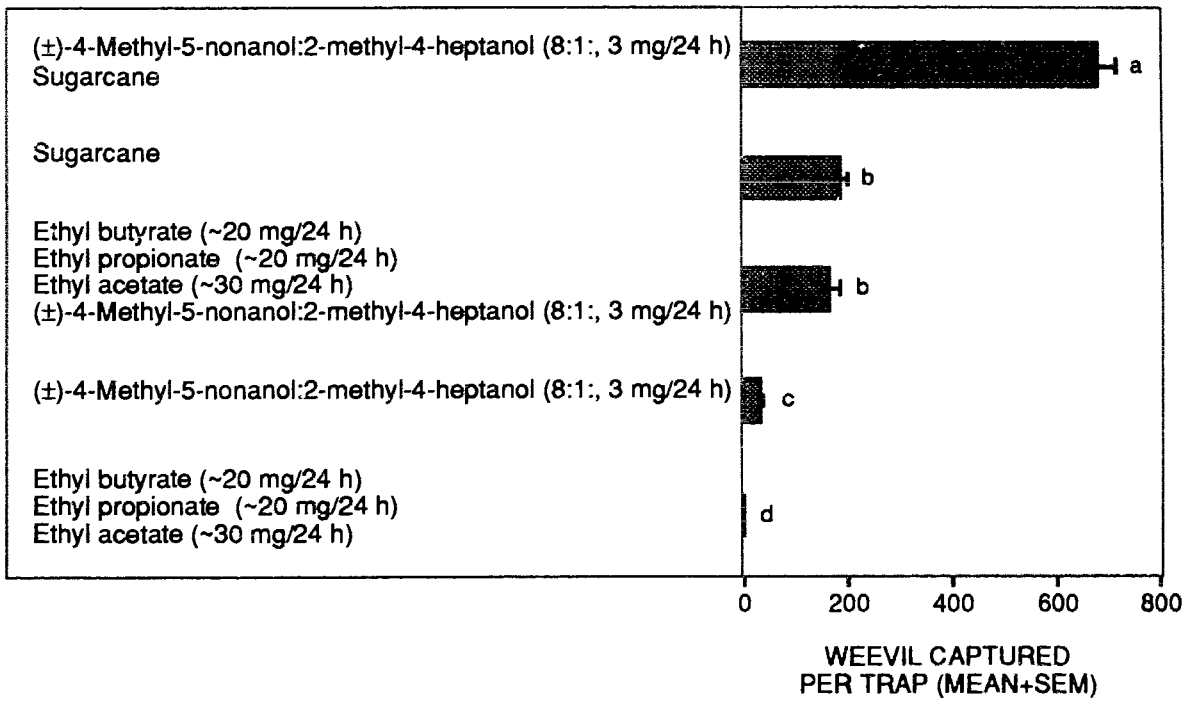


Figure 3.11. Mean (+SEM) captures of *WISW* in traps baited with a 8:1 mixture of **7:41** alone, 8:1 mixture of **7:41** and ternary combinations of ethyl acetate, ethyl propionate, ethyl butyrate or sugarcane. The sugarcane was pre-soaked in Sevin 80. Other treatments used detergent-laced water as the killing agent. The experiment (N = 9) was conducted in an oil palm plantation surrounding Coto, Costa Rica, 29 October-6 November 1994. Data transformed by $(x + 0.5)^{0.5}$ to approximate homogeneity are presented untransformed. ANOVA, $F = 176.01$; $df = 4, 40$; $p < 0.0001$. Means followed by the same letter are not significantly different (Bonferroni's *t*-test, $p < 0.05$).

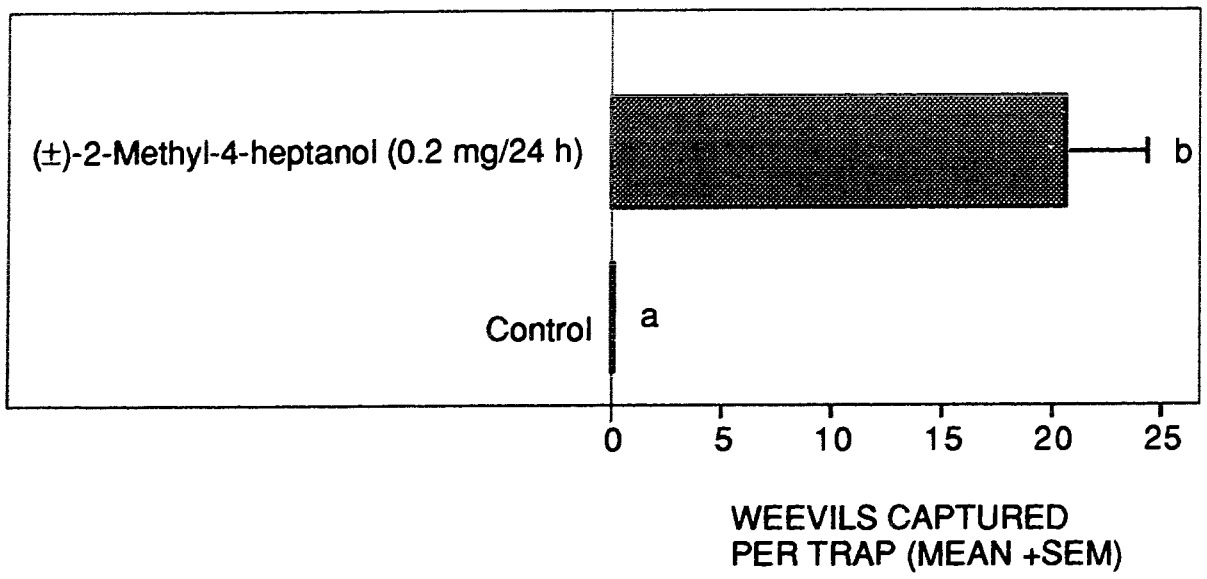


Figure 3.12. Mean (+SEM) captures of *P. distortus* in traps baited with alcohol **41**. The experiment (N = 12) was conducted in an oil palm plantation surrounding Coto, Costa Rica, 1-9 August 1995. Data transformed by $(X + 0.5)^{0.5}$ to approximate homogeneity are presented untransformed. ANOVA, F = 31.23; df = 1, 22; $p < 0.0001$. Means followed by the same letter are not significantly different (Bonferroni's *t*-test, $p < 0.05$).

3.4. Stereochemistry of Weevil-Produced Pheromones.

3.4.1. *M. hemipterus.*

Analysis of male-produced **7** on a Cyclodex B fused silica column (Figure 3.13) revealed that only the (4*S*,5*S*)-isomer was present. Since no separation of the enantiomers of **41** was possible on this column, formation of diastereoisomeric derivatives was necessary. Thus, GC analysis of the acetyllactate derivative[51] of male-produced **41** on a DB-1 column revealed that both enantiomers of **41** were present in the weevil extract in a 4:6 (*R*:*S*) ratio. Confirmation of this finding was obtained by EI-SIM-MS analysis of the derivatized weevil extract and standard (*R*)- or (*S*)-**41** [*m/z* = 115 (M^+-C_2H_3-$C_3H_4O_3$)].

3.4.2. *P. distortus.*

No configurational assignment was possible in this case, since this compound is produced by the insect (under the experimental conditions carried out in this work) in minute amounts (<50 pg/μL) (weevil-produced 2-methyl-4-heptanol is a small shoulder emerging at ~7.55 min, see Figure 3.3).

3.5. Synthesis of Individual Enantiomers of 2-Methyl-4-heptanol.

Different routes toward (*R*)- and (*S*)-2-methyl-4-heptanol were considered.

Allylborations of aldehydes[81] using *B*-allyldiisopinocamphenylborane or *B*-allyl bis(4-isocaranyl)borane are well known to produce homoallylic alcohols in good chemical yields and high enantiomeric excess (94-99 % ee).

Enzymatic kinetic resolution using PPL or Baker's yeast reduction are appealing methods,[82] however poor results have been obtained for simple non-functionalized alcohols.

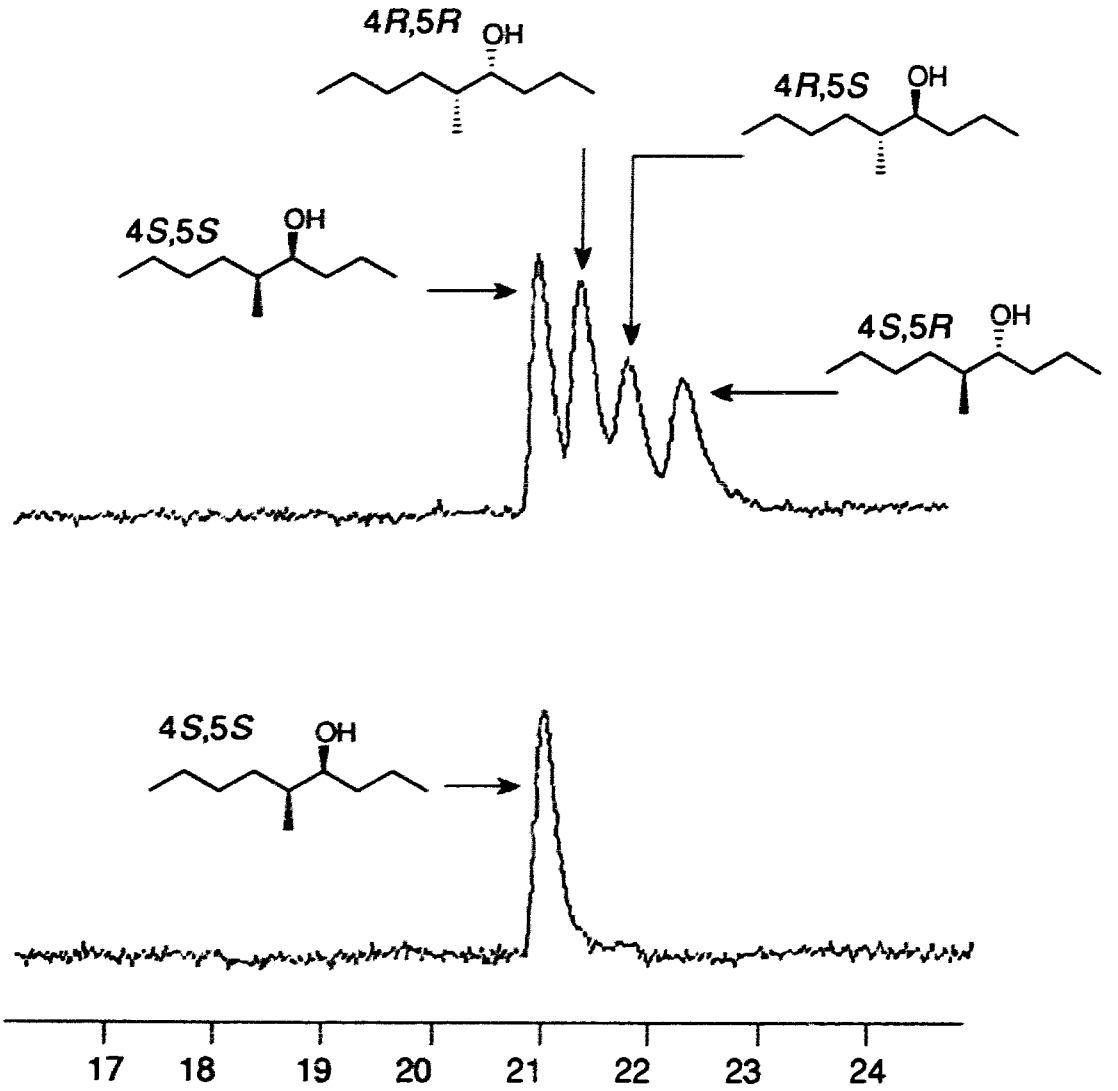
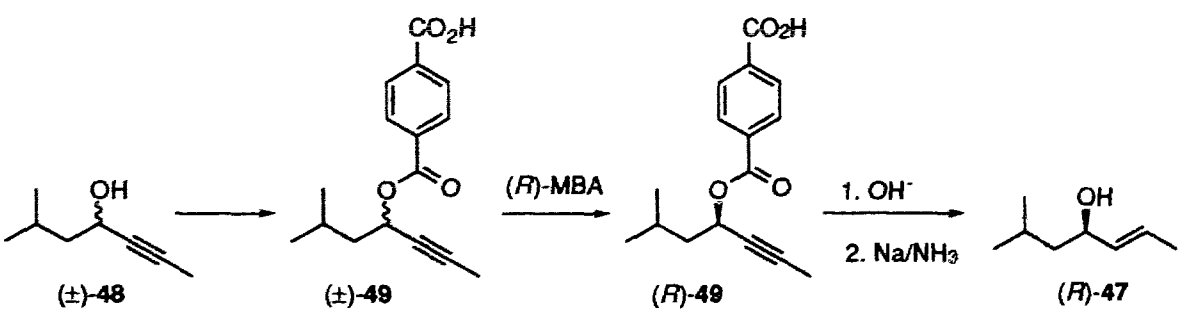


Figure 3.13. Selected ion chromatogram (*m/z* = 69, 87 and 101) of stereoisomeric and *M. hemipterus* produced **7**. Ion *m/z* 101 [(M^{+}-C_4H_9) was the base ion of the full scan mass spectrum in EI mode. Chromatography, Cyclodex-B fused silica column (30 m X 0.25 mm ID), isothermal 100°C; linear flow velocity of carrier gas 35 cm s^{-1}, split injection and injector temperature 220°C.

Sharpless kinetic resolution[44c] was used in the synthesis of the enantiomers of (*E*)-6-methyl-2-hepten-1-ol (**47**), the aggregation pheromone of the American palm weevil (90-92 % ee).[26a] Hydrogenation of either enantiomer can give access to the enantiomers of **41**.

(*R*,*E*)-6-Methyl-2-hepten-4-ol [(*R*)-**47**] and its antipode [(*R*)-**47**: 93 % ee, (*S*)-**47**: 96 % ee] have been prepared by Chan and coworkers[83] by resolution of the hemiphthalate (**49**) of 6-methyl-2-heptyn-4-ol [(±)-**48**] *via* (*R*)- or (*S*)-α-methylbenzylamines (MBA), alkaline hydrolysis and partial hydrogenation (Scheme 3.1).

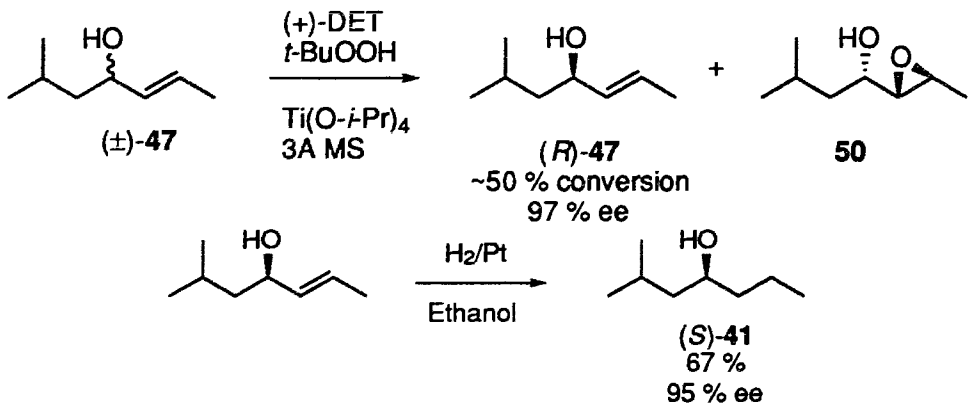


Scheme 3.1. Synthesis of enantiomers of **47** by Chan's procedure.

Mori and Ishigami,[84] synthesized (*R*)- and (*S*)-**47** in 98 % ee through a series of enzymatic kinetic resolutions (three cycles) of the corresponding acetates and propionates of **48**, combined with recrystallization of the alcohols (**48**) as 3,5-dinitrobenzoates (**49**). (*R*,*E*)-6-Methyl-2-hepten-4-ol was obtained in 5.4 % yield (9 steps, 98 % ee), while its antipode was produced in 7.1 % yield (6 steps) and 98 % ee.

Sharpless kinetic resolution[44c] was chosen as the synthetic method for synthesis of 2-methyl-4-heptanol enantiomers. Several reaction conditions were tested to optimize enantiomeric excess. Use of 50 mol % catalyst (as described in Chapter 2) in the presence of 3Å molecular sieves, gave (*R*,*E*)-**47** in 97 % ee

and (*S*,*E*)-**47** in 95 % ee. The reaction was monitored and stopped at 50 % conversion (~1.5-2 h at -20°C, E = 30-70). Optical purity was determined by gas chromatographic analyses of the corresponding acetyllactate derivatives (DB-1). Finally, hydrogenation of these alcohols gave (*R*)-**41** (32 % yield from (±)-**47**, 94 % ee) and (*S*)-**41** (27 % yield from (±)-**47**, 95 % ee) (Scheme 3.2). Enantiomeric excess was determined by gas chromatographic analysis of the acetyllactates on a DB-1 fused silica column. The corresponding acetates of (*R*)- and (*S*)-**41** separated on the Cyclodex B column, optical purity was verified using this column and revealed optical purities similar to those determined by the lactate analysis.



Scheme 3.2. Synthesis of **41** by Sharpless kinetic resolution of (±)-**47**.

3.6. Field Activity of Pheromone Stereoisomers

3.6.1. *M. hemipterus.*

Extensive field experiments[iv] in Costa Rica clearly demonstrated that (4*S*,5*S*)-4-methyl-5-nonanol, (4*S*,5*S*)-**7**, is the major aggregation pheromone of the West Indian Sugarcane Weevil (WISW), *Metamasius hemipterus sericeus*. After initial reports of this work,[65] Rochat *et al.*[29b] identified **7** as being a male specific compound in WISW and Mori *et al.*[66b] determined (4*S*,5*S*)-**7** was produced by WISW and was EAD active in this species. Equivalent attraction of male and female WISW to **7** establishes its function as an aggregation

pheromone rather than a sex pheromone. Individual enantiomers were released from glass capillaries (1 mm ID) cut 1 cm above the liquid meniscus, and placed in 300 µL capped plastic centrifuge tubes with two 4 mm diameter holes near the top. Each capillary tube released approximately 0.3 mg *per* day of **7** or **41** at 25°C. Field tests of candidate semiochemicals were conducted in commercial oil palm plantations near Coto, Costa Rica. Experimental design was the same as the one described in section 3.3.1 and employed pitfall traps. Stereoisomeric **7** and (4*S*,5*S*)-**7** were equally attractive (Figure 3.14) and attractiveness of the latter was enhanced by addition of (*R*)-, (*S*)- or (±)-**41** (Figure 3.14).

The (4*S*,5*S*)-stereoisomer of **7** present in WISW also serves as an aggregation pheromone in *Rhynchophorus* palm weevils (see Chapter 2). Presence and EAD-activity of **7** also in the American palm weevil, *R. palmarum* and in *Dynamis borassi* (Fabr.)[85] indicate that this compound is widespread and is present in at least three genera of tropical curculionids.

3.6.2. *P. distortus*

Field tests[iv] of candidate semiochemicals were conducted in commercial oil palm plantations near Coto, Costa Rica. The experimental design used was that described in 3.3.2. Individual enantiomers were released from glass capillaries (1 mm ID) cut 1 cm above the liquid meniscus, and placed in 300 µL capped plastic centrifuge tubes with two 4 mm diameter holes near the top. Each capillary tube released approximately 0.1 mg per day of (*R*)-, (*S*)- or (±)-**41** at 25°C. Due to variable results (Figures 3.15-3.18), it was not possible to demonstrate a conclusive biological response to either chiral isomer of **41** by *P. distortus*.

Contradictory results were obtained in several experiments. Figures 3.15 and 3.16 indicated synergism between (*R*)- and (*S*)-**41**. The occurrence of this

relationship is rare, being described only in the ambrosia beetle *Gnathotrichus sulcatus* Le Conte, which responds maximally to a 65:35 mixture of (*S*)- and (*R*)-6-methyl-5-hepten-2-ol, (sulcatol), its pheromone,[31a] and in the grain beetle *Cryptolestes turcicus* Grouvelle, which responds maximally to an 85:15 mixture of (*R*)- and (*S*)-(*Z,Z*)-5,8-tetradecadien-13-olide, its pheromone and to a 33:67 mixture of (*R*)- and (*S*)-(*Z*)-5-tetradecen-13-olide a synergist.[86] To verify this behavior, this experiment was repeated twice, (Figures 3.17 and 3.18). The latter experiments suggest racemic **41** and (*S*)-**41** are equally attractive to *P. distortus*. Thus, response of *P. distortus* to enantiomers of **41** could not be determined. Close observation of these four experiments hinted that response to enantiomer mixtures (dose response experiment) may give more information about *P. distortus* response to (*R*)- and (*S*)-**41**. A last experiment (Figure 3.19) was designed to address this point. The field test was conducted in commercial oil palm plantations near Coto, Costa Rica. Pitfall traps were buried in the ground and were approximately 20 m apart between treatments and 20 m apart between replicates. Individual isomers were released from glass capillaries using the same device described before. Each capillary tube released approximately 0.1 mg *per* day of 97.0 %, 89.0 % and 76.0 % (*R*)-**41**, racemic-**41**, 97.5 %, 89.0 % and 78.0 % (*S*)-**41** at 25°C. Results from this experiment explain why racemic- and (*S*)-**41** were equally attractive to *P. distortus* and the synergistic effect of (*R*)- and (*S*)-**41**, being optimal response at 1-2: 9-8 *R/S* ratio. Response by *P. distortus* is unusual among other weevils studied in this work, which field response is to only one enantiomer of their pheromones. Response of *P. distortus* to both enantiomers of its pheromone may signify some resource partition mechanism with competing insects.

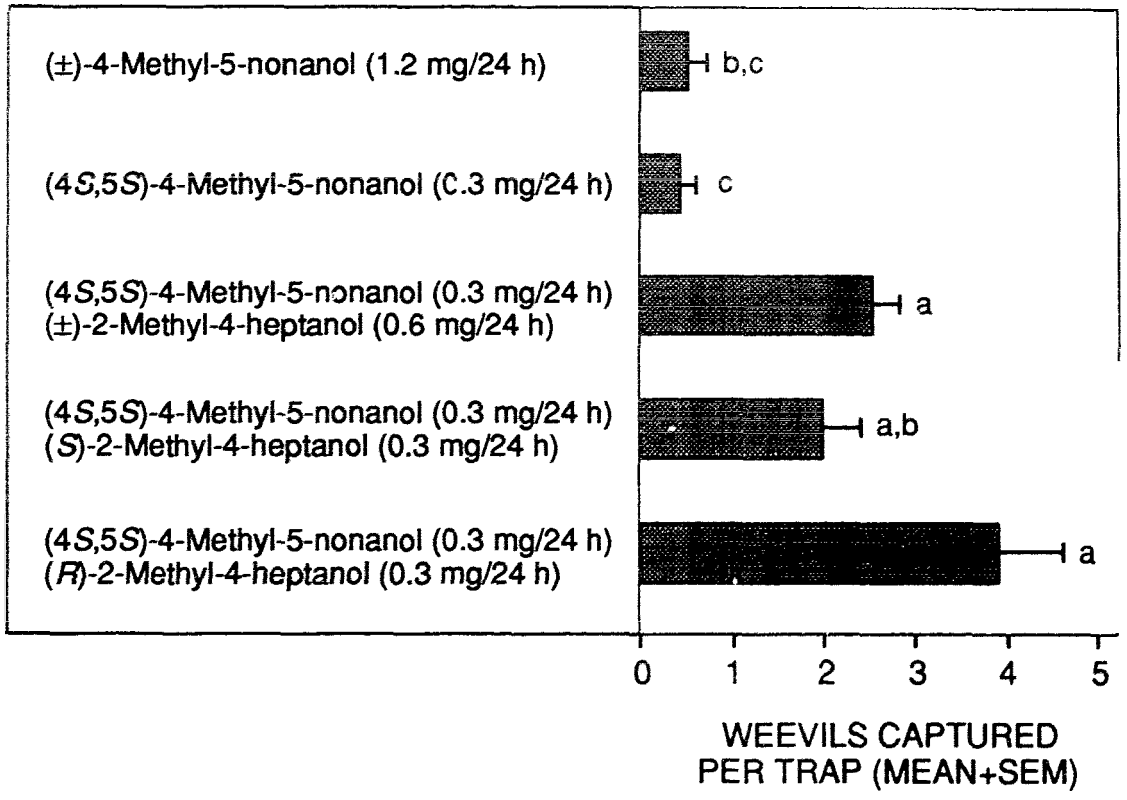


Figure 3.14. Mean (+SEM) captures of *WISW* in pitfall traps baited with (±)-**7** and (4*S*,5*S*)-**7** alone and combined with (±)-**41** , (*S*)-**41** or (*R*)-**41**. The experiment (N = 10) was conducted in an oil palm plantation surrounding Coto, Costa Rica, 11-24 August 1994. Data transformed by log(X + 0.5) to approximate homogeneity are presented untransformed. ANOVA, $F = 7.67$; $df = 4, 45$; $p < 0.001$. Means followed by the same letter are not significantly different (Bonferroni's *t*-test, $p < 0.05$).

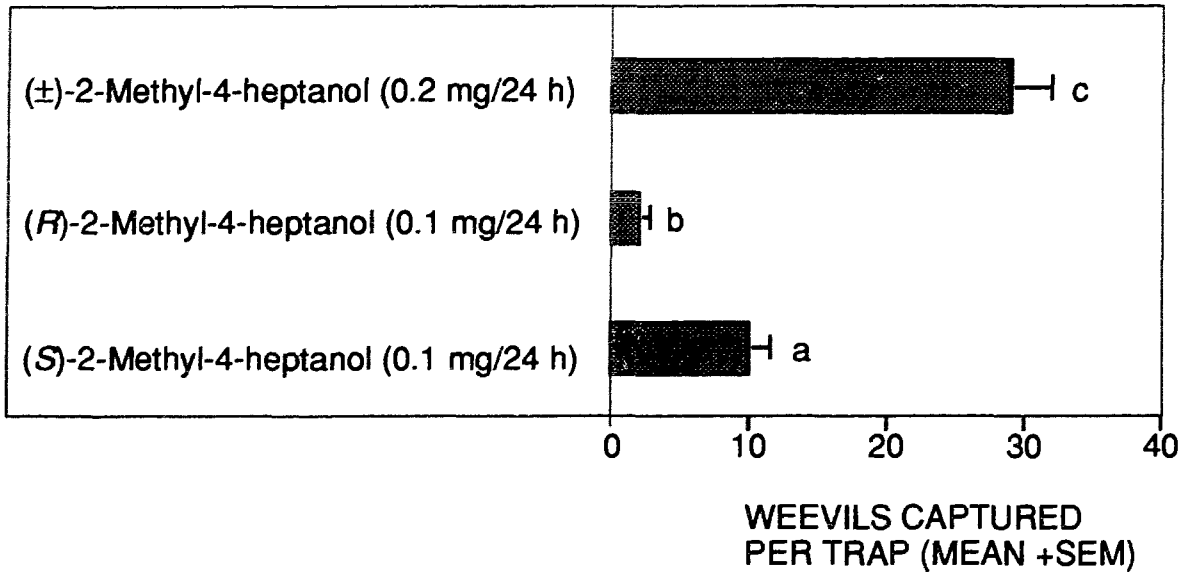


Figure 3.15. Mean (+SEM) captures of *P. distortus* in pitfall traps baited with (±)-**41** , (*S*)-**41** or (*R*)-**41**. The experiment (N = 10) was conducted in an oil palm plantation surrounding Coto, Costa Rica, 19 May to 3 June, 1994. Data transformed by log(X + 0.5) to approximate homogeneity are presented untransformed. ANOVA, F = 47.74; df = 2,27; p < 0.0005. Means followed by the same letter are not significantly different (Bonferroni's *t*-test, $p < 0.05$).

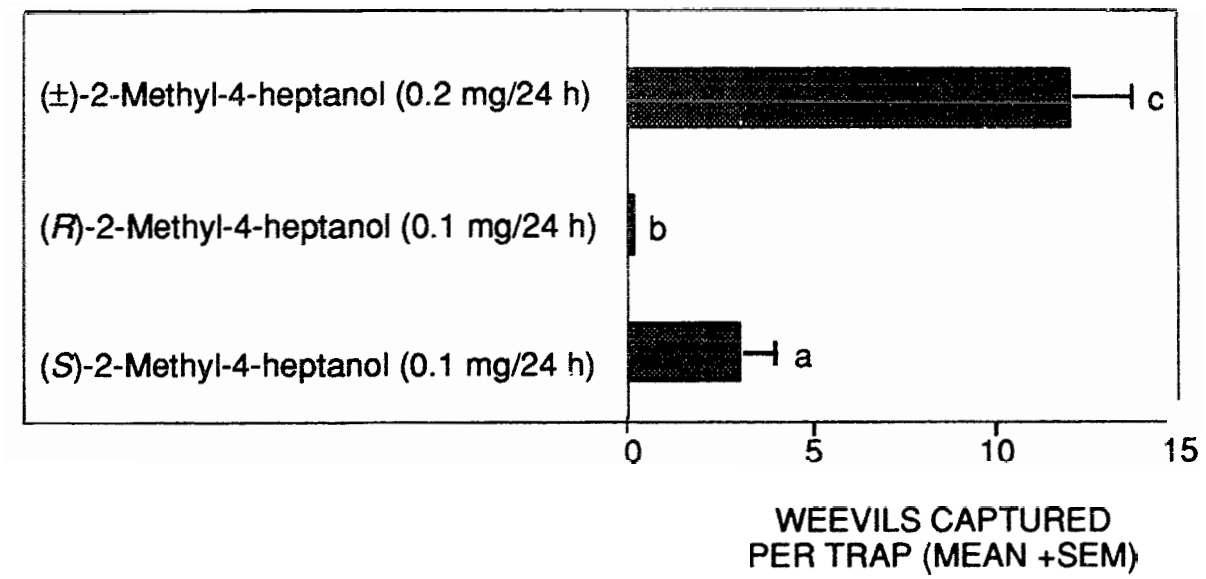


Figure 3.16. Mean (+SEM) captures of *P. distortus* in pitfall traps baited with (±)-**41** , (*S*)-**41** or (*R*)-**41**. The experiment (N = 10) was conducted in an oil palm plantation surrounding Coto, Costa Rica, May, 1994. Data transformed by log(X + 0.5) to approximate homogeneity are presented untransformed. ANOVA, followed by Bonferroni's *t*-test. Means followed by the same letter are not significantly different ($p < 0.05$).

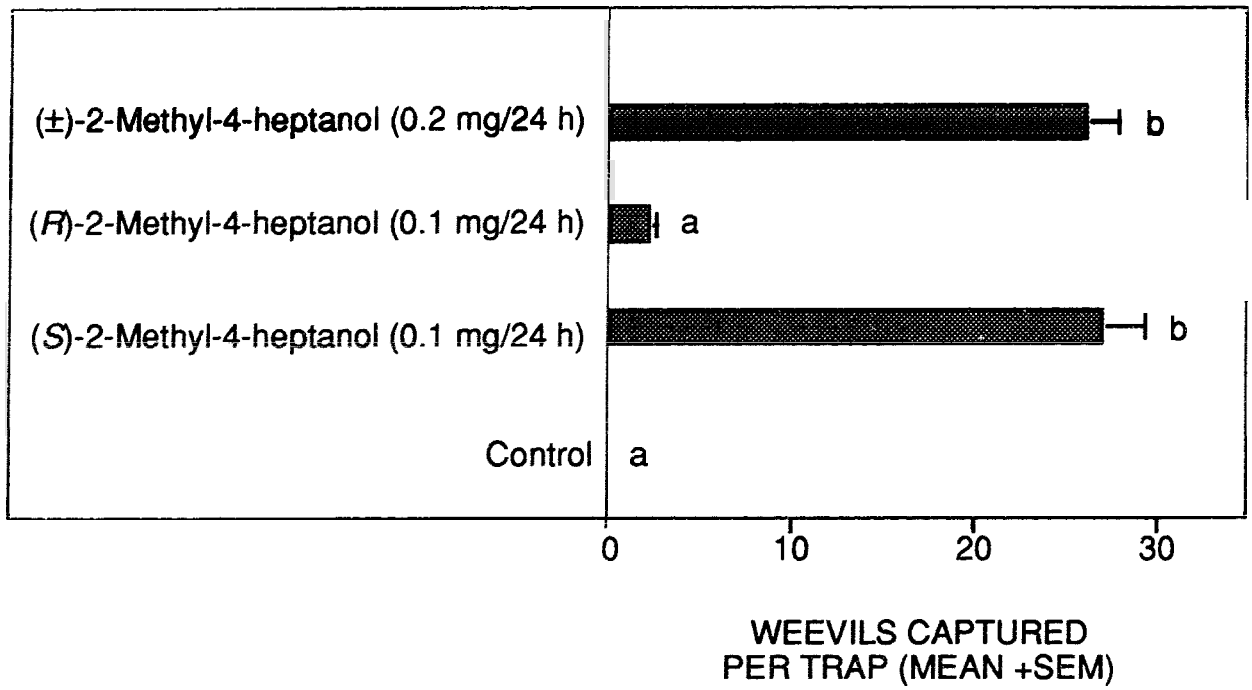


Figure 3.17. Mean (+SEM) captures of *P. distortus* in pitfall traps baited with (±)-**41**, (*S*)-**41** or (*R*)-**41**. The experiment (N = 10) was conducted in an oil palm plantation surrounding Coto, Costa Rica, 3-13 October, 1994. Data transformed by log(X + 0.5) to approximate homogeneity are presented untransformed. ANOVA, F = 49.58; df = 3,36; p < 0.0001. Means followed by the same letter are not significantly different (Bonferroni's *t*-test, $p < 0.05$).

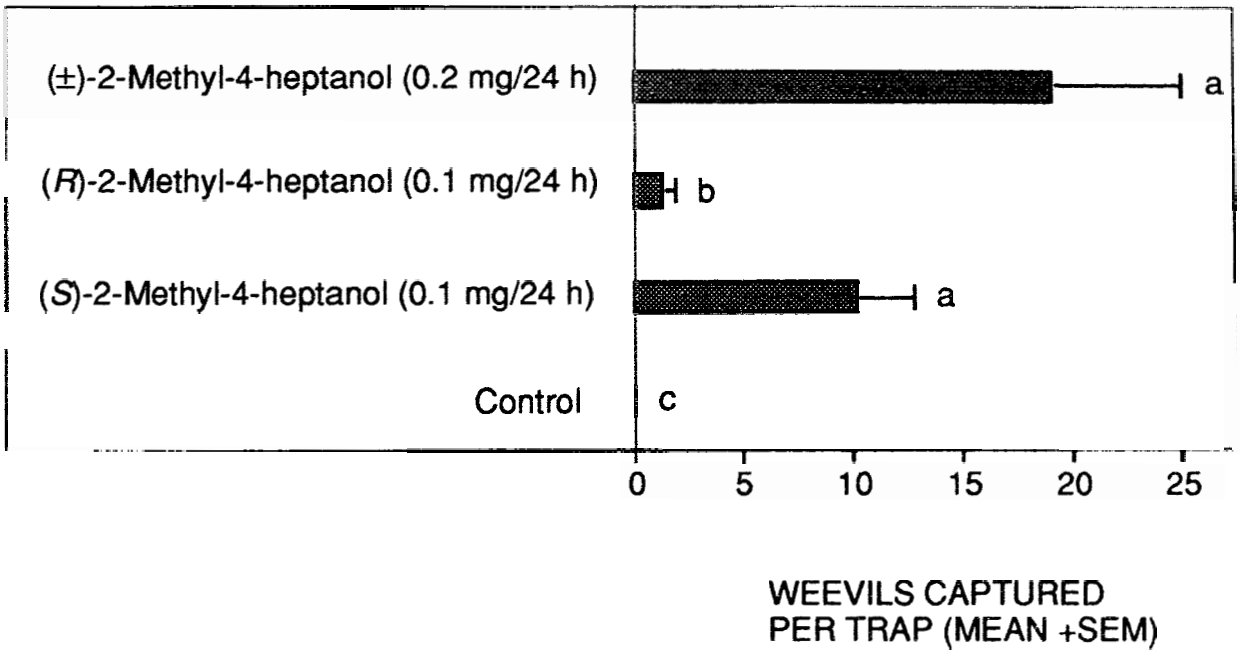


Figure 3.18. Mean (+SEM) captures of *P. distortus* in pitfall traps baited with (±)-**41**, (*S*)-**41** or (*R*)-**41**. The experiment (N = 10) was conducted in an oil palm plantation surrounding Coto, Costa Rica, 19 May to 3 June, 1994. Data transformed by log(X + 0.5) to approximate homogeneity are presented untransformed. ANOVA, $F = 29.44$; df = 3,36; $p < 0.0001$. Means followed by the same letter are not significantly different (Bonferroni's *t*-test, $p < 0.05$).

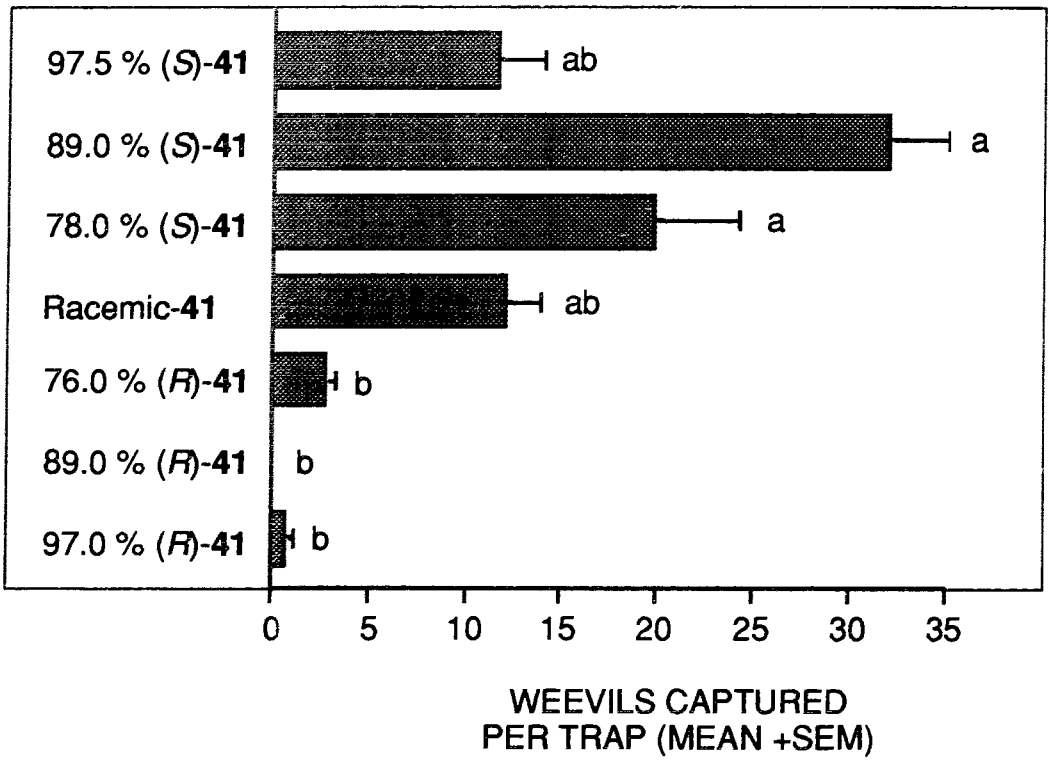
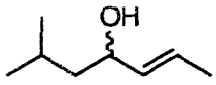


Figure 3.19. Mean (+SEM) captures of *P. distortus* in pitfall traps responding to enantiomer mixtures of (*S*)-**41** and (*R*)-**41**. The experiment (N = 8) was conducted in an oil palm plantation surrounding Coto, Costa Rica, 7-16 October 1995. ANOVA on ranked data with Tukey-Kramer means separation of all pairs. $F = 38.51$; $df = 6, 49$; $p < 0.0001$. Means followed by the same letter are not significantly different ($p < 0.05$).

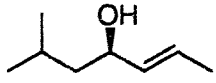
3.7. Experimental Section.

For general methods see Experimental Section Chapter 2.

For the synthesis of chiral isomers of 4-methyl-5-nonanol, see Chapter 2. 2-Methyl-4-heptanol (**41**), 2-methyl-4-octanol (**42**) were prepared from the corresponding Grignard reactions of suitable organomagnesium reagents and aldehydes and purified by vacuum distillation. Further oxidation of **41** and **42** with Jones' reagent yielded 2-methyl-4-heptanone (**44**) and 2-methyl-4-octanone (**45**). 2-Pentanol (**40**) was prepared by $NaBH_4$ reduction of commercially available 3-pentanone (**43**).

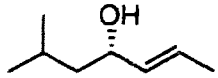


(*E*)-6-methyl-2-hepten-4-ol (±47). (*E*)-6-methyl-2-hepten-4-ol was prepared by reaction of isobutyl magnesium bromide and crotonaldehyde in diethyl ether. The compound purified by fractional distillation at reduced pressure (61°C @ 12 mm Hg) to give 80 % yield of ±**47**. ^1H NMR is in accordance with that reported by Mori and Ishigami.[84]

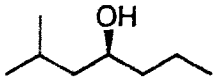


(*R,E*)-6-methyl-2-hepten-4-ol [(*R*)-47]. Titanium (IV) isopropoxide (2.28 mL, 7.4 mmol) in dry CH_2Cl_2 (80 mL) was mixed under argon with 0.5 g of 3A powdered, activated molecular sieves. After cooling to -78°C, diethyl (*2R,3R*)-tartrate (L-(+)-DET, 1.56 mL, 9.12 mmol) was added *via* syringe followed by addition of (*E*)-6-methyl-2-hepten-4-ol (1.84 g, 14.4 mmol) and 15 mmol of decane as internal standard. The mixture was stirred 15 min. prior to dropwise addition of precooled 6.6 M anhyd. *tert*-butyl hydroperoxide in CH_2Cl_2 (4.25 mL, 28 mmol). After the reaction warmed to -20°C it was stirred at this temperature for 0.5-1 h. The reaction was monitored by GC and was stopped at ~50 %

conversion. Aqueous work-up followed by column chromatography (2:8, Et_2O:pentane) gave (*R*)-**47** (0.75 g, 97 % ee) as a colourless liquid. ^1H NMR ($CDCl_3$, ppm): 0.89 (3H, d, J = 8.1 Hz), 0.91 (3H, d, J = 8.1 Hz), 1.36 (1H, m), 1.44 (2H, m), 1.70 (3H, d, J = 8.1 Hz), 1.90 (1H, brs), 4.08 (1H, q), 5.44 (1H, dd, J = 8.1, 16.2 Hz), 5.65 (1H, dq, J = 8.1, 16.2 Hz); ^{13}C NMR ($CDCl_3$, ppm): 137.76, 126.44, 71.33, 46.94, 28.23, 24.57, 22.92, 22.50, 22.25, 17.60. ^1H and ^{13}C NMR spectra were identical to those reported by Mori and Ishigami.[84]

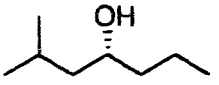


(*S,E*)-6-methyl-2-hepten-4-ol [(*S*)-47]. 0.86 g, 95 % ee. It was synthesized following the same procedure using diethyl (*2S,3S*)-tartrate (D-(-)-DET) as the epoxidation catalyst. ^1H and ^{13}C NMR spectra were identical to those reported by Mori and Ishigami.[84]



(*S*)-2-methyl-4-heptanol [(*S*)-41]. In an adaptation of the method of Brown,[87] a 50 mL-filtering flask was charged with a solution of (*R*)-**47** (0.73 g, 5.7 mmol) in dry methanol (20 mL) and 0.05 equiv.. of 5 % Pt/C. To the side arm of the flask, a rubber bulb was attached and secured with copper wire. The flask was capped with a large septum secured by wire. H_2 (5 psi) was injected until the rubber bulb inflated. The flask was stirred at room temperature until deflation of the balloon stopped indicating further H_2 was not required. GC monitoring of aliquots withdrawn from the reaction indicated completion after 3 h. The system was purged, then the mixture was filtered, diluted with water and extracted (3 X 10 mL) with Et_2O. Drying over $MgSO_4$ and solvent removal *in vacuo* afforded a light yellow liquid. The compound was purified by distillation at reduced pressure (70°C @ 15 mm Hg) to give (*S*)-**41** as a colourless liquid (0.51 g, 67 % yield, 95

% ee). $[\alpha]_D^{20}$ = +14.3° (c = 2.230, Et_2O); ^1H NMR ($CDCl_3$, ppm): 0.89 (3H, d, *J* = 7.5 Hz), 0.92 (3H, d, *J* = 7.5 Hz), 0.94 (3H, t, *J* = 7.5 Hz), 1.24 (1H, m), 1.38 (6H, m), 1.76 (1H, m), 3.77 (1H, m); ^{13}C NMR ($CDCl_3$, ppm): 69.69, 46.86, 40.26, 24.62, 23.28, 22.03, 18.68, 13.97; EI-MS *m/z* (relative intensity): 112 (M^+-18, 17), 87 (M^+-C_3H_7, 42). Anal. Calcd. for $C_8H_{18}O$: C, 73.78; H, 13.93. Found: C, 73.68; H, 13.85.



(*R*)-2-methyl-4-heptanol [(*R*)-41]. $[\alpha]_D^{20}$ = -10.20° (c = 2.280, Et_2O); 0.60 g, 69 % yield, 94 % ee. Anal. Calcd. for $C_8H_{18}O$: C, 73.78; H, 13.93. Found: C, 73.63; H, 13.81.

Chapter 4

Aggregation Pheromones of the African Rhinoceros Beetle, *Oryctes monoceros* (Olivier) and the Asian Rhinoceros Beetle, *Oryctes rhinoceros* (Linnaeus) (Coleoptera: Scarabacidae). The Coconut Rhinoceros Beetle.

4.1. Description of the Coconut Palm.

The coconut palm, *Cocos nucifera* Linnaeus, is one of the most important crops of the tropics. It occurs in all tropical and most subtropical regions, most abundantly in Asia and the Pacific. Both tropical South America and Malaysia have been suggested as the possible origin of the coconut. It was known in Portuguese East Africa in the 15th century. Ninety percent of the world's export crop is produced in Indonesia, the Philippines, Thailand, Ceylon, Malaysia and Oceania. Other exporting regions are East and West Africa, the West Indies, and Central and South America.[88a,b]

There is considerable variation in both the size and the period of development of the palm in its growing range. The fronds reach a length of 4-6.5 m each with 200-250 leaflets, which can approach 1 m in length. On average, the tree produces 12-16 new fronds per year. The upper surface of the leaflets is smooth and covered with a waxy layer; the lower surface also is smooth but is without wax, and it is on this surface that most insect pests (biting or sucking) live. At the centre of the crown of the palm, the young developing fronds are tightly compacted into an elongate terminal shoot called the spear or cabbage; severe injury to this growing point usually results in the death of the palm. The trunk of the palm attains a height of 18-21 m. Nuts are produced when trees are five years old, with highest production achieved between 15 and 50 years.

Productivity declines after 60 to 70 years when the tree is considered senile. The yield of nuts varies from 40 to 140 or more per tree per year.[88]

4.2. The African Rhinoceros Beetle. General Characteristics.

The African rhinoceros beetle, *Oryctes monoceros* (Olivier), is one of the most destructive pests of commercial coconut, oil and date palm in eastern Africa, the Seychelles and Madagascar.[8b] Eggs hatch in 7-9 days, the larval stage lasts 100-200 days and the pupal stage 14-21 days. The complete cycle from egg to adult occupies about six months.[88b] The eggs are laid in moist, decomposing vegetable matter. The adult is a large, black shiny beetle, about 4 cm long. It has a rhinoceros-type frontal horn which is well developed in the male, but short in the female. Adults rest during the day but fly strongly at night. Adults live for three to four months during which time they feed on unopened fronds and meristems of palms. With slight damage the leaves later unfold to show characteristic V-shaped cuts.[8b] Beetle attacks can kill young palms, provide entry points for diseases and other destructive insects (e.g., *Rhynchophorus phoenicis*), damage inflorescences and reduce photosynthetically active foliage, thereby diminishing oil and coconut production.[89] Introduction of pathogenic baculovirus, *Rhabdionvirus oryctes* Huger, suppressed populations of the rhinoceros beetle, *O. rhinoceros*, in parts of Asia,[89] but did not affect *O. monoceros* in Africa.[90] *O. monoceros* populations are currently managed by silvicultural methods,[91] removal of adults from young palms and removal of larvae from decomposing logs.

3.3. The Asian Rhinoceros Beetle. General characteristics.

The Asian rhinoceros beetle, *Oryctes rhinoceros* (Linnaeus), is one of the most important pests of coconut and oil palms in South East Asia.[92,93] It shares

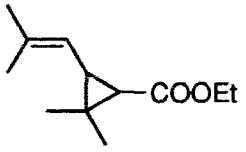
most of the same characteristics as *O. monoceros* in its attack of coconut and oil palm. Adult rhinoceros beetles burrow into the growing point of palms and feed on unopened fronds, causing damage to inflorescences and reduction in photosynthetic area, which decreases or delays fruit production.[94,95] Prolonged attacks can kill mature palms by defoliation, and young palms if the growing point is destroyed. The wounds produced by the beetle provide entry points for diseases and the palm weevils, *Rhynchophorus ferrugineus* (Olivier) and *R. vulneratus* (Panzer).[96,97]

O. rhinoceros also breed in decaying organic matter, such as felled rotting palms, and usually become a major problem in newly planted or replanted oil palm plantations. Covering fallen trunks with a rapidly growing ground cover[98] or shredding and burning of trunks are common practices to minimize *O. rhinoceros* populations.[95a] Although effective, shredding and burning is very expensive and has been banned in some parts of Southeast Asia to lower air pollution from the 4.5 million hectares of oil palm in the region.[99]

Treatment of breeding sites, such as stumps, with insecticidal drenches and routine application of granular insecticides (e.g., carbofuran) to the leaf axils of young oil palms, are recommended.[93] These techniques are currently considered economic,[95a] and are effective but present environmental and health risks and are labour intensive. Manual removal of beetles from palms and larvae from decomposing trunks is costly and very labour-intensive.[95a]

Limited success in managing *O. rhinoceros* populations has been achieved through introduction of the baculovirus, *R. oryctes*.[96,100] Introduction of the baculovirus to the Philippines reduced *O. rhinoceros* populations to 10-20% of prerelease levels but even low level populations of *O. rhinoceros* can cause significant damage.[89b,c] The baculovirus remains effective only if it infects new larval hosts or is repeatedly introduced, and the potential exists for *O. rhinoceros*

to develop resistance to the baculovirus after prolonged exposure.[89c] To be spread among a population the virus must be ingested by the carrier. Several compounds (e.g., geraniol, phenethyl butyrate, methyl eugenol, *trans*-2-hexenal and several chrysanthemumates), including ethyl chrysanthemumate (EC, rhinolure, **51**) have been recommended as lures for trapping *O. rhinoceros*,[98] but they are only moderately attractive.[89c,101]



51

O. rhinoceros adults are gregarious. More than one beetle can attack a given palm at the same time while a neighboring tree is unattacked.[102] Aggregation of adults in decaying palm trunks occurs during mating. Single and multiple pairs of adults occur in the same breeding site[89b] suggesting that *O. rhinoceros* is attracted to host kairomones and employs either an aggregation or sex pheromone or both.

4.4. Scarabaeid Pheromones.

Sex pheromones of diverse structure have been identified in several scarabaeids. For example, phenol (**52**) was found in *Costelytra zealandica* White,[103] (*R,Z*)-5-(1-decenyl)oxacyclopentan-2-one (**53**) in *Popillia japonica* Newman,[33] 2,6-dimethyl-5-heptenoic acid (**54**), hexadecanoic acid (**55**) and (*E*)-nerolidol (**56**) in *Kheper lamarcki* MacLeay,[104] methyl (5*Z*)-tetradec-5-enoate (**57**) in *Anomala rufocuprea* Motschulsky,[105] (*R,Z*)-5-(1-octenyl)oxacyclopentan-2-one (**58**) in *A. cuprea* Hope,[106] a mixture of **58** and (*Z*)-2-nonen-1-ol (**59**) in *A. daimiana* Harold,[107] **59** in *A. schonfeldti* Ohaus,[108] (*Z*)-(**60**) and (*E*)-7-tetradecen-2-one (**61**) in *Blitopertha orientalis*,[109] a 8:1 mixture of **58** and **53** in

A. octiescostata Burmeister,[110] a mixture of **58** and **53** with a minor presence of (*R,E*)-**58** in *A. albopilosa sakishimana* Nomura,[111] *L*-leucine (**62**) in *Holotrichia parallela* Motschulsky,[112] a 7:1 mixture of **60** and **61** in *Exomala orientalis* Waterhouse[113] and a 9:1 mixture of **60** and **61** in *A. orientalis* Waterhouse (Figure 4.1).[114]

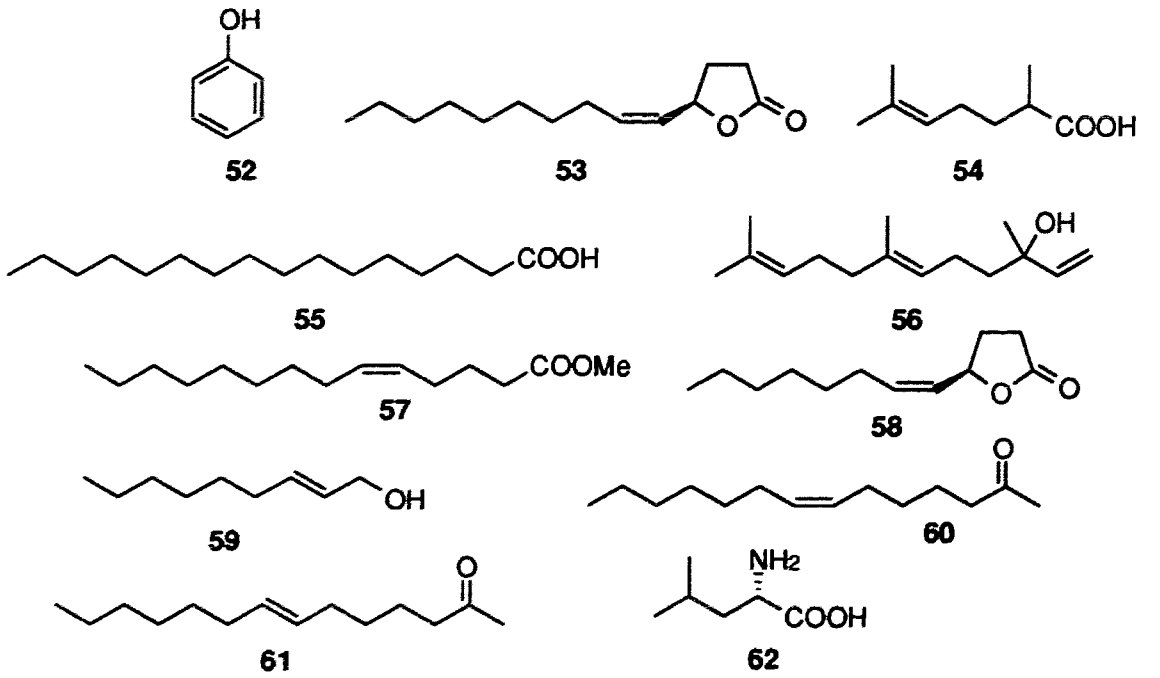


Figure 4.1. Known scarabaeid pheromones.

Due to the important pest status of *O. monoceros* and *O. rhinoceros*, identification, synthesis and field testing of candidate aggregation pheromones for these species was pursued.

4.5. Analysis and Identification of Male-Produced Volatiles.

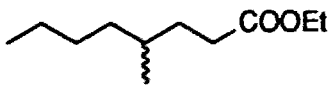
4.5.1. *O. monoceros*.

Fifteen males and eighteen females of *O. monoceros* were collected[i] in oil palm plantations 40-50 km northeast of Abidjan, Côte d'Ivoire and placed

[i] Collected by Dr. Allan C. Oehlschlager and Ms. Lilliana Gonzalez, and by Dr. Gerhard Gries and Ms. Regine Gries, Simon Fraser University.

together in a modified Nalgene desiccator and aerated for five days (for details, see experimental section Chapter 2). In a second experiment, eleven females and thirteen males were aerated separately for seven days. Porapak Q trapped volatiles were eluted with pentane and concentrated.

GC and GC-EAD analyses of Porapak Q trapped volatiles obtained from aerations of males, females or both sexes combined revealed two male-specific compounds (Figure 4.2), and several female specific compounds. Because aggregation pheromones have greater potential than sex pheromones (common characteristic in the scarabidae) for controlling *Oryctes* populations through mass trapping, research was focused on the identification of aggregation pheromones. The early eluting male-specific volatile elicited responses from male and female antennae (Figure 4.3). This male-specific compound was not detected by FID, GC-MS or EAD in female-produced volatiles (Figure 4.2). Analysis by GC-MS of the antennally active compound (Figure 4.4) indicated an ethyl ester (*m/z* = 141 indicated loss of an -OEt group) with a molecular weight of 186 and with a retention index (RI) of 1484 (SP-1000 fused silica column) which is lower than that of isomeric ethyl nonanoate (RI = 1539). Based on the increased intensity of the *m/z* 101 (M^+-C_6H_{13}) and *m/z* 129 (M^+-C_4H_9) fragmentation (Figure 4.4), it was hypothesized that the compound was ethyl 4-methyloctanoate (**63**).



63

Identical retention and mass spectrometric characteristics as well as comparable antennal activity of synthetic and male produced **63** confirmed this structural assignment.

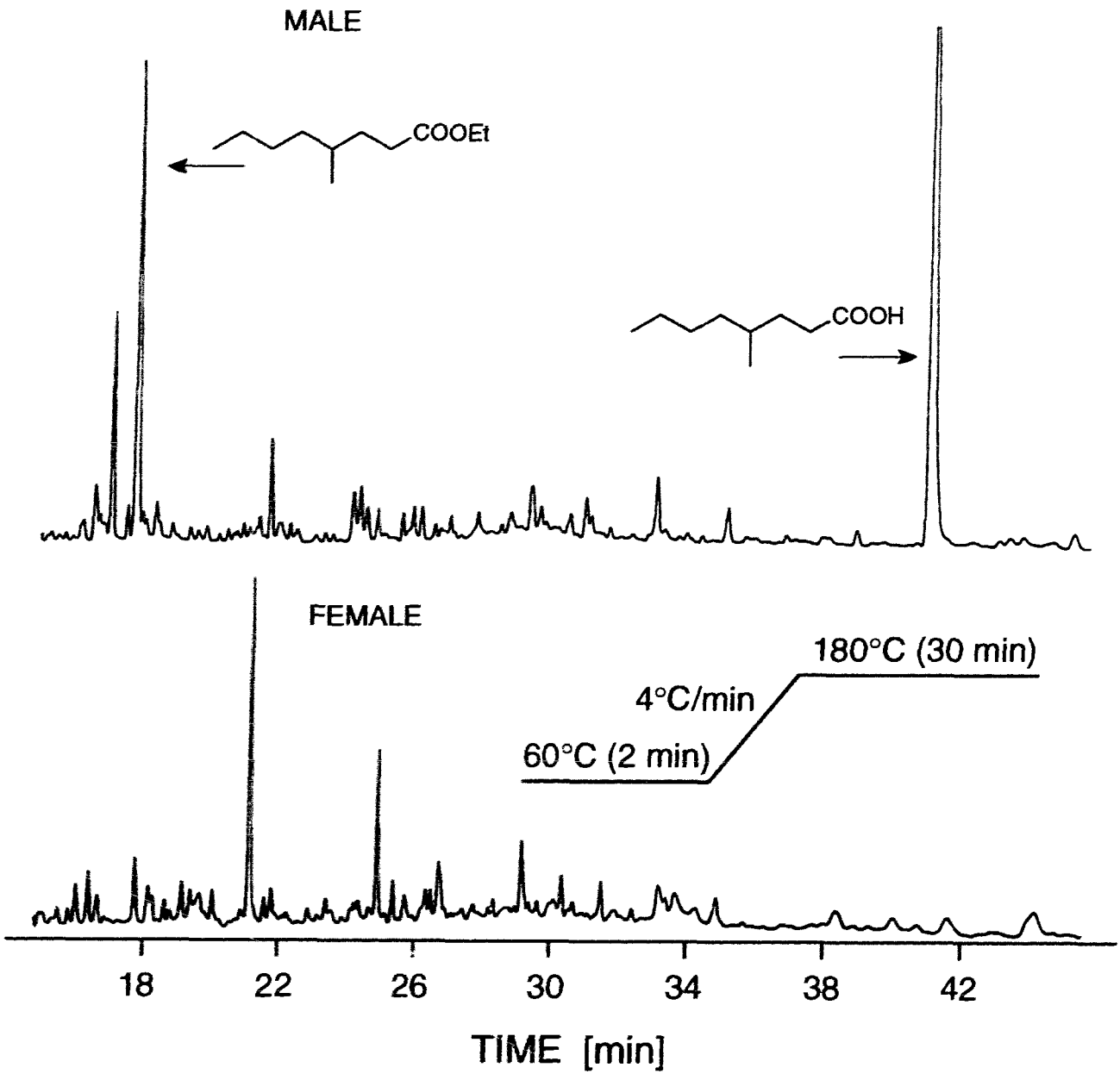


Figure 4.2. Gas chromatograms of volatiles from male (N = 13) and female (N = 11) *Oryctes monoceros* maintained in aeration chambers for 168 h without food. SP-1000 fused silica column (30 m X 0.5 mm ID).

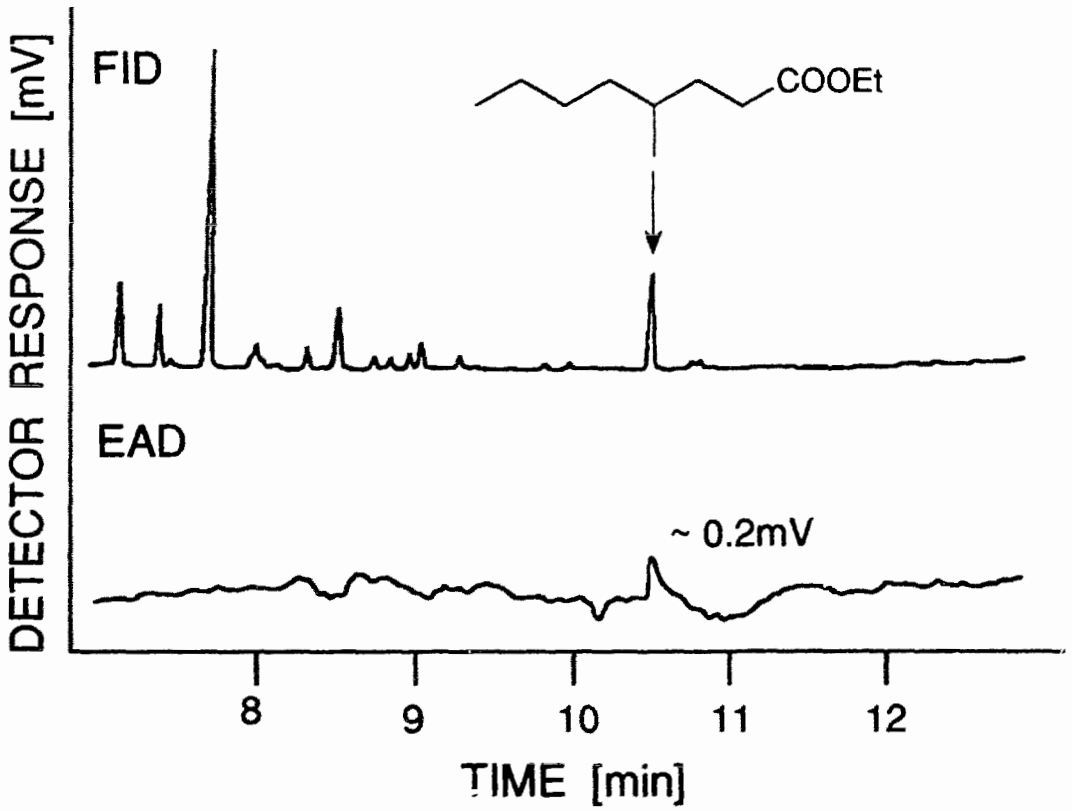


Figure 4.3. Representative recording (N = 9) of FID and EAD responses to volatiles obtained from aeration of male and female *Oryctes monoceros* combined. The antennal recording was carried out with an antenna of a female beetle. Chromatography: 1 min at 70°C, 10°C per min to 180°C; SP-1000 fused silica column (30 m X 0.25 mm ID).

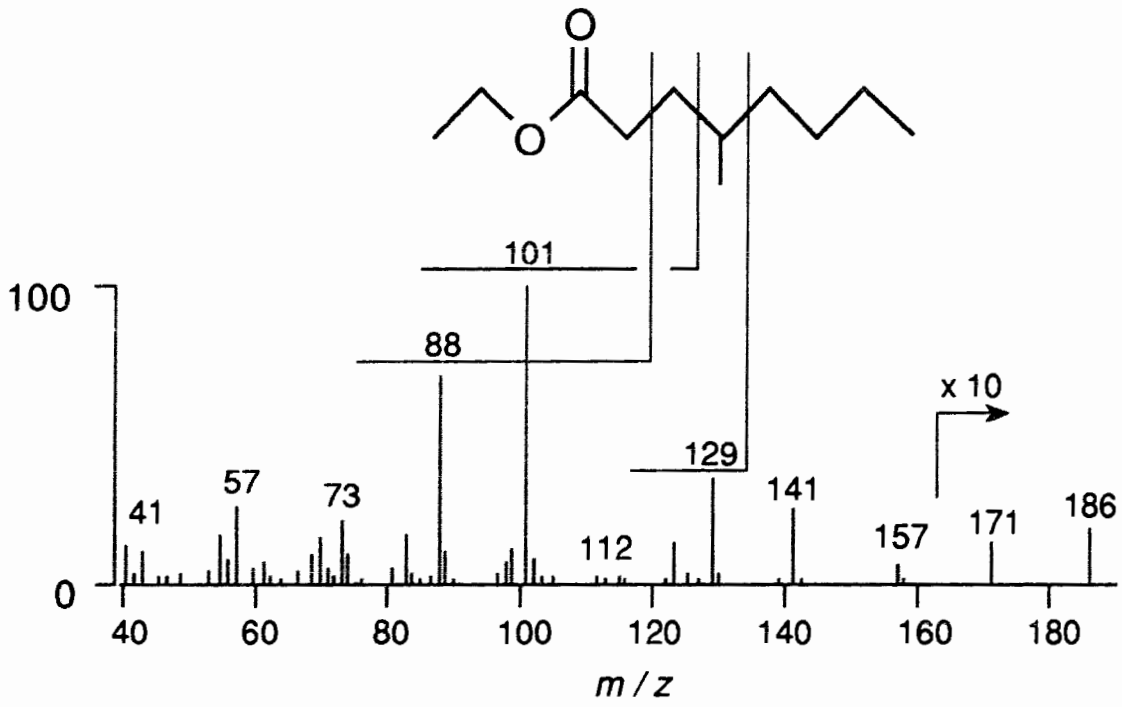


Figure 4.4. Electron impact (70 eV) mass spectrum of ethyl 4-methyloctanoate (**63**).

The second male-specific compound was found to be 4-methyloctanoic acid (**64**) by comparison of its retention time and mass spectrum to that of synthetic sample (see below).

4.5.2. *O. rhinoceros.*

Adults of *O. rhinoceros* were collected[ii] at Parungkuda, West Java, Indonesia. Fourteen females and sixteen males were separately aerated for one week in modified Nalgene desiccators containing sugarcane (for details, see experimental section Chapter 2). In a second series of aerations, ten females and ten males were aerated separately. Volatiles were eluted from the Porapak Q with pentane and concentrated.[10]

GC and GC-EAD analyses of Porapak Q-trapped volatiles obtained from aerations of either *O. rhinoceros* males or females revealed two abundant male-specific components (Figure 4.5), of which the early eluting volatile elicited antennal responses by male and female antennae (Figure 4.6). Retention and mass spectrometric characteristics of these two compounds were identical to ethyl 4-methyloctanoate, **63**, and 4-methyloctanoic acid, **64**. A second EAD-active compound (not visible in Figure 4.6) had a retention index (RI = 1392, SP-1000 fused silica column) indicative of ethyl 4-methylheptanoate, **65**. GC-MS in both electron impact and chemical ionization modes confirmed this structural assignment.

In laboratory bioassays (Y-tube olfactometer),[115] male-produced volatiles were equally attractive to walking male and female *O. rhinoceros*; female-produced volatiles were attractive only to males. Behavioral activity of synthetic **63** and **65** or both was verified and justified field tests of synthetic candidate pheromones. In the Japanese beetle, *Popillia japonica,* pheromonal attraction is

[ii] Collected by Ms. Rebecca Hallett, Department of Biological Sciences, Simon Fraser University.

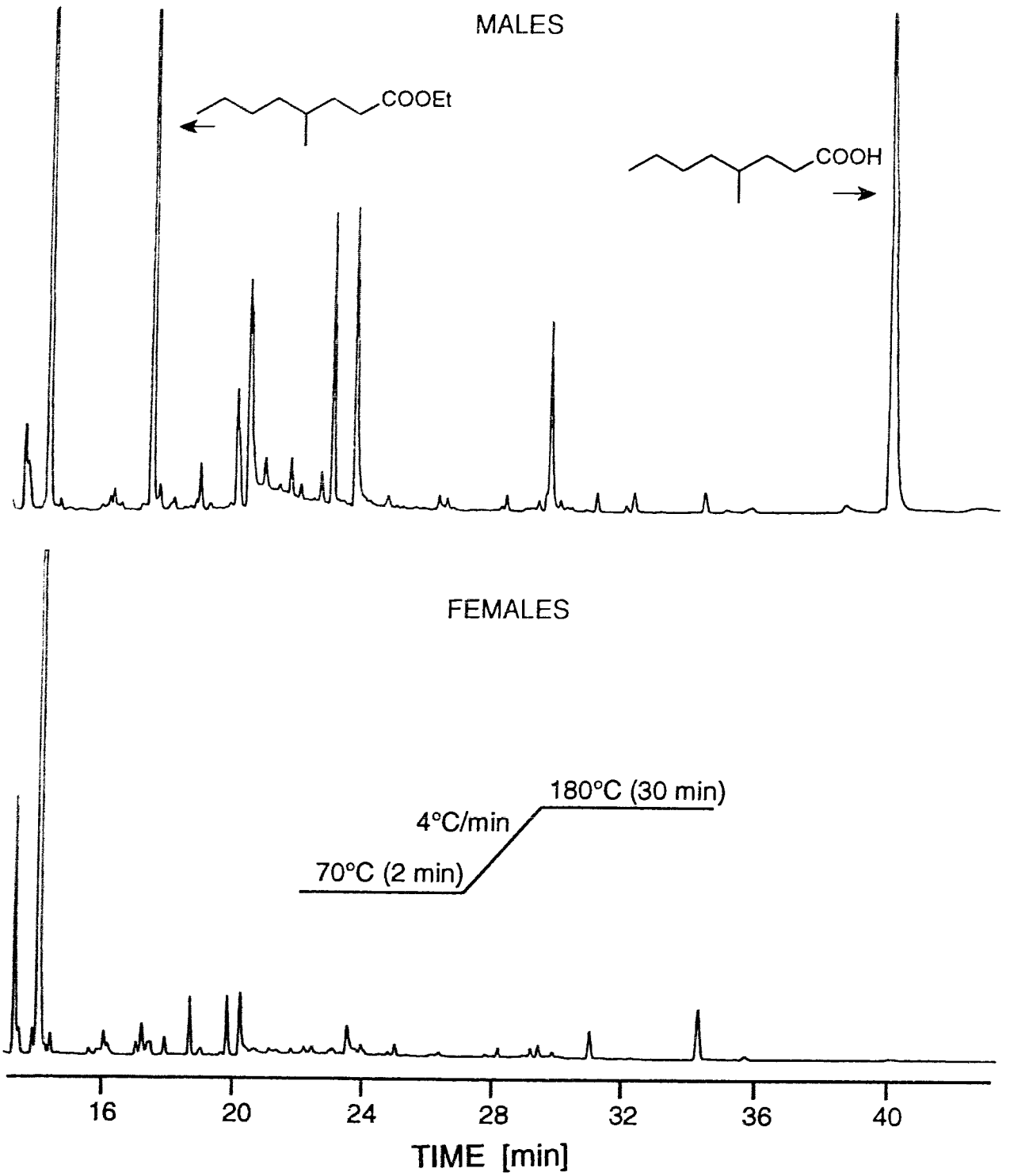


Figure 4.5. Gas chromatograms of volatiles from ten male and from ten female *Oryctes rhinoceros* maintained in aeration chambers for one week with sugarcane. SP-1000 fused silica column (30 m X 0.5 mm ID).

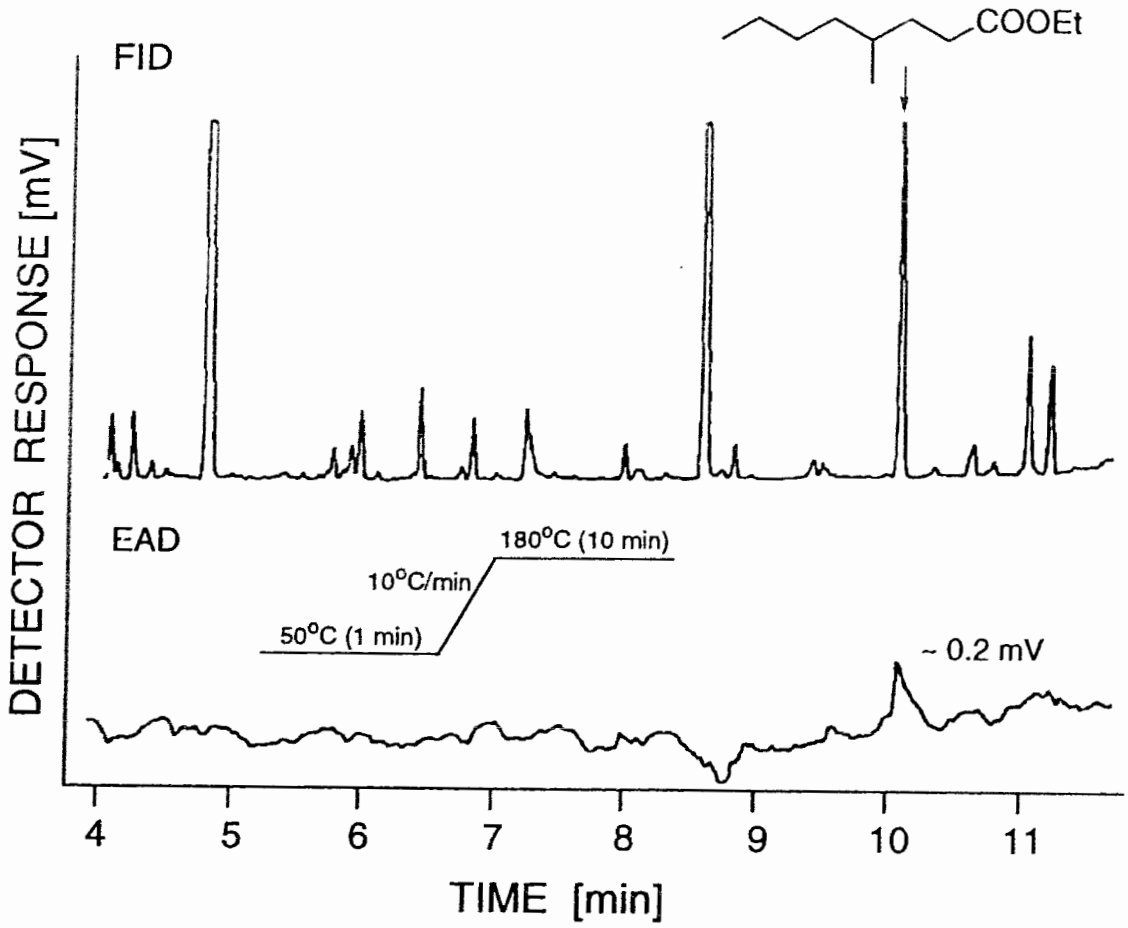


Figure 4.6. FID and EAD responses to volatiles obtained from male *Oryctes rhinoceros*. The antennal recording was carried out with an antenna of a female beetle. SP-1000 fused silica column (30 m X 0.25 mm ID).

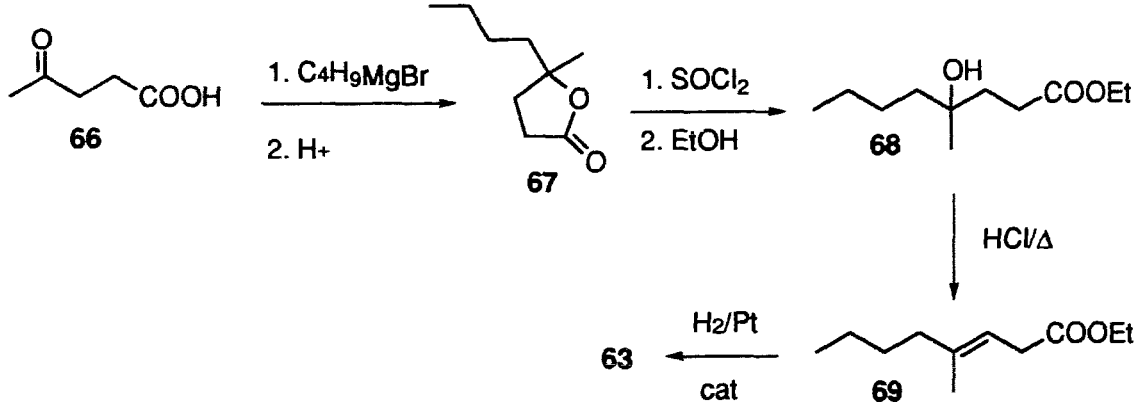
strongly inhibited by the presence of the non-natural pheromone enantiomer of its sex pheromone, (*R,Z*)-5-(1-decenyl)oxacyclopentan-2-one (**53**).[33] Therefore, investigation of the response of *O. rhinoceros* to individual enantiomers of **63** was also tested.

4.6. Syntheses of Candidate Pheromones.

4.6.1. Previous Synthesis of Racemic Ethyl 4-Methyloctanoate (63) and Ethyl 4-Methylheptanoate (65).

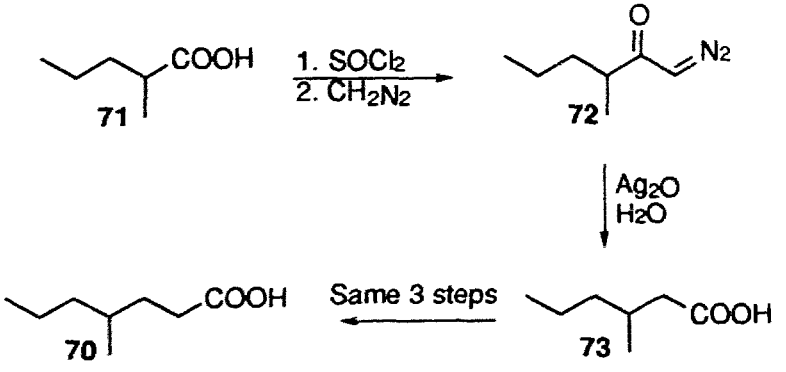
Methyl branched pheromones are very common.[116] There are several synthetic methods described for the synthesis of 4-methyl alkanoic acids and esters.

Ethyl 4-methyloctanoate, **63**, and ethyl 4-methylheptanoate, **65**, were prepared by Cason and coworkers (1944)[117] by reaction of ethyl levulinate or levulinic acid (**66**) with the corresponding Grignard reagent to produce a γ,γ-dialkylbutyrolactone (**67**). Treatment of the lactone with $SOCl_2$ followed by ethanol gave **68** which was converted by further acidic treatment to **69**. Hydrogenation of **69** gave **63** in overall yields of 50-60 % (Scheme 4.1).



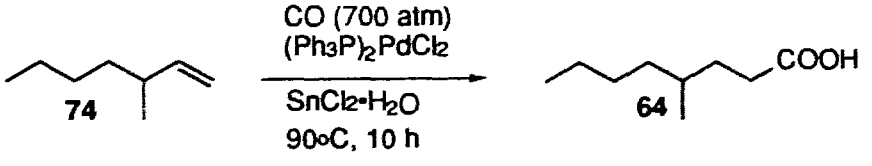
Scheme 4.1. Synthesis of **63** according to Cason and coworkers.

Vasi and Desai[118] prepared 4-methylheptanoic acid (**70**) from 2-methylpentanoic acid (**71**) using two successive Arndt-Eistert syntheses involving intermediates **72** and **73** (Scheme 4.2).



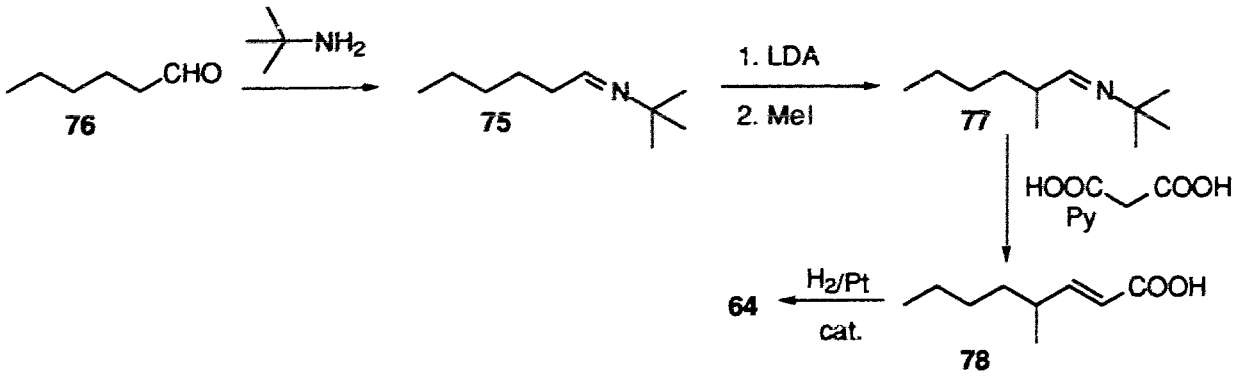
Scheme 4.2. Synthesis of **70** by Arndt-Eistert route.

Mrowca,[119] reported the synthesis of substituted carboxylic acids and esters by catalytic carboxylation or alkoxycarbonylation of unsaturated hydrocarbons (**64** was obtained in 86 % yield by the carbonylation of 3-methyl-1-heptene, **74**) (Scheme 4.3).



Scheme 4.3. Carbonylation of terminal alkenes.

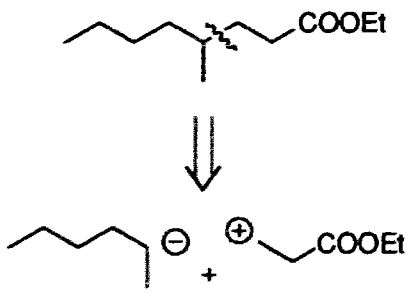
Finally, Sonnet and Baillargeon,[120] synthesized 4-methyloctanoic acid, **64**, in 53 % overall yield by methylation of the *N-t*-butylimine derivative (**75**) of hexanal (**76**) to give **77**. Condensation with malonic acid to **78** and hydrogenation gave **64** (Scheme 4.4).



Scheme 4.4. Synthesis of **64** by the method of Sonnet and Baillargeon.

4.6.2. Synthesis of 63 and 65 by Conjugate Addition Reaction.

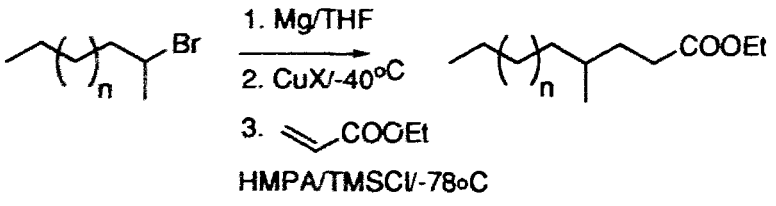
Retrosynthetic analysis of **63** and **65** reveals that such molecules can be assembled *via* conjugate addition of a suitable five or six carbon electron donor and a three carbon electron acceptor (Scheme 4.5). The candidate pheromones were prepared by conjugate addition of organocuprates to ethyl acrylate,[121] a shorter synthetic procedure than those of the earlier reports.



Scheme 4.5. Retrosynthetic analysis of ethyl 4-methyloctanoate.

The required cuprates were prepared by addition of 10 mol % CuCN to a solution of the corresponding Grignard reagent at -40°C. Subsequent addition of trimethylchlorosilane, HMPA and ethyl acrylate (2: 2: 1 ratio) in THF or Et_2O produced **63** or **65** in 40-68 % yield. Use of CuBr•DMS complex increased the yield of the conjugate addition by 10-15 % (Scheme 4.6). However, no further

attempts to optimize the reaction yields were made because **63** can also be prepared by the esterification of commercially available **64**.[122]

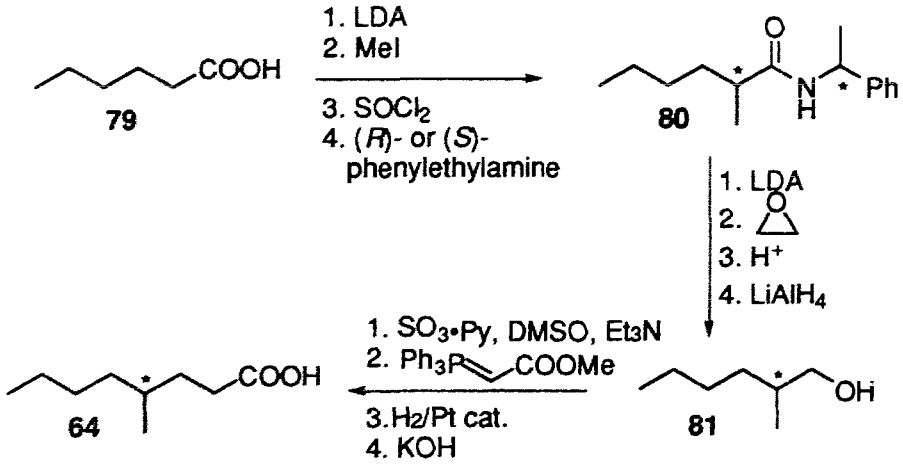


CuX = CuCN or CuBr•DMS

Scheme 4.6. Synthesis of **63** and **65** by conjugate addition of organocuprates to ethyl acrylate.

4.6.3. Chiral Synthesis of Ethyl 4-Methyloctanoate.

Because the methyl branch of the major candidate pheromone is remote from the functional group, synthesis must allow introduction of chirality at a remote location. Syntheses of (*R*)- and (*S*)-4-methyloctanoic acid [(*R*)- and (*S*)-**64**] in high optical purities (95.4 %) have been reported by Sonnet and Gazzillo.[123] Alkylation of hexanoic acid produced (**79**) 2-methylhexanoic acid, the acid chloride of which was treated with (*R*)- or (*S*)-α-phenylethylamine to give diastereoisomeric amides (**80**) which were separated by crystallization. The optically pure amides were *N*-hydroxyethylated and reduced to the corresponding 2-methylhexanols (**81**) which were oxidized and converted to the methyl 4-methyl-2-octenoates *via* a Wittig reaction of the resulting aldehyde with carbomethoxymethylene triphenylphosphorane. Hydrogenation and saponification afforded (*R*)-**64** and (*S*)-**64** in ~ 10 % overall yield (8 steps) (Scheme 4.7).



Scheme 4.7. Sonnet and Gazzillo's chiral synthesis of **64**.

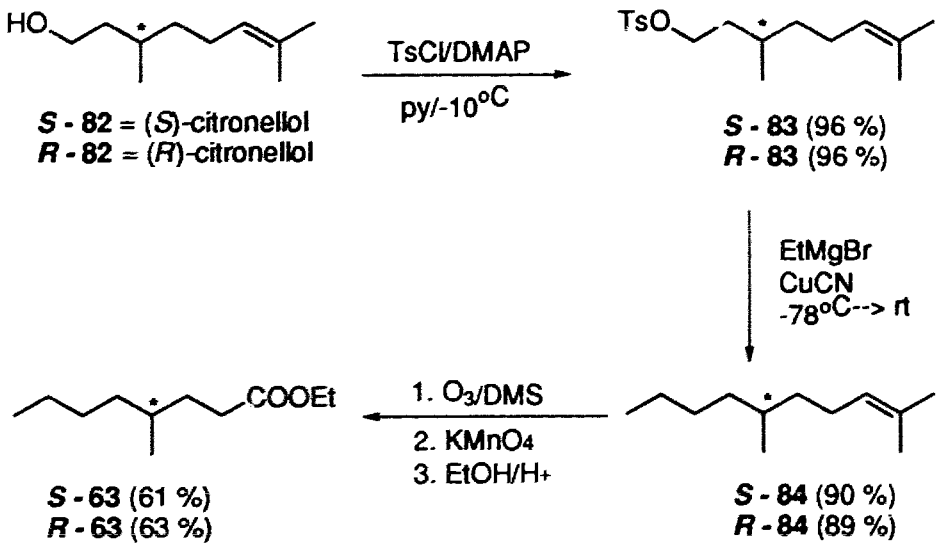
A more efficient route using highly enantiomerically enriched citronellol (**82**) was subsequently devised.[124,125] The citronellane skeleton is commonly used in the synthesis of natural products.[126] Modifications at both termini of the citronellane skeleton can be performed without perturbation of the chiral centre.[125]

The synthesis of (*S*)- and (*R*)-**63** commenced with tosylation of (*R*)- or (*S*)-citronellol, respectively.[126d] Chain extension *via* cuprate displacement of the tosylate **83**[50] produced the corresponding 2,6-dimethyl-2-decenes, **84**, in high yield. Ozonolysis followed by permanganate oxidation and esterification afforded (*S*)-**63** and (*R*)-**63** in yields of 45-47 % over five steps (Scheme 4.8).

Enantiomeric excess of (*R*)- and (*S*)-citronellol was determined by GC analysis (DB-1) of the amides of (*R*)-α-phenylethylamine of the corresponding citronellic acids.[123]

Attempts to determine the optical purity of **84**, **85** (**85** refers to the corresponding aldehydes obtained after ozonolysis of **84**), (*S*)-**63** or (*R*)-**63** by gas chromatography using a Cyclodex B fused silica column or NMR techniques were unsuccessful. ^{1}H NMR spectra in the presence of tris[3-(heptanofluoropropylhydroxymethylene)-(-)-camphorato)europium (III) [Eu(hfc)$_3$]

in CS_2 (1: 1 or 1: 2 ratio, ester: shift reagent)[127a] or the chiral solvating agent (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol in CCl_4 (1:1 or 1:2 ratio, ester: anthrylethanol)[127b,c] failed to display diastereoisomeric complexes with different chemical shifts. Since the above procedures have significant precedent in the literature and involve transformations remote from the stereogenic carbon, it was assumed that the optical purity of (*S*)-**63** and (*R*)-**63** was identical to that of the citronellol used as a precursor.



Scheme 4.8. Synthesis of ***S*-63** and ***R*-63** using enantiomerically enriched citronellol.

4.7. Behavioral Activity of Candidate Pheromones.

4.7.1. Field Experiments.

A. *O. monoceros.*

Ethyl 4-methyloctanoate (**63**) was tested[iii] in three- to four-year old oil palm plantation at the La Me Research Station, Côte d'Ivoire.[128] A four-treatment, eight-replicate experiment tested attraction of ethyl chrysanthemumate (**51**) and the candidate pheromone released at three rates (0.3, 3 and 30 mg *per* day, @

[iii] Conducted by Dr. Gerhard Gries and Ms. Regine Gries, Department of Biological Sciences, Simon Fraser University.

25°C). Plastic buckets[12] 1-2 m away from palms were employed as pitfall traps (side entrance holes at ground level, Figure 4.7) in a randomized complete block with traps at 27 m intervals and blocks 27-500 m apart. Petrolatum on the inner bucket surface below side entrances and a wet sponge treated with insecticide Evisect "S" (3 % thiocylam hydroxylate in water) at the bottom of the bucket, assured retention of captured beetles.

B. *O. rhinoceros.*

Experiments were conducted[iv] in one- or two-year old oil palm plantings at three P.T.P.P. London Sumatra Indonesia estates in North Sumatra, Indonesia. Specific locations are given in Figures 9-11. All experiments were set up as randomized complete blocks with intertrap and interblock distances of at least 27 and 54 m, respectively (for details see reference 115b). Traps were checked daily and captured beetles removed A 3-treatment, 10-replicate experiment (Figure 4.8) determined activity of the main candidate pheromone, ethyl 4-methyloctanoate, **63** (pitfall traps were used in this experiment as was suggested from *O. monoceros* experiments, however, later experiments in Indonesia showed vaned traps to be more efficient in trapping *O. rhinoceros*[115b]). In a second 12-replicate experiment (Figure 4.9) standard vane traps (Figure 4.7) were baited with **63** released at 0, 6, 9, 18, or 30 mg *per* day (to minimize interference between treatments, intertrap and interblock distances were increased to 54 and ≥63 m, respectively). In all experiments, no significant differences were found in the responses of male and female beetles and so catches were pooled by sex for analysis. Data from field experiments were transformed by log (x+1) if data were not normally distributed and were subjected to Analysis of Variance (General Linear Modeling) (Minitab, 1989).[61] If replicates

[iv] Conducted by Ms. Rebecca Hallett, Department of Biological Sciences, Simon Fraser University.

were run at different times or locations, data were analyzed for time x treatment or location x treatment interactions. Following ANOVA, multiple pair comparisons were made using Bonferroni's *t*-tests. If homoscedasticity was not improved by transformation, data were analyzed by X^2 tests.[61]

A 4-treatment, 10-replicate experiment tested attraction of beetles to racemic **63**, (*S*)-**63**, (*R*)-**63** (Figure 4.10), or a blank control in standard vane traps (Figure 4.8). (*S*)- or (*R*)-**63** were released at ~2 mg *per* day from eight 1 mm ID glass capillary tubes cut 1 cm above the meniscus and placed in capped 400 µL plastic centrifuge tubes with two 3 mm holes 1 cm below the top. Racemic **63** was released at ~4 mg *per* day from sixteen capillary tubes.

Attraction of beetles to **63**, 4-methyloctanoic acid (**64**), ethyl 4-methylheptanoate (**65**), and to ethyl chrysanthemumate (EC) was compared in several experiments. Also, pheromone-host material interactions were also tested.[116b]

4.8. Field Experiment Results.

4.8.1. *O. monoceros.*

Ethyl 4-methyloctanoate released at 30 mg *per* day attracted six males and five females in nine days, whereas the known attractant ethyl chrysanthemumate at the same release rate did not attract any *O. monoceros.* Lower release rates of pheromone were not attractive.

In assessing absolute trap captures, the low relative abundance of these very large insects must be taken into account. In 1992 for example, weekly removal of *O. monoceros* from palms revealed ~ 9 adults *per* hectare in these plantations (M. Zebeyou, Institut des Forêts (IDEFOR), Department des Plantes Oléagineux, Côte d'Ivoire, personal communication). Had the pheromone experiment been conducted in beetle-preferred coconut rather than oil palm

stands and not prior to but in the middle of the wet season during which *O. monoceros* is more abundant,[89] trap captures probably would be expected to be higher. Capture of eleven *O. monoceros* to **63** *versus* none to the known attractant EC clearly indicates superior attraction of the aggregation pheromone. Addition of yet unknown plant volatiles may enhance attraction of the aggregation pheromone. Capture rates might also be improved by optimizing pheromone release and trap design.

4.8.2. *O. rhinoceros.*

As for *O. monoceros*, compound **63** was confirmed in field experiments as the major male-produced aggregation pheromone of *O. rhinoceros* (Figure 4.8). Other geographically or temporally isolated scarabaeid beetles also utilize identical sex pheromones.[106,108] Compound **63** was ten times more attractive than **51**.[116b] A dose-response experiment (Figure 4.9) determined 9 mg *per* day of **63** was an optimal rate of release. Buried pitfall traps were more effective if they contained palm fruit bunches while vane traps were the most effective of all designs and captures were not improved by the addition of organic matter. Suspending vane traps at 2 m above ground increases captures by 2-3 times compare to ground level traps (Chong Teh BAL Plantations, Sabah Malaysia, unpublished). Suspended pheromone-baited vaned traps are now used in Malaysia as a method to manage *O. rhinoceros* populations (A.C. Oehlschlager, personal communication). Synergism between aggregation pheromones and host compounds has recently been shown for *A. octiescostata*,[110] and is known for palm weevils, *Rhynchophorus* spp (see Chapter 2). Synergistic volatiles are apparently produced early in the decomposition (fermentation) process, because freshly milled fruit bunches, but not decomposed palm tissue, enhanced pheromone attraction to pitfall traps.[115b] Ethyl 4-methylheptanoate, **65**, was

significantly more attractive than 4-methyloctanoic acid, **64**, but these compounds did not differ in attraction from EC. Based on results to date these two compounds cannot be classed as aggregation pheromones.

Racemic and (*S*)-**63** were similarly attractive to *O. rhinoceros* (Figure 4.10), indicating that (*S*)-**63** is a naturally produced isomer and (*R*)-**63** is not repellent.

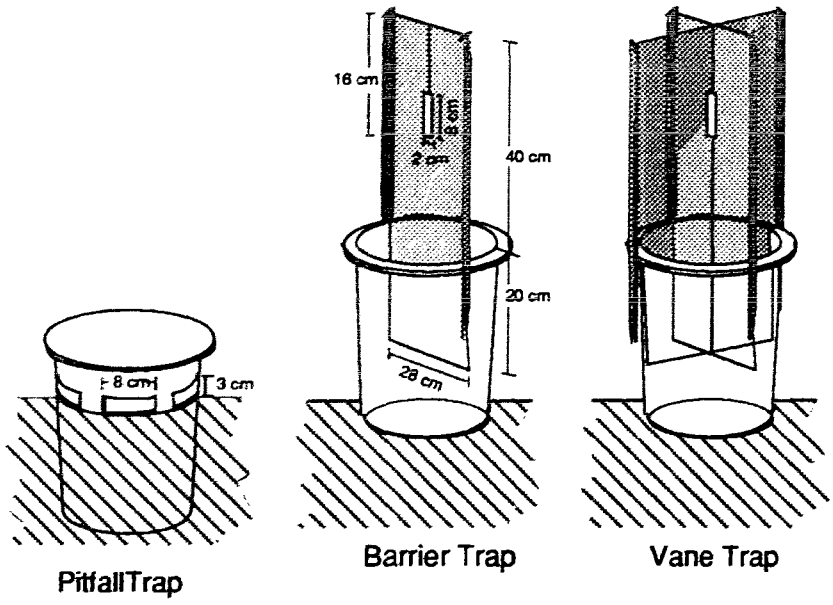


Figure 4.7. Trap designs used to capture *Oryctes rhinoceros*. **Pitfall trap**: 19 L black bucket buried in ground to allow beetles to enter through slots below rim; pheromone lure suspended within bucket from plywood lid. **Barrier and vaned trap**: 20 L white bucket with one or two unpainted sheet metal vanes extending 20 cm into bucket to prevent beetles from flying out; wooden slats on edge of vanes for reinforcement; pheromone lures suspended within slot to allow pheromone dissemination in all directions.

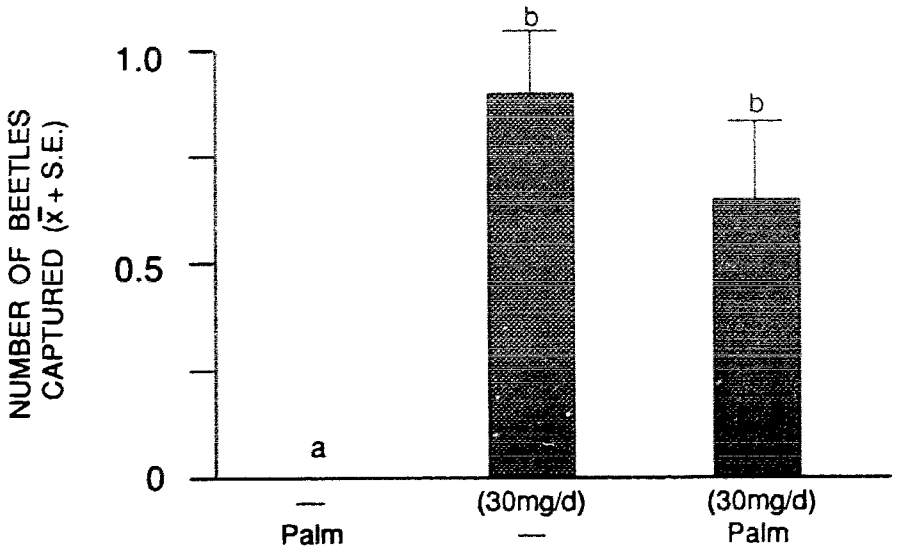


Figure 4.8. Attraction of *Oryctes rhinoceros* to ethyl 4-methyloctanoate, **63**, alone (released at 30 mg *per* day), decaying oil palm tissue alone or both together, in pitfall traps at Bah Lias and Rambong Sialang Estates, North Sumatra, Indonesia (14 - 22 and 16 - 23 October 1993, respectively); (N = 10). Data pooled as no locational differences were found (X^2= 2.2305, df = 1, p> 0.10). Treatment differences for pooled data, X^2= 13.036, df = 2, p<0.01. Bars superscripted by the same letter are not significantly different, pairwise X^2 tests, p< 0.05.

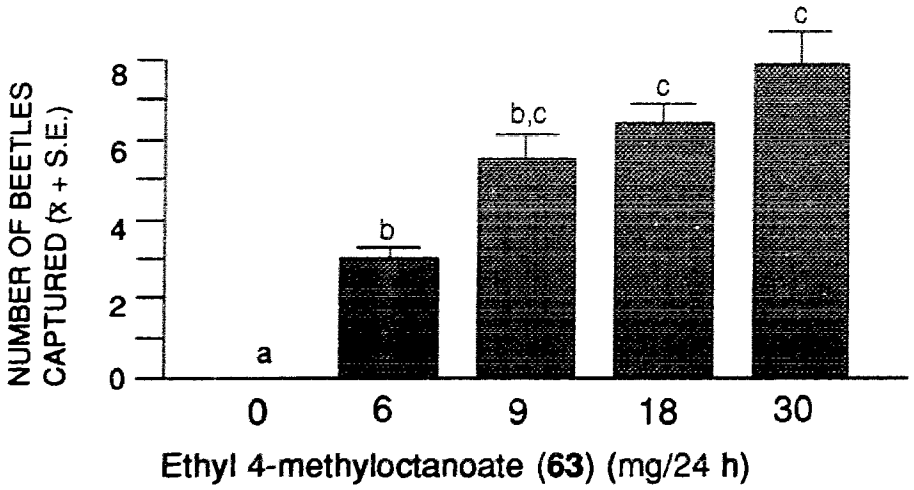


Figure 4.9. Attraction of *Oryctes rhinoceros* to **63** released at various rates from standard vane traps (24 May - 8 June 1994, Dolok) no organic matter present; (N = 12); ANOVA on log (x+1) transformed data, F= 49.84, df= 4, $p < 0.001$. Bars superscripted by same letter are not significantly different, Bonferroni's *t*-test, $p < 0.05$. Untransformed means presented.

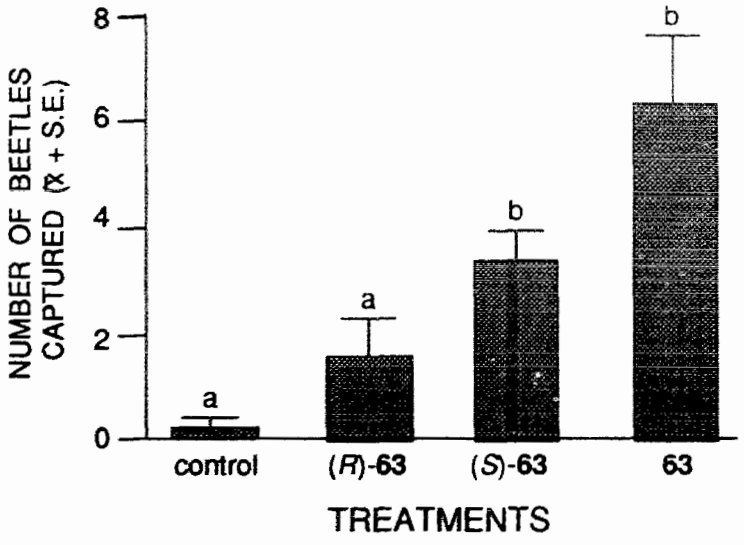
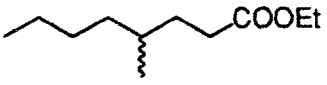


Figure 4.10. Attraction of *Oryctes rhinoceros* to standard vane traps containing stereoisomers of **63** at Rambong Sialang Estate (23 May-8 June 1994); (N = 10). ANOVA on log (x+1) transformed data, F= 24.04, df= 3, $p< 0.001$. Bars superscripted by the same letter are not significantly different, Bonferroni's t-test, $p< 0.05$. Untransformed means presented.

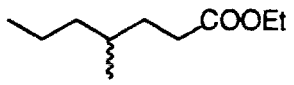
4.9. Experimental Section.

For general methods and volatile collection see Experimental Section Chapter 2.

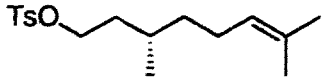
Copper cyanide and copper bromide dimethyl sulfide complex were purchased from Aldrich and transferred in a nitrogen glove bag. HMPA was fractionally distilled under vacuum from CaH_2, collected and stored over activated 4A molecular sieves under argon.



Ethyl 4-methyloctanoate (63). A solution of 2-hexyl magnesium bromide [prepared by reaction of 2-bromohexane (2.0 mL, 2.34 g, 14 mmol) and magnesium turnings (0.24 g, 10 mmol)] in dry Et_2O was cooled to -40°C, then CuCN (1.10 g, 12 mmol) or CuBr•DMS (2.50 g, 12 mmol) was added. After stirring the mixture 30 min, the flask was cooled to -78°C and a solution of ethyl acrylate (2.2 mL, 20 mmol), HMPA (4.0 mL, 23 mmol) and TMSCl (2.4 mL, 19 mmol) in dry Et_2O (10 mL) was added *via* cannula. After 30 min of stirring, the cold bath was removed and the reaction allowed to warm to room temperature. The reaction was then quenched with 3 M HCl at 0°C. The aqueous layer was extracted with Et_2O (3 X 25 mL), washed with saturated $NaHCO_3$ and NaCl, and dried over anhyd. $MgSO_4$. Distillation at reduced pressure (86°C @ 10 mm Hg) gave 0.80 g (56 % yield from CuCN) or 1.10 g (68 % from CuBr•DMS) of **63** as a colourless liquid. ^{1}H NMR ($CDCl_3$, ppm): 0.89 (3H, d, J = 8.1 Hz), 0.93 (3H, t, J = 8.1 Hz), 1.10 (1H, m), 1.24 (3H, t, J = 8.1 Hz), 1.34 (5H, m), 1.40 (2H, m), 1.66 (1H, m), 2.30 (2H, m), 4.10 (2H, q, J = 8.1 Hz); EI-MS *m/z* (relative intensity): 186 (M^+, 20), 141 (M^+-OC_2H_5, 40), 101 (M^+-C_6H_{13}, 100).



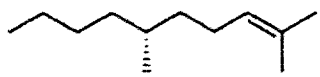
Ethyl 4-methylheptanoate (65). A solution of 2-pentyl magnesium bromide [prepared by reaction of 2-bromopentane (4.95 mL, 6.04 g, 40 mmol) and magnesium turnings (0.96 g, 40 mmol)] in dry Et_2O was cooled to -40°C, then CuCN (0.36 g, 8 mmol) was added. After stirring the mixture 30 min, the flask was cooled to -78°C and a solution of ethyl acrylate (2.75 mL, 25 mmol), HMPA (8.7 mL, 8.96 g, 50 mmol) and TMSCl (6.35 mL, 5.43 g, 50 mmol) in dry Et_2O (10 mL) was added *via* cannula. After 30 min of stirring, the cold bath was removed and the reaction allowed to warm to room temperature. The reaction was then quenched with 3 M HCl at 0°C. The aqueous layer was extracted with Et_2O (3 X 25 mL), washed with saturated $NaHCO_3$ and NaCl, and dried over anhyd. $MgSO_4$. Distillation at reduced pressure (80°C @ 10 mm Hg) gave 1.75 g (40 % yield, 95 % pure) of **65** as a colourless liquid. ^1H NMR ($CDCl_3$, ppm): 0.88 (6H, m), 1.10 (1H, m), 1.27 (3H, t, J = 8.0 Hz), 1.30 (2H, m), 1.40 (3H, m), 1.66 (1H, m), 2.30 (2H, m), 4.10 (2H, q, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, ppm): 174.16, 60.11, 36.97, 32.17 (2C), 31.95, 31.16, 19.99, 19.23, 14.23; CI-MS *m/z* (relative intensity): 172 (M^+, 3), 127 (M^+-OEt, 30), 101 (M^+-CO_2Et, 100).



(3*S*)-3,7-Dimethyl-6-octenyltosylate [(*S*)-83]. To (*S*)-citronellol, [(*S*)-**82**] (97-98 % ee) (3.13 g, 20 mmol) in dry pyridine (30 mL) was added dimethylaminopyridine (DMAP) (0.40 g, 3.2 mmol). The flask was cooled to -10°C and *p*-toluenesulfonyl chloride (3.82 g, 20 mmol) added in one portion. Stirring was continued for 5 h at -10°C with monitoring of aliquots by GC and TLC (9:1, pentane:Et_2O, R_f = 0.25). The mixture was then poured into an ice-cooled NaCl solution and extracted (2 X 30 mL) with Et_2O. The organic layer was

washed with 3 M HCl, saturated $NaHCO_3$, NaCl solution and dried over anhyd. $MgSO_4$. After concentration *in vacuo*, the residue was chromatographed on a column (9:1, pentane:Et_2O) to yield (*S*)-**83** (5.70 g, 96 %, 98 % pure) as a pale yellow oil; ^1H NMR ($CDCl_3$, ppm): 0.80 (3H, d, J = 8.8 Hz), 1.10 (1H, m), 1.20 (1H, m), 1.40 (1H, m), 1.50 (1H, m), 1.52 (1H, m), 1.56 (3H, s), 1.70 (3H, m), 1.90 (2H, m), 2.45 (3H, s), 4.02 (2H, m), 5.0 (1H, t, J = 8.8 Hz), 7.32 (2 H, d, J = 8.8 Hz), 7.80 (2 H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, ppm): 144.60, 133.41, 131.44, 129.79, 127.88, 124.34, 69.05, 36.72, 35.69, 28.93, 25.66, 25.27, 21.60, 19.06, 17.60 ppm; CI-MS *m/z* (relative intensity): 310 (M^+, 2), 138 (M^+-OSO_2-C_6H_4-CH_3, 50).

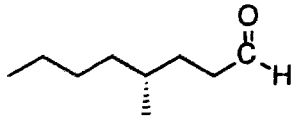
(3*R*)-3,7-Dimethyl-6-octenyltosylate [(*R*)-83]. A procedure similar to that described above was used for this synthesis: 5.61 g, 95 % yield, 98 % pure.



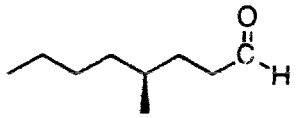
(*6R*)-2,6-Dimethyl-2-decene [(*R*)-84]. Ethyl magnesium bromide (60 mL, 0.18 mol, 3 M solution in Et_2O) was cooled to -40°C, then CuCN (1.62 g, 18 mmol) was added. After stirring the mixture 30 min, the flask was cooled to -78°C and (*S*)-**83** (5.00 g, 16 mmol) in dry THF (25 mL) added *via* cannula. After 30 min of stirring, the cold bath was removed and the reaction allowed to warm to room temperature. The progress of the reaction was followed by analysis of aliquots by GC and TLC (pentane, R_f = 0.54). Upon completion, the reaction was quenched with 3 M HCl at 0°C. The aqueous layer was extracted with Et_2O (3 X 25 mL), washed with saturated $NaHCO_3$ and NaCl, and dried over anhyd. $MgSO_4$. Column chromatography (pentane) afforded 2.42 g (90 % yield, 97 % pure) of (*R*)-**84** as a colourless liquid. ^1H NMR ($CDCl_3$, ppm): 0.88 (3 H, d, J = 7.3 Hz),

0.90 (3H, t, J = 7.3 Hz), 1.10 (2H, m), 1.30 (7H, m), 1.60 (3H, s), 1.70 (3H, s), 1.90 (2H, m), 5.10 (1H, t, J = 8 Hz); ^{13}C NMR ($CDCl_3$, ppm): 130.83, 125.16, 37.19, 36.68, 32.46, 29.29, 25.62 (2C), 23.01, 19.60, 17.55, 14.05; CI-MS *m/z* (relative intensity): 168 (M^+, 40); IR (neat): 2926, 1673, 1458, 1377, 1122, 1094, 984, 826 cm^{-1}; Anal. Calcd. for $C_{12}H_{24}$: C, 85.63; H, 14.37. Found: C, 85.69; H, 14.30.

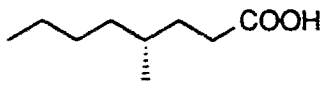
(*6S*)-2,6-Dimethyl-2-decene [(*S*)-84]. A procedure similar to that described above was used for this synthesis: 2.39 g, 89 % yield, 98 % pure. Anal. Calcd. for $C_{12}H_{24}$: C, 85.63; H, 14.37. Found: C, 85.78; H, 14.57.



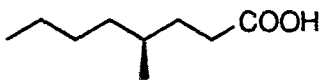
(*R*)-Methyloctanal [(*R*)-85]. Ozone was bubbled through a cold solution (-78°C) of (*R*)-**84** (2.30 g ,14 mmol) in a 1:1 mixture of CH_2Cl_2: MeOH (60 mL) and 1 g of $NaHCO_3$. When the characteristic blue colour appeared, indicating excess ozone, a stream of nitrogen was admitted to remove excess ozone. Dimethyl sulfide (5 mL) was added, the reaction mixture stirred overnight and concentrated *in vacuo* to one third of the volume, poured into water, extracted (3 X 30 mL) with Et_2O and dried over anhyd. MgSO4. Column chromatography (8:2, pentane:Et_2O, R_f = 0.55) afforded (*R*)-**85** (1.68 g, 87 % yield, 96 % pure) as a colourless liquid. ^1H NMR ($CDCl_3$, ppm): 0.90 (6H, m), 1.12 (1H, m), 1.30 (5H, m), 1.40 (2H, m), 1.64 (1H, m), 2.64 (2H, m), 9.75 (1H, s); ^{13}C NMR ($CDCl_3$, ppm): 202.87, 41.70, 36.36, 32.38, 29.16, 28.93, 22.91, 19.35, 14.05; CI-MS *m/z* (relative intensity): 143 (M^++ 1, 100); IR (neat): 2927, 2715, 1727, 1465, 1379, 1263, 1133, 1012, 896, 849, 729 cm^{-1}; Anal. Calcd. for $C_9H_{18}O$: C, 75.00; H, 12.76. Found: C, 75.09; H, 12.48.



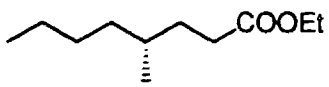
(*S*)-Methyloctanal [(*S*)-85]. A procedure similar to that described above was used for this synthesis: 1.65 g, 85 % yield, 98 % pure. Anal. Calcd. for $C_9H_{18}O$: C, 75.00; H, 12.76. Found: C, 74.98; H, 12.66.



(*R*)-4-Methyloctanoic acid [(*R*)-64]. (*R*)-Methyloctanal (1.60 g, 11 mmol) was added to a solution of $KMnO_4$ (3.6 g, 20 mmol) and Na_2CO_3 (0.7 g) in 75 mL of water and stirred at 0°C for 3 h then overnight at room temperature. The reaction mixture was centrifuged and the supernatant acidified with cold dil. H_2SO_4, extracted (3 X 25 mL) with Et_2O and dried over anhyd. $MgSO_4$. The solvent was removed *in vacuo* to give 1.78 g of (*R*)-**64** which was used for the next step without further purification. ^1H NMR ($CDCl_3$, ppm): 0.90 (6H, m), 1.12 (1H, m), 1.14 (3H, m), 1.60 (2H, m), 1.80 (1H, m), 2.35 (2H, m), 11.30 (1H, br. s).

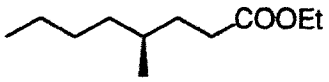


(*S*)-4-Methyloctanoic acid [(*S*)-64]. A procedure similar to that described above was used for this synthesis: 1.45 g.



(*R*)-Ethyl-4-methyloctanoate [(*R*)-63]. A dry ethanol solution of (*R*)-**64** (~100 mL) and a catalytic amount of concentrated. H_2SO_4 were refluxed for 5 h, cooled and diluted with water. This mixture was extracted (3 X 30 mL) with Et_2O, and the organic layer washed with saturated NaCl and dried over anhyd. $MgSO_4$. Column chromatography (9:1, pentane:Et_2O) gave 1.34 g of (*R*)-**63** (65

% yield based on (*R*)-**65**, 98 % pure). $[\alpha]_D^{20}$ = -1.67° (c = 1.345, $CHCl_3$), ^1H NMR ($CDCl_3$, ppm): 0.88 (3H, d, *J* = 8.1 Hz), 0.90 (3H, t, *J* = 8.1 Hz), 1.10 (1H, m), 1.24 (3H, t, *J* = 8.1 Hz), 1.30 (5H, m), 1.40 (2H, m), 1.66 (1H, m), 2.30 (2H, m), 4.10 (2H, q, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, ppm): 174.12, 60.14, 36.36, 34.42, 32.21, 31.97, 29.17, 22.94, 19.31, 14.25, 14.06; IR (neat): 2958, 2884, 1737, 1461, 1373, 1261, 11.73, 1108, 1032, 932, 855, 779, 732 cm^{-1}; Anal. Calcd. for $C_{11}H_{22}O$: C, 70.91; H, 11.91. Found: C, 70.99, H, 12.00.



(*S*)-Ethyl-4-methyloctanoate [(*S*)-63]. A procedure similar to that described above was used for this synthesis: 1.36 g, 66 % yield based on (*S*)-**65**, 98 % pure; $[\alpha]_D^{20}$ = +1.67° (c = 1.350, $CHCl_3$), Anal. Calcd. for $C_{11}H_{22}O$: C, 70.91, H, 11.91. Found: C, 70.82, H, 11.98.

Chapter 5

Aggregation Pheromones of the Mango Fruit Fly, *Anastrepha obliqua* (Macquart) (Diptera: Tephritidae): Efforts Toward New Syntheses of *Z,E*- and *E,E*-farnesenes

5.1. Distribution of the Genus *Anastrepha*.

There are approximately 4000 species of true fruit flies (the Tephritidae family), which are organized into 500 genera. Among the members of this group, the Mediterranean fruit fly, *Ceratitis capitata* (Wiedemann), is a well recognized pest that attacks over 250 varieties of fruits, nuts and vegetables. Small infestations in Florida and California have triggered multimillion dollar eradication programs.[129]

Flies in the genus *Anastrepha* (Diptera: Tephritidae) are among the world's most devastating agricultural pests. *Anastrepha* species are endemic to tropical and subtropical regions of the New World. Their range extends from southern United States to northern Argentina and includes most of the Caribbean Islands. Of the 184 species of *Anastrepha*, only seven are economically important: the South American fruit fly, *A. fraterculus* (Wiedemann), the South American curcubit fruit fly, *A. grandis* (Macquart), the Mexican fruit fly, *A. ludens* (Loew), the West Indies fruit fly, *A. obliqua* (Macquart), Sapote or Serpentine fruit fly, *A. serpentina* (Wiedemann), the guava fruit fly, *A. striata* (Schiner), and the Caribbean fruit fly, *A. suspensa* (Loew).[130a] The known host range of *Anastrepha* includes about 270 plant species in 41 families; there must be many unknown native hosts because more than half of *Anastrepha* species have no known host.[130b]

5.1.1. Control and Management of *Anastrepha*.

During the last 35 years,[130a] control of *Anastrepha* adults has employed of poisoned bait sprays and the use of food attractants in traps. These methods are considered ineffective and environmentally obnoxious. Detection of adults using traps baited with a mixture of protein (torula yeast, molasses or fermented fruit juices) in water is considered expensive and, even though females are captured preferentially, the method is regarded as inefficient. Quarantine regulations have been established to protect "pest free" areas, making trade in fresh fruits cumbersome. Methods of fruit clean-up vary from hot water or hot air treatments (mangoes, guavas and carambolas) to radiation and cold storage. Alternatives to manage *Anastrepha* populations[130a] include development of alternatives to standard hydrolyzed protein baits, better trap design (e.g., colour) and use of insect pheromones. Increased attention has been focused on trap design and improvement of baits,[131a-f] whereas the use of insect pheromones has been limited by their availability.[131g-p]

5.1.2. Pheromone Components in the *Anastrepha*.

Pheromones have been reported for the Mexican fruit fly, *A. ludens*,[131i,132a] which is known to attack citrus, mangoes and other crops in Mexico and Guatemala. This fly may seasonally migrate into citrus areas in the south-western United States. Pheromones are also known for the Caribbean fruit fly, *A. suspensa*,[131h,132b,c] a major pest of citrus, tropical fruits and nuts in the Caribbean and southern Florida. Males of both species share similar courtship, calling behavior and pheromonal components. Both *A. ludens* and *A. suspensa* synthesize and release[132a] (3*Z*)-3-nonen-1-ol (**86**), (3*Z*,6*Z*)-3,6-nonadien-1-ol (**87**), anastrephin (**88**), epianastrephin (**89**), suspensolide (**90**), *E,E*-farnesene (**91**), β-bisabolene (**92**) and α-trans-bergamotene (**93**). (*Z*)-β-Ocimene (**94**) was

found also in *A. suspensa*, whereas limonene (**95**) was exclusively detected in *A. ludens* (Figure 5.1).

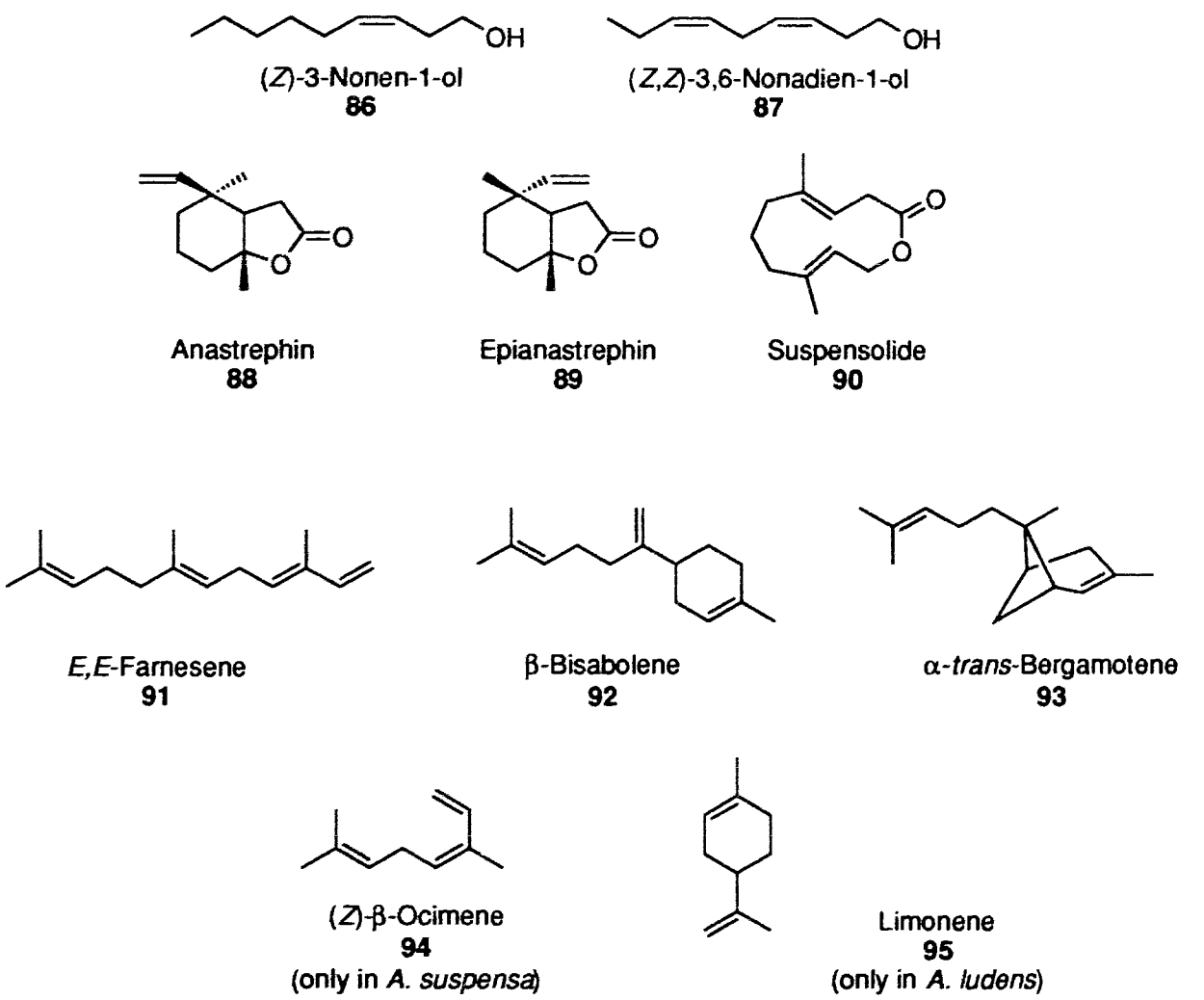


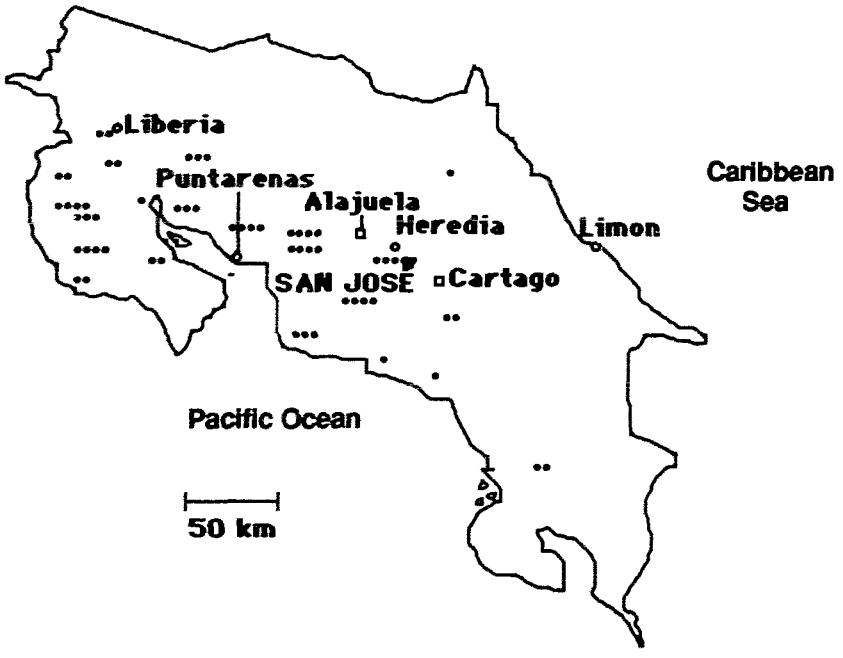
Figure 5.1. Pheromones of *A. ludens* and *A. suspensa*.

5.1.3. Ecology of the West Indies Fruit Fly, *Anastrepha obliqua* (Macquart).

Twenty eight species of *Anastrepha* are known to occur in Costa Rica.[133a] The most common species in commercially important fruit stands are *A. obliqua*, *A. striata*, and *A. serpentina*.[133b]

A. obliqua prefers mango, *M. indica* (L.) and represents 93-97 % of the species in attacked mangoes. It is believed to be attracted to mature fruit for

oviposition.[133c] In Costa Rica, mango is planted throughout the Central Valley and the tropical dry forest regions between the Central Valley and the Pacific coast (Figure 5.2).



• Infested collections
Jiron, L.F.; Hedstrõn, I. *Florida Entomol.* **1988**, *71*, 62.

Figure 5.2. Mango collections infested by *A. obliqua*.

Peak infestations of *A. obliqua* occur during the rainy season (May to September) with a second peak after the rainy season. The flies survive between crops as pupae in the soil.[133b] During April to June, *A. obliqua* changes host to the Spanish plum, *Spondias purpurea* or to any other common *Anacardiaceae* or *Sapotaceae* surrounding the plantation, assuring a year round population. Secondary hosts to *A. obliqua* are frequently used as live fences in mango plantations. In the southwest area of the country, *A. serpentina* can be found attacking mangoes with the same frequency as *A. obliqua*, whereas in the north-west, almost 100 % of mango is attack by *A. obliqua*. Monitoring and trapping of

A. obliqua is currently carried out by the use of MacPhail traps containing *Torula* yeast and 4 % sodium tetraborate or 50 % hydrolyzed soy protein in 50 % sodium tetraborate.[133d,e]

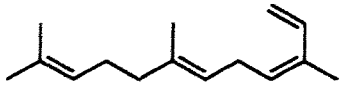
In the early 1990's parallel investigations by the United States Department of Agriculture (USDA) laboratories in Gainsville, Florida and Simon Fraser University in collaboration with the University of Costa Rica (UCR) in San Jose, Costa Rica began to identify species specific volatiles of *Anastrepha obliqua* which might exhibit pheromonal activity. These investigations were launched due to increased interest in Central America in growing mango (*M. indica*) which is a preferred host of *A. obliqua*. Both investigations determined that males produce sex specific compounds. The USDA investigation probed the biological activity of these compounds by a variety of laboratory bioassays while the UCR investigators collaborated with Simon Fraser University to determine electrophysiological activity of the male-specific volatiles.

5.1.4. Analysis and Identification of *A. obliqua* Male-Produced Volatiles.

Eighty seven male and ninety five female *A. obliqua*, reared at Simon Fraser University from pupae collected from the Experimental Station "Fabio Baudrit", University of Costa Rica, La Garita, Alajuela, Costa Rica, by Professor Luis F. Jiron, were aerated separately for 20 h in a modified Nalgene desiccator containing water, honeywater, mangoes and brewer's yeast. Collected volatiles were processed as usual (for details, see experimental section, chapter 2).[10]

Analyses of volatiles from males and females disclosed several male specific compounds (Figure 5.3). Gas chromatographic-electroantennographic (GC-EAD) detection revealed two male-specific compounds that elicited strong antennal response from male and female flies (Figure 5.4). Mass spectral

analyses in CI mode indicated the presence of a sesquiterpene with an *m/z* = 205 (M^++1) and an unsaturated alcohol *m/z* = 141 (M^++1) with a clear *m/z* = 123 (M^+-H_2O). Based on retention characteristics on three columns (SP-1000, DB-1 and DB-5) and by mass spectral comparisons,[131j,132a,134] the two EAD-active compounds and the third major male-specific compound were identified as (3*Z*,6*Z*)-3,6-nonadien-1-ol (**87**), *Z,E*-farnesene (**96**), and *E,E*-farnesene (**91**), respectively (Figure 5.5). The compounds occurred at approximate 52, 40 and 8 %, respectively.



Z,E-Farnesene
96

(3*Z*,6*Z*)-3,6-Nonadien-1-ol (**87**) and *E,E*-farnesene (**91**) have previously been reported as pheromonal components in *A. ludens* and *A. suspensa*, making the present finding taxonomically interesting. As pointed out by Rocca and coworkers[132a] the farnesol structure is exploited in the production of many of the pheromones of *Anastrepha*. Even though *E,E*-farnesene did not show EAD activity, its recurring presence in this genus suggested synthesis of both farnesenes should be executed.

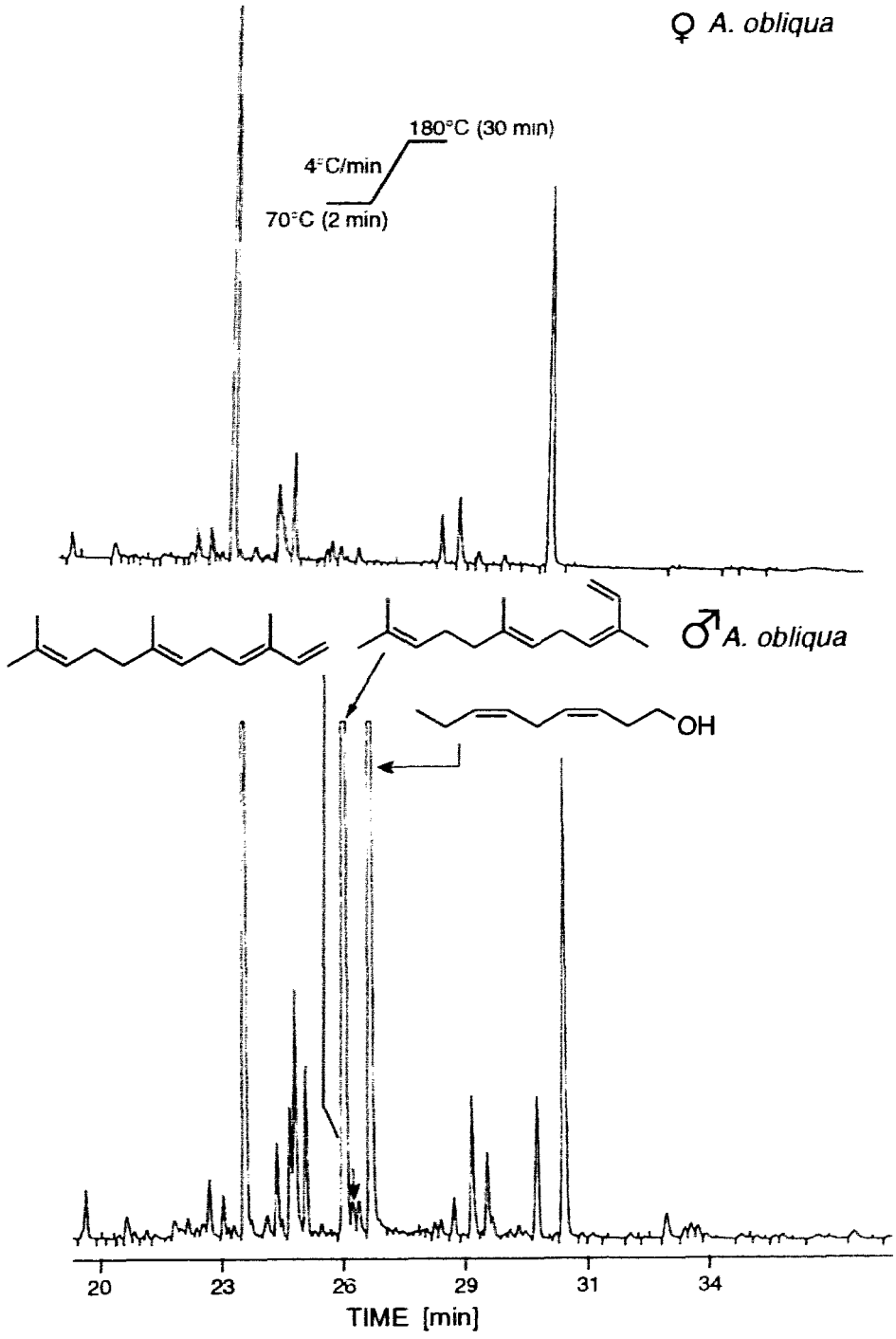


Figure 5.3. Gas chromatograms of volatiles from female (N = 95) and male (N = 87) *A. obliqua* maintained in aeration chambers for 20 h with food provision. Gas chromatographic conditions: linear flow velocity: 35 cm s^{-1}, injector and detector temperatures: 220°C, temperature programming: 70°C (1 min), 10°C min^{-1} to 180°C; SP-1000 fused silica column (30 m X 0.5 mm ID).

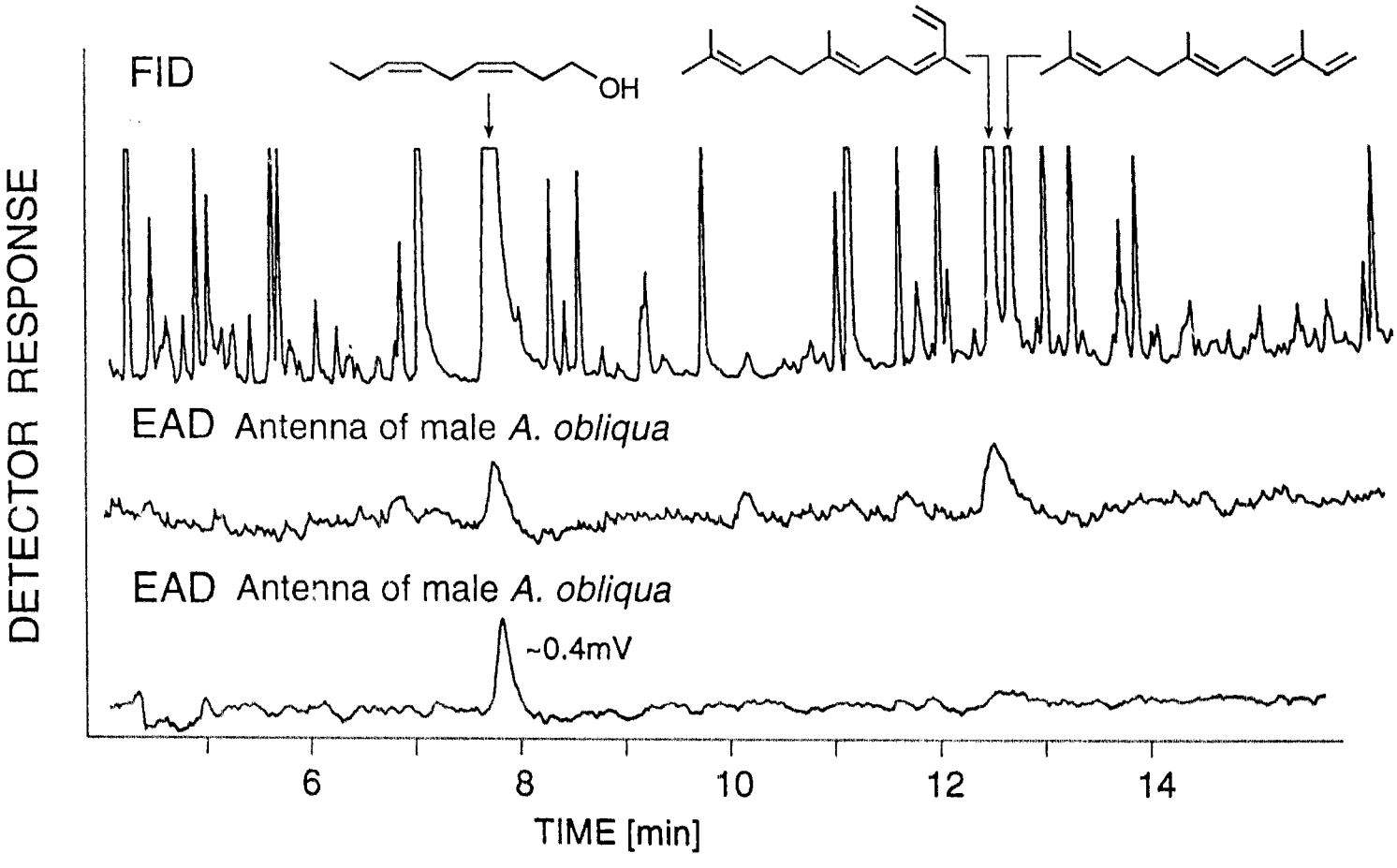


Figure 5.4. FID and EAD responses obtained from male *A. obliqua* chromatographed on a DB-5-coated fused silica column (1 min at 50°C, 10°C per min to 240°C. The antennal recordings were carried out with an antenna of male fly.

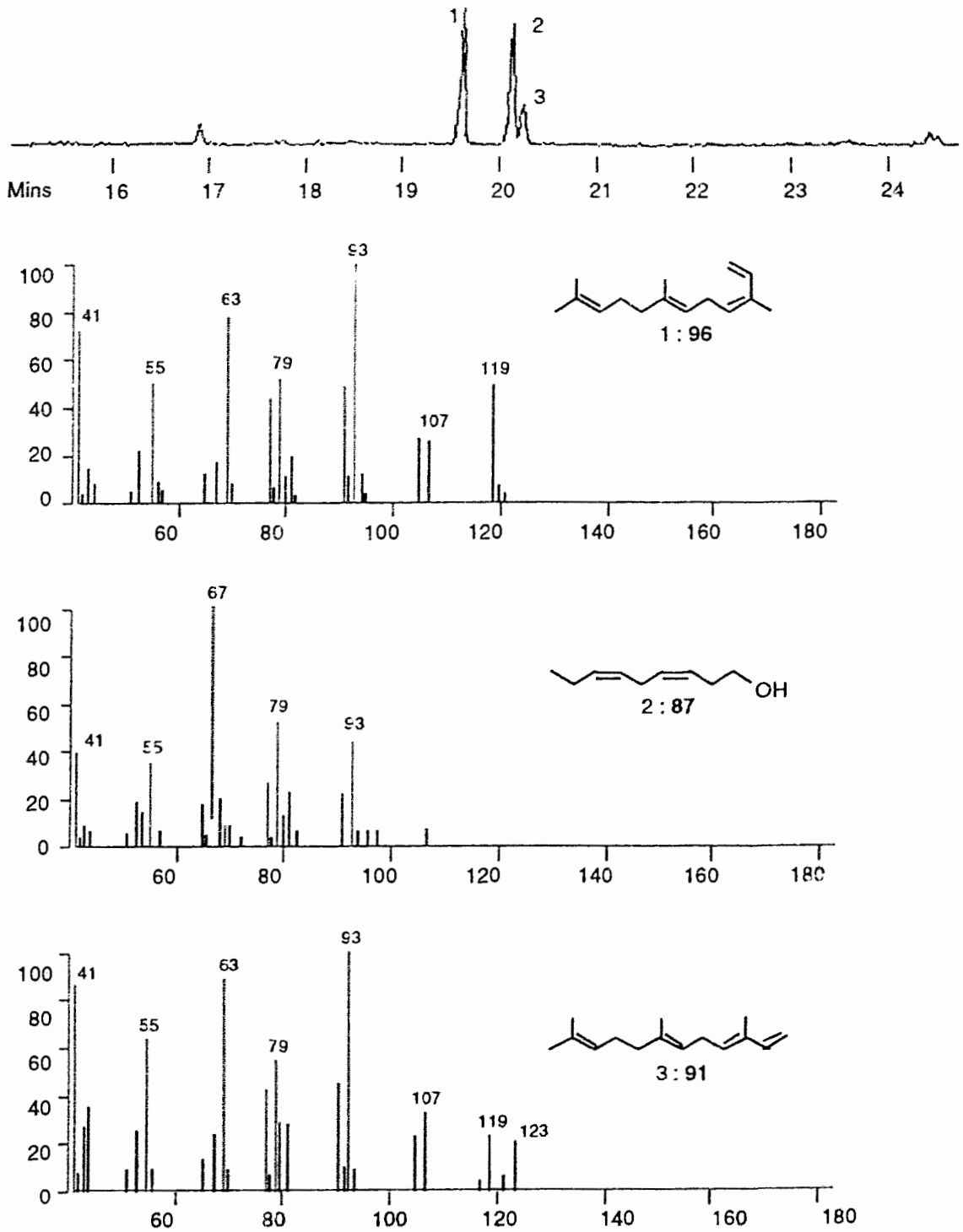


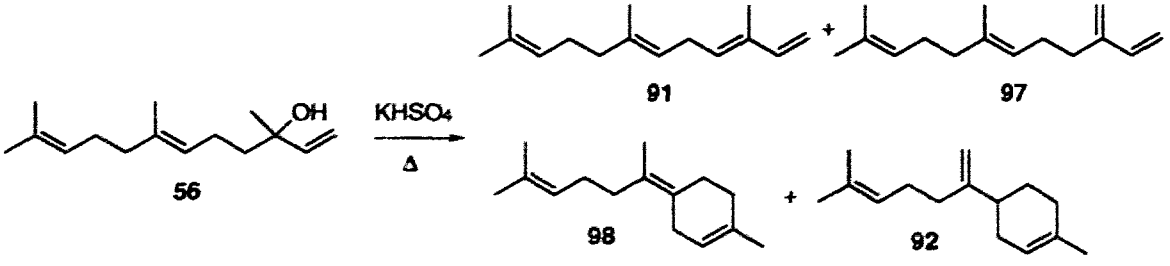
Figure 5.5. Mass spectra of produced *Z,E*-farnesene (**96**), (3*Z*,6*Z*)-3,6-nonadien-1-ol (**87**) and *E,E*-farnesene (**91**). Chromatography: linear flow velocity 35 cm s-1, injector and detector temperature: 260°C, temperature programming: 60°C, 10°C *per* min to 250°C; DB-1 fused silica column.

5.2. Synthetic Background.

5.2.1. Previous Syntheses of *E,E*-Farnesene.

E,E-Farnesene (**91**) has been found as a component in the trail pheromones of the ants *Aphenogaster longiceps*[135], *Myrmica rubra*[136], *Solenopsis* spp[137] and *M. scrabrinodis.*[138] It is also responsible for the formation of hard black brown patches in stored Granny Smith apples.[139] Previous syntheses of *E,E*-farnesene have been limited to the production of small amounts for identification purposes.

Brieger and coworkers,[140] reported one of the first synthesis of **91** in 1969. Dehydration of (*E*)-nerolidol (**56**) with $KHSO_4$, gave **91** as a mixture with β-farnesene (**97**), γ-bisabolene (**98**) and β-bisabolene (**92**) (Scheme 5.1).



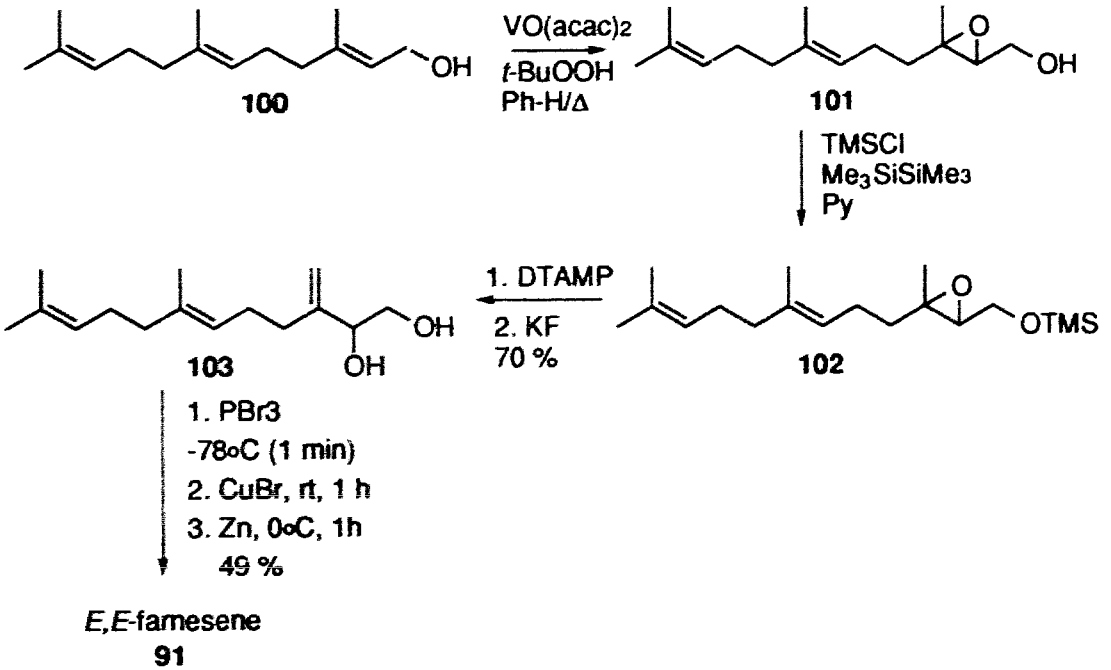
Scheme 5.1. Brieger's *E,E*-farnesene synthesis.

A yield improvement was obtained by isomerization of β-farnesene (**97**) using $RhCl_3$ as a catalyst. Even though **91** was attained in 57 % (by GC analysis), the presence of allofarnesene (**99**) and other isomers made this procedure synthetically ineffective (Scheme 5.2).

Scheme 5.2. Isomerization of β-farnesene.

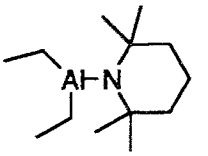
Since **91** easily isomerizes or self-condenses at high temperatures, Anet[134] modified Brieger's procedure of nerolidol dehydration by conducting the reaction in the presence of phosphoryl chloride ($POCl_3$) in pyridine at 50-70°C instead of 170°C. Yields of 25-35 % as a mixture with *Z,E*-farnesene and β-farnesene were obtained. Relatively pure compounds were obtained only after preparative gas chromatography. Anet's synthesis is the most commonly used, since it employs commercially available *E*- and *Z*-nerolidol and uses inexpensive reagents. However, the procedure gives low yields and requires chromatographic separations.

A more appealing route was published by Tanaka and coworkers[141] which takes advantage of the regiospecific epoxidation of *E,E*-farnesol (**100**) with vanadium acetylacetonate and *tert*-butyl hydroperoxide to give **101**. Protection to give **102** followed by isomerization to **103** with diethyl aluminum 2,2,6,6-tetramethylpiperidide (**104**) and elimination of the vicinal diol moiety gave **91** (Scheme 5.3).



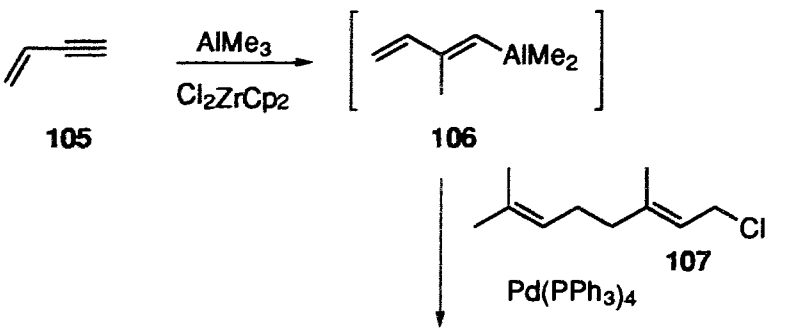
Scheme 5.3. Tanaka's synthesis of *E,E*-farnesene.

The key step in this procedure, is stereospecific epoxide isomerization[142] catalyzed by **104** to provide exclusively the *E*-allylic alcohol.



Diethyl aluminum 2,2,6,6-tetramethylpiperidide
104

Matsushita and Negishi[143a] executed an elegant synthesis of *E,E*-farnesene employing zirconium-catalyzed carboalumination[143b] of 1-buten-3-yne (**105**) to give **106** followed by palladium cross-coupling with geranyl chloride (**107**). The overall yield was 86 % and the isomeric purity was 98 % (Scheme 5.4).

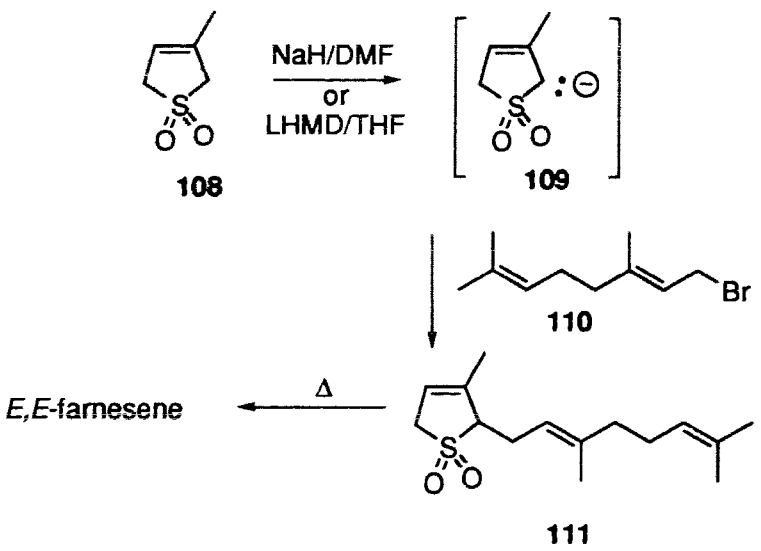


Scheme 5.4. Synthesis of *E,E*-farnesene *via* carboalumination of 1-buten-3-yne.

Despite its attractiveness, this procedure suffers from the lack of a commercial supply of 1-buten-3-yne.

Thermal rearrangements of sulpholenes to 1,3-dienes has been exploited by Chou's group.[144] Smooth conversion of 3-methyl-3-sulpholene (**108**) to carbanion (**109**) followed by alkylation with geranyl bromide (**110**) yielded

111.[145] Thermal rearrangement of the latter afforded *E,E*-farnesene in good isomeric and chemical yields. Unfortunately, 3-methyl-3-sulpholene (**108**) is no longer commercially available (Scheme 5.5).

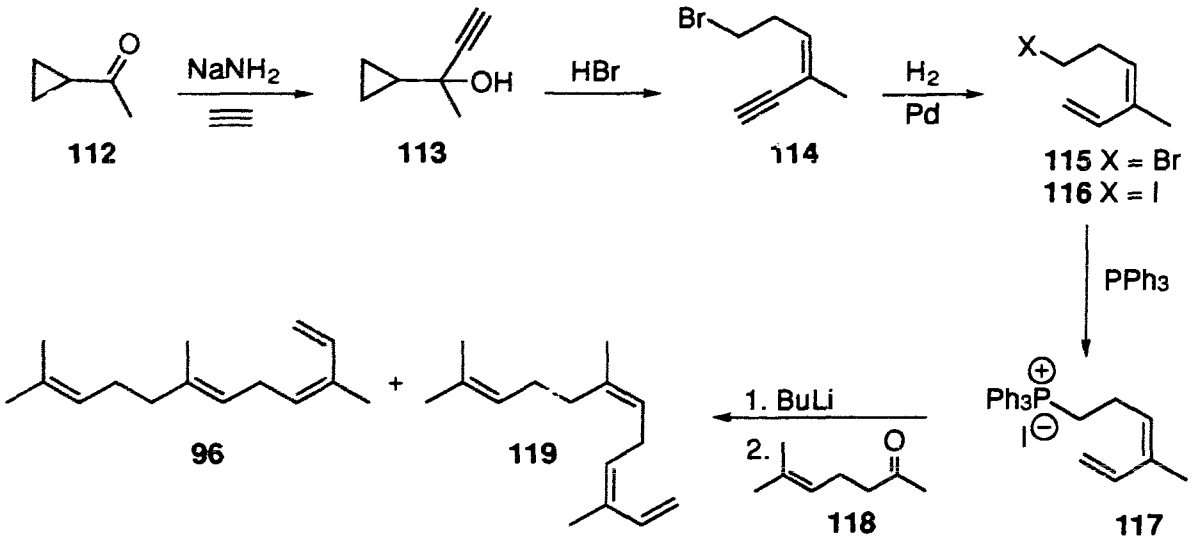


Scheme 5.5. Synthesis of *E,E*-farnesene *via* alkylation of 3-methyl-3-sulpholene.

5.2.2. Previous Syntheses of *Z,E*-Farnesene.

Synthesis of *Z,E*-farnesene (**96**) has received less attention. Only two methods have been reported. The first procedure is Anet's[134] dehydration of (*E*)-nerolidol which yields **96** as an isomeric mixture with *E,E*-farnesene. The second, reported by Morgan and Thompson,[146] affords an improved yield and a better regiocontrol. Methyl cyclopropyl ketone (**112**), was treated with sodium acetylide to give **113** which was then rearranged to the corresponding hexenyne bromide **114**. Selective hydrogenation gave **115** which was then converted to the corresponding iodide **116** before formation of the corresponding triphenylphosphonium salt (**117**). Wittig reaction with 6-methyl-5-hepten-2-one (**118**) afforded **96** and *Z,Z*-farnesene (**119**) in 70 % yield as a 1 : 1 mixture

(Scheme 5.6) which was separated by medium-pressure chromatography on SiO_2 impregnated with 20 % $AgNO_3$.



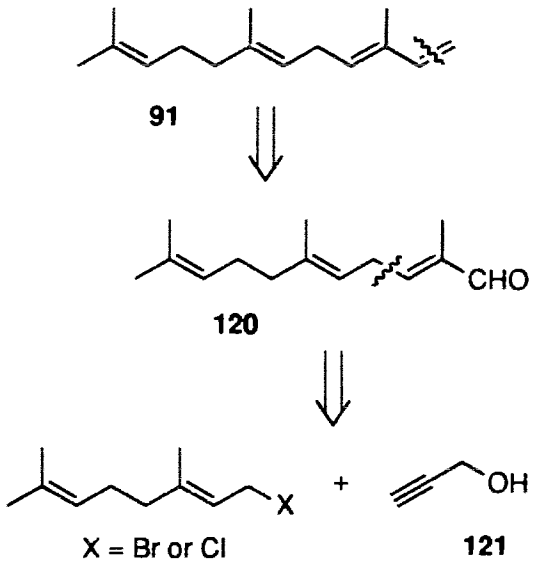
Scheme 5.6. *Z,E*-Farnesene synthesis by the Morgan-Thompson protocol.

5.3. Efforts Toward New Syntheses of *Z,E*- and *E,E*-Farnesenes.

5.3.1. *E,E*-Farnesene. Retrosynthetic Analysis.

Carboalumination of 1-buten-3-yne[143a] or thermal rearrangement of substituted 3-methyl-3-sulpholene[144] appear to be the best methods to obtain *E,E*-farnesene. Synthesis of 1-buten-3-yne[147] or 3-methyl-3-sulpholene[148] required by these routes is feasible. However, these methods require handling toxic, volatile chemicals and they increase the number of synthetic steps. A new synthetic scheme should render similar or better chemical yields and geometric purity.

Retrosynthetic analysis of **91** reveals that it can be constructed from the aldehyde **120**, which in turn can be assembled from coupling of 2-propyn-1-ol (**121**) and the geranyl skeleton (Scheme 5.7).



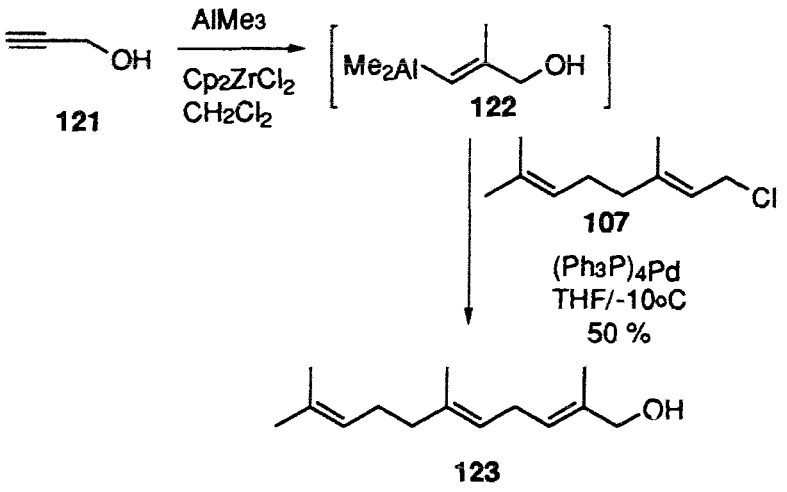
Scheme 5.7. Retrosynthetic analysis of *E,E*-farnesene

Synthesis of aldehyde **120** was approached by two methods. The first involved Zr-catalyzed carboalumination and palladium-catalyzed coupling reactions. The second commenced with reduction and vinyl iodide formation from a suitable derivative of **121**.

5.3.2. Zirconium-Catalyzed Carboalumination Route.

Rand and coworkers[149] have extended carboalumination to heterosubstituted (OH, $OSiMe_2t$-Bu, SPh or I) propargyl and homopropargyl derivatives. Regioselectivity is 92-98 % (*syn*-addition) and chemical yields are 41-87 %. Thus, a strategy similar to that utilized by Masushita and Negishi in the synthesis of **91**[143a] using propargyl alcohol (**121**) was envisioned.

Synthesis of **120** commenced with zirconium-catalyzed carboalumination of **121** followed by *in situ* palladium-catalyzed cross coupling of the alane intermediate (**122**) with geranyl chloride (**107**) to afford, after quenching, the *E*-allylic alcohol (**123**) in 50 % yield (Scheme 5.8). ^{1}H NMR and GC MS analyses indicated the formation of a new vinylic bond with and *E:Z* ratio of 94:6.



Scheme 5.8. Synthesis of allylic alcohol **123**.

Conversion of **123** to aldehyde **120** was achieved by Swern oxidation[150] in 74 % yield (Scheme 5.9). Since the anisotropic effect of the carbonyl group increases the chemical shift dispersion of the methyl region, the regioselectivity of the addition could be established by ^{1}H-^{1}H COSY, ^{1}H-^{13}C HETCOSY NMR and ^{1}H NMR nOe difference spectra at this stage. Based on COSY and HETCOSY correlations, the new *E*-connectivity of the major isomer was confirmed. A triplet at δ 6.46 (J = 6.7 Hz) was assigned to the two hydrogens on C-4. This signal showed a cross-peak in the COSY spectrum at δ 3.05 and δ 1.76 which indicated that this signal is due to the vinylic hydrogen β to the aldehydic carbon. The nOe difference spectrum confirmed the regiochemistry of the newly formed double bond. When the vinylic hydrogen at δ 6.46 was irradiated, a strong enhancement of the signals of the aldehydic hydrogen (δ 9.40) and the vinylic hydrogen at δ 5.18 were observed, verifying the *E*-geometry of the new trisubstituted double bond (Figure 5.6).

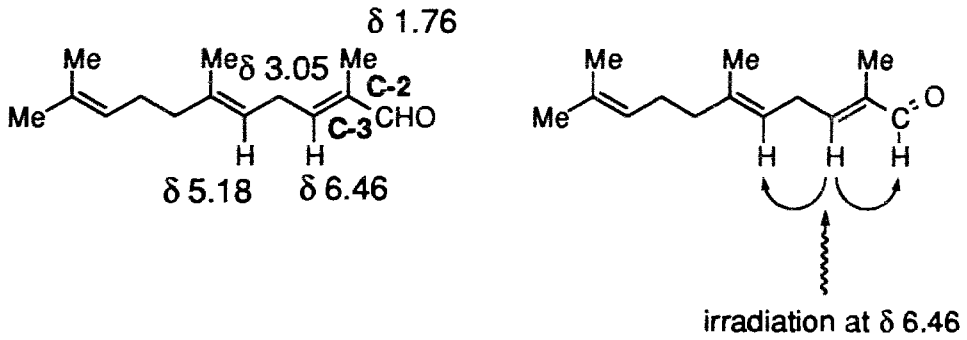
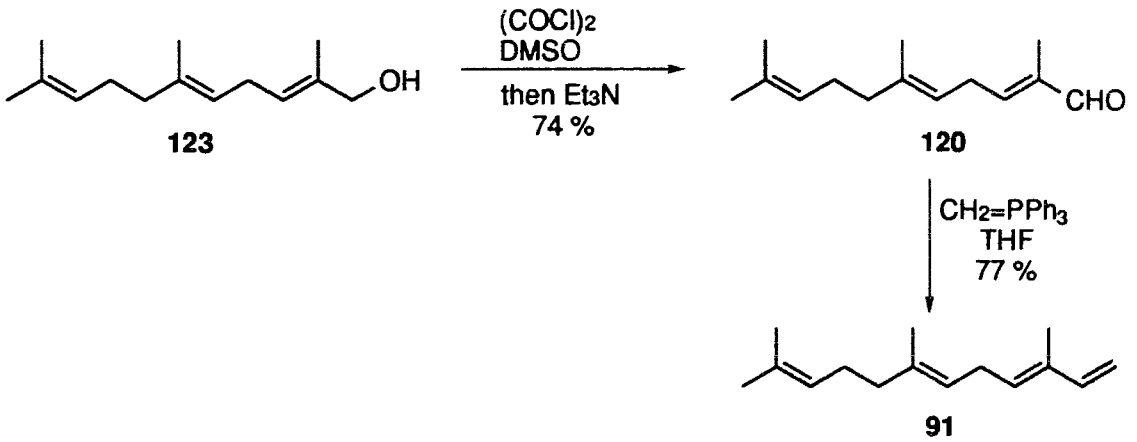


Figure 5.6. COSY and nOe correlations established for aldehyde **120**.

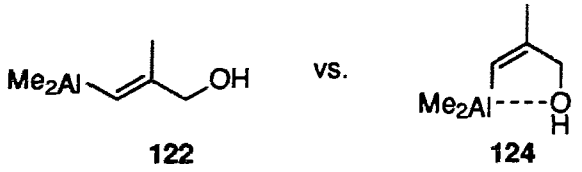
Subsequent Wittig methylenation using methylenetriphenylphosphorane afforded **91** in 77 % yield (28 % yield over three steps) (Scheme 5.9).



Scheme 5.9. Synthesis of *E,E*-farnesene by carboalumination of **121**.

Comparison of the ^{1}H NMR spectrum of **91** with that reported by Matsushita and Negishi[143a] and the MS fragmentation pattern to that reported by Anet[134] confirmed the structure of *E,E*-farnesene and an isomeric purity of 90 %. Although the synthetic target was obtained, the chemical yield is far from satisfactory (Matsushita and Negishi[143a] reported an 86 % yield whereas Spicer and coworkers[139c] reported a 74 % yield using Chou's procedure[145]). In addition, special attention is required for purification of the allylic alcohol, since residues of palladium cause side reactions, decreasing the yield and making

purification difficult. The *E*:*Z* ratio varies from 95:5 to 85:15 and is not easily controlled. This variation may be due to the interaction of the *Z*-alane (**122**) with the hydroxyl at the γ-position (**124**) (Figure 5.7). At this stage a second approach was envisioned.

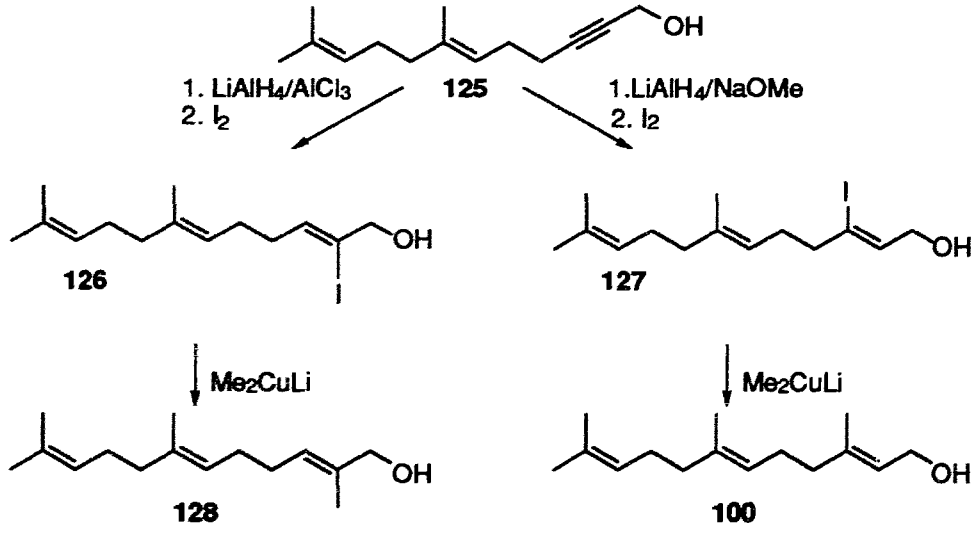


122 **124**

Figure 5.7. Contribution of *Z*-alane during Zr-catalyzed carboalumination.

5.3.3. Reduction of Propargylic Derivatives and Iodination Route.

In 1967 Corey and coworkers[151] introduced a stereoselective method to prepare trisubstituted alkenes *via* $LiAlH_4$ reduction of propargylic alcohols, iodination and subsequent alkylation. This methodology was exemplified by the synthesis of *E,E*-farnesol[151] (**100**) (Scheme 5.10) and the Cecropia juvenile hormone (JH-I).[152] Use of $LiAlH_4/AlCl_3$ resulted in iodination at the β-position (e.g., **126**) whereas $LiAlH_4$/NaOMe allowed substitution at the γ-position (e. g., **127**). Cuprate reaction with **127** gives **100** while reaction with **126** gives **128**.

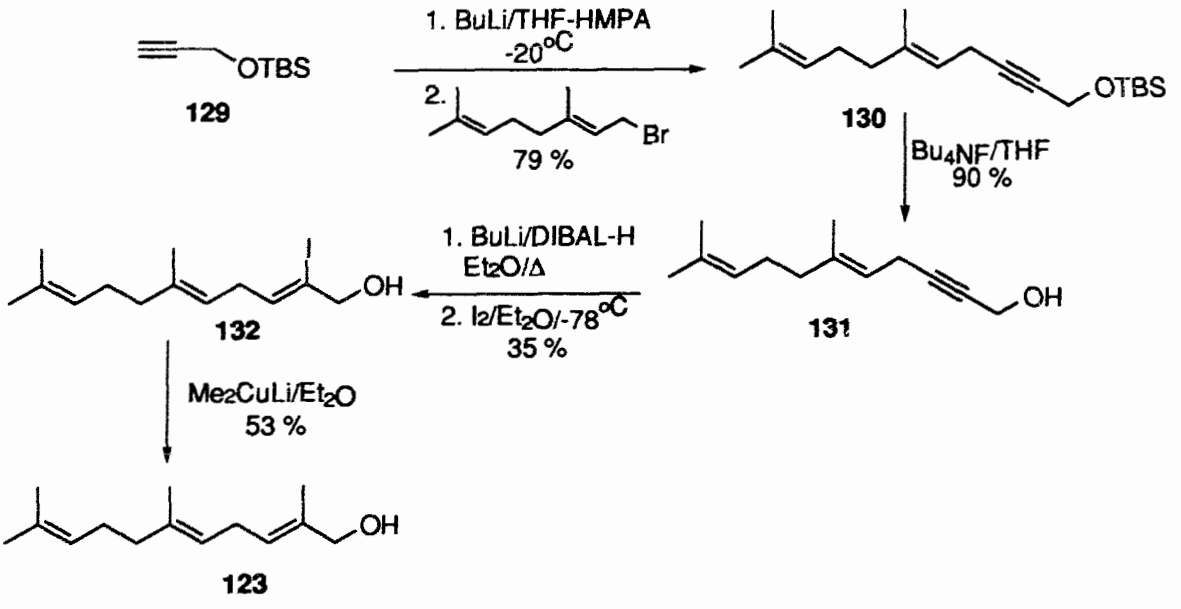


Scheme 5.10. Corey's synthesis of *E,E*-farnesol.

Thus, reduction of the appropriate alkynol with $LiAlH_4/AlCl_3$ would provide access to the β-vinyl iodide which could be methylated with $(CH_3)_2CuLi$ to the corresponding allylic alcohol **123**.

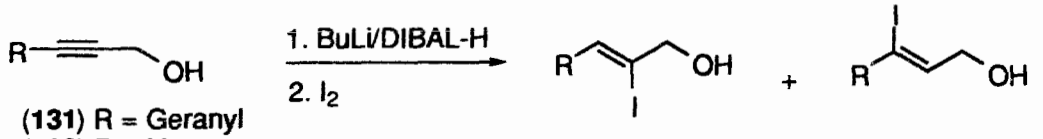
Synthesis of **123** by this route commenced with the protection of propargylic alcohol **121** to **129** in 98 % yield. Deprotonation of the latter with *n*-BuLi in THF-HMPA and alkylation with geranyl bromide (**110**) afforded **130**. Deprotection of **130** with Bu_4NF in THF gave **131**.[153] Reaction of **131** under Corey's protocol[151,152] produced an 1 : 1 mixture of the γ:β-vinyl iodide (**132**), as determined by ^1H NMR and GC analyses of the reaction mixture. Attempts to optimize the ratio of the two isomers failed. Use of DIBAL-H has been recommended by Corey and coworkers[154] to improve selectivity of the iodine substitution, this method was successfully utilized by this group in the total synthesis of α-santalol. Accordingly, reduction of **131** with DIBAL-H followed by treatment with iodine gave **132** in 35 % yield after separation by column chromatography from the γ-isomer. The structure of vinyl iodide **132** was confirmed by ^1H and ^{13}C NMR. ^1H NMR spectral analysis showed a triplet at δ 2.88 (J = 7.5 Hz) corresponding the CH_2 β to the iodide and a triplet for the vinylic hydrogen at δ 5.84 (J = 7.5 Hz) corresponding to the newly formed *E*-double bond. Reaction of **132** with Me_2CuLi in Et_2O at 0°C afforded **123** in 53 % yield (13 % yield over 5 steps) (Scheme 5.11).

Likewise, $LiAlH_4/AlCl_3$ or DIBAL-H reduction produced a mixture of the two isomers. In an attempt to optimize this step, examination of the reaction conditions using three other propargylic alcohols: 2-butyn-1-ol (**133** which gives **134**), 2-pentyn-1-ol (**135** which gives **136**) and 2-heptyn-1-ol (**137** which gives **138**) was performed (Table 5.1).



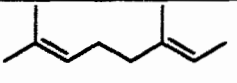
Scheme 5.11. Synthesis of **123** by DIBAL-H method.

Table 5.1. Isomeric composition obtained after DIBAL-H reduction of propargylic alcohols.



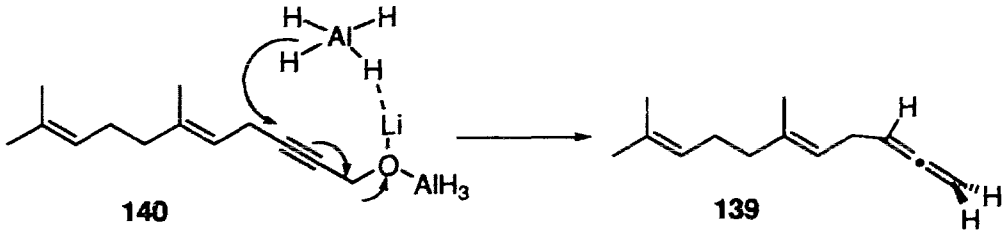
(**131**) R = Geranyl
(**133**) R = Me
(**135**) R = Et
(**137**) R = Bu

β-isomer γ-isomer

Entry	R	β : γ %*
1		55 45 (**132**)
2	Me	49 51 (**134**)
3	Et	64 36 (**136**)
4	Bu	67 33 (**138**)

(*) Relative ratio determined by ^{1}H NMR and GC.

The reaction temperature (20-23°C vs. 38-40°C), DIBAL-H : substrate ratio (1:1, 2:1, 3:1 or 10:1), reaction time (2, 3 or 7 days) and solvent effect (THF *vs.* Et_2O) were modified without significant change in the isomer ratio (Table 5.1 exemplifies some product ratios obtained). Increase in the amount of the allene (e.g., **139**) as a by-product (10-26 %) occurred with prolonged reaction times for the hydroalumination. This terminal allene arises from the elimination of aluminum alkoxide from **140** by a S_N2' mechanism (Scheme 5.12).



Scheme 5.12. Proposed formation of allene **139**.

Compound **139** was identified by its characteristic behaviour on TLC (R_f = 0.89, 8:2, pentane:Et_2O) and ^1H NMR spectrum, which presented a triplet at δ 5.83 (-<u>CH</u>=C=) (1H, J = 7.5 Hz), a multiplet at δ 4.37 (=C=<u>CH_2</u>) and a triplet at δ 2.81 (-<u>CH_2</u>-CH-C=) (2H, J = 7.5 Hz) (Figure 5.8).

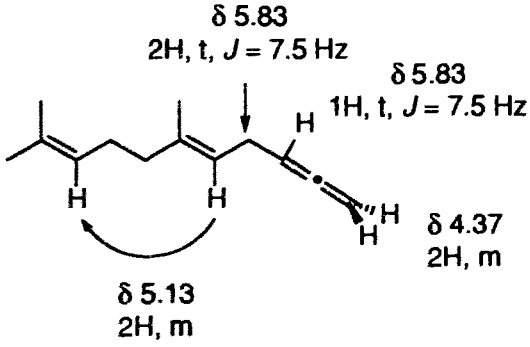
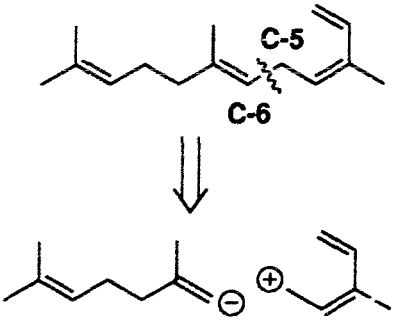


Figure 5.8. ^1H NMR assignment of allene **139**.

At this point a new strategy was devised for the synthesis of *E,E*-farnesene that is discussed in section 5.4.

5.3.4. *Z,E*-Farnesene. Retrosynthetic Analysis.

Based on the work of Morgan and Thompson,[146] a convergent synthesis of *Z,E*-farnesene (**96**) was envisioned. Disconnection between C-5 and C-6 revealed that synthesis of **96** should be possible through coupling of a suitable allylic cation and a vinyl anion equivalent (Scheme 5.13).



Scheme 5.13. Retrosynthetic analysis of *Z,E*-farnesene

A similar strategy was used by Negishi and coworkers in the synthesis of (*Z*)-3-methyl-2-alken-1-ols *via* Pd-catalyzed cross coupling of (*Z*)-3-iodo-2-buten-1-ol with organozinc compounds.[155] Here, the Zr-catalyzed carboalumination of 2-methyl-2-hepten-6-yne[156] (**141**) and the *in situ* Pd-catalyzed cross coupling of the respective alane with (*Z*)-1-chloro-3-methyl-2,4-pentadiene (**142**) was examined.

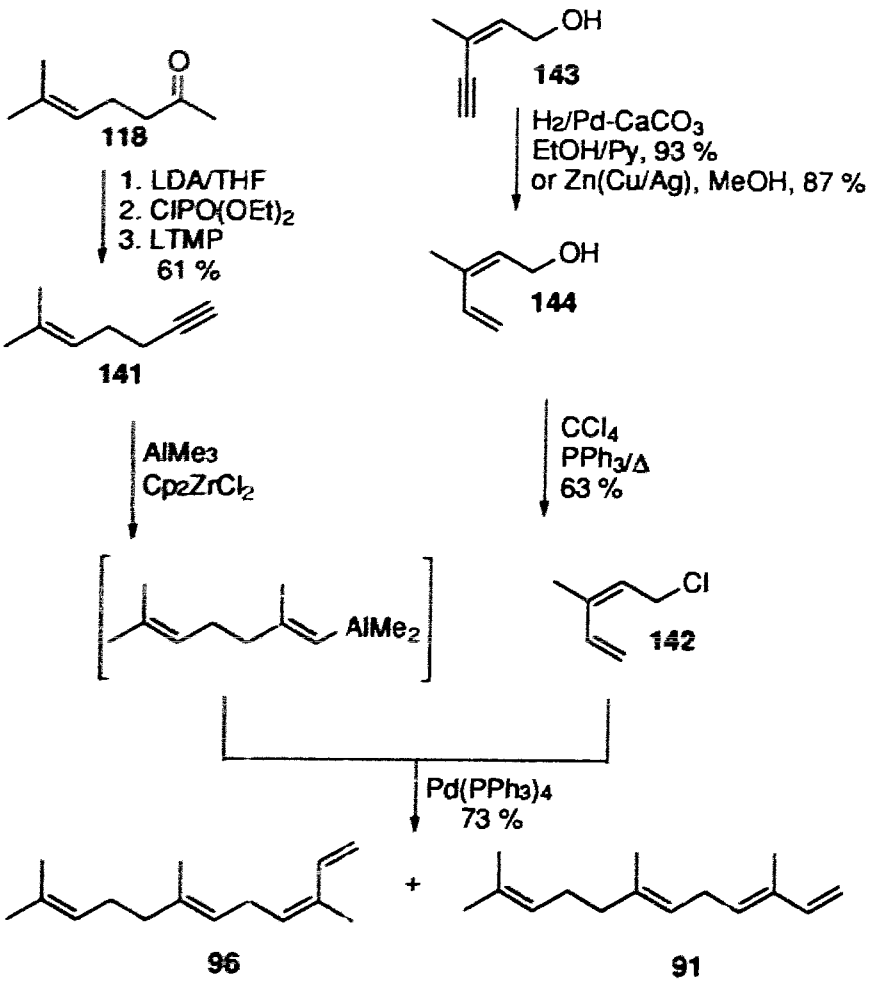
5.3.5. Synthesis of *Z,E*-Farnesene.

The synthesis commenced with the formation of 2-methyl-2-hepten-6-yne[156] (**141**) by the one pot procedure of Negishi and coworkers.[157] Thus, 6-methyl-5-hepten-2-one (**118**) was converted to its corresponding enolphosphate

which underwent β-elimination when treated with excess base to give alkyne **141** in 61 % yield. Commercially available (2*Z*)-3-methyl-2-penten-4-yn-1-ol (**143**) was selectively hydrogenated to **144**[158] in 93 % yield using Lindlar catalyst[159] or in 87 % yield using Zn(Cu/Ag).[160] Allylic chloride **142** was obtained in 63 % (95 % *Z*-isomer) yield by the method of Calzada and Hooz.[161] Carboalumination of **141**, followed by Pd-catalyzed coupling with **142** afforded a 1:1 mixture of *Z,E*- and *E,E*-farnesene in 73 % yield (Scheme 5.14). Separation of the mixture by column chromatography, according to the conditions reported by Evershed *et al.*[162], gave 40 mg of **96** (95 % isomerically pure) (Figure 5.9). The ^{1}H NMR spectrum[146] and MS fragmentation[134] are in agreement with the structure of *Z,E*-farnesene.

Cross coupling of γ,γ-disubstituted allylpalladium derivatives occurs with minimal stereochemical scrambling.[143a,163,164] Negishi[163] proposed that this reaction proceeds first by an oxidative addition to form the σ-allylpalladium complex (e.g. **145** σ-***Z***, Scheme 5.15), followed by attack of the alane *via* transmetallation and then reductive-elimination to form the corresponding alkene (**96**).

In opposition to Negishi's proposal,[143a] and to rationalize the isomerization suffered during the coupling, a π-allyl complex must be postulated as one of the plausible intermediates during the reaction. Rapid σ–π–σ (or π–σ–π) conversion would allows *E,Z* isomerization giving rise to an equilibrium between the σ–*Z* (**145** σ-***Z***) and σ-*E* (**145** σ-***E***) complexes. The preference of *E*- or *Z*- geometry is governed by the rate of isomerization, which depend on the lifetime of the π–complex,[164b] the favourable *syn* conformation of the η^3 complexes due to steric hindrance,[164g] and by the temperature of formation of the complex and the one of the cross-coupling reaction.[164k,l]



Scheme 5.14. Synthesis of *Z,E*-farnesene.

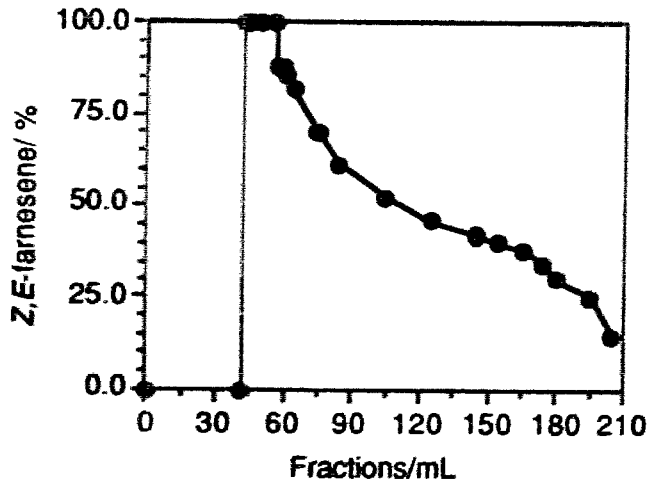
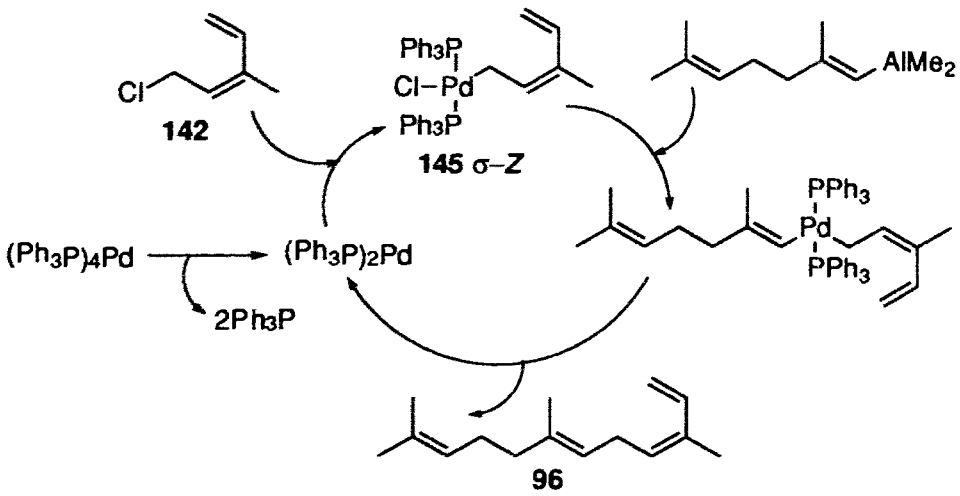
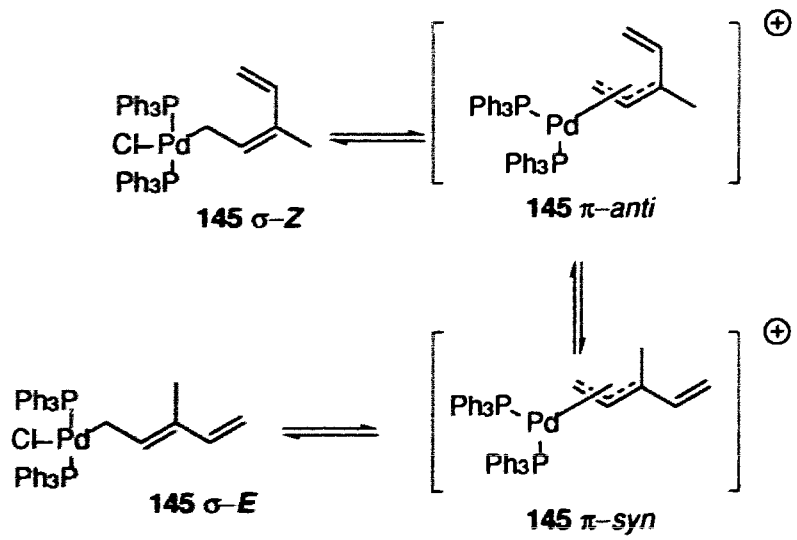


Figure 5.9. Separation of *Z,E*- and *E,E*- farnesenes by column chromatography.



Scheme 5.15. Formation of *Z,E*-farnesene by Pd-catalyzed reaction of alane intermediate and allyl chloride **142**.



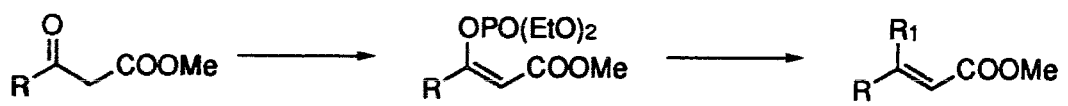
For isomerically fragile γ-monosubstituted allyl-Pd complexes both processes must be conducted below -45°C to avoid *E-Z* isomerization.[164k,l]

The coupling reaction was first performed, according to Negishi's procedure,[143a] which recommended use of room temperature. This led to a ~1:1 mixture of both farnesenes (Scheme 5.14). Execution of the reaction at 0°C, -20°C, -78°C (all reagents were pre-cooled at those temperatures before mixing) afforded no suppression of the isomerization. Inability to obtain *Z,E*- and *E,E*-farnesene, in appropriate chemical and isomeric yield by this route was the driving force to consider other alternatives as described below.

5.4. Selective Enolization of α,β-Unsaturated Ketones. Possible Route Toward the Synthesis of *Z,E*- and *E,E*-Farnesene.

The regio- and stereoselective enolization of a ketone, followed by trapping and alkylation can be envisioned as a route to the farnesenes. Enolphosphates and enoltriflates easily undergo coupling with dialkylcuprates[165] and react, under palladium catalysis, with organostannanes[166] to afford trisubstituted alkenes. This route will focus on the choice of enol derivatives to form the farnesenes.

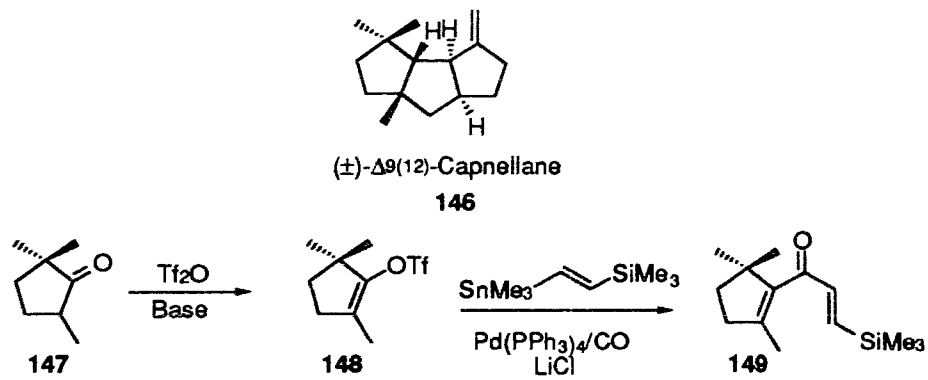
Sum and Weiler[165b] reported the synthesis of β-substituted-α,β-unsaturated esters by coupling dialkylcuprates and enolphosphates of β-ketoesters (Scheme 5.16).



Scheme 5.16. Weiler's synthesis of β-substituted α,β-unsaturated esters.

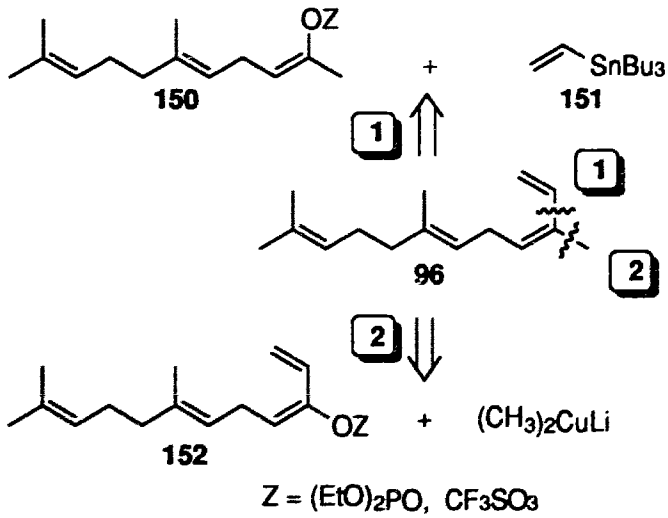
Scott and coworkers[166e] made use of the palladium-catalyzed reaction of organostannanes and enoltriflates in the total synthesis of (±)-$\Delta^{9(12)}$-capnellane

(**146**), in a repeated coupling sequence starting with cyclopentanone **147** and proceeding through intermediates **148** and **149** (Scheme 5.17).



Scheme 5.17. Stille's coupling of enoltriflates.

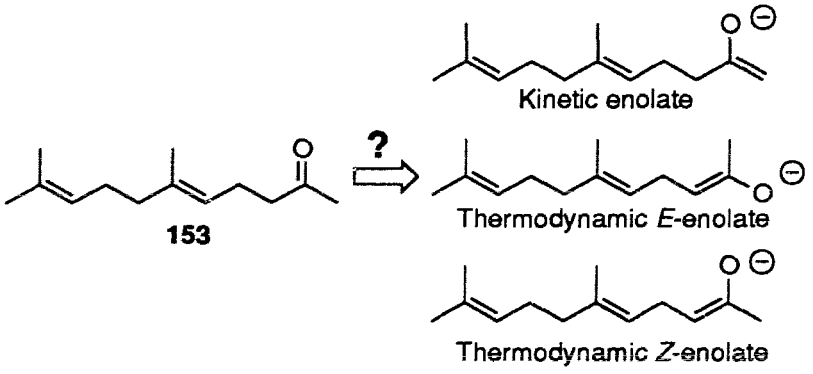
Retrosynthetic analysis of **96** under the premise of stereoselective enolate trapping, revealed the possibility of two pathways (Scheme 5.18). The first route requires reaction of the *Z*-enolate (**150**) with vinyl stannyl **151**. The second requires alkylation of the *E*-enolate of the appropriate α,β-unsaturated ketone (**152**). Similarly, formation of the *E*-enolate of **150** or the *Z*-enolate of the α,β-unsaturated ketone **152**, would allow stereoselective synthesis of *E,E*-farnesene.



Scheme 5.18. Retrosynthetic analysis of **96** based on stereoselective enolate trapping.

5.4.1. Strategy 1. Enolization of Geranylacetone.

To successfully execute this strategy preferential regiochemical (kinetic vs. thermodynamic) and stereoselective enolization (*E* vs. *Z*) must be achieved. (Scheme 5.19).



Scheme 5.19. Possible enolates from geranylacetone

Masamune and coworkers[167] reported selectivities of 70-90 % *Z* for 3-pentanone and cyclohexyl ethyl ketone by modification of the size of the substituents of the disilazide use as a base (e.g., Me_3Si vs. Me_2PhSi), while Evans *et al.*,[168] achieved *Z*-selectivities of 69-99% in the formation of boron enolates from aliphatic ketones using lutidine or diisopropylethylamine as bases. Capture of enolates with ethyl trimethylsilylacetate and tetrabutylammonium fluoride[169] also yielded enol derivatives with 86-100 % *Z* selectivity. High *E*-selectivity has been achieved by Corey and Gross[170] in the enolization of 3-pentanone employing lithium *tert*-octyl-*tert*-butylamide (LOBA) (2:98 *Z : E*).

Heathcock and coworkers[171] found lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylpiperidide (LTMP) produced predominantly (70-80:30-20, *E:Z*) *E*-enolate (**154*E***) with 3-pentanone (**43**) but predominantly (98:2 *Z : E*) *Z*-enolate (**154*Z***) with propiophenone. Generally, an increase in the size of the substituents attached to the carbonyl carbon increases the proportion of reaction proceeding *via* the *Z*-transition state when LDA or LTMP are used (e.g., 3-

pentanone vs. propiophenone) (Figure 5.10).[171] This is attributed to the low energy conformation of the ketone being the one in which methyl group, in this example (or C-C in general), is coplanar with the C-O bond, making the *Z*-enolate (**154*Z***) more favorable. The explanation given by Heathcock *et al.*[171] for the formation of the *E*-enolate (**154*E***), is based on steric interactions between the approaching base and the methyl group (e.g., CH_3 in **43**, R in general), since the base needs to approach the ketone over the face of the incipient enolate plane and not along the axis of the C-H bond (Figure 5.10).

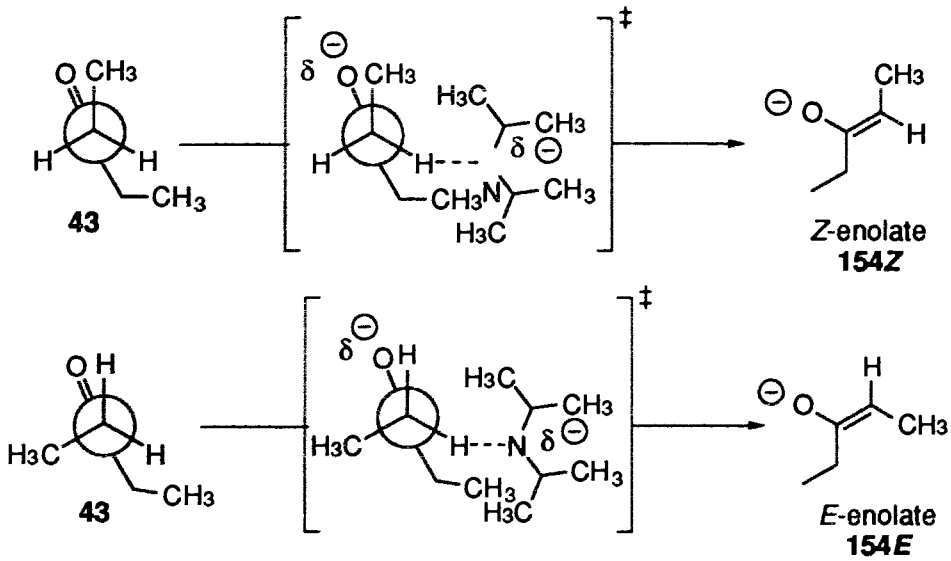


Figure 5.10. Heathcock's transition states.

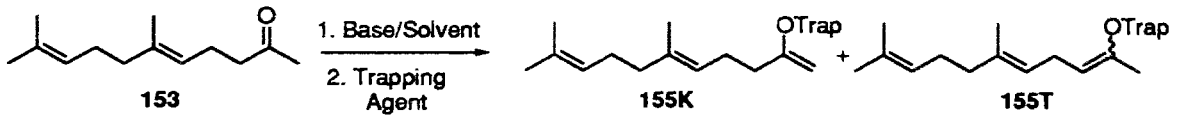
Molecular mechanical calculations,[172] suggest that *Z*-enolate formation is favored under thermodynamic conditions and by the use of small bases, non-complexing counter ions and solvents that can effectively solvate the cation. Under kinetic conditions, *Z*-enolates are favored if the carbonyl compound contains bulky substituents. The opposite is true for *E*-enolates. Under kinetic conditions, *E*-enolates are favored by coordinating counter ions, bulky bases and non-bulky ketone substituents. The influence of sterically demanding amides is

contradictory. Masamune and coworkers,[167] found that the *Z/E* ratio is significantly enhanced with increasing substituent size of the disilazides used, whereas Corey and Gross[170] and Nakamura *et al.*[169] found the opposite. Accordingly, it is expected that *E*-enolates will predominate when either LDA or LTMP react with saturated ketones with non-bulky substituents.

Formation of the thermodynamic *Z*-enolate of phenylacetone has been achieved by use sodium hexamethyldisilazide at room temperature, whereas use of lithium hexamethyldisilazide gave the thermodynamic *E*-isomer in a 90:10 *E*:*Z* ratio.[173] Use of bromomagnesium diisopropylamide has proven to be effective in the formation of thermodynamic enolates of α-substituted cyclic ketones.[166a,b;174] In addition to these two methods, the work of House and coworkers[175] bears on selective kinetic *vs.* thermodynamic enolate trapping. For the present work, lithium diisopropylamide (LDA), lithium 2,2,6,6-tetramethylpiperidide (LTMP), bromomagnesium diisopropylamide (*i*-Pr_2NMgBr) and KH were selected as bases for the enolization experiments and trapping groups were $ClPO(OEt)_2$ and $(CF_3SO_2)_2NPh$.

As can be seen in Table 5.2, the kinetic enols (**155 K**) were the only products obtained in all solvents (including the presence of HMPA, data not shown), reaction times and temperatures (-78°C, -30°C or equilibration at room temperature) when $ClPO(OEt)_2$ was the trapping reagent. Generation of the enoltriflate failed when *i*-Pr_2NMgBr, LDA or LTMP were used under the reaction conditions in Table 5.2. Unreacted starting material was recovered in most of the cases. Use of KH gave a 1:1 mixture of both kinetic (**155 K**) and thermodynamic (**155 T**) enolates; higher temperatures and prolonged reaction times caused the formation of several by-products without significant changes in the enolate ratio. Unambiguous differentiation of *E* and *Z* enolates products is possible by

Table 5.2. Enolization of geranylacetone (**153**).



153 155K 155T

Base/Solvent	Trapping Agent	*Ratio K : T / %
LDA/THF	$ClPO(OEt)_2$	97: 3
LDA/Et_2O	$ClPO(OEt)_2$	97: 3
LTMP/THF	$ClPO(OEt)_2$	96: 4
LTMP/Et_2O	$ClPO(OEt)_2$	97: 3
LDA/THF	TMSCl	95: 5
LTMP/Et_2O	TMSCl	95: 5
LDA/Et_2O	Tf_2NPh	N.R.
LTMP/Et_2O	Tf_2NPh	N.R.
i-Pr_2NMgBr	Tf_2NPh	N.R.
KH	$ClPO(OEt)_2$	43: 57
KH	Tf_2NPh	48: 52
KH/Δ, 16 h	Tf_2NPh	54: 46

(*) Product ratio determined by GC or ^1H NMR.

^{1}H NMR analysis (Figure 5.11). Based on these analyses, it was concluded that the thermodynamic *Z*-enolate was obtained in both triflate and chlorophosphate quenching reactions. The vinylic hydrogen, β to the oxygen and the γ methylene group in both derivatives presented characteristic chemical shifts. In the *Z*-isomer, the vinylic signal shifted upfield and the methylene signal shifted downfield compared to the *E*-isomer. ^{1}H NMR spectral comparisons of *E*- and *Z*-enolphosphates of α,β-unsaturated ketones derived from this work support this assignment. Lack of complete regiochemical control under the above conditions spurred investigation of a related strategy.

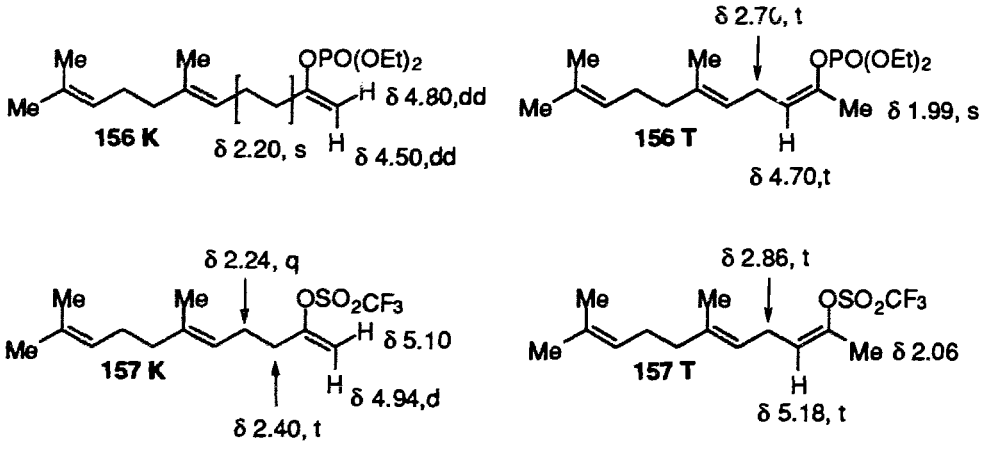


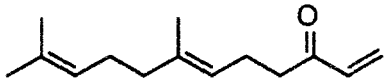
Figure 5.11. ^{1}H NMR comparison of kinetic and thermodynamic enolphosphates and enol triflates of **153**.

5.4.2. Selective Enolization of α,β-Unsaturated Ketones.

In comparison with studies of the regio- and stereoselectivity of enolizations of saturated ketones, there are few investigations of enolization of α,β-unsaturated ketones.[176] The production of silyl enol ethers from α,β-unsaturated ketones[177a-b] proceeds with poor *Z/E* selectivity while enolphosphate formation from methyl vinyl ketone[177c-d] pose no regiochemical or stereochemical problems.

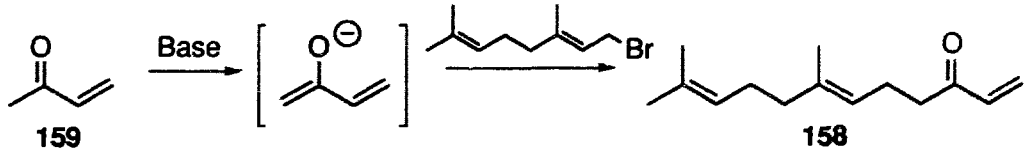
5.4.3. Synthesis of (6*E*)-7,11-Dimethyl-1,6,10-dodecatrien-3-one (158).

According to the proposed route in Scheme 5.18, the synthetic equivalent of the disconnected enolate is (6*E*)-7,11-dimethyl-1,6,10-dodecatrien-3-one (**158**).



158

This ketone has been synthesized by using: a) Diels-Alder reaction of methyl vinyl ketone and cyclopentadiene, followed by alkylation with geranyl bromide and a retro Diels-Alder reaction to give **158** in 60 % yield over 3 steps;[178] b) a five step procedure that commenced with condensation of diethyl malonate with geranyl bromide and subsequent transformation in a ~7 % yield over 5 steps[179] and c) a procedure similar to the one described in b), but wherein the first step consisted of a Claisen rearrangement giving a yield of 32 % over 5 steps.[180] In this work, alkylation of the enolate of methyl vinyl ketone (MVK, **159**) was anticipated to result in a one step production of **158** (Scheme 5.20).



159 **158**

Scheme 5.20. Proposed synthesis of **158**.

Several reactions were conducted without obtaining the anticipated coupling product (geranyl bromide was used in all the reactions as electrophile in a 1:1 or 1:1.2 MVK: geranyl bromide ratio) (Table 5.3). Variation of solvent and base, presence of HMPA (entry 3), presence of Lewis acid (entry 4), reaction

times, and the use of the trimethyl silyl ether of **159** (**160**) proved to be ineffective in promoting coupling.

The results obtained may be the result of rapid "Cα-protonation" due to an increase in the acidity of the N-H bond, in a phenomena that it is known as 'internal return" (addition of an electrophile to an enolate generated by an amide may increase the electron demand on the amine formed from the amide-enolate complex, causing an increase in the effective acidity of the N-H bond).[181] This "internal return" is held responsible for the frequent failure of deuteration of enolates generated by LDA and the reaction of enolates with electrophiles.[181a]

Table 5.3. Attempts to alkylate the enolate of MVK (**159**).

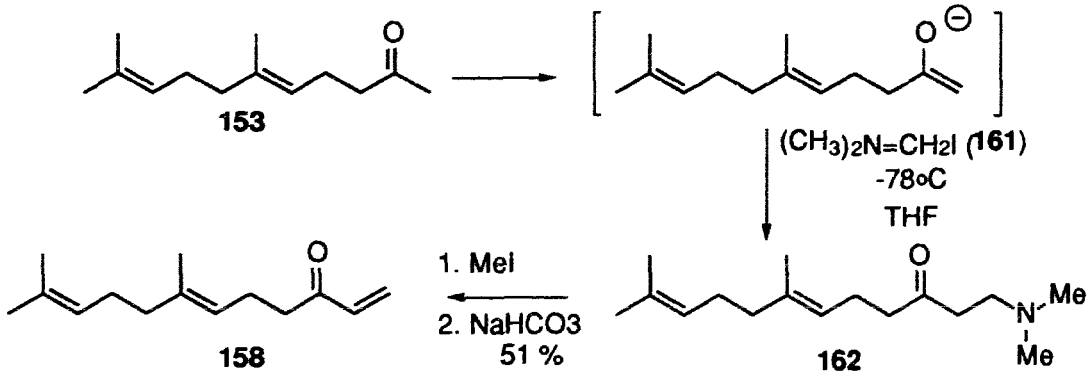
Entry	Susbtrate	Base	Solvent	T/°C	Result*
1	MVK	LDA	THF	-78	N.R.
2	MVK	LDA	Et_2O	-78	N.R.
3	MVK	LDA	THF HMPA	-78	N.R.
4	MVK	LDA	THF $ZnCl_2$	-78	N.R.
5	MVK	LTMP	THF	-78	N.R.
6	MVK	LTMP	Et_2O	-78	N.R.
7	MVK-TMS[a]	MeLi	THF	-78	N.R.

(*) Determined by GC analysis.
(a) 2-Trimethylsilyloxy-1,3-butadiene.

A shorter and more simple route for preparation of **158** was achieved by reaction of Eschenmoser's salt [*N,N*-dimethylmethyleneammonium iodide, $(CH_3)_2N{=}CH_2I$] and geranylacetone, **153**, following the method of Roberts and coworkers.[182] Similar procedures have been used to synthesize α-methylene

ketones *via* Wittig reactions[183a] or *via* Mannich reactions using *N*-methylanilinium trifluoroacetate as a Mannich salt.[183b-d] The results of these experiments are presented in Table 5.4.

Geranylacetone, **153**, was enolized (e.g., LDA, Table 5.4) and allowed to react with the Eschenmoser's (**161**) salt in THF. Upon work-up, the γ-ketoamine (**162**) was isolated and used to the next step without further purification. Permethylation with MeI and Hofmann elimination afforded **158** in 51 % yield (90 % isomeric purity) based on **153** after column chromatography (**163** was obtained in 48 % yield, 94 % isomeric purity, when LTMP was used as a base) (Scheme 5.21, Table 5.4).



Scheme 5.21. Synthesis of **158** *via* Mannich reaction of **153** and Eschenmoser's salt.

After several modifications, a mixture of **158** and **163** were obtained in ~50 % yield when LDA or LTMP were used as the base. The ratio change observed when LTMP was used is not understood since enolate trapping of geranylacetone (**153**), either using of LDA or LTMP, gave the kinetic enolate (**155 K**) in 90-95 % (see Table 5.2). ^{1}H NMR analysis clearly demonstrates the correct identification of **163** (Figure 5.12). Assignments of connectivity were verified by ^{1}H-^{1}H COSY and ^{1}H-^{13}C HETCOSY NMR spectra of **158** and **163**.

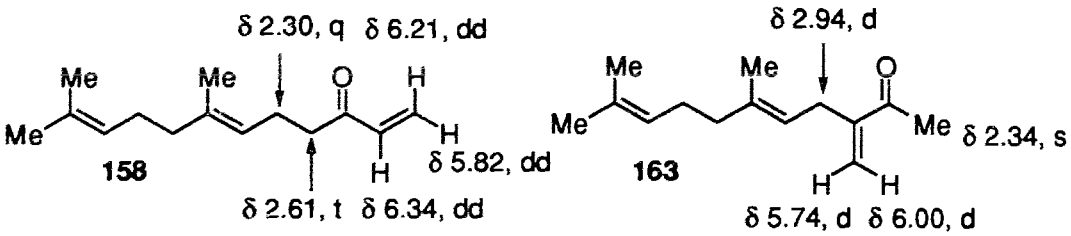
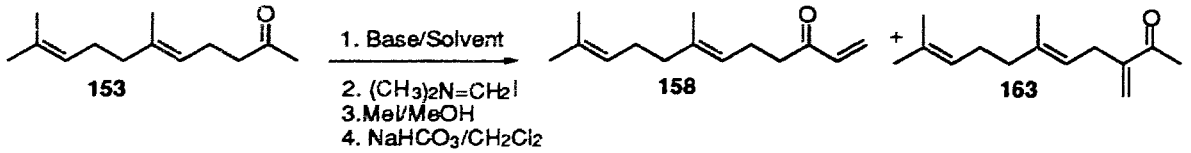


Figure 5.12. ^{1}H NMR comparison between **158** and **163**.

Table 5.4. Mannich approach toward the synthesis of **158**.



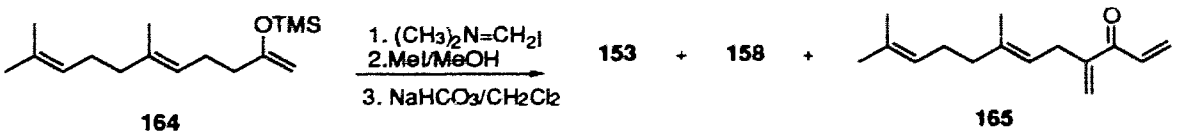
Base/Solvent	**158** : **163***
LDA/THF	81 : 19
LTMP/THF	17 : 83

(*) Use of HMPA as a co-solvent did not alter the product ratio in both cases. Product ratio was determined by GC and ^{1}H NMR.

Modification of the above procedure by reaction of the trimethylsilyl enolether (**164**) and Eschenmoser's salt was also studied.[184] Thus, **164**[185] was allowed to react with *N,N*-dimethylmethyleneammonium iodide in a 1:2 or 1:1 ratio. Double addition was obtained in the presence of an excess of Eschenmoser's salt, leading to **165** (55 % yield, 95 % pure after column chromatography) as a major product. Equivalent amounts of both reactants avoided double addition, but ~40 % the of the parent ketone was recovered (Table 5.5). The ^{1}H NMR spectrum of **165** revealed a doublet at δ 3.08 (J = 9.6 Hz) due to the CH_2 group β to the carbonyl. Integration of the vinylic region indicated the presence of seven hydrogens, including resonances characteristic

of the presence of an *exo*-methylene α' to the carbonyl at δ 5.80 (d, J = 0.8 Hz) and δ 5.96 (d, J = 0.8 Hz), and an methylene group [δ 5.80 (dd, J = 9.6, 0.8 Hz, δ 6.30 (dd, J = 16, 0.8 Hz) and δ 6.30 (dd, J = 16, 9.6 Hz)] both α to a carbonyl. Assignment of connectivities was verified by ^1H-^1H COSY and ^1H-^{13}C HETCOSY NMR spectra.

Table 5.5. Modified Mannich reaction



164 165

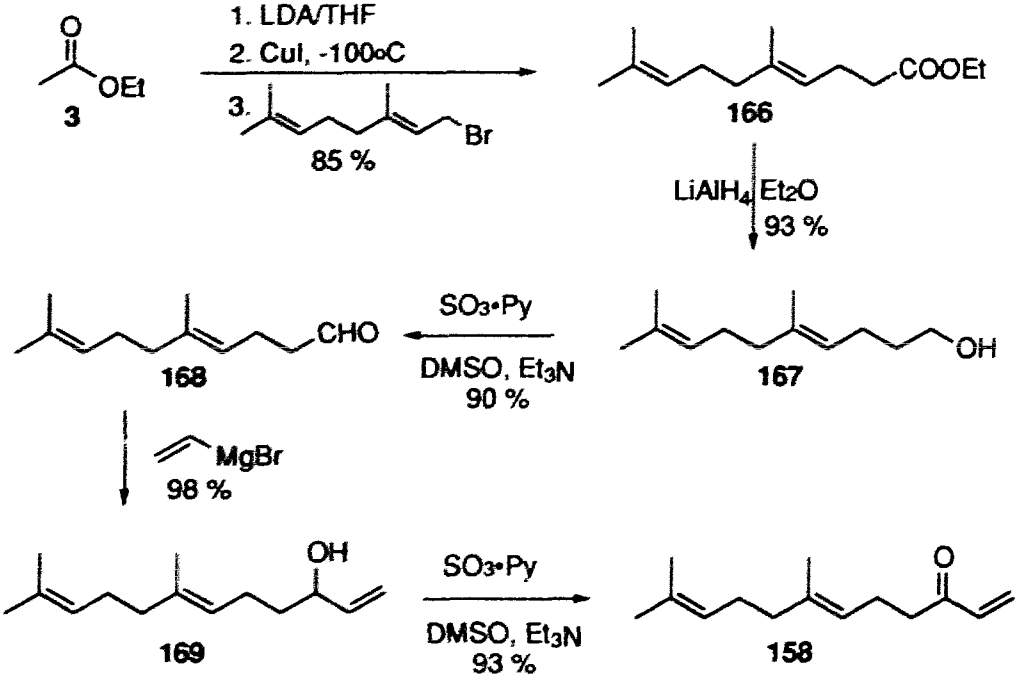
164 : Eschenmoser's salt	**153 : 158 : 165***
1 : 2	39 : 0 : 61
1 : 1	60 : 40 : 0

(*) Ratio was determined by GC analysis of reaction mixtures. Structure determination was by ^1H NMR analysis of purified compounds.

Since the Mannich reaction failed to give isomerically pure **158** in a reasonable yield, a modification of previous methods[179,180] was pursued.

The synthesis of **158** commenced with the alkylation of geranyl bromide by the lithium enolate of ethyl acetate (**3**) in the presence of CuI at -100°C to give **166**.[186] Reduction of **166** with $LiAlH_4$ gave the alcohol **167**. Oxidation of **167** using pyridine-sulfur trioxide complex and triethylamine in dimethyl sulfoxide[187] produced the desired aldehyde **168**. Grignard reaction of **168** with vinyl magnesium bromide gave the allylic alcohol **169** which was oxidized with pyridine-sulfur trioxide complex as in **169** to give **158** (65 % overall yield over 5 steps, Scheme 5.22). Efforts to reduce **166** directly to **168** using DIBAL-H (1 M

solution in THF or hexane, reaction temperature -78°C or -20°C) gave a mixture of unreacted ester and **167**, with trace amounts of aldehyde **168**. Reaction of vinyl magnesium bromide with **166** failed to give **158** (similar results were obtained in the presence of trimethylsilyl chloride).



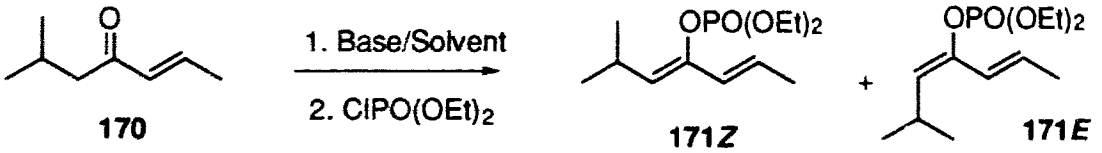
Scheme 5.22. Synthesis of **158**.

5.4.4. Strategy 2. Selective Formation of Enolphosphates of α,β-Unsaturated Ketones.

Initially, the effect of base and solvent on the *Z* : *E* selectivity of enolization of (*E*)-6-methyl-2-hepten-3-one (**170**) was investigated. Enolates were generated by reaction of **170** with LDA or LTMP in Et_2O or THF. This was followed by quenching with diethylchlorophosphate and analysis by gas chromatography and 400 MHz ^1H NMR spectroscopy to estimate the enolate ratio (both methods gave the same ratio of enolphosphates within experimental error). Use of LDA in Et_2O or THF (entries 1 and 2, Table 5.6) furnished mainly *Z*-enolphosphate (**171*Z***), while LTMP in Et_2O (entry 3, Table 5.6) rendered ~1 : 1

mixtures of **171*Z*** and **171*E***. Only the reaction of **170** with LTMP in THF furnished **171*E*** as a major product (entry 4).

Table 5.6. Effect of solvent and base on *E,Z*-selectivity of enolphosphate formation from **170**.



170 **171*Z*** **171*E***

Entry	Base/Solvent	% *Z* : *E*(*)	
1	LDA/Et_2O	89	11
2	LDA/THF	75	25
3	LTMP/Et_2O	43	57
4	LTMP/THF	13	87

(*) *Z* : *E* ratio were determined by GC and ^1H NMR. The two analytical methods revealed the same ratios within experimental error.

When each of these conditions were applied to **158**, (Table 5.7), use of LDA in Et_2O gave 95 % **172*Z*** (entry 1) while LTMP in THF gave ~1:1 mixtures of *E* and *Z* isomers of **172** (entry 2). Lithium dicyclohexylamide in THF (entry 3) also favoured the formation of the *Z*-enolate.

Lewis acids influence the stereoselectivity of enol formation.[188] Addition of $ZnCl_2$ to the enolate generating reactions listed in Table 5.6 did not appreciably alter the *Z* : *E* ratios (entries 4 - 7, Table 5.7).

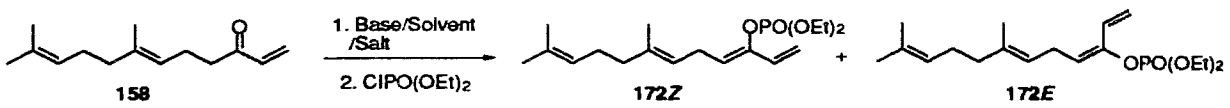
According to Collum and coworkers,[188h] substantial increases in *E* selectivity can be achieved when enolization of saturated ketones is conducted at

low ketone:base ratios. However, alteration of the **158**:base ratio, in the presence of Lewis acids, did not significantly increase the proportion of *E* enol product (Table 5.7).

Lithium cation coordination is considered to be an important influence on *E:Z*-enolate selectivity. Ireland *et al.*[188f,189] suggested that the increase in *Z*-enolate preference upon addition of HMPA demonstrates that strong solvation of lithium cation is a significant factor leading to formation of *Z*-enolates. Collum and coworkers[188g-h] obtained ^{6}Li and ^{15}N NMR evidence which suggests aggregation of LDA/LTMP and lithium salts. This group reported *Z/E* selectivities of 1:50 to 1:20 which were attributed to lithium cation coordination.[188h] In the present work, addition of 0.3-0.5 equivalents of LiBr or LiCl to reactions did not alter the *Z:E* enol ratio (entry 8). However, the *in situ* generation of LiBr from the bromonium salt of 2,2,6,6-tetramethylpiperidine (TMP•HBr), which avoids the necessity of handling of hygroscopic lithium salts gave a significant decrease in *Z/E* ratio (entry 9).

This methodology was extended to ketones **173-175** (Table 5.8). These ketones (**173-175**) were synthesized by oxidation (SO_3•Py complex) of (*E*)-4-octen-3-ol (**176**), (*E*)-2-octen-4-ol (**177**) and 1-octen-3-ol (**178**), respectively. Alcohols **176-177** were synthesized by Grignard reaction of the Grignard reagents derived from the respective alkyl bromides and aldehydes (for details see experimental section). *Z*-Enolate selectivities of 92-95 % were obtained using LDA-Et_2O (Table 5.8). *E*-Enolphosphates were obtained with selectivities of 80-90 % by use of TMP•HBr (*in situ* protocol). Isomeric ratios of enols were determined by analysis of crude reaction mixtures by gas chromatography and ^{1}H NMR. Purification of the enolphosphates by flash chromatography afforded *Z*-enolphosphates in 95-99 % isomerically pure form and *E*-enolphosphates 93-98 % isomerically pure. Structural assignments and isomeric purity were verified by

Table 5.7. Effect of base, solvent and salt on *Z/E* selectivity in enolphosphate formation from **158**



158 172Z 172E

Entry	Base/Solvent/Salt	Ratio *Z* : *E**	
1	LDA/Ether/NA[a]	95	5
2	LTMP/THF/NA[a]	55	45
3	Dicyclohexylamine/THF[a]	95	5
4	Lidicyclohexylamide/THF/$ZnCl_2$[a]	95	5
5	Lidicyclohexylamide/THF/$ZnCl_2$[b]	-	-[c]
6	LTMP/THF/$ZnCl_2$[a]	40	60
7	LTMP/THF/$ZnCl_2$[b]	50	50
8	LTMP/THF/LiX[d]	35	65
9	TMP•HBr/THF[a]	15	85
10	TMP•HBr/THF[b]	-	-[c]

NA: No salt added.
(*) Determined by ^1H NMR.
(a) Ratio ketone/base/phosphate 1: 1: 1.
(b) Ratio ketone/base/phosphate 1: 2: 2.
(c) No formation of the enolphosphate was detected.
(d) LiX: LiBr or LiCl. See text for comments.

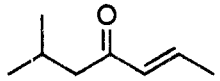
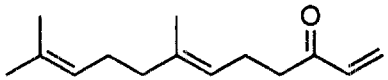
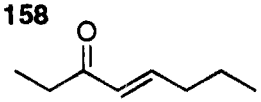
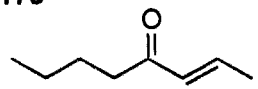
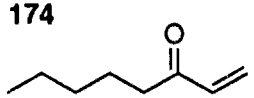
^{1}H NMR spectroscopy. nOe difference spectra or NOESY correlation of all enolphosphates confirmed geometry (Figure 5.13).

The ^{1}H NMR signals assignable to the vinylic hydrogens and hydrogens α to the phosphates of *Z*-enol phosphates are at a higher field than the corresponding signals of the *E* isomers (Figure 5.14).[190] The signal attributable to the methylene or methyl group β to the enol linkage is at lower field in the *Z*-isomers than in the *E*-isomer.

Attempts to increase yields by increasing reaction time (1h, 2h or overnight stirring), alteration of the amount of HCl used in the work-up, and variation in the sequence in which reactants were added did not significantly alter yields. Similar yields were reported by Liu and coworkers[177c] for the preparation of the enolphosphate of 3-buten-2-one (44 %). However, Ireland and Pfister[191] reported a 95 % yield for the preparation of the enolphosphate of coprostanone using NaH in DME and an 85 % yield of the enolphosphate of geranylacetone (**153**) was obtained when LDA, LTMP or TMP•HBr were used.

Analysis of the postulated transition states[171] for the formation of both *Z*- and *E*-enolates may help to understand the results obtained (Figure 5.15). Newman projections of **158** along C-3 and C-4 (Figure 5.15) depict proton abstraction by LDA and LTMP. In the lowest energy conformation for **158** either a large group or a small groups are coplanar to the C-O bond. By analogy with related systems the conformation in which the chain is eclipsed with the C-O bond and leads to *Z*-enolate formation is assumed to be the most stable conformer (**182*Z*** and **183*Z***, Figure 5.15) (formation under thermodynamic conditions). Moreland and Dauben,[172] have suggested *Z*-isomers arising from the more stable ketone conformers (e.g., **182*Z***) may be favoured under kinetic conditions if the size of the substituents attached to the substrates increase. In the

Table 5.8. *Z/E* Enolization of α,β-unsaturated ketones

Entry	Ketone	Reaction Conditions*	$OPO(OEt)_2$ H *Z*-enolphosphate	$OPO(OEt)_2$ H *E*-enolphosphate
1	 **170**	LDA/Ether LTMP/THF TMP•HBr/THF	89 (95)[a] (**171*Z***,48)[b] 13 (5) 8 (5)	11 (5) 87 (95)[a] (**171*E***, 45)[b] 92 (95)[a] (**171*E***, 49)[b]
2	 **158**	LDA/Ether LTMP/THF TMP•HBr/THF	95 (**172*Z***, 44)[b] 55 15 (5)[a]	5 45 85 (95)[a] (**172*E***, 40)[b]
3	 **173**	LDA/Ether LTMP/THF TMP•HBr/THF	92 (99)[a] (**179*Z***, 44)[b] 35 (3)[a] 10 (2)[a]	8 (< 1)[a] 65 (97)[a] (**179*E***, 45)[b] 90 (98)[a] (**179*E***, 46)[b]
4	 **174**	LDA/Ether LTMP/THF TMP•HBr/THF	92 (99)[a] (**180*Z***, 42)[b] 56 (10)[a] 17 (6)[a]	8 (< 1)[a] 44 (90)[a] (**180*E***, 45)[b] 83 (94)[a] (**180*E***, 44)[b]
5	 **175**	LDA/Ether LTMP/THF TMP•HBr/THF	95 (**181*Z***, 43)[b] 80 (7)[a] 20 (7)[a]	5 20 (93)[a] (**181*E***, 41)[b] 80 (93)[a] (**181*E***, 43)[b]

(*) *Z* : *E* ratio was determined by GC or ^{1}H NMR. The two analytical methods provided the same results within experimental errors.
(a) After column chromatography.
(b) Isolated chemical yield.

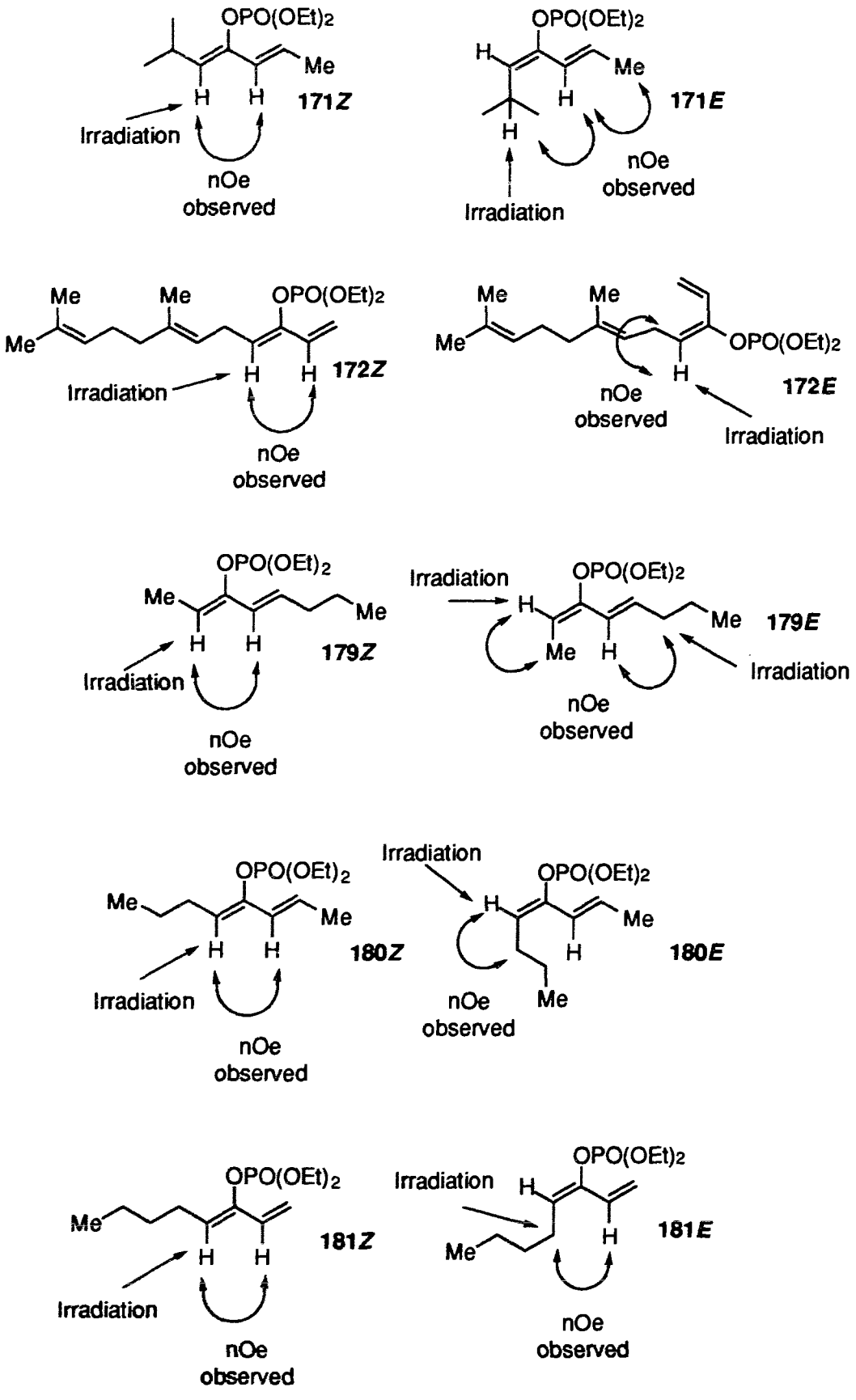


Figure 5.13. Observed nOe's of enolphosphates.

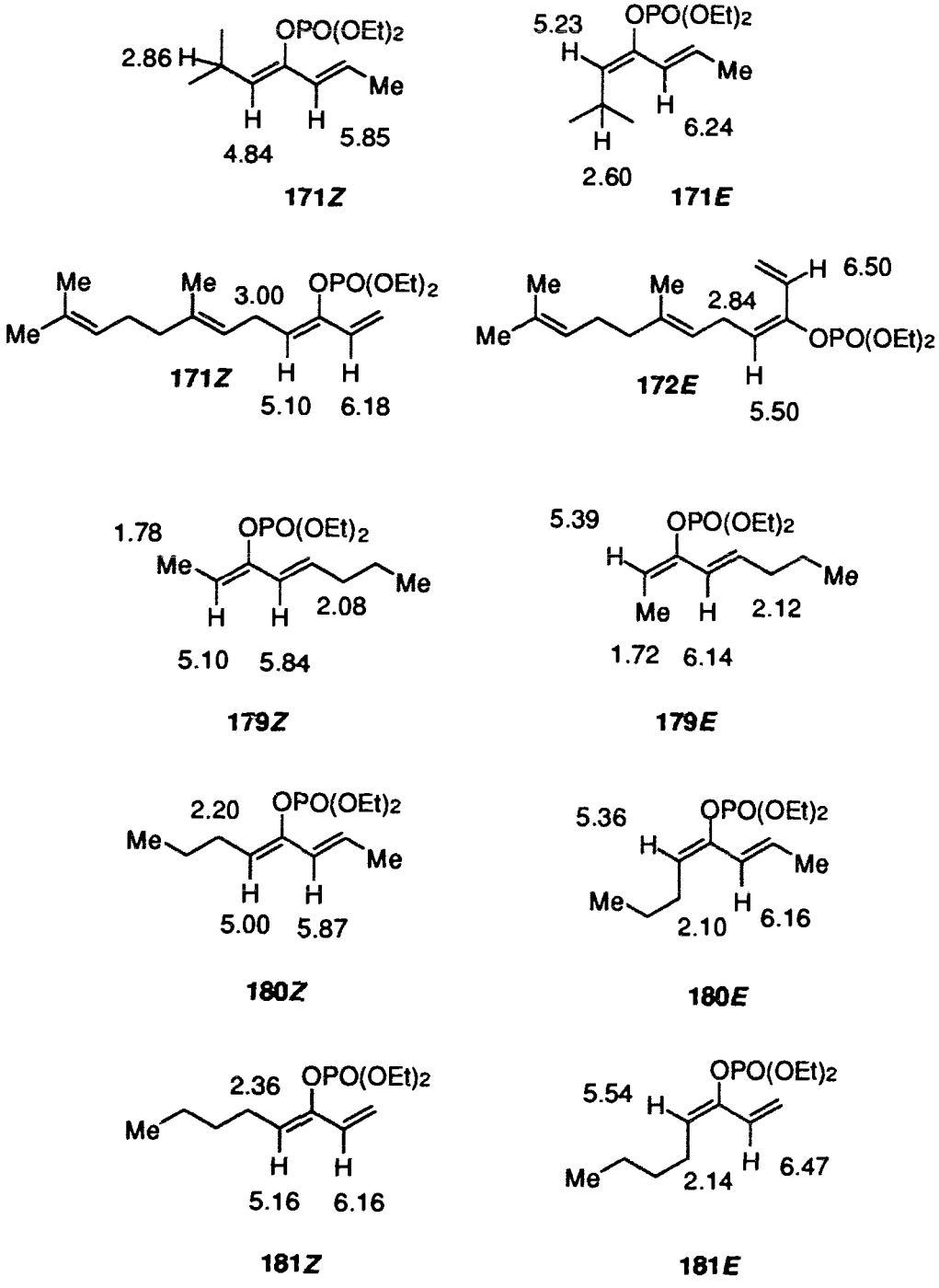


Figure 5.14. ^{1}H NMR *spectral features* ($CDCl_3$) *of synthesized* enolphosphates.

present case (e.g., **158**) substituents attached to C-3 and C-4 will generated steric interactions with an incoming base. Use of a base such as LDA should favour *Z*-enolate formation. Indeed, use of LDA favours *Z* enolate while use of LTMP gives rise to increased amounts of *E*-enolate (Table 5.8).

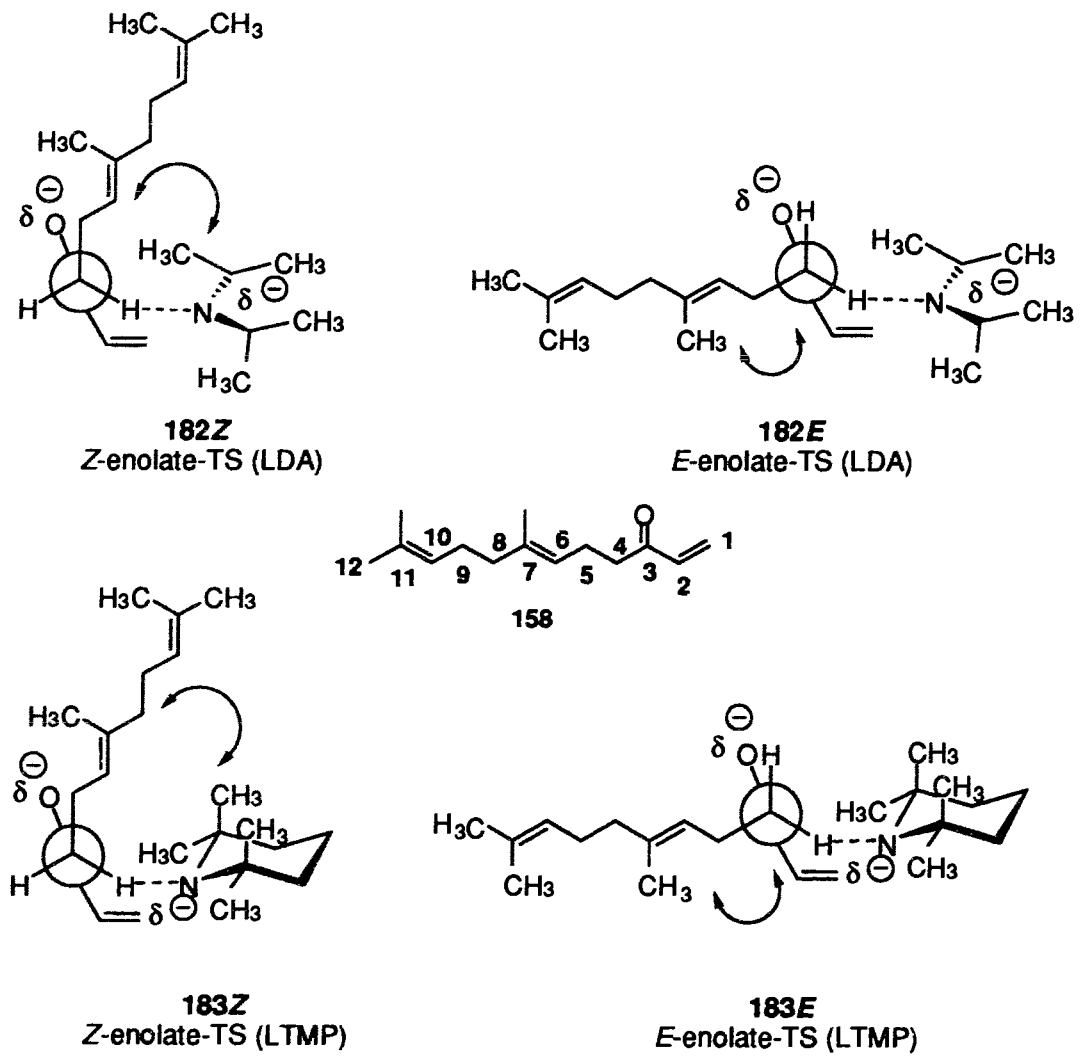
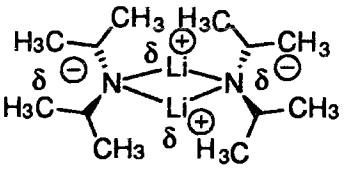
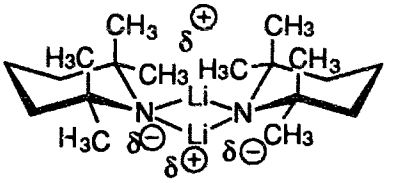


Figure 5.15. Proposed transition states for the enolization of **158**.

The selectivity observed in the *in situ* procedure (*in situ* generation of LiBr) may be rationalized by assuming LiX causes aggregation of LTMP in solution (**184a** and **184b**, Figure 5.16) and this aggregation favours the transition state leading to *E*-enolate.



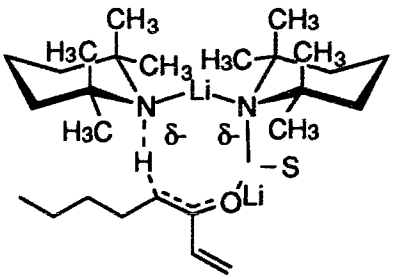
184a Dimeric LDA



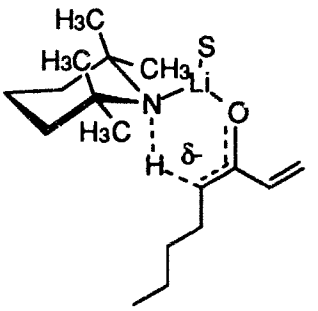
184b Dimeric LTMP

Figure 5.16. Proposed dimeric structures of LDA and LTMP.

In addition, LiBr can increase the complexation at the carbonyl oxygen increasing activation energy for generation of the *Z*-enolate and favouring the *E*-enolate transition state. This could occur through an open dimer (Figure 5.17a) or a cyclic monomer transition state (Figure 5.17b).[172,188h-j,189]



5.17a. Open dimer- transition state *E*-selectivity. Ketone **175**.



5.17b. Cyclic monomer-transition state *E*-selectivity. Ketone **175**.

Figure 5.17. Romesberg and Collum's proposed transition states.

5.4.5. Alkylation of Enolphosphates. Attempts Toward Synthesis of *Z,E*- and *E,E*-Farnesenes.

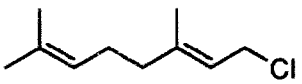
According to the procedure of Sum and Weiler,[165b] the isomerically pure enolphosphates **172*Z*** and **172*E*** were individually treated with $(CH_3)_2CuLi$ in Et_2O, with stirring for several days at 0°C in sealed Schlenk tubes under argon. Unreacted starting material was the only product isolated after work-up. No coupling product was formed from cuprates generated from CuBr•DMS complex or from CuI, even after varying the molar ratios 2 : 1, 5 : 1 and 10 : 1 (cuprate : enolphosphate). Reaction of **172*Z*** or **172*E*** with Bu_2CuLi, resulted in consumption of the enolphosphate but gave a complex mixture of hydrocarbons which were not identified.

5.6. Experimental Section.

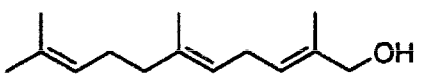
For general methods, including volatile collection see Experimental Section Chapter 2.

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl under nitrogen. Diisopropyl amine and dicyclohexylamine were freshly distilled from sodium under argon. Hexamethylphosphoric triamide (HMPA) was fractionally distilled under vacuum from CaH_2 and stored over 4A molecular sieves under argon. Diethylchlorophosphate and 2,2,6,6-tetramethylpiperidine were purchased from Aldrich and stored over 4A molecular sieves under argon. Iodine was purified by sublimation.

Unless otherwise stated, standard work-up refers to the combined organic extracts being washed with saturated NaCl, dried over anhyd. $MgSO_4$, filtered, and concentration of the filtrate *in vacuo*.

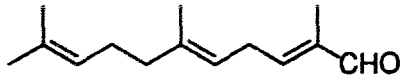


(2*E*)-1-Chloro-3,7-dimethyl-2,6-octadiene (geranyl chloride) (107). This was prepared in 90 % yield by the procedure described by Chappe *et al.*[192] ^1H NMR ($CDCl_3$, ppm): 1.61 (3H, s), 1.70 (3H, s), 1.75 (3H, s), 2.01 (2H, t, J = 7.5 Hz), 2.16 (2H, q, J = 7.5 Hz), 4.10 (2H, d, J = 7.5 Hz), 5.20 (1H, t, J = 7.5 Hz), 5.45 (1H, t, J = 7.5 Hz); FTIR (neat): 2969, 28.56, 1665, 1110, 834 cm^{-1}. ^1H NMR and IR spectra are in agreement with those reported in reference 161.



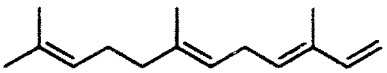
(2*E*,5*E*)-2,6,10-Trimethyl-2,5,9-undecatrien-1-ol (123). To a cold solution (-30°C) of neat trimethylalane (4.32 g, 5.74 mL, 60 mmol) and dichlorobis (η^5-cyclopentadienyl) zirconium (1.75 g, 6 mmol) in anhydrous CH_2Cl_2 (50 mL) was added under argon 2-propyn-1-ol (**121**) (1.68 g, 1.74 mL,

30 mmol). After stirring the mixture overnight at room temperature, geranyl chloride (**107**) (3.3 g, 19 mmol), tetrakis(triphenylphosphine)palladium (0.29 g, 0.25 mmol) in 20 mL on anhydrous THF were added at -30°C. The progress of the reaction was followed by analysis of aliquots by GC. The reaction mixture was stirred for 15 h at room temperature, treated with water (15 mL), and extracted with pentane-ether (1:1) (3 X 15 mL). Standard work-up and concentration *in vacuo,* left a residue that was purified by column chromatography (8:2, pentane:Et_2O, R_f = 0.04) yielding **123** (2.0 g, 50 % yield, 95 % pure) as a pale yellow oil. ^1H NMR ($CDCl_3$, ppm): 1.60 (3H, s), 1.62 (3H,s), 1.68 (3H, s), 1.70 (3H,s), 1.83 (1H, s), 2.00 (2H, t, *J* = 8.1 Hz), 2.06 (2H, q, *J* = 8.1 Hz), 2.75 (2H, t, *J* = 8.1 Hz), 4.00 (2H, s), 5.07 (2H, m), 5.38 (1H, t, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, ppm): 135.59, 134.53, 131.32, 125.18, 124.81, 122.28, 68.92, 39.64, 31.54, 25.61, 25.26, 17.62, 16.04, 14.03; CI-MS *m/z* (relative intensity): 191 (M^+-H_2O, 100); FTIR (neat): 3357, 1671, 1016, 898, 834 cm^{-1}; Anal. Calcd. for $C_{14}H_{24}O$: C, 80.71, H; 11.62. Found: C, 80.66; H, 11.34.

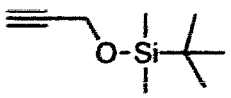


(2*E*,5*E*)-2,6,10-Trimethyl-2,5,9-undecatrienal (120). To a vigorously stirred solution of oxalyl chloride (1.52 g, 1.1 mL, 12 mmol) in CH_2Cl_2 (50 mL) at -60°C under argon was added dimethylsulfoxide (1.8 mL, 25 mmol) in 5 mL of CH_2Cl_2. The mixture was allowed to stir for ~ 5 min. A solution of **123** (1.40 g, 6.8 mmol) in CH_2Cl_2 (10 mL) was added over 5 min. After 30 min stirring, triethylamine (8 mL, 57 mmol) was added over 15 min and the mixture was allowed to warm to room temperature. Water (50 mL) was then added and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (3 X 15 mL). Standard work-up followed by flash chromatography (9.5 : 0.5, pentane:Et_2O, R_f = 0.50) gave **120** (1.00 g, 74 % yield, 95 % pure) as a pale

yellow oil. ^{1}H NMR ($CDCl_3$, ppm): 1.60 (3H, s), 1.68 (3H, s), 1.70 (3H, s), 1.76 (3H, s), 2.00 (2H, t, J = 6.7 Hz), 2.10 (2H, t, J = 6.7 Hz), 3.05 (2H, t, J = 6.7 Hz), 5.06 (1H, t, J = 6.7 Hz), 5.18 (1H, t, J = 6.7 Hz), 6.46 (1H, t, J = 6.7 Hz), 9.40 (1H, s); ^{13}C NMR ($CDCl_3$, ppm): 195.10, 152.96, 138.19, 131.32, 127.41, 124.01, 121.23, 39.61, 28.04, 26.43, 25.61, 17.65, 16.24, 15.23; EI-MS *m/z* (relative intensity): 206 (M^+, 25); FTIR (neat): 2970, 2920, 2856, 1678, 1193, 1123, 835 cm^{-1}; Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50, H; 10.75. Found: C, 81.30; H, 10.67.

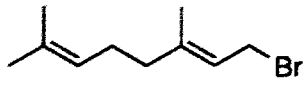


(3*E*,6*E*)-3,7,11-Trimethyl-1,3,6,10-dodecatetraene (91). This was prepared by Wittig reaction of **120** (0.56 g, 27 mmol) and methylenetriphenylphosphorane, generated from methyltriphenylphosphonium iodide (1.22 g, 28 mmol) and phenyl lithium (1.8 mL, 1.8 M solution in cyclohexane/Et_2O), according to the procedure of Leopold *et al.* for the synthesis of homogeraniol.[193] Chromatography using pentane (R_f = 0.49), gave **91** (0.30 g, 77 %) as a colourless liquid. ^{1}H NMR ($CDCl_3$, ppm): 1.60 (3H, s), 1.65 (3H, s), 1.70 (3H, s), 1.76 (3H, s), 2.02 (4H, m), 2.84 (2H, J = 8.1 Hz), 4.92 (1H, d, J = 8.1 Hz), 5.12 (2H, m), 5.10 (1H, d, J = 16.0 Hz), 5.46 (1H, t, J = 8.1 Hz), 6.38 (1H, dd, J = 8.1, 16.0 Hz); EI-MS *m/z* (relative intensity): 204 (M^+, 5), 123 (20), 119 (25). The ^{1}H NMR spectrum is in agreement with that reported by Matsushita and Negishi.[143a] The MS fragmentation is in agreement with those reported in references 134 and 136.

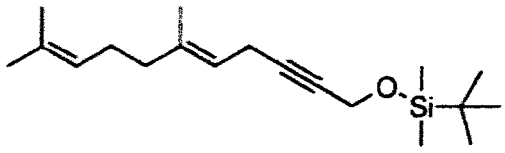


2-Propynyl *tert*-butyldimethylsilyl ether (129). To a solution of 2-propyn-1-ol (**121**) (2.48 g, 2.58 mL, 44 mmol) in CH_2Cl_2 (100 mL) and Et_3N (6.4

mL, 47 mmol) at -10°C was added TBSCl (6.9 g, 45 mmol) and DMAP (0.2 g). This mixture was allowed to reach room temperature and stirred overnight. The reaction mixture was poured into water (~75 mL). The organic phase was separated and the aqueous layer was extracted with Et_2O (3 X 30 mL). Standard work-up followed by vacuum distillation (36°C ~1 mm Hg) gave **129** (7.43 g, 98 % yield, > 99 % pure) as a colourless liquid. ^1H NMR ($CDCl_3$, ppm): 0.14 (6H, s), 0.90 (9H, s), 2.40 (1H, t, J = 2.2 Hz), 4.30 (2H, s); EI-MS *m/z* (relative intensity): 170 (M^+, 5), 113 (M^+- $C(CH_3)_3$, 100).

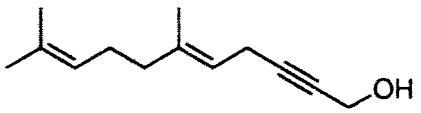


(2*E*)-1-Bromo-3,7-dimethyl-2,6-octadiene (geranyl bromide) (110). This was prepared according to the procedure of Katzenellenbogen and Lenox[194] in 96 % yield (95 % pure). ^1H NMR ($CDCl_3$, ppm): 1.60 (3H, s), 1.68 (3H, s), 1.71 (3H, s), 2.08 (4H, m), 4.02 (2H, d, J = 7.6 Hz), 5.06 (1H, t, J = 7.7 Hz), 5.51 (1H, t, J = 7.7 Hz).

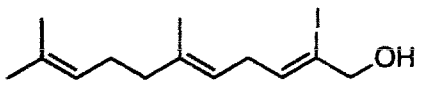


(5*E*)-6,10-Dimethyl-5,9-undecadien-3-ynyl *tert*-butyldimethylsilyl ether (130). To a solution of **129** (5.11 g, 30 mmol) in anhydrous THF (50 mL) at -20°C was added dropwise *n*-BuLi (12.2 mL, 2.45 M solution in hexanes). After stirring at this temperature for 3 h, geranyl bromide **110** (7.6 g, 35 mmol) in THF-HMPA (3:2, 40 mL) was added *via* cannula. This mixture was allowed to stir overnight. The reaction mixture was poured into water (~100 mL) and the aqueous layer was extracted with Et_2O (3 X 30 mL). Standard work-up followed by flash chromatography (9:1 pentane:Et_2O) afforded **130** (7.26

g, 79 % yield, 95 % pure) as a pale yellow liquid. ^{1}H NMR ($CDCl_3$, ppm): 0.14 (6H, s), 0.90 (9H, s), 1.58 (3H, s), 1.60 (3H, s), 1.68 (3H, s), 2.00 (2H, q, J = 8.2 Hz), 2.08 (2H, t, J = 8.2 Hz), 2.90 (2H, d, J = 8.2 Hz), 4.30 (2H, t, J = 2.3 Hz), 5.07 (1H, t, J = 8.2 Hz), 5.18 (1H, t, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$, ppm): 137.31, 131.55, 124.10, 118.76, 84.13, 78.23, 52.05, 39.63, 39.42, 26.54, 25.89, 25.79, 25.64, 18.34, 17.88, 17.65, 15.07, -5.08; CI-MS *m/z* (relative intensity): 307 (M^+1, 20); FTIR (neat): 2929, 2857, 2286, 2235, 1669, 1082, 837, 778 cm^{-1}.

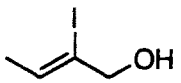


(5*E*)-6,10-Dimethyl-5,9-undecadien-3-yne (131).[153] To a solution of **130** (4.50 g, 15 mmol) in THF (50 mL) at room temperature was added tetrabutylammonium fluoride (30 mL, 1 M solution in THF, 30 mmol). This was stirred overnight at room temperature. Then water (~30 mL) was added and the mixture was extracted with Et_2O (3 X 20 mL). Standard work-up followed by flash chromatography using pentane:Et_2O (9:1, R_f = 0.05) as the eluant afforded **131** (2.51 g, 90 % yield, > 99 % pure). ^{1}H NMR ($CDCl_3$, ppm): 1.40 (1H, br s), 1.60 (3H, s), 1.64 (3H, s), 1.70 (3H, s), 2.06 (2H, q, J = 8.1 Hz), 2.10 (2H, t, J = 8.1 Hz), 2.95 (2H, t, J = 8.1 Hz), 4.25 (2H, t, J = 2.2 Hz), 5.06 (1H, t, J = 8.1 Hz), 5.18 (1H, t, J = 8 Hz); ^{13}C NMR ($CDCl_3$, ppm): 137.63, 131.53, 124.02, 118.53, 85.31, 77.85, 51.47, 39.42, 26.51, 25.63, 17.83, 17.66, 16.08; EI-MS *m/z* (relative intensity): 207 (M^+, 2), 191 (M^+-H_2O, 10); FTIR (neat): 3334, 2220, 1668, 1108, 1018, 821 cm^{-1}. The MS is in agreement with that reported in reference 153.

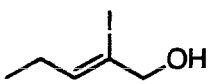


(2*E*,6*E*)-2- Iodo-6,10-dimethyl-2,5,9-undecatrien-1-ol (132). The propargylic alcohol **131** (1.45 g, 7.6 mmol) in anhydrous Et_2O (20 mL) at

-20°C, was treated successively with *n*-BuLi (2.1 mL, 2.45 M solution in hexane, 7.6 mmol) and DIBAL (23 mL, 0.8 M solution in THF) and the solution was heated ~ 38°C for 48 h. Excess hydride was decomposed with anhydrous ethyl acetate (1.5 mL). Iodine (17.3 g, 68.4 mmol) in Et_2O (100 mL) was added *via* cannula at -78°C, and the mixture was stirred at -78°C for 2 h. The mixture was poured into basic sodium thiosulfate, and the aqueous layer extracted with Et_2O (3 X 20 mL). Standard work-up followed by flash chromatography (8:2, pentane:Et_2O, R_f = 0.20; 3-iodo isomer R_f = 0.14) yielded **132** (0.85 g, 35 % yield, 96 % pure) as a pale yellow liquid. ^1H NMR ($CDCl_3$, ppm): 0.90 (1H, br s), 1.60 (3H, s), 1.66 (3H, s), 1.68 (3H, s), 2.00 (2H, q, J = 7.5 Hz), 2.08 (2H, t, J = 7.5 Hz), 2.88 (2H, t, J = 7.5 Hz), 4.25 (2H, d, J = 1.5 Hz), 5.07 (1H, t, J = 7.5 Hz), 5.14 (1H, t, J = 7.5 Hz), 5.84 (1H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, ppm): 137.47, 135.35, 131.25, 124.17, 119.70, 83.40, 71.72, 39.62, 35.04, 26.66, 25.65, 17.68, 16.52; CI-MS *m/z* (relative intensity): 320 (M^+, 2), 303 (M^+-H_2O, 45), 193 (M^+-I, 20); FTIR (neat): 3354, 1669, 1640, 1074, 1007, 833, 667 cm^{-1}.

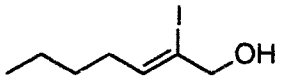


(2*E*)-2-Iodo-2-buten-1-ol (134β). This was prepared by the same procedure described for the preparation of **132**. Flash chromatography (8:2, pentane:Et_2O) gave **134β** in 30 % yield. ^1H NMR ($CDCl_3$, ppm): 1.89 (3H, d, J = 6.6 Hz), 2.60 (1H, br s), 4.25 (2H, s), 5.99 (1H, q, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, ppm): 132.50, 84.30, 74.75, 19.42.

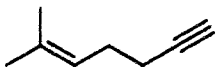


(2*E*)-2-Iodo-2-penten-1-ol (136β). This was prepared by the same procedure described for the preparation of **132**. Flash chromatography (8:2,

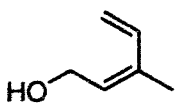
pentane:Et_2O) gave **136**β in 30 % yield. ^1H NMR ($CDCl_3$, ppm): 0.96 (3H, t, J = 8 Hz), 1.95 (1H, br s), 2.20 (2H, dq, J = 7.5 Hz), 4.25 (2H, s), 5.95 (1H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, ppm): 137.40, 82.60, 75.25, 27.40, 13.38.



(2*E*)-2-Iodo-2-hepten-1-ol (138β). This was prepared by the same procedure described for the preparation of **132**. Flash chromatography (8:2, pentane:Et_2O) gave **138**β in 30 % yield. ^1H NMR ($CDCl_3$, ppm): 0.94 (3H, t, J = 8 Hz), 1.38 (4H, m), 1.80 (1H, br s), 2.17 (2H, q, J = 7.6 Hz), 4.25 (2H, s), 5.90 (1H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, ppm): 136.59, 83.28, 74.97, 33.78, 31.50, 22.47, 14.01.



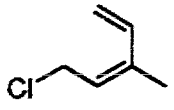
2-Methyl-2-hepten-6-yne (141). This was prepared in 61 % yield by the procedure described by Negishi *et al.*[157] ^1H NMR ($CDCl_3$, ppm): 1.63 (3H, s), 1.70 (3H, s), 1.95 (1H, t, J = 4.1 Hz), 2.20 (4H, m), 5.17 (1H, m); ^{13}C NMR ($CDCl_3$, ppm): 133.14, 122.62, 84.55, 68.09, 38.54, 31.45, 18.95, 17.77. CI-MS *m/z* (relative intensity): 109 (M^+, 100); FTIR (neat): 3313, 2119, 1674, 824 cm^{-1}. The ^1H NMR and MS spectra are in agreement with those reported by Sato *et al.*[156a]



(2*Z*)-3-Methyl-2,4-pentadien-1-ol (144).[158] **Method A.** In adaptation of the method of Brown,[87] a 50 mL-filtration flask was charged with a solution of (2*Z*)-3-methyl-4-pentyn-1-ol (**143**) (4.00 g, 40 mmol) in dry ethanol (80 mL), pyridine (10 mL) and Lindlar catalyst[159] (1.3 g of $Pd/CaCO_3$). A rubber bulb

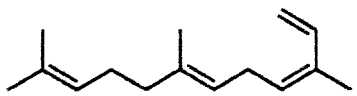
was secured with copper wire to the side arm of the flask. The flask was capped with a wire secured large septum. H_2 (5 psi) was injected until the rubber bulb inflated. The mixture was stirred at room temperature until no further deflation of the balloon indicated that H_2 uptake stopped. Monitoring of aliquots by GC indicated reaction completion after 24 h. The mixture was then filtered, diluted with water and extracted (3 X 25 mL) with Et_2O. Standard work-up followed by flash chromatography (1:1, pentane:Et_2O, R_f = 0.30) gave **144** (3.81 g, 93 % yield, >99 % pure). ^{1}H NMR ($CDCl_3$, ppm): 1.88 (3H, s), 1.92 (1H, s), 4.30 (2H, d, J = 8.0 Hz), 5.20 (1H, dd, J = 8.0, 1.2 Hz), 5.30 (1H, dd, J = 16.1, 1.2 Hz), 5.60 (1H, t, J = 8.0 Hz), 6.75 (1H, dd, J = 8.0, 16.1 Hz); ^{13}C NMR ($CDCl_3$, ppm): 135.64, 132.94, 128.62, 115.56, 58.39, 19.68; CI-MS *m/z* (relative intensity): 98 (M^+, 100); FTIR (neat): 3328, 1648, 995, 907 cm^{-1}.

Method B.[160b] Copper acetate monohydrate (1.32 g) was added to a suspension of zinc dust (13.12 g) in water (75 mL) and the mixture was stirred for 15 min. Silver nitrate (1.32 g) was added and stirring was continued for 15 min. The suspension was centrifuged, washed successively with water, methanol, acetone and Et_2O and re-suspended into 75 mL of methanol-water (1:1). A solution of **143** (2.26 g, 23.5 mmol) in 20 mL of methanol was poured into this suspension and the mixture was stirred for 3 days at room temperature. After dilution with water, the mixture was filtered through Celite and extracted with Et_2O (3 X 20 mL) and dried over Na_2SO_4. Concentration *in vacuo* gave **144** (2.10 g, 87 % yield) which was used without further purification (>99 % pure).



(2*Z*)-1-Chloro-3-methyl-2,4-pentadiene (142). To a dry 2-neck flask, equipped with a reflux condenser (to which was attached an argon inlet),

was added **144** (2.94 g, 30 mmol), 45 mL of dry CCl_4 and dry triphenyl phosphine (10.23 g, 39 mmol). This solution was stirred with heating to reflux for 1 h. The mixture was allowed to cool to room temperature; dry pentane was added until no additional precipitate was formed. The precipitate was filtered through a small pad of SiO_2, the residue cooled to -20°C and re-filtered. After *in vacuo* concentration **142** (2.22 g, 63 % yield, 95 % pure) was obtained and used without further purification. ^1H NMR ($CDCl_3$, ppm): 1.90 (3H, s), 4.20 (2H, d, J = 8.1 Hz), 5.27 (1H, dd, J = 8.1, 1.2 Hz), 5.37 (1H, dd, J = 16.3, 1.2 Hz), 5.60 (1H, t, J = 8.1 Hz), 6.76 (1H, dd, J = 8.1, 16.3 Hz); ^{13}C NMR ($CDCl_3$, ppm): 137.84, 132.11, 126.49, 116.89, 39.63, 19.73; CI-MS *m/z* (relative intensity): 118 (M^++2, 35), 116 (M^+, 100); FTIR (neat): 1598, 1640, 1686, 983, 915, 849, 788, 645 cm^{-1}.



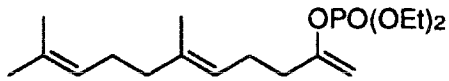
(3*Z*,6*E*)-3,7,11-Trimethyl-1,3,6,10-dodecatetraene (96). To a cold solution (-30°C) of neat trimethylalane (1.44 g, 1.90 mL, 20 mmol) and dichlorobis (η^5-cyclopentadienyl) zirconium (0.58 g, 2 mmol) in anhydrous CH_2Cl_2 (30 mL) was added under argon 2-methyl-2-hepten-6-yne (**141**) (1.00 g, 9.3 mmol). After stirring the mixture overnight at room temperature, **142** (1.2 g, 10 mmol), tetrakis(triphenylphosphine)palladium (0.58 g, 0.5 mmol) in 10 mL of anhydrous THF were added at -30°C. The progress of the reaction was followed by analysis of aliquots by GC. The reaction mixture was stirred for 15 h at room temperature, treated with water (10 mL), and extracted with pentane-Et_2O (1:1) (3 X 15 mL). Standard work-up and concentration *in vacuo,* left a residue that was purified by column chromatography (pentane, R_f = 0.31) to yield a 1:1 mixture of **91** and **96** (1.49 g, 73 % yield). Re-chromatography of the mixture using a 1 m column (15 mm OD) packed with 20 % $AgNO_3/SiO_2$ (Merck 60 , 230-400 mesh), and 19 : 1 pentane/Et_2O as a solvent, afford 50 mg of pure **96**. ^1H NMR ($CDCl_3$,

ppm): 1.60 (3H, s), 1.66 (3H, s), 1.70 (3H, s), 1.84 (3H, s), 2.01 (4H, m), 2.86 (2H, t, J = 8.1 Hz), 5.07 (1H, dd, J = 8.1, 1.5 Hz), 5.10 (2H, m), 5.20 (1H, dd, J = 16.2, 1.5 Hz), 5.34 (1H, t, J = 8.1 Hz), 6.82 (1H, dd, J = 8.1, 16.2 Hz); EI-MS *m/z* (relative intensity): 204 (M^+, 5), 119 (75). The MS fragmentation is in agreement with that reported in reference 136. The ^1H NMR spectrum is in agreement with that reported by Morgan and Thompson.[146]

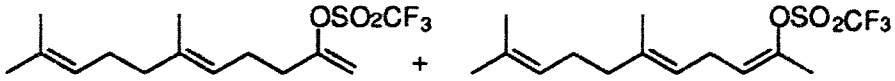
Enol Trapping General Procedure. Amide Method. To freshly distilled amine (diisopropylamine, 0.3 mL, 2.1 mmol or 2,2,6,6-tetramethylpiperidine, 0.36 mL, 2.1 mmol) in 15 mL of anhydrous solvent (THF or Et_2O), cooled to 0°C, 0.90 mL of *n*-BuLi (2.39 M in hexane) was added and the mixture was stirred for 30 min. After cooling the flask to -78°C, **153** (2.2 mmol in 10 mL of solvent) was added *via* cannula. After stirring at this temperature for 1 h, 0.35 mL (0.42 g, 2.42 mmol) of $ClPO(OEt)_2$ was added and the reaction was stirred overnight. Subsequent concentration of the solvent *in vacuo* and dilution of the residue with Et_2O gave an ether layer which was washed with cold dil. HCl, sat. $NaHCO_3$, sat. NaCl and dried over anhyd. $MgSO_4$. The solvent was concentrated *in vacuo* and the orange residue was purified by column chromatography (3:7, pentane:Et_2O as eluant).

Enol Trapping General Procedure. KH Method. Potassium hydride (0.13 g of a 35 % suspension in mineral oil, 1.1 mmol) was washed once with dry hexane and twice with anhydrous THF (10 mL each) under nitrogen and suspended in 15 mL of THF. A solution of **153** (0.25 mL, 1.1 mmol) in 10 mL of THF was added at -15°C *via* cannula and the mixture was allowed to warm to room temperature. After evolution of hydrogen had ceased, the solution was cooled to -15°C and neat $ClPO(OEt)_2$ (0.20 g, 0.17 mL, 1.2 mmol) or a solution of

N,N-bis(trifluoromethylsulfonyl) aniline (0.41 g, 1.2 mmol) in 10 mL of THF was added dropwise and stirring was continued at room temperature or heated at 60°C under argon. The solvent was removed *in vacuo*, the residue dissolved in diethyl ether and the extract was washed with cold dil. HCl, sat. $NaHCO_3$ and water. The ether extract was dried over anhyd. $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (phosphate: 1:1, pentane-ether, R_f = 0.15; triflate: 9:1, pentane:Et_2O, R_f = 0.64) to afford mixture reported in Table 5.2. Product ratio was estimated by ^1H NMR and GC.

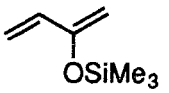


(5*E*)-2-Diethylphosphoryloxy-6,10-dimethyl-1,5,9-undecatriene (156K). ^1H NMR ($CDCl_3$, ppm) 1.34 (6H, t, J = 9.7 Hz), 1.59 (3H, s), 1.62 (3H, s), 1.70 (3H, s), 1.97 (2H, t, J = 9.7 Hz), 2.05 (2H, q, J = 9.7 Hz), 2.20 (4H, s), 4.16 (4H, q, J = 9.7 Hz), 4.50 (1H, dd, J = 3 Hz, $^4J_{P\text{-}H}$ = 1 Hz), 4.80 (1H, dd, J = 3 Hz, $^4J_{P\text{-}H}$ = 1 Hz), 5.06 (2H, m); ^{13}C NMR ($CDCl_3$, ppm) 155.54 ($J_{C\text{-}P}$ = 9 Hz), 136.17, 131.29, 124.28, 122.78, 96.88 ($J_{C\text{-}P}$ = 6 Hz), 64.15 ($J_{C\text{-}P}$ = 6 Hz), 39.65, 34.71, 26.70, 25.58, 25.01, 17.61, 16.04 ($J_{C\text{-}P}$ = 7 Hz); FTIR (neat) 2988, 2916, 1660, 1278, 1040, 870, 826 cm^{-1}; CI-MS *m/z* (rel intensity) 331 (M^++1, 15), 177 (45), 155 (100); Anal. Calcd. for $C_{17}H_{31}PO_4$: C, 61.80; H, 9.46. Found: C, 61.78; H, 9.55.

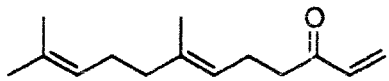


(*Z*)-6,10-Dimethyl-2-trifluoromethanesufonyloxy-2,5,9-undecatriene and (5*E*)-6,10-Dimethyl-2-trifluoromethanesufonyloxy-1,5,9-undecatriene (157). ^1H NMR ($CDCl_3$, ppm): 1.60 (12H, m), 1.60 (6H, s), 2.00 (6H, m), 2.06 (3H, s), 2.08 (6H, m, signal overlapped with -CH_3 group), 2.24 (2H, q, J = 7.5 Hz), 2.39 (2H, t, J = 7.5 Hz), 2.86 (2H, t, J = 7.5 Hz), 4.94 (1H,

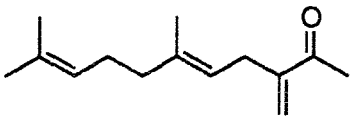
d, J = 2.7 Hz), 5.10 (5H, m), 5.18 (1H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, ppm): 156.72, 144.70, 137.68, 137.42, 131.50, 124.11, 121.49, 120.84, 119.74, 104.21, 39.62, 39.58, 34.02, 26.61, 25.63, 24.80, 24.60, 19.61, 17.65, 16.03; EI-MS *m/z* (rel intensity) 325 (50), 177 (100). Mixture 54:46 of **157K**:**157T** triflates.



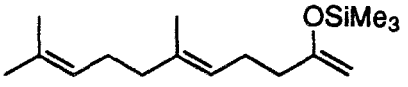
2-Trimethylsilyloxy-1,3-butadiene[177a] **(160).** Dry LiBr (3.48 g, 40 mmol) was placed in a oven-dried 2-neck flask under argon. The flask was then heated under vacuum for 30 min and then allowed to cool to room temperature under argon. Dry THF (10 mL) was added and the mixture was stirred until the salt dissolved. This solution was cooled to -20°C, followed by the successive addition of chlorotrimethylsilane (4.80 g, 5.6 mL, 44 mmol), 3-buten-2-one (MVK, **159**) (2.80 g, 3.3 mL, 40 mmol) and Et_3N (4.40 g, 6 mL, 44 mmol). The mixture was stirred for 1 h at -20°C and overnight at ~ 40°C. The mixture was diluted with cold pentane (20 mL) and poured into saturated NaCl solution (50 mL). The organic phase was separated and the aqueous layer extracted with cold pentane (3 X 10 mL). The combined pentane extracts were washed with cold water, cold saturated $NaHCO_3$, cold water and dried over anhydrous $MgSO_4$. Vacuum distillation (35-36°C @ 35 mm Hg) afforded **160** in 80 % yield. ^1H NMR ($CDCl_3$, ppm): 0.30 (9H, m), 4.40 (2H, s), 5.10 (1H, dd, J = 8.0, 1.2 Hz), 5.50 (1H, dd, J = 16.0, 1.2 Hz), 6.10 (1H, dd, J = 8.0, 16.0 Hz). The ^1H NMR spectrum is in agreement with the one reported by Hansson and Carlson.[177a]



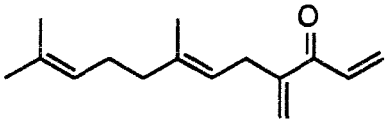
(6*E*)-7,11-Dimethyl-1,6,10-dodecatrien-3-one.[178-180] **Method A. (158).** To freshly distilled diisopropylamine (0.3 mL, 2.1 mmol) in 20 mL of anhydrous solvent THF, cooled to 0°C, 0.90 mL of *n*-BuLi (2.39 M solution in hexane) was added and the mixture was stirred for 30 min. After cooling the flask to -78°C, a solution of geranylacetone **153** (0.41 g, 0.47 mL, 2.1 mmol) in THF (10 mL) was added *via* cannula and the mixture stirred for 1 h. A slurry of Eschenmoser's salt (*N,N*-dimethylmethyleneammonium iodide) (0.78 g, 4.2 mmol) in THF (10 mL) was cooled to -78°C and added *via* cannula to the enolate mixture. After the addition was complete, the mixture was stirred at -78°C for 30 min and gradually allowed to warm to room temperature. The solvent was removed at reduced pressure, the residue dissolved in MeOH (15-20 mL) and an excess of MeI was added. The resulting mixture was stirred at room temperature for 24 h. The solvent was removed *in vacuo*, giving a white-yellow solid. The residue was suspended in CH_2Cl_2, a solution 5 % $NaHCO_3$ was added and the mixture was stirred until the solid dissolved. The organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (5 X 10 mL) and dried over anhydrous $MgSO_4$. After flash chromatography (9:1, pentane:Et_2O), **158** was obtained (0.21 g, 51 % yield, 95 % pure, isomeric purity: 90 %) as a pale yellow liquid. ^1H NMR ($CDCl_3$, ppm): 1.58 (3H, s), 1.62 (3H, s), 1.66 (3H, s), 1.98 (2H, t, J = 9.6 Hz), 2.06 (2H, q, J = 9.6 Hz), 2.30 (2H, q, J = 9.6 Hz), 2.61 (2H, t, J = 9.6 Hz), 5.07 (2H, m), 5.82 (1H, dd, J = 10.4, 1 Hz), 6.21 (1H, dd, J = 16.8, 1 Hz), 6.34 (1H, dd, J = 16.8, 10.4 Hz); ^{13}C NMR ($CDCl_3$, ppm): 200.40, 137.60, 136.70, 131.40, 127.60, 124.40, 124.30, 39.80, 39.70, 26.70, 25.60, 22.60, 17.60, 16.60; CI-MS *m/z* (relative intensity): 206 (M^+, 2); FTIR (neat): 2967, 2856, 1681, 1616, 1266, 1107, 914, 734 cm^{-1}.



(5*E*)-6,10-Dimethyl-3-methylene-5,9-undecadien-2-one (163). This was prepared by the procedure described for the preparation of **158**, but 2,2,6,6-tetramethylpiperidine was used as a base. Flash chromatography (9:1, pentane:Et_2O) gave **163** in 48 % yield (95 % pure, isomeric purity: 94 %). ^1H NMR ($CDCl_3$, ppm): 1.61 (6H, s), 1.67 (3H, s), 2.06 (4H, m), 2.34 (3H, s), 2.94 (2H, d, J = 8.4 Hz), 5.10 (2H, m), 5.74 (1H, d, J = 0.72 Hz), 6.00 (1H, d, J = 0.72 Hz); ^{13}C NMR ($CDCl_3$, ppm): 199.60, 148.21, 137.60, 131.43, 123.98, 124.33, 120.83, 39.65, 28.80, 26.67, 25.91, 25.60, 17.58, 15.93; CI-MS *m/z* (relative intensity): 207 (M^++1, 100); FTIR (neat): 2967, 2918, 2853, 1680, 1626, 1440, 1263, 1118, 1022, 974, 836 cm^{-1}; Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50, H; 10.75. Found: C, 81.28; H, 10.86.

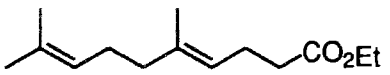


(5*E*)-6,10-Dimethyl-2-trimethylsilyloxy-5,9-undecadiene[185] (164). This was prepared from geranylacetone (**153**) in 92 % yield by the procedure described by Inoue *et al.*[185] ^1H NMR (CCl_4, ppm): 0.32 (9H, s), 1.72 (3H, s), 1.74 (3H, s), 1.80 (3H, s), 2.18 (8H, m), 4.06 (1H, s), 4.08 (1H, s), 5.18 (2H, m). CI-MS *m/z* (relative intensity): 267 (M^+, 100), 177 (20).

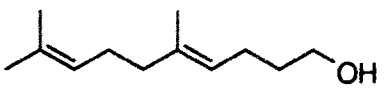


(6E)-7,11-Dimethyl-3-methylene-1,6,10-dodecatrien-2-one (165). To a stirred solution of Eschenmoser's salt (0.39 g, 2.1 mmol) in CH_2Cl_2 (25 mL), **164** (0.28 g, 1.05 mmol) in CH_2Cl_2 (10 mL) was added at room temperature. After stirring for 5 h the solvent was removed at reduced pressure,

the residue dissolved in MeOH (15-20 mL) and an excess of MeI was added. The resulting mixture was stirred at room temperature for 24 h. The mixture was quenched using the procedure described above for **158**. After flash chromatography (9:1, pentane:Et_2O), **165** was obtained (0.12 g, 55 % yield, 95 % pure, isomeric purity: 95 %) as a pale yellow liquid. ^1H NMR ($CDCl_3$, ppm): 1.58 (3H, s), 1.60 (3H, s), 1.68 (3H, s), 2.10 (4H, m), 3.08 (2H, d, J = 9.6 Hz), 5.10 (1H, t, J = 9.5 Hz), 5.18 (1H, t, J = 9.5 Hz), 5.77 (1H, dd, J = 9.6, 0.8 Hz), 5.80 (1H, d, J = 0.7 Hz), 5.96 (1H, d, J = 0.7 Hz), 6.30 (1H, dd, J = 16.0, 0.8 Hz), 6.80 (1H, dd, J = 16.0, 9.6 Hz); ^{13}C NMR ($CDCl_3$, ppm): 192.50, 148.09, 137.92, 132.49, 131.41, 128.60, 124.31, 124.16, 120.52. 39.73, 29.40, 26.58, 25.60, 17.62, 15.88; FTIR (neat): 2967, 2855, 1669, 1609, 1440, 1404, 1242, 1048, 981, 825 cm^{-1}; Anal. Calcd. for $C_{15}H_{22}O$: C, 82.52, H; 10.16. Found: C, 82.69; H, 10.30.

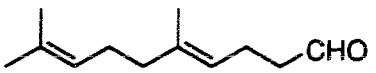


Ethyl (4*E*)-5,9-dimethyl-4,8-decadienoate[186] (166). This was prepared in 85 % yield by the procedure described by Kuwajima and Doi.[186] ^1H NMR ($CDCl_3$, ppm): 1.27 (3H, t, J = 8.0 Hz), 1.60 (3H, s), 1.64 (3H, s), 1.70 (3H, s), 1.99 (2H, t, J = 8.0 Hz), 2.07 (2H, q, J = 8.0 Hz), 2.30 (4H, m), 4.02 (2H, q, J = 8.0 Hz), 5.09 (2H, m); ^{13}C NMR ($CDCl_3$, ppm): 173.37, 136.60, 131.35, 124.25, 122.42, 60.16, 39.66, 34.60, 26.70, 25.61, 23.62, 17.63, 15.98, 14.25.

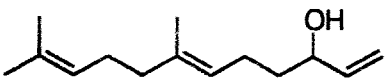


(4*E*)-5,9-Dimethyl-4,8-decadien-1-ol (167). To a suspension of $LiAlH_4$ (1.52 g, 40 mmol) in anhydrous ether (15 mL) at 0°C, was added dropwise, *via* cannula, a solution of ethyl (4*E*)-5,9-dimethyl-4,8-decadienoate (**166**) (7.75 g, 35.6 mmol) in anhydrous Et_2O (25 mL). After 2 h excess $LiAlH_4$ was destroyed at 0°C by slow addition of water. The resulting white precipitate

was filtered and rinsed with small portions of Et_2O (4 X 15 mL). Standard work-up followed by vacuum distillation (115°C @ 5 mm Hg) afforded **167** (5.53 g, 93 % yield, >99 % pure). ^1H NMR ($CDCl_3$, ppm): 1.30 (1H, br s), 1.60 (3H, s), 1.62 (3H, s), 1.69 (3H, s), 2.00 (2H, t, J = 8.3 Hz), 2.08 (6H, m), 3.66 (q, 2H, J = 8.3 Hz), 5.07 (1H, t, J = 8.3 Hz), 5.12 (1H, t, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$, ppm): 135.84, 131.39, 124.32, 123.80, 62.78, 39.74, 32.82, 26.72, 25.64, 24.31, 17.56, 15.97.

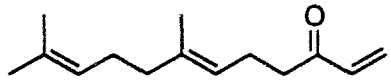


(4*E*)-5,9-Dimethyl-4,8-decadienal (168). (4*E*)-5,9-Dimethyl-4,8-decadien-1-ol (**167**) (3.96 g, 21.7 mmol) was dissolved in dry DMSO (170 mL) and dry Et_3N (35 mL) was added under argon. Pyridine sulfur-trioxide complex (SO_3•Py, 10.32 g, 74 mmol) was dissolved in DMSO (70 mL) and the solution was added *via* cannula. After stirring for 30 min, the mixture was poured into water (200 mL) and the product removed by extraction with Et_2O (5 X 20 mL). Standard work-up followed by vacuum distillation (92°C @ 3 mm Hg) gave **168** (3.51 g, 90 % yield, 96 % pure). ^1H NMR ($CDCl_3$, ppm): 1.57 (3H, s), 1.60 (3H, s), 1.70 (3H, s), 2.00 (2H, t, J = 8 Hz), 2.10 (2H, q, J = 8.1 Hz), 2.36 (2H, q, J = 8.1 Hz), 2.50 (2H, t, J = 8.1 Hz), 5.10 (2H, m), 9.76 (1H, t, J = 2.2); ^{13}C NMR ($CDCl_3$, ppm): 202.35, 136.90, 131.45, 124.08, 122.08, 43.95, 39.62, 26.64, 25.60, 20.93, 17.63, 16.02.

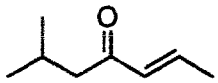


(6*E*)-7,11-Dimethyl-1,6,10-dodecatrien-3-ol (169). To a solution of vinyl magnesium bromide (20 mL, 1 M solution in THF, 20 mmol) in THF (15 mL) at 0°C **168** (3.51 g, 19.5 mmol) in THF (15 mL) was added *via* cannula. The mixture was warmed to room temperature and stirred for 1 h, then cooled to -10°C and saturated NH_4Cl solution was added until pH ~6. The organic phase

was separated and the aqueous layer was extracted with Et_2O (3 X 10 mL). Standard work-up followed by flash chromatography (7:3, pentane:Et_2O) gave **169** (4.01g, 98 % yield, 98 % pure) as a colourless liquid. ^1H NMR ($CDCl_3$, ppm) 1.57 (2H, m), 1.60 (3H, s), 1.62 (3H, s), 1.70 (3H, s), 2.00 (2H, t, J = 7.5 Hz), 2.10 (4H, m), 4.12 (1H, q, J = 7.5 Hz), 5.13 (3H, m, J_{cis} = 11.4 Hz, J_{gem} = 2.2 Hz), 5.22 (2H, dd, J = 16.1, 2.2 Hz), 5.89 (1H, ddd, J = 16.1, 11.4, 8.0 Hz); ^{13}C NMR ($CDCl_3$, ppm): 141.30, 135.84, 131.37, 124.33, 123.83, 114.42, 72.84, 39.73, 37.10, 26.71, 25.65, 23.91, 17.66, 16.01.



(6*E*)-7,11-Dimethyl-1,6,10-dodecatrien-3-one (158). This was prepared from **169** in 93 % yield by the procedure described for the preparation of **168**. The ^1H NMR spectrum is in agreement with that obtained for **158** prepared by the Mannich reaction.

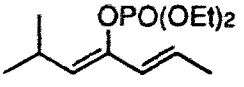


(*E*)-6-Methyl-2-hepten-4-one[195] (170). To a solution of (*E*)-6-methyl-2-hepten-4-ol (**47**, Chapter 2) (3.05 g, 23.8 mmol) in dry pentane (175 mL) was added MnO_2 (21 g, 0.24 mmol) at room temperature. After stirring for seven days, the mixture was filtered and the residue washed thoroughly with a small portion of Et_2O (5 X 5 mL). After distillation (65°C, 6 mm Hg) **170** was obtained (2.37 g, 79 % yield, 98 % pure) as a colourless liquid: ^1H NMR ($CDCl_3$, ppm) 0.90 (6H, d, J = 7.5 Hz), 1.89 (3H, dd, J = 7.5, 1.3 Hz), 2.15 (1H, septet, J = 7.5 Hz), 2.38 (2H, d, J = 7.5 Hz), 6.10 (1H, dq, J = 17, 1.3 Hz), 6.80 (1H, dq, J = 17.0, 7.5 Hz); ^{13}C NMR ($CDCl_3$, ppm): 200.18, 142.08, 132.45, 49.16, 25.12, 22.65 (2C), 18.07; 127 (M^++1, 100), 109 (M^+-H_2O, 6).

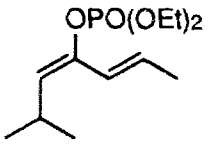
1. Enol Trapping. Effect of Solvent and Base. The procedure used for the enolization of geranylacetone (**153**) (amide method) was used with the corresponding ketones **158, 170, 173, 174** and **175**.

2. Salt Effect. After formation of the lithium amide (from *n*-BuLi addition to dicyclohexyl amine, diisopropyl amine, or 2,2,6,6-tetramethylpiperidine), 0.3-0.4 equiv. of $ZnCl_2$ (1 M solution in ether), LiBr or LiCl (dry under vacuum for 24 h at 150°C) in THF or Et_2O were added at 0°C with latter cooling to -78°C before addition of the ketone. Work-up and purification procedures were as in the general procedure above.

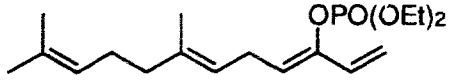
3. *In situ* LTMP-LiBr. A procedure similar to that used in enol trapping for **153** was employed. 2,2,6,6-tetramethylpiperidinium bromide,[188h] 0.50 g, 2.27 mmol prepared and diisopropyl amide were used. Ketones were used in a 2.2 mmol scale. Work-up and purification procedures were as above.



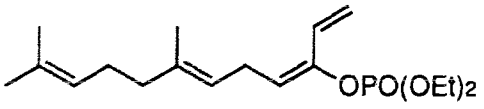
(2*E*,4*Z*)-4-Diethylphosphoryloxy-6-methyl-2,4-heptadiene (171*Z*). ^1H NMR ($CDCl_3$, ppm) 1.00 (6H, d, J = 8.8 Hz), 1.46 (6H, *pseudo* t, J = 8.8 Hz), 1.78 (3H, d, J = 8.8 Hz), 2.86 (1H, m), 4.18 (4H, m), 4.84 (1H, dd, J = 9.0, $^4J_{P-H}$ = 1.5 Hz), 5.85 (1H, dq, J = 15.5, 2.1 Hz), 5.95 (1H, dq, J = 15.5, 9.0 Hz); ^{13}C NMR ($CDCl_3$, ppm) 143.51, 126.49, 126.07, 125.2 (J_{C-P} = 6 Hz), 64.17 (J_{C-P} = 6 Hz), 25.32, 22.65, 16.11 (J_{C-P} = 7 Hz); FTIR (neat) 1667, 1634, 1271, 1032, 1003 cm^{-1}; EI-MS *m/z* (rel intensity) 263 (M^++1, 30), 155 (100); Anal. Calcd. for $C_{12}H_{23}PO_4$: C, 54.93; H, 8.84. Found: C, 54.79; H, 8.80.



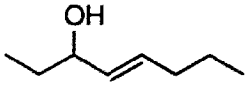
(2*E*,4*E*)-4-Diethylphosphoryloxy-6-methyl-2,4-heptadiene (171*E*). ^{1}H NMR ($CDCl_3$, ppm) 1.03 (6H, d, J = 9.0 Hz), 1.44 (6H, pseudo t, J = 9.0 Hz), 1.82 (3H, d, J = 9.0 Hz), 2.60 (1H, m), 4.15 (4H, m), 5.23 (1H, dd, J = 9.0, $^{4}J_{P\text{-}H}$ = 2.0 Hz), 6.04 (1H, dq, J = 15.5, 9.0 Hz), 6.24 (1H, dq, J = 15.5, 2.0 Hz); ^{13}C NMR ($CDCl_3$, ppm) 143.12 ($J_{C\text{-}P}$ = 9 Hz), 127.50, 122.62 ($J_{C\text{-}P}$ = 4 Hz), 121.54 ($J_{C\text{-}P}$= 6 Hz), 64.06 ($J_{C\text{-}P}$= 6 Hz), 26.09, 23.17, 17.96, 16.03 ($J_{C\text{-}P}$ = 6 Hz); FTIR (neat) 1662, 1618, 1270, 1034, 1005, 958, 791 cm^{-1}; EI-MS *m/z*: (rel intensity) 263 (M^{+}+1, 25), 155 (100); Anal. Calcd. for $C_{12}H_{23}PO_4$: C, 54.93; H, 8.84. Found: C, 54.95; H, 8.84.



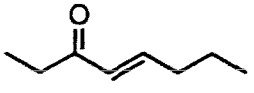
(3*Z*,6*E*)-3-Diethylphosphoryloxy-7,11-dimethyl-1,3,6,10-dodecatetraene (172*Z*). ^{1}H NMR (CD_3OD, ppm) 1.36 (6H, t, J = 6.8 Hz), 1.60 (3H, s), 1.66 (3H, s), 1.69 (3H, s), 2.00 (2H, t, J = 6.8 Hz), 2.09 (2H, q, J = 6.8 Hz), 2.95 (2H, dt, J = 6.75, 1.5 Hz), 4.19 (4H, m), 5.02 (3H, m, J_{cis} = 11.5 Hz), 5.19 (1H, dt, J = 6.8, $^{4}J_{P\text{-}H}$ = 2.3 Hz), 5.45 (1H, dquintet, J = 17.1, 0.5 Hz), 6.24 (1H, dd, J = 17.1, 11.5 Hz); ^{13}C NMR ($CDCl_3$, ppm) 145.30, 136.74, 131.94, 131.38, 124.26, 121.08, 120.12, 113.99, 64.32 ($J_{C\text{-}P}$ = 6 Hz), 37.63, 26.91, 25.60, 25.03, 17.63, 16.12 ($J_{C\text{-}P}$ = 7 Hz), 16.09; FTIR (neat) 1655, 1274, 1032, 863, 821 cm^{-1}; CI-MS *m/z* (rel intensity) 343 (M^{+}+1, 18), 219 (18), 189 (42), 155 (90); Anal. Calcd. for $C_{18}H_{31}PO_4$: C, 63.12; H, 9.13. Found: C, 62.85; H, 9.20.



(3*E*,6*E*)-3-Diethylphosphoryloxy-7,11-dimethyl-1,3,6,10-dodecatetraene (172*E*). ^{1}H NMR ($CDCl_3$, ppm) 1.36 (6H, t, J = 8.5 Hz), 1.60 (3H, s), 1.61 (3H, s), 1.72 (3H, s), 2.00 (2H, t, J = 8.5 Hz), 2.07 (2H, q, J = 8.5 Hz), 2.84 (2H, dt, J = 8.5, 2.5 Hz), 4.16 (4H, q, J = 8.5 Hz), 5.08 (2H, m), 5.21 (1H, dt, J = 10.5, 1.5 Hz), 5.50 (1H, tt, J = 8.5, $^4J_{P\text{-}H}$ = 2.5 Hz), 5.58 (1H, d, J = 16.5 Hz), 6.50 (1H, dddd, J = 16.5, 10.5, $^4J_{P\text{-}H}$ = 2.5 Hz); ^{13}C NMR ($CDCl_3$, ppm) 145.01, 136.70, 131.46, 126.74, 124.16, 121.18, 117.19, 115.55, 64.24 ($J_{C\text{-}P}$ = 6 Hz), 39.59, 26.67, 25.60, 25.12, 17.63, 16.11 ($J_{C\text{-}P}$ = 7 Hz), 16.07; FTIR (neat) 1653, 1274, 1030, 863, 825 cm^{-1}; CI-MS *m/z* (rel intensity) 343 (M^++1, 22), 219 (16), 155 (90); Anal. Calcd. for $C_{18}H_{31}PO_4$: C, 63.12; H, 9.13. Found: C, 62.80; H, 9.25.

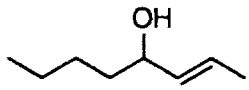


(*E*)-4-Octen-3-ol[196] (176). This was prepared from (*E*)-2-pentenal and ethyl magnesium bromide (3 M solution in Et_2O) in 72 % yield by the procedure described for the preparation of **169**. ^{1}H NMR ($CDCl_3$, ppm) 0.90 (6H, m), 1.50 (5H, m), 2.20 (2H, q, J = 8.0 Hz), 3.98 (1H, q, J = 8.0 Hz), 5.44 (1H, dd, J = 15.5, 8.0 Hz), 5.64 (1H, dt, J = 15.5, 8.0 Hz); ^{13}C NMR ($CDCl_3$, ppm): 133.03, 132.05, 74.51, 34.29, 30.24, 22.37, 13.59, 9.69; CI-MS *m/z* (relative intensity): 128 (M^+, 2), 111 (M^+-H_2O, 100).

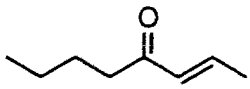


(*E*)-4-Octen-3-one[196] (173). This was prepared from **176** in 92 % yield by the procedure described for the preparation of **168**. ^{1}H NMR ($CDCl_3$,

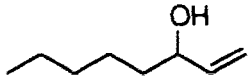
ppm) 0.96 (3H, t, J = 7.8 Hz), 1.09 (3H, t, J = 7.8 Hz), 1.50 (2H, sextet, J = 7.8 Hz), 2.20 (2H, q, J = 7.8 Hz), 2.57 (2H, q, J = 7.8 Hz), 6.07 (1H, dt, J = 16.0, 0 8 Hz), 6.80 (1H, dt, J = 16.0, 7.8 Hz); ^{13}C NMR ($CDCl_3$, ppm): 201.00, 146.68, 130.22, 34.40, 21.39, 15.22, 13.60, 8.15; CI-MS *m/z* (relative intensity): 127 (M^++1, 60), 109 (M^+-H_2O, 2).



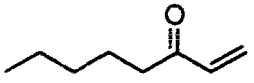
(*E*)-2-Octen-4-ol[197] **(177)** . This was prepared from (*E*)-2-butenal and *n*-BuLi (2.45 M solution in hexane) in 89 % yield by the procedure described for the preparation of **169**. ^{1}H NMR ($CDCl_3$, ppm) 0.90 (3H, t, J = 8.0 Hz), 1.32 (4H, m), 1.52 (2H, m), 1.72 (3H, d, J = 8.0 Hz), 2.18 (1H, s), 4.04 (1H, q, J = 8.0 Hz), 4.48 (1H, dd, J = 16.3, 8.0 Hz), 5.65 (1H, dq, J = 16.3, 8.0 Hz); ^{13}C NMR ($CDCl_3$, ppm): 134.56, 126.56, 73.12, 37.10, 27.67, 22.65, 17.58, 13.99; CI-MS *m/z* (relative intensity): 128 (M^+, 2), 111 (M^+-H_2O, 100).



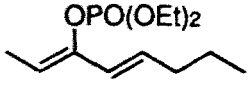
(*E*)-2-Octen-4-one[197] **(174)** . This was prepared from **177** in 93 % yield by the procedure described for the preparation of **168**. ^{1}H NMR ($CDCl_3$, ppm) 0.92 (3H, t, J = 7.5 Hz), 1.36 (2H, sextet, J = 7.5 Hz), 1.59 (2H, quintet, J = 7.5 Hz), 1.89 (3H, d, J = 7.5 Hz), 2.54 (2H, t, J = 7.5 Hz), 6.10 (1H, dt, J = 16.2 Hz, 1.6 Hz), 6.84 (1H, dq, J = 16.2, 7.5 Hz); ^{13}C NMR ($CDCl_3$, ppm): 200.52, 141.98, 132.02, 39.81, 26.44, 22.42, 18.06, 13.79; CI-MS *m/z* (relative intensity): 127 (M^++1, 100), 109 (M^+-H_2O, 4).



1-Octen-3-ol[198] **(178)** . This was prepared from hexanal and vinyl magnesium bromide (1 M solution in THF) in 90 % yield by the procedure described for the preparation of **169**. ^{1}H NMR ($CDCl_3$, ppm) 0.91 (3H, t, J = 8.4 Hz), 1.33 (6H, m), 1.55 (2H, m), 4.10 (1H, q, J = 8.4 Hz), 5.11 (1H, dd, J = 11.5, 1.0 Hz), 5.22 (1H, dd, J = 16.5, 1.0 Hz), 6.48 (1H, ddd, J = 16.5, 11.5, 8.4 Hz); ^{13}C NMR ($CDCl_3$, ppm): 141.46, 114.39, 73.26, 37.12, 31.78, 24.98, 22.57, 13.95; CI-MS *m/z* (relative intensity): 127 (M^+-1, 10), 111 (M^+-H_2O, 100).

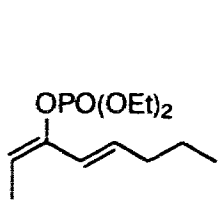


1-Octen-3-one[198] **(175)** . This was prepared from **178** in 90 % yield by the procedure described for the preparation of **168**. ^{1}H NMR ($CDCl_3$, ppm) 0.90 (3H, t, J = 8.8 Hz), 1.33 (4H, m), 1.64 (2H, q, J = 8.8 Hz), 2.57, (2H, t, J = 8.8 Hz), 5.80 (1H, dd, J = 12.2, 1.2 Hz), 6.20 (1H, dd, J = 17.6, 1.2 Hz), 6.34 (1H, dd, J = 17.6, 12.2 Hz); ^{13}C NMR ($CDCl_3$, ppm): 200.91, 136.68, 127.54, 39.71, 31.47, 23.76, 22.44, 13.84; CI-MS *m/z* (relative intensity): 127 (M^++1, 35), 109 (M^+-H_2O, 10).

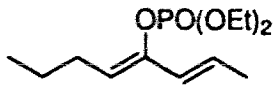


(2*Z*,4*E*)-3-Diethylphosphoryloxy-2,4-octadiene (179*Z*). ^{1}H NMR ($CDCl_3$, ppm) 0.91 (3H, t J = 7.5 Hz), 1.31 (6H, t, J = 7.5 Hz), 1.44 (2H, sextet, J = 7.5 Hz), 1.78 (3H, dd, J = 7.5, 3.5 Hz), 2.08 (2H, quintet, J = 7.5 Hz), 4.18 (4H, m), 5.10 (1H, dq, J = 7.5, $^4J_{P\text{-}H}$ = 2.0 Hz), 5.84 (1H, d, J = 16.2 Hz), 5.94 (1H, dt, J = 16.2, 7.5 Hz); ^{13}C NMR ($CDCl_3$, ppm) 145.41, 130.82, 125.11, 112.60 ($J_{C\text{-}P}$ = 6 Hz), 64.16 ($J_{C\text{-}P}$ = 6 Hz), 34.40, 22.33, 16.12 ($J_{C\text{-}P}$ = 7 Hz), 13.59, 11.38; FTIR (neat) 1707, 1668, 1615, 1268, 1023, 968 cm^{-1}; CI-MS *m/z* (rel intensity) 263

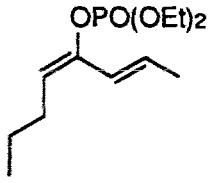
(M^++1, 40), 155 (100); Anal. Calcd. for $C_{12}H_{23}PO_4$: C, 54.93; H, 8.84. Found: C, 55.10; H, 9.01.



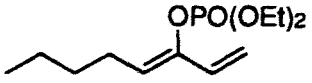
(2*E*,4*E*)-3-Diethylphosphoryloxy-2,4-octadiene (179*E*). ^{1}H NMR ($CDCl_3$, ppm) 0.92 (3H, t, J = 7.5 Hz), 1.45 (6H, t, J = 7.5 Hz), 1.55 (2H, sextet, J = 7.5 Hz), 1.72 (3H, dd, J = 7.5, 2.5 Hz), 2.12 (2H, q, J = 7.5 Hz), 4.16 (4H, dq, J = 7.5, 2.5 Hz), 5.39 (1H, dq, J = 7.5, $^4J_{P\text{-}H}$ = 2.5 Hz), 6.05 (1H, dt, J = 15.3, 7.5 Hz), 6.14 (1H, dd, J = 15.3, $^4J_{P\text{-}H}$ = 1.5 Hz); ^{13}C NMR ($CDCl_3$, ppm) 145.28, 132.61, 120.03 ($J_{C\text{-}P}$ = 6 Hz), 110.01 , 64.10 ($J_{C\text{-}P}$ = 6 Hz), 34.70, 22.32, 16.09 ($J_{C\text{-}P}$ = 7 Hz), 13.61, 11.41; FTIR (neat) 1705, 1659, 1623, 1272, 1025 cm^{-1}; CI-MS *m/z* (rel intensity) 263 (M^++1, 45), 155 (100); Anal. Calcd. for $C_{12}H_{23}PO_4$: C, 54.93; H, 8.84. Found: C, 54.74; H, 8.86.



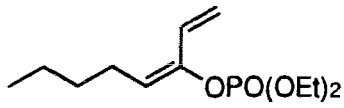
(2*E*,4*Z*)-4-Diethylphosphoryloxy-2,4-octadiene (180*Z*). ^{1}H NMR ($CDCl_3$, ppm) 0.91 (3H, t J = 7.1 Hz), 1.36 (6H, t, J = 7.1 Hz), 1.42 (2H, sextet, J = 7.1 Hz), 1.78 (3H, t, J = 7.1 Hz), 2.20 (2H, dq, J = 7.1, 1.4 Hz), 4.20 (4H, m), 5.00 (1H, dt, J = 7.1, $^4J_{P\text{-}H}$ = 2.0 Hz), 5.87 (1H, dd, J = 17.1, $^4J_{P\text{-}H}$ = 1.5 Hz), 5.96 (1H, dq, J = 17.1, 7.1 Hz); ^{13}C NMR ($CDCl_3$, ppm) 145.40 ($J_{C\text{-}P}$ = 9 Hz), 126.41, 125.85, 118.02 ($J_{C\text{-}P}$ = 6 Hz), 64.16 ($J_{C\text{-}P}$ = 6 Hz), 27.82, 22.36, 17.74, 16.11 ($J_{C\text{-}P}$ = 7 Hz), 13.77; FTIR (neat) 1710, 1660, 1610, 1270, 1025, 970 cm^{-1}; CI-MS *m/z* (rel intensity) 263 (M^++1, 66), 155 (100); Anal. Calcd. for $C_{12}H_{23}PO_4$: C, 54.93; H, 8.84. Found: C, 54.95; H, 8.99.



(2*E*,4*E*)-4-Diethylphosphoryloxy-2,4-octadiene (180*E*). ^{1}H NMR ($CDCl_3$, ppm) 0.92 (3H, t, J = 9.3 Hz), 1.34 (6H, t, J = 9.3 Hz), 1.42 (2H, sextet, J = 9.26 Hz), 1.82 (3H, d, J = 9.3 Hz), 2.10 (2H, dq, J = 9.3, 2.0 Hz), 4.18 (4H, quintet, J = 9.26), 5.36 (1H, dt, J = 9..3, $^4J_{P\text{-}H}$ = 2.0 Hz), 6.04 (1H, dq, J = 15.0, 9.3 Hz), 6.16 (1H, dq, J = 15.0, $^4J_{P\text{-}H}$ = 1.5 Hz); ^{13}C NMR ($CDCl_3$, ppm) 144.74, 127.46, 121.54 ($J_{C\text{-}P}$ = 5 Hz), 115.39 ($J_{C\text{-}P}$ = 4 Hz), 64.12 ($J_{C\text{-}P}$ = 5 Hz), 28.15, 26.37, 22.91, 16.09 ($J_{C\text{-}P}$ = 8 Hz), 13.57; FTIR (neat) 1709, 1663, 1620, 1273, 1030, 978 cm^{-1}; CI-MS *m/z* (rel intensity) 263 (M^++1, 44), 155 (100); Anal. Calcd. for $C_{12}H_{23}PO_4$: C, 54.93; H, 8.84. Found: C, 55.07; H, 8.94.



(3*Z*)-3-Diethylphosphoryloxy-1,3-octadiene (181*Z*). ^{1}H NMR ($CDCl_3$, ppm) 0.90 (3H, t J = 8 Hz), 1.36 (10H, m), 2.36 (2H, dq, J = 7.3, 1.5 Hz), 4.18 (4H, m), 5.08 (1H, dd, J = 11.2, 0.7 Hz), 5.16 (1H, dt, J = 6.5, $^4J_{P\text{-}H}$ = 2.0 Hz), 5.48 (1H, dd, J = 17.2, 0.7 Hz), 6.16 (1H, dd, J = 17.2, 11.2 Hz); ^{13}C NMR ($CDCl_3$, ppm) 145.59 ($J_{C\text{-}P}$ = 9 Hz), 132.02 ($J_{C\text{-}P}$ = 2 Hz), 121.40 ($J_{C\text{-}P}$ = 5 Hz), 113.76, 64.25 ($J_{C\text{-}P}$ = 6 Hz), 31.13 ($J_{C\text{-}P}$ = 2 Hz), 25.65, 22.40, 16.11 ($J_{C\text{-}P}$ = 7 Hz), 13.80; FTIR (neat) 1659, 1609, 1272, 1032, 979 cm^{-1}; CI-MS *m/z* (rel intensity) 263 (M^++1, 100), 155 (90); Anal. Calcd. for $C_{12}H_{23}PO_4$: C, 54.93; H, 8.84. Found: C, 54.77; H, 8.89.



(3*E*)-3-Diethylphosphoryloxy-1,3-octadiene (181*E*). ^{1}H NMR ($CDCl_3$, ppm) 0.90 (3H, t J = 8.5 Hz), 1.35 (10H, m), 2.14 (2H, dq, J = 8.5, 2.5 Hz), 4.20 (4H, m), 5.20 (1H, dt, J = 11, 1.5 Hz), 5.54 (1H, tt, J = 8.5, $^{4}J_{P\text{-}H}$ = 1.5 Hz), 5.58 (1H, dt, J = 15.5, 1.5 Hz), 6.47 (1H, dddd, J = 15.5, 11, $^{4}J_{P\text{-}H}$ = 1.5, 0.55 Hz); ^{13}C NMR ($CDCl_3$, ppm) 144.71, 126.76 ($J_{C\text{-}P}$ = 5 Hz), 118.51 ($J_{C\text{-}P}$ = 3 Hz), 115.23, 64.17 ($J_{C\text{-}P}$ = 6 Hz), 31.29, 22.88, 22.38, 16.08 ($J_{C\text{-}P}$ = 6 Hz), 13.74; FTIR (neat) 1662, 1615, 1278, 1034, 981, 849, 770 cm^{-1}; EI-MS *m/z* (rel intensity) 263 (M^{+}+1, 30), 155 (100); Anal. Calcd. for $C_{12}H_{23}PO_4$: C, 54.93; H, 8.84. Found: C, 54.66; H, 8.92.

Chapter 6

Transformation of Presumptive Precursors to Frontalin and *exo*-Brevicomin by Bark Beetles and the West Indian Sugarcane Weevil

6.1. Introduction. Biosynthesis of Bark Beetle Pheromones.

Plants often deter insect attack by production of cytotoxic terpenes. High levels of β-pinene and bornyl acetate in Douglas Fir confer resistance against the western spruce budworm, and (+)-3-carene has been suggested to be responsible for the resistance of western larch towards *Dendroctonus pseudotsugae* (Hopkins). Monoterpenes levels increase in lodgepole pine phloem tissue under attack by *D. ponderosae* (Hopkins).[199] Production of terpenes is induced when *Abies grandis* is attacked by bark beetles.[200] These secondary metabolites are also associated with host selection and pheromone biosynthesis in several species of bark beetles.

Pheromone production in the Scolytidae proceeds both *via* transformations of host volatiles and *de novo*.[30c-d,201] Evidence for conversion of plant derived terpenes to pheromones in Coleoptera is widespread.[202] Exposure of *Dendroctonus* beetles to α-pinene (**185**) results in production of *trans*-verbenol[203-205] (**186**), whereas *Ips* beetles convert α-pinene in oleoresin and myrcene (**187**) to verbenols, ipsdienol (**188**) and ipsenol (**189**), respectively (Figure 6.1).[203,204-211]

De novo biosynthesis of pheromones is also known. In the absence of myrcene *I. paraconfusus* (Lanier) produces ipsdienol (**188**).[212] Furthermore, *I. duplicatus* (Sahlb.)[213a,b] decreased its production of ipsdienol by 70 %, and myrcenol by 40 %, when compactin (an inhibitor of hydroxymethylglutaryl-coenzyme A, an enzyme that operates early in terpene biosynthesis prior the formation of mevalonate) was applied to the beetle's abdomen[213a] and even

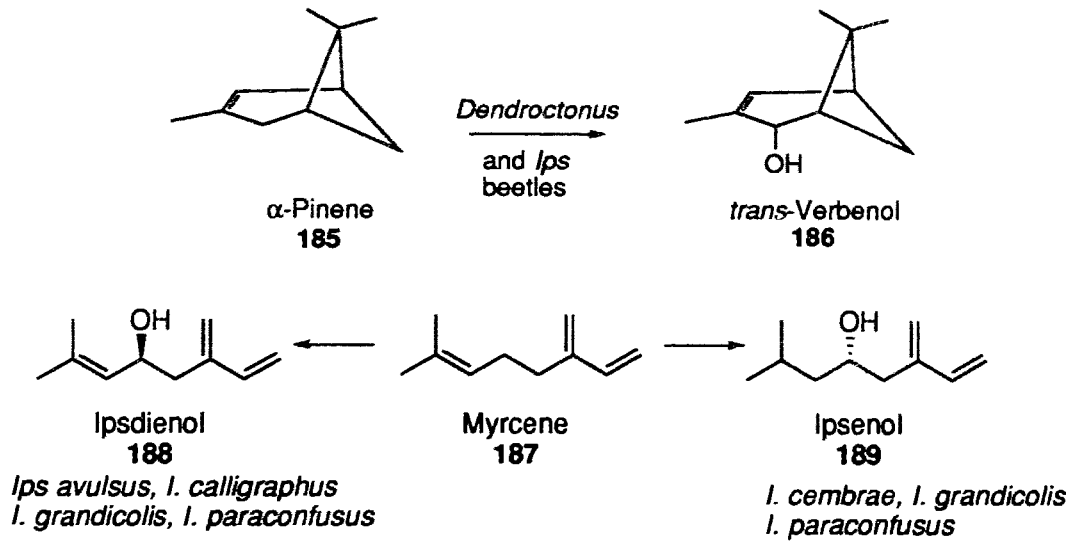


Figure 6.1. Oxidation of α-pinene and myrcene by bark beetles.

though pheromone production is stimulated by the addition of methoprene, addition of compactin blocked pheromone production.[213b] Pheromones of the boll weevil, *Anthonomus grandis* (Boheman), were originally hypothesized to be produced from host terpenes.[214] However, feeding experiments using radiolabelled acetate, mevalonate and glucose subsequently demonstrated[215] that these primary metabolites are a source of grandlure [(1*R*,2*S*)-(+)-1-methyl-1-(2-hydroxy)-ethyl-2-isopropenylcyclobutane (**190**), (*Z*)-3,3-dimethyl-$\Delta^{1,\beta}$-cyclohexene ethanol (**191**), (*Z*)-3,3-dimethyl-$\Delta^{1,\beta}$-cyclohexene acetaldehyde (**192**) and (*E*)-3,3-dimethyl-$\Delta^{1,\alpha}$-cyclohexene acetaldehyde (**193**), Figure 6.2]

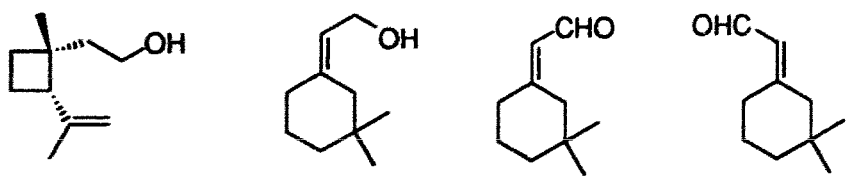
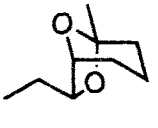
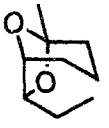


Figure 6.2. Pheromone components of the boll weevil.

Although bicyclic acetals represent an important group of scolytid aggregation pheromones, only for *exo*- (**194**) and *endo*-brevicomin (**195**) have detailed biosynthetic studies been reported.[216]

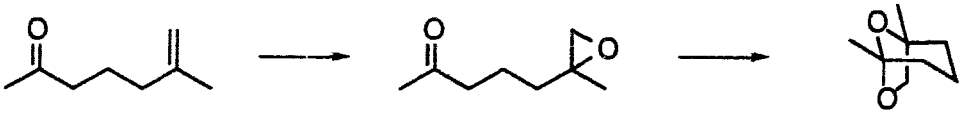


exo-Brevicomin
194



endo-Brevicomin
195

Frontalin (1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane, **196**) is an aggregation pheromone of several *Dendroctonus* beetles, including the Southern pine beetle, *Dendroctonus frontalis* (Zimmerman)[217] and the spruce beetle, *D. rufipennis* (Kirby).[218] 6-Methyl-6-hepten-2-one (**197**) has been suggested as a biosynthetic precursor of **196**.[4p,219] This possible precursor has been predicted as being derived from 6-methyl-5-hepten-2-one, sulcatone (**118**) or the corresponding alcohol, sulcatol.[4p] Thus, **196** has been envisioned to be formed from **197** by epoxidation (to form **198**) and cyclization in a process similar to that described for *exo*-brevicomin (Figure 6.3).[216b,219]



197 **198** Frontalin
196

Figure 6.3. Proposed biosynthetic route to frontalin.

The objectives of this study were to test the hypotheses, 1) that 6-methyl-6-hepten-2-one (**197**) is a biosynthetic precursor of frontalin in *D. rufipennis* and 2) that the biosynthesis of frontalin and *exo*-brevicomin from 6-methyl-6-hepten-2-one and (*Z*)-6-nonen-2-one, respectively, are specific to the beetles that utilize them as aggregation pheromones (Figure 6.4).

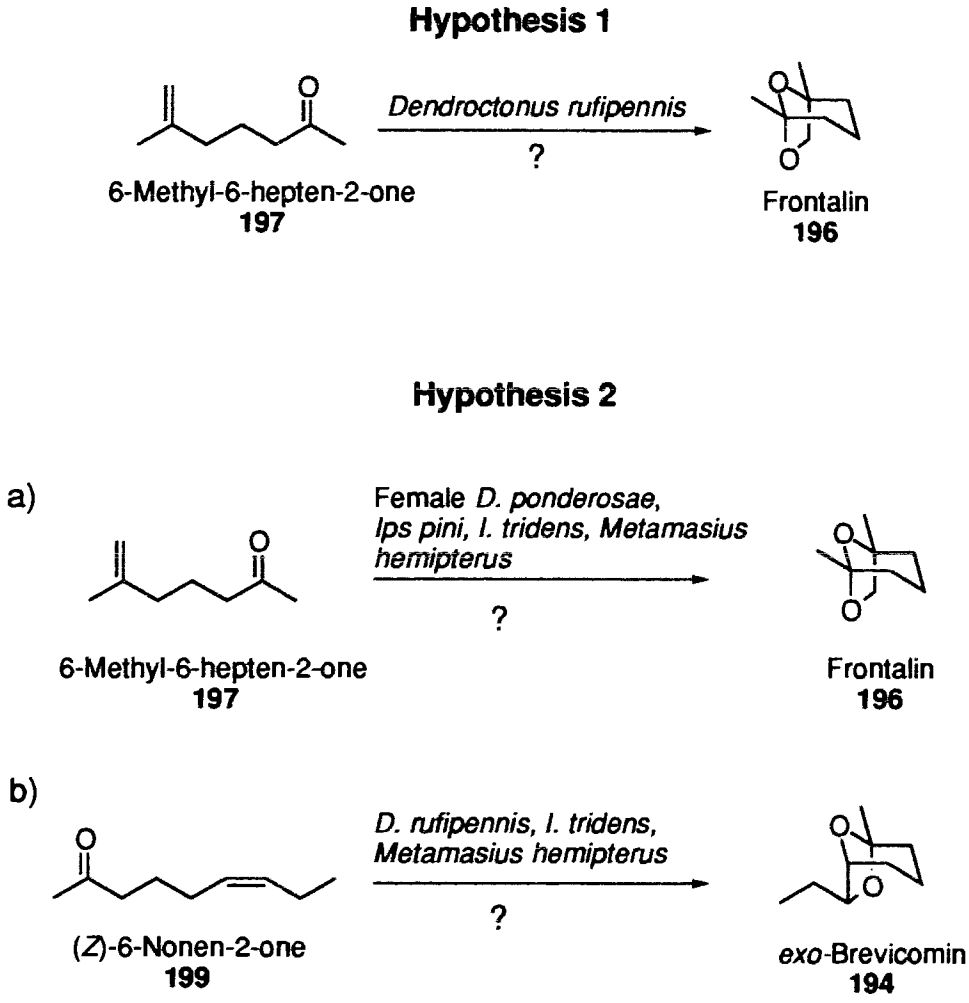
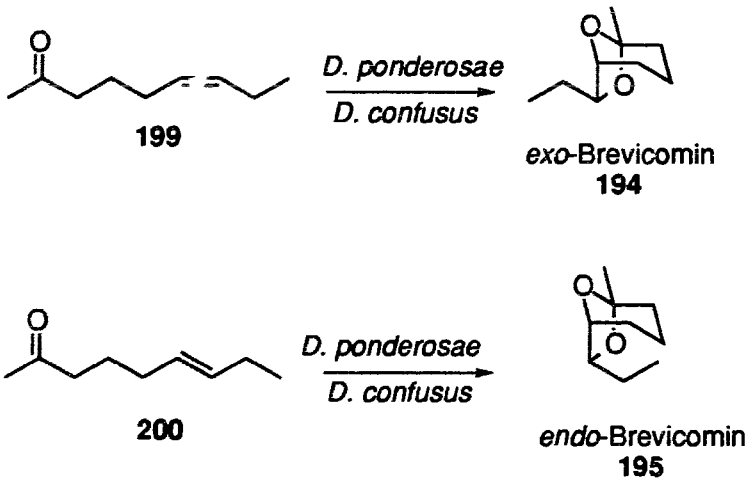


Figure 6.4. Presumptive precursor for frontalin biosynthesis by *D. rufipennis* (hypothesis 1) and production of frontalin and *exo*-brevicomin by *Ips* and *Metamasius* beetles (hypothesis 2).

6.2. Rationale.

Vanderwel and coworkers[216a] demonstrated the transformation of deuterated (*Z*)-(**199**) and (*E*)-6-nonen-2-one (**200**) to *exo*- and *endo*-brevicomin, respectively, by the mountain pine beetle, *Dendroctonus ponderosae* (Hopkins) and the western balsam bark beetle, *Dryocetes confusus* (Swaine).



The labelling pattern observed from the incorporation of ^{18}O-labelled precursors into **194** established that *D. ponderosae* converted (*Z*)-6-nonen-2-one to (+)-**194** by non-enantioselective oxidation of **199** followed by cyclization *via* either enantiomeric keto epoxides **201a** or **201b** (Figure 6.5).[216b] Analogous reasoning may be applied to the formation of frontalin in the spruce beetle.

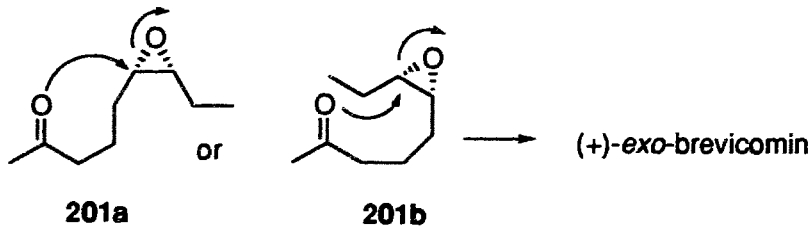
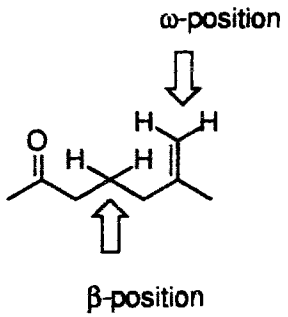


Figure 6.5 Proposed mechanism for the formation of (+)-**194** by bark beetles.

6.3. Synthesis of Frontalin Precursors.

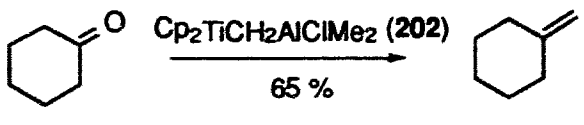
Based on the above arguments, 6-methyl-6-hepten-2-one was selected as the most logical precursor of frontalin. Two possible positions (β or ω-position) for deuterium label[220] were envisioned in 6-methyl-6-hepten-2-one:

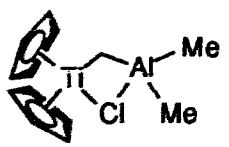


Deuteration at the ω-position might be achieved by Wittig reaction of monoprotected 2,6-heptanedione or by methylenation, catalyzed by $Zn/TiCl_4$, of a suitable precursor.[221] β-Deuteration could be achieved according to the procedure reported by Bartlett and coworkers.[222]

6.3.1. ω–Deuteration.

Methylenation of ketones using titanium compounds catalyzed by Lewis acids (e.g., **202**) was first reported by Tebbe and coworkers[223] in 1978. The advantages of this method are suppression of ketone enolization that normally occurs during Wittig protocols, improved yields and compatibility with several functional groups (e.g., lactones, esters, ethers, acetals, carboxylic acids).[224]



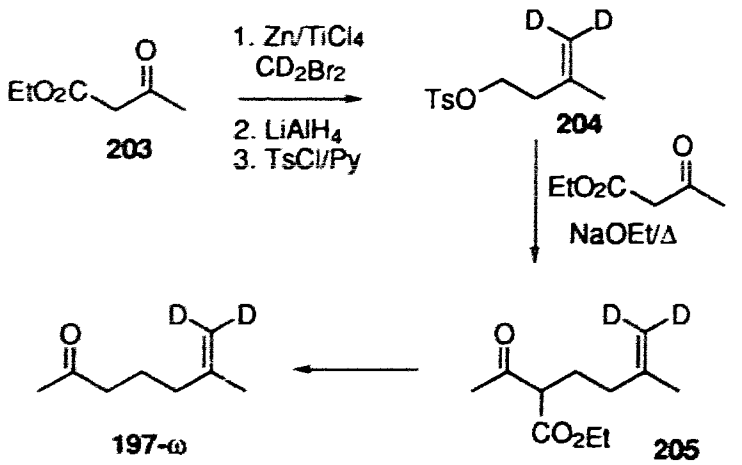


202

Similar efforts, based on modifications of Tebbe's catalyst (**202**), were pursued by Takai and coworkers[225] using Zn dust and several Lewis acids. Lombardo[221] applied a modified Takai procedure to the methylenation of

gibberellin norketone (93 % yield). Instead of the *in situ* procedure, Lombardo preformed the titanium complex (Zn-$TiCl_4$-CH_2Br_2) before addition of the ketone.

Synthesis of **197-ω** was thus envisioned by a three step procedure, starting with the methylenation of ethyl acetoacetate (**203**), conversion to the deuterio tosylate **204**, follow by alkylation (to form **205**) and decarboxylation (Scheme 6.1). Replacement of CH_2Br_2 by CD_2Br_2 would allow the introduction of the deuterium in the desired position.

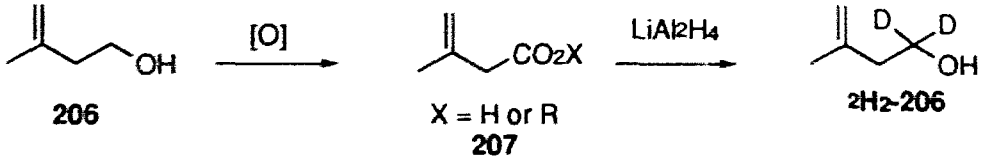


Scheme 6.1. Proposed synthesis of **197-ω**.

Several reactions were conducted using Lombardo's procedure with ethyl acetoacetate (**203**) and Zn-$TiCl_4$-CH_2Br_2. Zinc dust was activated by the procedure of Knochel[226] or Fieser and Fieser.[87] Starting material was recovered in all trials. No evidence of any methylenated product was obtained by analysis of reaction mixtures by spectroscopic methods. Tautomerization between the keto and enol forms of ethyl acetoacetate may account for the observed results.

6.3.2. β-Deuteration.

An alternate synthetic scheme can be used to incorporate deuterium at the β-position. Commercially available 3-methyl-3-buten-1-ol (**206**) can be converted to the carboxylic acid or ester (**207**) and reduced with $LiAl^2H_4$ (Scheme 6.2).



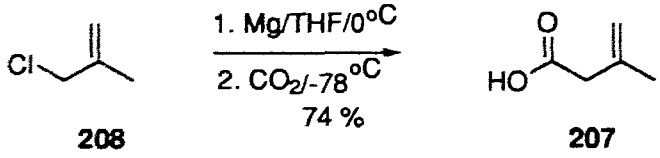
206 X = H or R **207** **$^2H_2$-206**

Scheme 6.2. Proposed synthesis of **$^2H_2$-206**.

Among the oxidation methods available for conversion of primary alcohols to carboxylic acids,[227] Jones' reagent was initially selected.[228] The resulting product was a mixture of **207** (X = H) (~45 % yield) and the corresponding ester with **206**. Similar results were obtained with calcium hypochlorite/HCl/*tert*-butanol.[229] Conversion of **206** directly to an ester by the method of Corey and Samuelsson[230] (CrO_3•Py complex/acetic anhydride/*tert*-butanol) was attempted. This process is considered to involve an oxidation to the aldehyde, then formation of the *tert*-butyl hemiacetal and then oxidation to the *tert*-butyl ester. When this method was applied to **206** mixtures of unreacted alcohol, acid and esters were obtained.

Alternative procedures to generate **207** (X = H) were considered. Reaction of CO_2 and 2-alkenylmagnesium halide (e.g., **208**) under Oppolzer's conditions[231] offered a possible alternative. One difficulty encountered in this process arises from coupling of the Grignard intermediate and unreacted alkenyl halide (**208**). Use of highly activated magnesium and low temperatures minimizes this reaction. Oppolzer and coworkers suggest activation of magnesium by evaporation of the metal into cooled THF. Replacement of this

active form of magnesium by activated magnesium dust (for details see experimental section) rendered 3-methyl-3-butenoic acid (**207**) in good yield (Scheme 6.3).



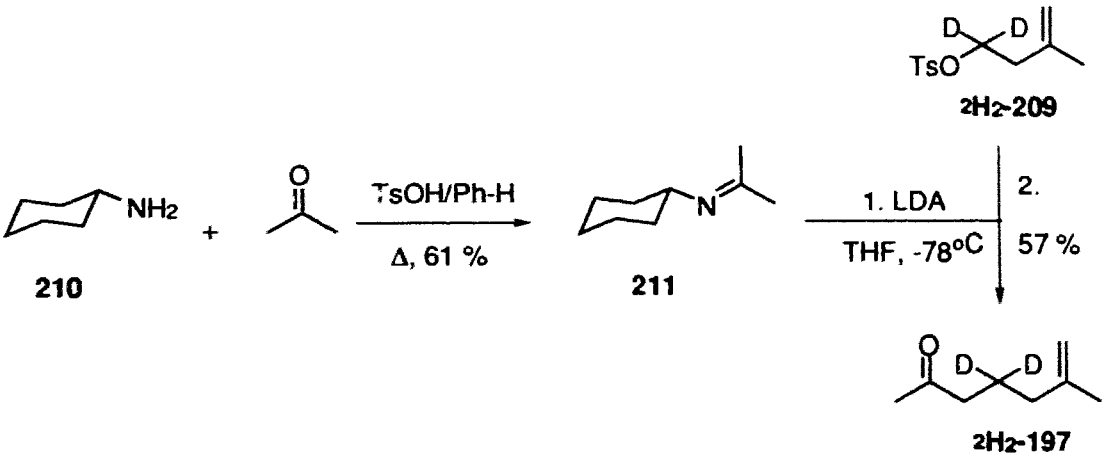
208 **207**

Scheme 6.3. Synthesis of 3-methyl-3-butenoic acid **207**.

Reduction of **207** with $LiAl^2H_4$ and tosylation afforded (1,1-$^2H_2$)-3-methyl-3-butenyltosylate (**$^2H_2$-209**) in 72 % overall yield from **207**. Deuterium enrichment (98 %) was determined by measurement of the intensity of the *m/z* 68 and 70 fragment ions which correspond to loss of M^+-$C_7H_7SO_3$. Deuterium content was also estimated by ^2H NMR (TsO-$\underline{CD_2}$- δ4.12, $CHCl_3$). According to Scheme 6.1, alkylation of sodium ethyl acetoacetate with tosylate **$^2H_2$-209**, hydrolysis and decarboxylation should produce ketone **197** (Scheme 6.1). This procedure was repeated several times using non-deuterated 3-methyl-3-butenyltosylate with overall yields of 10-30 %.

To avoid losses of deuterated material, a different route to **197** was conceived. The use of metalloimines in alkylation reactions is well known.[232] Therefore, 4,4-$^2H_2$-6-methyl-6-hepten-2-one (**$^2H_2$-197**) was prepared according to the procedure of Pearce and coworkers for the synthesis of 4,6-dimethyl-7-octadecen-3-one.[233] Alkylation of the lithium salt of the ketimine formed from cyclohexylamine (**210**) and acetone with **$^2H_2$-209** in THF gave, after hydrolysis, **$^2H_2$-197** in 57 % yield (98 % deuterium). Deuterium content was determined by measurement of the relative intensities of the *m/z* = 110 and 108 fragment ions which correspond to loss of H_2O from the molecular ion. These measurements were conducted by selective ion monitoring and verified by ^2H NMR (-$\underline{CD_2}$-

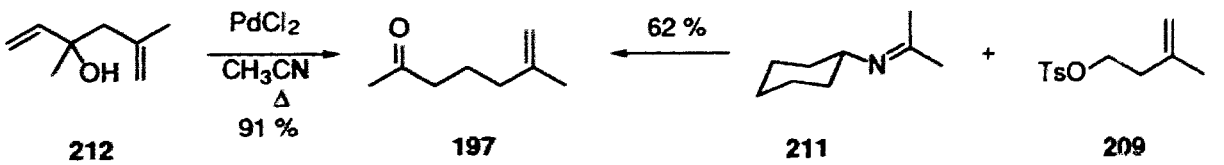
δ1.69, $CHCl_3$) (Scheme 6.4). Lithium diisopropylamide[234] gave a higher yield than the recommended base, ethyl magnesium bromide.[233,235]



Scheme 6.4. Synthesis of $^2H_2$-**197**.

6.3.3. Synthesis of 6-Methyl-6-hepten-2-one.

Synthesis of 6-methyl-6-hepten-2-one was achieved by alkylation of **211** by 3-methyl-3-butenyltosylate, **209**, in 62 % yield by the above procedure or in 91% yield by palladium-catalyzed [3,3] sigmatropic rearrangement[236] of 3,5-dimethyl-1,5-hexadien-3-ol (**212**) (Scheme 6.5).



Scheme 6.5. Synthesis of 6-methyl-6-hepten-2-one, **197**.

6.4. *In vivo* Experiments.

Spruce beetles, *Dendroctonus rufipennis* (Kirby), mountain pine beetles, *Dendroctonus ponderosae* (Hopkins), pine engravers, *Ips pini* (Say), *Ips tridens* (Mannerheim) and sugarcane weevils, *Metamasius hemipterus sericeus* (Olivier), were exposed to $^2H_2$-**197**, **197**, (*Z*)-6-nonen-2-one (**199**), 6-methyl-5-hepten-2-

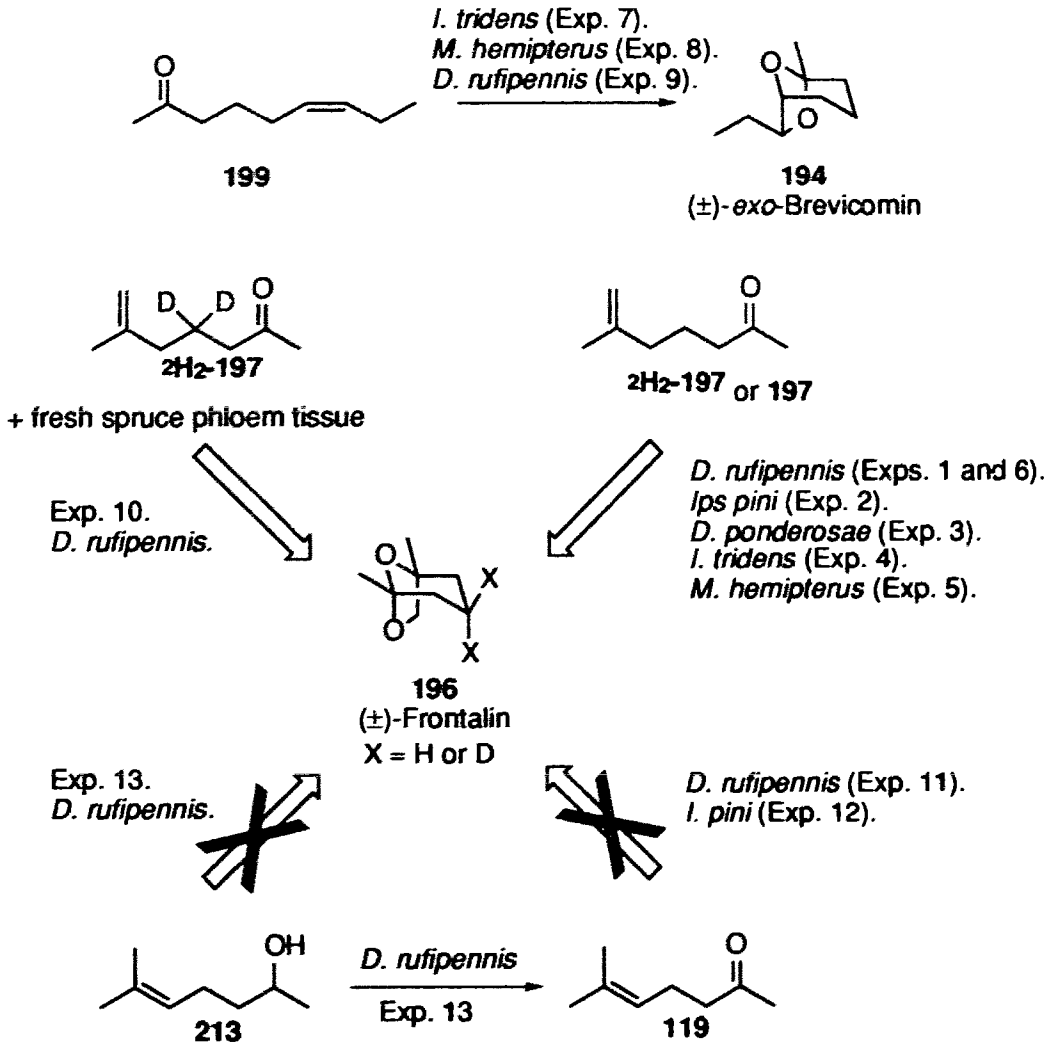
one (**119**) or 6-methyl-5-hepten-2-ol (**214**) as described in Scheme 6.6 and Table 6.1 (for details see experimental procedure).

6.4.1. *In vivo* Results.

Exposure of males and females *D. rufipennis* to (4,4-$^2H_2$)-6-methyl-6-hepten-2-one (**$^2H_2$-197**) (Exp. 1, Table 6.1), invariably resulted in production $^2H_2$-frontalin (**$^2H_2$-196**). The EI-mass spectrum of beetle-produced **196** clearly indicated enrichment of two deuteriums (*m/z* = 144, 114, 102) relative to non-deuterated **196** (*m/z* = 142, 114,100) (Figure 6.6). Male or female pine engravers exposed to **197** (Exp. 2, Table 6.1) also produced **196** as indicated by GC-MS and GC-MS-SIM analyses of beetle-produced volatiles. Further exposure of female *D. ponderosae* to **$^2H_2$-197** (Exp. 3, Table 6.1), and exposure of male and female *I. tridens* and *M. hemipterus* (Exps. 4-5, Table 6.1) to **197**, resulted in the production of deuterio- and protio-**196**, respectively.

Insects used in experiments 2-5 do not naturally produce **196**. Although **196** is a common aggregation pheromone in scolytids, it has never been reported for the genus *Ips*. Frontalin was also not detected in pheromone analysis of the curculionid *M. hemipterus*. Production of **196** by *Ips* and *Metamasius* during exposure to **197**, therefore, represents a non-specific and non-selective biotransformation. Similarly, neither *I. tridens*, *M. hemipterus* nor female mountain pine beetle naturally produce *exo*-brevicomin (**194**), but did so (Figure 6.8) when exposed to (*Z*)-6-nonen-2-one (**199**) (Exps. 7-9, Table 6.1), the proposed precursor for *exo*-brevicomin in male mountain pine beetle.

Enantioselective production of (+)-**196** by female *D. rufipennis* boring into logs of Engelmann spruce is known.[237] Gas chromatographic analyses on a Cyclodex-B column of volatiles produced by *D. rufipennis* exposed to **197** (Exp. 6) revealed **196** produced under these unnatural conditions was either racemic



Scheme 6.6. Summary of exposure experiments with scolytid and curculionid beetles.

Table 6.1 Exposure of scolydid and curculionids to presumed precursors of bicyclic acetal pheromones.

Exp.	Insect	Precursor[a]	Number of beetles exposed		Number of beetles control		Number of beetles *per* replicate	
			Males	Females	Males	Females	Males	Females
1	*D. rufipennis*	**$^2H_2$-197**	16	16	16	16	4	4
2	*I. pini*	**197**	70	70	70	70	10	10
3	*D. ponderosae*	**$^2H_2$-197**		8		8		4
4	*I. tridens*	**197**	40	40	40	40	10	10
5	*M. hemipterus*	**197**	4	4	2	2	1	1
6	*D. rufipennis*	**197**	20	20	16	16	4	4
7	*I. tridens*	**199**	40	40	40	40	10	10
8	*M. hemipterus*	**199**	4	4	2	2	1	1
9	*D. rufipennis*	**199**	12	12	8	8	4	4
10	*D. rufipennis*[b]	**$^2H_2$-197**	16	16	4	4	4	4
11	*D. rufipennis*	**118**	24	24	24	24	4	4
12	*I. pini*	**118**	50	50	50	50	10	10
13	*D. rufipennis*	**213**	24	24	4	4	4	4

(a) **$^2H_2$-197** = (4,4-$^2H_2$)-6-methyl-6-hepten-2-one; **197** = 6-methyl-6-hepten-2-one; **199** = (*Z*)-6-nonen-2-one; **118** = 6-methyl-5-hepten-2-one; **213** = 6-methyl-5-hepten-5-ol. (b) The beetles were exposed in the presence of fresh Engelmann spruce phloem.

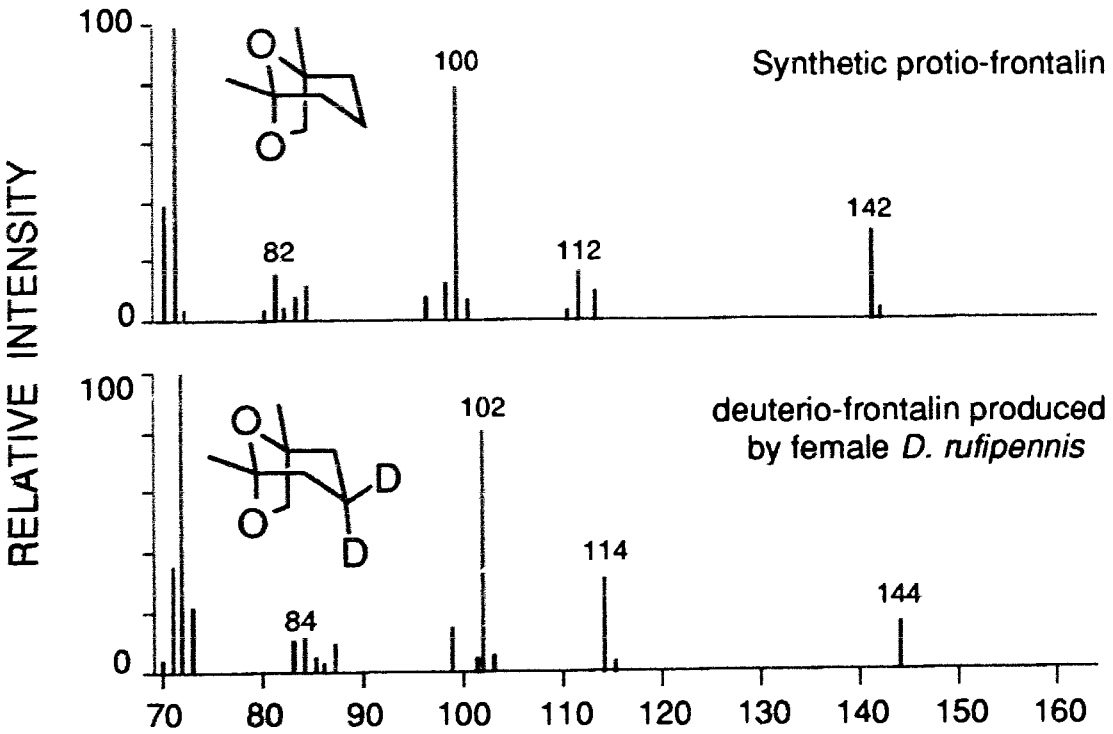


Figure 6.6. Mass spectra of synthetic protio-frontalin and deuterio-frontalin, produced by *D. rufipennis* upon exposure to (4,4-$^2H_2$)-6-methyl-6-hepten-2-one (**$^2H_2$-197**).

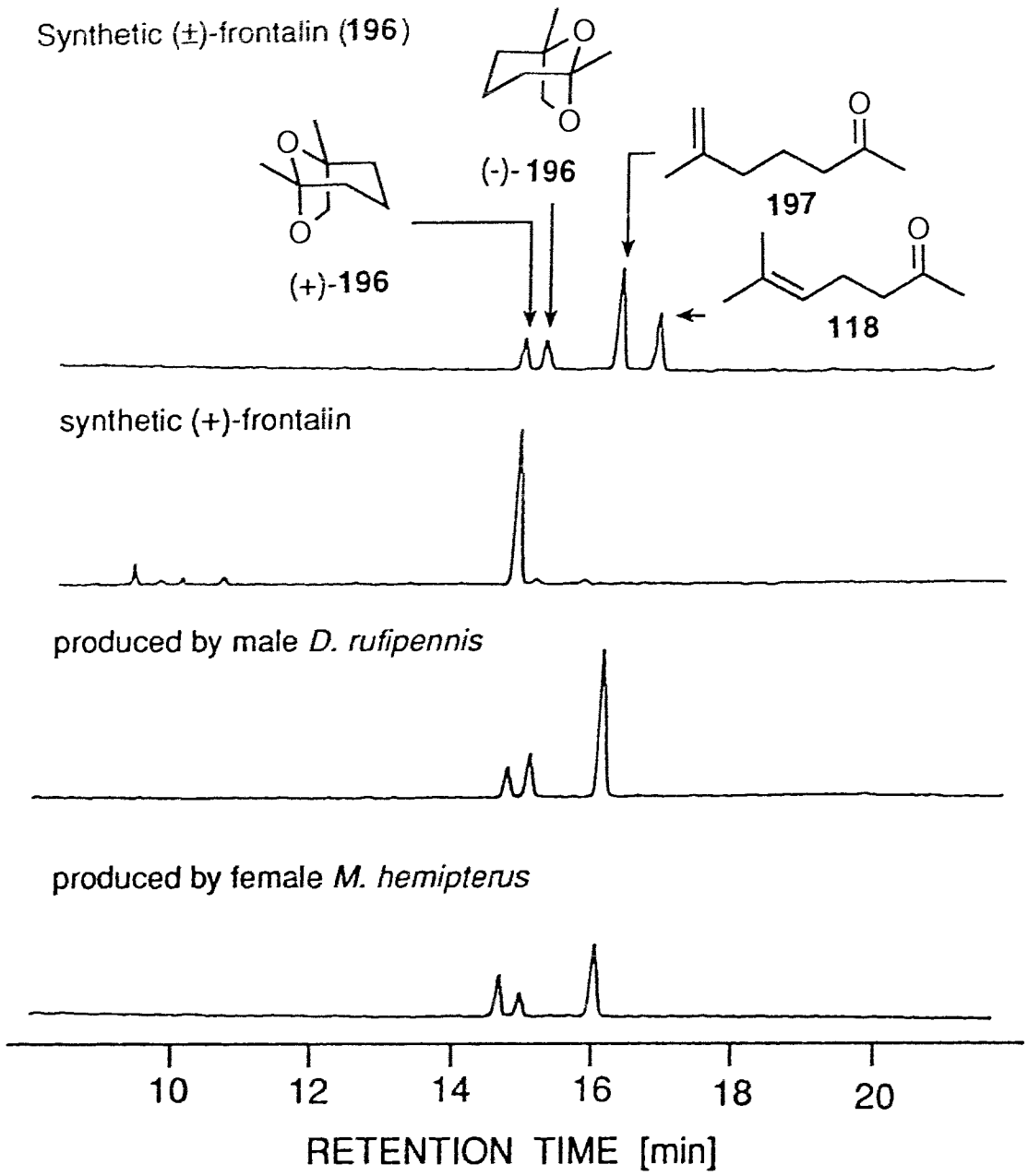


Figure 6.7. Gas chromatograms analyses of synthetic (±)- and (+)-frontalin (**196**), and **196** produced by *D. rufipennis* and *M. hemipterus* during vapour exposure to 6-methyl-6-hepten-2-one (**197**). Chromatograms for male and female beetles were virtually identical. Exposure of female *D. ponderosae* to deuterio-**197** resulted in the production of racemic deuterio-**196**. Chromatography: Cyclodex-B (30 m X 0.25 mm ID) column; 80°C isothermal; split injection; linear flow velocity of carrier gas: 35 cm s^{-1}; injector temperature: 220°C.

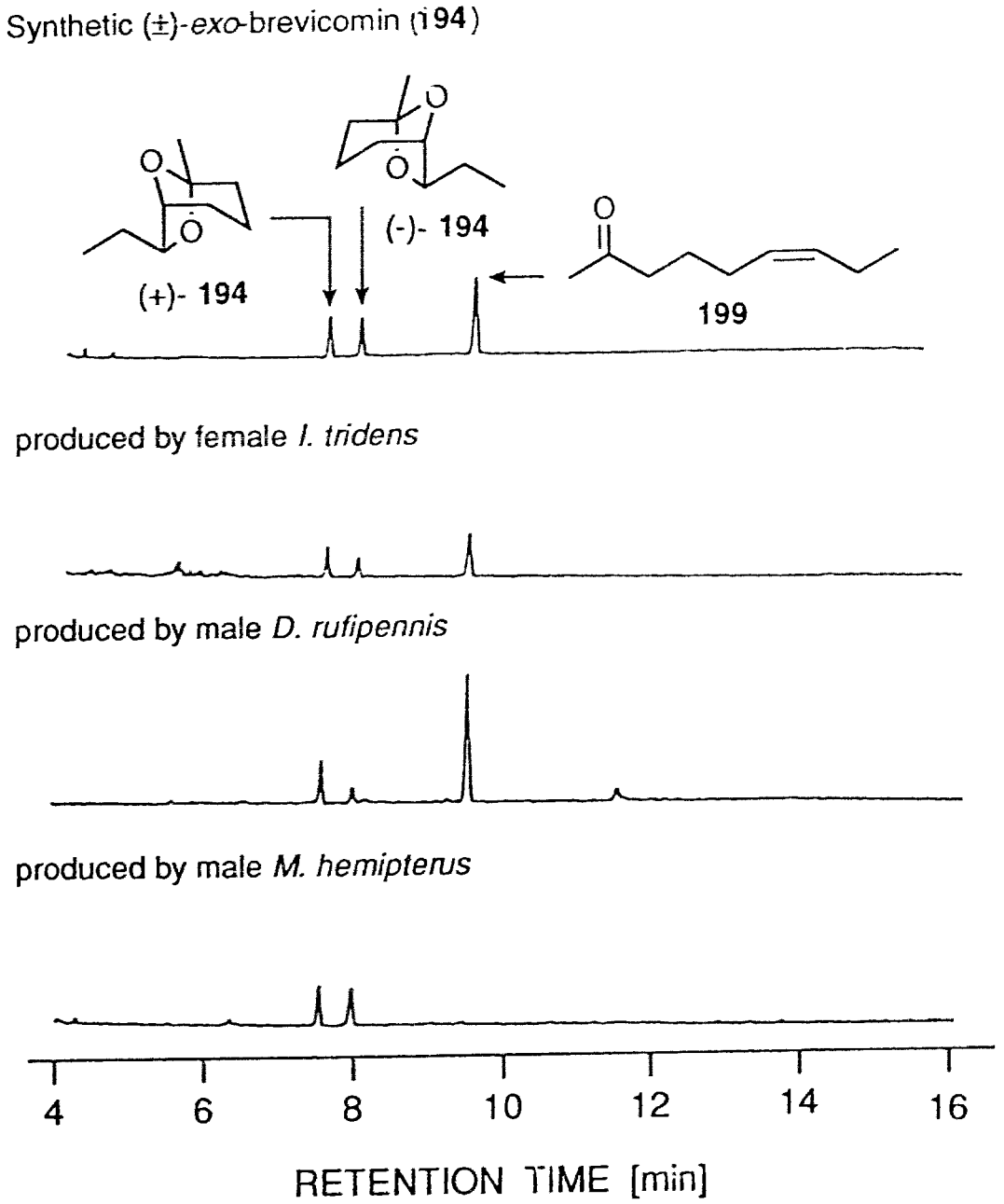


Figure 6.8. Gas chromatograms analyses of synthetic (±)-*exo*-brevicomin (**194**), and **194** produced by *I. tridens*, *D. rufipennis* and *M. hemipterus* during exposure to (*Z*)-6-nonen-2-one (**199**). Chromatograms for male and females were virtually identical. Chromatography: Cyclodex-B (30 m X 0.25 mm ID) column; 110°C isothermal; split injector; linear flow velocity of carrier gas: 35 cm s^{-1}; injector temperature: 220°C.

or of low enantiomeric excess (Figure 6.7). All insects exposed to **$^2H_2$-197** or **197** produced enantiomerically enriched **196**. When exposed to **197**, *D. rufipennis* produced more (-)-**196** (22-30 % ee) (Figure 6.7) while *D. ponderosae* produced (±)-**196** and *M. hemipterus* produces (+)-**196** which is 26-30 % ee (Figure 6.7). Similarly, (+)-**194** was produced (Exps. 7-9) in 42-56 % ee by *D. rufipennis*, in 27-30 % ee by *I. tridens* and in 0 % ee by *M. hemipterus* (Figure 6.8).

Feeding in phloem tissue or exposure to tree volatiles may be required for induction of enzymes mediating biosynthesis of **196**.[238] Thus, male and female *D. rufipennis* were separately exposed to fresh phloem disks laced with **$^2H_2$-197** (Exp. 10). Although beetles were observed to feed on phloem disks, the **$^2H_2$-196** produced possessed enantiomeric ratios comparable to those produced in the absence of phloem.

The presence of **197** in volatiles of male and female *D. rufipennis* would provide evidence that **197** is formed by these insects. A search for **197** and related compounds revealed only isomeric 6-methyl-5-hepten-2-one (**119**) in beetle-produced volatiles. Because **196** may be derived from isomerization of **119**[5b,220] or from oxidation and isomerization of 6-methyl-5-hepten-2-ol, beetles were also exposed to **119** [*D. rufipennis* (Exp. 11), *I. pini* (Exp. 12)] or to **213** [*D. rufipennis* (Exp. 13)]. Oxidation of **213** to **119** (Exp. 13) coupled with the lack of frontalin formation from **119** or **213** (Exps. 11-13) indicates that neither **119** or **213** are precursors of **196** under the conditions of these experiments.

Enantioselective conversion of **199** to (+)-*exo*-brevicomin by male mountain pine beetle[216] suggests that **199** may be a natural precursor. Failure to demonstrate enantioselective conversion of **197** to **196** by spruce beetle in this study does not eliminate the possibility that **197** is a natural precursor of **196**. During exposure experiments, **197** may have overloaded the pheromonal

biosynthetic apparatus, and non-specific oxidases may have operated to convert excess **197** to (±)-**196**. Attempts to avoid "overloading" were made by employing the same amount of **197** (0.1 μL) as **199** that was administered to *D. ponderosae* in the study of **194** biosynthesis. It is also possible that under the present experimental conditions the pheromonal biosynthetic apparatus in *D. rufipennis* was not triggered. Beetles were feeding naturally while exposed to **197**, but, the experiment lacked a preceding dispersal flight which may be a prerequisite for pheromone production (flight and starvation of male *I. pini* prior to myrcene exposure, however, reduced rather than enhanced ipsdienol production[239]). Finally, failure of spruce beetles to transform **197** to **196** with high enantiomeric purity may signal production of **196** by a route not involving **197** as a precursor. For example, *I. paraconfusus*, produces substantial quantities of ipsenol and ipsdienol while feeding on *Pinus sabiana* phloem with low levels of myrcene (< 0.01 μg/g), suggesting that precursors other than myrcene may be utilized for ipsenol and ipsdienol biosynthesis.[213a]

In conclusion, even though spruce beetles converted 6-methyl-6-hepten-2-one (**197**) to frontalin, lack of **197** in beetle volatiles and non-natural production of a mixture of enantiomers of frontalin rather than enantiomerically pure (+)-frontalin, do not support the hypothesis that **197** (under the conditions tested) is the frontalin precursor in spruce beetle. Production of frontalin and *exo*-brevicomin by scolytid and curculionid beetles, not naturally producing these bicyclic acetals, demonstrates widespread occurrence of non-specific polysubstrate monooxidases in these Coleoptera.[240]

6.5. Experimental Section.

For general methods see Experimental Section in Chapter 2.

Benzene and acetone were freshly distilled from activated 4A molecular sieves and anhydrous $CaSO_4$, respectively. Diisopropyl amine and cyclohexyl amine were freshly distilled from sodium under argon. Magnesium dust was washed several times with 5 % HCl, once with water, ethanol and Et_2O, and allowed to dry overnight in an oven at 140°C. Enantiomers of frontalin and *exo*-brevicomin were available from Pherotech Inc., Delta, B.C.

6.5.1. *In vivo Experiments.*

Spruce beetle-infested Engelmann spruce logs,[i] *Picea engelmannii* (Parry), were collected near MacKenzie, Princeton and Merritt, British Columbia (B.C.). Prior to use, MacKenzie and Princeton logs were stored at ~0°C for several months, whereas Merrit logs were immediately placed in cages at 22-25°C and 40-60 % relative humidity. Pine engravers, *Ips pini* (Say), and mountain pine beetles, *Dendroctonus ponderosae* (Hopkins) were obtained from infested lodgepole pine logs, *Pinus contorta* (var *latifolia* Engelman), collected near Princeton. *I. tridens* (Mannerheim) were obtained from infested Engelmann spruce logs near Slate Creek, B.C. The cut ends of all logs were sealed with hot paraffin wax to prevent desiccation. Emergent beetles were collected daily, sexed and used within 48 h. West Indian sugarcane weevils (WISW), *Metamasius hemipterus sericeus* (Olivier), were collected in the Palma Tica Oil Palm Plantation near Coto, Costa Rica.[ii]

In exposure experiments 1-9 and 11-13 (Table 6.1), insects were placed individually in capped vials,[239] containing 0 (control) or 0.1 μL of test chemical.

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[i] Collection by Ms. Therese Poland and Mr. Robert R. Setter, Department of Biological Sciences, Simon Fraser University.

[ii] Collection by Dr. Carlos Chinchilla, Palma Tica, Coto, Costa Rica.

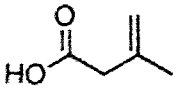
In Exp. 10 (Table 6.1, Scheme 6.1), each vial also contained a 25-30 mm disk of fresh spruce phloem. After 24 h at 18-22^{0}C, insects were crushed in dry ice-cooled pentane/ether (9:1, 250 μL), containing decane as internal standard. The crude extract was filtered through 1.5-2 cm of anhydrous $MgSO_4$ and pipetted onto a glass "boat" (4X1X1 cm) within a glass tube (20 cm long, OD 22 mm). This tube was placed inside a small. The inlet was connected to a charcoal filter (coconut shell, 50-80 mesh) and the outlet to a Porapak Q trap inserted into a dry ice/acetone cooled aluminum block. A slow nitrogen stream through the system for one hour, while the oven temperature was slowly increased to 90°C. Volatiles emanating from crude extract in the boat were captured on Porapak Q, eluted from it with Et_2O (1-2 mL) and concentrated for analyses. Groups of five samples were processed concurrently on a manifold of five pyrex glass tubes, each connected downstream to a Porapak Q trap. The solvent extracts were placed on glass wool in the pyrex tubes. A charcoal-filtered nitrogen stream was passed through the manifold for ~2 h, and trapped volatiles were eluted from Porapak Q with 1.5 mL of pentane and concentrated.

Volatiles from male and female spruce beetle feeding on suitable spruce logs were available from Professor G. Gries.[218,237]

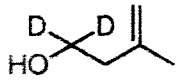
6.5.2. Analyses of Insect Extracts.

Volatile were analyzed by GC-mass spectrometry (MS) (Hewlett Packard 5985 B and Varian Saturn ion trap), employing fused silica columns (30 m X 0.25 mm ID; 0.25 mm film) coated with DB-1 or DB-5. Chiral determinations of frontalin and *exo*-brevicomin were carried out on a Cyclodex-B-coated column (30 m X 0.25 mm ID) which separates enantiomers with baseline resolution. Electron impact (EI, 70 eV) GC-MS analyses were conducted in both full scan and selected ion monitoring mode (SIM). A full scan mass spectrum of synthetic

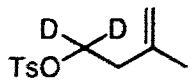
frontalin was obtained to select diagnostic ions. For GC-MSEI-SIM, synthetic frontalin, pentane or ether and concentrated insect extract were injected in split mode and analyzed by scanning for diagnostic ions.



3-Methyl-3-butenoic acid (207). 2-Methyl-1-propenyl magnesium chloride [prepared by Grignard reaction between 3-chloro-2-methyl-1-propene (**208**) (6.78 g, 7.4 mL, 75 mmol) and activated magnesium powder[232] (3.40 g, 0.14 mol) in THF at 0°C was cooled to -78°C. An excess of CO_2 gas was bubbled into the reaction for ~15 min. The mixture was stirred for 30 min then the cold bath was removed and the reaction allowed to warm to 0°C. Progress of the reaction was followed by analysis of aliquots by GC. Upon completion, the reaction was quenched with saturated NH_4Cl at 0°C. The aqueous layer was extracted with Et_2O (3 X 25 mL) and the combined organic layer concentrated *in vacuo*. The residue was brought to pH ~ 10 with 1 M NaOH. The basic layer was extracted with Et_2O (2 X 10 mL), acidified with cold dil. HCl, extracted with Et_2O (3 X 25 mL), washed with saturated NaCl and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed *in vacuo* and the residue distilled under reduced pressure (63-65°C @ 1 mm Hg) to give 5.55 g (98 % pure, 74 % yield). ^1H NMR[241] ($CDCl_3$, ppm): 1.85 (3H, s), 3.10 (2H, s), 4.90 (1H, d, J = 0.6 Hz), 4.97 (1H, d, J = 0.6 Hz) 11.92 (1H, br s); ^{13}C NMR ($CDCl_3$, ppm): 177.60, 137.91, 115.28, 43.08, 22.35.

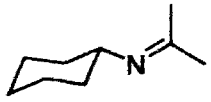


(1,1-$^2H_2$)-3-Methyl-3-buten-1-ol ($^2H_2$-206). To a suspension of $LiAl^2H_4$ (98 % atom % ^2H) (0.82 g, 19.5 mmol) in anhydrous ether at 0°C, was added dropwise, *via* cannula, a solution of 3-methyl-3-butenoic acid (**207**) (2.01 g, 20 mmol) in anhydrous Et_2O. After 0.5 h excess $LiAl^2H_4$ was destroyed at 0°C by slow addition of water. The resulting white precipitate was filtered and rinsed with small portions of Et_2O (4 X 10 mL). The solvent was removed by fractional distillation and the residue was used to the next step without further purification. EI-MS *m/z* (relative intensity): 88 (M^+, 42) 70 (M^+-H_2O, 90); FTIR (neat): 3440, 3069, 2973, 2931, 2255, 2168 cm^{-1}.

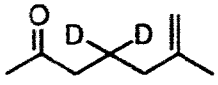


(1,1-$^2H_2$)-3-Methyl-3-butenyltosylate ($^2H_2$-209). To a solution of **$^2H_2$-206** in dry pyridine (30 mL) was added DMAP (0.56 g, 4.5 mmol). The flask was cooled to -10°C and *p*-toluenesulfonyl chloride (4.30 g, 22.5 mmol) added in one portion. Stirring was continued for 5 h at -10°C with monitoring of aliquots by GC and TLC (9:1, pentane/Et_2O, R_f = 0.20). The mixture was poured into ice-cooled NaCl solution and extracted (2 X 30 mL) with Et_2O. The organic layer was washed with 3 M HCl, saturated $NaHCO_3$, NaCl solution and dried over anhydrous $MgSO_4$. After concentration *in vacuo,* the residue was purified by column chromatography (9:1, pentane:Et_2O) to yield **$^2H_2$-209** (3.52 g, 72 % yield based on **207**, 98 % pure) as a pale yellow oil. ^1H NMR ($CDCl_3$, ppm): 1.66 (3H, s), 2.32 (2H, s), 2.44 (3H, s), 4.67 (1H, d, J = 0.8 Hz), 4.80 (1H, d J = 0.8 Hz), 7.36 (2H, dd, J = 8.0, 1.0 Hz), 7.80 (2H, dd, J = 8.0, 1.0 Hz); ^2H NMR ($CHCl_3$, ppm): 4.12; ^{13}C NMR ($CDCl_3$, ppm): 144.63, 140.17, 133.54, 129.77, 127.89, 113.04, 67.9 ($J_{C\text{-}^2H}$ = 16.7 Hz), 36.65, 22.29, 21.56; EI-MS *m/z* (relative intensity):

70 (M^+-$C_7H_7SO_3$, 100) (98 % deuterium enriched by correlation of 68/70 peaks); FTIR (neat): 3072, 2978, 2931, 2249, 2167, 1648, 1596, 1361, 1184, 1096, 1073, 959, 879, 816, 770 cm^{-1}; Anal. Calcd. for $C_{12}H_{14}{}^2H_2SO_3$: C, 59.98, H; 6.72. Found: C, 60.10; H, 6.79.

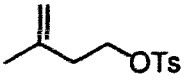


***N*-(1-Methylethylidine)cyclohexylamine (211).** A solution of anhydrous acetone (5.81 g, 7.34 mL, 0.1 mol), cyclohexylamine (**210**) (9.97 g, 11.4 mL, 0.1 mol), and *p*-toluenesulfonic acid (100 mg) in anhydrous benzene (100 mL) was refluxed in a Dean-Stark separator until no additional water was produced (~3 days). Benzene was removed and the residue distilled at reduced pressure (35-37°C @ 1 mm Hg) to yield **211** (8.34 g, 61 %, 95 % pure). ^1H NMR ($CDCl_3$, ppm): 1.28 (6H, m), 1.49 (2H, m), 1.76 (2H, m), 1.84 (3H, s), 1.98 (3H, s), 3.19 (1H, m); ^{13}C NMR ($CDCl_3$, ppm): 164.01, 59.39, 36.97, 33.65, 30.82, 29.41, 25.73, 25.08, 17.92; EI-MS *m/z* (relative intensity): 139 (M^+, 20), 124 (M^+-15, 100).

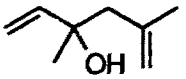


(4,4-$^2H_2$)-6-Methyl-6-hepten-2-one ($^2H_2$-197). To a stirred cold (-78°C) solution of LDA [prepared from 10 mmol of diisopropyl amine and 10 mmol of 2.45 M *n*-BuLi in hexanes at 0°C in THF] under a positive pressure of argon, was added **211** (1.38 g, 10 mmol) in THF (10 mL). After stirring for 45 min, a solution of **$^2H_2$-209** (2.42 g, 10 mmol) in THF (15 mL) was added dropwise *via* cannula and the resulting mixture was stirred for 3 h at -78°C. The mixture was quenched to slight acidity with 1 M HCl at 0°C. The organic layer was separated and the aqueous layer was extracted (2 X 10 mL) with Et_2O. The

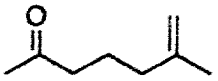
combined ether extracts were washed with saturated NaCl and dried over anhydrous $MgSO_4$. Column chromatography (9:1, pentane:Et_2O, R_f = 0.27) afforded **$^2H_2$-197** (0.63 g, 57 % yield, 95 % pure) as a pale yellow liquid. ^1H NMR ($CDCl_3$, ppm): 1.72 (3H, s), 2.02 (2H, s), 2.16 (3H, s), 2.40 (2H, s), 4.67 (1H, d, J = 1.0 Hz), 4.72 (1H, d J = 1.0 Hz); ^2H NMR ($CHCl_3$, ppm): 1.69; ^{13}C NMR ($CDCl_3$, ppm): 208.64, 144.98, 110.51, 42.81, 36.89, 29.84, 22.28 ($J_{C\text{-}^2H}$ = 16.7 Hz), 22.10; EI-MS *m/z* (relative intensity): 128 (M^+, 5), 110 (M^+-H_2O) 65 (98 % deuterium enriched by correlation of 110/108 peaks in SIM mode.); FTIR (neat): 3074, 2969, 2917, 2250, 2159, 1716, 1649, 1446, 1361, 1179, 962, 888 cm^{-1}.



3-Methyl-3-butenyltosylate (209). Commercially available (Aldrich) 3-methyl-3-buten-1-ol was tosylated using the same procedure described for the synthesis of (1,1-$^2H_2$)-3-Methyl-3-butenyltosylate (**$^2H_2$-209**). ^1H NMR ($CDCl_3$, ppm): 1.65 (3H, s), 2.35 (2H, t, J = 7.5 Hz), 2.44 (3H, s), 4.16 (2H, t, J = 7.5 Hz), 4.68 (1H, d, J = 1.4 Hz), 4.79 (1H, s, J = 1.4 Hz), 7.34 (2H, dd, J = 10.0, 1.0 Hz), 7.78 (2H, dd, J = 10.0, 1.0 Hz).



3,5-Dimethyl-1,5-hexadien-3-ol (212). This compound was prepared by reaction of 2-methyl-1-propenyl magnesium chloride and 3-buten-2-one.[236] ^1H NMR ($CDCl_3$, ppm): 1.30 (3H, s), 1.78 (3H, s), 1.86 (1H, s), 2.30 (2H, s), 4.77 (1H, d, J = 1.3 Hz), 4.92 (1H, d, J = 1.3 Hz), 5.04 (1H, dd, J = 10.7, 1.3), 5.23 (1H, dd, J = 17.3, 1.3 Hz), 5.96 (1H, dd, J = 10.7, 17.3 Hz); FTIR (neat): 3445, 3075, 2933, 1710, 1643, 1107, 920, 777 cm^{-1}



6-Methyl-δ-hepten-2-one (197): This compound was prepared by the alkylation of **210** by 3-methyl-3-butenyltosylate, **209**, according to the former procedure or by the palladium catalyzed [3,3] sigmatropic rearrangement of **212**. In the latter process **212** (4.74 g) and $PdCl_2$ (17.5 mg) in dry CH_3CN (35 mL) were stirred for ~72 h at room temperature. After filtration of the catalyst, distillation at reduced pressure (70-73°C @ 25 mm Hg) afforded 4.31 g of **197** (91 % yield, 98 % pure)]. ^1H NMR ($CDCl_3$, ppm): 1.72 (5H, m), 2.00 (2H, t, J = 7.7 Hz), 2.13 (3H, s), 2.44 (2H, t, J = 7.7 Hz), 4.68 (1H, d, J = 1.2 Hz), 4.73 (1H, d, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$, ppm): 208.30, 145.07, 110.62, 43.04, 37.11, 29.97, 22.20, 21.58.

General Conclusions

The identification of male-produced aggregation pheromones of *Rhynchophorus phoenicis, R. cruentatus, R. bilineatus, Oryctes monoceros, O. rhinoceros, Metamasius hemipterus sericeus* and *Paramasius distortus* is an important step towards understanding the biology and chemical ecology of these insects and further expands the development of management programs.

The four stereoisomers of 3-methyl-4-octanol, the aggregation pheromone of the African palm weevil, *R. phoenicis*, 5-methyl-4-octanol, the aggregation pheromone of the Palmetto weevil, *R. cruentatus* and 4-methyl-5-nonanol, the aggregation pheromone of the Asian palm weevils *R. bilineatus, R. ferrugineus* and *R. vulneratus* and the sugarcane weevil *M. h. sericeus* were synthesized by the Sharpless asymmetric epoxidation combined with diastereoselective epoxide opening. This strategy uses inexpensive reagents and allows the synthesis of the four diastereoisomers of the respective alcohols from common intermediates. Synthetic stereoisomers were baseline-separated on a Cyclodex-B fused silica column. Use of this column in gas chromatographic-electroantennographic (GC-EAD) and GC-mass spectrometric analyses revealed that only one stereoisomer, (*3S,4S*)-3-methyl-4-octanol, (*4S,5S*)-5-methyl-4-octanol and (*4S,5S*)-5-methyl-4-nonanol is produced by male *R. phoenicis*, male *R. cruentatus*, and male *R. bilineatus, R. ferrugineus, R. vulneratus* and *M. h. sericeus*, respectively and elicit good antennal responses by conspecific male and female weevils.

In field trapping experiments, these *syn*-isomers strongly enhanced attraction to fresh palm or sugarcane tissue, whereas other stereoisomers were behaviorally benign.

EAD-active host volatiles were identified. However, superior attraction of fresh host tissue indicated that additional unknown semiochemicals must be identified if the kairomonal effect is to be mimicked.

Male coconut rhinoceros beetles, *Oryctes monoceros* produces a single sex-specific compound and *O. rhinoceros*, produces three sex-specific compounds, ethyl 4-methyloctanoate, ethyl 4-methylheptanoate, and 4-methyloctanoic acid, the first of which is an aggregation pheromone in both species. Syntheses of these compounds involved conjugate addition of organocuprates to ethyl acrylate, whereas optically active isomers of ethyl 4-methyloctanoate were prepared from enantiomerically enriched citronellols. Field trapping experiments in Indonesia showed that ethyl (4*S*)-methyloctanoate and the racemic mixture were equally attractive to *O. rhinoceros.* Racemic ethyl 4-methyloctanoate was more effective in attracting *O. monoceros* (Africa) and *O. rhinoceros* (Indonesia) than ethyl chrysanthemumate, a previously recommended attractant.

(3*Z*,6*Z*)-3,6-nonadien-1-ol and *Z,E*-farnesene were identified in *Anastrepha obliqua* male volatiles as EAD active components. Efforts toward the synthesis of *Z,E*- and *E,E*-farnesenes (another major component of males extract in *A. obliqua*) were presented. Low chemical and isomeric yields hampered production of more than milligram quantities of *Z,E*- and *E,E*-farnesenes. However, regioselective formation of *E*- and *Z*-enolphosphates of α,β-unsaturated ketones, with regioselectivities >95 % were achieved.

(*Z*)-6-Nonen-2-one has recently been shown to be the biosynthetic precursor for the aggregation pheromone *exo*-brevicomin in mountain pine beetle, *Dendroctonus ponderosae* males. In this study, the following hypotheses were tested: 1) that 6-methyl-6-hepten-2-one is a biosynthetic precursor of the aggregation pheromone frontalin in the spruce beetle, *D. rufipennis* , and 2) that

frontalin and *exo*-brevicomin are produced from, respectively, 6-methyl-6-hepten-2-one and (*Z*)-6-nonen-2-one and that these aggregation pheromones are only produced by beetles that utilize them. Exposure of scolytids mountain pine beetle, spruce beetle, pine engravers, *Ips pini*, and *I. tridens*, and West Indian sugarcane weevil, *Metamasius hemipterus sericeus* to deuterio- or protio-6-methyl-6-hepten-2-one invariably resulted in the production of deuterio- or protio-frontalin. Similarly, exposure of *D. rufipennis*, *M. h. sericeus* and *I. tridens* to (*Z*)-6-nonen-2-one resulted in the production of *exo*-brevicomin. Experiments did not provide evidence that 6-methyl-6-hepten-2-one is the natural biosynthetic precursor of frontalin in spruce beetle. Thus, there was an: 1) absence of this compound in spruce beetle volatiles, 2) inability of this beetle to isomerize 6-methyl-5-hepten-2-one to 6-methyl-6-hepten-2-one, and 3) production of an enantiomeric mixture of frontalin rather than natural (+)-frontalin from this ketone. Production of enantiomerically enriched frontalin and *exo*-brevicomin by all the beetles reveal non-specific and non-selective biotransformations, and demonstrates occurrence of non-specific polysubstrate monooxidases in these Coleoptera.

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