

**“BABEȘ-BOLYAI” UNIVERSITY CLUJ-NAPOCA**  
**FACULTY OF CHEMISTRY AND CHEMICAL ENGINEERING**

**CARBON-CARBON COUPLING REACTIONS USED IN**  
**THE SYNTHESIS OF PHEROMONES**

**Thesis summary**

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**CLUJ-NAPOCA**

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**Keywords:**  $\omega$ -functionalized alkynylmercury derivatives, cross-coupling, monoene pheromone, diene pheromone, *Adoxophyes orana*, *Cydia pomonella*, attract and kill biotechnology.

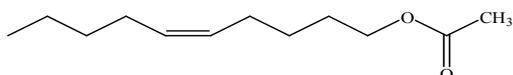
## INTRODUCTION

Pheromones are chemicals that can contribute to the control of pests explaining the interest shown towards this class of biologically active compounds and made use of the knowledge acquired in other specialty domains such as biology, physiology, ecology etc.

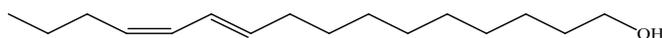
Over the years important developments were recorded toward establishing the chemical structure of pheromones which open the way to the synthetic approach in obtaining them.

The most studied pheromones are the sex pheromones of butterfly (*Lepidoptera*) (over 350 species were identified), flies (*Diptera*), bugs (*Coleoptera*), the tracks pheromones of ants (*Hymenoptera*) and termites (*Isoptera*).

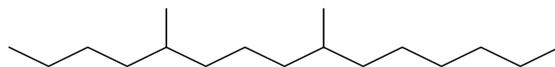
With few exceptions the sex pheromones of butterflies (*Lepidoptera*) are mono and di-olefins alcohols with long chain also their acetates and aldehydes with a 10 to 18 carbon atoms chain. In some butterfly families (*Geometridae*, *Arctiidae* and *Noctuidae*) were identified as pheromone polyenic hydrocarbon chains and their monoepoxydes.



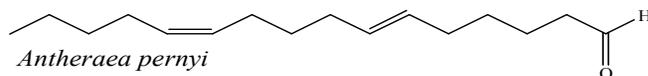
*Agrotis segentum*



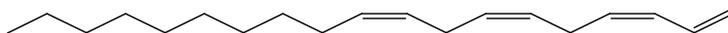
*Bombyx Mory*



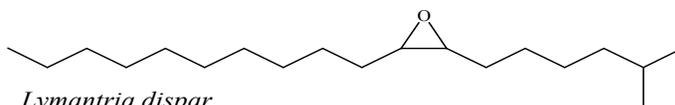
*Leucoptera coffeela*



*Antheraea pernyi*



*Operophtera brumata*



*Lymantria dispar*

The use of the pheromones in pest control as a non-polluting alternative of chemical insecticides is in-line with the efforts to attain the European Union standards.

The first part of the thesis presents a study about the carbon-carbon bond forming reactions in pheromones synthesis available in the literature.

The second part of the doctoral thesis touches: (i) the study and the synthesis of monoenic and dienic sex pheromones of some *Lepidoptera* by developing an original method of synthesis with high level of generalization, using for the first time mercury derivatives of the terminal-alkyne  $\omega$ -functionalised; (ii) preparation of an intermediate using a new synthesis method, this intermediate can be used in the synthesis of pheromones; (iii) establishing of an "attract and kill" biotechnique to be used in simultaneous control of some pests in pomiculture that are important from economic point of view.

The third part of the thesis presents the experimental part along with the synthesis methods of the intermediate and the final products.

The thesis is part of the "Raluca Ripan" Chemistry Research Institute's Natural Products Laboratory tradition.

## 2. ORIGINAL CONTRIBUTIONS

### 2.1. Using the functionalized alkynylmercury compounds in carbon-carbon bond formation

Synthesis of monoenic pheromones [152-156] was one of the concerns of the pheromone research team from the Natural Product Laboratory-Chemistry Research Institute "Raluca Ripan".

The current thesis develops an original method for synthesis of some monoenic and dienic pheromones by using  $\omega$ -functionalized alkynylmercury compounds.

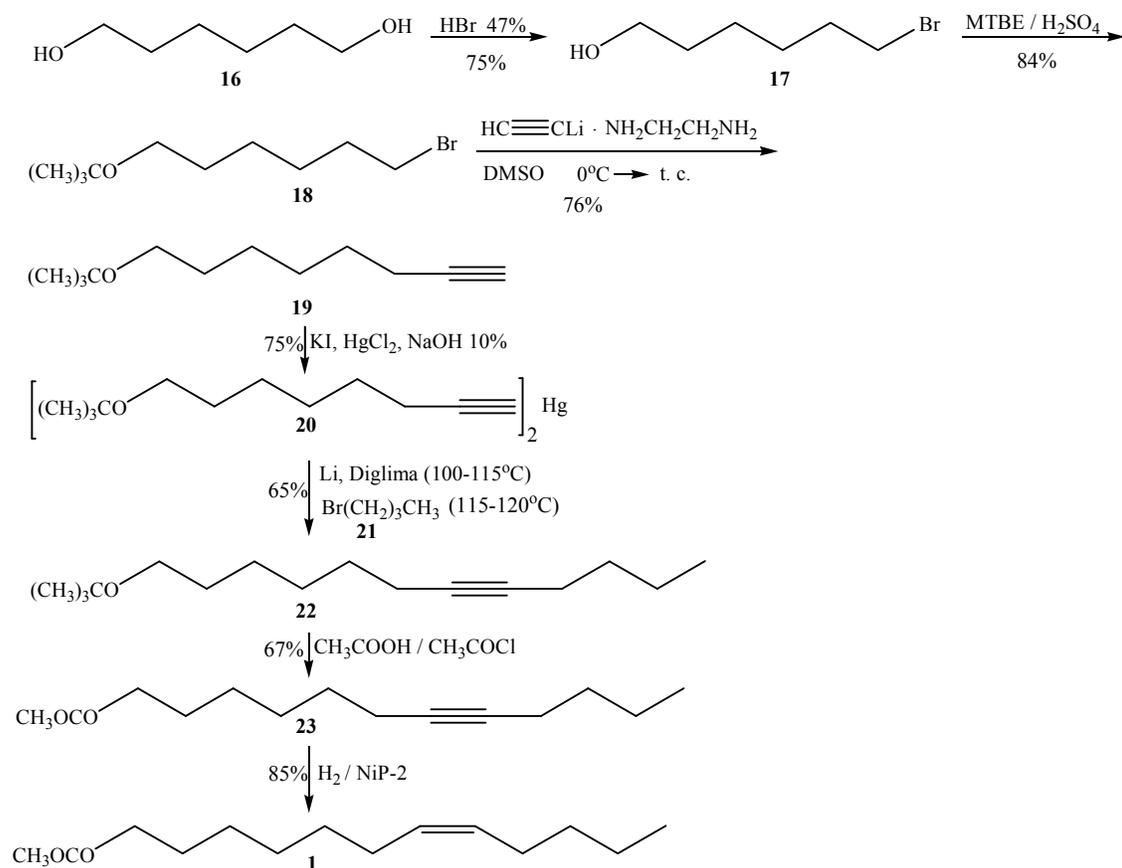
#### 2.1.1. The study of the synthesis of some monoenic pheromones with *Z* and *E* geometry

##### 2.1.1.1. Contributions to the synthesis of (*Z*)-7-dodecen-1-yl acetate

Bykov [158] synthesized the (*Z*)-7-dodecen-1-yl (**1**) acetate, the sex pheromone of *Trichoplusia ni* species, by using as a key reaction the stereoselective ethenolysis of 1,5-ciclooctadiene with ethylene in presence of  $\text{MoCl}_5/\text{SiO}_2\text{-SnMe}_4$  catalyst. Ujvari [159] uses as key step a stereoselective Wittig reaction between 7-acetoxiheptanal (**12**) and ilide generated from pentyltriphenylphosphonium bromide by sodium methylsulfinylmethanide.

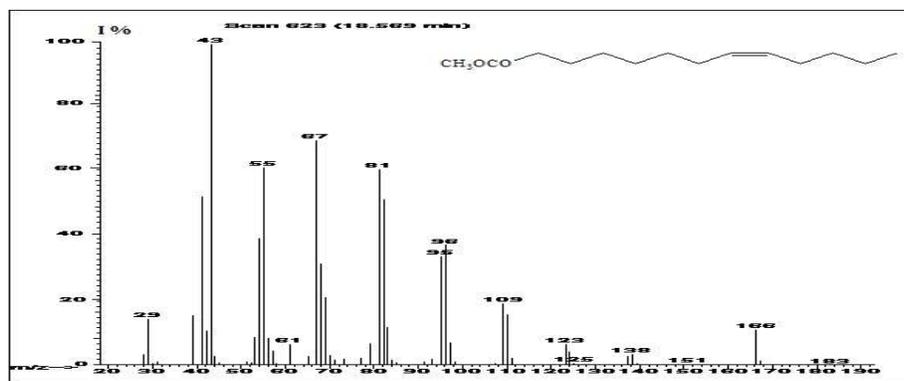
THE ORIGINAL PATH PROPOSED approaches the synthesis of (*Z*)-7-dodecen-1-yl acetate (**1**) starting from 1, 6-hexanediol (**16**). The key step of the synthesis is obtaining the di[*t*-butoxy-oct-7-yne]mercury (**20**) followed by the  $\text{C}_8 + \text{C}_4$  coupling sequence (Figure 2.1.1.1-5). The ( $\text{C}_8$ ) sinton **20** undergoes transmetallation reaction with lithium metal in diglyme, followed by alkylation with 1-brombutane ( $\text{C}_4$ ) (**21**). The GC analysis shows the resulted coupling product **22** with 85% purity. Compound **22** is converted into the corresponding acetate **23** using a mixture of acetyl chloride and acetic acid.

7-Dodecyne-1-yl acetate (**23**) was catalytic hydrogenated in ethyl alcohol with NiP-2 passivated with ethylene diamine. NiP-2 was obtained from nickel acetate and sodium borohydride, which is specific for the catalytic triple bond hydrogenation to the *cis* isomer [161]. Gas-chromatographic analysis shows the (*Z*)-7-dodecen-1-yl acetate (**1**) obtained with 96% purity.



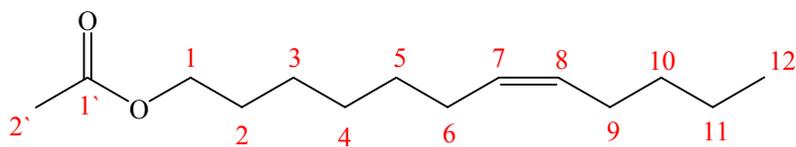
#### Scheme 2.1.1.1-5

On the mass spectrum of (*Z*)-7-dodecen-1-yl acetate (**1**), the main peak represents the *m/z* 43 fragment which is formed by cleavage of the alkoxy group, resulting the acilium ion (CH<sub>3</sub>CO<sup>+</sup>). The peak at *m/z* 61 is formed by a cleavage which implies a double transposition of hydrogen (CH<sub>3</sub>COOH<sub>2</sub><sup>+</sup>). The peak at *m/z* 166 is formed by the elimination of one acetic acid molecule from the molecular ion (Figure 2.1.1.1-2).



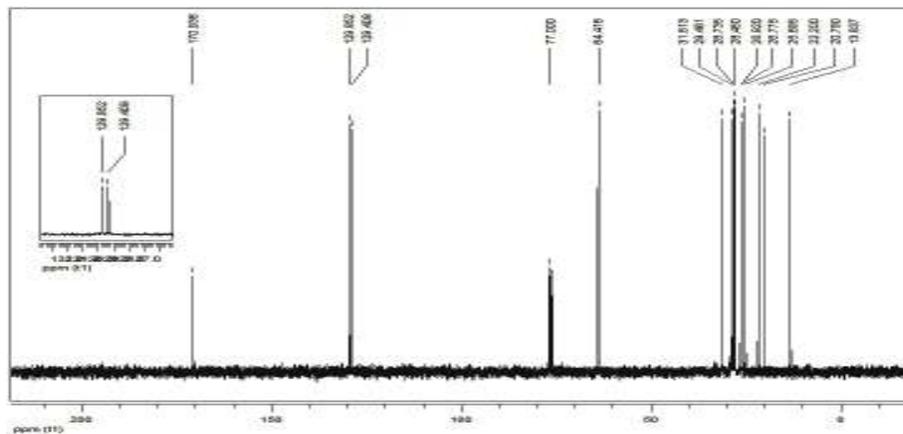
**Figure 2.1.1.1-2.** Mass spectrum of (Z)-7-dodecen-1-yl acetate (**1**)

Confirmation of the structure of (Z)-7-dodecen-1-yl acetate (**1**) was achieved by NMR spectroscopy ( $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$ ).



**Table 2.1.1.1-1.** Chemical shifts (ppm) of carbon atoms in (Z)-7-dodecen-1-yl acetate (**1**). Assignments based upon Refs. 162.

	$\delta$ (ppm)
$\text{C}_1$	64.1
$\text{C}_2$	28.4
$\text{C}_3$	25.6
$\text{C}_4$	29.4
$\text{C}_5$	28.7
$\text{C}_6$	26.7
$\text{C}_7$	129.4
$\text{C}_8$	129.8
$\text{C}_9$	26.9
$\text{C}_{10}$	31.8
$\text{C}_{11}$	22.2
$\text{C}_{12}$	13.8
$\text{C}_1$	170.9
$\text{C}_2$	20.7



**Figure 2.1.1.1-4.**  $^{13}\text{C}$ -NMR spectrum of (*Z*)-7-dodecen-1-yl acetate (**1**) ( $\text{CDCl}_3$ , 75 MHz)

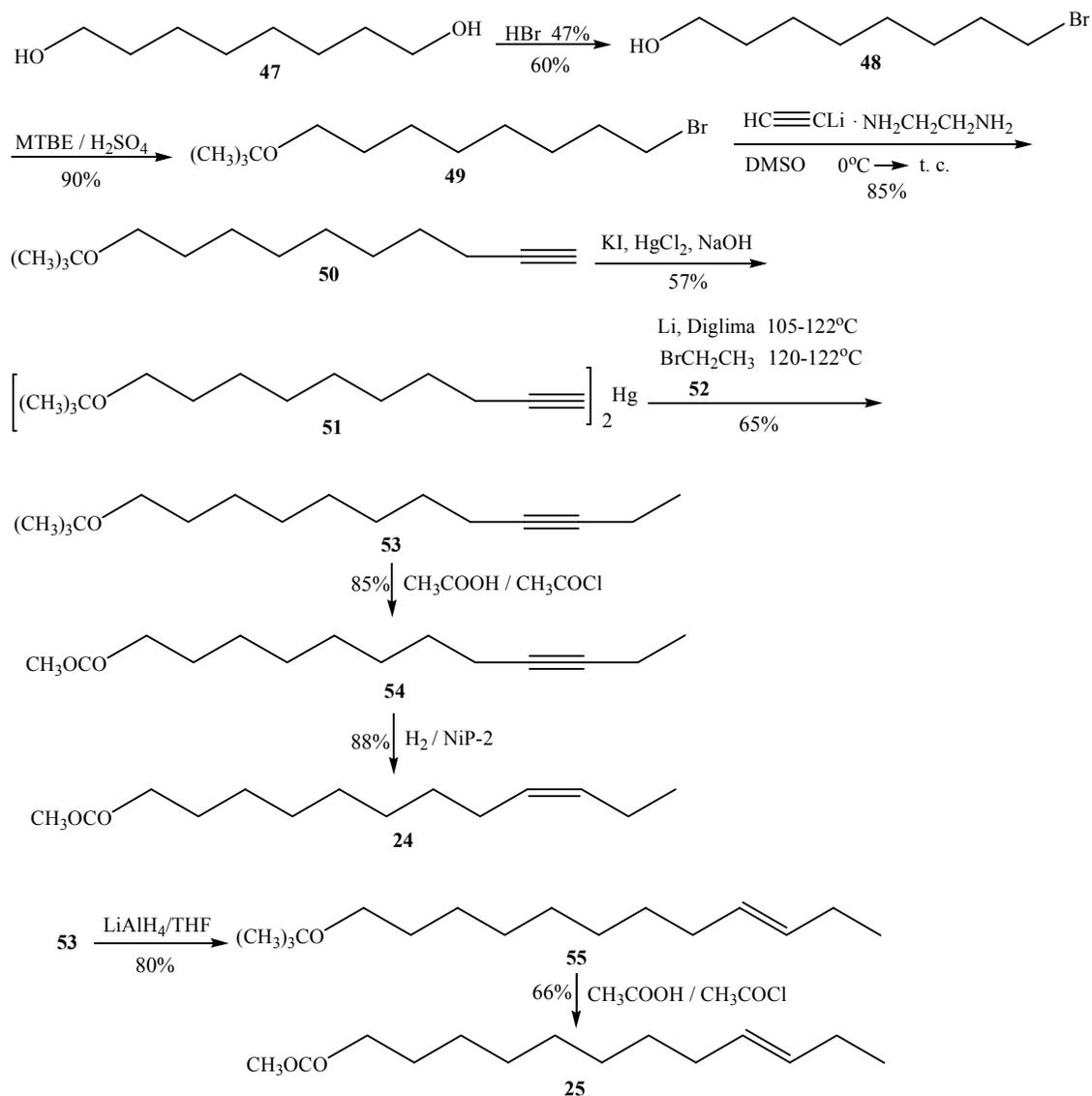
### 2.1.1.2. Contribution to the synthesis of (*Z*)-9-dodecen-1-yl acetate and (*E*)-9-dodecen-1-yl acetate

Bestmann [166] prepares (*Z*)-9-dodecen-1-yl acetate (**24**), the pheromone of *Paralobesia viteana* and *Eupocillia ambiguella pest species* by  $\text{C}_6 + \text{C}_6 = \text{C}_{12}$  coupling sequence, based on cross-coupling reaction between Grignard reagent ( $\text{C}_6$ ) and haloalkene ( $\text{C}_6$ ). Petrushkina [167] used cross-coupling reaction of (*Z*)-1-phenoxy-pent-2-ene with Grignard reagent to prepare (*Z*)-9-dodecen-1-yl acetate (**24**) by  $\text{C}_5 + \text{C}_7 = \text{C}_{12}$  coupling sequence, obtaining a mixture of three isomers at a ratio of 1:15:2, the major isomer being the target product.

Odinokov [169] synthesized (*E*)-9-dodecen-1-yl acetate (**25**), component of the sex pheromone of the *Sparganothis Pilleriana* and *Loxostege sticticalis* pest species in 10 steps, following acetylenic route by alkylation reaction of lithium acetylide in liquid ammonia with 1-(tetrahydropyranyloxy)-8-bromooctanol, followed by a second alkylation reaction. The starting material was 1,5-cyclooctadiene.

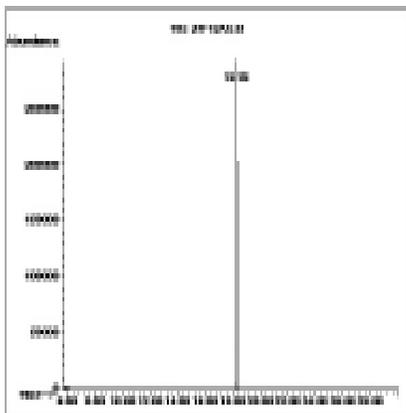
ORIGINAL ROUTE OF SYNTHESIS APPROACHED of the (*Z*)-9-dodecen-1-yl acetate (**24**) and (*E*)-9-dodecen-1-yl acetate (**25**) removed the disadvantages of others methods from literature and was realised by  $\text{C}_8 + \text{C}_2 = \text{C}_{10}$  and  $\text{C}_{10} + \text{C}_2 = \text{C}_{12}$  coupling scheme, followed by stereoselective hydrogenation, starting material being 1,8-octanediol (**47**) (Scheme 2.1.1.2-6). The key step of the synthesis is represented by

transmetallation reaction of di[*t*-butoxy-dec-9-yne]mercury (**51**) with lithium metal in diglyme and then alkylated with ethyl bromide (**52**) obtaining 1-*tert*-butoxy-dodec-9-yne (**53**) with 83% purity. The resulted acetylenic compound **53** is stereospecifically hydrogenated to the *Z* isomer by using NiP-2 catalyst, respectively *E* isomer by using LiAlH<sub>4</sub>. After the acetylation steps, (*Z*)- and (*E*)-9-dodecen-1-yl acetates are obtained with an isomeric purity > 99%.

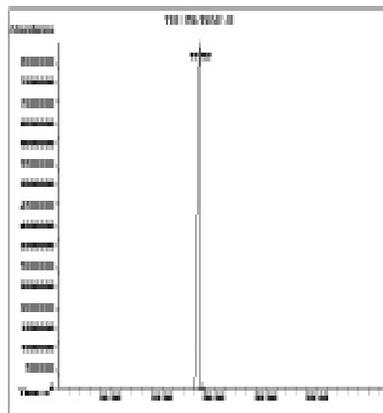


**Scheme 2.1.1.2-6**



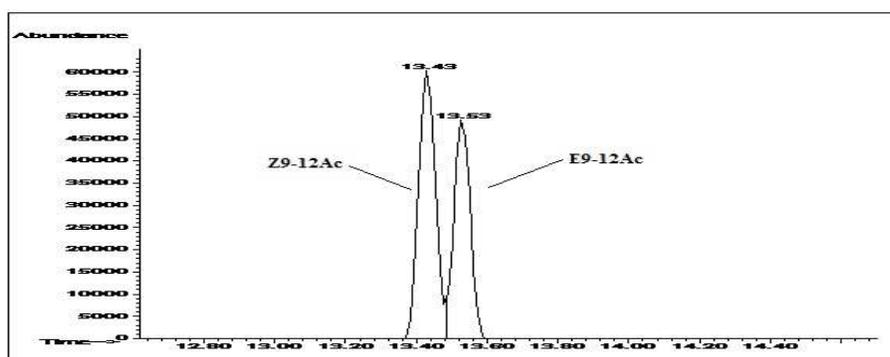


**Figure 2.1.1.2-3.** GC analysis of *(Z)*-9-dodecen-1-yl acetate (**24**)



**Figure 2.1.1.2-4.** GC analysis of *(E)*-9-dodecen-1-yl acetate (**25**)

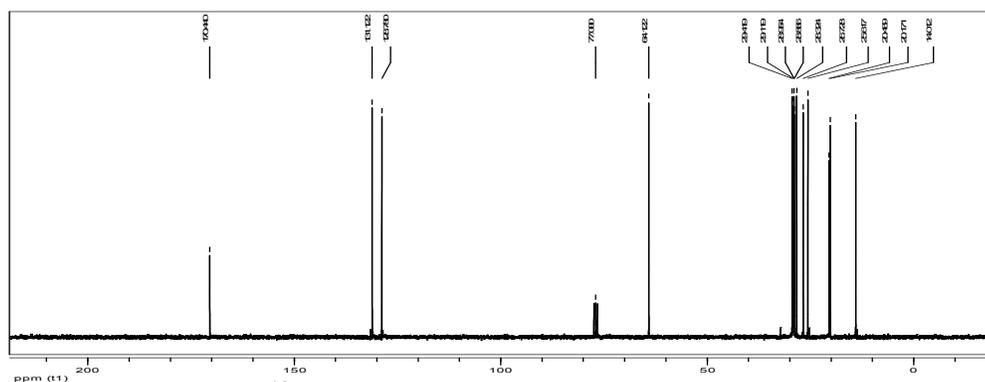
Identification of compounds separated by GC technique is an important step when mixtures of isomers are obtained. It has been made a test mixture of acetates with *Z* configuration, respectively *E* configuration. They were separated by GC analysis on a GC-MS device 5890 Series II - 5972 equipped with a capillary column DB-5MS. The analysis was performed with a temperature program between 100°-250°C at a temperature increase rate of 6°/min. It was observed that *(Z)*-9-dodecene-1-yl acetate (**24**) is more strongly retained on column (Figure 2.1.1.2-5).



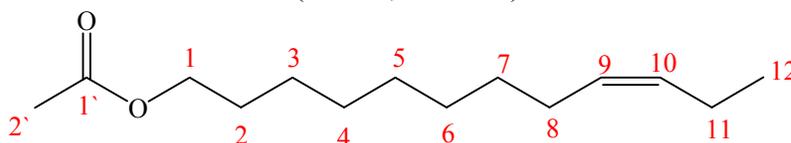
**Figure 2.1.1.2-5.** Separation of *(Z)*- and *(E)*-9-dodecen-1-yl acetates on capillary column DB-5MS 30m x 0.25 mm

The structure of the final compounds was confirmed by the NMR spectroscopy (<sup>1</sup>H-NMR, <sup>13</sup>C-NMR). Valuable information is obtained from the chemical shift of carbon atoms in  $\alpha$  position to the double bond. Geometric isomers is important for

pheromones structure, carbon atoms in  $\alpha$  position to the disubstituted double bond have different values of chemical shift, values which depend on the (*Z*)- or (*E*)- configuration of the adjacent double bond [162]. This type of dependence of chemical shift of the carbon atom of the allyl double bond geometry was observed in many olefinic compounds [174, 175]. 20.1 ppm chemical shift of allyl carbon in *Z*-alkenes can be observed to higher fields (Table 2.1.1.2-1), while the *E*-alkenes shows a 25.0 ppm chemical shift towards lower fields (Table 2.1.1.2-2).

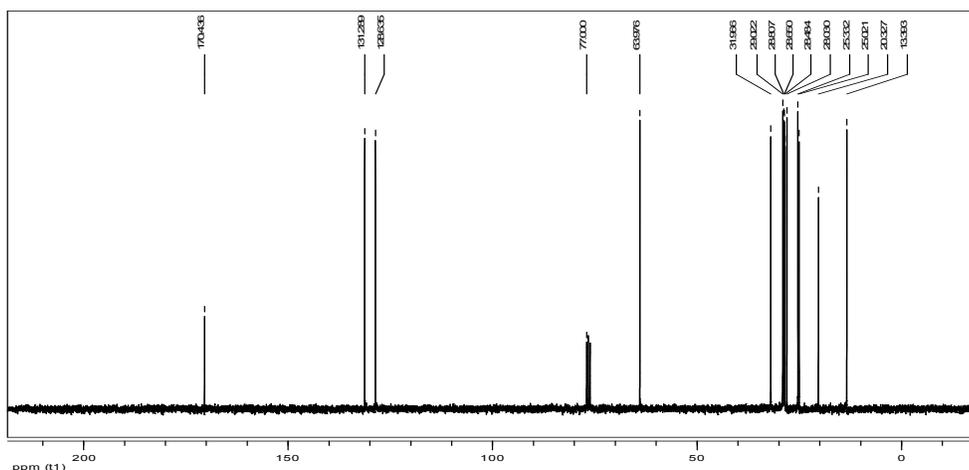


**Figure 2.1.1.2-8.**  $^{13}\text{C}$ -NMR spectrum of (*Z*)-9-dodecen-1-yl acetate (**24**) ( $\text{CDCl}_3$ , 75 MHz)

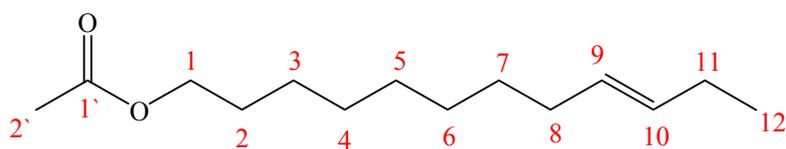


**Table 2.1.1.2-1.** Chemical shifts (ppm) of the carbon atoms in (*Z*)-9-dodecen-1-yl acetate (**24**) assigned according Refs. 162

	$\delta$ (ppm)
$\text{C}_1$	64.1
$\text{C}_2$	28.3
$\text{C}_3$	25.6
$\text{C}_4$	29.1
$\text{C}_5$	28.8
$\text{C}_6$	28.9
$\text{C}_7$	29.4
$\text{C}_8$	26.7
$\text{C}_9$	128.7
$\text{C}_{10}$	131.1
$\text{C}_{11}$	20.1
$\text{C}_{12}$	14.0
$\text{C}_{1'}$	170.4
$\text{C}_{2'}$	20.4



**Figure 2.1.1.2-9.**  $^{13}\text{C}$ -NMR spectrum of (*E*)-9-dodecen-1-yl acetate (**25**)  
( $\text{CDCl}_3$ , 75 MHz)



**Table 2.1.1.2-2** Chemical shifts (ppm) of the carbon atoms in  
(*E*)-9-dodecen-1-yl acetate (**25**) assigned according Refs. 162

	$\delta$ (ppm)
$\text{C}_1$	63.9
$\text{C}_2$	28.8
$\text{C}_3$	25.3
$\text{C}_4$	29.0
$\text{C}_5$	28.0
$\text{C}_6$	28.4
$\text{C}_7$	28.6
$\text{C}_8$	31.9
$\text{C}_9$	128.6
$\text{C}_{10}$	131.2
$\text{C}_{11}$	25.0
$\text{C}_{12}$	13.3
$\text{C}_1$	170.4
$\text{C}_2$	20.3

### 2.1.1.3. Contributions to the synthesis of (Z)-9-tetradecen-1-yl acetate

(Z)-9-tetradecen-1-yl acetate (**56**) was identified in the pheromonal "cocktail" of some insect pest from the Tortricidae and Noctuide [176] family of the *Lepidoptera* order, the main component of the sex pheromone of the *Adoxophyes reticulana* species, causing serious damage in pomiculture.

The literature listed a number of ways to synthesize (Z)-9-tetradecen-1-yl acetate [177-181, 122, 159 168].

Batista-Pereira [182] et al. synthesize (Z)-9-tetradecen-1-yl acetate (**56**) in four steps by alkylation reaction of 1-hexyne with 8-bromo-octane-1-ol at a temperature of  $-30^{\circ}\text{C}$  using HMPA as a solvent proved to be carcinogenic by inhalation, or DMI, the reaction being mediated of 2 equivalents of butyl-lithium. Francesco Naso [183] presents a method for obtaining of (Z)-9-tetradecen-1-yl acetate (**56**), which is based on the reaction of (Z)-1-bromo-2-phenylthioethene with Grignard reagents in the presence of catalysts of Ni (II) and Pd (II). Subbaraman and collaborators [185] developed a way of synthesizing (Z)-9-tetradecen-1-yl acetate (**56**) using Z-selective Wittig reaction of methyl-8-formyloctanoate and pentyltriphenylphosphonium bromide.

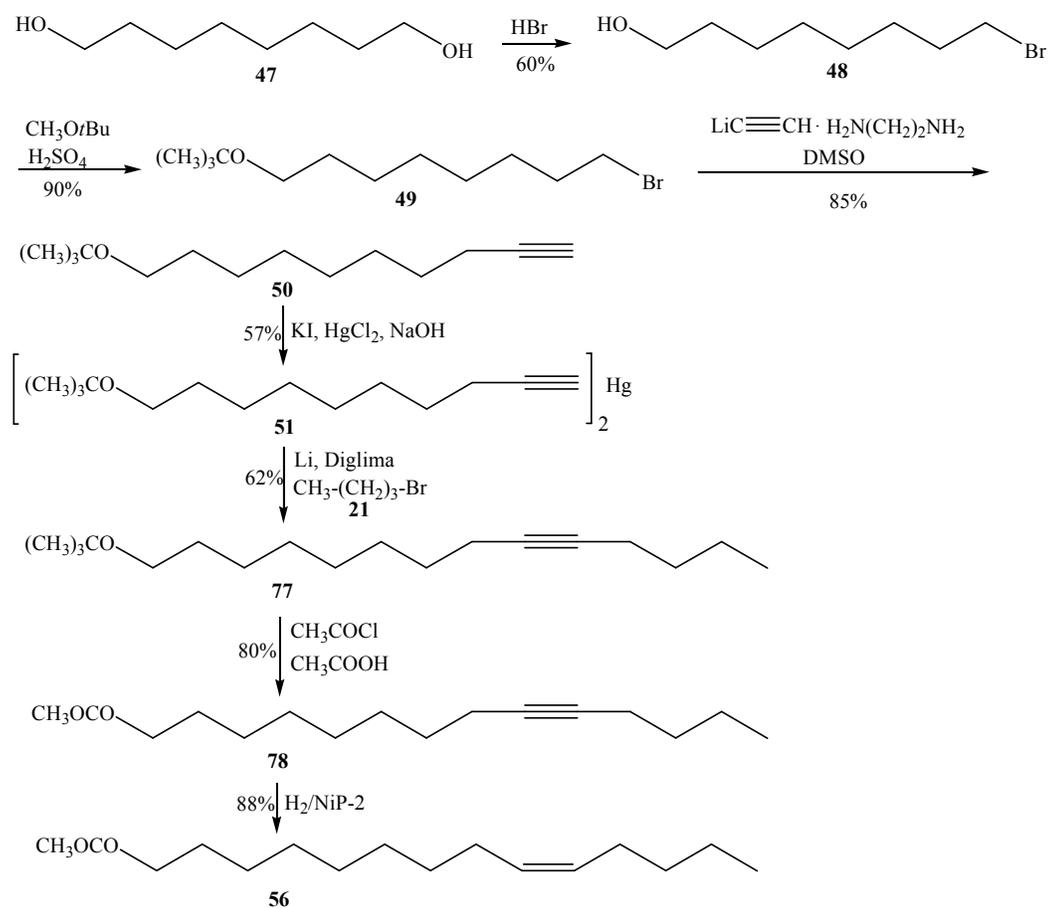
In the method developed by Batista-Pereira [182] the solvent used in alkylation reaction is hexamethylphosphoramide (HMPA) solvent proved to be carcinogenic by inhalation [186] or 1,3-dimethyl-2-imidazolidone. Also, the temperature of  $-30^{\circ}\text{C}$  is difficult to obtain and butyl-lithium requires special storage and handling conditions. Other synthetic routes mentioned involves a large number of steps and require special reagents.

PROPOSED SYNTHESIS METHOD removes the above disadvantages, in that is based on a C-alkylation reaction, using as intermediates, mercury derivatives of  $\omega$ -functionalized terminal acetylene [187]. The chain of 14 carbon atoms is achieved by the scheme  $\text{C}_8 + \text{C}_2 = \text{C}_{10}$  and  $\text{C}_{10} + \text{C}_2 = \text{C}_{14}$ , the intermediate being di[*t*-butoxy-dec-9-yne]mercury (**51**) (Figure 2.1.1.3-5).

The key step of the synthesis consists in the preparation of di[*t*-butoxy-dec-9-yne] mercury (**51**), its transmetallation reaction with lithium metal in diglyme and alkylation with 1-bromobutane (**52**), yielding 1-*tert*-butoxy-tetradec-9-yne (**77**). The

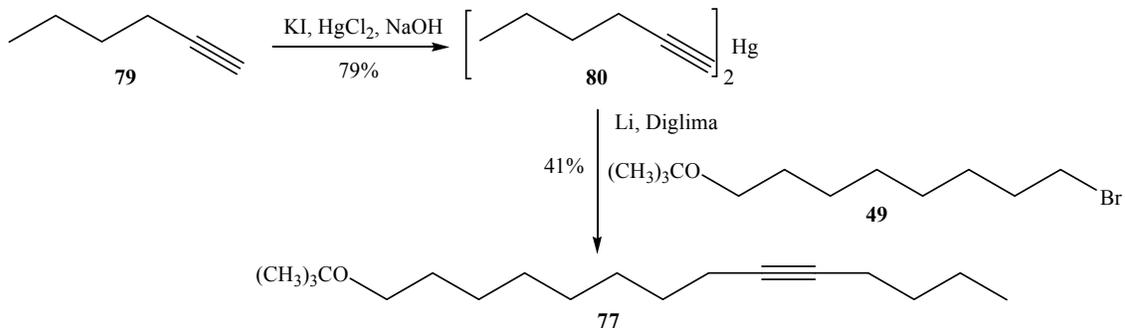
coupling product 1-*tert*-butoxy-tetradec-9-yne (**77**) was obtained with a purity of 80% determined by GC.

The acetylation of compound **77**, followed by stereoselective *cis* hydrogenation with NiP-2 [161] lead to (*Z*)-9-tetradecen-1-yl acetate (**56**) with 99% purity.



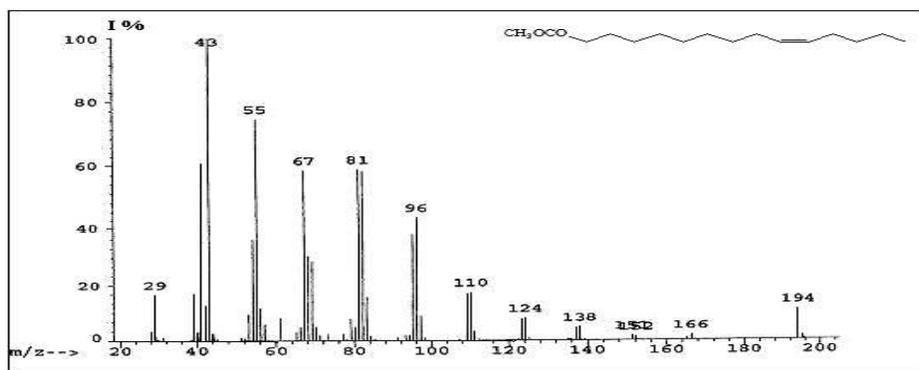
**Scheme 2.1.1.3-5**

(*Z*)-9-tetradecen-1-yl acetate (**56**) can be synthesized from 1-hexyne (**79**), transformed into di[hex-1-yne]mercury, followed by transmetallation reaction with lithium metal and alkylation with 1-*tert*-butoxy-8-bromo-octane (**49**), the reaction took place in diglyme [188,189] (Scheme 2.1.1.3-6). (*Z*)-9-tetradecen-1-yl acetate (**56**) was obtained with 94% purity.

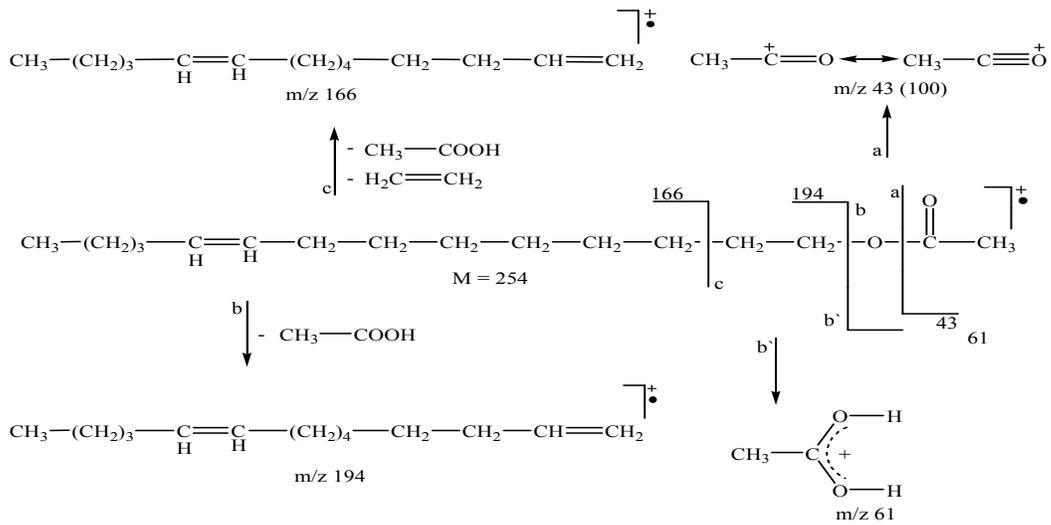


**Scheme 2.1.1.3-6**

(*Z*)-9-tetradecen-1-yl acetate (**56**) appears in the gas chromatogram at retention time  $T_R = 19.71$  and has prominent peaks in the mass spectrum at  $m/z$  43, 55, 96, 194, 166, characteristic splitting of esters and higher alkenes with general formula  $C_nH_{2n-1}$  (Figure 2.1.1.3-2, Scheme 2.1.1.3-8).



**Figure 2.1.1.3-2.** Mass spectrum of (*Z*)-9-tetradecen-1-yl acetate (**56**)



**Scheme 2.1.1.3-8**



#### 2.1.1.4. Contributions to the synthesis of (Z)- and (E)-11-tetradecen-1-yl acetates

(Z)-11-tetradecen-1-yl acetate (**81**) is a pheromone component of many insect species in the order *Lepidoptera*. Some economically important insect pests are: *Tortrix viridana* (green oak moth), *Adoxophyes reticulana* (summer fruit tortrix moth), *Archips podana* (fruit tree tortrix moth) and *Ostrinia nubilalis* (European corn borer moth).

Dzhemilev et al. [192] presents a method of synthesis of (Z)-11-tetradecen-1-yl acetate (**81**) based on Wittig reaction - coupling of propionic aldehyde with methyl-11-bromoundecanoate. Ratovelomanana et al. [193] synthesize (Z)-11-tetradecen-1-yl acetate (**81**) by cross-coupling reaction catalyzed by phosphine-palladium complex of the Grignard reagent with Z-1-chlorobutene.

(E)-11-tetradecen-1-yl acetate (**98**) was identified as the sex pheromone of the *Loxostege sticticalis* species (pest of legume crops, lucerne, pea), the main component of pheromones *Archips podana* species (fruit tree tortrix moth), *Ostrinia nubilalis* (European corn borer moth) and other harmful species.

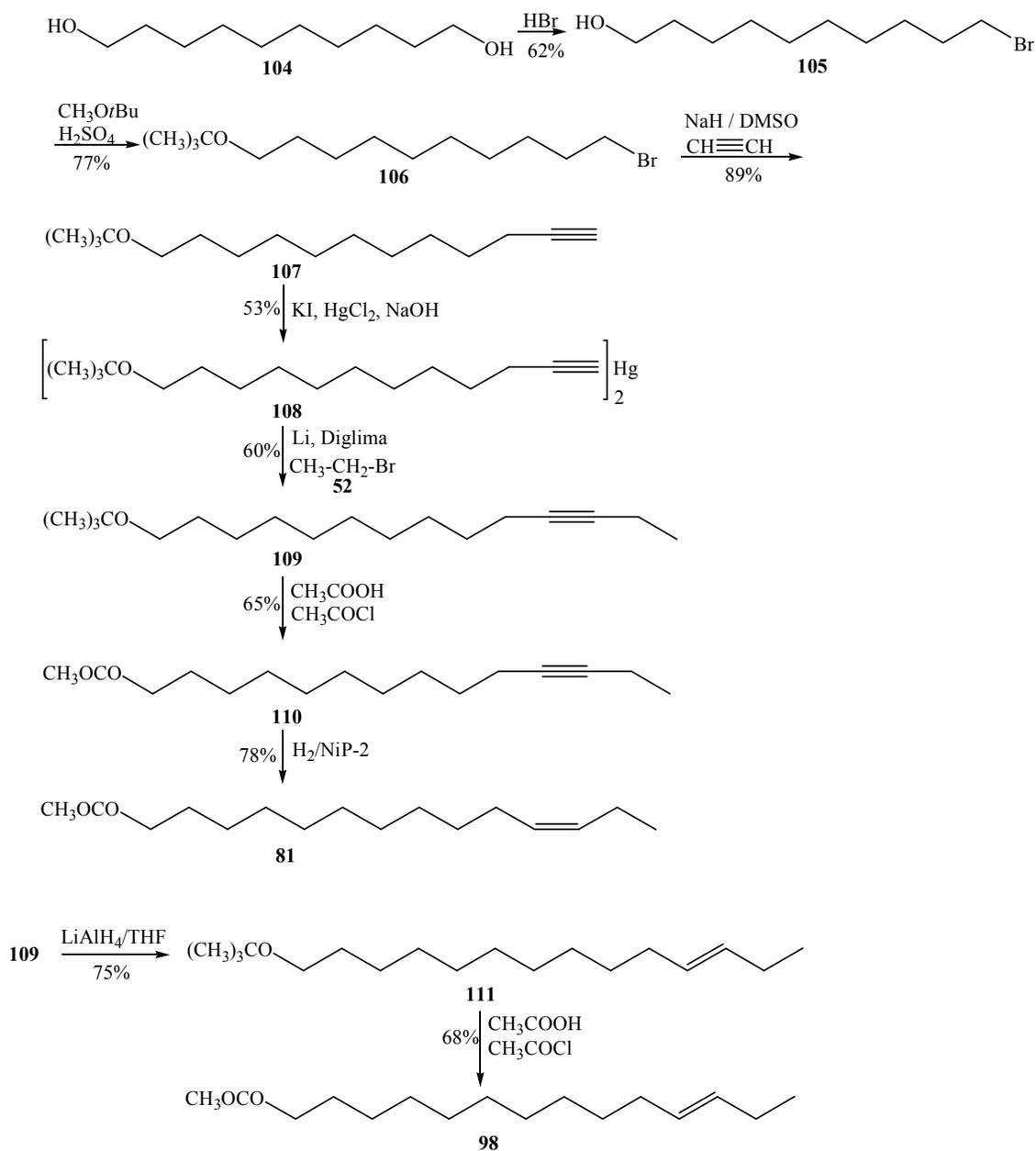
Shakhmaev [194] obtained (E)-11-tetradecen-1-yl acetate (**98**) using a Claisen rearrangement as key step 1-penten-3-ol with triethyl orthoacetate in the presence of acetic acid.

PROPOSED ALTERNATIVE PREPARATION of (Z) - and (E)-11-tetradecen-1-yl acetates (**81**, **98**) is based on the coupling sequences  $C_{10} + C_2 = C_{12}$  and  $C_{12} + C_2 = C_{14}$  [195]. The starting material used is 1, 10-decanediol (**104**) (Figure 2.1.1.4-5).

The first coupling reaction was effected by adding 1-*tert*-butoxy-10-bromodecane (**106**) to monosodiate acetylene, obtained *in situ* from DMSO and sodium hydride.

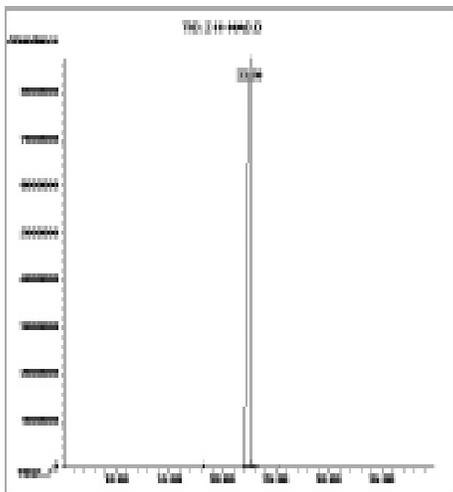
The second coupling reaction consisted in directly lithiated di[*t*-butoxy-dodec-11-yne]mercury (**108**) and then alkylated with ethyl bromide (**52**), obtaining 1-*tert*-butoxy-tetradec-11-yne (**109**). After acetylation and stereoselective reduction of 1-*tert*-butoxy-tetradec-11-yne (**109**) in the presence of NiP-2 catalyst gave (Z)-11-tetradecen-1-yl acetate (**81**) with > 99% isomeric purity.

(*E*)-11-tetradecen-1-yl acetate (**98**) was prepared with an isomeric purity > 99% by reducing of 1-*tert*-butoxy-tetradec-11-yne (**109**) with LiAlH<sub>4</sub> in THF, followed by acetylation.

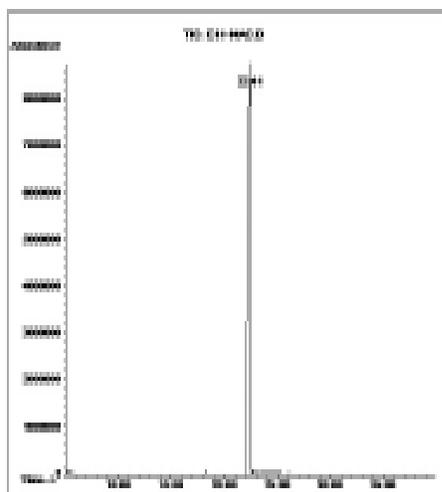


Scheme 2.1.1.4-5

Acetates of (*Z*)- and (*E*)-11-tetradecen-1-yl (**81**, **98**) appear in the gas chromatogram at retention times  $T_R = 22.58$  and  $T_R = 22.41$  (Figure 2.1.1.4-3, Figure 2.1.1.4-4).

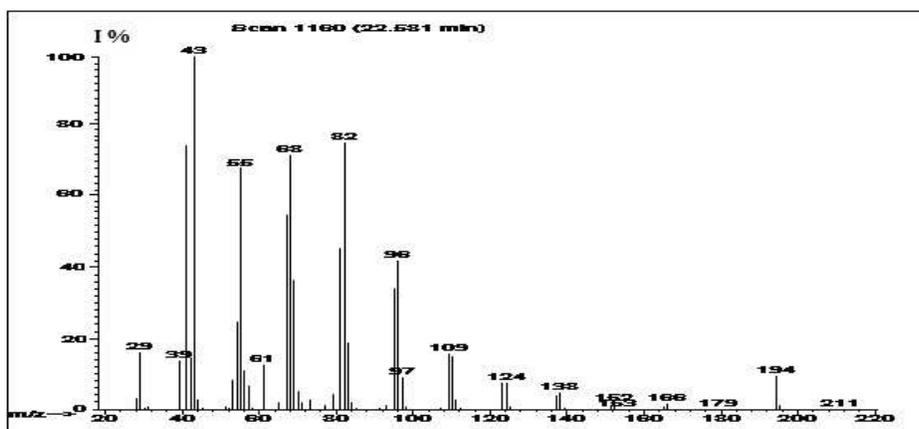


**Figure 2.1.1.4-3.** GC analysis of (*Z*)-11-tetradecen-1-yl acetate (**81**)



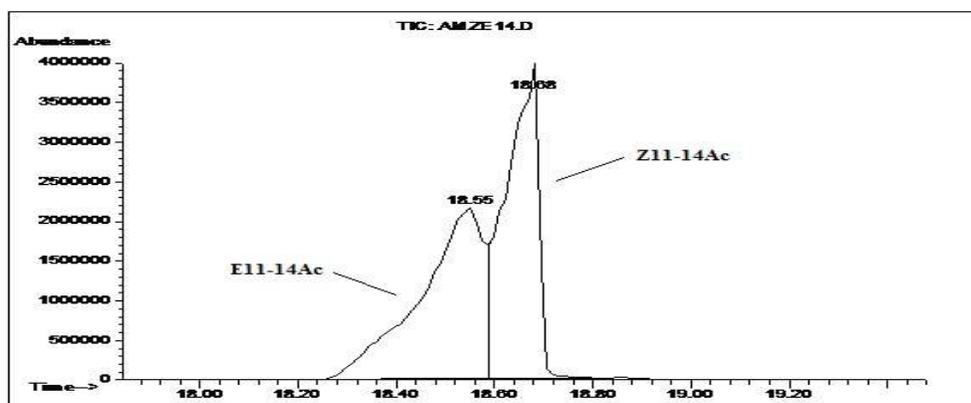
**Figure 2.1.1.4-4.** GC analysis of (*E*)-11-tetradecen-1-yl acetate (**98**)

The mass spectrum of the two acetates is identical, being characteristic esters and higher alkenes with general formula  $C_nH_{2n-1}$  (Figure 2.1.1.4-5). The peak at  $m/z$  194 is formed by cleavage of a molecule of acetic acid from molecular ion. Mass fragment  $m/z$  61 is formed through a fragmentation involving a double transposition of hydrogen ( $CH_3COOH_2^+$ ). Another important mass fragment appears at  $m/z$  43 ( $CH_3CO^+$ ), representing the base peak.



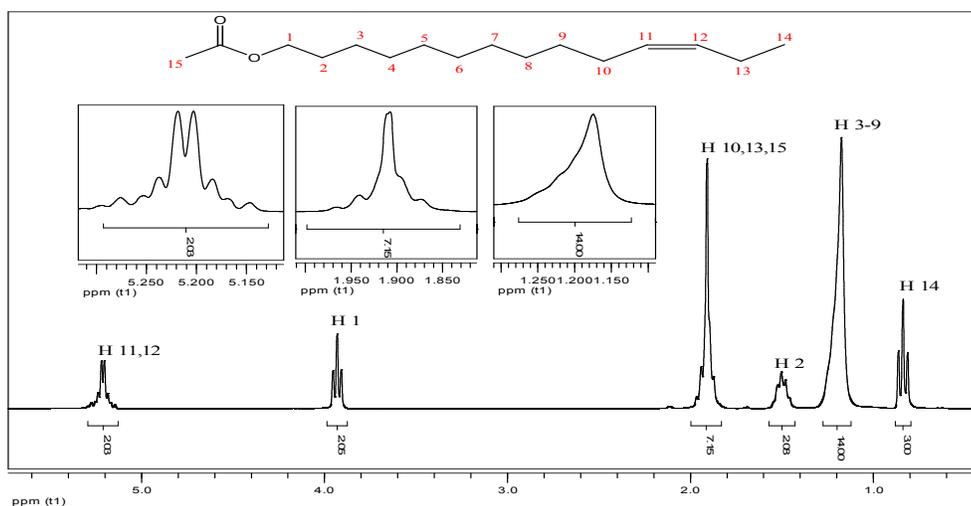
**Figure 2.1.1.4-5.** Mass spectrum of the (*Z*)- and (*E*)-11-tetradecen-1-yl acetates

For the separation of geometric isomers of acetates it is used gas chromatographic analysis performed on a GC-MS device 5890 II - 5972 equipped with a capillary column DB-5MS, 30 m x 0.25 mm. The analysis was performed with a temperature slope program between 100°-250°C at a rate of temperature increase of 6°/min. The stronger retention observed on the column is for (Z)-11-tetradecen-1-yl acetate (Figure 2.1.1.4-6).



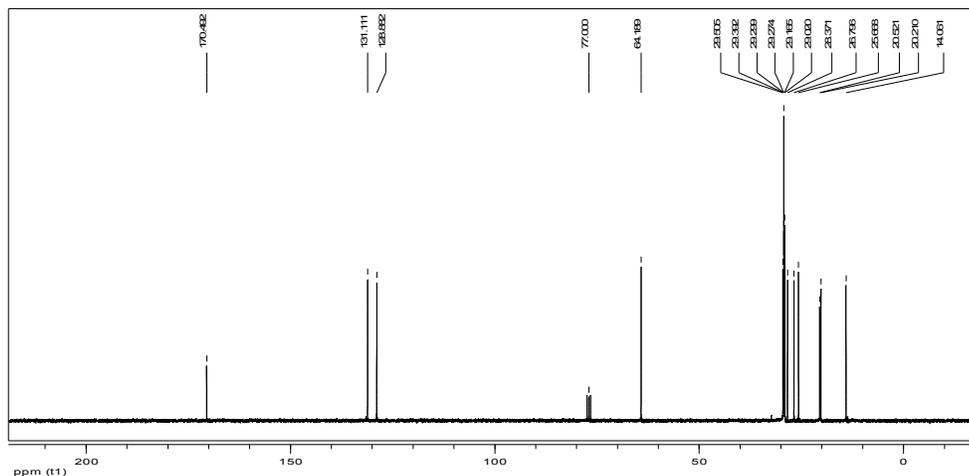
**Figure 2.1.1.4-6.** Separation of (Z)- and (E)-11-tetradecen-1-yl acetates on capillary column DB-5MS 30 m x 0.25 mm

Characterization with  $^1\text{H}$ -RMN and  $^{13}\text{C}$ -RMN spectrum of the (Z)- and (E)-11-tetradecen-1-yl acetates helped to confirm their structure.

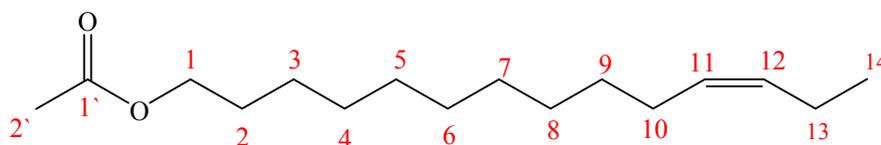


**Figure 2.1.1.4-7.**  $^1\text{H}$ -RMN spectrum of (Z)-11-tetradecen-1-yl acetate (81) ( $\text{CDCl}_3$ , 300 MHz)

Proton signals H 11, 12 (2H,  $J = 10.84$  Hz) appear as multiplets in the  $\delta$  5.15-5.29 ppm indicating a *cis* configuration of the double bond (Figure 2.1.1.4-7).

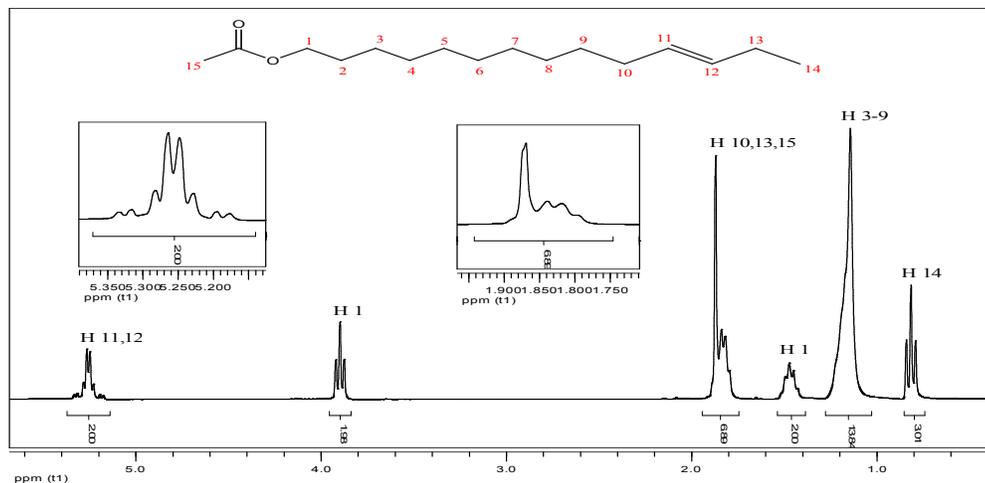


**Figure 2.1.1.4-9.**  $^{13}\text{C}$ -RMN spectrum of (*Z*)-11-tetradecen-1-yl acetate (**81**) ( $\text{CDCl}_3$ , 75 MHz)



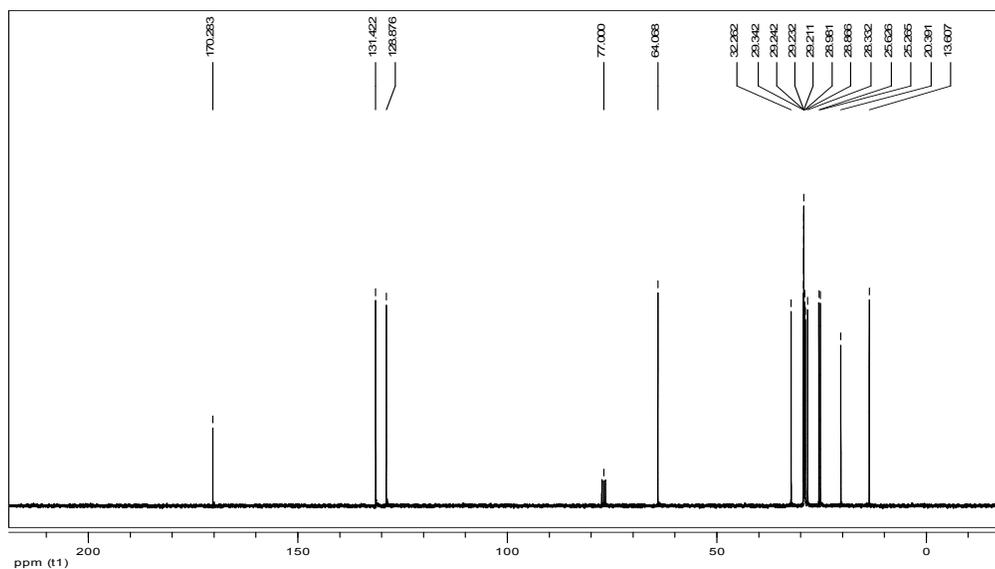
**Table 2.1.1.4-1.** Chemical shifts (ppm) of the carbon atoms in (*Z*)-11-tetradecen-1-yl acetate (**24**) assigned according **Refs. 194**

	$\delta$ (ppm)
$\text{C}_1$	64.1
$\text{C}_2$	28.3
$\text{C}_3$	25.6
$\text{C}_4$	29.3
$\text{C}_5$	29.0
$\text{C}_6$	29.1
$\text{C}_7$	29.2
$\text{C}_8$	29.2
$\text{C}_9$	29.5
$\text{C}_{10}$	26.7
$\text{C}_{11}$	128.8
$\text{C}_{12}$	131.1
$\text{C}_{13}$	20.2
$\text{C}_{14}$	14.0
$\text{C}_1$	170.4
$\text{C}_2$	20.5

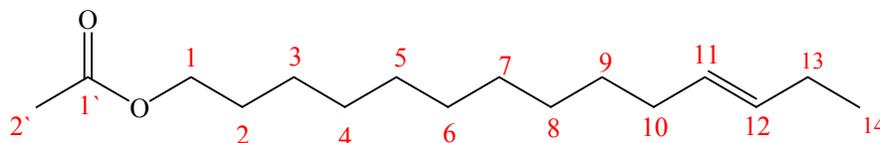


**Figure 2.1.1.4-8.**  $^1\text{H}$ -RMN spectrum of (*E*)-11-tetradecen-1-yl acetate (**98**) ( $\text{CDCl}_3$ , 300 MHz)

Proton signals H 11, 12 (2H,  $J = 15.51$  Hz) appear as multiplets in the  $\delta$  5.17-5.33 ppm indicating a *trans* configuration of the double bond (Figure 2.1.1.4-8).



**Figure 2.1.1.4-10.**  $^{13}\text{C}$ -RMN spectrum of (*E*)-11-tetradecen-1-yl (**98**) ( $\text{CDCl}_3$ , 75 MHz)



**Table 2.1.1.4-2.** Chemical shifts (ppm) of the carbon atoms in (*E*)-11-tetradecen-1-yl acetate (**24**) assigned according Refs. 194

	$\delta$ (ppm)
$C_1$	64.0
$C_2$	28.3
$C_3$	25.6
$C_4$	29.3
$C_5$	28.8
$C_6$	28.9
$C_7$	29.2
$C_8$	29.2
$C_9$	29.2
$C_{10}$	32.2
$C_{11}$	128.8
$C_{12}$	131.4
$C_{13}$	25.2
$C_{14}$	13.6
$C_1$	170.2
$C_2$	20.3

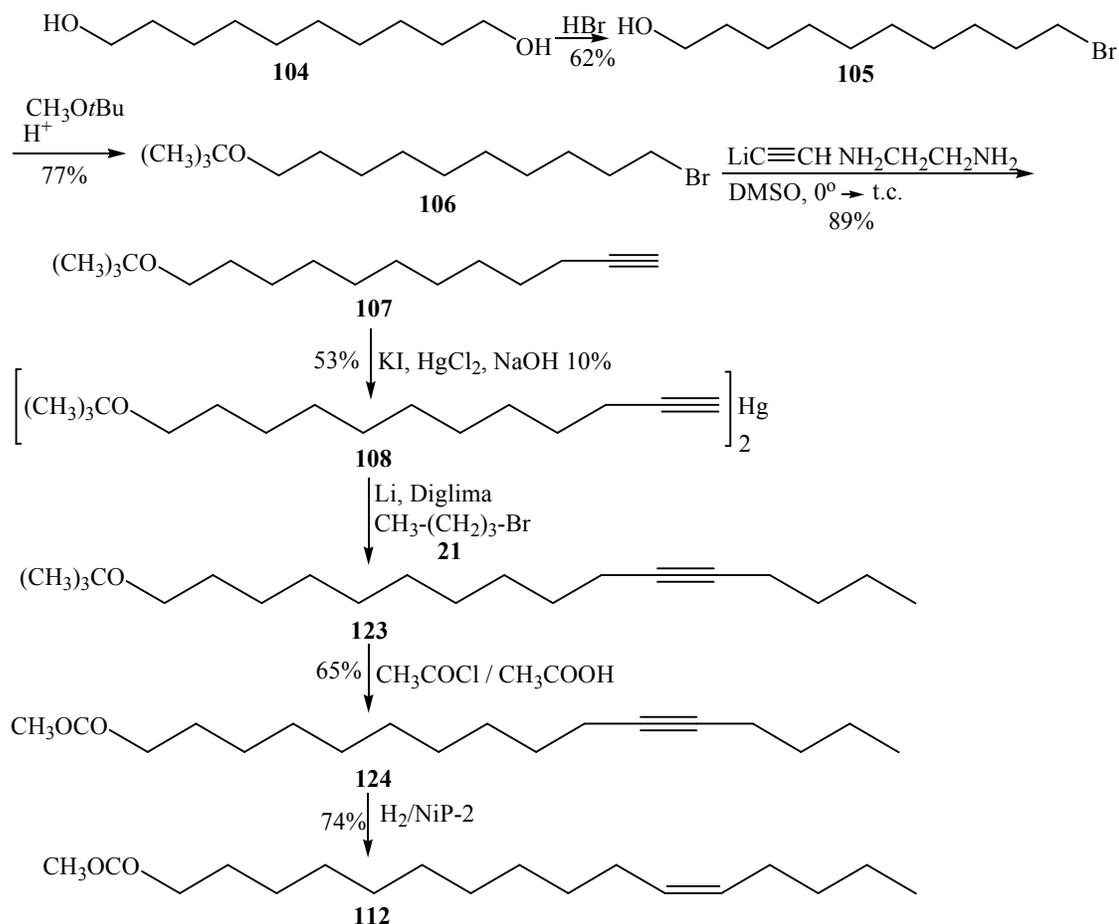
### 2.1.1.5. Contribution to the synthesis of (*Z*)-11-hexadecen-yl acetate

(*Z*)-11-hexadecen-yl acetate (**112**) is the main component of the sex pheromone of *Mamestra brassicae* species, the pest of cabbage crops.

Brown and collaborators [200] propose a method of synthesis of (*Z*)-11-hexadecen-1-yl (**112**) based on organoborane chemistry. Fiandanese et al. [201] prepared (*Z*)-11-hexadecen-1-yl acetate (**112**) by cross-coupling reactions catalyzed by complexes with Pd (II) and Ni (II). Schaub et al. [202] are using *Z*-stereoselective Wittig reaction for the synthesis of (*Z*)-11-hexadecen-1-yl acetate (**112**) and Nesbitt et al. [203] acetylene way in which 1-hexyne is lithiated with lithium amide in liquid ammonia and then alkylated with 1-tetrahydropiraniloxy-10-bromo-decane.

IN ELABORATED METHOD synthesis of (*Z*)-11-hexadecen-1-yl acetate (**112**) has the key step coupling reaction of  $C_{12}$  and  $C_4$  using a mercury derivative of  $\omega$ -

functionalized alkyne **108** and 1-bromobutane (**21**) (Figure 2.1.1.5-4). Di[*t*-butoxy-dodec-11-yne]mercury (**108**) is obtained by coupling sequence C<sub>10</sub> + C<sub>2</sub>, C<sub>10</sub> being 1-*tert*-butoxy-10-bromodecane (**106**) and C<sub>2</sub> lithium acetylides-ethylenediamine complex, followed by precipitation of ω-functionalized 1-alkyne.



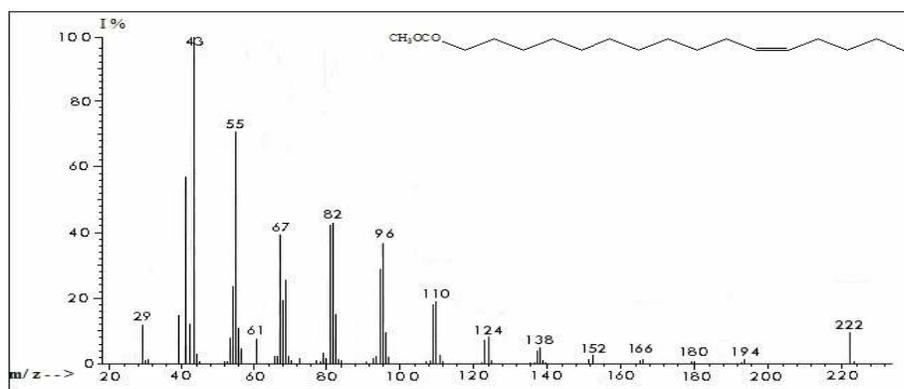
**Scheme 2.1.1.5-4**

C<sub>12</sub> + C<sub>4</sub> coupling sequence consist of a step of di[*t*-butoxy-dodec-11-yne]mercury (**108**) transmetallation with lithium metal in diglyme, a reaction that takes place between 100°-105°C for 3 hours, followed by the alkylation reaction with 1-bromobutane (**21**). Bromide **21** is added to 90°C while stirring the mixture of the reaction for 4 hours at 120°-123°C, then 1-*tert*-butoxy-hexadec-11-yne (**122**) with a purity of 50% is obtained. Compound **123** was acetylated with acetic acid and acetyl

chloride followed by catalytic hydrogenation reaction with NiP-2 to obtain (*Z*)-11-hexadecen-1-yl acetate (**111**) with a purity of 90 % determined by gas chromatography.

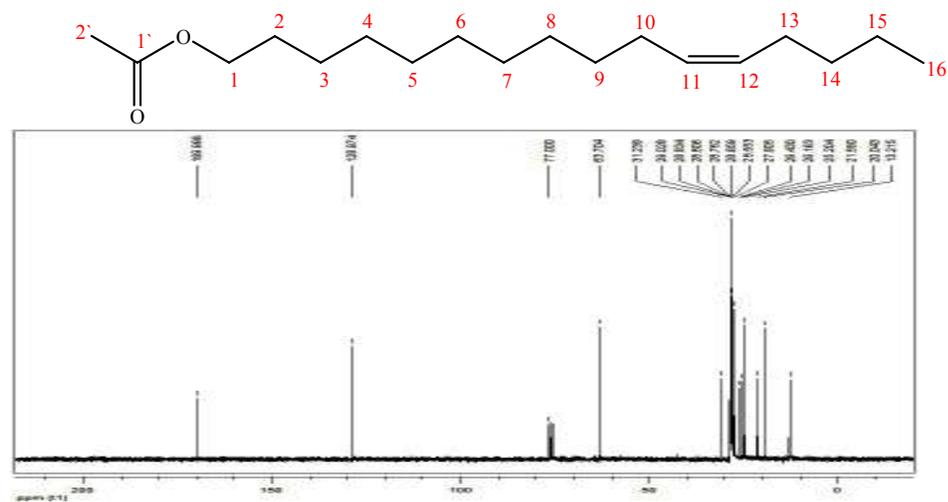
Analysis of reaction products was achieved by GC - MS coupling.

(*Z*)-11-hexadecen-1-yl acetate (**112**) appears in the gas chromatogram at retention time  $T_R = 25.39$  and has characteristic fragmentation of acetates in the mass spectrum (Figure 2.1.1.5-2).



**Figure 2.1.1.5-2.** Mass spectrum of (*Z*)-11-hexadecen-1-yl acetate (**112**)

Chemical structure of (*Z*)-11-hexadecen-1-yl acetate (**112**) was confirmed by NMR spectroscopy.



**Figure 2.1.1.5-3.**  $^{13}\text{C}$ -RMN spectrum of (*Z*)-11-hexadecen-1-yl acetate (**112**)  
( $\text{CDCl}_3$ , 75 MHz)

In the  $^{13}\text{C}$ -NMR spectrum of (Z)-11-hexadecen-1-yl acetate (**112**) the corresponding signal for C1' carbon atom can be observed which appears downfield at  $\delta$  169.9 ppm due to linking with the oxygen atom, the signal corresponding to the C<sub>11</sub> and C<sub>12</sub> carbon atoms appears at  $\delta$  128.9 ppm, the signal corresponding to the C<sub>1</sub> carbon atom was found at  $\delta$  63.7 ppm, the signals corresponding to carbon atoms of methylene groups appear at  $\delta$  31.2, 29.0, 28.8, 28.8, 28.7, 28.6, 28.5, 27.9, 26.4, 26.1, 25.2, 21.5 ppm, the signal corresponding to C<sub>16</sub> carbon atom appears at  $\delta$  13.2 ppm and the corresponding signal for C<sub>2</sub>' carbon atom appears at  $\delta$  20.0 ppm. (Figure 2.1.1.5-3)

### 2.1.2. Studies about synthesis of dienic pheromone of the (9Z,12E)-tetradeca-9,12-dien-1-yl acetate

(9Z,12E)-tetradeca-9,12-dien-1-yl acetate (**125**) is the main component or within the pheromonal mixture of many species of insect pests of the order *Lepidoptera*, family *Pyralidae*, this family including deposits pest. Some representatives are significant: *Plodia interpunctella* (indian meal moth), *Ephestia kuhniella* (mediterranean flour moth), *Cadra cautella* (almond moth), *Ephestia elutella* (tobacco moth), *Cadra figuliella* (raisin moth) [204-208].

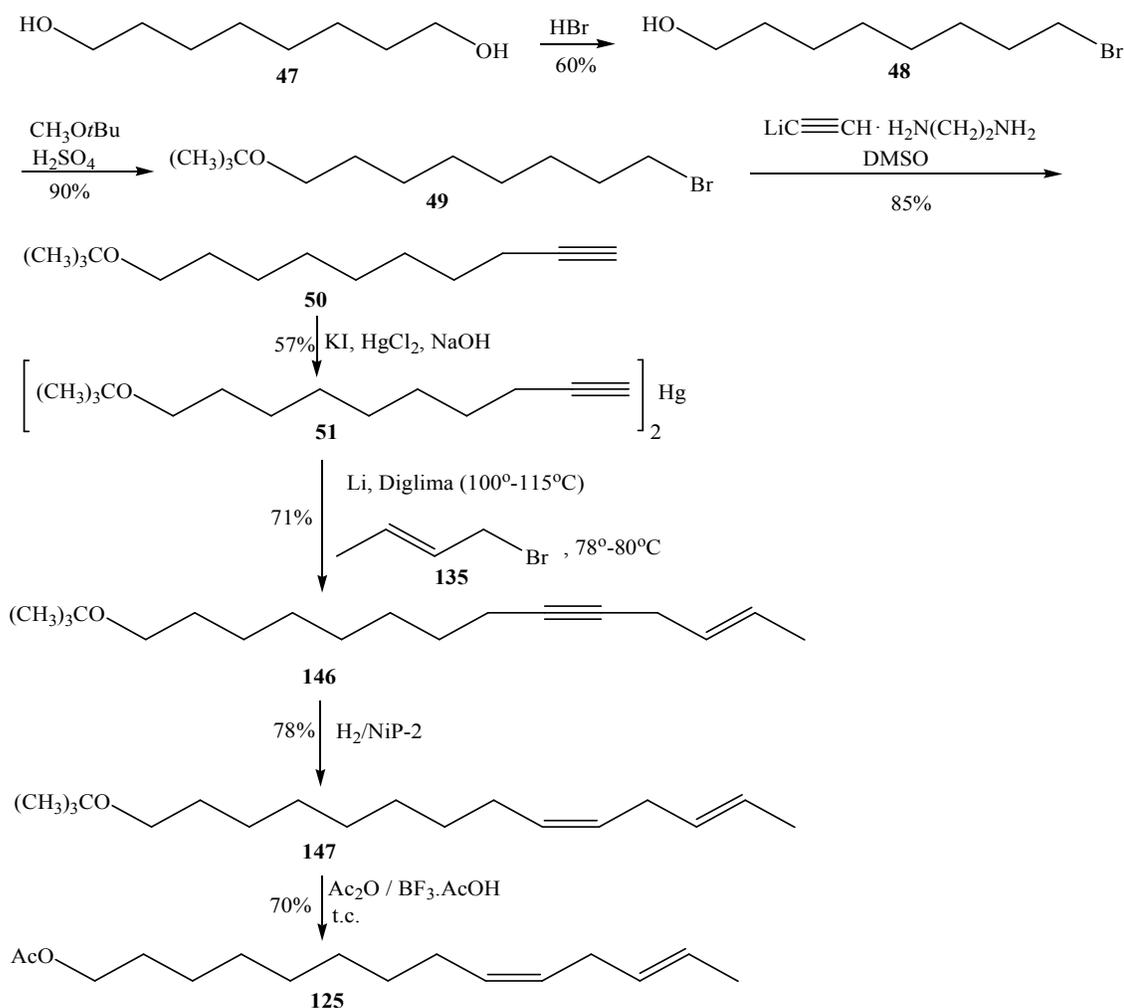
Numerous methods have been developed for preparing (9Z,12E)-tetradeca-9,12-dien-1-yl acetate [209-217].

Hornyanszky and collaborators [218] synthesize (9Z,12E)-tetradeca-9,12-dien-1-yl acetate using Wittig reaction as key step starting from the (E)-pent-3-enoic acid methyl ester. Matveeva et al. [221] describe the synthesis of (9Z,12E)-9,12-tetradecadiene-1-yl acetate (**125**) in 9 steps, synthesis based on the cross-coupling reaction of alkynyl cuprate and crotyl halides, resulting in a mixture of geometric isomers of tetradec-12-en-9-yn-1-ol (E-isomer is 83% and Z-isomer 9%) and branched enyne alcohol (8%).

IN PROPOSED SYNTHESIS METHOD (9Z,12E)-tetradeca-9,12-dien-1-yl acetate (**125**) was prepared by the scheme  $\text{C}_8 + \text{C}_2 = \text{C}_{10}$ ,  $\text{C}_{10} + \text{C}_4 = \text{C}_{14}$ .

The route involves, as the key reaction, the use of the mercury derivative of the  $\omega$ -functionalised-1-alkyne **51** as intermediate. Metil-*tert*-butyl ether was used under

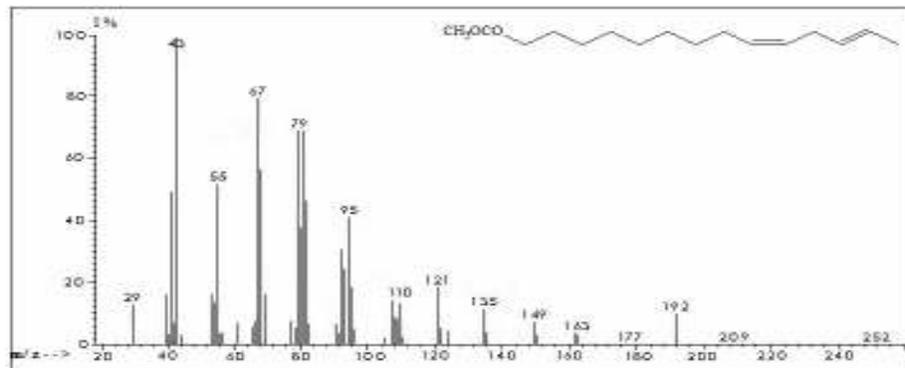
acid catalysis to protect the –OH function of the 8-bromo-octane-1-ol (**48**). The first coupling reaction took place by adding the compound **49** to monosodiate acetylene.  $\omega$ -Functionalised-1-alkyne **50** is separated from the reaction mixture with Nessler reagent as mercury compound **51**. The second coupling reaction consisted in directly lithiated of mercury compound **51** and then alkylated with crotyl bromide (**135**) obtaining 1,4-enyne system **146**. The obtained 1,4-enyne system **146** undergoes stereoselective hydrogenation reaction with NiP-2, from which 1,4-diene system **147** is obtained. Through transacetylation reaction of the compound **147** with acetic anhydride in the presence of boron trifluoride acetic acid complex at room temperature resulted (9*Z*,12*E*)-tetradeca-9,12-dien-1-yl acetate (**125**) (Figure 2.1.2-5).



**Scheme 2.1.2-5**

Isomeric mixture is obtained consisting of (9Z,12E)-tetradeca-9,12-dien-1-yl acetate (**125**) (82%) and (9Z,12Z)-tetradeca-9,12-dien-1-yl acetate (13%).

Final and intermediate products were analyzed by GC-MS.



**Figure 2.1.2-4.** Mass spectrum of (9Z,12E)-tetradeca-9,12-dien-1-yl acetate (**125**)

By GC-MS analysis (Figure 2.1.2-4) of the (9Z,12E)-tetradeca-9,12-dien-1-yl acetate (**125**) was marked out the following: (i) the presence in the mass spectrum of base peak  $m/z$  43 ( $\text{CH}_3\text{CO}^+$ ); (ii) elimination of neutral molecules  $\text{CH}_3\text{-COOH}$  resulting in fragment  $m/z$  192; the presence of double transposition ion  $m/z$  61( $\text{CH}_3\text{-COOH}_2^+$ ); (iii) the presence of fragments of mass  $m/z$  95 resulting from the cleavages in  $\alpha$  to the double bond in position 9 of hydrocarbon chain; (iv) mass fragment  $m/z$  252 corresponds to the molecular peak.

The structure of (9Z,12E)-tetradeca-9,12-dien-1-yl acetate (**125**) was confirmed by NMR spectroscopy.

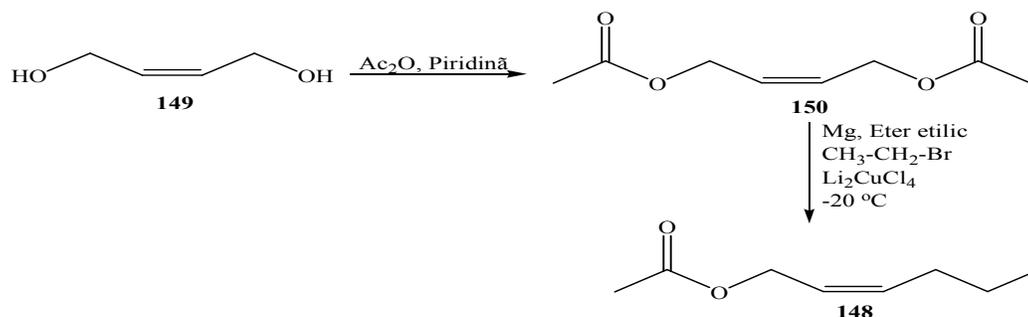
## 2.2. Using Grignard reagents in carbon-carbon bond formation

Allyl activated alkyl acetates are known to be coupled with Grignard reagents in the presence of  $\text{Li}_2\text{CuCl}_4$  catalyst [234].

In this study attempted the coupling reaction of an allyl activated diacetate with Grignard reagent in the presence of  $\text{Li}_2\text{CuCl}_4$  catalyst (Scheme 2.2-1).

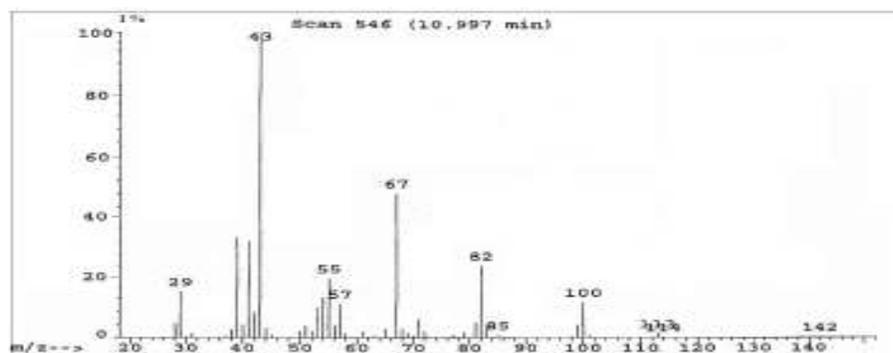
*Cis*-2-butene-1,4-diol (**149**) was used as a starting material. Acetylation reaction of *cis*-2-butene-1,4-diol (**149**) was performed with acetic anhydride in pyridine, the

corresponding diacetate **150** is obtained with a purity of 98% determined by gas chromatography. Key step is the cross-coupling reaction of *cis*-1,4-diacetoxy-2-butene (**150**) with ethyl magnesium bromide in anhydrous ethyl ether, the reaction was catalyzed by  $\text{Li}_2\text{CuCl}_4$ . (*Z*)-2-hexen-1-yl acetate (**148**) is formed with a small yield.

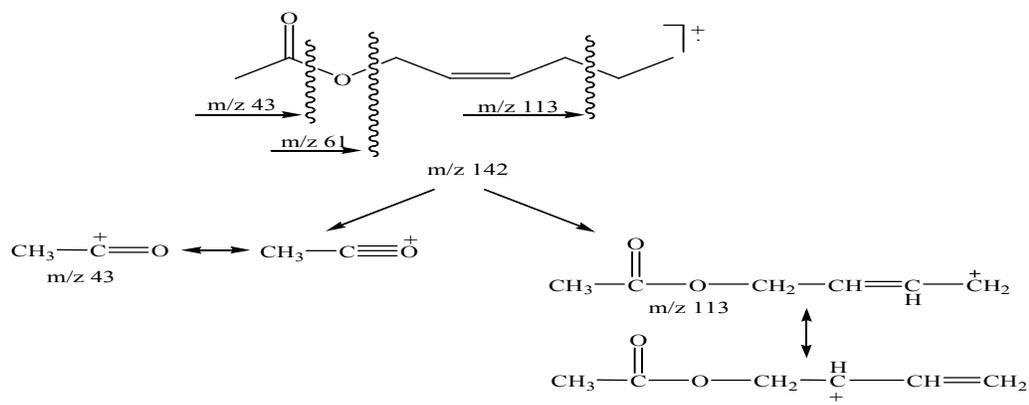


**Scheme 2.2-1**

(*Z*)-2-hexen-1-yl acetate (**148**) also has characteristic fragmentation of acetates. Mass fragment  $m/z$  43 corresponds to the base peak and mass fragment  $m/z$  142 corresponds to the molecular peak (Figure 2.2-2, Scheme 2.2-3).



**Figure 2.2-2.** Mass spectrum of (*Z*)-2-hexen-1-yl acetate (**148**)



**Scheme 2.2-3**

### 2.3. Experiments on the use of pheromonal products in bio-monitoring by "attract and kill" biotechnology of the *Adoxophyes reticulana* (summer fruit tortrix moth) and *Cydia pomonella* (codling moth) species

#### Elements of novelty

- Control of *Adoxophyes reticulana* species by "attract and kill" biotechnology
- Simultaneous control using a single product over the *Adoxophyes reticulana* and *Cydia pomonella* pest species by "attract and kill" biotechnology

The summer fruit tortrix moth *Adoxophyes reticulana* and *Cydia pomonella* are the most frequent pests of economic importance for the apple plantations in Romania. The population of these species often exceeds the economic threshold of pest, and thus signifies special damages for orchards.



*Adoxophyes reticulana*



The way of damage

A more recent onset of the direct control by using the semiochemical compounds is "attract and kill" biotechnology involving a substrate with controlled emission combined with synthetic pheromones and insecticide. The subject matter offers an environmentally friendly solution for bio-monitoring and control mentioned species.

The sex pheromone of the *Adoxophyes reticulana* species has in its composition two active components (*Z*)-9-tetradecen-1-yl acetate (**56**) and (*Z*)-11-tetradecen-1-yl acetate (**81**) at a rate of 9:1. Pheromones are used to attract adult males with the bait containing a contact insecticide that kills insect after it has reached the source.

AR MESSAGE and AC SIGNAL pheromone products have been formulated to be selective and effective in integrated control of *Adoxophyes reticulana* and *Cydia pomonella* species by "attract and kill" biotechnology in which composition falls (Z)-9-tetradecen-1-yl acetate (**56**) and (Z)-11-tetradecen-1-yl acetate (**81**), prepared in this doctoral thesis by the original method of synthesis.

Testing the efficacy of the products is carried out in partnership with the University of Agronomical Sciences and Veterinary Medicine Cluj-Napoca, Research and Development Institute for Pomiculture Pitesti-Mărăcineni, Research and Development Institute for the protection of Plants Bucuresti, Research and development station for Pomiculture Bistrița, Research and production station for Pomiculture Mures within the framework of the research project funded by the National Center of Management Programs, PN II Program, Contract 61040.

### **2.3.1. Testing product's efficacy AR MESSAGE administered to apple for control *Adoxophyes reticulana* (summer fruit tortrix moth) species**

AR MESSAGE product has the following composition: (Z)-9-tetradecen-1-yl acetate (9 parts) and (Z)-11-tetradecen-1-yl acetate (1 part). Active substances was dispersed in hydrophob gel where to a insecticide was added. The product was placed in a dosage pump. The pheromonal product AR MESSAGE was applied manually with a metering pump on the branches of trees in apple orchards under the form of droplets.

#### **2.3.1.1. Presentation of results**

##### **➤ Research-Development Institute for Pomiculture Pitești-Mărăcineni**

In 2008 AR MESSAGE product was administered in two experimental orchards, respectively ICDP Pitesti-Mărăcineni and SCDP Voinești to control summer fruit tortrix moth – *Adoxophyes reticulana*.

The efficacy results of the AR MESSAGE product to control summer fruit tortrix moth *Adoxophyes reticulana* in 2008 are presented in Tables 1 and 2.

**Table 1.** Fallen fruit

Variant	Total fruits observed	From which		Frequency of attack (F%)	Efficacy (E%)
		Healty (Nr.)	Attacked (Nr.)		
MESAJ AR Florina	307	301	6	1,9	95,5
MESAJ AR Generos	500	497	3	0,6	97,8
Standard	129	120	9	6,9	93,2
Untreated control	294	162	132	44,8	-

**Table 2.** Fruits from tree

Variant	Total fruits observed	From which		Frequency of attack (F%)	Efficacy (E%)
		Healty (Nr.)	Attacked (Nr.)		
MESAJ AR Generos	500	499	1	0,2	96,2
Standard	300	292	8	2,6	73
Untreated control	300	271	29	9,6	-

➤ **Research-Development Institute for Plant Protection București**

The effectiveness of 81.63% which was calculated for the variant treated with specific pheromone of summer fruit tortrix moth by "attract and kill" method comparable to that of the standard chemically treated (88.77%) demonstrates the possibility of using this method with good quality and harvest amount.

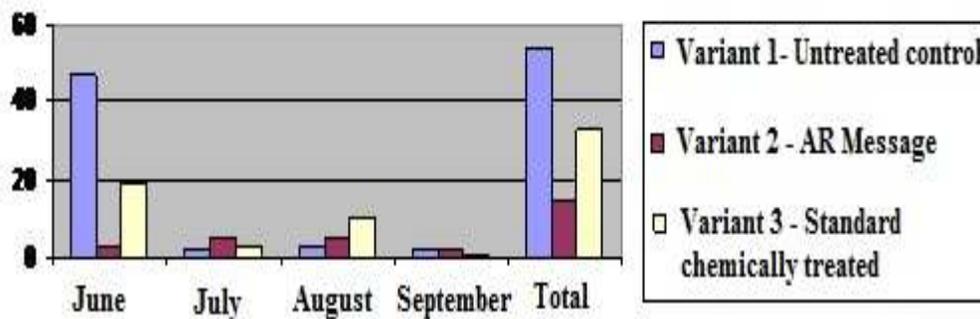
**Table 1.** The effectiveness of the AR MESSAGE product in control of the summer fruit tortrix moth *Adoxophyes reticulana*

Variant	G1		G2	
	% attack on leaves	Effectiveness (%)	% attack on fruits	Effectiveness (%)
MESAJ AR	0,6	76,92	1,8	81,63
Standard	0,8	69,23	1,1	88,77
Untreated control	2,6	-	9,8	-

➤ **Research-Development Institute for Pomiculture Bistrița**

”Attract and kill” biotechnique can give good results if they reach pest levels thresholds medium or small as occurred in the experimental year 2008. Very low level of 15 catches in the Variant 2 treated with AR MESSAGE and across from the 54 catches in untreated control Variant 1 shows significant reduction of adult flight in 2008 [236].

**The dynamics of butterflies captured per month depending on the variants of the experiment**



**Figure 3**

**2.3.2. AC SIGNAL efficacy testing administered to apple for simultaneous control of the *Adoxophyes reticulana* and *Cydia pomonella* (codling moth) species**

AC SIGNAL product was formulated to simultaneously control the *Adoxophyes reticulana* and *Cydia pomonella* species, two major pests of apple by ”attract and kill” biotechnique.

Active substances: **(Z)-9-tetradecen-1-yl acetate** (8 parts), **(Z)-11-tetradecen-1-yl acetate** (2 parts), **(8E,10E)-dodeca-8,10-dien-1-ol** (10 parts).

Active substances were dispersed in hydrophob gel where to an insecticide was added, a component that determines death of the attracted male. The product is placed in aluminum tubes.

### 2.3.2.1. Presentation of results

#### ➤ Research-Development Institute for Pomiculture Pitești-Mărăcineni

Frequency of attack produced by codling moth - *Cydia pomonella* (G1) to SCDP Voinești, 2009

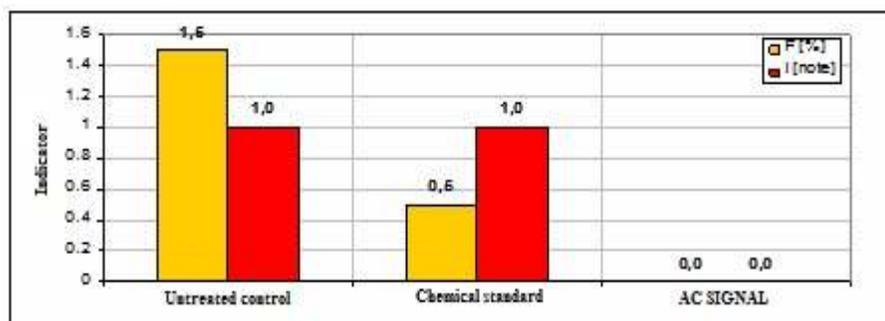


Figure 1

From the analysis of Figure 1 can be seen that the SCDP Voinești where the first generation of codling moth in the lot was treated with AC SIGNAL product, the attack rate was 0 compared to the lot treated with standard chemicals where the value of this indicator was 0,5%. Compared to the untreated control lot the attack rate was 1.5%. As the intensity of pest attack grew, the lot treated with AC SIGNAL product was 0 compared with untreated control standard lot where the attack intensity was quantified with 1.

Frequency of attack produced by summer fruit tortix moth- *Adoxophyes reticulana* (G1) to SCDP Voinești, 2009

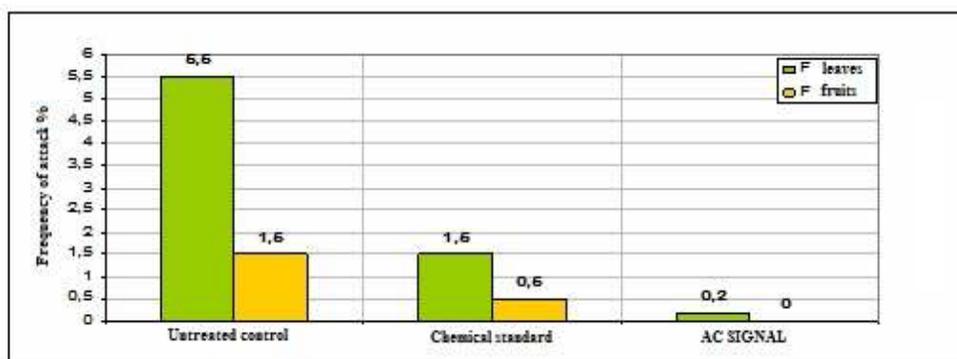


Figure 2

From Figure 2 we can see that Voinești the leaves attack rate on the lot treated with AC SIGNAL product the on was 0.2% compared to lot treated with standard products where the rate was 1.5%. Compared to the untreated control lot attack frequency was 5.5%.

With regard to pest attack on fruit skin, in the lot treated with AC SIGNAL product the skin fruit was intact, (attack rate 0) compared to the group treated with chemicals where the rate was 0.5%. Compared to the untreated control lot the fruit attack frequency was 1.5%.

➤ **Research-Development Institute for Plant Protection București**

**Table 2.** AC SIGNAL efficiency in controlling the summer fruit tortrix moth *Adoxophyes reticulana* and codling moth *Cydia pomonella* (Generation I), SCDPP Voinești, Dâmbovița, 2009

Variant	<i>Adoxophyes reticulana</i>				<i>Cydia pomonella</i>	
	leaves		fruits		% attack	Efficacy(%)
	% attack	Efficacy (%)	% attack	Efficacy (%)		
<b>SEMNAL AC</b>	<b>0,3</b>	<b>96,51</b>	<b>0,1</b>	<b>98,76</b>	<b>0,8</b>	<b>87,69</b>
Standard	3,2	62,79	2,4	70,37	0,6	90,77
Untreated control	8,6	-	8,1	-	6,5	-

The efficacy registers (87,69% – 98,76%) at the treated lot with the mixture containing pheromones specific to the two pests by ”attract and kill” biotechnology were higher then those registered at the standard chemically treated (62,79% - 90,77%) showing the possibility of the use of this method in control of these dangerous pests for apple orchards.

### 3. GENERAL CONCLUSIONS

- I. This doctoral thesis has approached the study of the synthesis of some monoene and diene pheromones using for the first time mercury derivatives of some  $\omega$ -functionalized 1-alkyne. A new method of synthesis of highly generalization using functionalized alkynylmercury compounds was developed.
- II. By the original synthesis method developed were prepared 8 pheromone with chain length of 12, 14 and 16 carbon atoms. Of the eight synthesized pheromones 7 are monoene pheromones with *Z* and *E* geometry with the double bond in position 7, 9 and 11 and a diene pheromone with double bonds in positions 9 and 12.
- III.  $\omega$ -Functionalized alkynylmercury compounds were used for the first time in the preparation of pheromones with different chain lengths of carbon atoms, respectively different positions of the double bond in the chain, being stable compounds which may be isolated from the reaction medium and require no special conditions for storage or handling. Through these  $\omega$ -functionalized mercury derivatives pheromones were prepared with a purity > 90%.
- IV. The intermediate (*Z*)-2-hexen-1-yl acetate was synthesized by a new synthesis method using cross-coupling reaction of ethylmagnesium bromide with *cis*-1,4-diacetoxy-2-butene in the presence of  $\text{Li}_2\text{CuCl}_4$  catalyst. This intermediate can be used in pheromone synthesis if the yield can be improved.
- V. Intermediates and final compounds prepared were analyzed by gas chromatography coupled with mass spectrometry, the structure of the final product having been confirmed by NMR spectroscopy ( $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR).

- VI. (Z)-9-tetradecen-1-yl acetate and (Z)-11-tetradecen-1-yl acetate were prepared by the original method of synthesis developed used in the formulation of pheromone products AR MESSAGE and AC SIGNAL tested in field conditions.
- VII. AR MESSAGE product have been used to control of the summer fruit tortrix moth *Adoxophyes reticulana* by "attract and kill" biotechnology.
- VIII. AC SIGNAL product was used in simultaneous control of the two major pests of apple trees, the *Adoxophyes reticulana* and *Cydia pomonella* species, by "attract and kill" biotechnology.
- IX. The results presented on the use of AR MESSAGE and AC SIGNAL in control of the *Adoxophyes reticulana* and *Cydia pomonella* species under field conditions by "attract and kill" biotechnology showed a good efficiency of the products, respectively a frequency of attack comparable with that in the chemical standard. Based on the results on the effectiveness of these products can be considered to be used in integrated control systems.
- X. Some of the results obtained in elaborating of this doctoral thesis has been exploited in the form of three papers, a patent, 4 communications in the country and 5 communication abroad.

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