# Syntheses of (E)-5/6- and (E)-6/7-Nonenyl Acetate Mixtures as Melon Fly (*Dacus cucurbitae* Coquillet) Attractants

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Foi desenvolvido um método geral para obtenção de misturas de (E)-5/6 e (E)-6/7-acetato de nonenila. Acilação da morfolino-enamina de ciclopentanona (**1a**) e cicloexanona (**1b**) com cloreto de butirila e de propionila, respectivamente, seguida de abertura do anel, forneceu os ácidos 6-ceto e 7-cetononanóicos (**3-6**, **3-7**). Redução ($NaBH_4$) da carbonila cetônica, com subsequente desidratação ($H_3PO_4/P_2O_5$) dos ésteres metílicos correspondentes, levou a uma mistura E,Z dos 5/6 e 6/7-nonenoatos de metila. Os isômeros E e Z foram separados por cromatografia em coluna, e estes últimos foram isomerizados ($HNO_2$) aos primeiros, aumentando assim a quantidade total dos isômeros biologicamente ativos E. Redução ($LiAlH_4$) do grupamento éster, com subsequente acetilação ($Ac_2O$,Py), levou às misturas desejadas.

A general method has been developed to obtain (E)-5/6- and (E)-6/7- nonenyl acetate mixtures by acylating the morpholine enamine of cyclopentanone (**1a**) and cyclohexanone (**1b**) with butyryl and propionyl chloride, respectively, followed by ring-opening to 6-keto- and 7-ketononanoic acids (**3-6**, **3-7**). Reduction ($NaBH_4$) of the keto group and subsequent dehydration ($H_3PO_4/P_2O_5$) of the corresponding methyl esters gave E,Z-mixtures of methyl 5/6- and 6/7-nonenoates. E and Z isomers were separated by column chromatography and the latter isomerised ($HNO_2$) to the former, thus increasing the total amount of the biologically active E isomers. Reduction ($LiAlH_4$), of the ester group and subsequent acetylation ($Ac_2O$, Py) led to the title mixtures.

**Key words:** *synthesis, (E)-nonenyl acetates, mixtures,* Dacus cucurbitae.

## Introduction

(E)-6-Nonenyl acetate is known as the best synthetic attractant regarding control and eradication of the melon fly (*Dacus cucurbitae* Coquillet)[1] and because the corresponding free alcohol has been identified as the main component of the male *Ceratitis capitata* Wiedemann sex pheromone[2], many syntheses of these two parent compounds have been published[3]. However, particular care has been paid to the regio- and stereo specific formation of the C-C double bond and as a result, poor yields and specific reaction requirements have limited the application of these processes on a large scale.

Therefore, we sought to develop a general method to obtain, via non-controlled formation of the C-C double bond, (E)-5/(E)-6- and (E)-6/(E)-7-nonenyl acetate mixtures (see Scheme), based on the reported data[1] that biological response of the female melon fly to individual (E)-5-, (E)-6- and (E)-7-nonenyl acetates shows an attractancy index relationship of 47:66:35, whereas Z-diasteroisomers of all nonenyl acetates are totally devoid of activity.

## Method

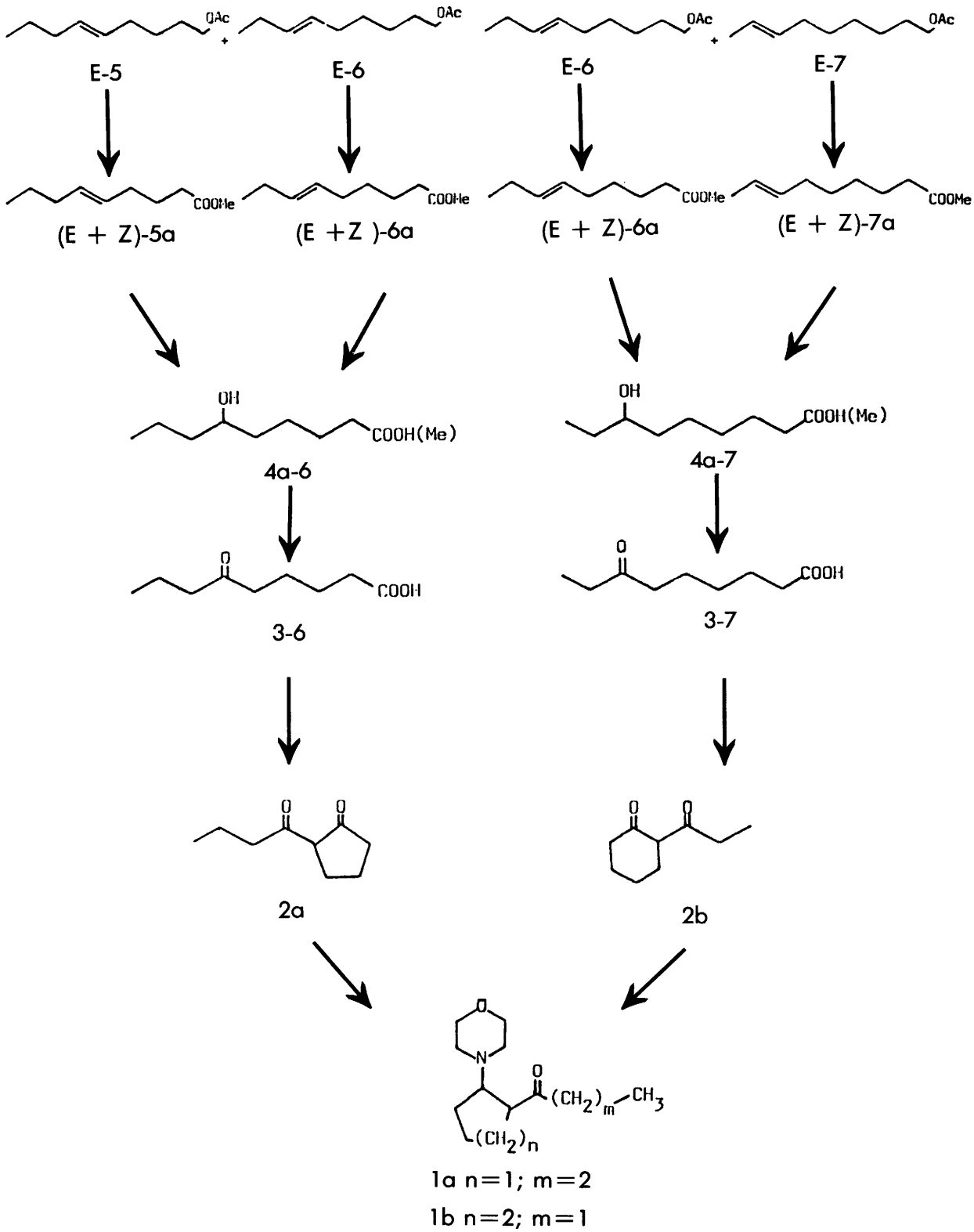
Retrosynthetic considerations led us to the conclusion that enamines should be suitable general precursors as they allow chain elongation by reaction with electrophiles; in fact, enamine acylation[4] provided an efficient synthetic route to 6-keto- and 7-ketononanoic (**3-6** and **3-7**) which were converted into the corresponding 6- and 7-hydroxyacids (**4-6** and **4-7**) by $NaBH_4$ reduction. Since both compounds contain the proper functionalized skeleton, next work was centered on introduction of the C-C double bond and to produce the final mixtures with total E-configuration and known compositions.

Dehydration of alcohols under acidic conditions is one of the most common ways of forming a C-C bond; acidic reagents must be fairly strong and must have a non-nucleophilic counter-ion to avoid substitution. The usually efficient $POCl_3$-pyridine dehydration system gave, in our hands, poor yields (38%), whereas better results (60-65% yield) were obtained[5] with $H_3PO_4/P_2O_5$ and the methyl esters of the respective hydroxyacids. Structural similitudes of the regio- and stereoisomers in dehydration products (**5a**/**6a** and **6a**/**7a**) render unreliable any direct quantitative analysis either by GLC or spectroscopy due to the limitations of available instruments.

Consequently, E and Z isomers in either mixture were separated by column chromatography giving E:Z ratios of 2:1 of **5a**/**6a** and 1.6:1 for **6a**/**7a**. Total amount of the biologically active E-isomers was increased by Z to E isomerization by *in situ* generated nitrous acid[6].

All attempts to attain separation of the regioisomers failed and lack of pure and authentic samples of **5a**, **6a**

## SCHEME


OAc
E-5
E-6
E-6
E-7
COOMe
(E + Z)-5a
(E + Z)-6a
(E + Z)-6a
(E + Z)-7a
OH
COOH(Me)
4a-6
4a-7
O
COOH
3-6
3-7
2a
2b
N
(CH2)m CH3
(CH2)n
1a n=1; m=2
1b n=2; m=1

and **7a**, to be used as standards, prevented direct GLC analysis. Hence, oxidative cleavage of each one of the dehydration mixtures was carried out with the potassium periodate-permanganate reagent[7] and available glutaric, adipic and pimelic dimethyl esters were used as references in the GLC analysis of the respective oxidation produts. Compositions of **5a/6a** (46:54%) and **6a/7a** (51:49%) were calculated from the corresponding glutaric/adipic and adipic/pimelic dimethyl esters relationships.

Finally, conversion of the -COOMe functional group into $-CH_2OAc$ was performed in mild conditions ($LiAlH_4$ and $Ac_2O$, pyridine)[8] to avoid any modification of position or geometry of the C-C double bond.

The method described herein involves readily available starting materials and reagents, feasible large-scale reactions performed in normal conditions and high yields. As the easy availability and low cost of an efficient lure is of prime importance in programs to controle or eradicate destructive pests, such as the melon fly, synthetic advantages might render this method competitive enough to compensate a lower biological activity of the obtained (E)-nonenyl acetate mixtures compared with that of pure (E)-6-nonenyl acetate.

## Experimental

All compounds were identified by their physical and spectroscopic properties. IR spectra were recorded on a Perkin Elmer 599 spectrometer. $^1H$ NMR spectra were obtained in $CC\ell_4$ solutions, with TMS as internal standard, on a Varian EM-360L spectrometer. GLC analyses were performed on a Varian 3700 - FID.

*6-ketononanoic acid* (**3-6**): according to literature procedures[4a], cyclopentanone afforded **3-6** (61%) by acylating the morpholine enamine with butyryl chloride, b.p. (150-153)° C/0.701Pa.

M.p. (37-38)°C (lit.[4b]37-38°C); IR (melted film) 3700-2800 (OH), 1715(keto CO), 1710(acid CO), 950(OH) $cm^{-1}$; NMR $\delta$ ppm 0.9-1.5(m,9H), 2.1 (t,4H), 2.4(t,2H), 10.8(s,1H).

*Methyl 6-hydroxynonanoate* (**4a-6**): $NaBH_4$ (2.14g, 56mmol) was added to a solution of **3-6** (9g, 52 mmol) in 5% aqueous NaOH (35ml). After heating at 45°C for 1h with magnetic stirring, usual workup gave **4-6** (85%) which, without further purification, was converted into the methyl ester (99%) by treament with diazomethane[8], b.p. (125-128)°C/0.701Pa.

IR (neat) 3350(OH), 1740(CO), 1115(COOR) $cm^{-1}$; NMR $\delta$ ppm 0.9(t,3H), 1.5 (m,8H), 2.2(m,3H), 2.4(s,1H), 3.5(s,3H).

*Methyl (E/Z)-5/6-nonenoate* (**5a/6a**): stereoisomeric mixture of **5a/6a** (4.11g, 65%) was obtained by dehydration of **4a-6**(7g, 36 mmol) with $H_3PO_4/P_2O_5$(90:2.4 mmol), as described in the literature[5], except that steam distillation was used to isolate the product. After extraction with ether, usual workup gave a yellow oil which was chromatographed on a $AgNO_3$-silica gel column[9] using hexane-$CHC\ell_3$ (9:1) as eluent. Regioisomers were not separated; E-stereostructure was assigned to the less polar major product and Z-stereostructure to the more polar minor product. The validity of these assignments was estabilised by TLC ($AgNO_3$-silica gel plates, hexane-$CHC\ell_3$, 9:1) and IR spectral comparison: methyl (E)-5/6 nonenoates (**E-5a/6a**, 2.81g, 68%), $R_f$ values 0.63 and 0.58; IR (neat) 970 and 920 $cm^{-1}$ (trans HC=CH); NMR $\delta$ ppm 3.5(s, 3H), 5.2(m,2H,HC=); methyl (Z)-5/6 nonenoates (**Z-5a/6a**, 1.30g, 32%), $R_f$ values 0.37 and 0.40; IR (neat) lack of 970 and 920 $cm^{-1}$ absorption bands; NMR, virtually identical with **E-5a/6a**.

*Isomerization of Z* **-5a/6a**: **2-5a/6a** (1.3g, 7.6 mmol) was warmed under nitrogen at (70-75)°C for 1 h with aqueous $NaNO_2$ (2M, 1.7ml) and $HNO_3$ (2M, 0.2ml)[6]. The oily residue was chromatographed as described above to give **E-5a/6a** 0.97g, 75%). After E-structure confirmation by TLC and IR spectral comparision, this fraction was added to the previously obtained to sum up total **E-5a/6a**(3. 78g, 91% yield from **5a/6a**).

*Determination of 5a/6a composition:* a sample of **5a/6a** was oxidized with potassium periodate-permanganate as described in the literature[7]. After treatment with diazomethane, the oxidation products were analized by GLC as methyl and dimethyl esters (3% SP-SE 30; 3m×2mm; (170-200)°C; 4°C/min; $N_2$); retention time data were identical with those of authentic samples of glutaric and adipic dimethyl esters.

*(E)-5/6-nonenyl acetates* (**E-5/6**): reduction[8] by $LiAlH_4$ of **E-5a/6a** afforded the mixture of the corresponding E-alkenols which, without further purification, were converted into the acetates with acetic anhydride-pyridine[8]. The product was purified by passage through a silical gel column and assigned structure confirmed by TLC ($AgNO_3$-silica gel plates, hexane-$CHC\ell_3$, 9:1) and spectral analyses: **E-5/6** (3.21g, 85%); $R_f$ values 0.63 and 0.58; IR (neat) 1750(CO), 1240, 1050(COOR), 970,920(trans HC=CH) $cm^{-1}$; NMR $\delta$ ppm 3.9(t,2H,-$CH_2OOCCH_3$), 5.2(m,2H,HC=).

(E)-6/7-nonenyl acetate mixture (**E-6/7**) was obtained in a similar manner according to the sequence; 7-ketononanoic acid (**3-7**; 57% yield from cyclohexanone), b.p. (144-147)°C/1.052Pa.

M.p. (42-43)°C (lit.[4b]41.5-42.5°C); methyl 7-hydroxynonanoate (**4a-7**, 85% yield from **3-7**), b.p. (120-125)°C/1.052Pa;

methyl (E/Z)-6/7-nonenoate (**6a/7a**; 60% yield from **4a-7**); methyl (E)-6/7-nonenoate (**E-6a/7a**; 61% yield from **6a/7a**). $R_f$ values 0.58 and 0.52; methyl (Z)-6/7-nonenoate (**Z-6a/7a**; 39% yield from **6a/7a**), $R_f$ values 0.40 and 0.45; IR and NMR data in agreement with all assinged structures and virtually undistinguishable from those given above for the corresponding compounds and mixtures derived from cyclopentanone.

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