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THE USE OF TETRAHYDROFURAN DERIVATIVES IN SYNTHESIS OF COMPONENTS OF SEX PHEROMONE OF THE ORIENTAL FRUIT MOTH

N. G. HOBOSYAN [1,2*], S. A. HOVAKIMYAN [2], K. V. BALYAN [1], H. S. NERSISYAN [1], H. B. SARGSYAN [1], J. A. CHOBANYAN [1]

[1] *Institute of Organic Chemistry, STC of Organic and Pharmaceutical Chemistry of NAS RA*
[2] *Kh. Abovian Armenian State Pedagogical University, Armenia*

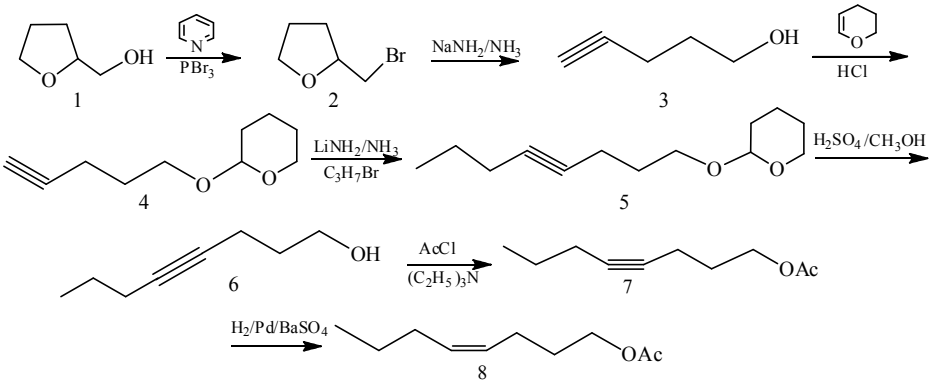
Based on available reagents: tetrahydrofurfuryl alcohol and tetrahydrofuran, the technologically easily implemented method of synthesis of the active component of the sex pheromone of Oriental Fruit Moth *Grapholitha Molesta* with predominant content of (*Z*)-dodec-8-enyl acetate by two synthon C_8+C_4 scheme was developed. The condensation stage of C_4 and C_8 was performed in the presence of dilithium tetrachlorocuprate.

***Keywords*:** sex pheromone, oriental fruit moth, two-synthon strategy, tetrahydrofuran, tetrahydrofurfuryl alcohol, column chromatography.

Introduction. The synthesis of natural compounds is one of the most promising part of contemporary organic chemistry. The realization of these tasks requires developing the methods, which will allow creating biologically active substances with certain structure [1, 2]. In series of natural low molecular weight bioregulators the pheromones differ by their multifunctional action and application importance. At present the structure of hundreds of insects' pheromones is known [3–7]. The majority of those pheromones was successfully synthesized and tested against plants pests as well as for determination of their shelf life. The most promising is the use of pheromones in extermination and disorientation of male insects, which will essentially decrease the quantity of the pesticides now in use. Oriental moth is widely spread throughout the territory of the Republic of Armenia. It causes big damage to horticulture (apricot, peach, pear and quince). Thus we consider the importance to review the literature data concerning this insects pheromone and to develop simple methods of its synthesis [8, 9]. It is known that the active ingredients of oriental moth pheromone are cis- and trans-dodec-8-enyl acetates. The known up to now in the literature methods of synthesis of these monoen compounds from technological point of view are not easy at all, since the starting reagents are not available and they can be synthesized by the reactions of alkylacetylenes with alkylpropargyl halides.

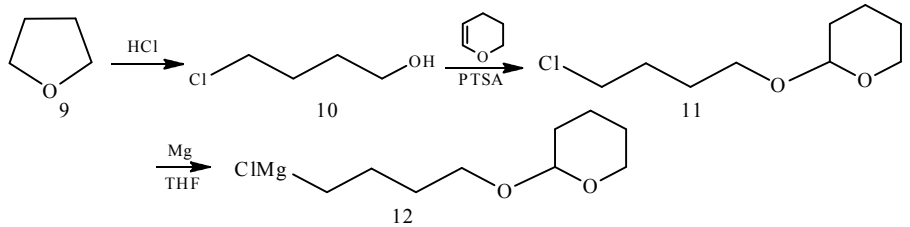
* E-mail: ninahobosyan@mail.ru

Results and Discussion. We synthesized the (*Z*)-dodec-8-enylacetate major component of the pheromone of the oriental fruit moth by the two-synthon C_4+C_8 strategy, which involves the use of tetrahydrofuran and its available derivatives in the process of obtaining both components. The starting reagent for the synthesis of synthon C_8 is was tetrahydrofurfuryl alcohol (**1**), which was converted into the corresponding bromide (**2**) by the reaction with phosphorus tribromide in pyridine. Tetrahydrofurfuryl bromide (**2**) was fissioned with sodium amide in ammonia to give pent-4-yn-1-ol (**3**), the alcohol group of which was protected by a tetrahydropyranyl group (Scheme 1). By the alkylation of 2-(pent-4-ynyloxy)tetrahydro-2*H*--pyran (4) with propyl bromide in the presence of lithium amide the corresponding ether (5) was obtained. Then, the pyranyl protecting group was removed and oct-4-yn-1-ol (6) was synthesized. Acetylene alcohol (6) was acylated with acetyl chloride in triethylamine medium. The cis-hydrogenation of the internal triple bond of acetate (7) was carried out in the presence of the Pd/$BaSO_4$ system to obtain the C_8-component (*Z*)-oct-4-enylacetate (8):



Scheme 1.

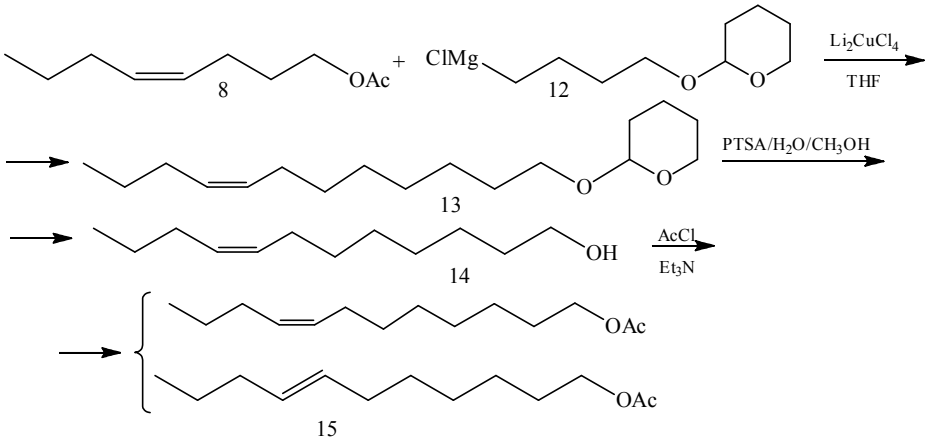
The C_4-component was obtained from tetrahydrofuran (9) by the reaction with hydrogen chloride resulting in the formation of 4-chlorobutane-1-ol (10). By protecting the functional alcohol group of the latter compound by tetrahydropyranyl ether group it is quite easy to obtain the corresponding Grignard reagent (12) according to the following reaction (Scheme 2):



Scheme 2.

It should be noted that the Grignard reagent more easily can be obtained from the bromoderivative of the pyranyl ether however according to our studies in that case more reaction by-products (~30%) are formed. The C_8+C_4 condensation reaction carried out at –10÷5°*C* in tetrahydrofuran medium at a molar ratio of

reactants of 1:1.1 in the presence of dilithium tetrachlorocuprate, as a result of which tetrahydropyranyl ether of cis-dodec-8-en-1-ol was formed. Further, by the action of a catalytic amount of p-TSA in methanol, tetrahydropyranyl protection was removed. The resulting dodec-8-en-1-ol (14) was acylated with acetyl chloride in the presence of triethylamine to give the targeted (*Z*)-dione-8-ethylacetate (15) and isolated by column chromatography (Scheme 3):



Scheme 3.

According to the GLC data, the target product contains up to 93% (*Z*)-dodec-8-ethylacetate and presumably (*E*)-dodec-8-ethylacetate. This is indicated by the presence of two absorption bands in the IR spectrum corresponding to *E* (969 cm^{-1}) and *Z* (723 cm^{-1}) double bonds. Probably, in the process of condensation, a partial inversion of the (*Z*) double bond of the C_8 component takes place, as a result of which the content of the (*E*)-isomer increases in the target product.

Thus, the synthesis of the sex pheromone of the oriental fruit moth *Grapholitha molesta* was carried out on the basis of available tetrahydrofuran derivatives.

Experimental Part. ^{1}H NMR spectra (300.07 and 75.46 *MHz* respectively) of the solutions in DMSO-d_6–CCl_4 (1:3) were recorded on a Varian Mercury-300 VX spectrometer at 303 *K* relative to internal TMS. The reaction progress was monitored by TLC using Silufol UV-254 plates, developing with $KMnO_4$ and iodine vapor. GLC analysis was performed using a LHM-80MD instrument (model 3) (1.5 *m* column, AW-NMDC sorbent soaked with 10% Carbovax-20M, rate of carrier gas 40 *mL*/*min*, detector temperature 200°*C*, evaporator temperature 250°*C*). IR spectra were recorded on Nicolet AVATAR 330 FT-IR spectrophotometer and the reported wave numbers are given in cm^{-1}. Tetrahydrofurfuryl bromide was obtained by Smith [10]. THF was distilled from sodium and benzophenone before used.

*Pent-4-yn-1-ol (**3**).* 600 *mL* of condensate ammonia was cooled to –45°*C*, 0.5 *g* of iron (III) nitrate, 22 *g* (0.945 *mol*) of sodium were added and mixed until sodium was converted to the amide. Further, at –40°*C* for 25–30 *min*, 45 *g* (0.27 *mol*) of tetrahydrofurfuryl bromide (**2**) was added and stirred for 2 *h*. The reaction mixture was stand at room temperature for 12 *h*, neutralized with saturated hydrochloric acid solution, and extracted with diethyl ether (3×50 *mL*).

The organic layer was dried over sodium sulfate. Removal of the solvent and subsequent distillation gave 18.00 *g* of **3** in 80% yield, b.p. 70–71°*C* (29 *mm* Hg), n_D^{20} 1.4443. ^{1}H NMR spectra, *δ*, *ppm*; *J*, *Hz*: 1.65 m (2H, CH_2); 2.05 t (1H, HC≡C, *J*=2.5); 2.2 *m* (2H, CH_2C≡); 3.5 t (2H, CH_2OH, *J*=6.4); 4.1 s (1H, OH). IR, *v*, cm^{-1}: 1045, 1140, 1205, 1425 (C–O), 2125 (C≡C), 3300 (C≡CH), 3350 (OH).

*2-(Pent-4-yn-1-yloxy)tetrahydro-2H-pyran (**4**)*. The mixture of 18.0 *g* (0.21 *mol*) pent-4-yn-1-ol (3) and 18.5 *g* (0.22 *mol*) dihydropyran was cooled to 0°*C*, 0.2 *mL* of concentrated hydrochloric acid was added dropwise and the mixture was stirred at 25°*C* for 18 *h*. The reaction mixture was neutralized by the addition of 0.5 *g* of crystalline potassium hydroxide, stirred for 15 *min*, and filtered. Removal of the solvent and subsequent distillation gave 32.0 *g* of **4** in 91% yield, b.p. 103–105°*C* (11 *mm* Hg), n_D^{20} 1.4542. ^{1}H NMR spectra, *δ*, *ppm*; *J*, *Hz*: 1.5–1.86 m (8H, CH_2); 2.1 t (H, HC≡C, *J*=2.5); 2.3 m (2H, CH_2C≡); 3.3–3.9 m (4H, CH_2O); 4.58 s (1H, O–CH–O). IR: *v*, cm^{-1}: 1035 (C–O), 2125 (≡CH), 2875, 2945 (CH).

*2-(Oct-4-yn-1-yloxy)tetrahydro-2H-pyran (**5**)*. 500 *mL* of ammonia was condensed, cooled to –50°*C*, 0.3 *g* of iron (III) nitrate and 2 *g* of lithium was added. 32 *g* of 2-(pent-4-yn-1-yloxy)tetrahydro-2*H*-pyran (**4**) was added dropwise to the reaction mixture, stirred for 1 *h* and 32 *g* (0.26 *mol*) of propyl bromide was added dropwise over 30 *min* so that the temperature of the reaction mixture did not rise above –40°*C*. The reaction mixture was stirred for 1 *h* and stand at 25°*C* for 12 *h*, then neutralized with saturated HCl solution, and extracted with diethyl ether (3×50 *mL*). The organic layer was dried over sodium sulfate. Removal of the solvent and subsequent distillation gave 27 *g* of the compound 5 in 68% yield, b.p. 144–146°*C* (11 *mm* Hg), n_D^{20}1.4599. ^{1}H NMR spectra, *δ*, *ppm*; *J*, *Hz*: 0.95 t (3H, CH3, *J*=6.4); 1.45–1.86 m (10H, CH_2); 2.1–2.3 m (4H, CH_2C≡); 3.3–3.9 m (4H, CH_2O); 4.57 s (1H, O–CH–O). IR, *v*, cm^{-1}: 1035 (C–O), 2225 (C≡C), 2875, 2945 (CH).

*Oct-4-yn-1-ol (**6**)*. To 300 *mL* of methanol was added 20 *mL* of concentrated sulfuric acid and stirred at 5°*C* for 15 *min*, the temperature was brought to 20°*C*, 2-(oct-4-yn-1-yloxy)tetrahydro-2*H*-pyran (**5**) 27 *g* (0.13 *mol*) was added and stirred for 5 *h*. The mixture was neutralized with a solution of sodium carbonate, extracted with diethyl ether, dried with magnesium sulfate. Removal of the diethyl ether and subsequent distillation gave 10 *g* of 2 oct-4-yn-1-ol (**6**) in 61% yield, b.p. 100°*C* (12 *mm* Hg). ^{1}H NMR spectra, *δ*, *ppm*; *J*, *Hz*: 0.95 t (3H, CH_3, *J*=6.4); 1.45–1.6 m (4H, CH_2); 2.18 m (4H, CH_2C≡); 3.45 m (2H, CH_2OH); 3.95 t (1H, OH). IR, *v*, cm^{-1}: 2225 (C≡C), 3400–3500 (OH).

*Oct-4-ynyl Acetate (**7**)*. A mixture of 160 *mL* of absolute ether, 12 *mL* of triethylamine and 10 *g* (0.08 *mol*) of oct-4-yn-1-ol (**6**) was cooled to –12°*C*, stirred for 10 *min* and was added dropwise 7.0 *g* (0.09 *mol*) of acetyl chloride, exotherm was observed up to –6°*C* and stirred at this temperature for 1.5 *h*. The precipitated crystals were filtered and washed with diethyl ether the ether extracts were treated with 2 *M* hydrochloric acid, then with sodium carbonate and sodium chloride solutions respectively. The organic layer was dried over sodium sulfate. Removal of the solvent and subsequent distillation gave 10 *g* of oct-4-ynyl acetate (**7**) in 74% yield, b.p. 97–105°*C* (12 *mm* Hg), n_D^{20} 1.4379, R_f 0.75 (hexane : diethyl ether = 2 : 1). ^{1}H NMR spectra, *δ*, *ppm*; *J*, *Hz*: 1.0 t (3H, CH_3, *J*=6.4); 1.4–1.8 m (4H, CH_2);

2.0 s (3H, CH_3C=O); 2.1–2.3 m (4H, CH_2C≡); 4.1 t (2H, CH_2O, *J*=6.4). IR, *v*, cm^{-1}: 2225 (C≡C), 3400–3500 (OH).

*(Z)-Oct-4-enyl Acetate (**8**).* To 10 *g* (0.06 *mol*) of oct-4-ynyl acetate (**7**) were added 3 *mL* of pyridine, 150 *mL* of methanol and hydrogenation at a temperature of 25°*C* in the presence of 1.2 *g* of $Pd/BaSO_4$ catalyst. After 9 *h*, the mixture was filtered, extracted with ether (3×50 *mL*), the extracts were treated with 5% hydrochloric acid, washed with water. The organic layer was dried over sodium sulfate. Removal of the solvent and subsequent distillation gave 9.4 *g* of oct-4-ynyl acetate (**7**) in 92% yield, b.p. 97–105°*C* (12 *mm* Hg), R_f 0.72 (hexane : diethyl ether=3:1). ^{1}H NMR spectra, *δ*, *ppm*; *J*, *Hz*: 1.01 t (3H, CH_3, *J*=6.4); 1.4 m (2H, CH_2CH_3), 1.65 m (2H, $\underline{CH_2}CH_2OAc$); 2.01 m (4H, $\underline{CH_2}CH$=CH), 2.09 s (3H, $COCH_3$); 4.15 t (2H, $\underline{CH_2}OCOCH_3$, *J*=6.4); 5.42 m (2H, =CH). IR, *v*, cm^{-1}: 1610 (CH=CH), 723 (*Z*).

*2-(4-Chlorobutoxy)tetrahydro-2H-pyran (**11**).* 94 *g* (0.87 *mol*) of 4-chlorobutan-1-ol was cooled up to –5°*C*, 75.6 *g* (0.9 *mol*) of dihydropyran was added dropwise, followed by 1 *g* of concentrated hydrochloric acid and stirred at 18°*C* for 18 *h*. The reaction mixture was neutralized by 1.6 *g* of crystalline potassium hydroxide, stirred for 15 *min* and filtered. Futher distillation gave 116 *g* of **11** in 69.3% yield, b.p. 120°*C* (12 *mm* Hg), n_D^{20} 1.4589. ^{1}H NMR spectra, *δ*, *ppm*; *J*, *Hz*: 1.4–1.9 m (10H, CH_2); 3.3–3.5 m (2H, CH_2O); 3.6–3.8 m (4H, CH_2O, CH_2Cl); 4.5 m (1H, O–CH–O). IR, *v*, cm^{-1}: 1035 (C–O), 2875, 2945 (CH).

*(Z)-2-(Dodec-8-enyloxy)tetrahydro-2H-pyran (**13**).* In 90 *mL* of absolute tetrahydrofuran, a Grignard reagent (12) was prepared by reacting 2.5 *g* of Mg and 17 *g* (0.088 *mol*) of 2-(4-chlorobutoxy)tetrahydro-2*H*-pyran (**11**). Separately, 0.5 *g* of Li_2CuCl_4 was dissolved in 12 *mL* of absolute tetrahydrofuran, 9.4 *g* (0.055 *mol*) of (*Z*)-oct-4-enyl acetate was added, cooled to –10°*C* and the Grignard reagent (12) obtained by the above method was added. The mixture was stirred for 1 *h* at 0°*C*, then 2 *h* at 25°*C*, further treated with 90 *mL* of saturated ammonium chloride solution, the organic layer was separated, the aqueous layer was extracted with ether (3×30 *mL*) and dried with sodium sulfate. After removal of the ether, 12 *g* of a crude residue was obtained and transformated without distillation.

*(Z)-Dodec-8-en-1-ol (**14**).* To 55 *mL* of methanol at 0°*C* was added 7 *mL* of concentrated sulfuric acid, stirred for 10 *min*, then at 20°*C* 12 *g* of an unreacted residue containing (*Z*)-2-(dodec-8-enyloxy)tetrahydro-2*H*-pyran (**13**) was added. The reaction mixture was stirred at 20°*C* for 10 *h*, neutralized with sodium carbonate, extracted with ether and dried with sodium sulfate. After the ether was removed, 7.2 *g* of a residue was obtained, which was chromatographed on a column containing 100 *g* of silica gel (40–100 *mcm*) (hexane : ether = 4 : 1) portionwise over 2.4 *g* and gave of the 4.2 *g* of (*Z*)-dione-8-en-1-ol (14). ^{1}H NMR spectra, *δ*, *ppm*; *J*, *Hz*: 1.01 t (3H, CH_3, *J*=6.4); 1.22–1.40 m (12H, CH_2); 1.96 m (4H, $\underline{CH_2}CH$=CH); 3.45 m (2H, $\underline{CH_2}OH$), 3.95 m (1H, OH); 5.42 m (2H, =CH). IR, *v*, cm^{-1}: 1610 (CH=CH), 723 (*Z*), 3400–3500 (OH).

*(Z)-Dodec-8-ethylacetate (**15**).* 42 *mL* of triethylamine, 4.2 *g* (0.023 *mol*) of (*Z*)-dodec-8-en-1-ol were added at –5°*C* to 50 *mL* of absolute ether, stirred for 10 *min*. The mixture was cooled to –10°*C*, 3 *mL* of acetyl chloride was added and stirred for another 1 *h*. The temperature was raised to 25°*C* and stirring was continued for 3 *h* at this temperature. The mixture was filtered, and the residue was

washed with ether. The organic extracts were treated with 40 *mL* of 2 *M* hydrochloric acid, neutralized with a solution of sodium carbonate, washed with water and dried with sodium sulfate. After removal of the ether, the residue was portionwise (×3) chromatographed on a column containing 70 *g* of silica gel (40–100 *mcm*) (hexane:ether=3:1) and gave 3 *g* (62%) of (*Z*)-dodec-8-ethylacetate (**15**). ^{1}H NMR spectra, δ, *ppm*; *J*, *Hz*: 0.91 t (3H, CH_3, *J*=7.6); 1.27–1.36 m (10H, CH_2); 1.62 m (2H, $\underline{CH_2}CH_2O$); 1.98–2.00 m (4H, $\underline{CH_2}$–CH=CH–$\underline{CH_2}$); 2.03 s (3H, $COCH_3$), 4.0 t (2H, CH_2OAc, *J*=6.8); 5.38 m (2H, CH=CH). IR, *v*, cm^{-1}: 1610 (CH=CH), 723 (*Z*). Calculated, %: C 74.58, H 11.42. $C_{14}H_{26}O_2$. Found, %: C 74.29, H 11.58.

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