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Stereodirectional Synthesis of the Main Component of Pheromone (9*Z*,12*E*)-Tetradeca-9,12-dienyl Acetate by Cross-coupling*

E. D. Matveeva, A. S. Erin, I. F. Leshcheva, and A. L. Kurts

Moscow State University, Moscow, 119899 Russia

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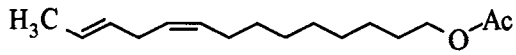
Abstract—By cross-coupling of alkynyl cuprate with crotyl halides was synthesized (9*Z*,12*E*)-tetradeca-9-12-dienyl acetate, the main component of pheromones of several insect species Lepidoptera. The assignment of the chemical shifts of diene system was performed by ^{1}H and ^{13} NMR spectroscopy.

The (9*Z*,12*E*)-tetradeca-9-12-dienyl acetate (**I**), the main component of pheromone of insects Ephestia Kuehniella and Plodia Interpunctella, cereal pests, are synthesized by several methods [1–3].

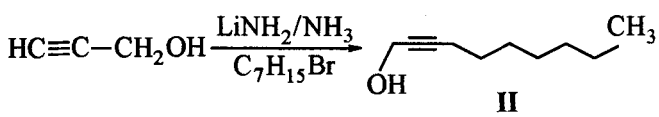


I

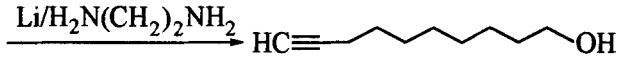
We described in [1] a successful stereospecific synthesis of this pheromone using as key stage salt-less version of Wittig reaction: The attained stereospecific purity of the diene was 98%. The target of this study was the synthesis of pheromone **I** by cross-coupling of lithium homocuprate with crotyl chloride and crotyl bromide.

We studied formerly the cross-coupling of various primary and secondary allyl halides with lithium dialkynyl cuprates as a model reactions of regioselective 1,4-enyne synthesis [4]. We found the conditions affording 96–97% of regioselective cross-coupling.

For the multistage stereodirectional synthesis of pheromone **I** was chosen as starting compound dec-2-yn-1-ol (**II**) that was prepared by alkylation of dilithium salt of propargyl alcohol with heptyl bromide in liquid ammonia.



II



III

Preparation of the terminal decinol (**III**) without impurities of allenes, dienes, and nonterminal alkyne resulted from treating dec-2-yn-1-ol (**II**) with lithium 2-aminoethylamide in ethylenediamine at 60–70°C [5]. The terminal decynol was obtained in 82% yield in chromatographically pure state and was characterized by ^{13}C NMR spectra.

The next stage of the synthesis required tetrahydropyranyl protection of the hydroxy group, and the corresponding tetrahydropyranyl decynyl ether was obtained in 95% yield and 97% purity and was used without further purification.

The second components in cross-coupling were crotyl halides. E-isomer of crotyl chloride of 99% purity was prepared by procedure developed by us previously consisting in replacement of hydroxy group in crotyl alcohol with chlorine by treating with triphenylphosphine complex with ethyl trichloro-

Table 1. Isomeric composition of coupling products of 9-decyn-1-ol homocuprate with crotyl halides

Halide	Overall yield, %	Isomeric composition, %			Yield of pure isomer IV, %
		IV	V	VI	
Crotyl bromide[a]	88	83	9	8	68
Crotyl chloride[a]	85	89	5	6	71
(*E*)-1-Chlorobut-2-ene	82	95	1	4	75

[a] A mixture of isomers was used.

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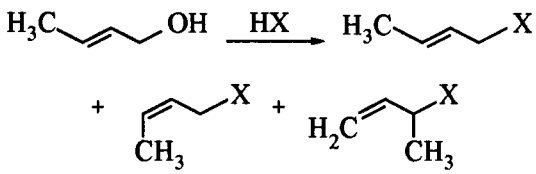
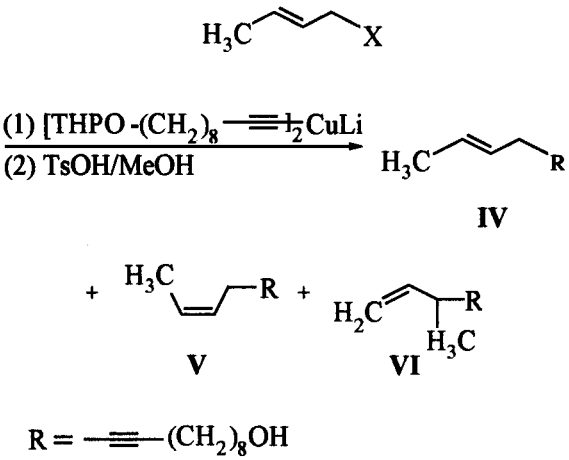
acetate [6]. Besides we used in coupling a mixture of *E*- and *Z*-1-chlorobut-2-enes obtained in reaction of crotyl alcohol with hydrochloric acid. Crotyl bromide disregarding the method of its preparation always contains three isomeric bromides: *E*- and *Z*-1-bromobut-2-enes, and 3-bromo-1-ene.



X = Cl, Br.

The products of cross-coupling between terminal alkynyl cuprate and crotyl halides were studied and the yields of reaction products were evaluated after elimination of tetrahydropyranyl protective group by treating with *p*-toluenesulfonic acid in methanol. The structure and isomer ratio was estimated from GLC, ^{1}H and ^{13}C NMR data.

In Table 1 are presented the data on isomeric composition of the coupling products for crotyl bromide, crotyl chloride, and individual E-1-chlorobut-2-ene.

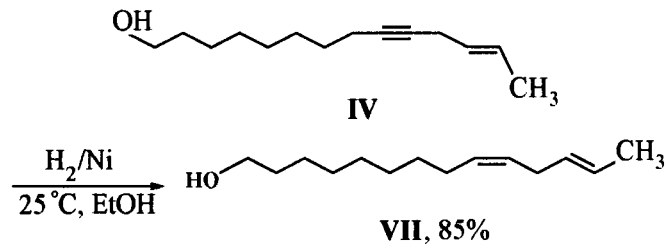


R = $-\equiv-(CH_2)_8OH$

At the use in reaction of mixtures of isomeric chlorides and bromides the regio and stereoselectivity of the reaction are relatively low (83–90%). As was expected the purest cross-coupling product (95%), *E*-tetradec-12-en-9-yn-1-ol (**IV**), was obtained from the pure *E*-1-chlorobut-2-ene. Further purification of enynol **IV** was carried out by low temperature crystallization from hexane at -30÷-50°C. Two recrystallizations with more homogeneous product and tree-four with less pure compound resulted in isomeric purity of compound attaining 98–99%.

In the ^{1}H NMR spectrum of *E*-tetradec-12-en-9-yn-1-ol appear signals of protons at the double bond, those from methyl and methylene groups characteristic of hex-4-en-1-yn-1-yl fragment in the carbon backbone. The vicinal coupling constant of the olefinic protons amounting to 15 Hz evidences *trans*-configuration of the double bond. A characteristic feature of the ^{1}H NMR spectrum of the coupling product, alcohol IV, is the appearance of a coupling constant ^{1}J 2.5 Hz in the signals of methylene groups at the triple bond corresponding to the long-range spin-spin coupling through the triple bond and unambiguously confirming the enyne system formation.

Enynol **IV** obtained was reduced with hydrogen over P-2Ni catalyst in the presence of ethylenediamine [7]. The reaction was monitored with GLC, since the initial E-tetradec-12-en-9-yn-1-ol and (9*Z*,12*E*)-tetradeca-9,12-dien-1-ol (**VII**) notably differ in retention times.



VII, 85%

The reduction proceeds with a high yield (85%), and the reaction product **VII** according to GLC is of 98% purity and contains no more than 1% of isomeric dienes and less than 1% of alkenol.

Acylation of (9*Z*, 12*E*)-tetradeca-9,12-diene-1-ol (**VII**) with acetic anhydride in tetrahydrofuran in the presence of pyridine afforded the corresponding acetate **I** in 93% yield. The completion of acylation was checked by GLC. It is important since according to published data the attractive activity of pheromone for some insect species is suppressed in the presence of unacylated (9*Z*, 12*E*)-tetradeca-9,12-diene-1-ol. The isomer (9*Z*, 12*E*-**I**) obtained according to GLC, ^{1}H and ^{13}C NMR data is of 99% isomeric purity (impurity 1% of *Z*,*Z*-isomer) and of 98% general purity.

The isolated data on ^{1}H NMR spectrum of this compound cannot serve as reliable confirmation of the double bonds configuration in the diene system. However, since both ^{1}H and ^{13}C NMR spectra and also retention time of the compound obtained by cross-coupling and that previously prepared by Wittig reaction coincide, we can conclude on formation of pheromone **I**.

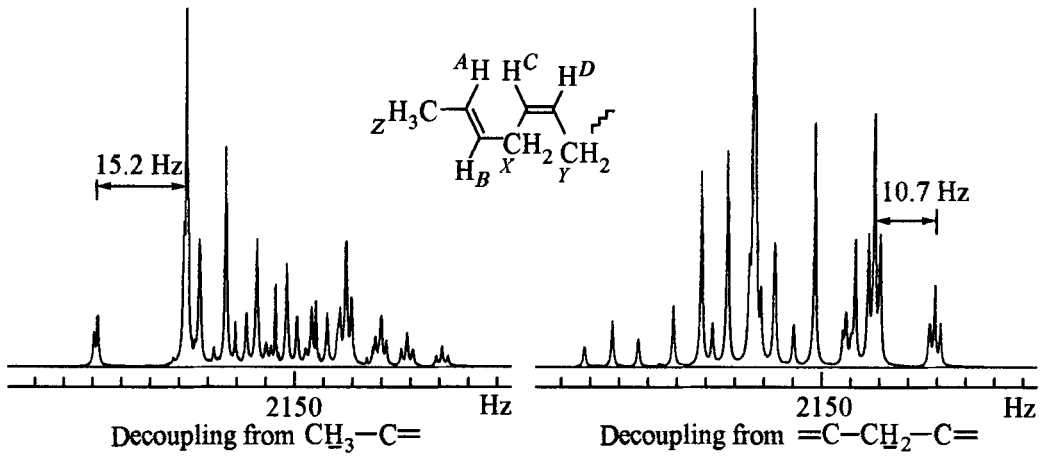


Fig. 1. Diene region of double resonance spectra with selective decoupling from methylene and methyl protons.

The assignment of the signals of the olefinic protons belonging to the 1,4-diene system and evaluation of the coupling constants was performed with the help of double resonance ^{1}H NMR spectra with selective decoupling from the protons of the neighboring groups; this procedure considerably simplified the spectrum.

The simulated diene region of the spectrum constructed according the data of the double resonance experiments with selective decoupling from methyl and methylene protons adjacent to the diene fragment is presented in Fig. 1.

From the spectra with selective decoupling from CH_3 and $=C-CH_2-C=$ group we were able to determine the chemical shift of *A* and *D* protons (5.435 and 5.380 ppm respectively) and their coupling constants with the residual two protons amounting respectively to 15 and 11 Hz. These findings unambiguously confirm the 9*Z*,12*E*-configuration of the dienyl acetate obtained.

A detailed analysis and simulating of the spectra enabled us to establish all the chemical shifts and coupling constants of the olefinic protons. The values obtained are listed in Table 2.

The diene region of the spectrum of compound **I**, both experimental and simulated proceeding from the spectral parameters obtained, is shown in Fig. 2. The spectra virtually exactly coincide, also the double resonance spectra; thus the spectral parameters are evaluated with high precision.

The analysis of ^{13}C NMR spectra, also those obtained without proton decoupling, provided the possibility to assign the signals to the carbons of the diene fragment. The assignment was based on coupling constants and multiplicity of the carbon signals. The chemical shifts are given in Table 2. Note that the thorough analysis of the ^{13}C NMR spectra recorded without proton decoupling enabled us to refine the assignment of the chemical shifts of carbon atoms *B* and *D*.

Table 2. Parameters of ^{1}H and ^{13}C NMR spectra of (9*Z*,12*E*)-tetradeca-9,12-dienyl acetate (400 MHz, $CDCl_3$)

Group	*A*	*B*	*C*	*D*	*X*	*Y*	*Z*
δ, ppm	5.425	5.385	5.340	5.380	2.71	2.02	1.65
δ_C, ppm	124.86	127.56	129.48	130.16	30.30	[a]	17.71
Coupling constant, $J_{H,H}$, Hz							
A	–	15.1	–	–	–1.5	–	5.8
B		–	–	–	6.5	–	–1.3
C			–	10.7	6.3	–1.5	–
D				–	–1.5	7.3	–

[a] We did not succeed in exact assignment of the signal.

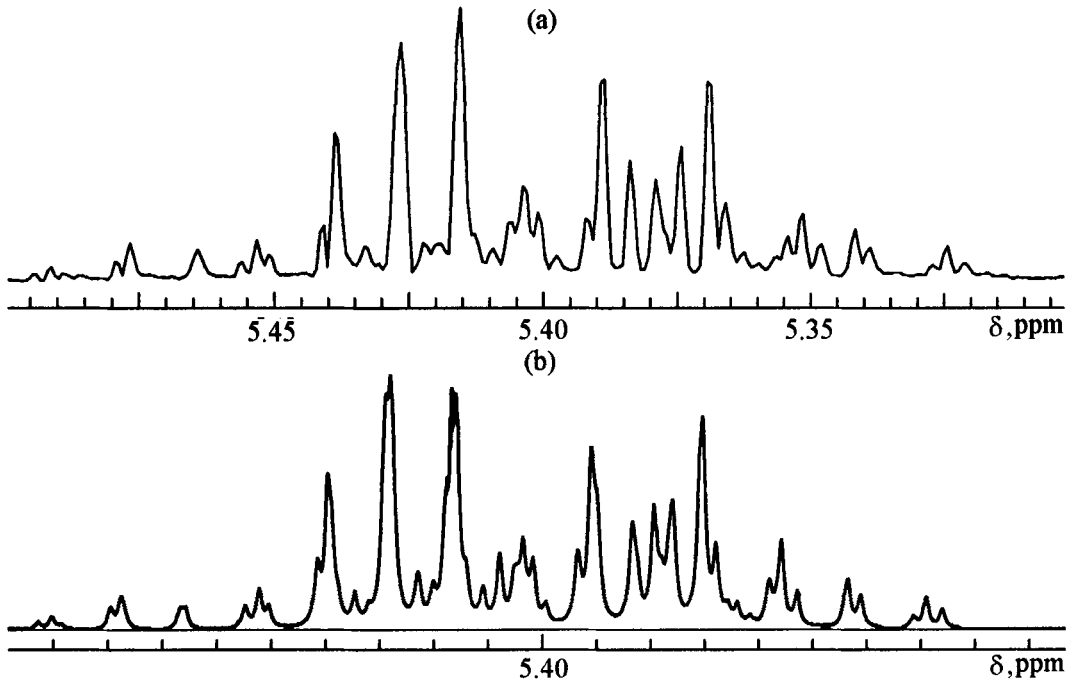


Fig. 2. Proton signals region of 1,4-diene system in experimental (a) and simulated (b) spectra.

Attractive activity of the synthetic pheromone **I** was tested both in laboratory and in the field on insects Ephestia Kuehniella; it was comparable with the biological activity of a natural sample.

Thus the cross-coupling reaction permitted synthesis of 1,4-dienic pheromones of high stereochemical purity and biological activity.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were registered on Varian VXR-400 instrument at operating frequency 400 MHz for protons, solvent $CDCl_3$, internal reference TMS.

Isomeric composition and purity of compounds was determined by GLC on Chrom-5 device, flame-ionization detector, quartz capillary column (25000 × 0.25 mm), stationary phase SE-30, carrier gas helium. In the data on GLC analyses given below are indicated: evaporator and detector temperature; column temperature; retention time, min; content, %; substance.

Computer treatment and simulation of spectra was performed using software package ACD/Spec Manager, ACD/CNMR DB, and ACD/HNMR DB (Version 3.5, ACD Inc).

The synthesis of E-1-chlorobut-2-ene was described in [6].

(9Z,12*E*)-9,12-tetradecadienyl acetate (I). To a solution of 0.535 g (2.5 mol) of 9.12-tetradecadien-1-ol (**VII**) and 0.24 g (3 mmol) of pyridine in 10 ml of THF was added 0.24 g (3 mmol) of acetyl chloride. The mixture was stirred till completion of the reaction (GLC monitoring). Then 1 ml of 1% hydrochloric acid and 20 ml of hexane was added, the organic layer was separated, washed with 2 ml of 5% sodium hydrogen carbonate, and dried with calcium chloride. The solvent was distilled off. We obtained 0.595 g (93%) of 9,12-tetradecadienyl acetate. GLC: 200, 182, 6.28, 1% of alcohol **VII**; 7.50, 98% (9Z,12*E*)-tetradeca-9,12-dienyl acetate (**I**); 7.62, 1% (9*E*,12*E*)-tetradeca-9,12-dienyl acetate.

Dec-2-yn-1-ol (II). In a three-neck flask equipped with a stirrer, inlet and outlet tubes for ammonia at cooling with acetone–solid carbon dioxide mixture was liquified 200 ml of ammonia dried by passing through two columns packed with solid potassium hydroxide. The inlet tube for ammonia was removed, and at stirring was added into the flask a little metallic lithium. As dark-blue color appeared was added 0.04 g (0.1 mmol) of iron(III) nitrate nonahydrate. The hydrogen evolution started, and the mixture turned grey-black. Gradually (within about 0.5 h) was added 0.58 g (0.083 mol) of lithium, each addition was done when hydrogen evolution ceased. Still at cooling to the mixture obtained was added a solution of 2.24 g (0.04 mol) prop-2-yn-1-ol in 10 ml

of ethyl ether. The mixture was stirred for 0.5 h, and gradually a solution of 7.16 g (0.04 mol) of heptyl bromide in 15 ml of ether was added. The mixture was stirred for 2 h still at cooling. The reaction mixture obtained was left overnight for completing the reaction and evaporating ammonia. Then the mixture was quenched with 10 ml of 1M HCl. The reaction products were extracted with ether (3× 30 ml), the combined extracts were washed with water (2×10 ml), with 5% solution of HCl (2×10 ml), and with 10 ml of 5% solution of sodium hydrogen carbonate. On drying with sodium sulfate and removing solvent the residue was distilled. Yield 4.62 g (75%), bp 110–113°C (10 mm). ^{13}C NMR spectrum, δ_C, ppm: 85.94, 78.16 (C≡C); 50.75 (CH_2O); 31.47, 28.58, 28.41, 22.36, 18.47 [$(CH_2)_6$–]; 13.74 (CH_3). GLC: 150, 136, 5.64, 99.5% of 2-decyn-1-ol.

Dec-9-yn-1-ol (III). In 20 ml of anhydrous ethylenediamine under argon at stirring was dissolved 0.7 g (0.1 mol) of lithium that was added by small portions, each next portion after complete dissolution of the previous one. The solution obtained was cooled to 0°C, and 3.1 g (0.02 mol) of dec-2-yn-1-ol was added thereto. The mixture was stirred for 2 h at heating to 60–70°C, then was cooled to 0°C. The reaction mixture was quenched with 50 ml of water, the reaction products were extracted into ether (3×20 ml), the extract was washed with 1M HCl, 5% solution of sodium hydrogen carbonate, and dried with sodium sulfate. The solvent was distilled off, and the residue was distilled in a vacuum. We obtained 2.54 g (82%) of 9-decyn-1-ol, bp 105–108°C (10 mm). GLC: 150, 136, 4.85, 98% of 9-decyn-1-ol. ^{13}C NMR spectrum, δ_C, ppm: 68.2 (HC≡), 84.6 (≡C–), 62.4 (C–O), 32.6, 29.3, 29.1, 28.7, 28.4, 25.7, 18.3 (CH_2).

10-Tetrahydropyranyloxydec-1-yn was obtained along standard procedure by reaction of decynol **III** with 3,4-dihydro-2*H*-pyran in the presence of catalytic quantity of hydrochloric acid. Yield 95%. GLC: 200, 182, 7.55, 98% OF 10-tetrahydropyranyloxydec-1-yn.

Coupling of 10-tetrahydropyranyloxydec-1-yn with 1-bromo-2-butene. To a solution of 1.71 g (7 mmol) of 10-tetrahydropyranyloxydec-1-yn in 40 ml of THF at cooling to 0°C under argon was added 3.5 ml (7 mmol) of 2 M butyllithium solution in hexane, the mixture was stirred for 0.5 h, and dropwise was added 1.1 g (8 mmol) of crotyl bromide. The solution was stirred for 4 h at room temperature. Then 0.1 ml of water and 10 ml of hexane was added. The solution obtained was filtered through silica gel, eluting with ethyl ether. The solution was evaporated, the residue was dissolved in 20 ml of methanol, and 0.05 g of *p*-toluenesulfonic acid was added. The mixture was stirred for about 12 h. The solvent was distilled off, 20 ml of hexane was added to the residue, and the extract obtained was washed with 5% solution of sodium hydrogen carbonate (3×10 ml), dried with sodium sulfate, and the solvent was distilled off in a vacuum. We obtained 1.32 g (88%) of a mixture of geometrical isomers tetradec-12-en-9-yn-1-ol (**IV, V**), and 11-methyltridec-12-en-9-yn-1-ol (**VI**). GLC: 200, 182, 5.63, 8% of allylic isomer **VI**; 7.04, 83% of *E*-isomer (**IV**); 7.10, 9% of *Z*-isomer (**V**).

Coupling of 10-tetrahydropyranyloxydec-1-yn with 1-chloro-2-butene. The reaction was performed as above with 1 g (4.2 mmol) of 10-tetrahydropyranyloxydec-1-yn, 2.1 ml (4.2 mmol) of 2 M butyllithium solution in hexane, and 0.45 g (5 mmol) of 1-chloro-2-butene. The workup was carried out as above. We obtained 0.79 g (82%) of a mixture of geometrical isomers tetradec-12-en-9-yn-1-ol (**IV, V**), and 11-methyltridec-12-en-9-yn-1-ol(VI). GLC: 200, 182, 5.63, 4% of allylic isomer VI; 7.04, 95% of *E*-isomer (**IV**); 7.10, 1% of *Z*-isomer (**V**).

Purification of E-tetradec-12-en-9-yn-1-ol (IV). A solution of 0.73 g of the mixture of enyne alcohols in 10 ml of hexane was slowly cooled at stirring to –50°C. The separated precipitate was filtered off. The procedure was repeated monitoring the purity of the product by GLC. We obtained 0.63 g (86, or 71% with respect to tetrahydropyranyl decynyl ether) *E*-tetradec-12-en-9-yn-1-ol (**IV**). ^{1}H NMR spectrum, δ, ppm: 5.67 d.q (1H, CH_3–C<u>H</u>=, *J* 15.2 Hz), 5.42 d.t (1H, =C<u>H</u>–CH_2, *J* 15.2 Hz), 3.63 t (2H, O–CH_2), 2.86 m (2H, =C–CH_2–C≡), 2.17 t.t (2H, ≡C–CH_2), 1.68 d.q (3H, CH_3), 1.2–1.6 m [12H, $(CH_2)_6$]. ^{13}C NMR spectrum, δ_C, ppm: 126.2, 125.9 (2C, C=C), 82.0, 77.6 (2C, C≡C), 63.0 (1C, C–O), 32.7, 29.3, 29.1, 29.0, 28.8, 25.7, 22.0, 18.8 (8C, CH_2), 17.6 (1C, CH_3). GLC: 200, 182, 7.02, 98% of *E*-isomer (**IV**); 7.12, 1% of *Z*-isomer (**V**).

(9Z,12E)-Tetradeca-9,12-dien-1-ol (VII). To a solution of 0.124 g (0.5 mmol) of nickel acetate pentahydrate in 15 ml of 96% ethanol under hydrogen atmosphere was added by a syringe 0.02 g (0.5 mmol) of sodium borohydride in 5 ml of ethanol. After stirring for 10 min 0.06 g (1 mmol) of ethylenediamine in 5 ml of ethanol was added, and the stirring continued for 10 min more. Then was added a solution of 0.63 g (3 mmol) of E-tetradec-12en-9-yn-1-ol (**IV**) in 5 ml of ethanol. The reaction

progress was monitored by hydrogen absorption and with the use of GLC. After disappearance of the initial enynol 10 ml of ether was added to the mixture, and it was filtered through a layer of silica gel that was then washed with ether (20 ml). The ether solution was evaporated, 15 ml of hexane was added to the residue, the solution was washed with 10 ml of 1% HCl solution, 10 ml of 5% sodium hydrogen carbonate solution, and dried with calcium chloride. The solvent was distilled off. We obtained 0.535 g (85%) of 9,12-tetradecadien-1-ol. ^{1}H NMR spectrum, δ, ppm: 5.32–5.50 m (4H, CH_3-C<u>H</u>=), 3.63 t (2H, O-CH_2), 2.71 t.t (2H, =C-CH_2-C=), 2.02 q (2H, =C-CH_2), 1.65 d.q (3H, CH_3); 1.56 m (2H, CH_2), 1.24–1.37 m (10H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 130.3, 129.6, 127.6, 125.0 (4C, C=C), 62.9 (1C, C-O), 32.7, 30.4, 29.6, 29.4, 29.3, 29.2, 27.0, 25.7 (8C, CH_2), 17.8 (1C, CH_3). GLC: 200, 182, 6.30, 99% of (9*Z*,12*E*)-tetradeca-9,12-dien-1-ol.

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