CONCLUSIONS

A short synthesis of R,E-14-methyl-8-hexadecenal (trans-trogodermal) from 1,1-ethylenedioxy-8-acetoxy-9-decene and R-(−)-1-bromo-4-methylhexane was realized.

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PHEROMONES OF COLEOPTERA.

COMMUNICATION 6. SYNTHESIS OF R,Z-14-METHYL-8-HEXADECENAL (cis-TROGODERMAL)

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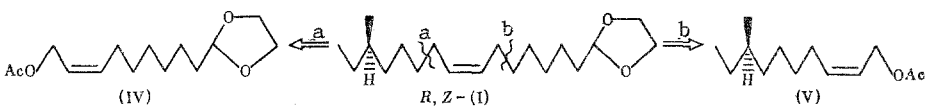
UDC 542.91:547.382.3:632.76

R,Z-14-Methyl-8-hexadecenal [cis-trogodermal (I)] is an aggregation pheromone of skin beetles of the genus *Trogoderma* – *T. granarium, T. variabile, T. inclusum* – which are dangerous pests of food supplies [1-3]. The known methods for the synthesis of R,Z-I are based on the use of R-(+)-citronellol [4], S-(−)-citronellol [5, 6], and S-β-butanolide [7] as sources of the chiral R-fragment and on the construction of a Z-double bond via cis addition of a diorganocuprate to acetylene [7] or catalytic hydrogenation [4-6].

A new simple synthesis of optically active R,Z-trogodermal from the following accessible starting compounds is described in the present communication: R-1-bromo-4-methylhexane (II), which is obtained from technical-grade S-3,7-dimethyl-2,6-octadiene ("dihydromyrcene"), and Z-4-chloro-2-buten-1-ol (III), which is obtained from technical-grade Z-butene-1,4-diol. Compound II serves as a precursor of the chiral fragment, and III serves as the precursor of the Z-olefinic fragment of the I molecule. For the construction of the carbon chain of the pheromone we selected a scheme based on the condensation of Z-disubstituted primary allyl acetates with Grignard reagents.



This type of coupling makes it possible to obtain vinyl derivatives with various degrees of substitution and high stereospecific purities [8, 9]. Starting from structure I, for the coupling reaction one must synthesize either achiral acetate IV or chiral acetate V. Compound IV was obtained via the following scheme:

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Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 4, pp. 906-910, April, 1987. Original article submitted November 4, 1985.

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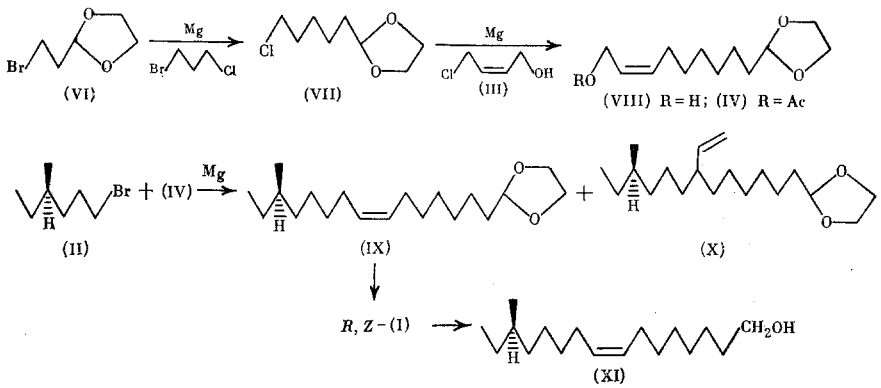
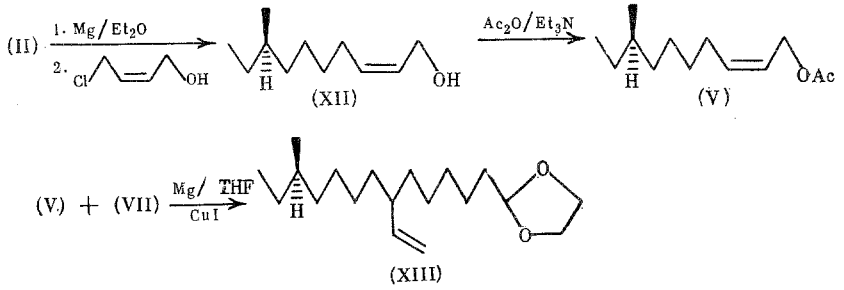


The reaction of 1-bromo-3-chloropropane and an MgBr derivative prepared from 1-bromo-3,3-ethylenedioxypropane (VI) in tetrahydrofuran (THF) at 0°C in the presence of Li_2CuCl_4 (1 mole %) gave homologous C_6 chloride VII in 73% yield. For the introduction of the Z-double bond, 6,6-ethylenedioxyhexylmagnesium chloride, prepared from VII, was treated with one equivalent of CuI with subsequent alkylation with Z-4-chloro-2-buten-1-ol (III) in THF–ether to give hydroxyacetal VIII in 71% yield. Allyl acetate IV was obtained in 88% yield by acetylation of VIII. The last two reactions both proceed with complete retention of the Z-configuration of the double bond and give individual isomers IV and VIII [according to the results of capillary gas–liquid chromatography (GLC) and PMR spectra].

The final condensation of allyl acetate IV with a Grignard reagent prepared from R-(−)-bromide II was carried out in THF in the presence of CuI or Li_2CuCl_4. It was established that a quantitative yield of the reaction products is observed when a II:IV:CuI molar ratio of 3:1:0.5 is used. The condensation proceeds regiospecifically as S_N2 substitution of the allylic acetoxy group in acetate IV. The yield of R,Z-1,1-ethylenedioxy-14-methyl-8-hexadecene (IX) is 92%; the yield of regioisomeric acetal X, which corresponds to an S_N2' reaction, is only 6-8%. Separation of structural isomers IX and X with a column packed with silica gel impregnated with $AgNO_3$ gave a sample of "linear" Z-acetal IX, the degree of geometrical purity of which was 92-94% (according to the results of capillary GLC and the PMR spectrum). Thus, the S_N2 reaction between allyl acetate IV* and the organocuprate obtained from bromide II proceeds with high stereospecificity relative to the allylic double bond. With allowance for chromatographic separation, the yield of Z-acetal IX is 70%. Optically active R,Z-trogodermal (I) was obtained in quantitative yield in the hydrolysis of acetal IX. The overall yield of the R,Z-I obtained by this method is ~26% based on starting bromoacetal VI. By the action of $NaBH_4$, aldehyde I was converted quantitatively to R,Z-14-methyl-8-hexadecen-1-ol [cis-trogodermol (XI)] – a minor component of the pheromone secretion of *T. variabile* and *T. inclusum* [1, 3]. The IR and PMR spectra of I and XI correspond to the published spectra (see [4, 6]). The αD^{20} value of −3.3° found for I corresponds to ~55% optical purity of the pheromone (see [4]).

In order to exclude excess chiral bromide II we investigated the possibility of obtaining Z-acetal IX in the reaction of chiral acetate V with an organocuprate obtained from chloroacetal VII. To obtain V, a Grignard reagent prepared from R-bromide II was treated with Z-chlorobutenol III, and the resulting alcohol XII was acetylated. The acetate V obtained in this way was subjected to reaction with an organocuprate prepared from chloride VII, magnesium, and CuI under conditions similar to those described above for the preparation of IX. However, the formation of "linear" acetal IX did not occur in the presence of CuI or Li_2CuCl_4 under these conditions or under other conditions that we tested. The only product of the reaction of acetate V with an organometallic derivative of chloroacetal VII was "branched" acetal XIII, which is formed as a result of substitution of the S_N2' type. The difference between XIII and isomeric acetal IX was established reliably by capillary GLC and from the PMR spectra; thus a multiplet of olefin protons appears at δ 5.35 ppm in the spectrum of IX, whereas signals of a CH_2=CH group show up at 4.92 and 5.52 ppm in the spectrum of XIII.

*The degree of geometrical purity of starting Z-chlorobutenol III and technical-grade Z-2-butene-1,4-diol is also ~94%.



The sharp difference in the reactivities of monotypic allyl acetates IV and V in monotypic reactions with two different organocuprates is worthy of separate consideration.

EXPERIMENTAL

Analysis by GLC was carried out with a Biokhrom-1 chromatograph with a flame-ionization detector using glass capillary columns with dimensions of 52 m × 0.27 mm and 50 m × 0.28 mm packed with OU-101 and XE-60, respectively. The IR spectra of solutions in CCl_4 (if not specified otherwise) were recorded with a UR-20 spectrometer. The PMR spectra were obtained with Tesla BS-467 (60 MHz) and Bruker WM-250 (250 MHz) spectrometers. Optical rotation was measured with a Perkin–Elmer-141 polarimeter.

Silica gel L 40/100 μm (Chemapol, Czechoslovakian SSR) and Al_2O_3 (neutral activity III) were used for column chromatography. The solvents and liquid reagents were distilled prior to their use. The starting R-1-bromo-4-methylhexane (II) was obtained in 85% yield from R-4-methylhexanol by the action of PBr_3 in pyridine (Py) [10]; 1-bromo-3,3-ethylenedioxypropane (IV) was obtained in 60% yield by treatment of acrolein with anhydrous HBr in ethylene glycol [11]. The synthesis of Z-4-chloro-2-buten-1-ol (III) in 42% yield was accomplished by the action of $SOCl_2$ in Py on Z-2-butene-1,4-diol by the method in [12].

1-Chloro-6,6-ethylenedioxyhexane (VII). A solution of a Grignard reagent obtained from 2.8 g of Mg and 18.1 g (0.1 mole) of bromoacetal VI in 50 ml of THF under Ar (the start of the reaction was initiated with I_2 and a few drops of EtBr at 45-50°C) was added to a stirred (at −10°C) solution of 14.2 g (90 mmole) of 1-chloro-3-bromopropane and 1.1 g of Li_2CuCl_4 in 40 mm of dry THF, after which the mixture was stirred at −5°C for 3 h, diluted with ether, and decomposed with saturated NH_4Cl solution. The organic layer was washed successively with $NaHCO_3$ solution, H_2O, and saturated NaCl solution and dried with $MgSO_4$. Fractionation gave 11.8 g (73%) of VII with bp 83°C (2 mm) and n_D^{18} 1.4586. PMR spectrum (CCl_4, δ, ppm): 1.1-1.9 m [$(CH_2)_4$], 3.45 t (CH_2Cl, J = 6.5 Hz), 3.8 m (OCH_2CH_2O), 4.7 t (OCHO, J = 4 Hz).

Z-10,10-Ethylenedioxy-2-decen-1-ol (VIII). A stirred (at ~20°C) solution of a Grignard reagent obtained from 0.96 g of Mg and 5.34 g (30 mmole) of chloride VII in 15 ml of THF was treated dropwise with a solution of 1.5 g of III in 10 ml of absolute ether, after which the mixture was refluxed for 2 h, cooled to 0°C, and decomposed with 30 ml of saturated NH_4Cl solution. The organic layer was worked up as described above, the solvent was removed, and the residue was maintained at 100°C (0.1 mm) for 30 min. This procedure gave 2.6 g (71%) of VIII with $n_D^{17.5}$ 1.4748. The chromatographically homogeneous (greater than 92%, according to GLC data) substance was used in the next step without additional purification.

Z-1-Acetoxy-10,10-ethylenedioxy-2-decene (IV). A mixture of 2.14 g (0.01 mole) of alcohol VIII, 20 ml of dry CH_2Cl_2, 1.2 g of Ac_2O, and 5 ml of Et_3N containing a catalytic amount of 4-dimethylaminopyridine was maintained at ~20°C for 48 h, after which it was diluted with H_2O and extracted with ether (three 50-ml portions). The organic layer was washed successively with saturated $CuSO_4$ solution, saturated NaCl solution, and H_2O and dried with $MgSO_4$. The solvent was removed by distillation, and the residue was filtered through silica gel to give 2.25 g (88%) of acetate IV with n_D^{16} 1.4650. IR spectrum (ν, cm^{-1}): 1734 (C=O), 730 (cis-CH=CH). PMR spectrum ($CDCl_3$, δ, ppm): 1.0-1.7 [10H, $(CH_2)_5$], 1.96 s (3H, CH_3CO), 2.0 m (2H, CH_2C=), 3.8 m (4H, OCH_2CH_2O), 4.55 m (2H, =CH_2O), 4.75 t (1H, J = 4 Hz, OCHO), 5.25-5.45 m (2H, −CH=CH−).

R,Z-1,1-Ethylenedioxy-14-methyl-8-hexadecene (IX). A 0.76-g sample of CuI and (dropwise) a solution of 0.77 g of acetate IV in 3 ml of THF were added successively to a vigorously stirred (at −10°C) solution of a Grignard reagent obtained from 0.26 g of Mg and 1.8 g (0.01 mole) of bromide II in 6 ml of dry THF, after which the mixture was stirred at −10°C for

2 h, heated to ~20°C for 2 h, decomposed with saturated NH_4Cl solution, and extracted with ether (three 50-ml portions). The combined organic layers were washed with saturated NaCl solution and water and dried over $MgSO_4$. The solvent was removed by distillation, and the residue (1.22 g), which contained hydrocarbons, due to coupling of the Grignard reagent, and acetals IX and X in a ratio of 93:7, was chromatographed on 60 g of SiO_2 and 12 g of $AgNO_3$. Gradient elution from hexane to ether (up to 10% of the latter) gave 0.63 g (71%) of acetal IX (Z:E = 93.7) in the form of an oil with n_D^{20} 1.4606 and α_D^{20} −2.4° (C 2.6, $CHCl_3$). IR spectrum (ν, cm^{-1}): 2960, 2930, 2860, 1460, 1410, 1380, 1145, 1040, 945, 730. PMR spectrum ($CDCl_3$, 250 MHz, δ, ppm): 0.84 d (3H, CH_3, J = 6.5 Hz), 0.86 t (3H, CH_3, J = 6.5 Hz), 1.0-1.5 (17H, CH_2, CH), 1.63 m (2H, CH_2CHO), 2.02 m (4H, $CH_2CH{=}CHCH_2$), 3.85-3.96 m (4H, OCH_2CHO), 4.84 (1H, OCHO, J = 5 Hz), 5.35 m (2H, CH=CH). Found, %: C 77.30; H 11.86. $C_{19}H_{36}O_2$. Calculated, %: C 77.03; H 12.16.

R,Z-14-Methyl-8-hexadecenal (I). A mixture of 0.25 g of IX, 3 ml of AcOH, and 3 ml of H_2O was refluxed for 3 h, after which it was cooled and neutralized with $NaHCO_3$ solution. The mixture was extracted with ether (three 20-ml portions), and the extract was dried with $MgSO_4$. The ether was removed by distillation, and the residue was filtered through a layer of SiO_2 to give 0.2 g (97%) of R,Z-I with n_D^{20} 1.4581 and α_D^{20} −3.3° (C 3.2, ether), which corresponds to ~55% optical purity [see [7]: n_D^{25} 1.4541 and α_D^{22} −5.96°(C 1.06, $CHCl_3$)]. IR spectrum (ν, cm^{-1}): 2960, 2940, 2860, 2721, 1730, 1460, 1410, 1380, 970, 920, 730. PMR spectrum (250 MHz, $CDCl_3$, δ, ppm): 0.84 d (3H, CH_3, J = 6.5 Hz), 0.86 t (3H, CH_3, J = 6.5 Hz), 1.0-1.7 m (17H, CH_2, CH), 2.02 m (4H, $CH_2CH{=}CHCH_2$), 2.43 m (2H, $CH_2C{=}O$), 5.34 m (2H, CH=CH), 8.65 t (1H, CHO, J = 1.8 Hz).

R,Z-14-Methyl-8-hexadecen-1-ol (XI). A 0.04-g sample of $NaBH_4$ was added in portions at 0-5°C to a solution of 0.2 g of R,Z-I in 5 ml of Me_2CHOH, after which the mixture was maintained at 0-5°C for 1 h and at 20°C for 2 h. It was then worked up in the usual way to give 0.2 g (99%) of alcohol XI in the form of an oil with n_D^{20} 1.4601 and α_D^{20} −2.7° (C 3.2, $CHCl_3$), which corresponds to ~51.0% optical activity [see [4]: n_D^{20} 1.4583 and α_D^{20} −5.43° (C 2.2, $CHCl_3$)]. IR spectrum (ν, cm^{-1}): 3320, 3010, 2960, 2920, 2855, 1470, 1055, 720. PMR spectrum (250 MHz, $CDCl_3$, δ, ppm): 0.85 d (3H, CH_3, J = 6 Hz), 0.86 t (3H, CH_3, J = 6 Hz), 1.0-1.8 m (19H, CH_2 and CH), 2.04 m (4H, $CH_2CH{=}CHCH_2$), 3.40 broad s (OH), 3.68 t (2H, CH_2O, J = 6.5 Hz), 5.36 t (2H, CH=CH, J = 5 Hz).

R,Z-8-Methyl-2-decen-1-ol (XII). A stirred (at ~20°C) solution of a Grignard reagent obtained from 0.51 g of Mg and 3.6 g of bromide II in 8 ml of ether was treated dropwise with a solution of 1.1 g of III in 8 ml of ether, after which the mixture was refluxed for 2 h, cooled to 0°C, and decomposed with 30 ml of saturated NH_4Cl solution. The organic layer was worked up as described above. Fractionation gave 1.5 g (80%) of alcohol XII with bp 60-70°C (0.1 mm), n_D^{19} 1.4520, and α_D^{20} −2.7° (C 9.8, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3340, 2960, 2940, 2850, 1660, 1380, 1040. PMR spectrum ($CDCl_3$, δ, ppm): 0.85 m (6H, CH_3), 1-1.5 m (9H, CH_2 and CH), 2.0 m (2H, $CH_2C{=}$), 3.6 broad s (OH), 3.95 m (2H, CH_2O), 5.42 m (2H, CH=CH).

R,Z-1-Acetoxy-8-methyl-2-decene (VI). A mixture of 1.4 g of alcohol XII, 20 ml of dry CH_2Cl_2, 1.0 g of Ac_2O, and 4 ml of Et_3N containing a catalytic amount of 4-dimethylaminopyridine was maintained at 20°C for 48 h, after which it was diluted with water and extracted with ether. The usual workup and fractionation gave 1.56 g (90%) of acetate VI with bp 80°C (0.1 mm), n_D^{20} 1.4450, and α_D^{20} −2.1° (C 4.2, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3020, 2960, 2930, 2876, 2860, 1740, 1470, 1380, 1230, 1030, 970. PMR spectrum ($CDCl_3$, δ, ppm): 0.85 m (6H, CH_3), 1-1.5 m (9H, CH_2 and CH), 1.95 s (3H, CH_3CO), 2.0 m (2H, $CH_2C{=}$), 4.55 m (2H, $=CCH_2O$), 5.45 m (2H, CH=CH). Acetate VI was used in the next step without additional purification.

12R, 7RS-1,1-Ethylenedioxy-7-vinyl-12-methyltetradecane (XIII). A 0.45-g sample of CuI and (dropwise) a solution of 0.45 g (~2.1 mmole) of acetate VI in 5 ml of THF were added successively to a stirred (at −10°C) solution of a Grignard reagent obtained from 0.26 g of Mg and 1.8 g (0.01 mole) of chloride VI in 7 ml of THF, after which the mixture was stirred at −10°C for 1 h, heated at 20°C for 2 h, decomposed with saturated NH_4Cl solution, and extracted with ether. The subsequent usual workup of the extract gave 0.62 g of XII, which was chromatographed on 50 g of Al_2O_3. Gradient elution from hexane to ether (up to 5% of the latter) gave 0.54 g (86%) of XII in the form of an oil with n_D^{19} 1.4607 and α_D^{20} −1.8° (C 4.2, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3080, 2960, 2940, 2860, 1640, 1465, 1415, 1380, 1145, 1040, 945, 915. PMR spectrum (250 MHz, $CDCl_3$, δ, ppm): 0.85 d (3H, CH_3, J = 6.5 Hz), 0.87 t

(3H, CH_3, J = 6.5 Hz), 1.0-1.5 m (19H, CH_2 and CH), 1.65 m (2H, CH_2CHO), 1.92 m (1H, CHC=), 3.86 and 3.97 m (4H, OCH_2CH_2O), 4.85 t (1H, OCHO, J = 6 Hz), 4.92 and 5.52 m (3H, $CH=CH_2$).

CONCLUSIONS

The simple synthesis of optically active R,Z-14-methyl-8-hexadecenal (cis-trogodermal), the principal components of the aggregation pheromone of *Trogoderma granarium*, was accomplished. The synthesis was based on the use of R-1-bromo-4-methylhexane and Z-4-chloro-2-buten-1-ol as the sources of the chiral and olefin fragments.

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TRANSFORMED STEROIDS.

160. REACTION OF 20,20-DIMETHOXY-16α,17α-EPOXYPREGN-5-ENE-3β,21-DIOL-20-ONE WITH PYRIDINE THIOCYANATE AND CARBETHOXYHYDRAZINE

A. V. Kamernitskii and A. M. Turuta

UDC 542.91:547.92

Using the acetolysis of 20,20-dimethoxy-16α-17α-epoxypregn-5-ene-3β,21-diol-20-one (I) as an example, it was shown that this compound enters into a stereo- and regiospecific reaction of cis-opening of the oxide ring that proceeds in the presence of carbethoxyhydrazine (CEH). The reaction results in the addition of an anion [^-OAc, $^-(NH)_2CO_2Et$] to the C^{17} atom from the α-region of the steroid molecule, with a stage of formation of a 20-carbethoxyhydrazone preceding the oxide opening [1].

In the present work, it was found that this path of the reaction is not the only one when other nucleophilic agents competing with CEH at the first stage of the process are used to effect the oxide (I) opening. The reaction of 20,20-dimethylacetal (I) with Py·HSCN and CEH in EtOH under standard conditions [2, 3] proceeds with the formation of a complex mixture, from which components (II), (III), (IVa), (Va), shown in the scheme below, were isolated. Dicarbethoxyhydrazones (II), (III) are formed by the expected path [3] (path *a*): as a result of the initial substitution of 20,20-dimethylacetal group by a hydrazone group [1, 4], followed by cis-opening of the oxide ring by thiocyanate ion with attack at C^{17}, intramolecular cyclization of the 16α,17α-thiocyanohydrin intermediate thus formed, and the condensation of pregn-5-ene-3β,21-diol-20-one-[17α,16α-d]-2'imino-1,3'-oxathiolane with excess CEH [3]. The

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Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 4, pp. 911-914, April, 1987. Original article submitted November 21, 1985.