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AN EFFICIENT TOTAL SYNTHESIS OF PROPYLURE, THE HIGHLY ACTIVE SEX ATTRACTANT FOR THE PINK BOLLWORM MOTH*

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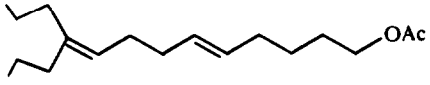
Abstract—The total synthesis of *trans*-1-acetoxy-10-(n-propyl)trideca-5,9-diene (propylure), a substance which induces highly active sexual response in the male bollworm moth has been accomplished using several novel synthetic methods. The efficiency of the techniques employed are demonstrated by an overall yield of 31% for the sex attractant.

THE SEX ATTRACTANT of the pink bollworm moth, *Pectinophora gossypiella Saunders*, a destructive cotton pest was isolated and characterized[1] several years ago and its structure stated to be *trans*-1-acetoxy-10-(n-propyl)trideca 5,9-diene, **1**. The total synthesis of the substance was accomplished[1] and verification of its pheromone behavior was shown by the high degree of sexual excitement induced in the male bollworm species. The synthetic approach to **1**, designated by the trivial name "propylure" was performed in 0·2% overall yield and several subsequent syntheses[2–5] reported since 1967 were likewise characterized by low yields, product mixtures, and/or lengthy procedures.



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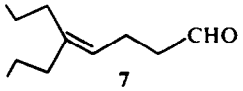
During the course of studies designed to evaluate the synthetic utility of dihydro-1,3-oxazines as precursors to a variety of aldehydes,[6] it was felt that an efficient synthesis of the aldehyde **7** would provide a key intermediate for the synthesis of the pheromone. Thus, routine coupling of **7** with the Wittig reagent of the bromoacetate **9** should lead to the gross structure of propylure. This report describes our efforts in this respect



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and the modifications and innovations employed which indeed resulted in a new and efficient total synthesis of a highly active form of the pheromone. Each of the synthetic operations proceeded in good yield and purification of intermediates along the sequence were limited only to the aldehyde **7** and the pheromone, **1**. The overall yield of propylure was slightly over 30% (Scheme 1).

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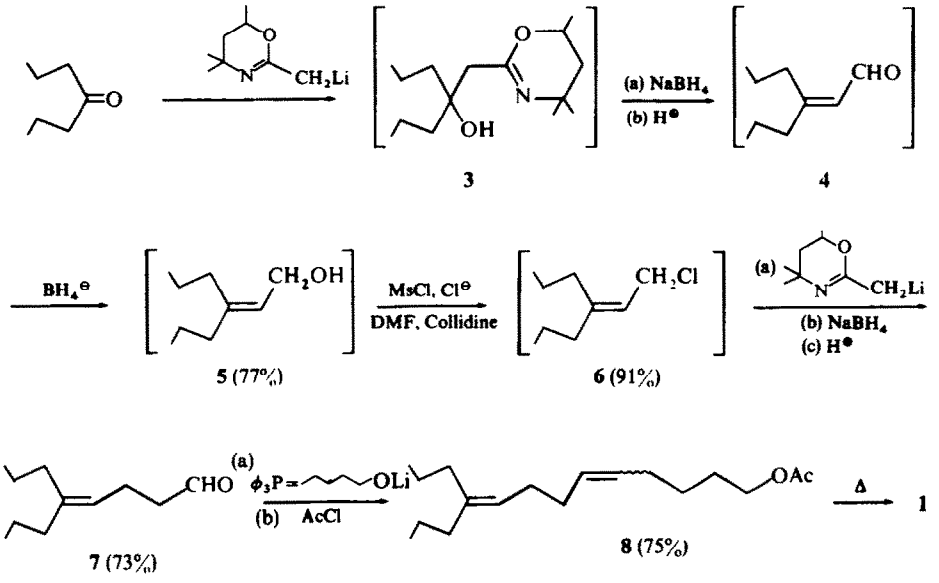
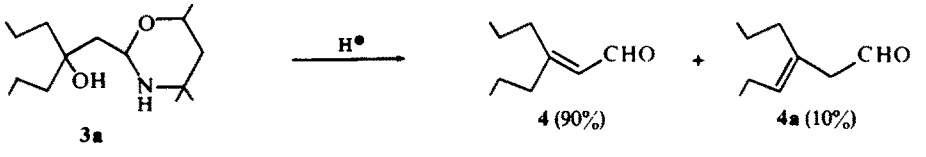
SCHEME 1.*



* Products in brackets were crude products and were utilized without purification by distillation.

Reaction of 4-heptanone with the lithio salt of 2,4,6.6-tetramethyl-5,6-dihydro-1,3-oxazine in THF at $-78°$ produced the adduct **3**, after work-up, in 96·4% crude yield. Without purification, the C=N link of the oxazinyl carbinol was reduced in EtOH-THF at $-40°$ with aqueous $NaBH_4$ at an apparent pH of 5–7 to the tetrahydro-1,3-oxazine **3a** (98% crude) and then subjected to hydrolysis in dilute oxalic acid solution to the unsaturated aldehyde, **4**. Examination of the aldehyde, obtained in 73% yield from 4-heptanone, revealed that it contained 10% of the non-conjugated aldehyde **4a**. due to two available modes of dehydration. The product mixture was readily discernible by NMR examination and integration of the vinyl and formyl signals.

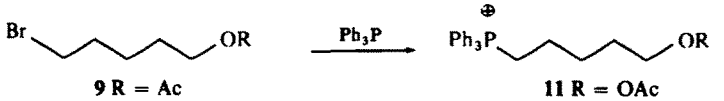


Since the synthetic approach called for efficient arrival to the allylic alcohol **5**, the aldehyde mixture was then subjected to reduction in abs EtOH with $NaBH_4$. The alcoholic products obtained were analyzed by VPC and found to contain 82% of the desired allylic alcohol (**5**) and a mixture of the homoallylic and saturated alcohol. Thus. this method of converting **4** to **5** was less than satisfactory due to side reactions. A recent study[7] of $NaBH_4$ reductions of conjugated aldehydes and ketones has shown that considerable amounts of saturated and homallylic alcohols accompany the product under a variety of different solvent systems.

It was subsequently found that $NaBH_4$ could be added directly to the aqueous oxalic acid solution utilized in the cleavage of the tetrahydro-1,3-oxazine after

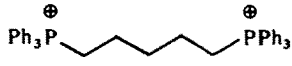
neutralization with bicarbonate. The allylic and homoallylic alcohols were produced in the same ratio (9:1) as the aldehyde mixture obtained ealier,* and no saturated alcohol was present.

The fact that a mixture of unsaturated alcohols were obtained did not cause any concern with regard to the next step in the pheromone synthesis. This was due to the fact that the allylic chloride **6** required to proceed was expected to react smoothly with the oxazine anion. The homoallylic chloride which was anticipated to also form in the conversion of **5** to **6** is not sufficiently electrophilic to react with the oxazine anion.[7] A variety of standard techniques[8] for carrying out the preparation of the allylic chloride were examined and all met with unsatisfactory results. A study was initiated to examine feasible means of preparing the allylic chloride **6** and success was realized after a series of trials which culminated in a novel and facile method.[9] Treatment of the allylic alcohol **5** (containing 10% of the homoallylic alcohol derived from **4a**) at 0° in DMF containing one equivalent each of LiCl and s-collidine with one equivalent of MsCl led to the allylic chloride in excess of 90% yield contaminated with approximately 10% of the homoallylic mesylate. Since the allylic chloride was rather unstable to heat it was not possible to purify it by distillation, nor was it feasible to effect purification by thin layer or column chromatography due to decomposition and rearrangement characteristics. The crude chloride was therefore used directly in the reaction with the lithio dihydro-1,3-oxazine to obtain the homologated aldehyde **7** by the standard procedure of alkylation, reduction, and cleavage. It is noteworthy that the homoallylic mesylate present in **6** did not interfere with the aldehyde preparation and **7** was obtained pure in 73% yield from the chloride mesylate mixture. The overall yield of **7** from 4-heptanone was 40%. The remainder of the synthesis leading to propylure anticipated to be routine, did not fulfill expectations. The bromoacetate **9** was readily prepared from tetrahydropyran and acetyl bromide.[10] Attempts to prepare the phosphonium salt **11** using triphenyl phosphine in benzene led only to an extremely hygroscopic semi-solid which resisted all attempts at crystallization.



9 R = Ac
10 R = H

11 R = OAc
12 R = OH



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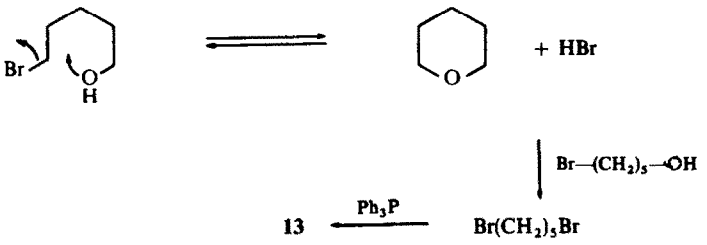
Additional efforts to utilize the crude phosphonium salt in the Wittig reaction with the aldehyde **7** resulted in only trace quantities of the desired product (**8**). Attention was then turned to the bromoalcohol, **10** since it has been reported[11] that β-hydroxyethylbromide and γ-hydroxypropyl bromide gave the corresponding phosphonium salts and underwent normal Wittig couplings *via* their phosphorane derivatives. When 5-bromo-1-pentanol was treated with triphenylphosphine in dry benzene

* The use of an aqueous buffered solution to retard solvent addition and/or double bond migration in the reduction of conjugated carbonyl compounds appears to be a useful method for overcoming the problems mentioned in reference 8. This technique is currently under investigation in our laboratories.

and heated to reflux only the *bis*-phosphonium salt (**13**) was obtained. It was subsequently discovered that freshly distilled 5-bromopentanol contained HBr and even after removal of the acid, more was found to be present several hours later. Thus, the equilibrium generating tetrahydropyran and HBr and the subsequent process which converts the bromopentanol to the dibromide had to be circumvented (Scheme 2).

SCHEME 2.



It was also found that 5-bromopentanol in refluxing benzene was extensively converted to dihydropyran and 1,5-dibromopentane. This difficulty was overcome by adding an acid scavenger (K_2CO_3) to the solution of the bromopentanol and triphenylphosphine in MeCN which gave the desired crystalline 5-hydroxypentyl phosphonium salt, **12**.

The salt, suspended in THF was treated with two equivalents of n-BuLi and produced the O-lithiophosphorane which was then treated with the aldehyde **7**. After the red color of the phosphorane had been discharged 1·2 equivalents of acetyl chloride were added and in this fashion, both Wittig coupling and acylation took place in a single operation affording **8** as a mixture containing predominantly the *cis* isomer in 80% yield. Although there have been reports that the steric course of the Wittig reaction could be controlled by appropriate selection of solvents,[12] or the use of proton donors to equilibrate the betaines[13] none of these modifications resulted in any significant change in isomer distribution.

The analysis of the *cis-trans* mixture was less than satisfactory using a variety of VPC conditions since distinct separation of the peaks could not be obtained. The most useful technique for determination of the mixture lay with the intensity of the 970 cm^{-1} peak characteristic of the *trans*-olefin. Comparisons of IR spectra with authentic material provided the guidelines for isomer purity.

The active propylure was readily obtained by thermal isomerization (250°) in the presence of Se as described by Stowell.[5] On recovery of the material the spectral properties were virtually identical with that of the natural active material.* It should be noted that the propylure is active so long as the *cis*-isomer constitutes less than 15% of the mixture. Mixtures containing 15% *cis*-isomer failed to cause a sexual response.[14]

In order to ascertain the authenticity and degree of activity of the synthetic material from this study, a sample was submitted for insect sexual response upon the male bollworm moths. The results, kindly supplied by Dr. Martin Jacobson of the United

* We thank Dr. John Stowell, Louisiana State University in New Orleans, for a copy of the IR spectrum of propylure.

States Department of Agriculture, Entomology Research Division, Beltsville, Maryland, stated:

"Of the 50 caged male moths in the laboratory exposed to the air from a pipet containing the compound vapors, 75 per cent showed typical sexual excitement, consisting of frenzied flight, abdominal bending, and copulatory attempts. The material is therefore highly active." These results are consistent with a mixture of *cis*- and *trans*-isomers containing 98 ± 2 *trans*-product.[14]

EXPERIMENTAL*

2-(2-*Hydroxy*-2-n-*propyl*) n-*pentyl*-4,4,6-*trimethyl*-5,6-*dihydro*-1,3-*oxazine* (**3**). A 500 ml three-necked flask equipped with a magnetic stirring bar, a 75 ml addition funnel topped with a rubber spetum, and a nitrogen inlet tube was successively evacuated and flushed with nitrogen. Anhydrous THF (100 ml) and 14·1 g (0·10 mole) of 2,4,4,6-tetramethyl-4,5-dihydro-1,3-oxazine[15] were added from a syringe through the rubber septum. The stirred solution was cooled to −78° (Dry Ice–acetone bath) and 69·0 ml (0·11 mole. 1·6 M) of n-BuLi in hexane was injected into the addition funnel. The n-BuLi was added dropwise over a period of 1 hr. Approximately 1 hr after the addition a yellow precipitate formed. This was indicative of complete anion formation. The anion may not precipitate if more than the above quantity of solvent is employed. A solution of 4-heptanone (11·5 g, 0·10 mole) in THF (25 ml) was added slowly to the anion solution at −78° when the yellow color gradually became paler. After the addition was complete the mixture was allowed to slowly warm to room temp when it was poured onto ice-water and acidified with 9N HCl. The acidic solution was extracted three times with pentane and then carefully basified with 40% NaOH. Extraction with ether, drying (K_2CO_3) and evaporation gave the oxazine (24·7 g) **3** as a yellow oil (96·4%). ν_{max}(film): 3320 (OH) 1665 cm^{-1} (C=N); NMR (CCl_4): τ 4·75 (1H, s, OH) 5·5–6·1 (1H, m, $CH_3C\underline{H}$—O), 7·85 (2H, s, N=C—CH_2), and 8·0–9·3 (25H, m).

2-(2-*Hydroxy*-2-*n*-*propyl*) *n*-*pentyl*-4,4,6-*trimethyl*-2,3,5,6-*tetrahydro*-1,3-*oxazine* (**3a**). To a 600 ml beaker was added 100 ml of THF, 100 ml of 95% EtOH, and the crude dihydrooxazine (21·3 g) obtained in the preceding experiment. The mixture was cooled between −35 and −40° with an acetone bath to which Dry Ice was added as needed. HCl (9 N) was added to the magnetically stirred solution until an approximate pH of 7 was obtained. The $NaBH_4$ solution was prepared by dissolving 3·78 g (0·10 mole) in a minimum amount of water (~4–5 ml) to which 1 drop of 40% NaOH had been added. The $NaBH_4$ solution and the 9N HCl solution were added to the stirred solution alternately so that pH 6–8 was maintained. The pH was monitored by periodic checks with pH paper. After addition of this borohydride solution was complete, the solution was stirred with cooling for an additional hour (pH 7 was maintained by the occasional addition of HCl aq). The contents were poured into 100 ml of water and made basic by the addition of 40% NaOH aq. The layers were separated and the aqueous solution extracted with ether. The combined organic extracts were washed with 100 ml of sat. NaCl aq and dried over anhyd K_2CO_3. Concentration of the extracts gave 21·2 g (98%) of **3a** as a pale yellow oil which solidified at low temps. ν_{max}(film): 3380 cm^{-1} (OH, NH): NMR (CCl_4): τ 5·2–5·8 (1H, m, N—CH), 5·69 (1H, broad s, OH), 5·9–6·6 (1H, m, CH—O), 8·0–9·3 (28H, m).

Oxalic acid cleavage of the tetrahydro-oxazine (**4a**). A mixture of the tetrahydro-oxazine (**4a**) (56·4 g), oxalic acid (108 g) and water (300 ml) was boiled for 40 min. After cooling, the solution was extracted with ether. The combined ether extracts were dried (K_2CO_3), filtered and evaporated to give 23·5 g (73%) of a mixture of 3-n-propyl-hex-2-en-1-al (**4**) (90%) and 3-n-propyl-hex-3-en-1-al (**4a**) (10%). ν_{max}(film): 1730 (CO), 1690 (CO), 1640 cm^{-1}; NMR (CCl_4): τ −0·2 (0·9H, d, J = 5Hz, CHO), 0·13 (0·1H, m, CHO), 4·05 (0·9H, d, J = 5Hz, C=CH—CO), 4·4–4·7 (0·1H, m, C=CH), 6·8–8·0 (4H, m), 8·0–8·7 (4H, m), and 8·8–9·2 (6H, m).

Reduction of aldehyde mixture (**4**) *and* (**4a**). A solution of the aldehyde mixture (1·93 g) in abs EtOH (25 ml) was treated dropwise with stirring with a solution of $NaBH_4$ (0·52 g) in 2 N NaOH (0·4 ml) diluted with water (5 ml). Stirring was continued at room temp for 3 hr when the EtOH was removed under reduced pressure and the residue diluted with water (10 ml) and extracted with ether (50 ml). The extract was dried ($MgSO_4$), filtered and evaporated to leave a pale yellow liquid (1·84 g, 94·5%).

VPC (10% Carbowax 20 M on Chromosorb P at 140°) showed the mixture to contain 82% of 3-propyl-2-hexen-1-ol (**5**). The remaining material of the mixture consisted of 3-propyl-3-hexen-1-ol and another component, not characterized but possibly the saturated alcohol.

* Microanalyses performed by Atlantic Microlabs, Inc., Atlanta, Georgia.

A pure sample of the alcohol (**5**) was collected from the VPC instrument. ν_{max}(film): 3320 (OH), 1672 cm^{-1}; NMR (CCl_4): τ 4·3–4·7 (1H, t, J = 4·2Hz, C=CH), 5·7–6·0 (2H, d, J = 4·2Hz, CH_2O), 7·3 (1H, broad s, OH), 7·7–8·2 (4H, m, $(CH_2)_2C$=C), 8·2–8·8 (4H, m), and 8·8–9·3 (6H, m).

Cleavage of the tetrahydro-oxazine (**3a**) *followed by an 'in situ' reduction to* **5**. The procedure for the oxalic acid cleavage is the same as described earlier. After cooling, the aqueous mixture was carefully neutralized with solid $NaHCO_3$. EtOH (95%, 300 ml) was then added followed by the dropwise addition of a solution of $NaBH_4$ (6·8 g) in 2N NaOH (3 ml) diluted with water (50 ml). After the effervescence subsided the mixture was stirred for a further 3 hr at room temp when it was acidified with 6N HCl and extracted with ether. The ethereal extracts were dried and concentrated to give 24 g (77%) of a mixture of 3-propyl-2-hexen-1-ol (**17**) (90%) and 3-propyl-3-hexen-1-ol (**18**) (10%).

1-*Chloro*-3-(*n-propyl*)-*hexene*-2 (**6**). A solution of 3·95 g LiCl in DMF (80 ml) was added to a solution of 13·21 g (0·093 mole) **5** in 2,4,6-collidine (12·4 g). The mixture was cooled to $-5°$ under N_2 and 11·8 g of MsCl added at a rate that kept the reaction temp below 0°. The resulting suspension was stirred at 0° for 1·25 hr and then poured onto ice water. The quenched mixture was extracted with ether-pentane (1:1) and the latter extracts washed successively with cold sat $Cu(NO_2)_2$ aq until the intensification of the cupric ion color was no longer evident. The organic solvent extracts were dried and concentrated at room temp giving 13·25 g (93%) of the crude allylic chloride. The product was unstable to heat (>80°), silica or alumina and was utilized in the next step in its present state of purity (~90% from NMR integration). The product contained approximately 10% (NMR) of the homoallylic mesylate. ν_{max}(film): 1650 cm^{-1}; NMR (CCl_4): τ 4·2–4·6 (1H, t, J = 5Hz, C=CH), 5·7–6·0 (2H, d, J = 5Hz, CH_2Cl), 7·7–8·1 (4H, m), 8·1–8·8 (4H, m), and 8·8–9·3 (6H, m).

Upon treatment of a sample of allylic chloride with ethanolic $AgNO_3$, there appeared an immediate copious precipitate of AgCl.

5-(*n-Propyl*)-4-*octene*-1-*al* (**7**)

(a) *Alkylation of* (**6**) *with lithio-oxazine*. Utilizing the procedure described above for alkylation of 4-heptanone, 10·5 g of the crude allylic chloride was treated with the oxazine anion prepared from 9·25 g tetramethyl-5,6-dihydro-1,3-oxazine, 32 ml n-BuLi (2.25 M) in 75 ml THF. Upon work-up there was obtained 13·3 g (76%) of the alkylated oxazine, b.p. 98–99° (0·23 mm); ν_{max}(film); 1660 cm^{-1}; NMR (CCl_4): τ 4·5–4·9 (1H, m, C=CH), 5·5–6·2 (1H, m, CH—O), 7·4–8·3 (8H, m), and 8·3–9·3 (21H, m).

(b) *Reduction of alkylated dihydro*-1,3-*oxazine*. The procedure described earlier was employed with 2·24 g of the above oxazine and 0·34 g $NaBH_4$. The tetrahydro-1,3-oxazine (2·12 g, 94%) was obtained as a colorless oil [ν_{max}(film) 1650 cm^{-1}, NMR (CCl_4) τ 4·6–5·0 (1H, t, C=CH), 5·6–6·0 (1H, m, N—CH), 6·0–6·6 (2H, m, NH and CH—O), 7·7–8·2 (8H. m), 8·2–9·3 (21H, m)].

(c) *Cleavage to* **7**. The tetrahydro-1,3-oxazine (11·0 g) was hydrolyzed in boiling oxalic acid (20·8 g in 60 ml water) solution for 1·25 hr and gave 5·9 g (85%) crude aldehyde. Distillation (54–55°/0·01 mm) gave pure **7** in 73% yield. ν_{max}(film): 2700, 1724 cm^{-1}; NMR (CCl_4): τ 0·0 (1H, m. CHO), 4·6–5·0 (1H, m, C=CH), 7·4–7·8 (4H. m). 7·8–8·2 (4H. m), 8·2–8·85 (4H, m), 8·85–9·4 (6H, m); (Calc. for $C_{11}H_{20}O$: C. 78·51; H. 11·98. Found: C, 78·54; H. 12·05%).

5-*Bromopentan*-1-*ol* (**10**). Prepared by a modification of the procedure reported by Ames and Islip.[16] To a solution of 5-bromopentyl acetate (67·8 g) in 95% EtOH (150 ml) was added 2N NaOH (180 ml) and the mixture shaken until homogeneous. After standing at room temp for 3 hr the EtOH was removed under reduced pressure and the organic residue extracted with ether. The combined ethereal extracts were dried (K_2CO_3), filtered and distilled to give 5-bromopentan-1-ol (29·6 g, 72%) as a colorless liquid, b.p. 62°/0·5 mm. (lit.[18] b.p. 75–76°/0·5 mm). ν_{max}(film): 3280 cm^{-1} (OH).

5-*Hydroxypentyltriphenylphosphonium bromide* (**12**). A solution containing 2·84 g **10**, 4·47 g triphenylphosphine in 15 ml MeCN was treated with 2·38 g K_2CO_3 and the suspension heated at reflux for 4 hr. The cooled solution was filtered and diluted with 150 ml of anhyd ether. The solid was collected, washed with ether and dried. 2·9 g (40%) m.p. 190–191°. ν_{max} ($CHCl_3$): 3280 cm^{-1} (OH); NMR ($CDCl_3$): τ 1·9–2·5 (15H, m, aromatic), 5·9 (1H, s, OH), 6·0–6·7 (4H, m), and 8·0–8·6 (6H, m).

Cis *and* trans-1-*Acetoxy*-10-(*n-propyl*)*trideca*-5,9-*diene* (**8**). A suspension of the phosphonium salt. **12** (3·1 g) in dry THF (50 ml) at room temp under nitrogen was treated dropwise with n-BuLi (9·95 mL 1·8 M) in hexane. The red phosphorane was stirred for 20 min when a solution of the aldehyde **7** (1·26 g) in THF (20 ml) was added dropwise. The resulting pale yellow suspension was stirred for an additional 30 min and AcCl (0·65 ml) was added. After 15 min, the mixture was poured into water and the organic layer removed by ether extraction. The extracts were dried ($MgSO_4$), filtered and concentrated producing a residue which was triturated with cold pentane to remove triphenylphosphine oxide. Concentration of the pentane

solution and distillation of the residue gave 1·51 g (72%) pure *cis*- and *trans*-propylure, b.p. 128° (1·0 mm).

The isomeric mixture showed a single peak on VPC (column 18', 10% UC-W 98 80-100 S, 211°, retention time 23 min). The active pheromone, which is the *trans*-product was reported to possess a strong band at 970 cm^{-1} in the IR. The product obtained showed only weak absorption in this region. (Calc. for $C_{18}H_{32}O_2$: C, 77·09; H, 11·50. Found: C, 77·37; H, 11·39%).

Isomerization leading to the active pheromone. A mixture of 0·035 g Se powder and 0·440 g **8** was heated in an evacuated sealed tube at 250° for 1 hr. Upon washing the tube with ether and concentrating the solution, there was obtained after distillation (b.p. 128° 1·0 mm) 0·390 g of a straw yellow liquid which exhibited a strong absorption at 970 cm^{-1} in the IR. Although VPC analysis still showed a single peak. this material was submitted to the United States Department of Agriculture for sexual response.

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