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Insect Pheromone Synthesis: New Methodology

Multiple syntheses of two attractants illustrate the evolution of new concepts and techniques.

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Insect pheromones were defined by Karlson and Luscher (*1*) as chemical "substances secreted by an individual [insect] and received by a second individual, in which they elicit a specific reaction. . . ." They are the agents of a chemical communication system, and as such they may serve to attract and excite members of the opposite sex or simply, for example, to aggregate both sexes, to signal alarm, or to demark a trail leading to a food source (*2, 3*).

Interest in insect pheromones stems from several areas. Isolated insect antennae provide physiologists with model systems in which to study pheromone reception and sensory transmission (*4*); manipulation of pheromone concentrations facilitates studies of insect behavior and sociality (*5*), and the potent attractant properties of certain insect pheromones provide economic entomologists with novel means for controlling insect pest populations (*3, 6*). In the last case, the use of pheromone-baited traps to monitor regions of suspected infestations (in order to direct the selective application of conventional insecticides) and the application of large quantities of pheromonal compounds (to cause confusion and reduce mating efficiency) appear most promising.

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Synthesis and Pheromone Structure Elucidation

Although powerful spectroscopic techniques available in many chemical laboratories are generally sufficient to elucidate unambiguously the structure and stereochemistry of most new natural products, this is rarely the case with insect pheromones. While the structures of insect pheromones have usually proved to be relatively simple, the quantity of material available for structural characterization is often extremely limited. Individual insects contain only nanogram amounts of pheromone; therefore, large numbers of insects still provide only microgram quantities. Mass spectroscopic and gas chromatographic analysis of a new pheromone, and similar analysis of its hydrogenolytic and ozonolytic fragments, will often delineate its basic structural features; and the ingenious technique of subtractive gas chromatography, developed for pheromone characterization (*7*), can provide information about functional groups with nanogram samples. But in the field of insect pheromones synthetic chemistry still maintains one of its traditional roles, that of providing the confirmation of a proposed structure through synthesis by an unambiguous route. In fact, in most cases, synthetic efforts have proved essential to the elucidation of the correct structural and stereochemical features of pheromones. It is expected, of course, that synthetic material will be relied on for any major field uses of insect pheromones, because natural supplies are so limited.

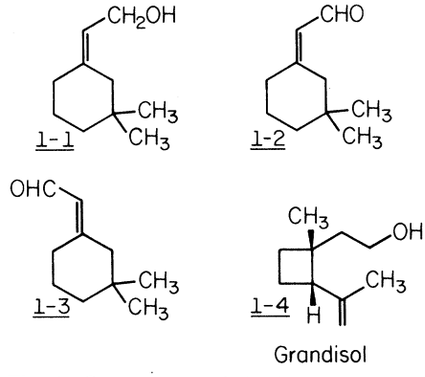


Fig. 1. Components of the boll weevil sex attractant "grandlure" (*10*).

The structures of many insect pheromones are relatively simple linear olefinic alcohols or esters, and often the application of traditional synthetic methods suffices for the efficient synthesis of these compounds. However, there are a number of cases where these pheromone structures have been sufficiently complex so as to be a test of skill for the synthetic chemist. In these instances, one can trace with each compound a characteristic development that proceeds through two distinct phases. In the first stage, synthetic efforts are geared to the preparation of the compound by a route that, while perhaps not efficient or stereospecific, will be sufficiently unambiguous to resolve all remaining structural and stereochemical questions. Thereafter, a premium is placed on syntheses that are either simple and efficient or ones that illustrate particularly novel conceptual or methodological features. Thus, one often finds certain insect pheromones selected repeatedly as synthetic targets to establish the utility of newly described synthetic procedures.

In this article, I trace such an evolution of synthetic logic and methodology

that is associated with the pheromones of two insects—both cotton pests—the boll weevil and the pink bollworm moth. A number of other reviews provide more comprehensive coverage of pheromone synthesis (*8, 9*).

Boll Weevil Sex Attractant

Workers at the Agricultural Research Laboratory of the U.S. Department of Agriculture Laboratory at State College, Mississippi, found that young female boll weevils (*Anthonomus grandis*, Boheman) are attracted by a pheromone emitted by young males (*10*). In 1966, work began on the isolation and identification of the chemical nature of the boll weevil sex attractant. Nearly 5 million boll weevils and 50 kilograms of weevil excrement (frass) provided starting material for the extensive separation procedures that were required.

This investigation provided a particular challenge because the active pheromone proved to be a mixture rather than a single chemical. Therefore, in order to use bioassays to follow activity during the fractionation procedures, separate fractions had to be remixed in different compositions (*10*). Work was completed in 1969, when it was reported that the pheromone consisted of four components that acted synergistically; together these are termed "grandlure" (from the species name *grandis*) (Fig. 1); no one of the four alone had more than 10 percent of the activity of the mixture (*11*).

Three of the components are rather ordinary cyclohexylidine monoterpenes (**1-1**, **1-2**, **1-3**) (*12*); their syntheses were described by the original workers (*11, 13, 14*) and have been refined by more recent efforts (*15, 16*). Structurally, the most intriguing component is the cyclobutane alcohol **1-4** termed "grandisol."

Several structural and chemical features in this molecule should be noted. Biosynthetically, it appears to be of terpene origin; γ-geraniol has been suggested as its precursor (*16*), yet it is unlikely that biogenetic-type synthesis will be fruitful because of the strain of the four-membered ring (*16*). The relative stereochemistry (*cis* versus *trans*) of the two larger ring substituents (ethanol and isopropenyl) was not evident from spectroscopic analysis of natural grandisol; therefore, solution of this point required either stereochemically unambiguous synthesis or syntheses of both *cis* and *trans* isomers for spectroscopic comparison. The isomerization of the double bond under acid conditions, from its terminal, disubstituted position to the exocyclic, tetrasubstituted position (see **2-6**) can be perceived as a potential pitfall.

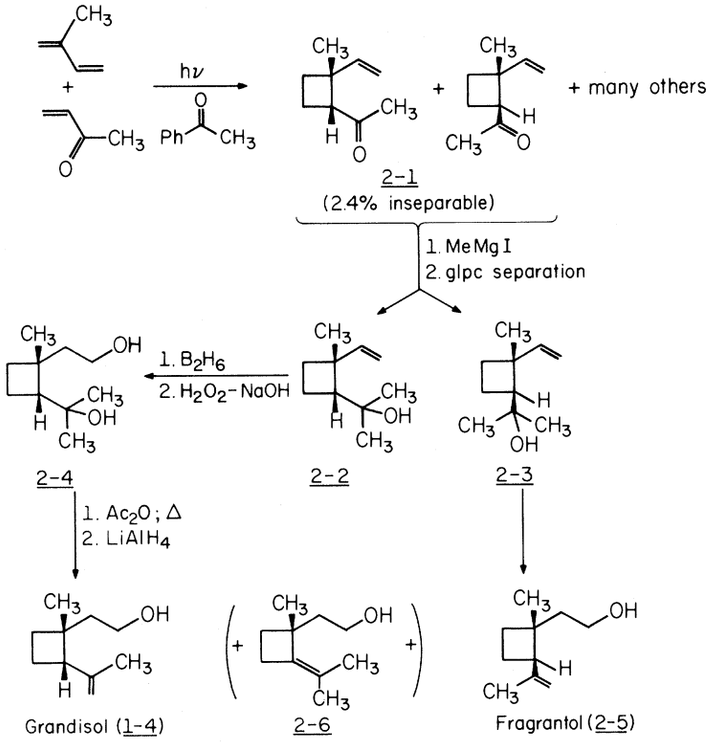


Fig. 2. The first synthesis of grandisol (*14*).

Photochemical Syntheses of Grandisol

At the time that the structure of grandisol was reported, one of the most successful methods for the synthesis of alkyl substituted cyclobutanes was the photochemical cycloaddition of olefins to unsaturated ketones (*17*). This reaction provided the basis for most of the early grandisol syntheses.

The workers who isolated and characterized grandisol also provided its first syntheses (*10, 13, 14*) (Fig. 2); although it was nonstereospecific and inefficient, this synthesis did establish the *cis* stereochemistry of grandisol as shown in **1-4**. The acetophenone-sensitized photocycloaddition of methyl vinyl ketone and isoprene provided in 2.4 percent yield a nonseparable mixture of the *cis* and *trans* acetylcyclobutanes **2-1**. The stereoisomeric alcohols **2-2** and **2-3** resulting from methyl Grignard addition, however, were separable by gas-liquid partition chromatography (GLPC), and each was individually converted further to grandisol (**1-4**) or its *trans* isomer (**2-5**) by hydroboration and oxidation, followed by dehydration and hydrolysis. Both products were contaminated with the structural isomer **2-6**. With both stereoisomers in hand, the assignment of grandisol as the *cis* isomer could be made unambiguously by proton magnetic resonance (PMR) analysis.

The *trans* isomer **2-5** was found to be 100- to 200-fold less active than the *cis* in the laboratory assay of weevil attraction (*14*). It is interesting, however, that this isomer is also a natural product that was later isolated from the roots of *Artemisia fragrans* Willd (*18*) and termed fragrantol.

The clarification of the stereochemistry of grandisol paved the way for more efficient, stereospecific syntheses. Three closely releated routes (Fig. 3) also relied on photocycloaddition to construct the cyclobutane moiety. In these cases stereochemical control was achieved by constraining the *cis*-oriented substituents within a five- or six-membered ring containing an unsaturated ketone or lactone. Different approaches were taken in the elaboration of the side chains from the fused bicyclic photoaddition products.

In the most straightforward approach, Gueldner *et al.* (*19*) provided for the ethanol functionality by utilizing an unsaturated lactone (**3-1**) in the photocycloaddition. Addition of two equivalents of methyllithium to the photoadduct **3-2** assembled all the required carbon atoms. A small percentage of the ketone inter-

mediate in the transformation of **3-2** to **2-4** epimerized, forming some *trans* diol **2-3**, but this was easily removed by recrystallization. The *cis* diol **2-4** was identical with that prepared by their earlier route (Fig. 2) and was converted, as in their previous sequence, to grandisol. Although this synthesis avoided the formation of all but a few percent of the *trans* isomer (**2-5**), considerable product was lost as the exocyclic olefin (**2-6**) because of the acidic conditions used to dehydrate **2-4**.

The Zoecon synthesis by Zürfluh *et al.* (*20*) (Fig. 3) involved a more complex series of reactions to convert the photoaddition product (**3-4**) of ethylene and cyclohexenone into grandisol, but the more controlled construction of the isopropenyl group improved the overall yield. An additional double bond was introduced into **3-4** by a standard bromination-dehydrobromination process. Selective 1,2-addition of methyllithium then gave the allylic alcohol **3-6**, which was then subjected to osmium tetroxide–periodate oxidation. This cleavage proceeds with the excision of the carbon originally situated α to the carbonyl group and unmasks from the unsaturated ketone an acetyl group and an acetic acid group. The *cis* relationship between these two groups that is expected from the method of synthesis can be further ascertained by the ready lactonization of the alcohol produced by borohydride reduction of the acetyl group in **3-7** and by the base-catalyzed isomerization of the methyl ester of **3-7** to a mixture predominating in the more stable *trans* isomer. The acid itself (**3-7**) was converted to grandisol by Wittig methylenation, followed by hydride reduction. This process permits construction of the isopropenyl group without the danger of double bond isomerization.

More recently, Cargill and Wright (*21*) have used a related, abnormal ozonolytic cleavage in a grandisol synthesis (Fig. 3). In this case the photoadduct of a cyclopentenone and ethylene (**3-8**) was condensed with acetone or an aromatic aldehyde and then reacted with methyllithium to give the allylic alcohol **3-10**. Ozonolysis, followed by treatment with base gave the same keto acid (**3-7**) produced by the Zoecon synthesis. The overall yield by this route is very high, and a mechanism proposed for the ozonolytic cleavage is shown in **3-11**.

Ayer and Browne (*22*) have used an intramolecular photocyclization to synthesize grandisol (Fig. 3). The starting material is a naturally occurring terpene, eucarvone (**3-12**), which contains all of the ten atoms in the final product. The initial photocyclization reaction used to form **3-13** had been described by Buchi and Burgess in 1960 (*23*), but Ayer improved the yield of **3-12** substantially by systematically investigating the effect of different solvents. After hydrogenation of **3-13**, all that remained was to transpose the carbonyl group to a position adjacent to the *gem*-dimethyl function

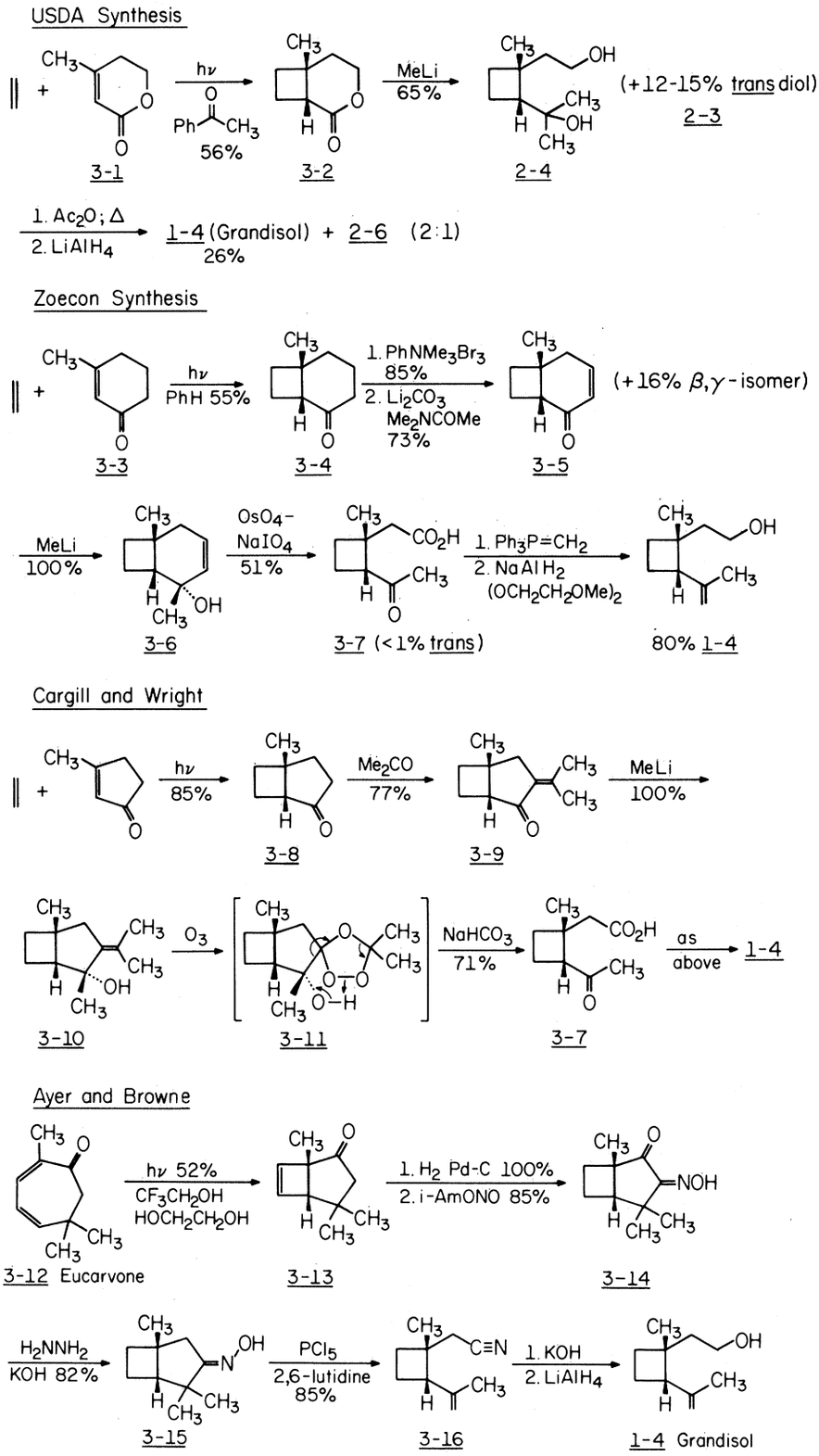


Fig. 3. Grandisol syntheses based on photocyloadditions; the USDA synthesis is described in (*19*), Zoecon in (*20*), Cargill and Wright in (*21*), and Ayer and Browne in (*22*).

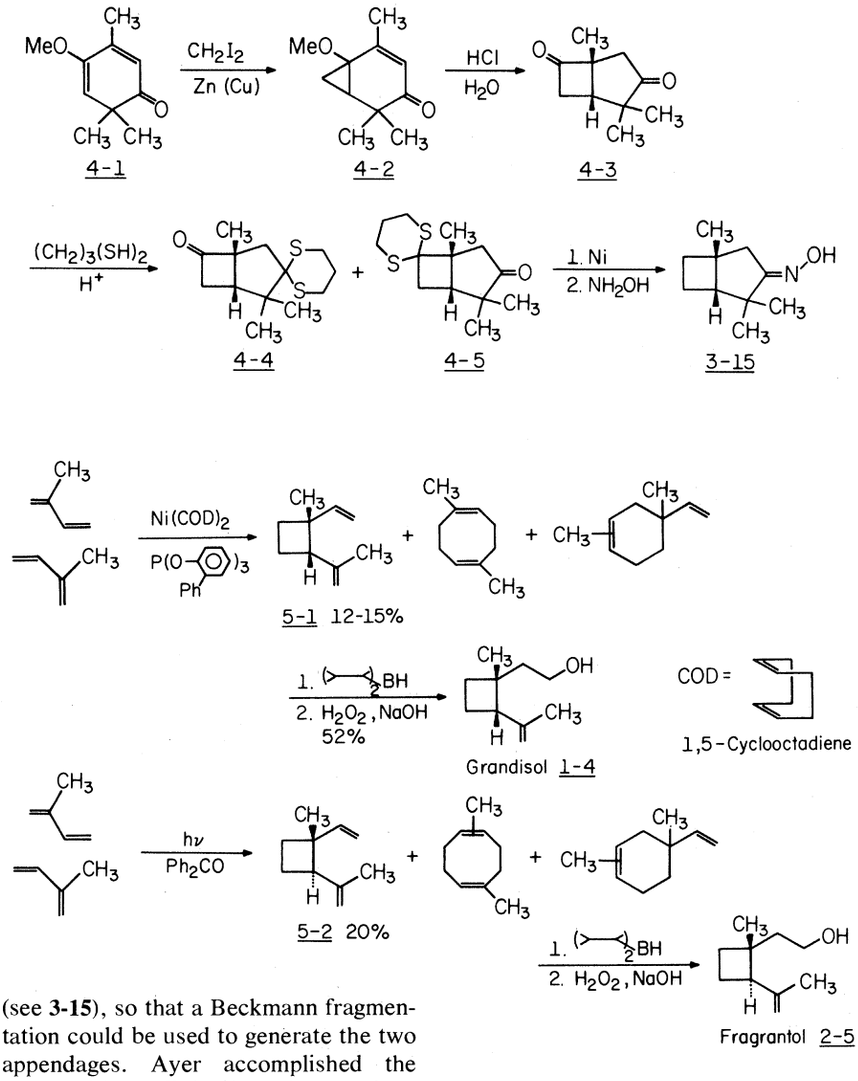


Fig. 4 (top). Grandisol syntheses by Golob (*24*) and Wenkert (*25*). Fig. 5 (bottom). Syntheses of grandisol (*27*) and fragrantol (*28*) starting from isoprene.

(see **3-15**), so that a Beckmann fragmentation could be used to generate the two appendages. Ayer accomplished the transposition efficiently using a nitrosation-Wolff-Kishner reduction sequence, but only after several other alternative procedures had failed. Fragmentation of the oxime **3-15** proceeded well under carefully defined conditions that avoided the generation of protic acids; again, typical procedures used for Beckmann fragmentations resulted in the undesired isomerization of the double bond to the exocyclic position. Finally, conversion of the nitrile **3-16** to grandisol proceeded without incident.

It is instructive to reexamine how increasingly efficient sequences were developed for conversion of the initial, photochemically produced cyclobutanes (**3-2**, **3-4**, **3-8**, and **3-13**) into grandisol.

Grandisol Syntheses Based on New Methodology

Several very different approaches have been taken to the synthesis of grandisol; each demonstrates a method for cyclobutane synthesis that was developed only subsequent to the structural elucidation of the attractant component.

To demonstrate the utility of an α-oxycyclopropyl carbonium ion rearrangement in natural products syntheses, Golob (*24*) and Wenkert (*25*) prepared grandisol, starting from compound **4-2**, a cyclopropyl ether (*26*) (Fig. 4). In acid, this ether underwent the desired rearrangement to the fused bicyclic dione **4-3**. The cyclobutane ketone in **4-3** was removed by a thioketalization-desulfurization sequence (through **4-5**) that was not completely specific; the undesired thioketal **4-4** could be recycled back through **4-3**, however. Treatment of the appropriate monoketone with hydroxylamine gave oxime (**3-15**), which was the same as that produced photochemically by Ayer and Browne (*22*); the final steps to grandisol closely parallel the earlier route (Fig. 3).

In a two-step synthesis of grandisol (Fig. 5), Billups *et al.* (*27*) used a zerovalent, biscyclooctadienylnickel-phosphite complex to dimerize isoprene. The desired *cis* cyclobutane diolefin **5-1** constituted about 12 to 15 percent of the complex product mixture, but it could be separated from unreacted isoprene and other cyclic dimers by a low-temperature distillation; above room temperature it isomerized to 1,5-dimethyl-1,5-cyclooctadiene. It is interesting that no other cyclobutane-containing products are formed in this transition metal–catalyzed dimerization. Selective hydroboration-oxidation of compound **5-1** sufficed to complete the synthesis.

This route closely resembles that in an unpublished synthesis of fragrantol by Corey, Katzenellenbogen, and Libit (Fig. 5), which was completed before the stereochemistry of grandisol was reported (*28*). In this case the *trans* cyclobutane diolefin isomer **5-2** was isolated by GLPC from a mixture of dimers produced by the photosensitized irradiation of isoprene (*29*).

A recent synthesis by Stork and Cohen (*30*) (Fig. 6) illustrates the application of a new cyclization of epoxynitriles. Studies in model systems had shown that when the anion derived from a δ,ϵ-oxidonitrile (**6-6**) cyclized, preferential formation of cyclobutylcarbinol rather than the cyclopentanol occurred, because of the required colinear arrangement between the attacking anion and the bond to the departing oxygen. This can be achieved only by attack on the proximal (δ) rather than the distal (ϵ) carbon-oxygen bond (see **6-6**).

The epoxynitrile required for the grandisol synthesis **6-3** was prepared by standard reactions, and it possessed all but one of the carbon atoms ultimately needed. The cyclization efficiently furnished the cyclobutylcarbinol **6-4**, 95 percent of which had the nitrile *trans* to the carbinol, and thus the protected ethanol function *cis* to the potential isopropenyl group. A two-step sequence converted the nitrile to the methyl group (**6-5**), and the differentially protected diol was elaborated to grandisol in a routine fashion. Care was required only at the final stage, where the tetrahydropyranyl ether protecting group had to be removed under conditions that were sufficiently mild to avoid isomerization of the double bond. The final product contained only 6 percent fragrantol. This stereospecificity reflects the steric factors operating during the cyclization (see **6-7**): Because of its large size the nitrile ion must adopt an orientation that is *trans* to the epoxide group.

Recently, Babler reported another ap-

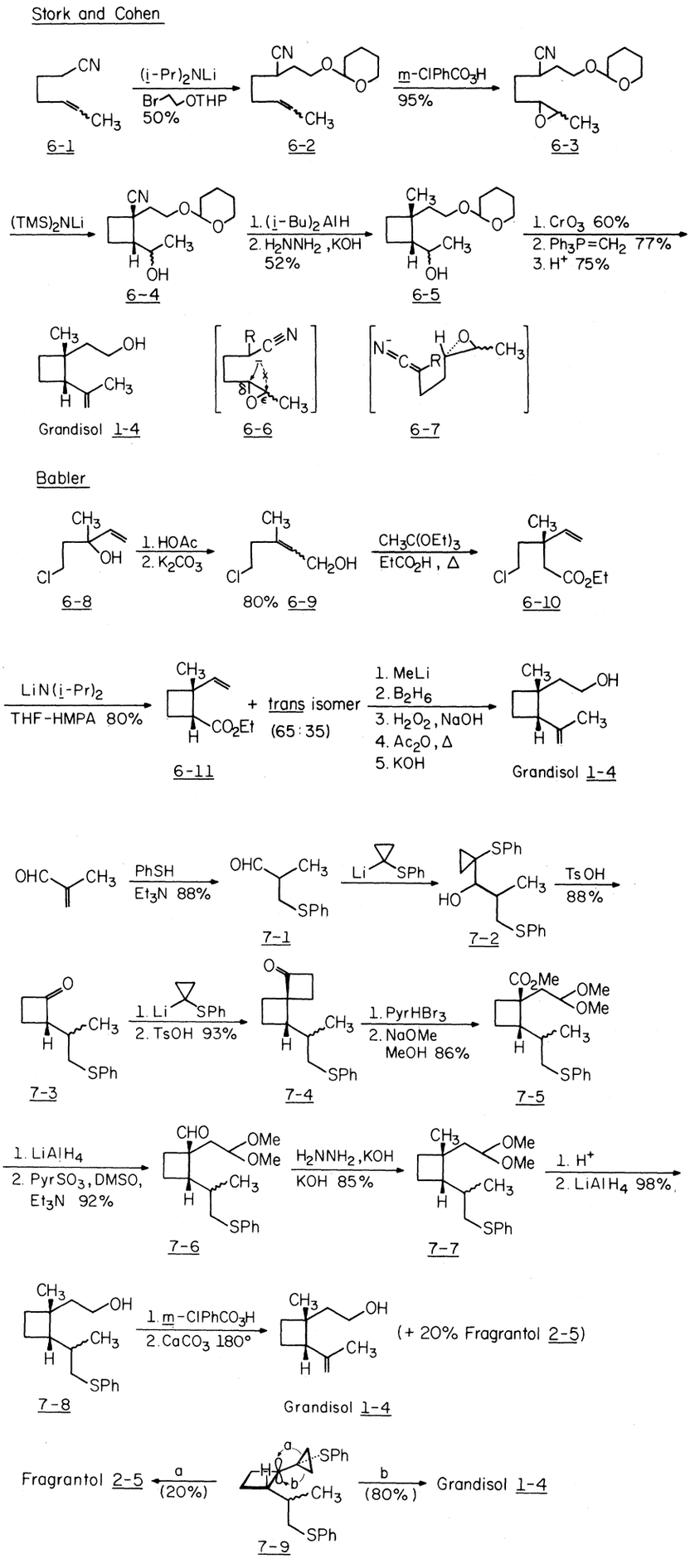
Fig. 6 (top). Grandisol synthesis by anionic cyclizations. The synthesis of Stork and Cohen is described in (*30*), that of Babler in (*31*). Fig. 7 (bottom). Grandisol syntheses by Trost and Keeley (*33*).

proach to grandisol, based on an anionic cyclization (*31*) (Fig. 6). The allylic orthoester rearrangement of Johnson *et al.* (*32*) was applied to the chloroalcohol **6-9** to produce the δ-chloroester **6-10**, which in the key step was cyclized in 80 percent yield to a 65:35 mixture of the *cis* and *trans* substituted cyclobutanes (**6-11**). A sequence of now familiar steps produced grandisol, admixed presumably with the exocyclic isomer **2-6**.

A grandisol synthesis by Trost and Keeley (*33*) (Fig. 7) is again illustrative of recently developed synthetic methodology. Here, a new reagent is used twice in succession, first to form the cyclobutane ring and then to introduce the two geminal alkyl substituents (methyl and ethanol). An intriguing conceptual feature of this synthesis is that it begins at the isopropenyl end of grandisol and progresses sequentially to the ethanol function.

The isopropenyl group in methacrolein, destined to be the isopropenyl group in grandisol, is protected as the thiophenol adduct (**7-1**). The cyclobutanone is then elaborated by a two-step process developed by Trost (*34*), which involves the use of an extremely versatile reagent, lithiocyclopropyl phenyl sulfide. The cyclopropylcarbinol adduct (**7-2**) rearranges readily to the cyclobutanone **7-3**. With the ring formed, the two remaining substituents are introduced by a process termed by Trost "seco alkylation." First, the cyclobutyl annelation is repeated with the formation of a fused spiro heptanone system **7-4**, then the new cyclobutanone ring is fragmented by a haloform-type cleavage. This gives the required one- and two-carbon substituents (**7-5**), suitably differentiated to permit their elaboration into the methyl and ethanol functions, respectively, by a series of routine steps to **7-8**. Finally, the isopropenyl group is regenerated by oxidation of the sulfide to the sulfoxide, followed by thermal elimination of phenylsulfenic acid (C_6H_5SOH), a process that does not produce any of the exocyclic isomer (**2-6**).

This synthesis produced grandisol mixed with 20 percent of the *trans* isomer, fragrantol (**2-5**). It is interesting to trace back to the origin of this isomeric contaminant. In the second cyclobutyl annelation sequence, rearrangement of the cyclopropylcarbonium ion (**7-9**) can proceed in two different fashions: one (path *a*) places the carbonyl carbon of



the spiro system *cis* to the protected isopropenyl function, while the other (path *b*) places these groups *trans*. The latter process is favored (80 to 20), and it is the one that leads to grandisol.

An Asymmetric Synthesis of Grandisol

The grandisol synthesis by Hobbs and Magnus (*35*) (Fig. 8) shares a feature of the Ayer and Browne synthesis (Fig. 3) in that it starts with a natural product. In this case, however, the natural product, (−)-β-pinene is a single enantiomer, and the goal of the synthesis is the preparation of enantiomerically pure grandisol, a feat not achieved by any of the other syntheses.

(−)-β-Pinene contains a cyclobutane ring that is preserved throughout the synthesis. This ring has four substituents; two are methyl groups, and the other two form part of the three-carbon bridge. The only functional group is a double bond, and it is the site from which a series of rather intricate manipulations originate.

The first stage of the synthesis involves the selective functionalization of the methyl group that is *endo* with respect to the trimethylene bridge, and its elaboration into the ethanol group. Hydration of the double bond in β-pinene gives the well-known pinan-2β-ol (**8-1**) (*36*). The new hydroxyl group, which is close to the *endo* methyl group, is converted to the nitrite ester and photolyzed. This procedure, which was devised by Barton (*37*), involves an intramolecular hydrogen transfer and converts the *endo* methyl group into an aldoxime (**8-2**). Hydrolysis to the aldehyde and conversion to the olefin **8-3**, followed by selective hydroboration-oxidation, gives the diol **8-4**. This multistep sequence results in the addition of a $-CH_2OH$ group specifically to the *endo* methyl group in β-pinanol, so that now two of the three substituents on the cyclobutane ring of grandisol are in completed form.

The second stage of the synthesis involves the elaboration of the three-carbon bridge into the isopropenyl group. Also required is the removal of the fourth substituent on the cyclobutane, together with an extra carbon atom. The same hydroxyl group provides the site of functionalization to achieve these transformations.

The primary hydroxyl in the diol **8-4** can be acetylated selectively, and the tertiary one is then dehydrated to a 2:1 mixture of exocyclic and endocyclic olefins (**8-5**). Allylic oxidation of this mixture to the unsaturated ketone **8-6**, followed by hydrogenation, gives the saturated ketone **8-7**. This ketone undergoes an efficient, photochemical Norrish type I cleavage, revealing the isopropenyl group in **8-8**. All that remains is the removal of the extra carboxaldehyde function from **8-8** by decarbonylation and the deprotection of the hydroxyl group. The *cis* stereochemistry of the ethanol and isopropenyl substituents is the direct consequence of the initial intramolecular functionalization reaction, and throughout the whole synthesis the chirality originally present in the starting material is preserved. The synthetic material is dextrorotatory; this agrees in sign with the rotation of natural grandisol that was determined on a crude sample (*11*).

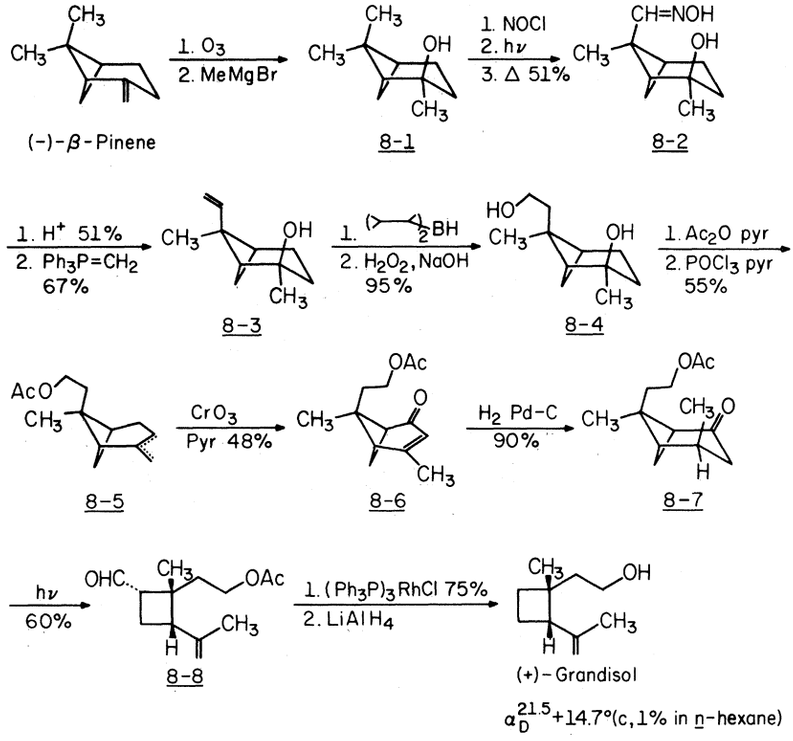


Fig. 8. Asymmetric synthesis of grandisol by Hobbs and Magnus (*35*).

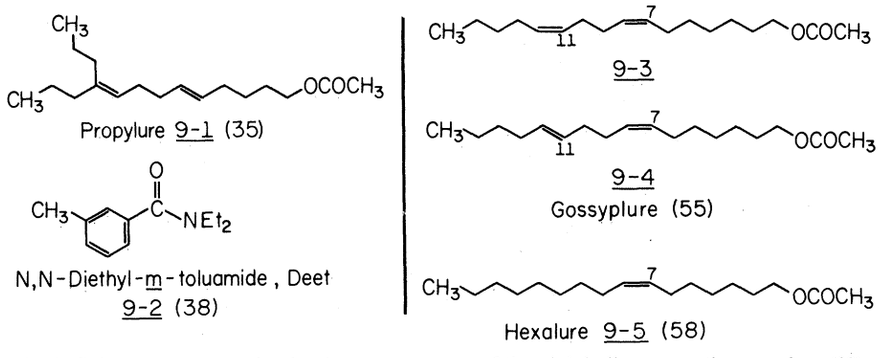


Fig. 9. Substances reported to be the sex attractant of the pink bollworm moth: propylure (*38*), Deet (*41*), gossyplure (*58*), and hexalure (*63*).

Sex Attractant of the Pink Bollworm Moth: Propylure

One of the more intriguing sagas in the field of pheromone synthesis concerns the sex attractant of the pink bollworm moth, *Pectinophora gossypiella* (Saunders) which, like the boll weevil, is also a destructive pest in cotton-growing areas. In 1966, Jones, Jacobson, and Martin (*38*) at the U.S. Department of Agriculture (USDA) Laboratory in Beltsville, Maryland, reported the isolation of the pheromone from 850,000 virgin female moths (2 days old) by a procedure utilizing extensive chromatographic separa-

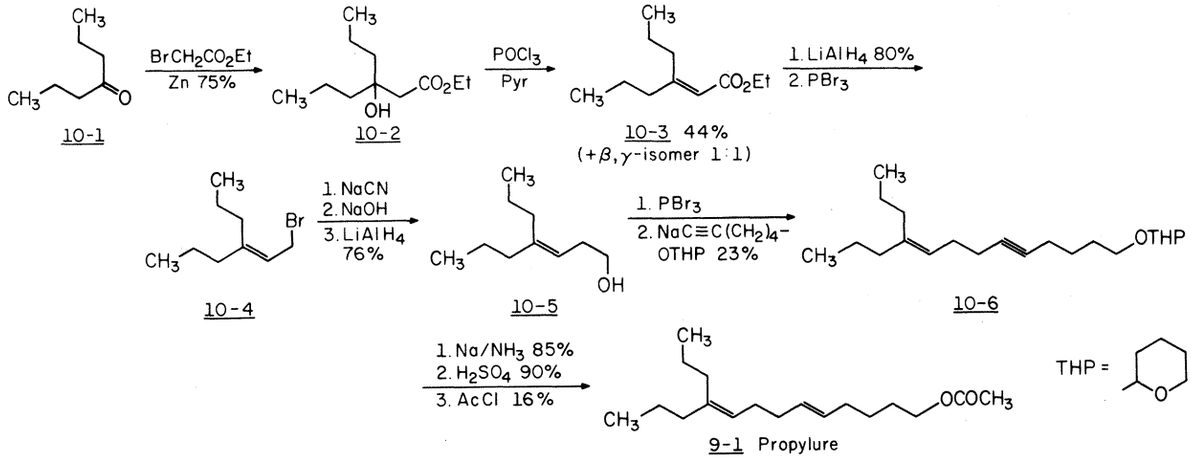


Fig. 10. An early synthesis of propylure by Jones *et al.* (*38*).

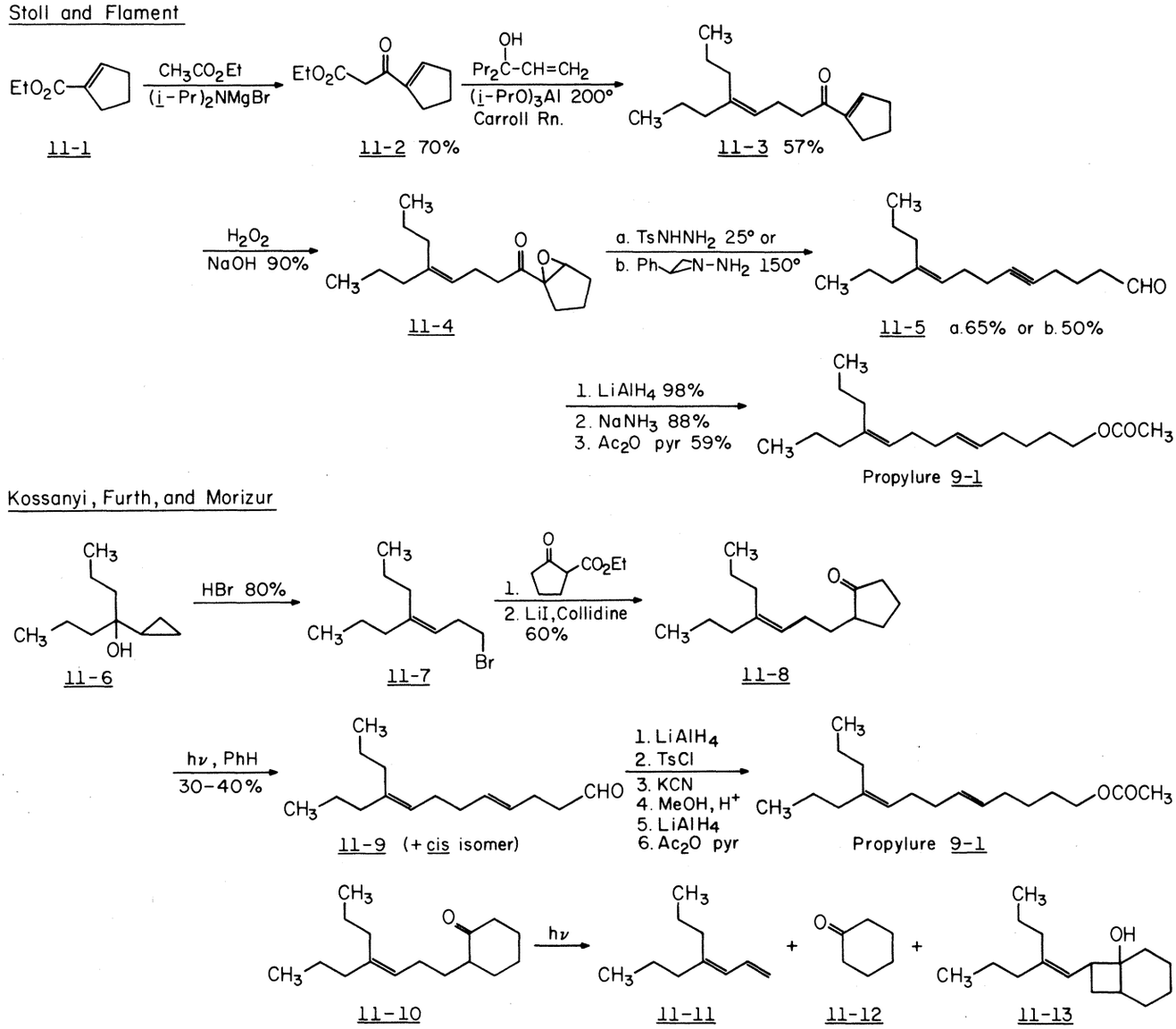


Fig. 11. Propylure syntheses involving ring scission. The Stoll and Flament synthesis is described in (*45*), and that of Kossanyi *et al.* in (*47*).

tions. They related that this material was attractive to male pink bollworm moths, and on the basis of spectroscopic and degradative evidence they assigned an intriguing structure to this substance; most curious was the trisubstituted olefin unit bearing two propyl substituents, which is unique in nature and led to the common name "propylure" (Fig. 9).

Propylure has had a particular appeal to synthetic organic chemists, and has served as the testing ground for many new methods of stereospecific di- and trisubstituted olefin syntheses, and of 1,5-diene syntheses. Jones *et al.* (*38*) presented a rather laborious synthesis of propylure as part of the structure proof (Fig. 10), and soon thereafter a similar synthesis was reported by Eiter *et al.* (*39*). Both of these syntheses involved first the formation of the trisubstituted olefinic unit (**10-3** in the Jones synthesis) by a sequence involving a Reformatsky reaction that gave a mixture of α,β and β,γ double bond isomers. Further elaboration by Jones *et al.* (*38*) was done by homologation with cyanide ion and then acetylide alkylation, followed by dissolving metal reduction, deprotection, and acetylation, to give the *trans* disubstituted olefin (**9-1**) stereospecifically. Eiter *et al.* (*39*) used a Wittig condensation to give the disubstituted olefin; as this reaction is not stereospecific, his product was a mixture of geometric isomers at C-5.

A controversy about propylure began when Eiter found that his synthetic material was biologically inactive, and he challenged the validity of the initial structural assignment (*39*). The USDA workers countered by describing a reinvestigation (*40*) in which they found that the *trans* isomer of propylure was highly attractive in a laboratory bioassay (*41*), but that the 5-*cis* isomer was not only inactive, but was capable of blocking the activity of the *trans*; as little as 15 percent contamination by the *cis* isomer destroyed all activity. Other examples where pheromonal activity was masked by isomeric contaminants were known at the time (*40*); thus, it appeared imperative that future syntheses of propylure provide material free from structural or stereoisomers.

Shortly thereafter, an efficient synthesis by Pattenden (*42*) combined the *trans* stereospecificity of the dissolving metal reduction of acetylenes in forming the unsaturation at C-5 with the regiospecificity of the Wittig reaction in making the C-9 double bond to provide an unambiguous synthesis of *trans* propylure. His material was judged to be active by the USDA workers. Related syntheses (also not shown) were reported by Stowell (*43*) and by Meyers and Collington (*44*).

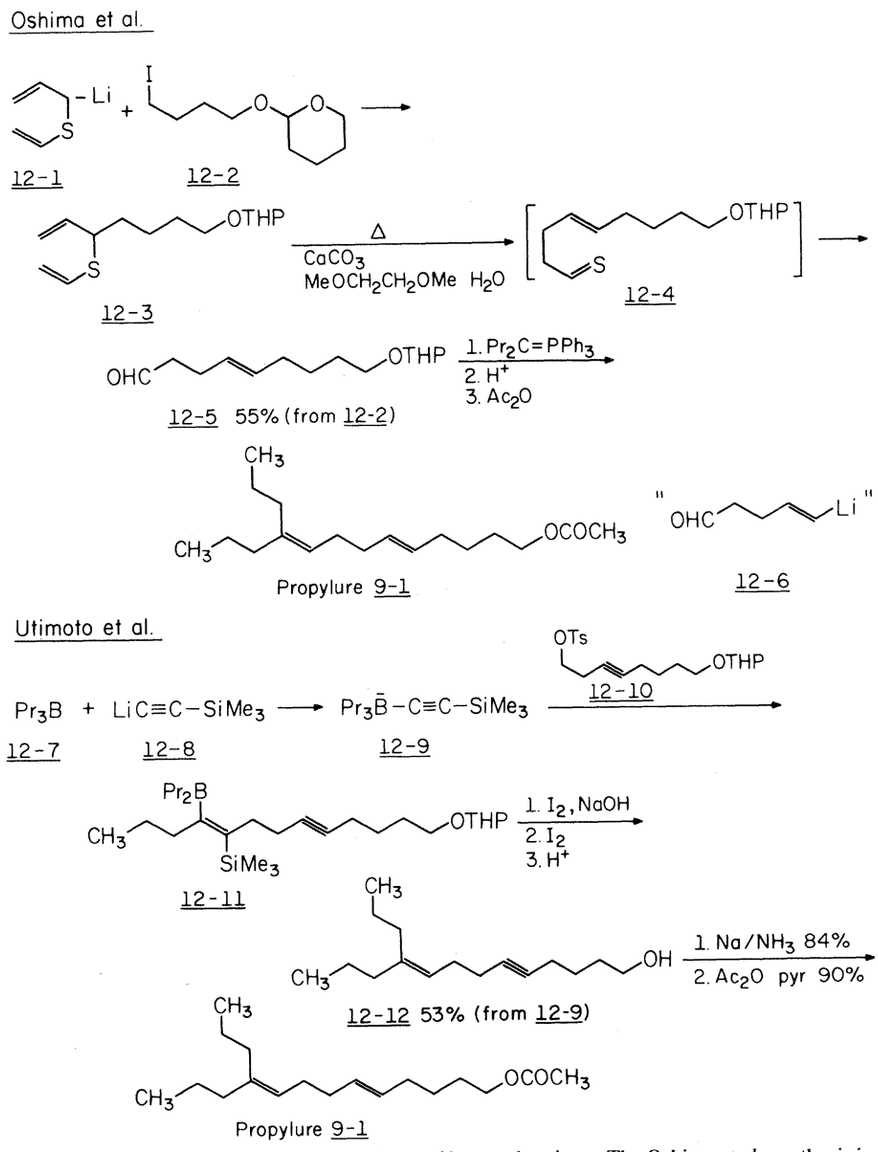


Fig. 12. Propylure syntheses based on sulfur and boron chemistry. The Oshima *et al.* synthesis is described in (*50*), and that of Utimoto *et al.* in (*55*).

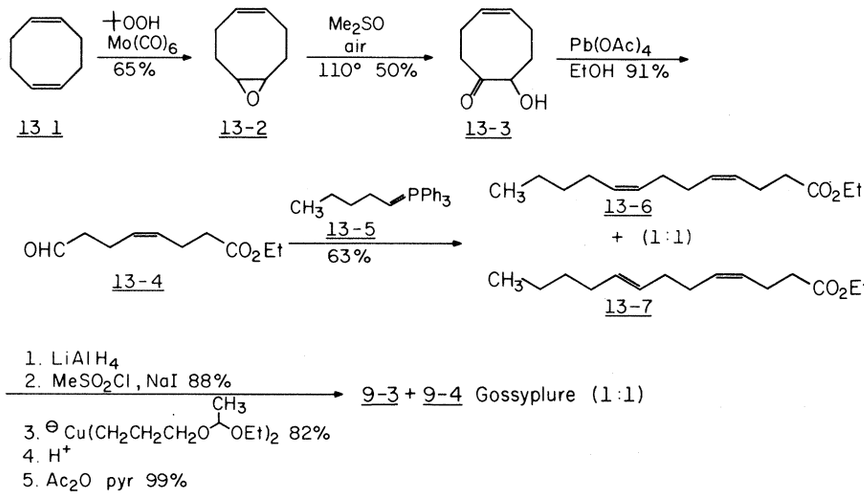
Recent Syntheses of Propylure

More recent syntheses of propylure display impressive conceptual diversity and technical sophistication. Two syntheses use carbocyclic units to generate in a controlled fashion the disubstituted olefin and terminal oxygen functionality. Stoll and Flament (*45*) (Fig. 11) used the Carroll rearrangement to prepare an unsaturated cyclopentenyl ketone **11-3**. This intermediate contains the completed trisubstituted olefin and all the remaining carbon atoms needed to complete the synthesis. Application of the Eschenmoser-Tanabe cleavage (*46*) of the epoxy ketone **11-4** reveals acetylene and carboxaldehyde functions; the requisite three methylenes separating these groups were predetermined by the ring size of the cyclic ketone. Straightforward reactions then complete the synthesis.

While different in detail, a related method was presented by Kossanyi, Furth, and Morizur (*47*). A homoallylic bromide unit containing the trisubstituted olefin (**11-7**) was synthesized by means of a rearrangement reaction described by Julia *et al.* (*48, 49*) and then used to prepare the unsaturated cyclopentanone **11-8**. When irradiated in benzene, this ketone underwent a photochemical Norrish type 1 cleavage. This generated the olefinic aldehyde **11-9** (as a mixture of *cis* and *trans* isomers), which then needed to be homologated [compare grandisol synthesis by Hobbs

and Magnus (*35*) (Fig. 8)] in order to complete the synthesis.

It is unfortunate that this homologation cannot be avoided simply by using the related substituted cyclohexanone **11-10**; this compound undergoes predominately a photochemical Norrish type 2 cleavage, which gives side chain scission (**11-11** and **11-12**), and forms a cyclobutanol (**11-13**).



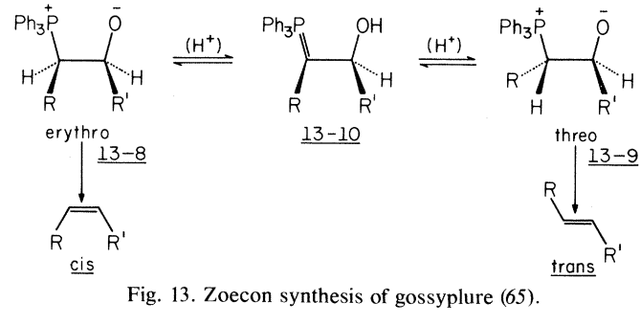


Fig. 13. Zoecon synthesis of gossyplure (*65*).

Propylure Syntheses Based on Sulfur and Boron

Two other recent syntheses of propylure illustrate the use of modern reagents which contain hetero atoms (in these cases sulfur and boron). These reagents are used to achieve a particular reactivity or charge stability that assists in key reactions that form carbon-carbon bonds; the hetero atoms are subsequently removed. Oshima and co-workers (*50*) describe the use of lithiated allyl vinyl sulfide (**12-1**). This reagent can be alkylated selectively in the α-position to give **12-3** which subsequently undergoes a [3,3] rearrangement (Fig. 12). Removal of sulfur reveals that the five carbons in the reagent **12-1** have added to the original chain (**12-2**) as a synthetic equivalent or "synthon" (*51*) for the δ-metalated γ,δ-unsaturated aldehyde (**12-6**). Stereoselectronic factors in the transition state of [3,3] rearrangements (*52*) ensure that the disubstituted double bond in **12-5** is formed *trans* with very high stereoselectivity. This product can then be elaborated to propylure by simple steps.

Vig *et al.* (*53*) reported a closely related synthesis of propylure in which an allyl vinyl ether, similar in structure to the thioether **12-3**, was rearranged stereospecifically, and Cookson and Hughes (*54*) described yet another approach based on Claisen and Cope rearrangements.

A propylure synthesis by Utimoto and co-workers (*55*) utilizes two boron to carbon transfer reactions to construct the trisubstituted olefin unit and illustrates the great potential for organoboranes in natural products synthesis (*56*). A borate complex (**12-9**) formed between tripropylborane (**12-7**) and a trimethylsilyl-protected acetylide (**12-8**) is induced to transfer a propyl group to the triple bond by the action of an electrophile (acetylenic tosylate **12-10**). In **12-11** a second propyl group is transferred and the boron is eliminated by the action of iodine and base. Removal of the trimethylsilyl group, by a second iodine exposure, followed by other standard steps, completes this synthesis.

The two organoborane transfer steps have precedent (*57*), but thus far such reactions have not enjoyed wide use in natural products synthesis. Such elegant illustrations will certainly help to rectify this situation.

Reinvestigation of the Pink Bollworm Moth Pheromone: Gossyplure

These numerous syntheses of propylure evolved in parallel with the conceptual and methodological advances of synthetic organic chemistry. It is a testament to the appeal of this molecule that they were forthcoming, despite the lingering controversy concerning the biological activity of propylure and its identity as the true pheromone of the pink bollworm moth (*39–41*).

In 1973, Hummel and co-workers (*58, 59*) reported the results of a reinvestigation of the attractive components from the pink bollworm moth. They were unable to detect propylure or Deet (*41*) in insect extracts and found instead that the attractive material, active both in laboratory and field bioassay, was a 1:1 mixture of 7,11-*cis,cis*- and *cis,trans*-hexadecadienyl acetates **9-3** and **9-4**. To this mixture they gave the common name "gossyplure." Both of the 7-*trans*-hexadecadienyl acetate isomers were not only inactive, but as little as 10 percent contamination with these markedly reduced the attractiveness of the mixture of **9-3** and **9-4**. The 1:1 ratio of 7-*cis* isomers was also essential for full attractiveness (*60, 61*).

While structurally less interesting, such linear dienyl acetates are more closely related to pheromones identified from other lepidoptera (*9, 61*). In fact, in an empirical screen of synthetic compounds, the USDA workers (*62, 63*) had found that 7-*cis*-hexadecenyl acetate (a close structural analog to gossyplure, termed "hexalure" **9-5**) was attractive to male pink bollworm moths in the field.

Gossyplure Syntheses

A number of syntheses of gossyplure have appeared. Most of them involve the separate preparation of the 7,11-*cis,cis*- and 7,11-*cis,trans*-hexadecadienyl acetate isomers by a suitable sequence of triple bond reduction by dissolving metals, catalytic hydrogenation over deactivated palladium (Lindlar) catalysts, or Wittig olefination reactions (*59, 64*). The pheromone is then constituted by mixing the separately synthesized isomers to a 1:1 ratio. A more unusual approach

was taken by the Zoecon group (*65*) where a method was sought for simultaneous preparation of the two isomers in precisely a 1:1 ratio. Their route proceeds as follows.

As both of the pheromone components have the 7-*cis* geometry, the stereochemistry at this position was established early and unambiguously (Fig. 13). Starting with *cis,cis*-1,5-cyclooctadiene (**13-1**), selective epoxidation with a molybdenum catalyst and further air oxidation and unsymmetrical cleavage by lead tetraacetate furnished the olefinic ester carboxaldehyde **13-4**. This intermediate embodies a *cis*-olefin destined to become the C-7 unsaturation, an aldehyde that is situated appropriately for elaboration of the other olefin unit, and an ester (suitably differentiated from the aldehyde to permit the selective chain extension required to complete the reaction). Anderson and Henrick made a study of the factors influencing the stereochemistry of the Wittig reaction (*65*). Normally, the ylide **13-5** would add to the aldehyde **13-4** to give predominately an erythro adduct (see structures **13-8** to **13-10**), which would then undergo elimination of triphenylphosphine oxide to give the *cis* olefin. They found that by adding ethanol after adduct formation, they could catalyze equilibration between the *erythro* (**13-8**; yields *cis* olefin) and *threo* adducts (**13-9**; yields *trans* olefin) through an alkoxy ylide intermediate (**13-10**). By suitable adjustment of time and temperature, they were able to reproducibly form a 1:1 mixture of the *cis,cis* and *cis,trans* isomers (**13-6** and **13-7**). Subsequent trishomologation of the iodide derived from the diene esters gave the isomeric acetates that comprise gossyplure.

The syntheses of the pheromones described in this article illustrate a progressive evolution of synthetic methodology that involves both the development of new conceptual insights in synthetic strategies and the discovery and exploitation of new reactions and reagents. They are a testament to the vitality of the field of synthetic organic chemistry.

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