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THE SYNTHESIS OF INSECT SEX PHERMONES†

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INTRODUCTION

During the past 10 years there has been a rapidly expanding interest in the chemical identification and synthesis of insect pheromones,[1-4] at least partially in an effort to provide alternatives to the use of insecticides for the control of insect populations. The identification of a phermone and the development of a practical chemical synthesis allow the necessary biological research to be carried out to determine whether or not the compounds can be used to interfere with the normal behavior of the insect species and to aid in successful pest control. Although no pheromone has to date been fully registered for use in crop protection,‡ progress has been made in the application of several pheromones in pest control programs and some experimental use permits have been granted by the U.S. Environmental Protection Agency. Survey and monitoring traps incorporating synthetic sex pheromones have been widely used for measuring the presence and abundance of pest populations and are commercially available. Many different experiments aimed at insect control have also been carried out with varying success using mass trapping, host baiting, and communication disruption techniques.[5-9]

This review is concerned with the synthesis of selected insect sex pheromones (see Refs. 10–13) and includes much of our own unpublished work. The choice of compounds discussed is based principally on the types of pheromones of potential practical use in agriculture with the inclusion also of a few chemically interesting structures of little economic importance. The compounds discussed have been grouped by chemical type within the

†Contribution No. 55 from the Research Laboratory of Zoecon Corporation.

‡However, (*Z*)-9-tricosene is used by Zoecon Corporation to increase the effectiveness of a fly bait containing insecticides. This is the first commercial U.S. EPA registered product using a sex pheromone for insect control purposes.

orders covered. This review is designed to be informative and critical and is not intended to be comprehensive. Experimental details have been emphasized in an effort to make this report helpful to research workers with varying degrees of expertise in this field.

I. LEPIDOPTERA

The majority of the pheromones discussed in this review are produced by moth species belonging to the order Lepidoptera (moths and butterflies). Most of the identified sex pheromones from moth species are unsaturated straight-chain aliphatic alcohols, acetates, or aldehydes.[1-4] Reproductive isolation of the various species is effected by many factors and chemical specificity of the pheromone is one important factor for reducing cross-attractancy. In the family Tortricidae, for example, structural variation is exhibited through changes in the functional moiety (acetate, alcohol, or aldehyde), the double-bond position, the configuration (*Z* or *E*) or number of double bonds, or the carbon-chain length.[14] Many insect species also use more than one attractant chemical as an aid to reproductive isolation.[14,15] The sex pheromone often consists of a particular blend of a number of components, some species using various mixtures of *Z* and *E* isomers, some utilizing acetate-alcohol or acetate-aldehyde mixtures, and some using mixtures of positional isomers. The different rates of release of a pheromone into the air stream by different species also have an impact on the effectiveness.

For many lepidopterous pheromones a precise mixture of the *Z* and *E* isomers of the double bond(s) is necessary if the synthetic material is to be an effective attractant in the field. For example, the main component of the sex pheromone for the oriental fruit moth, *Grapholitha molesta*, is (*Z*)-8-dodecen-1-yl acetate but optimum attraction of the males in the field requires the presence of about 7% of the (8*E*)-isomer (although this isomer has not yet been characterized from the female).[16] The pure *Z* isomer is *not* effective as an attractant for males in the field. For the male lesser appleworm moth, *Grapholitha prunivora*, attractancy to (*Z*)-8-dodecen-1-yl acetate is best when *ca.* 2.2% of the *E* isomer is present although this species is attracted by the pure *Z* isomer.[16] Similarly, (*Z*)-11-tetradecen-1-yl acetate is the principal component of the sex pheromone of the European corn borer, the Iowa Strain, *Ostrinia nubilalis*, and of the redbanded leafroller, *Argyrotaenia velutinana*, but the geometrically pure (*Z*)-isomer is only weakly attractive to males of these species. The presence of about 3% and 6–8%, respectively, of the (11*E*)-isomer is necessary for optimum attraction (although neither species is attracted to the pure *E* isomer alone).[17,18] The pheromone isolated from female redbanded leafrollers was found subsequently to contain *ca.* 9% of the (11*E*)-isomer.[18] In contrast, field tests with (*E*)-9-dodecen-1-yl acetate, the sex pheromone of the European pine shoot moth, *Rhyacionia buoliana*, have shown that the addition of as little as 2% of the *Z* isomer to a biologically active sample of the synthetic *E* isomer (already containing 1.1% of the *Z* isomer) almost completely inhibits the attraction of males.[19]

The purity of the synthetic pheromones is generally of critical importance. The problem of inhibitors requires that synthetic methods be devised that give materials of very high chemical purity and of known stereochemical composition. The synthetic sex pheromone must not be contaminated with inhibitor chemicals which can cause a decrease in the response of males to the attractant.[7,14] The frequent finding that the synthetic pheromone which is the most attractive in field trials is not isomerically pure but a mixture of geometrical isomers in a specific proportion makes it essential that the stereochemical purity of the synthetic compounds be accurately known. Synthetic products have generally been analyzed by IR spectrometry or by gas liquid chromatography (glc) (e.g. Refs. 16–18, 20). Small quantities of pure isomers have been obtained by preparative glc (e.g. Ref. 17) or by thin layer chromatography (tlc) on silver nitrate-impregnated silica gel (e.g. Ref. 18). High-performance liquid chromatographic (hplc) methods have recently been developed for both the analysis and the separation of olefinic isomers.[21] This technique often allows the isolation of sufficient amounts of the geometrically pure isomers for bioassay in the field. Crystallization of synthetic intermediates (and sometimes of the pheromone itself) at low temperature has often been a valuable aid in the preparation of pure isomers.

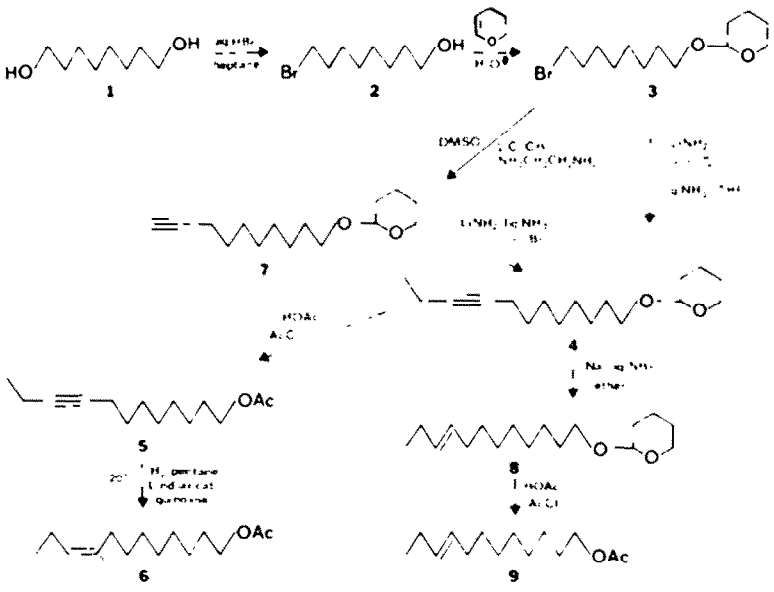
The structures of many of these lepidopterous sex pheromones are deceptively simple but their efficient synthesis in high stereochemical purity has offered considerable synthetic challenge.

(1) *Aliphatic monoene alcohols and acetates*

(a) *Acetylenic routes.* e.g. *(Z)-9-Dodecen-1-yl acetate.* The main component of the sex pheromone produced by the female grape berry moth, *Paralobesia viteana*, has been shown to be (*Z*)-9-dodecen-yl acetate (**6**).[22] As an example of a general route often used to prepare this type of attractant, the synthesis of this compound is outlined in Scheme 1.[23] These experimental conditions are typical of what has been used in the literature. Variations and recent improvements are discussed subsequently. Thus, 1,8-octanediol (**1**) was heated with 42% hydrobromic acid at 90°, under conditions of continuous extraction with hot heptane to give 8-bromo-1-octanol (**2**) in 90% yield. Purification of **2** was readily accomplished on a laboratory scale by column chromatography on Florisil or silica gel. The tetrahydropyranyl ether **3** was prepared in 80% yield (after distillation† *in vacuo* in the presence of a trace of K_2CO_3) using dihydropyran and a trace of conc hydrochloric acid‡ as the catalyst at 0–10°. The alkylation step was carried out by forming the lithium salt of 1-butyne with excess lithium amide in dry liquid ammonia with tetrahydrofuran (THF) added as a co-solvent, adding the bromide in THF, and stirring the mixture for 5 hr at −30° under reflux. This procedure gave **4** in 85% yield which was then converted directly to the acetate **5** with acetyl chloride and glacial acetic acid (2 hr under reflux) in 85% yield (distilled). Partial hydrogenation of the triple bond in **5** over Lindlar catalyst in pentane at room temperature with synthetic quinoline added, gave **6** in 92% isolated yield. After column chromatography (on silica gel) the pheromone **6** was obtained in a purity (as the *Z* isomer) of 97% by glc analysis in an overall yield of 48% from **1**. The material was also shown to contain 2.5% of the *E* isomer **9**. Optimum field activity for attracting male grape berry

†Distillation of the halo-ether is usually unnecessary but if it is carried out it should be done at as low a temperature as possible.

‡In many cases conc sulfuric acid is a better catalyst for this reaction and gives higher yields of the tetrahydropyranyl ether.



Scheme 1.

moths is obtained with the *Z* isomer **6** containing 4% of the *E* isomer **9**.[24]

There are many variations in this type of synthetic route. The heptane (or toluene, etc.) continuous extraction method for the conversion of a polymethylene glycol to a ω-halo-1-alkanol generally gives a good yield of product (especially for bromo alcohols) contaminated by only a few percent of the starting diol and of the dihalide.[23,25,26] On a large scale the crude product can be purified by first cooling an ether solution and collecting the crystalline diol by filtration and then treating the filtrate (after removal of the ether) with triethyl borate, and stripping off the ethanol-triethyl borate azeotrope. The dihalide is then distilled off *in vacuo* and the residue treated with methanol (or with NaOH-brine) to regenerate the halo-alcohol.[27] An alternative large-scale purification procedure involves partitioning the crude bromo alcohol between hexane and aqueous methanol.[28] Reaction of the glycol (e.g. **1**) with 1.2 equiv. of PBr_3 in benzene gives a mixture of dibromide:diol:bromo alcohol in the ratio of *ca.* 10:40:50 and the bromo alcohol can be separated (in *ca.* 35% overall yield) from this mixture by column chromatography (Florisil) or by the triethyl borate procedure described above.[27] 5-Halo-1-pentanols can also be prepared in high yield by the opening of tetrahydropyran with acetyl chloride (or acetyl bromide) and a zinc chloride catalyst, followed by hydrolysis of the intermediate halo acetates.[29]

The alkylation of an 1-alkyn-1-ide ion with a primary alkyl halide such as **3** can be carried out under a wide variety of conditions (e.g. Refs. 30 and 31). To overcome the low solubility of higher alkyl halides and of metal 1-alkyn-1-ides (especially the sodium salts) in liquid ammonia, other solvents have been investigated both alone and as co-solvents with liquid ammonia. The use of lithium salts of 1-alkynes in liquid ammonia with THF as the co-solvent gives good yields with alkyl bromides when efficient stirring is used.[31] Excess lithium amide is often used as the base and although commercial lithium amide can be used, freshly prepared material is preferable. Alkyl chlorides generally give low yields under these conditions. Dipolar aprotic solvents such as dimethylformamide,[32] dimethyl sulfoxide,[30,33] and hexamethylphosphoric triamide (HMPT)[26,32c,33b,34-36] have been used successfully. For example, dimethylformamide has been used as a solvent alone,[32] or mixed with xylene,[32c] or THF.[34a] Rutledge investigated briefly the alkylation of sodium acetylide in HMPT but preferred the use of dimethylformamide-xylene mixtures.[32c] Later, Normant suggested the use of HMPT or of HMPT-THF mixtures for the alkylation of sodium 1-alkynides.[34] The preferred method for general laboratory synthesis with alkyl chlorides or bromides appears to be the alkylation of lithium 1-alkyn-1-ides in HMPT-tetrahydrofuran (or HMPT alone).[26,35,36] The reaction is rapid at 0–25° (the temperature should be kept below 25° in general) and the yields are usually high. The lithium alkynides can be generated in THF at 0° with 1.6 M *n*-butyllithium in hexane[26,35,36] or less readily with lithium amide in THF (at 65°).[36] For large scale laboratory runs the use of 90% by weight *n*-butyllithium in hydrocarbon, available from Ventron Corp, has the advantages of keeping the reaction volume small and increasing the yield of the alkylation product.[37] The alkylation of sodium salts of 1-alkynes under these HMPT–THF conditions is less satisfactory as some dehydrobromination of alkyl bromides such as **3** often occurs.[31] Many of the acetylenic *alcohols* obtained in these types of syntheses (after removal of the protecting group) can be purified by crystallization from pentane at low temperatures (e.g. 11-tetradecyn-1-ol, m.p. 25–6°).

The use of dimethyl sulfoxide as the reaction solvent is best restricted to alkylations utilizing the commercially available lithium acetylide-ethylenediamine complex,[38] (or to when it is a co-solvent with liquid ammonia for the alkylation of sodium acetylide[30]), since the alkylation of higher lithium (or sodium) alkynides in dimethyl sulfoxide often gives low yields.[33,39] The metalation of the dimethyl sulfoxide is a competing reaction and it appears that the equilibrium favors the methyl sulfinylmethide (dimsyl) anion over the sodium or lithium alkynide for all alkynes higher than acetylene itself.[39] Even with the use of the lithium acetylide-ethylenediamine complex the yields can vary greatly with the concentration of the

reactants[23,38b] and with the order of addition of the reactants.† Many of the aliphatic monoene acetate pheromones have been synthesized via a variation in Scheme 1 in which the bromide 3 is treated with the lithium acetylide-ethylenediamine complex to give 7 and further alkylation of the 1-alkyne anion with an alkyl halide then gives 4 (e.g. Ref. 38*c*). Dioxane has also been used as a solvent at temperatures of 100–150° for the alkylation of higher lithium alkynides which are soluble in hot dioxane.[31,38c,40]

The hydroxy group of a ω-hydroxy-1-alkyne can be effectively protected against alkylation by conversion to the corresponding lithium alkoxide. Selective carbon alkylation of the dilithium compound with one equiv. of an alkyl halide can be readily achieved.[30,41] Unprotected ω-bromo-1-alkanols can also be used to alkylate lithium alkynides in the presence of an extra equivalent of a lithium reagent (either lithium amide or an excess of the lithium alkynide) to generate the lithium alkoxide.[26,41a] Similarly, ω-haloalkanoic acids may be utilized to alkylate lithium alkynides[35b,41c,42] or even sodium alkynides[31b,42] without additional protection of the carboxyl group, and the dilithium salt of ω-acetylenic acids can also be alkylated selectively on carbon with alkyl halides.[35b]

In these alkylations one should be aware that 1-alkynes can be isomerized to 2-alkynes with excess lithium acetylide in HMPT or in HMPT-tetrahydrofuran at room temperature.[33b,43] Prolonged heating of 1-alkynes in homogeneous solution with sodium amide in dimethyl sulfoxide also is reported to give 2-alkynes.[44a]‡ One should also keep in mind that polymetalation of terminal and internal acetylenes can occur with n-butyllithium in ether or hexane at room temperature,[45] although this side reaction does not appear to be a problem with one equiv. of *n*-butyllithium at temperatures below 10° (the reaction temperature should preferably be kept below 0° during the formation of 1-alkyn-1-ides with *n*-butyllithium).

The partial selective catalytic hydrogenation of alkynes such as 5 over Lindlar catalyst [Pd–$CaCO_3$–$Pb(OAc)_2$] in the presence of synthetic quinoline generally gives high yields of the corresponding *Z* olefin.[46] Non-polar solvents such as pentane or hexane are to be preferred, in general, over alcohols for these hydrogenations.[46a,b] When the reaction is carried out at room temperature the product usually contains 1.5–3.5% of the corresponding *E* isomer, and if the temperature is allowed to rise during the reaction (particularly in alcoholic solvents) the percentage of the *E* isomer increases (usually up to 5–10%).[20a,21,47] Gutmann and Lindlar recommended[46a] that the selective hydrogenation of triple bonds to *Z* double bonds be carried out at relatively low temperatures (10–20°), and ice-bath temperature has also been used.[48] It is generally thought that stereomutation of the *Z* olefin under the hydrogenation conditions over palladium catalysts, in general, occurs only in the presence of hydrogen and is not a problem until the acetylenic compound is completely hydrogenated, and that the formation of the *E* isomer occurs only via isomerization of the *Z* isomer.[46c,49] We have found that if the partial hydrogenation of alkynes such as 5 is carried out over Lindlar catalyst[50] (poisoned by synthetic quinoline) *at lower temperatures* (−10 to −30°) in pentane, hexane, or hexane–THF, the *Z* olefin obtained *contains* ≤0.5% *of the* E *isomer.*[51] Analysis of an aliquot removed during one such hydrogenation indicates that the small amount of the *E* isomer produced is formed throughout the reaction and not only after the disappearance of all of the acetylene[51] (see Ref. 46*c*, 49).§ Other catalysts such as palladium-on-barium sulfate (poisoned by synthetic quinoline),[26,52] "P-2 nickel" (with ethylenediamine),[53] and other nickel catalysts[46c] have been employed successfully in place of the Lindlar catalyst for the selective hydrogenation of triple bonds to *Z* double bonds.

As an alternative method to the selective hydrogenation, an alkyne such as 4 or 5 may be hydroborated with a sterically hindered reagent (e.g. disiamylborane), and protonolysis of the vinylboron intermediate with a carboxylic acid then gives the corresponding *Z* alkene.[54,55] This method generally gives high yields of pure olefins (>98% *Z* isomer), but if disiamylborane is used in this reduction procedure it should be freshly prepared. Occasionally anomalous results have been obtained with the resulting olefin containing from 5–80% of the *E* isomer.[56,57]

The preparation of the corresponding pure *E* isomer (e.g. 9) is usually conveniently accomplished by the reduction of the alkyne (e.g. 4) with metallic sodium (or lithium) in liquid ammonia.[58] This reaction is preferably carried out by the addition of the alkyne in ether *to* a mixture of sodium in liquid ammonia. The alternative reverse addition procedure usually gives incomplete reduction of the triple bond.[59] An increase in the amount of liquid ammonia in relation to the starting alkyne is advisable for the reduction of high molecular weight alkynes (carbon chain longer than *ca.* 13 C atoms) to avoid incomplete reduction due to solublility problems.[60] The olefin product is usually very pure *E* isomer with little or no detectable *Z* isomer.[20a,47,60] For example, reduction of 0.1 mol of 2 - (11 - tetradecyn - 1 - yloxy)tetrahydropyran with 3 equiv. of metallic sodium in ether (150 ml) and liquid ammonia (500 ml) at −30° for 4 hr with efficient stirring gave (*E*)-2-(11-tetradecen-1-yloxy)tetrahydropyran in 87% yield with no detectable *Z* isomer.[61] During this reduction procedure the 1-ethynyl group of a non-conjugated diyne can be protected as the sodium salt by reaction with sodamide in liquid ammonia. Reduction of such a sodium salt with sodium reduces only the disubstituted triple bond with the formation, after hydrolysis, of the non-conjugated (*E*)-enyne.[62] (*E*)-Isomers can also be prepared in high yield by reduction of the corresponding alkynes with lithium aluminum hydride (LAH) in an ether solvent.[63] For example, reduction of 2-methyl-7-octadecyne in diglyme at 140° gave (*E*)-2-methyl-7-octadecene in *ca.* 92% yield containing no detectable *Z* isomer.[63b]

The synthesis by Holan and O'Keefe of (*Z*)-8-dodecen-1-yl acetate (13), a sex pheromone of the oriental fruit moths, *Cydia molesta* and *Grapholitha molesta*, is out-

†Addition of the dry complex to a solution of the alkyl bromide in dimethyl sulfoxide at 15° gave the best results in our hands[38d] (see Ref. 38*b*).

‡In contrast, multipositional isomerization of various internal alkynes to 1-alkynes has been achieved using potassium 3-aminopropylamide in 1,3-diaminopropane as the solvent. For example, 2- and 3-undecyn-1-ol are both converted to 10-undecyn-1-ol in high yield under these conditions.[44b]

§If only a very slow uptake of hydrogen occurs (or none at all) the Lindlar catalyst may be too strongly poisoned or else impurities in the substrate may have further deactivated the catalyst. Filtering the mixture and adding fresh catalyst to the filtrate often results in a satisfactory hydrogen uptake.

lined in Scheme 2 as an example of a modification of Scheme 1.[55] Alkylation of the lithium salt of 1-pentyne with 1-chloro-6-iodohexane gave the chloro alkyne **11** (see Ref. 64) which was converted to the carboxylic acid **12** via the corresponding nitrile. The intermediate acid allowed purification at this step by means of the acid salt. (*Z*)-7-Dodecen-1-yl acetate, a pheromone of the cabbage looper, *Trichoplusia ni* has been prepared by synthetic routes similar to Scheme 2,[65a] and also by modifications of Scheme 1.[65b,c] (*Z*)-7-Dodecen-1-ol is a potent inhibitor of this pheromone in the field and care must be taken to ensure that the synthetic acetate contains no residual alcohol.[66]

Leznoff and Fyles[67] have used an insoluble polymer as a support in the synthesis of *Z* monoene acetates by a route similar to that outlined in Scheme 1. The insoluble polymer phase (polymer-bound trityl chloride) is effective in monoblocking the starting symmetrical diol (see **1**). Cleavage with acid after the alkylation step gave the acetylenic alcohols (and polymer-bound trityl alcohol) which were converted to the *Z* acetates (see **6**) by hydrogenation and acetylation in the normal manner. The recovered polymer can be recycled and this polymer-support method has the potential, at least on a small scale, to be adapted to an automated procedure.

(b) *Wittig and special routes.* Several of the *Z* monoene acetates and related compounds have been synthesized by the Wittig reaction[68] between an aliphatic non-stabilized triphenylphosphonium ylide and the corresponding aliphatic aldehyde, either in a nonpolar solvent in the absence of lithium salts ("salt-free")[69] or in a dipolar aprotic solvent such as dimethylformamide,[70] dimethyl sulfoxide,[71] or hexamethylphosphoric triamide.[71,72] Under these conditions the Wittig condensation affords predominantly the *Z* monoenes usually containing *ca.* 6% of the corresponding *E* isomer. Bestmann *et al.*[69b] recently observed that when the phosphonium ylides were generated with sodium bis(trimethylsilyl)amide in tetrahydrofuran and the condensation was carried out at −78°, a *Z*:*E* ratio in the disubstituted olefin product of 98:2, respectively, was obtained. In many cases the preparation of the ω-oxygen-functionalized aldehyde or of the ω-functionalized phosphonium salt is lengthy or proceeds in low yield and the alternative acetylenic route is preferable (e.g. Ref. 26).

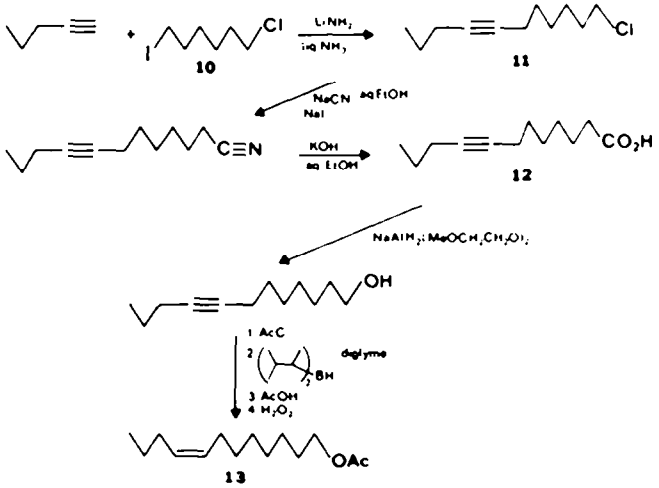
A number of alternative synthetic routes have been used for the synthesis of the *E* monoene acetates such as **9**. For example, (*E*)-7-dodecen-1-yl acetate was prepared utilizing the stereoselective procedure of Crombie and Harper[73] which involved the ring scission of 2-butyl-3-chlorotetrahydropyran with granulated sodium in ether to give (*E*)-4-nonen-1-ol followed by a somewhat lengthy chain extension via diethyl malonate and then carboxylation of a Grignard reagent.[65b] The *E* acetate prepared by this route was shown, by careful glc analysis, to contain 1.3% of the *Z* isomer.[20a] This method is therefore not as stereoselective as the previously discussed sodium-liquid ammonia reduction of a triple bond which affords entirely the *E* isomer.[20a]

A stereoselective general synthesis of *E* olefins was recently described whereby the lithio derivatives of γ-substituted allyl-phosphonates are alkylated exclusively at the α-position by a variety of alkyl halides. The allylic phosphonates are then reduced (with double bond migration and loss of the phosphonate group) by treatment with LAH in ether at 0° to give exclusively *E* olefins.[74] For example, alkylation of the lithio derivative of diethyl 2-butenylphosphonate (**15**) with the bromide **14** (at −60°) gave the phosphonate **16** which was reduced and the protecting group removed to give (*E*)-11-tetradecen-1-ol (**17**) in 73% yield (Scheme 3). This short stereoselective route should be useful on a laboratory scale.

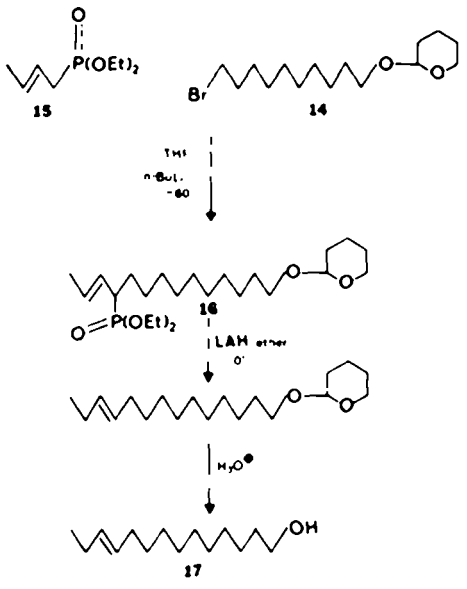
The [3,3]-sigmatropic rearrangement of allylic dithiocarbamates has also been developed as a method for the stereoselective synthesis of *E* alkenyl acetates (Scheme 4).[75] For example, alkylation of the lithio derivative of **18** at −55° with n-butyl iodide gave **19** which was rearranged by heating in chloroform under reflux to give **20** (96% yield from **18**) containing no detectable *Z* isomer. Further alkylation with **21** followed by reductive removal of the dimethyldithiocarbamate group with lithium in ethylamine at −60° and then acetylation gave (*E*)-7-dodecen-1-yl acetate (**22**) in high yield.[75] Even though the yields in this scheme are high the requirement of low reaction temperatures for three of the steps would limit its application on a large scale.

(2) *Monoene aldehydes*

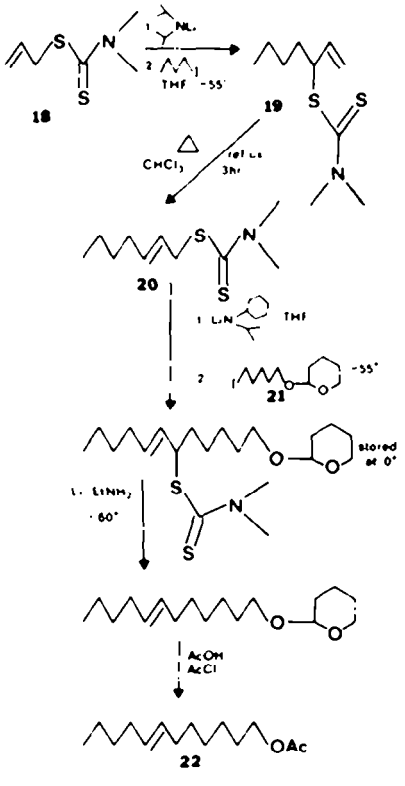
Both *E*[76] and *Z*[77,78] alken-1-als have been identified as sex pheromones of insects. Thus (*Z*)-9-tetradecen-1-al (**23**) and (*Z*)-11-hexadecen-1-al (**24**) are components (in



Scheme 2.



Scheme 3.

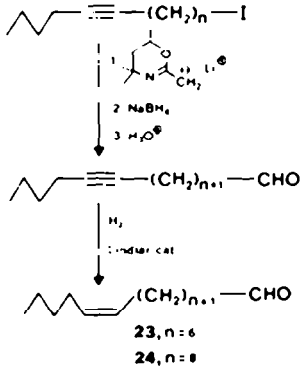


Scheme 4.

the ratio 1:16, respectively) of the sex pheromone of the tobacco budworm, *Heliothis virescens*,[77a,b] and (*Z*) - 11 - hexadecen - 1 - al, has been isolated from the corn earworm, *Heliothis zea*,[77a,c] but appears to be an inhibitor for this insect species in the field.[77c] In these investigations the aldehydes were synthesized by the oxidation of the corresponding primary alcohols with the chromium trioxide-pyridine complex in dichloromethane,[77a,c,78,79] or by alkylation of the lithium salt of 5,6 - dihydro - 2,4,4,6 - tetramethyl - 1,3 - (4H) - oxazine with an alkynyl halide followed by reduction with $NaBH_4$ and acid hydrolysis to the acetylenic aldehyde, and hydrogenation over Lindlar catalyst (Scheme 5),[77b,80] or by heating the primary alken-1-yl mesylate with dimethyl sulfoxide and $NaHCO_3$.[76,81]

However, for the preparation of several hundred gram quantities of pure aldehydes these methods are not very satisfactory. For example, the oxidation of a primary alcohol with the chromium trioxide-pyridine complex is limited in the scale on which it can be carried out by the low solubility of the complex (resulting in high solvent volumes), and by the requirement of a 6:1 mole ratio of complex to alcohol for rapid, complete conversion to aldehyde.[79] In attempts to overcome these difficulties several new methods have recently been developed for the oxidation of alcohols to aldehydes (and ketones), including the use of chromium trioxide and 3,5-dimethylpyrazole in CH_2Cl_2,[82] pyridinium chlorochromate in CH_2Cl_2,[83] chromyl chloride and pyridine in CH_2Cl_2 (plus added t-butyl alcohol),[84] dimethyl sulfide and N-chlorosuccinimide in toluene (followed by Et_3N),[85a] dimethyl sulfoxide-chlorine in CH_2Cl_2 (followed by Et_3N),[85b] chromium trioxide in HMPT,[86] and N-methyl-morpholine-N-oxide in acetone catalyzed by ruthenium compounds.[87]

For the large scale synthesis of (*Z*)-9-tetradecen-1-al (**23**) and (*Z*)-11-hexadecen-1-al (**24**) we have investigated the oxidation of the corresponding primarily alcohols by both a modified Collins procedure[88a] and the use of the dimethyl sulfide-*N*-chlorosuccinimide procedure.[88b] The use of the CrO_3-3,5-dimethylpyrazole method[82] was unsatisfactory and gave a poor yield of aldehyde.[88c] The modified Collins procedure involved the portionwise addition of the reagent. Thus, one equiv. of (*Z*)-11-hexadecen-1-ol (containing 0.4% of the *E* isomer) was added to 3.5 equiv. of the dipyridyl-CrO_3 complex in CH_2Cl_2 containing a 10% excess of pyridine. After 10 minutes at 20° the reaction ceased at 50–60% completion and on cooling to 10°, a further 5.5 equiv. of pyridine and 2.5 equiv. of CrO_3 were added with stirring. After an additional 0.5 to 1 hr at room temperature the reaction was complete and was worked up. This procedure was carried out routinely on a 1 mole scale and enabled the use of about 50–70% of the normal volume of CH_2Cl_2. After filtration in pentane through a short column of Florisil and distillation at 0.1 mm yields of *ca.* 75% of **24** were obtained.† Recrystallization from pentane at −70° gave



Scheme 5.

†The pot residue was mainly the C-32 ester derived from two alcohol residues; this ester was also obtained with the usual Collins procedure.

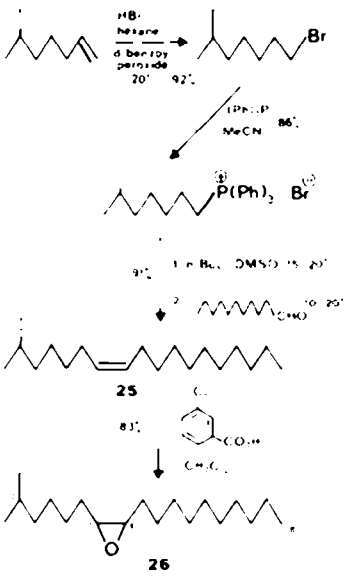
(*Z*)-11-hexadecen-1-al (**24**) of ≥98.5% purity (containing 0.4% of the *E* isomer).[88a] The method of Corey and Kim[85a] was found to be even more satisfactory for large laboratory scale oxidations.[88b] For example, addition of 0.6 mol of (*Z*)-9-tetradecen-1-ol to 0.9 mol of *N*-chlorosuccinimide-dimethyl sulfide complex at −30° in toluene followed, after 1.5 hr, by treatment with triethylamine (initially at −65° then at −5°) gave after workup and filtration in hexane through a short column of Florisil, the aldehyde containing about 8% of (*Z*)-9-tetradecen-1-yl methylthiomethyl ether as the only major impurity.[85a] Repeated recrystallization from pentane at −75° gave the aldehyde **23** in 80% yield, (99.5% purity with 0.2% *E* isomer; isomer ratio was determined by careful glc analysis of 9,10-epoxytetradecan-1-ol, derived by LAH reduction and epoxidation).[88b,†]

(3) *Epoxide*

cis - 7,8 - Epoxy - 2 - *methyloctadecane*. The gypsy moth, *Porthetria*(*Lymantria*) *dispar*, is a serious pest of forest, shade, and orchard trees in Europe and in the northeastern parts of the United States of America. The principal sex pheromone emitted by the female of this species has been shown to be *cis* - 7,8 - epoxy - 2 - methyloctadecane (disparlure, Disparmone[R] attractant; **26**).[90] Experiments with both enantiomers indicate that the *cis*-(+)-isomer [(7*R*,8*S*)-(+)-disparlure] is the natural sex pheromone with the *cis*-(−)-isomer showing only weak or no activity and both enantiomers of *trans*-disparlure showing essentially no activity.

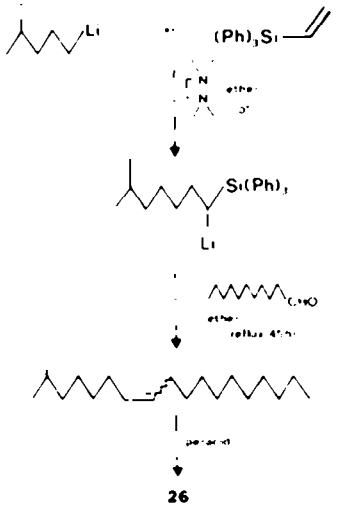
These results imply that the male gypsy moths have a chiral receptor system in their olfactory organ.[91] Racemic *cis*-disparlure attracts male moths, although the activity is somewhat lower than that shown by the *cis*-(+)-isomer alone.[91b,c] The racemic disparlure has been used extensively in traps for monitoring populations and in field tests aimed at the control of the gypsy moth,[9,92] and this pheromone has been synthesized by a number of routes. The intermediate olefin, (*Z*)-2-*methyl*-7-octadecene (**25**), which has been isolated from the female gypsy moth, is reported to inhibit male attraction to the pheromone **26**,[91] and hence care must be taken to ensure that synthetic samples of the epoxide for use in trapping studies, contain <0.5% of this olefin. No reduction in activity of the racemic *cis* isomer was observed when the *trans*-isomer was added,[90] and hence removal of the *trans*-isomer for synthetic preparations does not appear to be critical.

Bierl *et al.*[90] synthesized the pheromone by a Wittig reaction route according to Scheme 6, with an overall yield of 60%. Anti-Markownikoff addition of hydrogen bromide to 6-methyl-1-heptene gave 1-bromo-6-methylheptane which was converted to the corresponding triphenylphosphonium salt. Wittig condensation with 1-undecanal using n-butyllithium in dimethyl sulfoxide gave the olefin **25** as a mixture of *ca.* 88% of the *Z* isomer and 12% of the *E* isomer. Epoxidation with *m*-chloroperbenzoic acid followed by column chromatography of the product on silica gel-silver nitrate gave the pure *cis*- and *trans*-isomers of the pheromone. Bestmann and Vostrowsky[94a] carried out this same Wittig reaction in HMPT as the solvent (using a solution of



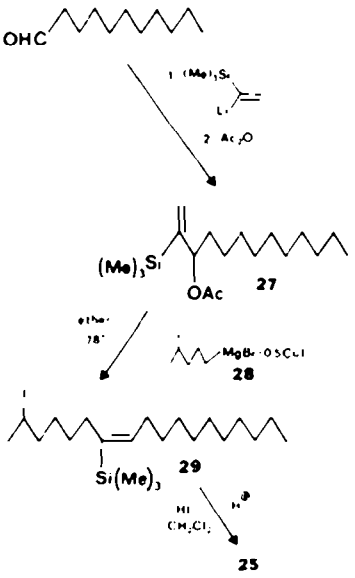
Scheme 6.

potassium in HMPT as the base) and obtained **25** as a mixture of 94% of the *Z* isomer and 6% of the *E* isomer. More recently, Bestmann *et al.*[94b] generated this ylide with sodium bis(trimethylsilyl)amide in THF and carried out the Wittig condensation at −78°. Under these conditions a 75% yield of **25** was obtained containing ≤2% of the *E* isomer. A 1:1 mixture of the *cis*- and *trans*-isomers of **26** has also been prepared by condensation of 1-undecanal with 1-triphenylsilyl-6-methyl-heptyllithium (Scheme 7) followed by epoxidation.[95] This mixture was biologically active in the field for the trapping of male gypsy moths. The *Z* olefin **25** has recently been prepared in 65% overall yield from 1-undecanal via a stereoselective route utilizing an organosilane intermediate (Scheme 8).[96] Reaction of 1-undecanal with α-trimethylsilylvinyllithium at −78° followed by acetylation gave **27** in 80% yield. The reaction of **27** with the organocopper-magnesium complex **28** at 78° proceeded with allylic rearrangement to give the vinylsilane **29**, which was protodesilylated with acid to the *Z*-alkene **25** (*Z*:*E* = 87:13).

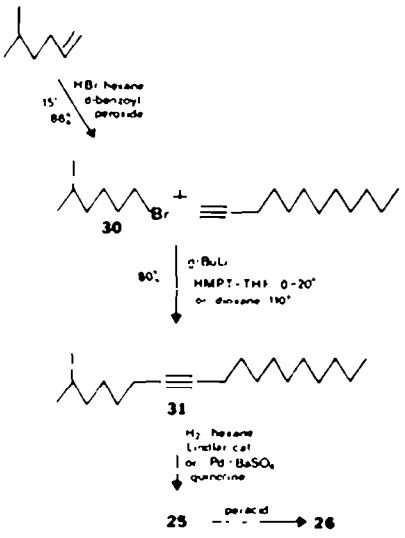


Scheme 7.

†Sulfur by-products in the crude aldehyde were shown to catalyze isomerization of the double bond. Thus, a sample of the crude product after being held at 105° for 4 hr contained 15% of the *E* isomer (see Ref. 89).[88b]



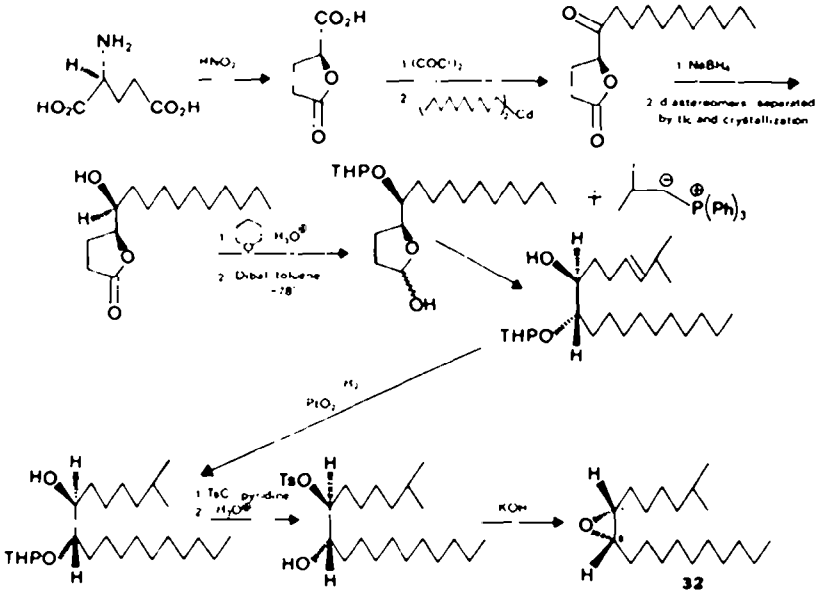
Scheme 8.



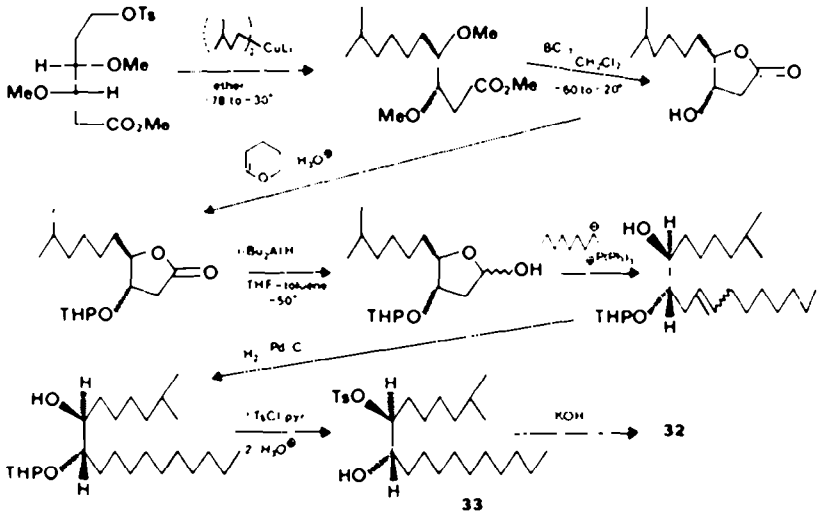
Scheme 9.

The pheromone **26** has also been synthesized via 2-methyl-7-octadecyne (**31**).[97,98] For example,[97] alkylation of sodium acetylide in dimethylformamide with n-decyl bromide gave 1-dodecyne in 80% yield. Anti-Markownikoff addition of anhydrous hydrogen bromide to 5-methyl-1-hexene gave 1-bromo-5-methylhexane (**30**), which was purified (to >99% purity) by spinning-band distillation and used to alkylate the lithium salt of 1-dodecyne in dioxane at 110° under pressure, giving a 60% yield of pure **31**. Partial hydrogenation in pentane over Lindlar catalyst (poisoned with quinoline) then gave the *Z* olefin **25** (containing 2.1% of the *E* isomer) which was treated with peracid to give the *cis*-epoxide **26** (Scheme 9).

Similar routes to **31** were also developed by Eiter,[98a] Shamshurin *et al.*[98b] Kovalev *et al.*[98c] and Sheads and Beroza.[98d] The last authors utilized improved reaction conditions in the alkylation step. Thus the lithium salt of 1-dodecyne was treated with the bromide **30** in HMPT-THF at 0° (see Ref. 98*c*) to give a higher yield (80%) of the acetylene **31** (Scheme 9). Hydrogenation of **31** in hexane over 5% palladium on barium sulfate poisoned with quinoline at room temperature gave **25** as a mixture of *ca.* 96% *Z* and 4% *E* isomers.[98d] The olefin, 2-methyl-7-octadecene has also been prepared, as a mixture of *Z* and *E* isomers, in low yield by a transition metal-catalyzed olefin cross-metathesis reaction between 1-dodecene and 7-methyl-1-octene.[99a] Pilot plant scale quantities of disparlure have been prepared by both Wittig and acetylenic routes (see Schemes 6 and 9).[100] The elegant synthesis of *cis*-(+)-disparlure (**32**) by Iwaki *et al.*, was carried out as outlined in Scheme 10[91a] starting from (*S*)-(+)-glutamic acid. The *cis*-(+)-isomer, obtained in <5% overall yield, was contaminated with *ca.* 6% of its (−)-enantiomer, and the *cis*-(−)-isomer, prepared by a modification of Scheme 10 was contaminated



Scheme 10.

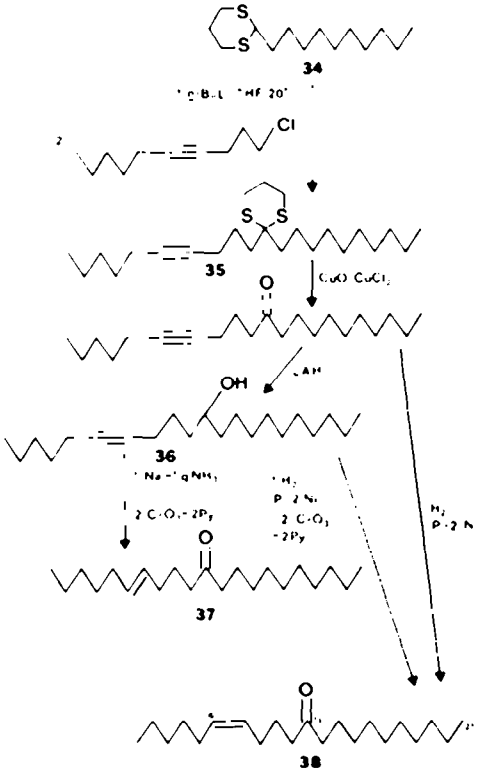


Scheme 11.

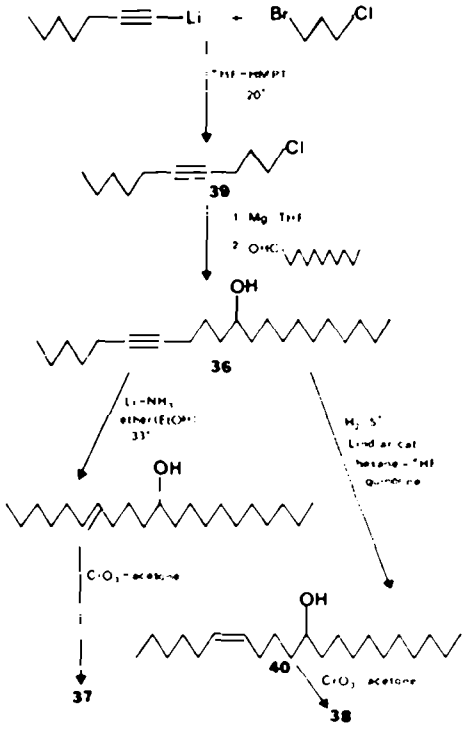
with 6% of its (+)-enantiomer. More recently, Mori *et al.*[91b] prepared the pure disparlure enantiomers in higher optical purity (>98%) starting from L-(+)-tartaric acid. For example, (7*R*,8*S*)-(+)-disparlure (**32**) was prepared as outlined in Scheme 11. The crystalline nature of the tosyloxyalcohol **33** enabled its ready purification.

(4) *Ketone*

(*Z*)-6-*Heneicosen*-11-*one*. The principal component of the sex pheromone (produced by the female) of the Douglas-fir tussock moth, *Orgyia pseudotsugata*, a severe defoliator of firs in western North America, has been identified as (*Z*)-6-heneicosen-11-one (**38**).[101] This structural type is unusual for a lepidopterous sex pheromone. The *Z* and *E* isomers of this pheromone have been synthesized by the routes outlined in Scheme 12[101] and Scheme 13,[102] and surprisingly both isomers attract male moths in laboratory bioassays and in field trials although the natural *Z* isomer is considerably more attractive than is the *E* isomer in laboratory bioassays.[101] In Scheme 12 the anion, generated from 2-n-decyl-1,3-dithiane (**34**) with n-butyllithium was alkylated with 1-chloro-4-decyne to give **35**. Hydrolysis of the dithiane with cupric chloride and cupric oxide followed by reduc-



Scheme 12.



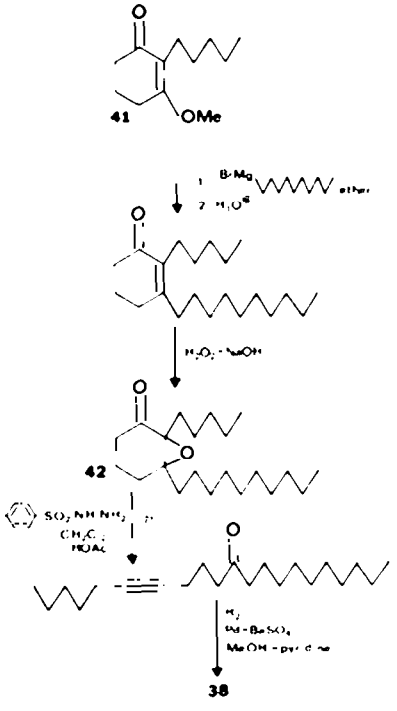
Scheme 13.

tion with LAH gave 6-heneicosyn-11-ol (**36**). Reduction of the triple bond with sodium in liquid ammonia and oxidation of the alcolol group gave the *E* isomer **37**. Catalytic hydrogenation of **36** over P-2 nickel catalyst poisoned with ethylenediamine[51] and oxidation of the alcohol group gave the pheromone **38** which was shown to be >97% pure by careful glc analysis of the derived epoxide.[101] In Scheme 13 the same alcohol **36** was prepared by reaction of the Grignard reagent prepared from **39**, with 1-undecanal. The intermediate hydroxyacetylene **36** and the *Z* hydroxy olefin **40** were both purified by crystallization from pentane at −35°. The pheromone **38** prepared by this scheme was shown to be 96% pure (as the *Z* isomer) and to contain *ca.* 2% of the *E* isomer (by glc analysis of the derived epoxide).[102] A further synthesis of the *Z* isomer **38** has been recently reported (Scheme 14).[103] The 21 C chain with the required 1,5-relationship between the ketone and acetylene functions was introduced in one step by a fragmentation reaction. Thus, Eschenmoser cleavage[104] of the α,β-epoxy ketone **42** with *p*-toluene-sulfonylhydrazine gave 6-heneicosyn-11-one in 71% yield. Partial hydrogenation then gave the pheromone **38** in 60% overall yield from the enol ether **41**.

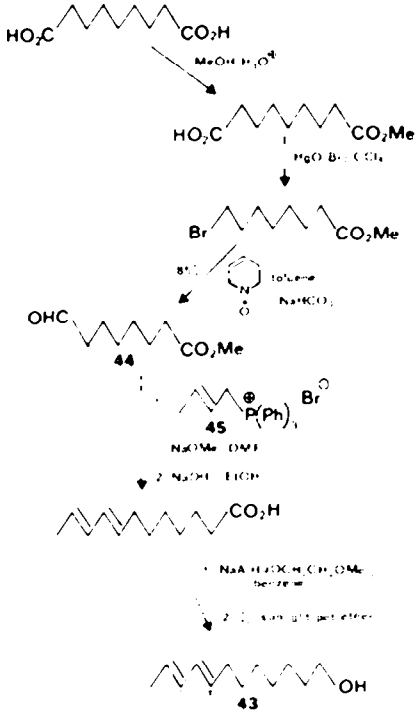
(5) *Conjugated dienes*

(a) (8E,10E)-8,10-*Dodecadien*-1-*ol*. The codling moth, *Laspeyresia pomonella*, (Tortricidae: Olethreutinae) is a major world wide pest of apple orchards. On the basis mainly of electroantennogram studies of model compounds and of female extracts Roelofs *et al.* proposed[105] that the sex pheromone of the codling moth was (8*E*,10*E*)-8,10-dodecadien-1-ol (**43**; Codlemone[‡] attractant) and its presence in female abdominal tips was later established by Beroza *et al.*[106] The synthetic compound has been shown to be very attractive to male moths in the field and is of considerable value as a survey tool.[105] Field trials with the geometrical isomers of **43** have shown that the pure *E,E* isomer **43** is by far superior to the other three isomers in attractiveness to males and that the other geometrical isomers appear to inhibit the male response when mixed with **43**.[107] The acetate ester of **43** has been shown to inhibit the attraction of male codling moths to either the synthetic sex pheromone **43** or to virgin moths.[108,109‡] A number of other chemicals such as undecanol,[108] ethers and esters of **43**,[109] and monoene esters such as (*Z*)-8-dodecen-1-yl acetate,[112] have also been shown to inhibit the attraction of male codling moths to **43**. This pheromone is of considerable practical importance and the various synthetic routes discussed below illustrate some of the methods available for the synthesis of conjugated *E,E* dienes. The early syntheses are of little use in preparing quantities of **43**, but they are discussed in this section to demonstrate the development of the more practical routes. Even though the sorbyl halide route (Scheme 19) is only of moderate use it is discussed in detail as this work led finally to the preferred route to **43** which is outlined in Scheme 20.

The first synthesis of **43** was carried out by Roelofs *et al.* as outlined in Scheme 15.[105] Wittig reaction of the triphenylphosphonium salt **45** [prepared from (*E*)-1-bromo-2-butene] with methyl 8-oxooctanoate (**44**) in dimethylformamide using sodium methoxide as the base, and using a large excess (10 equiv.) of the ylide, followed by hydrolysis, purification *via* the acid, and reduction gave **43** as a mixture of isomers estimated[105] to contain *ca.* 75% of the 8*E*,10*E* isomer and 25% of the 8*Z*,10*E* isomer. Isomerization with iodine and sunlight in pentane



Scheme 14.



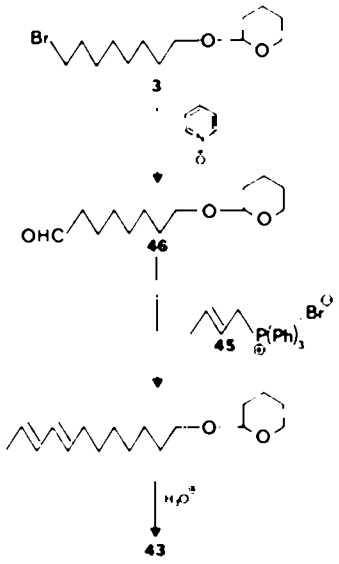
Scheme 15.

‡The acetate ester of **43** has recently been identified as the primary component of the sex pheromone of the female pitch pine tip moth, *Rhyacionia rigidana*,[110] and has also been found to be a good attractant for the male pea moth, *Laspeyresia nigricana*, in the field.[111]

gave the crude 8*E*,10*E* isomer in low yield. To obtain pure **43** this product was acetylated and the acetates were chromatographed on silver nitrate-impregnated silica gel-G thin layer plates developed with benzene.[105,107] Saponification of the material extracted from the upper edge of the higher Rf band then gave a small quantity of **43** (91% 8,10-dienols by glc analysis; 98% 8*E*,10*E* isomer[113]). This lengthy route is not useful for preparing more than a small quantity of **43**. The iodine-sunlight isomerization conditions gave impure **43** in low yield and the 8,10-dodecadienol fraction of this reaction product contained only *ca.* 50% of the 8*E*,10*E* isomer (plus 34% of the 8*Z*,10*E* isomer, and 16% of the 10*Z* isomers) by glc analysis,[113] although this mixture was active in the field.[105,107]

We initially prepared the 8,10-dienol as a mixture of isomers by modifications of the above Wittig approach, such as Scheme 16.[114] The oxidation of ethyl 8-bromooctanoate and of the bromo ether **3** (from Scheme 1) with pyridine N-oxide[115] in toluene in the presence of sodium bicarbonate, in our hands gave the corresponding aldehydes in only 50% yield. The normal Wittig reaction of triphenylphosphonium (*E*)-2-butenylide with ethyl 8-oxooctanoate in ether in the presence of lithium bromide (ylide generated with n-butyllithium) gave in high yield a mixture of isomers containing (by glc analysis) 45% of the 8*E*,10*E* isomer, 39% of the 8*Z*,10*E* isomer, and 16% of the two 10*Z* isomers. Reduction of the ester with LAH gave the dienol. This mixture, containing 45% of **43**, was active as a sex attractant in both field and laboratory tests.[116] Acetylation of a sample of this mixture and column chromatography of the acetate isomers on silica gel–25% $AgNO_3$ gave the *E*,*E* acetate (95% *E*,*E* isomer by glc analysis) in low yield. The Wittig reaction of the aldehyde **46** (Scheme 16) with this partially stabilized ylide was studied in detail (Table 1).[114] The isomer ratio in the product was not significantly different under "salt-free" conditions[68,69,117] from that obtained under normal Wittig reaction conditions. Even the *E* olefin procedure (Table 1; entry 4), whereby the primary Wittig intermediate is α-metallated,[117] did not give an increase in the amount of 8*E*,10*E* isomer in the product. These results are in sharp contrast to those obtained when saturated aliphatic *nonstabilized* triphenylphosphonium ylides react with aliphatic aldehydes.[68] As a follow-up to this study, the bromo ether **3** was converted to its triphenylphosphonium salt (isolated as an oil) and the Wittig reaction with (*E*)-2-buten-1-al (using potassium t-butoxide in dimethylformamide) was carried out. After hydrolysis only a 10% yield of 8,10-dienols was obtained containing 77% of the 8*Z*,10*E* isomer, 20% of the 8*E*,10*E* isomer **43**, and 3% of the 10*Z* isomers.[114]

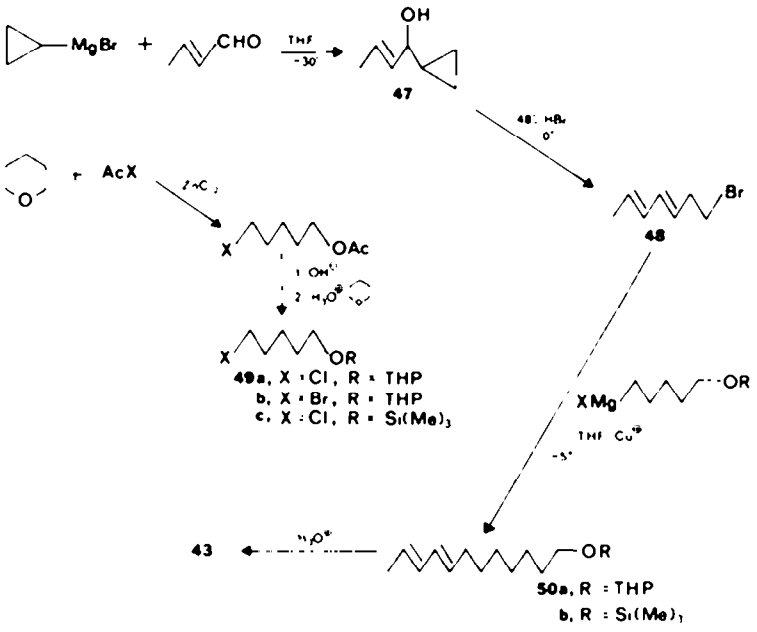
The above schemes were not satisfactory for the large scale preparation of **43**, and the stereoselective synthesis outlined in Scheme 17 was a considerable improvement.[118] Ring opening of the secondary cyclopropylcarbinol **47** with 48% aqueous hydrobromic acid at 0° according to the method of Julia[119] gave in 90% yield the homoallylic bromide **48**. Glc analysis of the latter indicated that it was a mixture of the 3*E*,5*E* isomer (90%) and the 3*Z*,5*E* isomer (10%); however, in view of the final isomer ratio obtained in the synthetic product, it



Scheme 16.

Table 1. Reaction of **46** with triphenylphosphonium (*E*)-2-butenylide

REACTION CONDITIONS	PRODUCT (After removal of protecting group)			
	Isolated Yield %	Isomer Ratio		
		8E,10E (43)	8Z,10E	10Z isomers
1. "Salt-Free" ($NaNH_2$, Liq NH_3, -33°, NH_3 removed then ether added followed by filtration).[68,117]	65	54	28	11 and 7
2. n-BuLi, ether	69	50	30	13 and 7
3. tert-BuOK, dimethylformamide	60	41	40	12 and 8
4. Schlosser's α-metallation of primary Wittig intermediate (ether as solvent).[117]	42	44	36	12 and 8



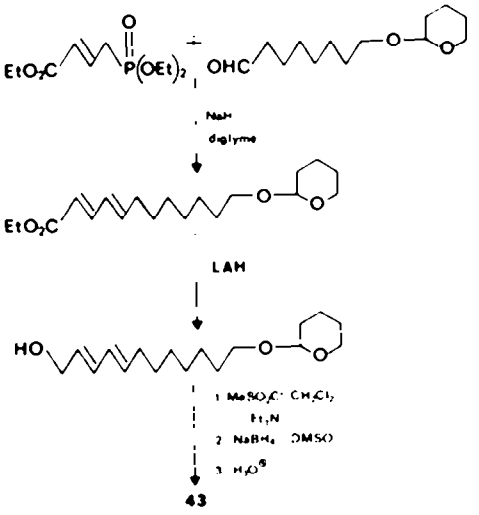
Scheme 17.

probably only contained *ca.* 80% of the 3*E*,5*E* isomer. Coupling of the Grignard reagents prepared from C-5 halo ethers **49** in THF with the C-7 homoallylic bromide **48** (see Ref. 120) was carried out at −5° using catalytic quantities (*ca.* 0.3%) of dilithium tetrachlorocuprate[121] to give **50** in good yields (85%). Hydrolysis of the protecting group in **50a** [*p*-toluenesulfonic acid in aqueous methanol, 50° for 2 hr] or **50b** [aqueous ethanol, 2 hr under reflux] gave, after distillation, the free alcohol in high yield containing 79% of the *E*,*E*, isomer **43** along with 9% of the 8*Z*,10*E* isomer and 12% of the 10*Z* isomers. This material readily crystallized at 5° and recrystallization from pentane at −5° gave a high recovery of the pure *E*,*E* isomer **43** (m.p. 29–30°; >99.5% pure by glc analysis).

The alternative coupling procedure, that of reaction of the Grignard prepared from **48** with **49b** under cuprous salt catalysis as above, gave a 60% yield (after distillation) of **50a** but the product contained only 68% of the *E*,*E* isomer, indicating some loss of stereochemistry either during the formation of the Grignard reagent from **48** or during the coupling reaction (see Ref. 120). This route (Scheme 17) has been used by us to prepare multi hundred gram batches of **43** in a very high state of purity.

The (8*E*,10*E*)-dienol **43** is highly crystalline which allows its ready separation from mixtures. When the desired *E*,*E* isomer is separated from a mixture of 8,10-dodecadienol isomers by low temperature crystallization, the mother liquor fraction typically still contains *ca.* 20% of residual *E*,*E* isomer. This mixture of geometrical isomers can be readily equilibrated by heating without solvent with 1% by weight of benzenethiol[89] at 100° for 30 min to give a mixture containing *ca.* 60% of the *E*,*E* isomer (equilibration of the pure 8*E*,10*E* isomer **43** also gives the same mixture).† Crystallization of this equilibrium mixture gives pure **43** and the mother liquor may again be re-equilibrated. When this process was repeated three times on 240 g of a mother liquor fraction containing 90% of 8,10-dodecadien-1-ol isomers, no dodecadienol was lost and no new impurities were produced in significant amounts.[122] This equilibration-crystallization sequence reduces the requirement for a highly stereoselective synthesis of **43**.

Many other synthetic routes to **43** (and its geometric isomers) have been investigated by us and by other workers in this field. Vig *et al.* have published a synthesis of **43** whereby they generated the *E*,*E* diene system *via* a phosphonate condensation, followed by removal of the C-12 functional group by reduction of the mesylate with $NaBH_4$ in dimethyl sulfoxide (Scheme 18).[123] However, their product was not crystalline and the purity is not discussed by the authors so that the stereoselectivity of their synthesis of the dienol **43** is not known.



Scheme 18.

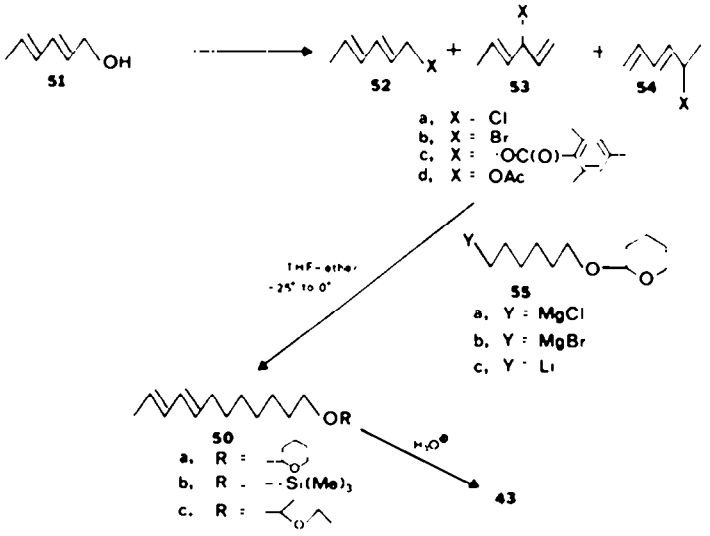
†Monoenes such as (*Z*)-8-dodecen-1-yl acetate (**13**) can also be readily equilibrated to give a mixture of the *Z* and *E* isomers (ratio 1:3, respectively) by heating without solvent with 1% by weight of benzenethiol (1 hr at 100°).[89]

We also carried out a detailed investigation of the synthesis of **43** starting from (2*E*,4*E*)-2,4-hexadien-1-ol (sorbyl alcohol, **51**) and the corresponding aldehyde and acid in attempts to develop inexpensive routes to **43**. As part of our work we studied the coupling reaction of sorbyl halides with C-6 organometallic reagents.[124†] It has been observed many times before that the reaction of monoene allylic halides with non-allylic organometallic reagents almost invariably produces mixtures of isomeric olefins. Either member of a primary-secondary pair of isomeric allylic chlorides or bromides usually yields a similar complex mixture of unsaturated products. Of the expected cross-coupled products the compound derived from the primary C atom of the allylic system usually predominates, but varying amounts of dienic hydrocarbons are also produced resulting from the homo-coupling of two allylic fragments.[125] In our work we found that treatment of the pure 2*E*,4*E* dienol **51** with 1 equiv. of thionyl chloride in ether in the presence of one equiv. of tri-n-butylamine[126] gave a 90% distilled yield of a mixture of allylic chlorides **52a** and **53a** in the ratio *ca.* 7:3, along with a few percent of **54a** (Scheme 19). Coupling of this isomeric mixture with the Grignard reagent **55a** in ether–THF, followed by acid hydrolysis of the protecting group gave a complex mixture of products. The 8,10-dodecadien-1-ol *portion* of the product was shown by glc analysis to contain *ca.* 75% of the 8*E*,10*E* isomer but the crude product contained other dienol and tetraene compounds along with dodecamethylene glycol (which apparently formed both during the preparation of the Grignard reagent and during the coupling reaction). Fractional distillation of the product *in vacuo* to remove the large fraction of volatile hydrocarbons (40–50%) and the C-12 diol, and crystallization of the alcohol fraction (containing 8,10-dodecadienols and other dienols in the ratio *ca.* 3:1) from aqueous methanol at 0° gave the pure 8*E*,10*E* isomer **43** in an overall yield from **52a** plus **53a** of 10 to 30%. The reaction products obtained in this study with sorbyl derivatives were somewhat more complicated than those obtained previously by other authors with crotyl derivatives. For example, reaction of 2-buten-1-ol with thionyl chloride in ether in the presence of tri-n-butylamine is reported to give exclusively 1-chloro-2-butene[126] whereas treatment of 2-buten-1-ol with thionyl chloride in dilute ether solution gave almost entirely 2-chloro-3-butene.[126] Coupling of either of these allylic chlorides with n-butylmagnesium halide,[127a,b] or n-butyllithium[127b,128] gave mainly 2-octene and only traces of dienic products. Similar results have been obtained with phenyllithium,[128,129] and phenylmagnesium bromide.[129a] The reaction of phenyllithium in ether with pure (*E*)-1-chloro-2-butene gave mainly (*E*)-1-phenyl -2-butene [plus 3-phenyl-1-butene and (*E*)-1-methyl-2-phenylcyclopropane] with no geometric isomerization during the course of the reaction[129b] (see Ref. 127*b*). In contrast to these results, coupling reactions of sorbyl halides with organometallic reagents such as **55a–c** and **56** gave complex mixtures usually containing up to 50% of unidentified unsaturated hydrocarbon products (see Ref. 127*c*).‡ Fractional distillation of the sorbyl chloride mixture gave pure **52a**, but coupling this isomer with the Grignard reagent **56** gave a similar complex mixture of products from which pure **43** was isolated as above in 15% yield. Treatment of the dienol **51** with thionyl chloride in ether solution[126] at 0–5° (20 hr) gave an 80% distilled yield of a mixture of **52a**, **53a** and **54a** in the ratio *ca.* 25:65:10, respectively. Coupling of this mixture with the Grignard reagent **56** in ether–THF gave a similar mixture of products to that described above. A number of other unsuccessful attempts were made to convert sorbyl alcohol to the corresponding halides without allylic rearrangement. For example, variations in the conditions of Stork *et al.*,[130] Collington and Meyers,[131] and the use of CCl_4-hexamethylphosphorous triamide in ether,[132] all gave mixtures of **52a**, **53a** and **54a** plus recovered starting dienol **51**.

Reaction of sorbyl alcohol with PBr_3 (0.4 mol equiv.) in ether at −40° (2.5 hr) gave a mixture of **52b** and **53b** in

†These coupling reactions are discussed in detail since our results with sorbyl derivatives were in many cases surprisingly different from those obtained previously by other authors with crotyl derivatives.

‡The coupling of the sorbyl chloride mixture **52a** plus **53a** with the organolithium reagent **55c** in ether–THF at −25° gave a similar mixture of products to that described above with the Grignard reagent **55a**.



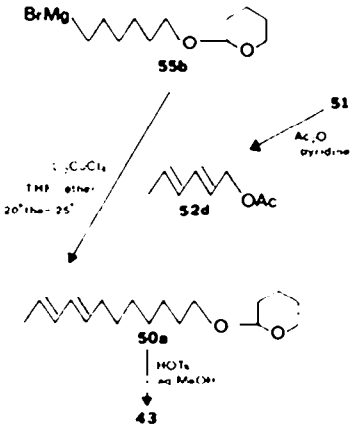
Scheme 19.

the ratio *ca.* 1:1, whereas at 0° (20 hr) with 0.5 mol equiv. of PBr_3 in ether a mixture of **52b**, **53b** and **54b** was obtained in the approximate ratio 70:10:20, respectively.† Treatment of the sorbyl bromide mixture (see Ref. 127*c*) with the Grignard reagent **55b** in ether–THF (with or without added HMPT, see Ref. 130) gave a complex mixture of products similar to that described above (for the reaction of **52a** and **53a** with **55a**) from which pure **43** was isolated as above in *ca.* 15% yield (from **51**). Reaction of the organolithium reagent **57** with the sorbyl bromide mixture in THF at −20° in the presence of a catalytic quantity of dilithium tetrachlorocuprate (see Ref. 121) gave a similar complex mixture of products and **43** was isolated in an overall yield of 17% (from sorbyl bromide) after recrystallization.[133] Reaction of sorbyl mesitoate (**52c**) with excess of the Grignard reagent **55b** in ether–THF under reflux (with or without added HMPT) gave mostly unidentified volatile products with only traces of 8,10-dodecadienols (see Ref. 134).

The preparation of **43** from sorbyl bromide has also been carried out by other groups.[109,135,136] Butt *et al.* report a 25–30% yield of 8,10-dodecadien-1-ol containing 75% of the *E,E* isomer **43** from the coupling of **55a** with sorbyl bromide (prepared with PBr_3) followed by spinning-band distillation of the product.[135] Essentially the same route, with crystallization of the distilled product, was used by George *et al.*[109] and by Mori,[136] to obtain pure **43**.

Finally we investigated[137] the coupling of sorbyl acetate (**52d**) and its allylic isomer **53d** with organomagnesium and organolithium reagents under copper(I) catalysis, and also with lithium diorganocuprate complexes, as a method of preparing **43**.[137] Allylic *halides* are highly reactive towards lithium dialkylcuprate reagents,[96,138–142] as well as towards Grignard and organolithium reagents as discussed above.[125,127–129,141] Although good yields have been reported (e.g. Ref. 140), the cross-coupling reaction of lithium dialkylcuprates with allylic halides often proceeds with considerable allylic rearrangement[138,141,142] and is accompanied by side reactions, especially the formation of homo-coupled products. For example, the reaction of lithium diethylcuprate with 1-bromo-2-butene in ether was reported to give only 15% of cross-coupled products along with 42% of a mixture of C-8 diene dimers formed from the homo-coupling of the allylic bromide.[143a] The reaction of allylic halides with aliphatic Grignard reagents in the presence of copper salts (e.g. $CuCl_2$) can also give complex mixtures of products containing large amounts of homo-coupled products.[141]‡ Previous studies of the coupling of allylic *esters* with lithium dialkylcuprate reagents to give alkylated olefins have been reported,[96,140,141,144–147] and in our work we observed that secondary and tertiary allylic acetates react rapidly at −10° with cuprate complexes in ether to give mainly the products derived from the displacement of the acetate group with allylic rearrangement.[145] With these substrates polymeric alkylcopper reagents were found to give only partial conversion to alkylated olefin.[145a] Alkylation via direct displacement of the acetoxy group with lithium dialkylcuprates can be the preferred reaction pathway for primary allylic acetates.[140,146] Recently Fouquet and Schlosser have reported that allylic (and benzylic) acetates react with Grignard reagents in the presence of catalytic amounts of copper(I) salts to give good yields of cross-coupled products.[148] For example, they reported that mixing (*E*)-2-buten-1-yl acetate, n-butylmagnesium bromide, and a catalytic amount of Li_2CuCl_4 in THF–ether at −78° and warming to room temperature gave a 62% isolated yield (88% yield based on glc analysis) of (*E*)-2-octene along with 9% of 5-methyl-5-nonan-ol (from the competitive uncatalyzed attack on the acetate carbonyl). Similarly, (*Z*)-2-octene was obtained in 50% yield from (*Z*)-2-buten-1-yl acetate, so that these coupling reactions with primary allylic acetates were reported to be both regio- and stereoselective. These authors also noted (without discussing any details) that secondary and tertiary allylic acetates react with Grignard reagents, in the presence of copper(I) catalysts, with allylic rearrangement.[148a]

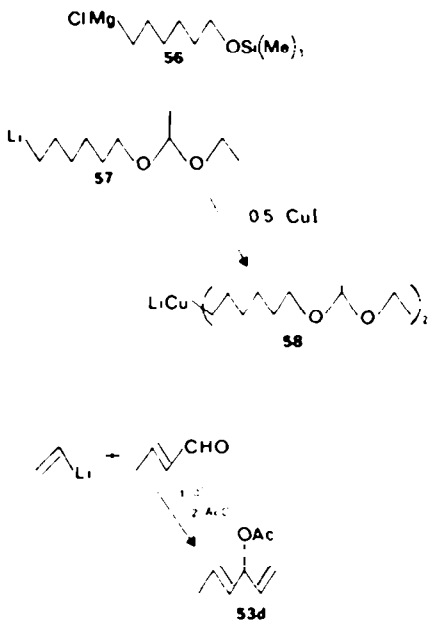
The reactions of both (*E,E*)-sorbyl acetate (**52d**) and its secondary allylic isomer **53d** with the organocuprate complex **58**, and with the Grignard reagent **55b** in the presence of a catalytic amount of Li_2CuCl_4 (Scheme 20) were studied.[137] The cuprate complex **58** reacted regio- and stereo-selectively with **52d** to give a 65% isolated yield (after removal of the protecting group and purification by preparative tlc) of **43** containing almost entirely (99.7%) the *E,E* isomer. Displacement with allylic rearrangement was a minor reaction pathway with these reactants. Under the same conditions the secondary allylic acetate **53d** reacted with **58** with almost entirely allylic rearrangement to give (after removal of the protecting group and tlc) a 61% isolated yield of a mixture of the 8*E*,10*E* and 8*Z*,10*E* isomers of **43** in the ratio of *ca.* 4:1, respectively. Reaction of the Grignard reagent **55b** with **53d** in the presence of a catalytic amount of Li_2CuCl_4 also proceeded with allylic rearrangement to give a 40% yield of a mixture of the 8*E*,10*E* and 8*Z*,10*E* isomers of **50a** in the ratio 45:55, respectively. Reaction of the lithium reagent **57** with sorbyl acetate (**52d**) in the presence of Li_2CuCl_4 as a catalyst gave a negligible amount of **50c** and attack on the acetate carbonyl with the formation of **51** was the major reaction. However, coupling of the Grignard reagent **55b** with **52d** in the presence of Li_2CuCl_4 gave a 60% yield of a mixture of



Scheme 20.

†Sorbyl bromide is not as stable as the chloride and should be stored cold (see Ref. 125); allylic bromides are known to isomerize much more readily than the corresponding chlorides.

‡In contrast, when copper(I) salts are used to catalyze the reaction between Grignard reagents and primary *alkyl* bromides (or iodides) in THF at 0° the yields of cross-coupled products are high and the formation of homo-coupled dimers is a very minor reaction.[121]



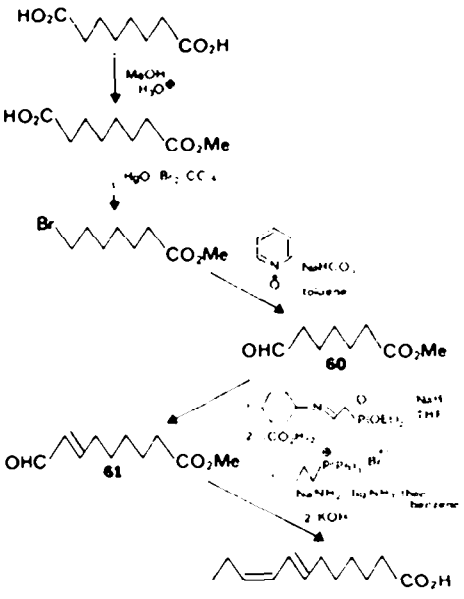
the isomers of **50a**, containing 85% of the 8*E*,10*E* isomer, 3% of the 8*Z*,10*E* isomer and 12% of the two 10*Z* isomers. This last reaction was scaled up as a practical method of preparing **43**. Thus a commercial batch of sorbyl alcohol containing *ca.* 75% of the *E,E* isomer and 25% of the *E,Z* isomer was acetylated and the acetate was coupled with the Grignard reagent **55b** in the presence of dilithium tetrachlorocuprate (0.2%) in ether–THF at −20°, then at room temperature (mixing at −78° was found not to be necessary; see Ref. 148*a*). The coupling occurred regio-selectively with no significant allylic rearrangement and with no substantial change in the stereochemistry of the diene system (the diene fraction contained *ca.* 75% of the *E,E* isomer). The crude product, after acidic hydrolysis to remove the protecting group, contained **43** contaminated with a small amount of **51** and considerable 1,12-dodecanediol. Dimerization of the C-6 fragment apparently occurs as a side reaction both during the preparation of the Grignard reagent **55b** and during the coupling reaction. The reaction product was cooled to −20°, rewarmed to 20° and extracted with hexane. The hexane-soluble fraction was filtered through a column of Florisil, and crystallization of the product from pentane at −20° gave a 40% yield of the pure *E,E* isomer **43**. This synthetic procedure is the overall preferred method of preparing **43**. We have also investigated the stereoselective coupling of sorbyl benzoate (see Ref. 145*b*) with **55b** under copper(I) catalysis and obtained similar yields (50–60%) of pure **43**.[149]

(b) (7*E*,9*Z*)-7,9-*Dodecadien*-1-*yl acetate*. The European grapvine moth, *Lobesia botrana* (Tortricidae; subfamily Olethreutinae) is an important pest of vineyards in southern Europe. The *L. botrana* females have been shown to produce (7*E*,9*Z*)-7,9-dodecadien-1-yl acetate (**59**) and the synthetic sex pheromone has been found to be highly attractive to *L. botrana* males in the field.[150–152] The various syntheses of this pheromone discussed below illustrate some of the methods now available for the stereoselective synthesis of conjugated (*E,Z*)-dienes.

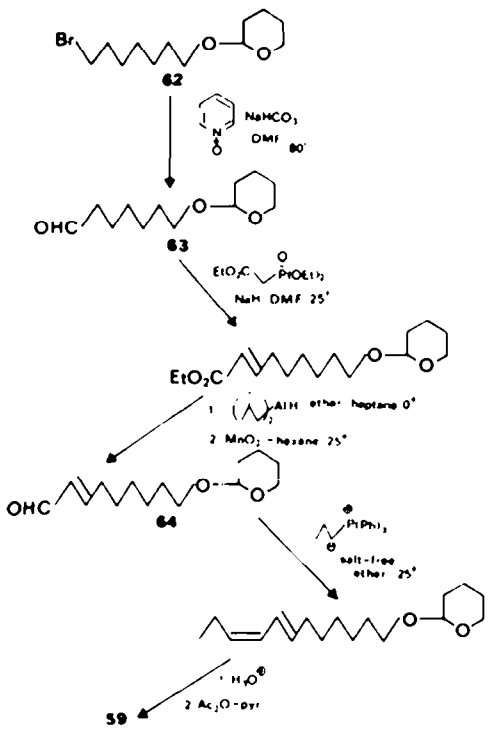
The initial synthetic route to **59** by Roelofs *et al.*,[150a,c] is outlined in Scheme 21 (see Scheme 15). Methyl 7-oxoheptanoate (**60**) was prepared via pyridine N-oxide oxidation[115] of methyl 7-bromoheptanoate. The aldehyde **60** was then converted to the α,β-unsaturated aldehyde **61** *via* use of the anion generated from diethyl 2-(cyclohexylimino)ethylphosphonate.[153] The crude α,β-unsaturated aldehyde was treated with triphenylphosphonium n-propylide in benzene (under essentially "salt-free" conditions; see Ref. 68) and the product was hydrolyzed to the acid. Reduction of the latter with sodium dihydrobis(2-methoxyethoxy)aluminate and acetylation of the resulting alcohol gave **59** (in 30% crude yield from **60**; purity *ca.* 70% of total 7,9-isomers). This lengthy scheme produced somewhat impure **59** in low overall yield. The crude **59** was purified by preparative glc to give a diene mixture containing 88% of the desired 7*E*,9*Z* isomer, plus 8% of the 7*E*,9*E* isomer, and 4% of the 7*Z*,9*Z* isomer. This synthetic material was attractive to *L. botrana* males in the field.[150a,c]

Initially we prepared **59** by a similar route (Scheme 22).[154] However, the pyridine N-oxide oxidation of **62** usually gave yields of only 30–50% of **63**. Dimethylformamide (at 80°) could be used in place of toluene with this substrate but we were unable to improve the overall yield above 50%. The α,β-unsaturated aldehyde **64** was prepared in three steps since we found the diethyl 2-(cyclohexylimino)ethylphosphonate reagent difficult to prepare reproducibly. The "salt free" reaction of this aldehyde in ether with triphenylphosphonium n-propylide (prepared with $NaNH_2$ in liquid NH_3; see Ref. 68) followed by acid hydrolysis and acetylation gave a product containing, by glc analysis (see Refs. 150*b*, 152), 88% of the 7*E*,9*Z* isomer **59** and 12% of other isomers (8.5% of the 7*E*,9*E* isomer, 2.5% of the 7*Z*,9*Z* isomer and 1% of the 7*Z*,9*E* isomer).

However, these routes (Schemes 21 and 22) were unsatisfactory as we were interested in developing a practical scheme which could be used to prepare **59** stereoselectively on a large scale. Such a route is out-



Scheme 21.



Scheme 22.

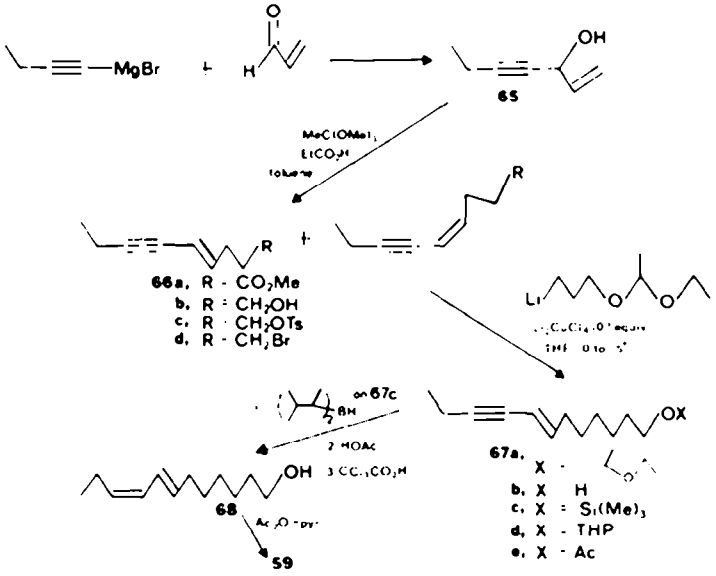
lined in Scheme 23.[152] 1-Hepten-4-yn-3-ol (**65**) was heated with trimethyl orthoacetate in toluene (propanoic acid catalyst)[155] to give, in 50% yield from acrolein, methyl 4-nonen-6-ynoate (*E*:*Z* ratio of *ca.* 4:1; see Ref. 156).†

†In one run using triethyl orthoacetate and adding the catalyst in portions during the reaction the overall yield of ethyl ester was 70%.[157]

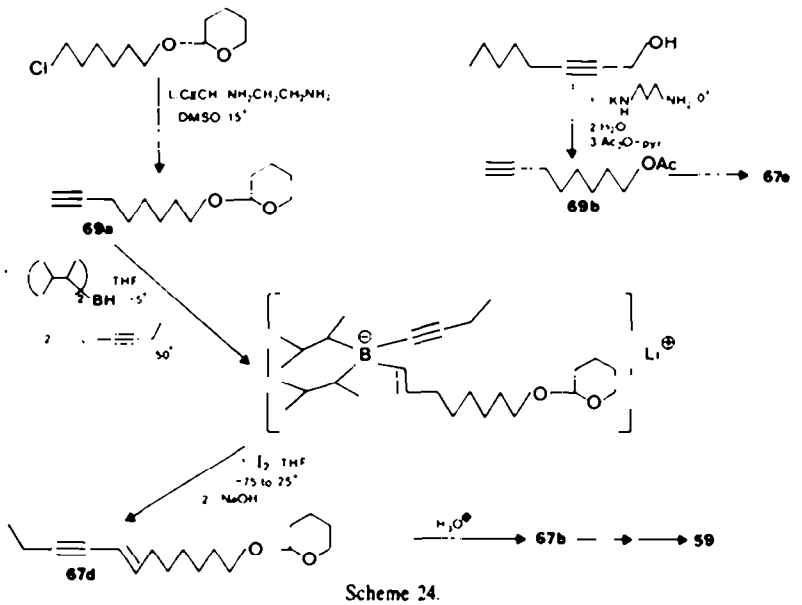
‡Care must be taken in the distillation of dienes such as the pheromone **59**. In one distillation of a 30 g batch (bath temperature 125°, head temperature 75–102°; *ca.* 45 min) at 0.06 mm, partial isomerization (*ca.* 9%) to the 7*E*,9*E* isomer occurred.[157]

The pure *E* isomer can be readily obtained by distillation of the isomer mixture **66a** on a spinning-band column, but such a separation is unnecessary at this stage. Conversion of the ester (*E*,*Z* isomers in ratio 4:1) to the bromide **66d** (70–80% yield) and coupling of the latter with 3-[(1-ethoxy)ethoxy]propyllithium[158] using a catalytic quantity of dilithium tetrachlorocuprate (-5°, 1 hr)[68] gave **67a**. Acid hydrolysis (trichloroacetic acid in aqueous THF, 60° for 1 hr) then gave the crude alcohol which was *crystallized from pentane at* −35° to give (*E*)-7-dodecen-9-yn-1-ol (**67b**) (99% purity by glc analysis) in 50–60% over-all yield from **66d**. The pure (*E*)-enyne alcohol **67b** was converted to the trimethylsilyl ether **67c**, (Me_3SiCl–Et_3N in CH_2Cl_2). Selective hydroboration of the acetylene group of **67c** with an equimolar amount of bis(3-methyl-2-butyl)borane (0°, 2 hr in THF) followed by protonolysis of the vinylboron intermediate with acetic acid (65°, 5 hr),[159,161] and then alkaline H_2O_2 treatment to remove boron-containing impurities, followed by acid hydrolysis of the residual protecting group (CCl_3CO_2H in methanol, 25° 1 hr) gave the 7*E*,9*Z* diene **68**. Crystallization from pentane (or hexane) at −50° gave a 77% yield (from **67b**) of **68** (≥98% purity). Acetylation of **68** then gave the sex pheromone **59**. The pheromone synthesized by this route was shown by glc analysis to contain 97.5% of the 7*E*,9*Z* isomer and 1.8% of the 7*E*,9*E* isomer.‡

Scheme 23 depends on the efficient synthesis of the key intermediate, (*E*)-7-dodecen-9-yn-1-ol (**67b**) (m.p. *ca.* −10 to −15°) which can be readily purified to ≥99.5% by crystallization from pentane or hexane at low temperatures (−30° to −45°) (the dienol **68** crystallizes much less readily than the enynol **67b**). We also synthesized **67b** by the stereoselective procedure outlined in Scheme 24 (see Negishi *et al.* Ref. 161*a*).[162] The overall yield (from **69a**) of pure **67b** (99.5% purity) after crystallization (pentane −35°), was only *ca.* 20%.[162] Although the conversion of the acetylene **69a** to **67d** is carried out in one pot, the reaction is difficult to follow, and is not practical on a large scale. The route outlined in Scheme 23 is preferable in our hands for large scale synthesis. Negishi[161b] has recently prepared **59** via



Scheme 23.

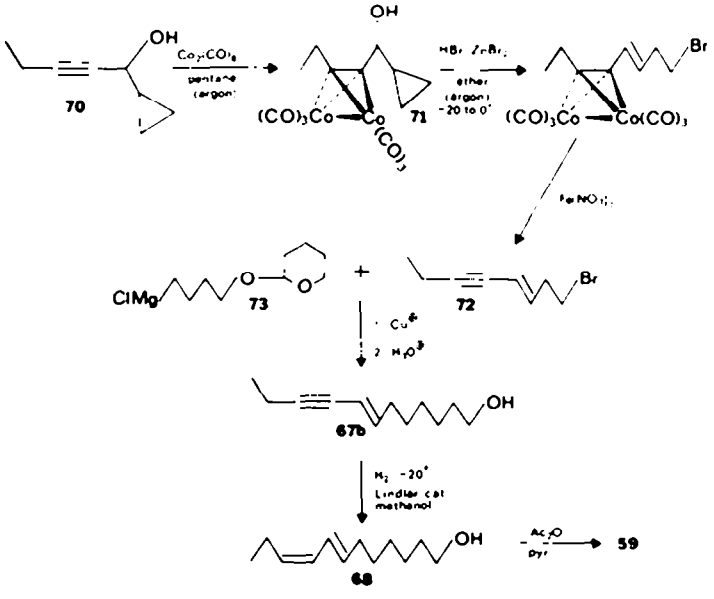


Scheme 24.

a modification of the procedure in Scheme 24, and has carried out the conversion of the (*E*)-enyne group to the (*E,Z*)-diene by both partial reduction of the triple bond with powdered zinc in aqueous n-propanol,[163] as well as by the hydroboration-protonolysis procedure used above (Scheme 23). These authors used 7-octyn-1-yl acetate (**69b**) instead of **69a** in their scheme and they prepared this terminal acetylene by treating 2-octyn-1-ol with potassium 3-aminopropylamide (acetylene "zipper" reaction)[44b] followed by acetylation. The obtained a 60% yield in the conversion of 7-octyn-1-yl acetate (**69b**) into the *E* enyne **67e** under these modified conditions.

We also attempted to prepare the 7*E*,9*Z* isomer **59** by reduction of the triple bond in the tetrahydropyranyl ether of (*Z*)-9-dodecen-7-yn-1-ol to the *E* olefin using lithium diisobutylmethylaluminum hydride.[164] However, presumably due to steric hindrance, the triple bond in the (*Z*)-enyne reacted very slowly, and mixtures of *Z* and *E* isomers were obtained on hydrolysis.[165] Initially the hydroalumination of the triple bond appeared to give predominantly (*E*)-vinylalanate but prolonged reaction times gave mostly *Z* olefin on hydrolysis.

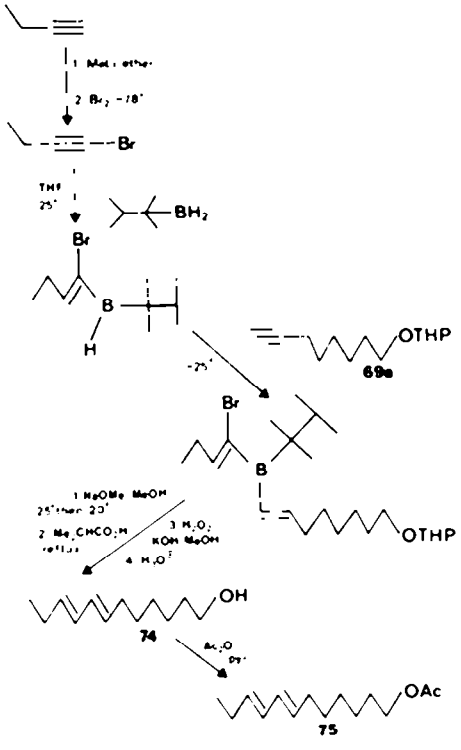
Descoins and Samain have also prepared the pheromone **59** via the (*E*)-enyne **67b** (Scheme 25).[166,167] They found that treatment of 1-cyclopropyl-2-pentyn-1-ol (**70**) with hydrobromic acid[119,168] gave mainly (*Z*)-1-bromo-3-octen-5-yne (*Z* and *E* isomers in the ratio 67:33). These workers therefore cleverly modified the stereochemistry of the cyclopropyl ring opening by temporarily increasing the steric hindrance of the acetylenic linkage through the preparation of a complex between the triple bond and dicobalt octacarbonyl. Treatment of the complex **71** with hydrobromic acid (plus $ZnBr_2$) followed by oxidation of the product with ferric nitrate gave the *E* homoallylic bromide **72** in 65% over-all yield with *ca.* 99% stereoselectivity.[166] Coupling of this bromide [Cu(I)



Scheme 25.

catalysis] with the Grignard reagent **73** gave, after acid hydrolysis, the enyne **67b** (96% *E* isomer) in 80% yield (see Scheme 17, Ref. 118). They then selectively hydrogenated the recrystallized **67b** (>99% *E* isomer) in methanol at −20° over a small amount of specially prepared Lindlar catalyst (with no added quinoline) to give the dienol **68** (92% 7*E*,9*Z*; 8% 7*E*,9*E*) in *ca.* 40–60% yield after spinning band distillation.[165] Pure dienol was obtained by preparative glc and acetylated to give **59**. However the hydroboration-protonolysis procedure described in Scheme 23 is much preferable to any catalytic hydrogenation method for such a conjugated enyne system.† In an alternative synthetic route to **59**, Descoins had also independently carried out the Claisen rearrangement described in Scheme 23 to give ethyl 4-nonen-6-ynoate.[165] The *E* isomer, obtained by spinning band distillation, was reduced (LAH) and the alcohol hydrogenated at −20° over a trace of Lindlar catalyst in methanol. The resulting (4*E*,6*Z*)-4,6-nonadien-1-ol (90% 4*E*,6*Z* isomer; 60% yield from ester) was then homologated to **59**. However this modified scheme, as initially carried out, is less attractive than that described in Scheme 23.[165]

We prepared the conjugated 7*E*,9*E* isomer **75** by a thexylborane procedure (Scheme 26)[170] developed by Negishi and Yoshida.[171] This is an excellent, versatile, general procedure for the synthesis of conjugated *E*,*E* dienes and is highly stereoselectivive. In Scheme 26 the



Scheme 26.

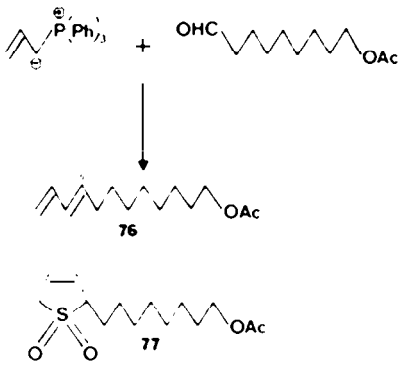
alcohol **74** was obtained in 40% distilled yield from the acetylene **69a** and contained >98% of the 7*E*,9*E* isomer by glc analysis.‡ Descoins also prepared the 7*E*,9*E* isomer **75** by a scheme analogous to that previously developed to prepare (8*E*,10*E*) - 8,10 - dodecadien - 1 - ol (Scheme 17).[118] Coupling of 1-bromo-3,5-octadiene (90% *E*,*E* isomer) with the Grignard reagent **73** (catalytic amount of dilithium tetrachlorocuprate) in THF gave, after acidic hydrolysis, a 70% yield of **74** (90% *E*,*E* isomer). Crystallization from pentane (−30°) gave pure **74** (>99% *E*,*E* isomer; m.p. *ca.* 5–6°) which was acetylated to **75**.

(c) (*E*)-9,11-*Dodecadien*-1-*yl acetate*. The red bollworm moth, *Disparopsis castanea* is a major pest of cotton in Malawi, Rhodesia, Mozambique and South Africa. A multi-component mixture of physiologically active compounds, containing 9,11-dodecadien-1-yl acetate (*E*:*Z* isomers in the ratio *ca.* 80:20), (*E*)-9-dodecen-1-yl acetate, 11-dodecen-1-yl acetate, and 1-dodecanyl acetate, was isolated from female abdominal tips.[172] The most abundant component of this mixture was the diene **76**, but on its own this compound was found to be only weakly attractive to male moths. However, addition of the non-attractive compound, 11-dodecen-1-yl acetate, to the diene in the ratio occurring naturally in the excised female glands (*ca.* 1:4, respectively) resulted in a mixture which was highly attractive to male moths under field conditions.[172] The effect of the *E* isomer content on the attractiveness of **76** (in combinations of **76** with 11-dodecen-1-yl acetate) has been evaluated and it was found that the level of the *E* isomer necessary for maximum male attraction was between 88–93%, with field catches diminishing rapidly if less than 7 or more than 13% of the *Z* isomer was present in the mixtures.[172c] The field-attractive, synergistic combination of 9,11-dodecadien-1-yl acetate (*E*:*Z* isomers in the ratio *ca.* 9:1) and 11-dodecen-1-yl acetate in the ratio 4:1 has been termed dicastalure.[172c] The non-attractive compound (*E*)-9-dodecen-1-yl acetate, also isolated from the female, was found to be potent inhibitor and almost completely prevented male orientation when volatilized alongside virgin females in traps. 1-Dodecanyl acetate was found to have no apparent effect on male response to pheromone-baited traps and is probably a pheromone precursor.[172c] In field studies it was also found that **76** and 11-dodecen-1-yl acetate *inhibited* male attraction to virgin females when used individually (but not as the 4:1 combination) and in addition (*Z*)-9-dodecen-yl acetate and 11-dodecen-1-ol were strong inhibitors of male attraction.[172c]

The pure *E* and *Z* isomers of **76** were required for the initial field testing, both separately and combined in known ratios. Wittig condensation between triphenylphosphonium 2-propenylide and 9-oxonon-1-yl acetate (prepared by ozonolysis of oleyl acetate in CS_2 and reduction with Ph_3P) in ether in the presence of lithium bromide gave a 70% yield of the diene containing the *E* and *Z* isomers in the ratio 3:2 (Scheme 27).[172a,173] Alterations in solvent polarity in the Wittig reaction gave *E*:*Z* ratios in the range 4:1 to 3:7 but attempts to obtain greater stereoselectivity were unsuccessful. Separation of the isomers of **76** was very difficult and only partial resolution was obtained by chromatography on silica gel–$AgNO_3$. However, treatment of the Wittig product with liquid sulfur dioxide at −20° followed by chromatography on Florisil (to remove the unreacted *Z* isomer) gave the 1,4-cyclo-addition product **77**. Thermolysis of

†Partial hydrogenation of *conjugated* enynes and of diynes using Lindlar catalyst is not very selective and usually gives mixtures containing ≤40% of the desired conjugated diene (see Refs. 58*b*, 163*a*, 169).

‡Such conjugated *E*,*E* dienes cannot be prepared, in general, by the reduction of conjugated diynes with sodium in liquid ammonia.[171]

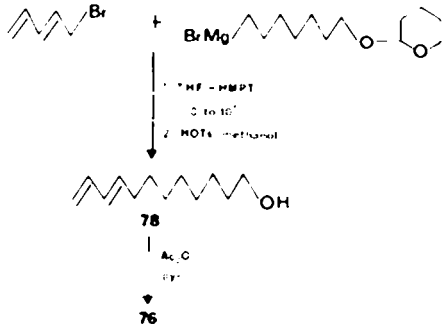


Scheme 27.

the sulfolene **77** occurred stereospecifically[174] to give the *E* diene **76** (99+ % purity) in high yield. The *Z* isomer of **76** was isolated in good yield by treating the Wittig product with excess tetracyanoethylene in THF at room temperature which selectively reacted with the *E* isomer. Chromatography of the product on Florisil enabled the separation of the *Z* isomer from the Diels–Alder adduct of the *E* isomer **76**.[173]

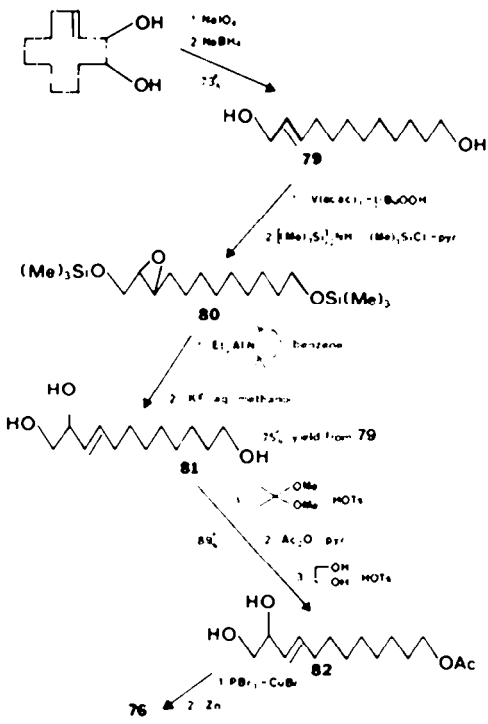
Mori prepared **76** by alkylation of the Grignard reagent prepared from 2-(7-bromo-1-heptyloxy)tetrahydropyran (**62**), with (*E*)-2,4-pentadien-1-yl bromide in HMPT–THF (Scheme 28). Acid hydrolysis of the product gave a crude alcohol mixture which was crystallized from light petroleum at −78° to give the partially purified alcohol **78** in low yield.† Acetylation of **78** gave the impure dienyl acetate (purity *ca.* 85%) which was shown to contain the *E* and *Z* isomers in the ratio 85:15 respectively.[136] The diene **76** has also been prepared by Tanaka *et al.* as an application of their general method for the conversion of an allylic alcohol into a 1,3-diene system utilizing the regio- and stereo-selective opening of an oxirane ring (Scheme 29).[175] Thus treatment of the epoxy silyl ether **80** with diethylaluminum 2,2,6,6-tetramethylpiperidide followed by removal of the silyl groups, gave the triol **81**. Reaction of the acetoxy diol **82** with phosphorus tribromide in ether in the presence of cuprous bromide followed by the addition of excess zinc powder gave the diene **76**.

(d) (9*Z*,11E)-9,11-*Tetradecadien-1-yl acetate*. The Egyptian cotton leafworm, *Spodoptera littoralis*, is a widespread polyphagous pest of cotton plants and of various vegetable crops in southern Europe, Africa and



Scheme 28.

†Mori found that this alcohol was an oil at room temperature and it did not crystallize readily at low temperature and therefore it could not be as easily purified by recrystallization as could the codling moth pheromone **43**.



Scheme 29.

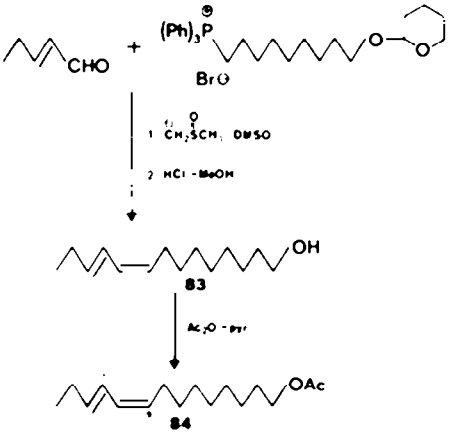
the Middle East. The female moth was reported by Nesbitt *et al.*[172a] to produce a complex of four compounds: 1-tetradecanyl acetate, (*Z*)-9-tetradecen-1-yl acetate, (*E*)-11-tetradecen-1-yl acetate, and (9*Z*,11*E*)-9,11-tetradecadien-1-yl acetate (**84**). Field trapping evaluation of these components showed that only the diene **84** was necessary for long range male moth attraction.[176] In baited traps, (*Z*)-9-tetradecen-1-yl acetate was found to almost completely inhibit the attraction of male moths to the diene **84** or to virgin females, but no marked attraction or inhibition of attraction was shown for the other two components isolated by Nesbitt *et al.* from the female moth. Nor was any synergistic action demonstrated for these two compounds when they were used in combination with the diene **84**.[176a] The pure 9*Z*,11*E* isomer **84** was found by Campion *et al.*[176a,d] to be much more attractive to male moths in the field than material of 70% purity (containing 15% of the 9*Z*,11*Z* isomer and 15% of the 9*E*,11*Z* isomer) and the 9*Z*,11*Z* isomer was found to be only slightly attractive to male moths.[176d] In contrast, Kehat *et al.*[176f] found that their purified synthetic 9*Z*,11*E* isomer (92% purity) was significantly *less* efficient in attractiveness than the partially purified synthetic attractant (72% 9*Z*,11*E* isomer).

The sex pheromone of *Spodoptera litura*, a serious pest of vegetable crops in the south-western part of Japan, has been shown to be a synergistic mixture ("litlure") of the (9*Z*,11*E*)-diene **84** and (9*Z*,12*E*)-9,12-tetradecadien-1-yl acetate.[177] Both of these esters only evoked a weak, behavioral laboratory, male response when used alone but were much more active when mixed together in specific ratios. The optimum ratio of the synthetic 9*Z*,11*E* and 9*Z*,12*E* acetates for *S. litura* male moth response was found to be *ca.* 9:1, respectively.[177] Tamaki and Yushima also reported[177a,178] that these same two esters were biologically active components (in the ratio 20:1, respectively) of the sex pheromone of *S. littoralis* (see Refs. 172*a*, 176). They reported that the optimum

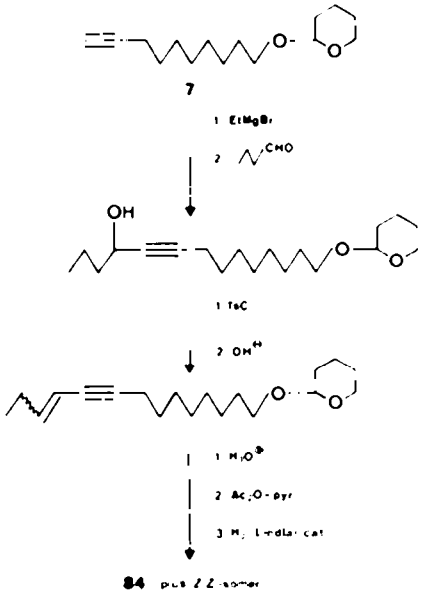
ratio of 9*Z*,11*E*:9*Z*,12*E* isomers for behavioral, laboratory response for this species was between 5:1 and 20:1. In contrast, in the field trapping studies of Neumark *et al.*,[176c] the 9*Z*,12*E* isomer was found to have an inhibitory effect on the attractancy of the 9*Z*,11*E* diene **84** at ratios of 1:20 and 1:50. However, admixture of the 9*Z*,12*E* isomer with **84** at ratios of 1:500 to 1:1600 were synergistic,[176c] increasing male moth catches of *S. littoralis* up to 2.5 fold. Kehat *et al.*[176f] found that addition of *ca.* 1% of the 9*Z*,12*E* isomer to *purified* **84** strongly enhanced the attraction. In field trapping experiments with **84** the addition of N-octyl-N'-phenyl-*p*-phenylenediamine (UOP 688) as an antioxidant was found by Neumark *et al.*[176b,c] to increase the longevity of the pheromone (see however Ref. 176*f*).

Nesbitt *et al.* first synthesized the (9*Z*,11*E*)-diene **84** by a Wittig condensation between (*E*)-2-pentenyltriphenylphosphonium bromide and 9-oxonon-1-yl acetate, and separation of the resulting isomers by argentation chromatography and preparative glc.[172a] This route was not stereoselective and thus they subsequently prepared **84** by a Wittig reaction between (*E*)-2-penten-1-al and a saturated alkyl ylide (Scheme 30) in dry dimethyl sulfoxide with sodium methylsulfinylmethide ("dimsyl sodium") as the base, followed by acidic hydrolysis and acetylation. This procedure gave a 53% yield of the diene as a mixture of the 9*Z*,11*E* and 9*E*,11*E* isomers in the ratio, 80:20. The 9*E*,11*E* isomer was selectively removed (as its Diels–Alder adduct) by treatment of this mixture with the appropriate amount of tetracyanoethylene in THF to give an overall yield of 38% of **84** containing *ca.* 1.5% of the 9*Z*,11*Z* isomer.[179] Goto *et al.*[180] also prepared **84** by the similar Wittig condensation of 9-acetoxynonyltriphenylphosphonium bromide with (*E*)-2-penten-1-al (see Scheme 30) in dimethyl sulfoxide using "dimsyl sodium" as the base (at 5°). These authors obtained a 74% yield of dienes containing 85–90% of **84** and 10–15% of the 9*E*,11*E* isomer. The latter diene was removed from the mixture by the formation of its Diels–Alder adduct with excess tetracyanoethylene, as above. These authors found that the alternative Wittig condensation of (*E*)-2-pentenyltriphenylphosphonium bromide with 9-oxonon-1-yl acetate gave a mixture of **84** and the 9*E*,11*E* isomer in various ratios depending on the solvent polarity and on the base used: in benzene (potassium t-butoxide), 40:60; in glyme (n-butyllithium), 50:50; and in dimethyl sulfoxide (dimsyl sodium), 60:40.[180] The diene **84** has also been prepared by a Wittig reaction between (*E*)-2-penten-1-al and 9-hydroxynonyltriphenylphosphonium bromide (see Scheme 30) in HMPT (n-butyllithium as the base) followed by acetylation of the product.[176c]

Acetylenic routes have also been utilized to synthesize **84**. Tamaki *et al.*[177a] prepared a mixture of the 9*Z*,11*E* and 9*Z*,11*Z* isomers, in presumably low yield, by Scheme 31 and isolated **84** by preparative glc. We prepared the diene from (*E*)-3-hexen-1-yne (**85**) via alkylation, hydroboration, and protonolysis as outlined in Scheme 32.[181] Pure **85** was obtained by spinning band distillation at atmospheric pressure of a mixture of the *E* and *Z* isomers which was prepared[182] from 1-hexyn-4-ol via[183] the *p*-toluenesulfonate (see Refs. 184, 185). Alkylation of the lithio derivative of **85** with 2-(8-bromo-1-octyloxy)tetrahydropyran in liquid ammonia-THF, followed by acid hydrolysis of the crude product and crystallization from pentane at low temperature, gave an 80% yield of pure (*E*)-11-tetradecen-9-yn-1-ol (**86**), m.p. 11°. The alcohol was protected as its trimethylsilyl derivative and the triple bond was hydroborated with 1.1 equiv. of disiamylborane in THF at −5° and the vinyl-boron intermediate was protonolyzed with acetic acid at 65°. After treatment with alkaline hydrogen peroxide to remove residual boron-containing impurities the product was purified by crystallization from pentane at −60° to give the pure alcohol **83** in 85% yield from **86** (see Scheme 23, Ref. 152). Acetylation gave **84** in 98.7% purity containing 0.5% of the *E*,*E* isomer.[181]† By a sequence analogous to Scheme 32 the 9*Z*,11*Z* isomer was prepared beginning with (*Z*)-3-hexen-1-yne. Isomerization of (9*Z*,11*Z*)-9,11-tetradecadien-1-ol (m.p. 17°) with benzenethiol[89] and repeated recrystallization from pentane gave the *E*,*E* alcohol (m.p. 25°) in 80% yield which

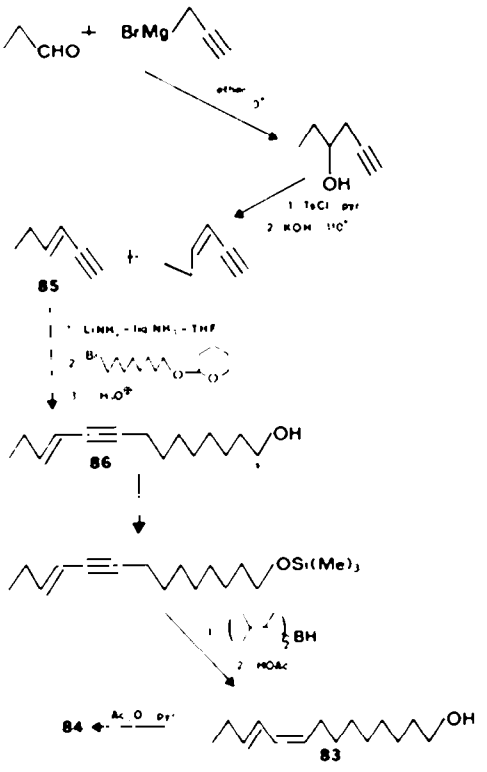


Scheme 30.

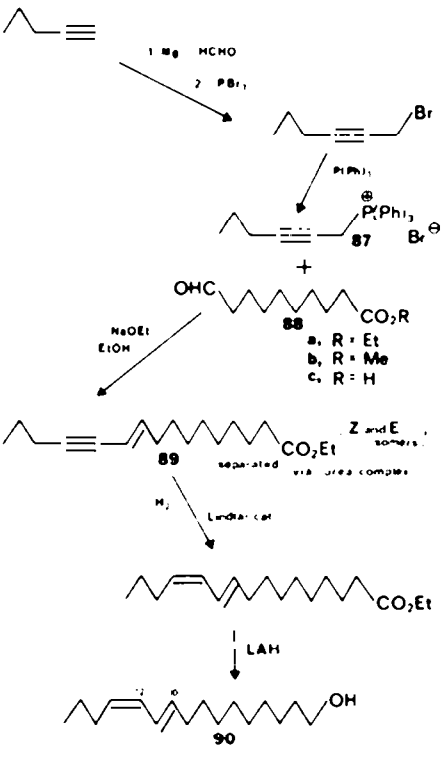


Scheme 31.

†When the pure 9*Z*,11*E* isomer **84** was distilled on a large scale (b.p. 111° at 0.26 mm) the distillate was found to contain *ca.* 3% of the *E*,*E* isomer and hence, in general, such dienes should not be distilled (see **59**, Scheme 23). The *E*,*E* isomer contaminant in this experiment was removed by selective urea clathration.



Scheme 32.

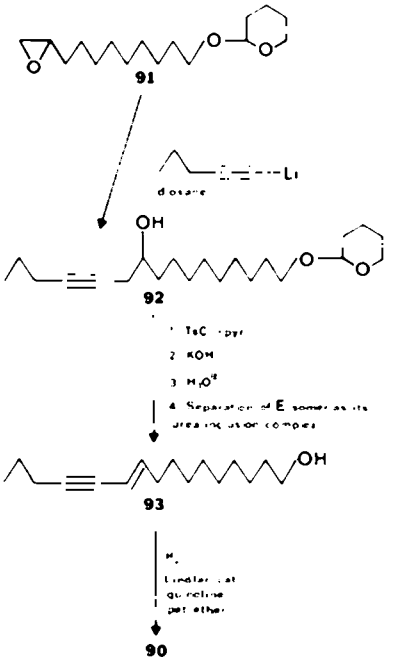


Scheme 33.

on acetylation gave the *E,E* acetate of 99.4% purity.[181]

(e) (10*E*,12*Z*)-10,12-*Hexadecadien*-1-*ol*. The isolation of lepidopterous sex pheromones was pioneered by Butenandt *et al.*[184] who, after almost 20 years of experimental work, starting with the glands from 500,000 females, identified (10*E*,12*Z*)-10,12-hexadecadien-1-ol (bombykol; **90**) as a pheromone of the female silkworm moth, *Bombyx mori*. The four geometric isomers of the conjugated dienol **90** were synthesized for comparison with the physiochemical and biological properties of the natural pheromone and the 10*E*,12*Z* isomer was found to be by far the most attractive to male silkworm moths in laboratory bioassays leaving no doubt that the natural pheromone is mainly the 10*E*,12*Z* isomer (although the potency of the natural material was considerably lower than that of synthetic **90**).[184-186]

In Scheme 33,[184,185] the pheromone was prepared non-stereoselectively via the Wittig condensation of triphenylphosphonium 2-hexynylide with ethyl 10-oxodecanoate (**88a**) (NaOEt in ethanol). The product from this reaction contained the *E* and *Z* isomers in approximately equal amounts and the *E* isomer **89** was separated by repeated recrystallization of its urea inclusion complex from methanol (the *Z* isomer remained in solution). The conjugated (*E*)-enyne **89** was then selectively hydrogenated over Lindlar catalyst (in petroleum ether with added quinoline) and the crude product was reduced with LAH. The resulting dienol was purified by treatment with urea in methanol.† Impurities were removed as their precipitated urea inclusion complexes with most of the desired diene **90** remaining in solution. The product from the mother liquors was then repeatedly recrystallized from petroleum ether at low temperature to give the pure (10*E*,12*Z*)-dienol **90**.



Scheme 34.

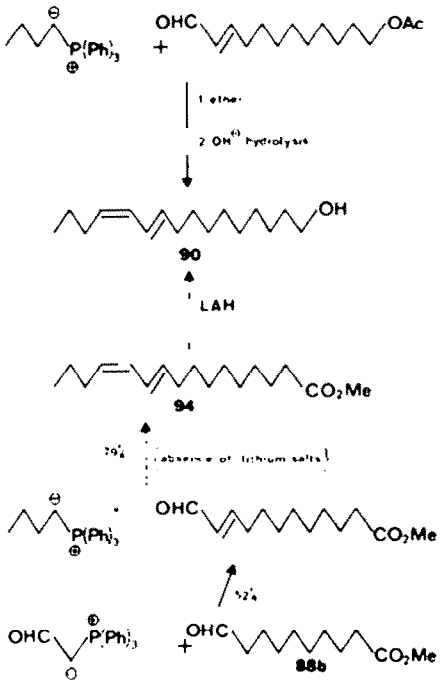
The pheromone **90** was also prepared (Scheme 34)[184,185] by an acetylenic route whereby the lithium salt of 1-pentyne was condensed with the epoxide **91** to give **92**. Dehydration *via* the *p*-toluene-sulphonate derivative and removal of the protective group gave a mixture of the *E*

†The partial hydrogenation of conjugated enynes such as **89** over Lindlar catalyst is not selective and usually gives mixtures (see Refs. 58*b*, 163*a*, 169).

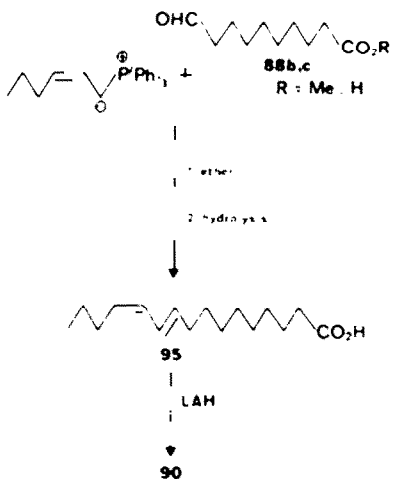
and *Z* enynols with the latter predominating. The *E* isomer **93** was separated as its urea inclusion complex and was purified by crystallization from petroleum ether at low temperature. Hydrogenation of **93** over Lindlar catalyst (in petroleum ether with quinoline added), precipitation of inclusion-forming impurities with urea, and low-temperature recrystallization as before, gave the pure pheromone **90**. These authors obtained **90** in low overall yields and made extensive use of urea inclusion complexes[187] and of low temperature recrystallization to purify the intermediates and the final dienols.

Truscheit and Eiter[188] prepared bombykol *via* the Wittig condensation of triphenylphosphonium n-butylide with (*E*)-12-acetoxy-2-dodecen-1-al (Scheme 35), which gave mostly the required 10*E*,12*Z* isomer plus a small amount of the 10*E*,12*E* isomer. The latter was removed by precipitation as its urea inclusion complex. These authors also used the Wittig condensation between triphenylphosphonium (*Z*)-2-hexenylide and the corresponding saturated aldehyde (Scheme 36) to prepare **90** (see Refs. 184, 185).[188] However, the alternative Wittig reaction in Scheme 35 was more stereoselective for the required 10*E*,12*Z* isomer. The mixture of dienoic *acids* from Scheme 36 was fractionally crystallized from petroleum ether to give the *Z*,*Z* acid (m.p. 34–35°) and the required 10*E*,12*Z* acid **95** (m.p. 25–26°). Recently, Bestmann *et al.*[188] also prepared **90** by a Wittig condensation between methyl (*E*)-12-oxo-10-dodecenoate and triphenylphosphonium n-butylide, in the absence of lithium salts,[69b] followed by reduction of the resulting ester **94** with LAH (Scheme 35). The dienol thus obtained contained *ca.* 92% of the required *E*,*Z* isomer **90**.

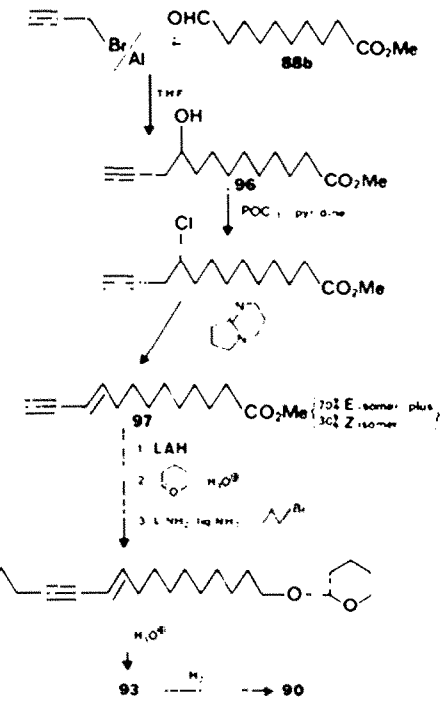
An alternative acetylenic route used to prepare bombykol is outlined in Scheme 37.[189] Dehydration of the alcohol **96** *via* the chloride, gave the enyne **97** as a mixture of *E* and *Z* isomers in the ratio *ca.* 7:3. Reduction of **97**, protection of the hydroxy group, alkylation with propyl bromide, hydrolysis, and crystallization of



Scheme 35.



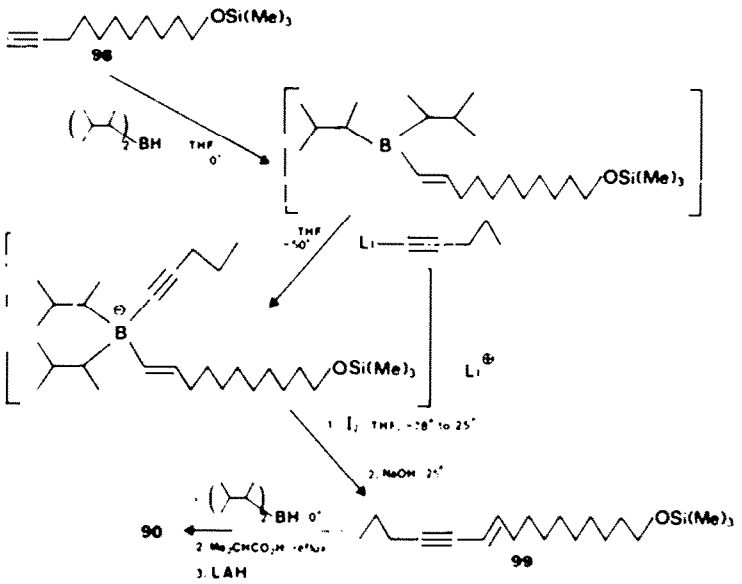
Scheme 36.



Scheme 37.

the product from petroleum ether at −20° gave the pure *E*-enyol **93** (see Scheme 34). Hydrogenation of **93** in methanol (no added quinoline) over a modified Lindlar catalyst gave impure bombykol. The *E*,*E* isomer was removed as its urea inclusion complex and the residue was repeatedly recrystallized from petroleum ether at −40° to give pure **90**.

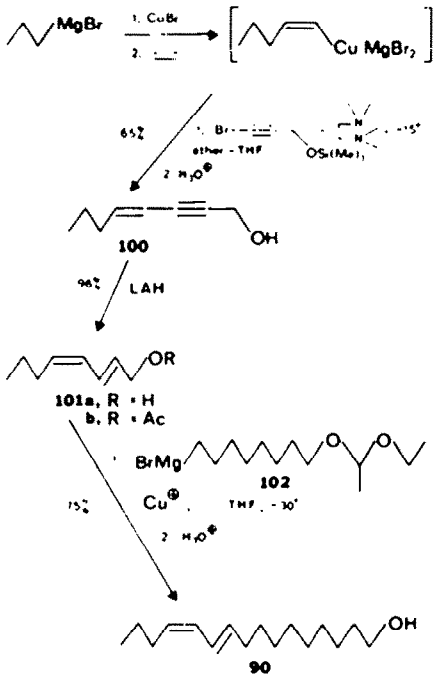
More recently Negishi *et al.*[161a] prepared bombykol as an application of their stereoselective synthesis of conjugated (*E*)-enynes (Scheme 38). Thus addition of disiamylborane to the acetylene **98** gave an alkenylborane which was treated with the lithium salt of 1-pentyne and the resulting complex was treated with iodine and sodium hydroxide to produce, in a highly stereoselective (>99%) manner the conjugated (*E*)-enyne **99** in 63% yield from **98**. The enyne **99** was then converted into **90** *via* hydroboration with 1 equiv. of disiamylborane (0°,



Scheme 38.

1 hr) followed by protonolysis with isobutyric acid and treatment of the butyrate ester thus obtained with LAH. As discussed previously (see Schemes 23 and 32) this hydroboration-protonolysis procedure for the conversion of conjugated enynes into dienes is far superior to partial hydrogenation over Lindlar catalyst (see Schemes 33, 34 and 37).

Finally, a synthesis of bombykol has been briefly described by Normant *et al.* as an application of their synthesis of conjugated enynes and dienes via vinylcopper intermediates (Scheme 39).[189] The propargylic alcohol **100** was converted in high yield to the (*E,Z*)-dienol **101a** by reduction with LAH. The allylic acetate **101b** was then coupled with the Grignard reagent **102** in



Scheme 39.

the presence of a catalytic quantity of Cu(I)[148] to give, after hydrolysis, the pheromone **90** (see Scheme 20[135]).

(6) *Nonconjugated dienes*

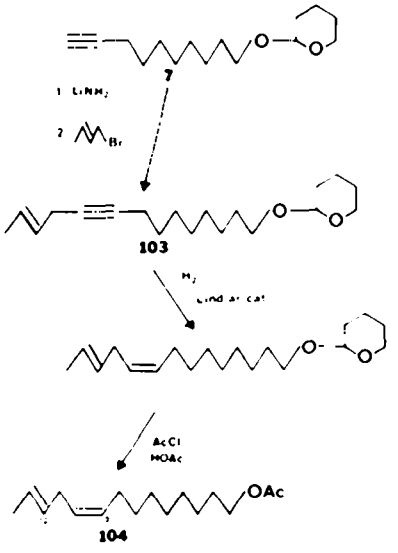
(a) (9Z,12E)-9,12-*Tetradecadien*-1-*yl acetate*. The almond moth, *Cadra cautella*, and the Indian meal moth, *Plodia interpunctella*, are serious pests of stored grain and dried fruits and these species are widely distributed in the Temperate and Tropical Zones of the world. Males of the almond moth respond to the crude pheromone extracted from females of the Indian meal moth and *vice versa*. A component of the sex pheromone of both of these species has been isolated from virgin female moths and identified as (9*Z*,12*E*)-9,12-tetradecadien-1-yl acetate (**104**).[190] It is the major component of the sex stimulatory and attractant pheromone of the female Indian meal moth, but in the female almond moth other components [including (*Z*)-9-tetradecen-1-yl acetate] are present that are necessary, in addition to **104**, for the elicitation of a normal response in almond moth males.[190a,c] Males of each of these species are preferentially attracted to females of their own species when females of the other species are present, and it appears that females of both species emit multiple-component pheromones which aid in isolating these species.[190c] The diene **104** has been identified, along with (*Z*)-9-tetradecen-1-yl acetate, as part of the sex pheromone of the female southern armyworm moth, *Spodoptera*(*Prodenia*) *eridania*.[191] The compound **104** has also been identified as a sex pheromone produced by the females of the Mediterranean flour moth, *Anagasta kühniella*,[190d,192] the tobacco moth, *Ephestia elutella*,[193] the beet armyworm, *Spodoptera exigua*,[194] the raisin moth, *Cadra figulilella*,[195] and also *Spodoptera litura*.[177] The behavioral response of male Indian meal moths to **104** is inhibited by the synthetic 9*Z*,12*Z* isomer of **104** in laboratory bioassays whereas the response of male almond moths is not affected by the presence of this isomer.[196]

It has also been found that the synthetic 9*E*,12*Z* and 9*E*,12*E* isomers of **104** inhibit the laboratory behavioral response of male Indian meal moths to the synthetic sex pheromone **104** when mixed individually in the ratio of 1:1 with **104**.[197] More recently it was found that female

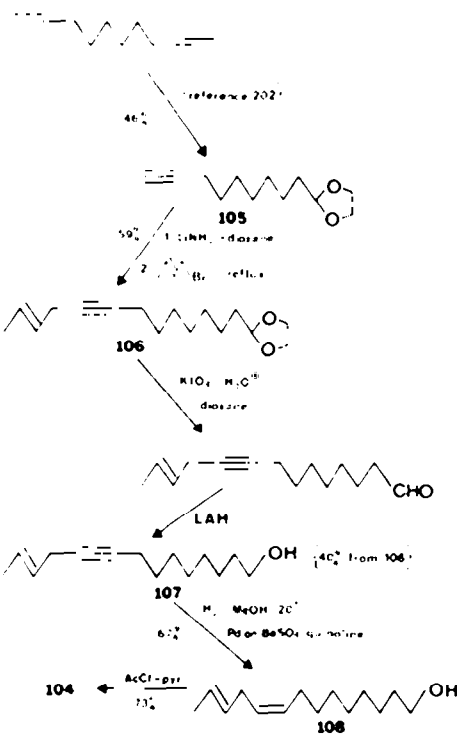
Indian meal moths release (9*Z*,12*E*)-9,12-tetradecadien-1-ol which inhibits the response of male almond moths to **104**.[198] Thus, it is important to have pure synthetic **104** for pheromone studies with these insect species. It must be emphasized that the identifications of **104** as a sex pheromone discussed above were initially made, in general, using laboratory bioassays which measure stimulatory activity and *short-range* attractiveness of a sex pheromone. Recently it has been reported that neither **104** nor (*Z*)-9-tetradecen-1-yl acetate were attractive, alone or in combination, to native male *Spodoptera exigua* or *S. eridania* in field tests using pheromone-baited sticky traps.[199a] Also, in an attempt to disrupt their mating, natural populations of *Plodia interpunctella* and *Cadra cautella* were continuously exposed to synthetic **104** [or to **104** plus (*Z*)-9-tetra-decen-1-yl acetate] in commercial peanut storage facilities. However, mating activity based on spermatophore counts of wild females sampled at intervals from the test buildings was *not* reduced in comparison to that of control females.[199b] The criterion of effectiveness in this study was the mating activity of the wild females rather than inhibition of attraction of wild males to caged laboratory-reared females. This lack of inhibitory effect of synthetic material on mating appears to indicate the existence of other important overriding mating stimuli.[199b,c] In another *laboratory* study, synthetic **104** (with and without an added antioxidant) was found to reduce the mating frequency of *P. interpunctella* held in enclosed environments. The effectiveness of any dose of **104** was markedly increased as the population density of moths decreased.[199d]

The pheromone **104** is an example of a (*Z*,*E*)-1,4-diene having "skipped" or "methylene-interrupted" double bonds. The synthesis of the corresponding (*Z*,*Z*)-1,4-dienes, typically present in poly-unsaturated fatty acids, has been extensively studied.[200] The diene **104** was synthesized initially as outlined in Scheme 40.[191] Coupling 2-(8-chloro-1-octyloxy)tetrahydropyran with lithium acetylide in dimethyl sulfoxide gave **7** in 74% yield. Reaction of the lithium salt of **7** with (*E*)-1-bromo-2-butene in dioxane gave the enyne **103** (29% yield) which was partially hydrogenated over Lindlar catalyst (86% yield) and the product treated with acetic acid and acetyl chloride under reflux to give, in 93% yield, the pheromone **104**. A similar route was used by Su *et al.*, (Scheme 41)[201] beginning with 1,9-decadiyne and crotyl alcohol. The acetal **105** was prepared from 1,9-decadiyne in 46% yield as described previously[202] and the lithium salt of **105** was coupled with (*E*)-1-bromo-2-butene in dioxane under reflux (16 hr) to give **106** in 59% yield. The alternative coupling of the Grignard reagent of **105** (prepared with ethylmagnesium bromide) with (*E*)-1-bromo-2-butene in THF *in the presence of* cuprous chloride and cuprous cyanide under reflux (36 hr) gave only a 29% yield of **106**. Hydrolysis of **106** and reduction gave **107** which was partially hydrogenated over 5% palladium on $BaSO_4$ to give the dienol **108**. Acetylation of **108** then gave the pheromone **104**, which after distillation was further purified by glc. Fukami *et al.*, have prepared all four possible isomers of **104** and their synthesis of the 9*Z*,12*E* isomer was similar to that outlined in Scheme 40.[192b]

The preparation of the 1,4-enynes **103** (Scheme 40)[191] and **106** (Scheme 41)[201] by coupling of lithium 1-alkyn-1-ides with (*E*)-1-bromo-2-butene in dioxane is noteworthy since the reaction of strongly basic *alkali* 1-alkyn-1-ides with allylic halides often gives a complex mixture of products. In addition to the formation of allylic rearrangement products and isomerization products (conjugated enynes) the initial 1,4-enyne can undergo abstraction of a proton (from the skipped methylene group) and further alkylation.[203,204] In a study of the reaction of sodium 1-alkyn-1-ides with allylic halides in liquid ammonia it was found that complex isomeric mixtures of mono-, di- and tri-allylation products were obtained.[204] For example, reaction of sodium 1-propyn-1-ide with one equiv. of 1-chloro-2-butene in liquid ammonia gave a mixture containing *ca.* 40% mono- and 55% di-allylation



Scheme 40.

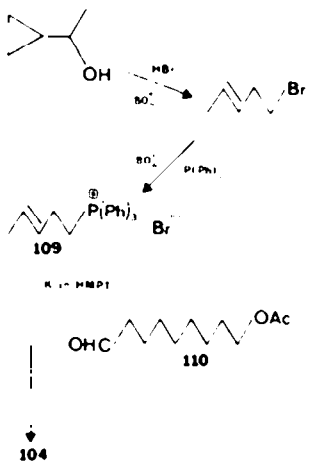


Scheme 41.

products. Reaction of sodium 1-butyn-1-ide gave an even more complex mixture of products under these conditions.[204] 1,4-Enynes can be prepared by the cuprous salt catalyzed coupling of 1-alkynylmagnesium halides with allylic halides in ether[205a] or in THF.[203,205b,c] In the absence of a cuprous salt catalyst little or no reaction occurs between an acetylenic Grignard reagent and an allylic halide in ether solution,[203,205a] although in THF as the solvent the reaction does proceed slowly.[206] The variant on this method of coupling allylic halides with free terminal alkynes under the influence of amines and catalytic amounts of cuprous salts (Cadiot–Chodkiewicz conditions) is not very useful for the synthesis of substituted 1,4-enynes, as the normal allylation product and the isomeric allylic rearrangement product are formed in similar amounts, irrespective of the substitution on the allylic halide.[207] The reaction of preformed cuprous 1-alkyn-1-ides with allylic halides in dipolar aprotic solvents also proceeds with partial allylic rearrangement. For example, the reaction of cuprous 1-heptyn-1-ide with 1 - bromo - 2 - butene in HMPT (at 25° in the presence of NaCN) gave in 76% yield a mixture of 9-undecen-6-yne and the isomeric allylic rearrangement product 8-methyl-9-decen-6-yne, in the ratio 3:1, respectively.[208] Both (*Z*)- and (*E*) - 1 - chloro - 2 - butene react with cuprous phenylacetylide (at 75° in the absence of solvent) to give the same isomeric enyne mixture, consisting of (*E*) - 1 - phenyl - 4 - hexen - 1 - yne and 3 - methyl - 1 - phenyl - 4 - penten - 1 - yne in the ratio 3:1, respectively.[209]

We synthesized the 1,4-enyne **103** (contaminated with *ca.* 9% of the allylic rearrangement product) in 75% yield by the coupling of (*E*)-1-bromo-2-butene in THF (3 hr under reflux), in the presence of cuprous chloride,[205] with the Grignard reagent prepared from **7** (with ethylmagnesium bromide).[38d] Conversion of **103** to the corresponding acetate and fractional distillation on a spinning band column gave the pure enyne acetate (free of the allylic isomer). The enyne **103** was also prepared in 60% yield (after separation from 15% of the allylic isomer) by the reaction of the Grignard reagent of **7** with (*E*)-1-chloro-2-butene (THF under reflux) using cuprous cyanide as the catalyst.[210] In an attempt to minimize the formation of the allylic rearrangement product, the reaction with (*E*)-1-chloro-2-butene was carried out in THF at 24° (15 hr) in the presence of lithium dichlorocuprate. Under these conditions using the lower reaction temperature, the product contained only 4.4% of the allylic isomer. After acid hydrolysis to remove the protecting group and crystallization of the product from hexane and ethyl acetate at −35°, a 72% yield of pure (*E*)-12-tetradecen-9-yn-1-ol (**107**; m.p. 18°) was obtained. Partial hydrogenation of the triple bond in **107** over Lindlar catalyst in THF–hexane (containing synthetic quinoline) at 0 to −5° gave the (9*Z*,12*E*)-dienol **108** which was recrystallized from hexane at −55° (96% yield from **107**) and acetylated with acetic anhydride and pyridine. The pheromone obtained by this route was found, by glc analysis, to be 98.1% pure **104** (as the 9*Z*,12*E* isomer).[210]

The pheromone has also been prepared by the Wittig condensation (Scheme 42) between triphenylphosphonium (*E*)-3-pentenylide and 9-acetoxy-1-nonanal (**110**) using either potassium in HMPT[211a] or dimsyl



Scheme 42.

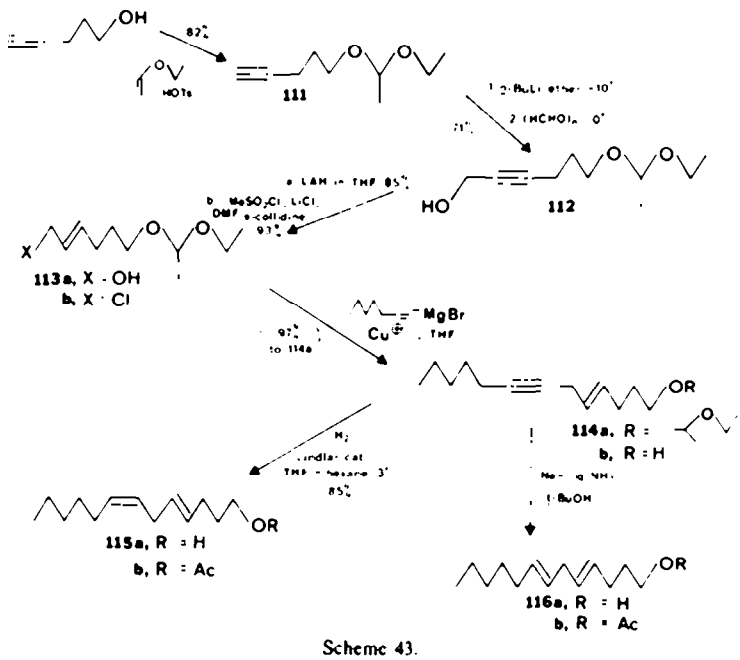
sodium in dimethyl sulfoxide.[211b] Under the former conditions a yield of 40% was obtained with the product containing 95% of the 9*Z*,12*E* isomer, plus 5% of the 9*E*,12*E* isomer.[211a] In the latter case a 53% distilled yield was obtained and the product contained 9% of the 9*E*,12*E* isomer which was removed by argentation chromatography (hplc on a silver nitrate-Florisil column).[211b] The homoallylic bromide used to prepare the crystalline phosphonium salt **109** was synthesized in 80% yield via the Julia rearrangement of 1-cyclopropylethanol with aqueous hydrobromic acid.[119]

The 1,4-diene **104** was found to autooxidize significantly on exposure to air at room temperature after only a few hours.[210] Irradiation in air with sunlight gave a mixture of (9*Z*,11*E*) - 13 - hydroperoxy - 9,11 - tetradecadien - 1 - yl acetate and (10*E*,12*E*) - 9 - hydroperoxy - 10,12 - tetradecadien - 1 - yl acetate.[212] Addition of 2,6 - di - *tert* - butyl - 4 - methylphenol (BHT) to **104** was effective at preventing autooxidation without producing any mating inhibitory effects.[212] The antioxidant N - phenyl - N′ - octyl - 1,4 - phenylene - diamine has also been added (5% by volume) to **104** to stablize the pheromone for use in laboratory mating disruption studies.[199d] The addition of a mixture of 0.2% BHA, 0.2% BHT, and 0.1% citric acid is even more effective than the use of 0.2% N,N′-dioctyl-1,4-phenylenediamine or of 0.2% BHT at preventing air oxidation of the 1,4-diene **104**.[210]

(b) (4E,7Z)-4,7-*Tridecadien*-1-*yl acetate*. The potato tuberworm moth, *Phthorimaea operculella*, is a widely distributed pest of solanaceous crops. A component of the sex pheromone has been isolated from the extracts of female abdominal tips and identified as the unusual odd-cabon-chain compound, (4*E*,7*Z*) - 4,7 - tridecadien - 1 - yl acetate (**115b**).[213a,c]† The sex pheromone of the potato tuberworm moth does contain a second active ester component[213a] which has recently been identified as (4*E*,7*Z*,10*Z*) - 4,7,10 - tridecatrien - 1 - yl acetate,[215] and found to be more attractive than the diene ester **115b**. However the 1,4-diene **115b**, by itself, is a useful attractant for male moths in the laboratory and in the field.[213a,214c] The compound **115b** is the first odd-carbon-chain acetate to be identified as a sex pheromone of a lepidopterous species.

The synthetic route we followed to prepare the pheromone **115b** is outlined in Scheme 43.[213] 4-Pentyn-1-ol was converted to the mixed acetal **111** with ethyl vinyl

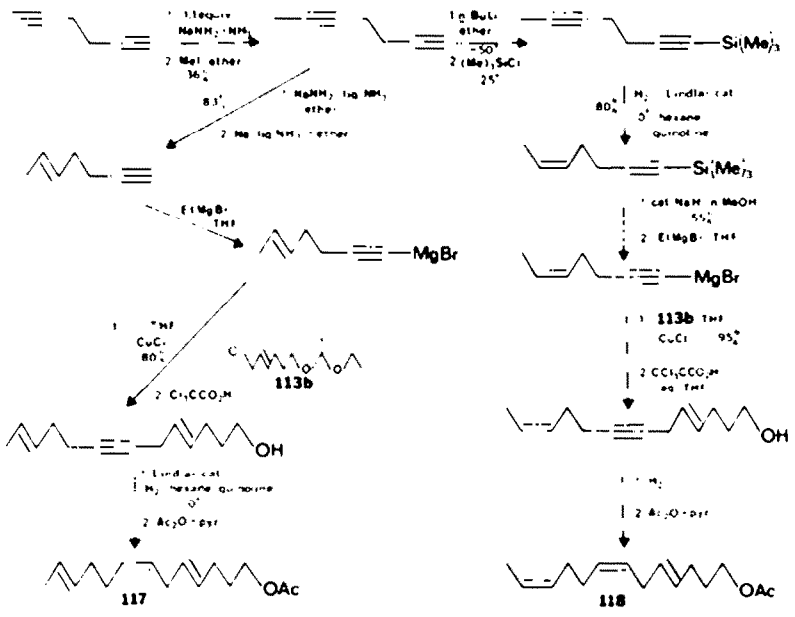
†In an unsuccessful attempt to elucidate the structure of this pheromone it was found that a synthetic isomeric mixture of 7,11-tridecadien-1-yl acetates showed some attractancy for male potato tuberworm moths in the field.[214a,c]



Scheme 43.

ether to protect the alcohol function.[158] Treatment of **111** with n-butyllithium gave the lithium salt which reacted with paraformaldehyde in ether–THF to give the acetylenic alcohol **112** in 71% yield. Stereoselective reduction of **112** with LAH in THF under reflux gave the (*E*)-allylic alcohol **113a** in 85% yield. This alcohol was converted to the desired allylic chloride **113b** in 93% yield by the method of Collington and Meyers (using methanesulfonyl chloride, lithium chloride, and 2,4,6-trimethylpyridine in dimethylformamide at 3°).[131] The formation of **113b** under these conditions proceed without any detectable allylic rearrangement or loss of stereochemistry and without any attack on the acid-sensitive acetal protecting group. Coupling of the allylic chloride **113b** with 1-heptynyl-1-magnesium bromide (prepared from 1-heptyne and ethylmagnesium bromide in THF under reflux for 2 hr) was achieved by heating the two reactants in THF under reflux (4.5 hr) in the presence of a catalytic quantity of cuprous chloride.[203,205] Hydrolysis of the crude coupling product **114a** with trichloracetic acid in aqueous THF and crystallization of the distilled alcohol from pentane at −70° gave the enyne alcohol **114b** (98.8% purity by glc analysis) in 60% yield. Selective partial hydrogenation of the triple bond in **114b** over Lindlar catalyst in hexane–THF (containing synthetic quinoline) at 3° followed by acetylation gave the 4*E*,7*Z* diene acetate **115b** (98% purity by glc analyses) in 17% overall yield from 4-pentyn-1-ol.[213] Glc analysis of the corresponding benzoate showed this material to contain 0.7% of the 4*E*,7*E* isomer (**116b**). This inactive 4*E*,7*E* isomer was prepared in 60% yield by reducing the 1,4-enyne alcohol **114b** with lithium (1% sodium) in liquid ammonia-THF in *the presence of ethanol*, followed by acetylation of the resulting dienol **116a**. The product prepared by this method was found to contain none of the 4*E*,7*Z* isomer but did contain 9% of a mono-olefin byproduct formed by over-reduction, presumably via lithium amide catalyzed conjugation of the diene or of the enyne and subsequent reduction. In an attempt to prepare (*E*,*E*)-1,4-dienoic acids it was reported by Gunstone and Jie that reduction of 1,4-diynes with lithium in liquid ammonia-THF (in the absence of any added alcohol) gave *only* a mixture of (*E*)-monoenoic acids.[58a] For example, a 6,9-diynoic fatty acid under these conditions gave a mixture of the 6*E* (15%), 7*E* (36%), 8*E* (33%) and 9*E* (16%) enoic acids.[58b] Thus, such reduction of 1,4-diynes are usually accompanied by, or preceded by, base-catalyzed isomerization to a compound with conjugated unsaturation and this is then reduced to the monoene level. Treatment of 1,4-enynes with metal amides (Li, Na, K and Ca) in liquid ammonia has been shown to give rapid rearrangement to (*E*)- and (*Z*)-1,3-enynes (with the *Z* isomer predominating).[216] However, there is a report of the successful reduction of 9,12-octadecadiynoic acid to (9*E*,12*E*)-9,12-octadecadienoic acid with sodium in liquid ammonia-diethyl ether at room temperature in an autoclave.[205c] In a further study of the above reduction of the 1,4-enyne **114b** we found that the reaction of **114b** with sodium in liquid ammonia-THF in the presence of t-butyl alcohol gave less overreducation than in the presence of ethanol. No 4*E*,7*Z* isomer was formed under these conditions and the (4*E*,7*E*)-dienol **116a**, after crystallization from pentane at −60°, was obtained in 70% yield with a purity of 95% and contained 2.4% of a dihydro byproduct.[217] Dahm also successfully reduced a 1,4-enyne system to the corresponding 1,4-diene with sodium in liquid ammonia in the presence of t-butyl alcohol, in preparing isomers of **104**.[218] The 1,4-dienes **115b** and **116b** were stabilized by the addition of 0.1% of BHT and stored under nitrogen to prevent autooxidation.

In an unsuccessful attempt to identify the second active ester component of the sex pheromone of the potato tuberworm moth,[215] the two trienes (4*E*,7*Z*,11*E*)- and (4*E*,7*Z*,11*Z*)-4,7,11-tridecatrien-1-yl acetate (**117** and **118**, respectively) were prepared as outlined in Scheme 44.[217] Although neither of these trienes is a natural pheromone, both gave positive electroantennogram responses [but less than that of the natural (4*E*,7*Z*,10*Z*)-triene] and in field trapping studies the (4*E*,7*Z*,11*E*)-triene **117** was a potent attractant for male moths, being more active than virgin females.[219]



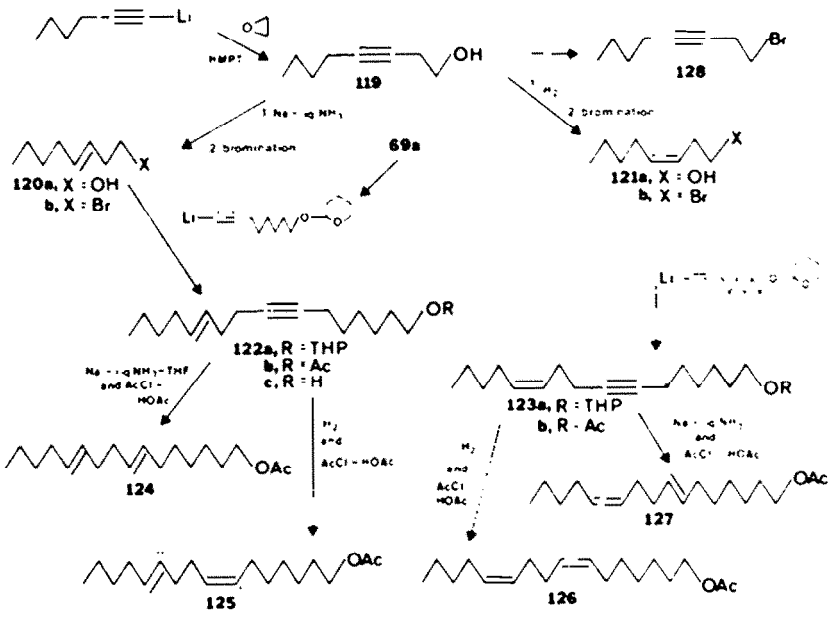
Scheme 44.

(c) (7Z,11E)- *and* (7Z,11Z)-7,11 - *Hexadecadien* - 1 - *yl acetate*. The pink bollworm moth, *Pectinophora gossypiella* is a very destructive pest of cotton in many areas of the world. The sex pheromone of this species was originally assigned the structure (*E*) - 10 - n - propyl - 5,9 - tridecadien - 1 - yl acetate (propylure),[220] and even though synthetic propylure exhibited very little biological activity in the field, many different syntheses of this 1,5-diene were carried out.[13] However, after considerable controversy the sex pheromone released by the female pink bollworm moth was identified as a *ca.* 1:1 mixture of (7*Z*,11*E*)- and (7*Z*,11*Z*) - 7,11 - hexadecadien - 1 - yl acetates and this mixture was given the name gossyplure.[221,223] The 1:1 combination of the 7*Z*,11*E* isomer **125** and the 7*Z*,11*Z* isomer **126** was by far the most attractive mixture to male moths in field tests in the USA.[221,222] Addition of as little as 10% of either the 7*E*,11*Z* or the 7*E*,11*E* isomer greatly diminished the attractiveness of the 1:1 mixture of **125** and **126**.[222] All four of the individual geometric isomers were inactive alone in field trapping studies, and other two-component mixtures showed little activity.[222] Considerable field testing has been carried out with gossylplure in studies designed to monitor the presence of, or to control the pink bollworm (by trapping and by communication disruption techniques).[223b,224–226] Field trials in Malawi have shown that gossyplure is very attractive to male pink bollworm moths, and the ratio of geometrical isomers was found to be critical for optimal field attraction.[224] However, in Malawi a mixture of 55–60% of the *Z*,*Z* isomer **126** in combination with 45–40% of the *Z*,*E* isomer **125** performed significantly better than all other isomer ratios, including the 1:1 optimal ratio reported in the USA.[221,222]

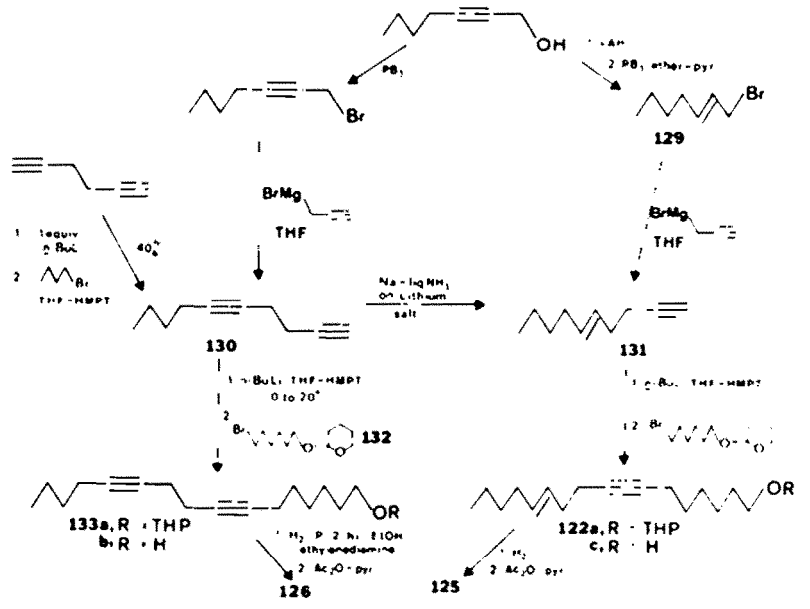
Through empirical screening of synthetic compounds, (*Z*) - 7 - hexadecen - 1 - yl acetate (hexalure)[227] was found to be an attractant for male pink bollworm moths both in the laboratory and in the field and hexalure was used extensively prior to the identification of gossyplure.[223,225] The 7*Z*,11*E* isomer **125** has also been identified as a sex pheromone of the female Angoumois grain moth, *Sitotroga cerealella*.[228] The other three geometric isomers appeared to have almost no biological activity for this species. The two gossylplure components **125** and **126** have been prepared separately via acetylenic intermediates,[222,228,229,230a,231,232] by allylic Grignard coupling,[222,230b] and by Wittig olefination reactions.[230a,231] The pheromone has then been constituted by mixing the separate isomers in a 1:1 ratio. In a different approach we prepared directly the required 1:1 mixture of isomers by a single synthetic scheme involving the stereochemical control of the Wittig olefination reaction.[68,234]

Su and Mahany[228a] prepared all four of the possible geometrical isomers in moderate overall yields by an acetylenic route using 3-octyn-1-ol (**119**) and 2 - (6 - chloro - 1 - hexyloxy)tetrahydropyran (Scheme 45). This general route was considerably improved by Disselnkötter *et al.* who obtained overall yields of 31–34% from **119**.[231] The latter group prepared the homoallylic bromides **120b** and **121b** from the corresponding alcohols in *ca.* 85% yields by use of triphenylphosphine dibromide in dioxane containing pyridine, whereas the former workers used phosphorus tribromide in ether–pyridine and only obtained 50–56% yields of the bromides. The coupling reactions of the bromides **120b** and **121b** with the lithium salt of **69a** were carried out in dioxane at 100° (22–25% yields)[228] or in diglyme at 110° (62–66% yields).[231] Under the latter conditions the acetylenic bromide **128** underwent dehydrobromination (see Ref. 58*b*).[231] The *E* configuration in **120a**, **124** and **127** was generated by sodium-liquid ammonia reduction of a triple bond, and the *Z* configuration in **121a**, **125** and **126** was formed by selective hydrogenation of a triple bond over either palladium on calcium carbonate in ethanol (with added quinoline)[228] or over a modified Lindlar catalyst in petroleum ether (no added quinoline).[231] By capillary glc all four of the geometrical isomers, **124–127**, could be separated and the isomeric purities of the products could be established.[231] Using Scheme 45, Disselnkötter *et al.* prepared **126** in a purity of 95.7% (containing 2.4% of **125** and 1.9% of **127**) and **125** in a purity of 97.1% (containing 1.4% of **126** and 1.5% of **124**).[231]

Mori *et al.* synthesized **125** and **126** by Grignard



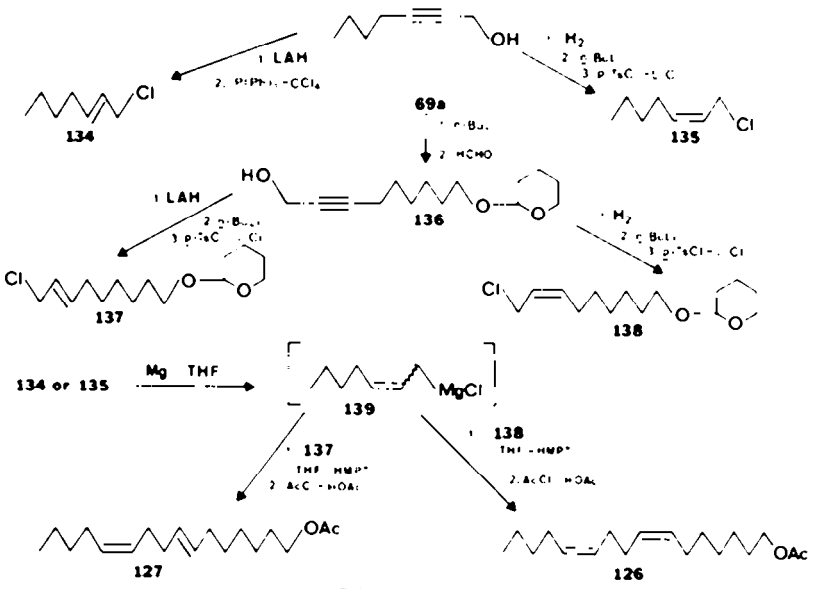
Scheme 45.



Scheme 46.

coupling reactions as outlined in Scheme 46.[229] Coupling of propargylmagnesium bromide with 1-bromo-2-heptyne and with the crude allylic bromide **129** gave the diyne **130** and the enyne **131** in crude yields of 79% and 63%, respectively. Both products contained some allenic impurities but after alkylation of the lithium salts of crude **130** and **131** with the bromide **132** in HMPT–THF and chromatography of the products on alumina, the diyne **133a** and the enyne **122a** were obtained in yields of 62% and 87%, respectively. Acidic hydrolysis to remove the protecting group, followed by partial hydrogenation of the alcohols **133b** and **122c** over P-2 nickel[53] and then acetylation, gave the pheromone components **126** (32% yield from 1-bromo-2-heptyne) and **125** (47% yield from **129**). Bierl *et al.*[222] prepared the 7*Z*,11*E* isomer **125** starting from 1,5-hexadiyne. Monoalkylation[58b,231] of the monolithium salt of this diyne with 1-bromobutane in HMPT–THF followed by fractional distillation gave a 40% yield of 1,5-decadiyne (**130**) (Scheme 46). Reduction of the lithium salt of **130** with sodium in liquid ammonia (see Ref. 62) gave (*E*)-5-decen-1-yne (**131**) which was then converted to **125** by a similar route to Scheme 46.

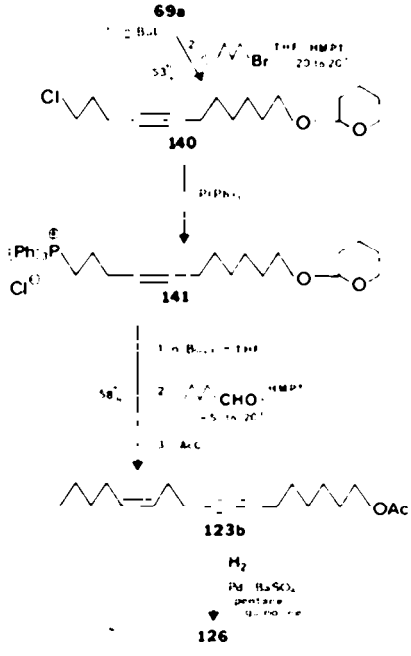
Bierl *et al.*[222] also prepared all four isomers, in low yield, by the coupling of allylic halides with an allylic Grignard reagent (Scheme 47).[222,230b] A study was made of the coupling of the allylic Grignard reagent **139** prepared from 1-chloro-2-heptene (**134** or **135**), with the *E* and *Z* allylic chlorides **137** and **138**. It is known that both members of a pair of isomeric alkyl-substituted allylic halides form Grignard reagents that are chemically indistinguishible,[125,236] and that such reagents appear to exist in diethyl ether solution, at room temperature, as a



Scheme 47.

rapidly equilibrating mixture of *Z* and *E* isomers with the equilibrium well on the side of the structures with the magnesium covalently bonded to the primary carbon.[125,236,237] In ether solution the coupling of either member of a primary-secondary pair of allylic chlorides with an alkyl-substituted allylic Grignard reagent gives a mixture of dienes in which the products having a primary allylic residue coupled to a secondary one usually predominate.[125,236] Sonnet *et al.*[230a] found that coupling of the allylic Grignard reagent **139** with the allylic chlorides **137** and **138** in THF gave mixtures containing 85–90% of secondary coupled products (not further investigated). In the case of **137** the primary coupled, unbranched product contained a *Z*:*E* ratio at the generated 11-ene double bond of 43:57, respectively. In anticipation of suppressing secondary coupling and preserving the geometry of the 7-ene double bond, these reactions were also carried out in the presence of HMPT.[130] Indeed, the reaction of the allylic Grignard reagent **139** with the allylic chlorides **137** and **138** in THF, containing 18% HMPT as a cosolvent, gave only 45–50% of secondary coupled products, but surprisingly, in the unbranched products of primary coupling, the 11-ene double bond originating from the Grignard portion had almost entirely (94–96%) the *Z* configuration.[230b] Thus the 7*Z*,11*Z* isomer **126** could be prepared from the coupling of **139** with **138** in the presence of HMPT, followed by acetolysis, and the 7*E*,11*Z* isomer **127** could be prepared via the reaction of **139** with **137**. The isomers **124** and **125** were prepared in low yield by the coupling reaction in the *absence* of HMPT followed by separation of the resulting mixtures by preparative glc followed by silver nitrate-silica gel column chromatography; however, this scheme is unsatisfactory for their preparation and the isomer **125** could not be obtained free of **127**.

In view of the limited success of this method for preparing the dienes via the coupling of allylic Grignard reagents (Scheme 47), Sonnet set out to develop an alternative practical route for the preparation of **125** and **126** using a Wittig condensation (Scheme 48).[230a] Alkylation of the lithium salt of **69a** with 1-bromo-3-chloropropane in HMPT–THF gave **140** in 53% yield. Treatment of **140** with triphenylphosphine gave the phosphonium salt **141** which was converted to the ylide with n-butyllithium. Condensation of this ylide with 1-pentanal in HMPT–THF and acetolysis of the product gave the enyne **123b** (58% yield from **141**) containing the *Z* and *E* isomers in the ratio 96:4 (see Ref. 68). Partial hydrogenation of the triple bond then gave the *Z*,*Z* isomer **126** in a purity of 93% (containing *ca.* 3.5% of the 7*Z*,11*E* isomer **125** and 3.5% of the 7*E*,11*Z* isomer **127**). However, Sonnet was unable to modify the Wittig conditions to stereoselectively obtain the other required isomer, **125**. Subsequently, Sonnet[230c] isomerized the 7*Z*,11*Z* and 7*Z*,11*E* isomers (as their tetrahydropyranyl ethers) to the 7*E*,11*E* and 7*E*,11*Z* isomers, respectively, by the method of Vedejs and Fuchs (treatment of the bis-epoxides with lithium diphenylphosphide and then

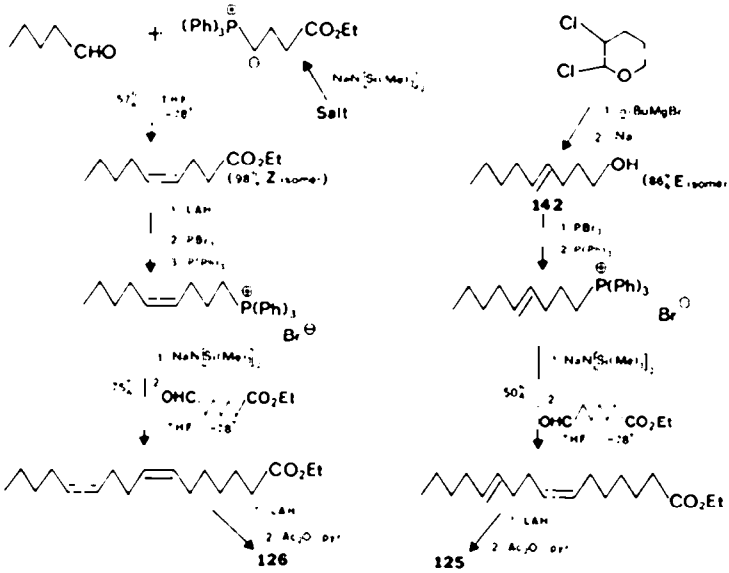


Scheme 48.

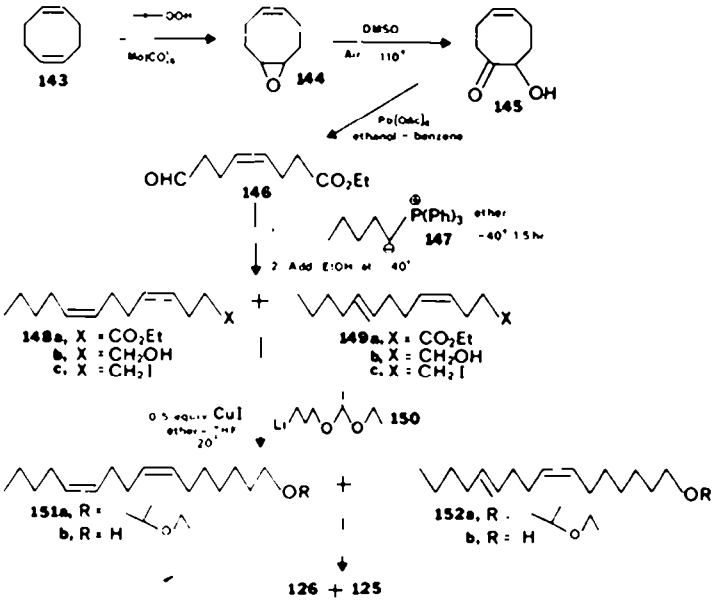
methyl iodide).[218] The proximity of the double bonds in these dienes did not cause any side reactions during these isomerization reactions. Sonnet reported that he was unable to cleanly prepare the 7*E*,11*Z* and 7*E*,11*E* isomers by sodium-liquid ammonia reductions of the corresponding 1,5-enyne or 1,5-diyne system (see however, Scheme 45).[230c] For example, reduction of the 7,11-diyne **133a** with excess sodium in liquid ammonia containing t-butyl alcohol produced a mixture containing 72% of the *E*,*E* diene, 5% each of two cyclic products, and 18% of other dienes.[230c] Presumably the proximity of the unsaturated centers led to side reactions.

Bestmann *et al.*[231] prepared the isomers **125** and **126** separately by means of Wittig condensations (Scheme 49). They observed that generation of non-stabilized ylides with sodium bis(trimethylsilyl) amide in THF was more convenient than the previous method (using sodium amide in liquid ammonia and subsequent replacement of the ammonia by another solvent; see Refs. 68, 69*a*), and these conditions gave highly (*Z*)-stereoselective olefin formation due to the absence of lithium salts (with or without the removal of the sodium bromide).[69a] The stereoselectivity was also found to be temperature dependent and by operating at −78° the *Z*:*E* ratio in the disubstituted olefin product was 98:2, whereas at 20° the ratio was 94:6 (see Ref. 68). By this route the *Z*,*Z* isomer **126** was obtained in 94.5% purity (Scheme 49), but the 7*Z*,11*E* isomer **125** was prepared in only 83.7% purity due to the lower stereoselectivity obtained in the preparation of (*E*)-4-nonen-1-ol (**142**).

We prepared gossyplure directly by a single synthetic scheme involving the controlled partial equilibration of the intermediate adducts in a Wittig reaction (Scheme 50).[68,234] Since both of the 7*E* isomers inhibit the at-



Scheme 49.



Scheme 50.

traction of pink bollworm males to the pheromone,[222] we defined the stereochemistry at this double bond by choosing a starting material already possessing a *Z* olefinic bond. This was achieved by taking advantage of the stereochemistry present in the readily available (*Z,Z*)-1,5-cyclooctadiene (**143**) and carrying out a selective, nonsymmetrical cleavage of one of the double bonds, which provided an intermediate containing not only the required functional groups but also the *Z* double bond. Thus oxidation of **143** with either one equiv. of *m*-chloro-perbenzoic acid or with t-butyl hydroperoxide (in the presence of molybdenum hexacarbonyl) gave the monoepoxide **144** in 65–70% yield. Bubbling air through a solution of **144** in dimethyl sulfoxide at 110° gave a 50% yield (after chromatography) of the α-ketol **145**, and lead tetraacetate (1 equiv.) cleavage of **145** in benzene-ethanol gave the aldehyde-ester **146** in 91% yield. A study was then made of the factors influencing the stereochemical outcome of the Wittig reaction of the aldehyde **146** with triphenylphosphonium n-pentylide (**147**). It was known that aliphatic nonstabilized triphenylphosphonium ylides react with aliphatic aldehydes such as **146** in nonpolar solvents (e.g. benzene or THF) in the absence of inorganic ions ("salt-free"), to give predominately erythro intermediate adducts which undergo elimination of triphenylphosphine oxide to give the *Z* olefins (>90%).[68,69] The same result is obtained in the presence (or absence) of lithium salts if the reaction is carried out in a dipolar aprotic solvent such as dimethylformamide, dimethyl sulfoxide, or hexamethylphosphoric triamide. In non-polar solvents the stereochemistry of the olefin product is dependent on the nature of the inorganic salt present.[117,239] A normal Wittig reaction between **146** and **147** in ether in the presence of lithium bromide, gave a 78:22 ratio of **148a**:**149a**, respectively, and a "salt-free" reaction in benzene at 0° gave a 94:6 ratio of **148a**:**149a**, respectively. However, when the ylide **147** (prepared from the phosphonium bromide salt with n-butyllithium) was allowed to react in ether (in the presence of LiBr) with the aldehyde **146** at −40° for 1–1.5 hr, followed by the slow addition of ethanol to the intermediate adduct (**153** or **154**), and the resulting reaction mixture was allowed to remain *ca.* 10 min at −40° prior to warming to room temperature, then a 1:1 mixture of **148a** and **149a** was reproducibly obtained (in 60–65% yield). The aldehyde and ylide presumably react initially in ether to give a betaine (**153**) or an oxaphosphetane (**154**) with predominately the erythro configuration, and the subsequent addition of ethanol at −40° facilitates the partial equilibration of this adduct, prior to olefin formation, to give some of threo adduct and hence an increase in the proportion of the *E* isomer in the olefin product. The equilibration appears to occur via the removal, by lithium ethoxide in ether-ethanol, of the proton on the carbon adjacent to the phosphorous atom in the protonated betaine **155** (i.e. the β-hydroxyphosphonium salt **155** gives reversibly the β-hydroxy ylide **156**). Longer times of equilibration of the Wittig intermediate (with ethanol) at lower temperatures gave increasing proportions of the *E* isomer **149a** up to a maximum of *ca.* 75%, but this method is unlikely to give more than 80–90% of the *E* isomer with these reactants.[68] To complete the synthesis of gossyplure, a functionalized three-carbon unit was coupled with the appropriate derivative of **148a** + **149a**. Thus, reduction of the 1:1 mixture of esters **148a** + **149a** with LAH gave the alcohols which were converted to the iodides in 88% yield (from the esters) via the corresponding mesylates. The iodides **148c** plus **149c** were then coupled in ether–THF at 20° with the lithium dialkylcuprate complex[158] prepared from the lithium reagent **150**,[158] to give the mixture of acetals **151a** plus **152a**. Mild acidic hydrolysis gave the 1:1 mixture of the alcohols **151b** and **152b** in 82% overall yield from the iodides. Finally, acetylation of the alcohol mixture gave gossyplure (1:1 mixture of **126** and **125**) in a purity of 99%.[68,234]

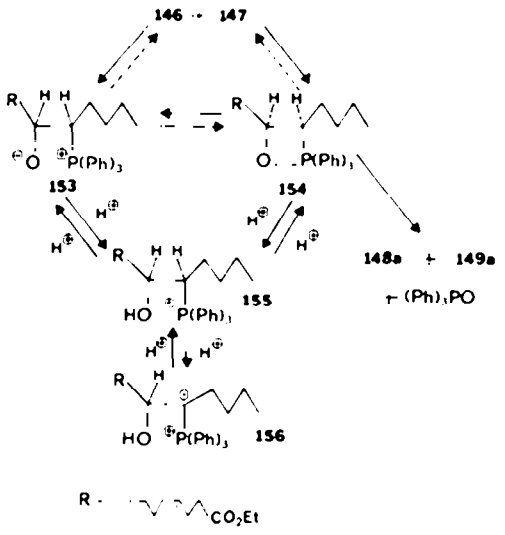
(d) (3*E*,13*Z*)- *and* (3*Z*,13*Z*) - 3,13 - *Octadecadien* - 1 - *yl acetate.* The lesser peachtree borer, *Synanthedon pictipes*, and the closely related species the peachtree borer, *Sanninoidea exitiosa*, are isolated reproductively by the different male responses to two geometrical isomers. Thus (3*E*,13*Z*) - 3,13 - octadecadien - 1 - yl acetate (**159**) was isolated and identified as a pheromone from the female lesser peachtree borer, whereas the corresponding 3*Z*,13*Z* isomer **160** was identified as a pheromone from the female peachtree borer.[240] Pure synthetic samples of these compounds strongly attracted the respective males of these species in field bioassays. These two C-18 isomers possess the longest carbon chain of any diene acetate isolated thus far from a lepidopterous species and identified as a sex pheromone.

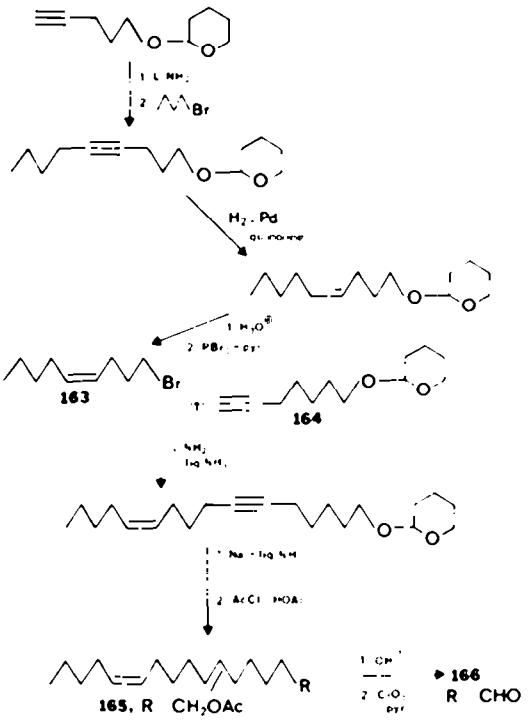
Sanninoidea exitiosa males did not respond to the *E,Z* isomer **159**, and low concentrations of it in the *Z,Z* isomer did not interfere with their response to the *Z,Z* isomer. Mixed in a 1:1 ratio with the *Z,Z* isomer, the *E,Z* isomer did appear to inhibit the *S. exitiosa* male response,[240a] although it has also been reported that traps baited with a mixture containing *ca.* 93% of the *Z,Z* isomer plus 7% of the *E,Z* and *Z,E* isomers were considerably more attractive to *S. exitiosa* males in the field than were traps baited with only the *Z,Z* isomer.[240b] In contrast, as little as 0.5% of the *Z,Z* isomer **160** in the *E,Z* isomer significantly inhibited the response of *Synanthedon pictipes* males to their pheromone, the *E,Z* isomer **159**. This strong inhibition of the response of males of one species (*S. pictipes*) by the pheromone of the other species (*S. exitiosa*) reinforces their reproductive isolation.[240a,c]

All four geometrical isomers of 3,13-octadecadien-1-yl acetate were synthesized by acetylenic routes (Scheme 51).[240a] The *Z,Z* isomer **160** was prepared by partial hydrogenation of the diyne **157** and the *E,Z* isomer **159** was prepared by sodium-liquid ammonia reduction of the enyne **158**. The isomers were purified by preparative glc to give the compounds **159–162** each containing *ca.* 3–5% of one or more of the other isomers. The *Z,Z* isomer **160** prepared in this way, was attractive to *S. exitiosa* males in the field but the synthetic *E,Z* isomer **159** was only slightly attractive to *S. pictipes* males. Further purification of the isomers by repeated hplc on a silica gel-silver nitrate column gave materials of 99.5% purity. The *purified E,Z* isomer **159** was then as attractive to the male *S. pictipes* moths as was the natural pheromone. Neither of these two pure isomers attracted the other species, nor were the *E,E* and *Z,E* isomers attractive to either species.†

(e) (6*E*,11*Z*) - 6,11 - *Hexadecadien* - 1 - *yl acetate. Antheraea polyphemus* is a wild silkmoth which occurs in the United States of America and in Canada from coast to coast. The sex pheromone isolated from the female abdominal tips of this species has been shown to contain (6*E*,11*Z*) - 6,11 - hexadecadien - 1 - yl acetate (**165**) as the

†Recently, a 1:1 mixture of the *E,Z* and *Z,Z* isomers was found to be a potent sex attractant for male cherry tree borer moths (*Synanthedon hector*).[241]





Scheme 52.

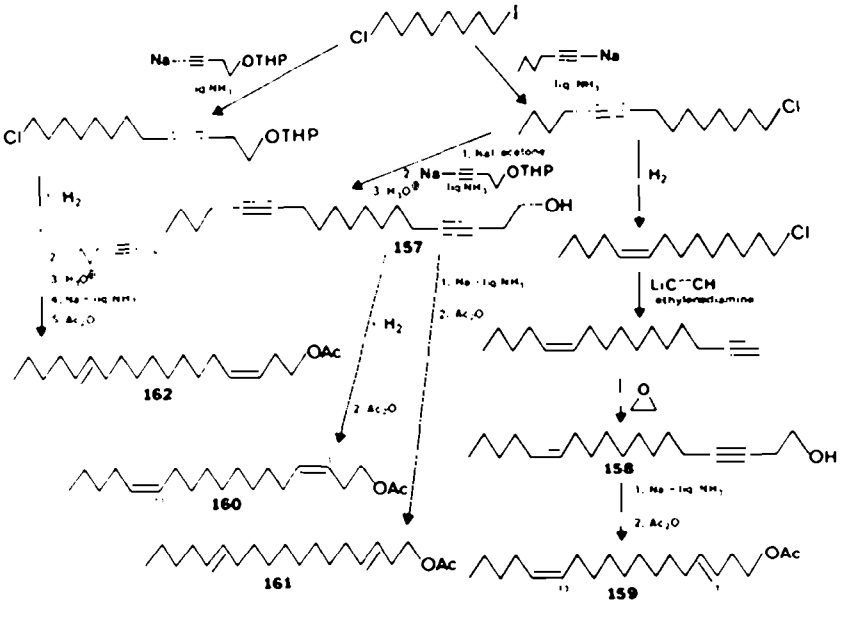
primary component and the corresponding aldehyde **166**, as a secondary component, and a *ca.* 9:1 mixture of the acetate and aldehyde, respectively, was found to be highly attractive to wild males in the field.[242] The acetate **165** and the aldehyde **166** were synthesized starting with 4-pentyn-1-ol and 1,5-pentanediol (Scheme 52). The coupling of (*Z*)-4-nonen-1-yl bromide (**163**) with the acetylene **164** proceeded in low yield. The overall yield of **165** and **166**, after purification by preparative glc, was only about 1% but efforts were not made to optimize the yields.[242]†

II. COLEOPTERA

Coleoptera (beetles and weevils) is the largest order of insects. The sex pheromones of beetles and weevils are structurally diverse and attractants may be produced by the male and/or the female of the species.

(a) (−)-*Methyl* (E)-2,4,5-*Tetradecatrienoate.* Males of the bean weevil, *Acanthoscelides obtectus*, produce a short-range sex pheromone which attracts the virgin female weevils, and (−)-methyl (*E*)-2,4,5-tetradecatrienoate (**170**) has been isolated from hexane extracts of the male and tentatively identified as a component of this pheromone.[243,244] Fractions containing this material usually attracted the virgin female weevils, although occasionally, negative results were obtained. This

†An improved synthesis of this pheromone (by a modification of Scheme 52) has been recently developed; J. P. Kochansky, R. T. Cardé, E. F. Taschenberg and W. L. Roelofs, *J. Chem. Ecol.* 3, in press (1977).

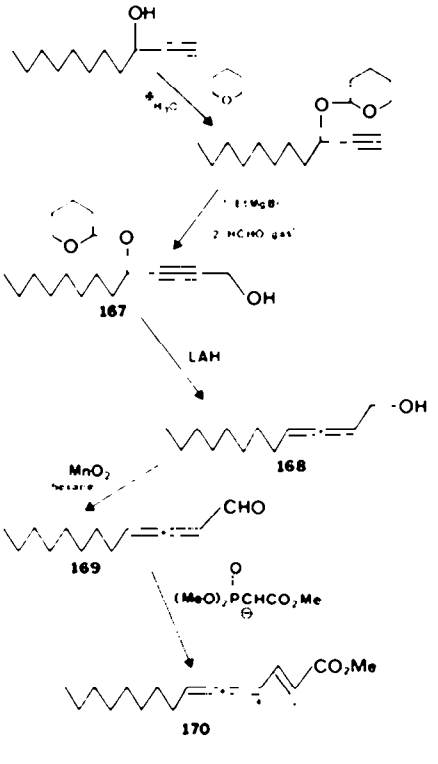


Scheme 51.

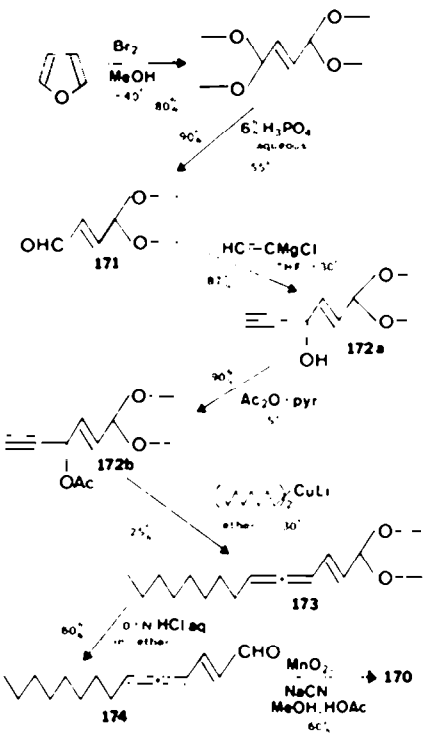
is the first example of an allenic sex pheromone and a number of syntheses have been developed for this interesting compound. The pure compound is unstable and polymerises readily, although it can be stored for prolonged periods in dilute solution in hexane at low temperatures.[243]

The first synthesis of racemic **170** was carried out by Landor *et al.*, (Scheme 53)[245] using their general method for the preparation of allenic alcohols.[246] Thus, reductive elimination of the 2-tetrahydropyranyloxy group from 4 - (2 - tetrahydropyranyloxy) - 2 - dodecyn - 1 - ol (**167**) with excess LAH gave 2,3-dodecadien-1-ol (**168**) which was oxidized with active manganese dioxide in hexane to the unstable allenic aldehyde **169**. Condensation of the crude aldehyde with the anion of trimethylphosphonoacetate (in dimethoxyethane at 60°) and repeated chromatography (over acidic alumina) gave the allenic ester **170**. No yields were quoted in this short paper.

We synthesized the racemic ester **170** utilizing the reaction of a lithium dialkylcuprate with a propargylic allylic acetate to generate the required allene-ene system (Scheme 54).[247] Reactions of lithium dialkylcuprates with isolated allylic esters (to give alkylated olefins),[144,145] propargylic acetates (to give alkylated and non-alkylated allenes),[248] and α-acetylenic epoxides (to give alkylated α-hydroxyallenes)[249] have been reported. We initially explored the reaction of lithium dialkylcuprates with 3 - acetoxy - 1 - penten - 4 - yne (**175**) and found the major product was **176**, resulting from addition to the triple bond, and that the alkylation of the double bond[144,145] to give **177** was only a minor reaction. For example, when *R* was *n*-octyl and the alkylation was carried out in ether at - 30°, a 52% yield of **176** plus **177** was obtained in the ratio 9:1, respectively.[247] Thus, to synthesize the pheromone we alkylated the dimethyl acetal **172b** with



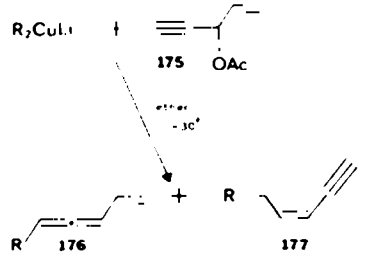
Scheme 53.

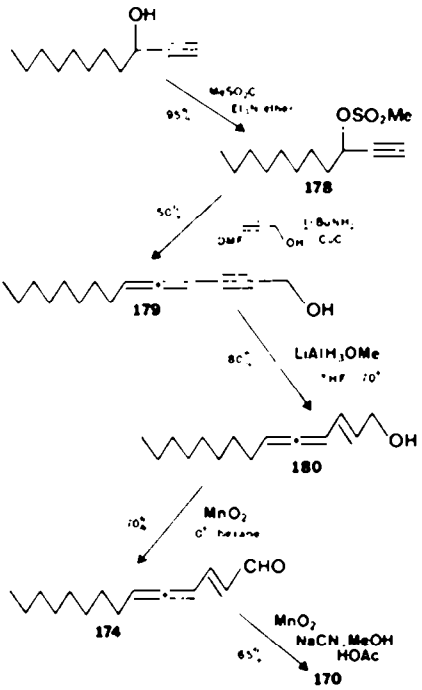


Scheme 54.

lithium dioctylcuprate in ether at −30° to give a 25% isolated yield of the allene **173** (purified by preparative tlc). The acetal **172b** was prepared in 78% yield (as in Scheme 54) from (*E*) - 4,4 - dimethoxy - 2 - buten - 1 - al (**171**), which was synthesized from furan.[250] Careful hydrolysis of **173** with 0.1 N aqueous HCl in ether gave the unstable aldehyde **174** (60% yield) which was then oxidized in methanol with manganese dioxide-sodium cyanide[251] to the methyl ester **170**. This allenic ester is unstable at room temperature and partially decomposes on distillation *in vacuo*, but it can be stored as a 10% solution in hexane at −20°. This synthetic, racemic sample (purity 91% by glc analysis) was found to be active in laboratory bioassays on female bean weevils (as an excitant and as a short range attractant),[252,253] but was not as attractive as the natural (−)-material.[243]

More recently another synthesis was developed which also proceeded through the allenic aldehyde **174** (Scheme 55).[254] Baudouy and Gore applied their general method of preparing α-vinylallenic alcohols[255] to the synthesis of **170** with the key step being the conversion of **179** to the (*E*)-enallene **180** in high yield and with high stereoselectivity. Thus, coupling the mesylate of 3-hydroxy-1-undecyne with propargylic alcohol in the presence of t-butylamine and cuprous chloride[256] gave the allenynol **179**. Reduction of **179** with lithium methoxyaluminum





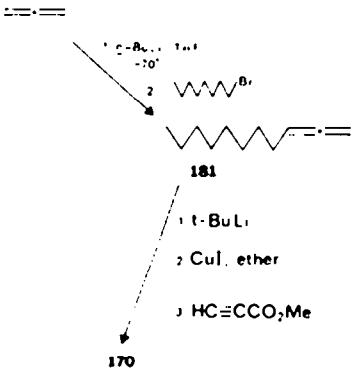
Scheme 55.

hydride gave exclusively the stable *E* alcohol **180** in 80% yield, which was then converted to **170** by the method of Corey *et al.*[251]

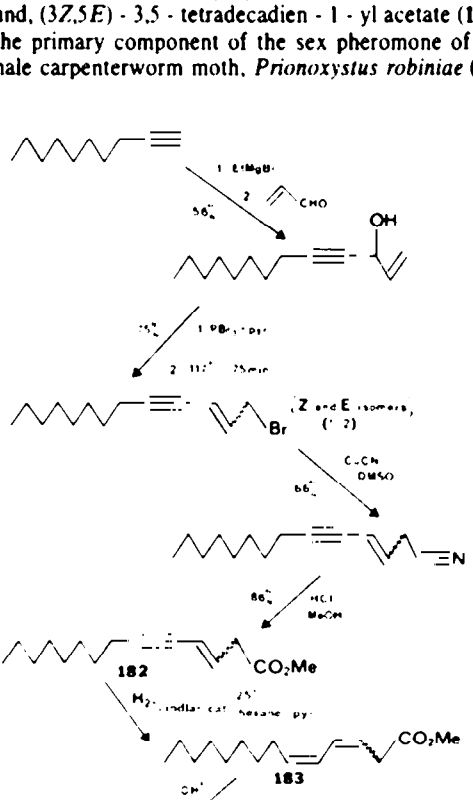
Michelot and Linstrumelle synthesized **170** by the use of allenic lithium reagents (Scheme 56).[257] Conversion of the alkylated allene **181**[258] into its lithium diallenylcuprate complex and addition of the latter to methyl propynoate (see Ref. 259) gave the pheromone **170** in unspecified yield.†

(b) (3*E*,5*Z*)-3,5-*Tetradecadienoic acid.* The principal component of the sex pheromone produced by the female black carpet beetle, *Attagenus megatoma*, has been identified as (3*E*,5*Z*)-3,5-tetradecadienoic acid (megatomoic acid, **184**).[260] The response of the male to synthetic **184** seemed to be slightly weaker than to the total extract of the female beetles, suggesting the possible presence of other unidentified components of the sex pheromone. None of the other three geometrical isomers of **184** were anywhere near as attractive to the male beetles, nor did they mask the attractiveness of the *E*,*Z* isomer. A mixture of the conjugated 3*E*,5*Z* diene **184**, and the 3*Z*,5*Z* isomer was prepared[261] in low purity by the sequence shown in Scheme 57 based on the procedure described by Celmer and Solomons,[262] for the synthesis of methyl (3*E*,5*Z*)-3,5-tridecadienoate. In the crude dienoic ester **183**, prepared by partial hydrogenation of the conjugated enyne **182** (mixture of *Z* and *E* isomers in the ratio *ca.* 1:2) over Lindlar catalyst, the 3*E*,5*Z* and 3*Z*,5*Z* isomers together comprised only 65% of the product (see Refs. 58*b*, 163*a*, 169). Hydrolysis of **183** gave the crude acid which contained only 50% of the required 3*E*,5*Z* isomer **184** and 22% of the *Z*,*Z* isomer. The 3*Z*,5*E* isomer **185** (along with the 3*Z*,5*Z* isomer) was prepared as outlined in Scheme 58. This route made extensive use of preparative glc to purify intermediates. The *E*,*E* isomer was obtained by isomerization (I_2-light) of the *E*,*Z* or *Z*,*E* methyl esters followed by hydrolysis. Small amounts of all four of the pure isomeric acids were prepared by mild alkaline hydrolysis of the corresponding methyl esters which were isolated by preparative glc from the synthetic mixtures.[261] The synthesis of the sex pheromone **184** described by these workers is not a practical route to the conjugated *E*,*Z*-diene system (see Schemes 23, 32 and 38).

Recently it has been proposed that a related compound, (3*Z*,5*E*) - 3,5 - tetradecadien - 1 - yl acetate (**187**), is the primary component of the sex pheromone of the female carpenterworm moth, *Prionoxystus robiniae* (Le-

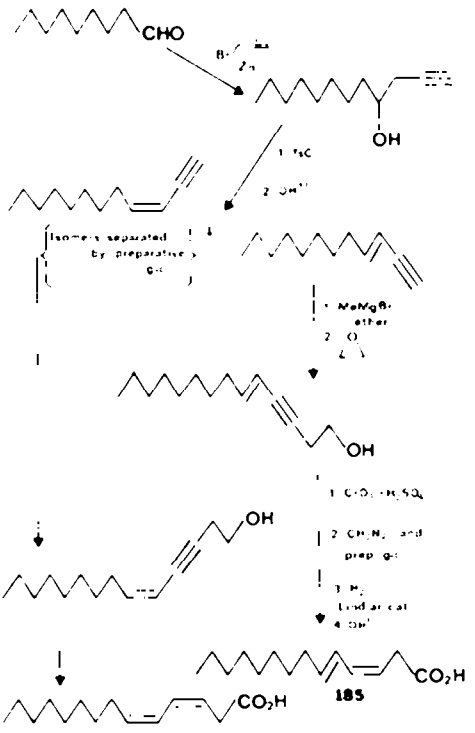


Scheme 56.

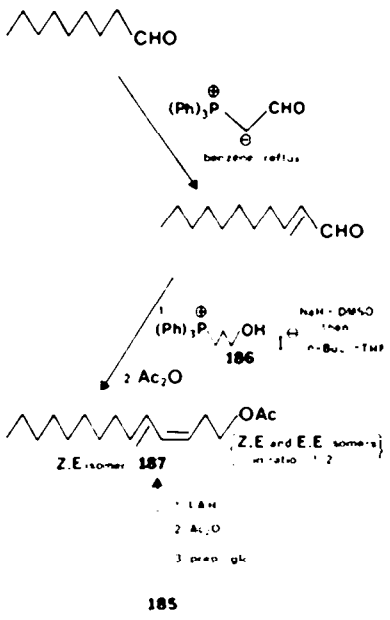


Scheme 57.

†The racemic pheromone has also been recently synthesized from methyl 4,5-tetradecadienoate via the reaction of its lithium enolate with diphenyl diselenide to give the α-phenylseleno ester, which on treatment with $NaIO_4$ in aqueous THF gave **170**; P. J. Kocienski, G. Cernigliaro and G. Feldstein, *J. Org. Chem.* **42**, 353 (1977).



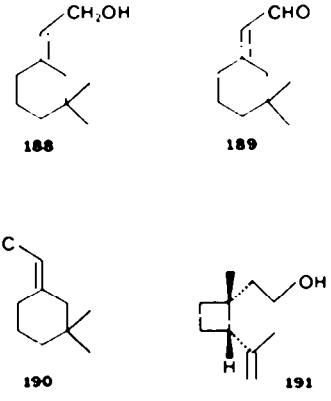
Scheme 58.



Scheme 59.

pidoptera).[261] Although this compound has not been positively identified from the female extract, it was indicated to be a natural pheromone by electroantennogram analyses of female gland extracts and of synthetic standards. The synthetic diene **187**, which corresponded in glc retention time with the primary pheromonal component of the female extract, was active in the laboratory and was a good attractant for male moths in the field. All four geometrical isomers of the 3,5-diene were synthesized and bioassayed in the laboratory and in the field.[261] The (3*Z*,5*Z*)-and (3*E*,5*Z*)-tetradecadien-1-yl acetates were prepared by a modification of the route used by Rodin *et al.*[261] to prepare the corresponding carboxylic acids (see Scheme 57). The *E* and *Z* isomers of **182** were separated by preparative glc and each was partially hydrogenated over Lindlar catalyst. The individual dienoic esters were reduced with LAH and the products acetylated. Purification of the diene acetates by preparative glc then gave the 3*Z*,5*Z* and 3*E*,5*Z* isomers of **187**. The 3*Z*,5*E* isomer **187** was initially obtained by reduction of the impure acid **185** (Scheme 58) with LAH followed by acetylation and purification by preparative glc. Subsequently, the 3*Z*,5*E* and 3*E*,5*E* isomers were synthesized as shown in Scheme 59. A Wittig condensation was carried out in dimethyl sulfoxide—THF with 2-undecen-1-al and the ylide generated from the salt **186** (see Ref. 169). This reaction, after acetylation of the product, gave a mixture of the 3*Z*,5*E* and 3*E*,5*E* acetates in the ratio 1:2, respectively. Initially, samples of the individual isomers were obtained by preparative glc. Distillation of the acetates on a spinning-band still failed to completely separate the mixture but did give one fraction containing the 3*Z*,5*E* isomer **187** in a purity of 95% and a still-pot residue containing 98% pure *E*,*E* isomer. Hplc was used to prepare a 99+% pure sample of the sex attractant **187**. In field tests (and in laboratory bioassays) the *Z*,*Z*, *E*,*Z* and *E*,*E* isomers were not attractive to males, and while the *Z*,*Z* and *E*,*Z* isomers appeared to inhibit the attractiveness of the *Z*,*E* isomer **187** the *E*,*E* isomer did not. Addition of up to 20% of the *E*,*E* isomer to the *Z*,*E* isomer did not appear to inhibit the response of males to **187**. This is fortuitous since the method of synthesis (Scheme 59) gave a mixture of these two isomers, and the *E*,*E* isomer was difficult to remove completely from the sex attractant **187** on a practical scale.

(c) (+)-cis-2-*Isopropenyl*-1-*methylcyclobutaneethanol*. Male boll weevils, *Anthonomus grandis*, produce a pheromone that is highly attractive to females in the laboratory and to both sexes in the field. An aggregating response is obtained from both sexes in early and late season, but primarily females are attracted to the male weevils in mid-season, indicating a true sex pheromone at this time of year. This pheromone has been isolated and identified by Tumlinson *et al.*[264] as a synergistic mixture of the four compounds **188–191** (collectively called "grandlure"). When combined in the proper proportions, mixtures of these four synthetic compounds elicit behavioral responses in the laboratory and in the field (both as an aggregation and a sex pheromone) identical to those produced by the natural pheromone.[261,266] Grandlure has been used extensively in



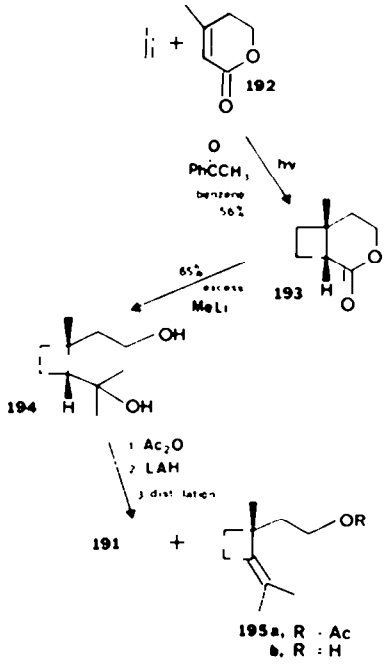
the field in traps and in trap crops in experiments designed to monitor and also to control the boll weevil.[265,266]

The three components **188–190** of grandlure are cyclohexylidene monoterpenoids and their synthesis has been described by straight-forward routes.[264,267] Of considerably more synthetic interest is the cyclobutane alcohol component **191**, termed "grandisol". The natural material is the (+)-isomer and it has *cis*-stereochemistry. The corresponding racemic *trans*-isomer has also been synthesized and was found to be at least 100- to 200-fold less active than the racemic *cis*-isomer in laboratory bioassays.[264] Interestingly, the *trans*-isomer (optical rotation unspecified) is also a natural product and has been isolated from the roots of *Artemisia fragrans* (a plant of the family Compositae), and termed fragranol.[268]

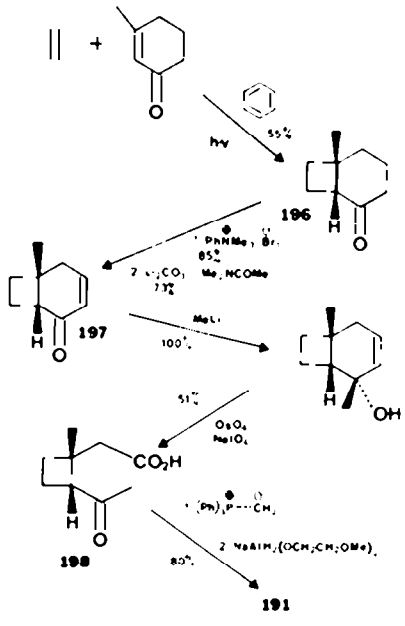
The various synthetic procedures used to prepare grandisol (**191**) have been recently reviewed in detail by Katzenellenbogen.[13] Several of the early synthesis of racemic **191** involved a photochemical step which severely limits the quantity of material that can be prepared. Almost all of the syntheses of **191** described in the literature are lengthy and involve steps that would be difficult to scale up to prepare the quantities required for field use. However, these synthetic studies have resulted in useful new methods for the formation of cyclobutane rings.[13] Until 1973, the synthetic route of Gueldner *et al.* (Scheme 60)[269] was used by USDA workers to prepare a total of *ca.* 1 kg of racemic **191** for field studies.[266] This method has now been replaced by the elegant, nonphotochemical procedure of Billups *et al.* (Scheme 62).[270] The procedure of Gueldner *et al.* relied on the photocycloaddition of ethylene to the unsaturated lactone **192** (photosensitized by acetophenone) to form the cyclobutane ring. Stereochemical control was achieved by constraining the *cis*-substituents within the lactone ring. The side chains were then elaborated from the fused bicyclic photoaddition product (Scheme 60).[269] Thus, addition of the photoadduct **193** to excess methyllithium gave the diol **194** which was purified by recrystallization (to remove 12–15% of the *trans*-diol formed by epimerization of the intermediate methyl ketone). Treatment of the diol with acetic anhydride under reflux gave, in 90% yield, a mixture of the acetate of **191** and the structural isomer **195a** in a 2:1 ratio, respectively. Other attempted methods of dehydration were even less satisfactory. Reduction of the acetate mixture with LAH and fractional distillation of the diols on an annular, spinning-band-still removed the undesired isomer **195b** and gave pure **191**.

The Zoecon stereoselective synthesis (Scheme 61)[271] was somewhat more lengthy but did not produce the structural isomer **195b**. Thus photochemical cycloaddition of ethylene to 3-methyl-2-cyclohexenone (1% solution in benzene) gave the bicyclic photoadduct **196**, which was brominated with phenyltrimethylammonium tribromide and the α-bromoketones were dehydrobrominated to give the unsaturated ketone **197**. Addition of methyllithium and then cleavage of the double bond by osmium tetroxide-catalyzed sodium periodate oxidation gave directly the keto-acid **198** containing less than 1% of the *trans*-isomer. Reaction of **198** with 2.5 equiv. of triphenylphosphonium methylide in THF–dimethyl sulfoxide followed by hydride reduction gave racemic grandisol (**191**) containing only 3% of the undesired *trans*-isomer. Pure **191** was obtained by preparative glc.

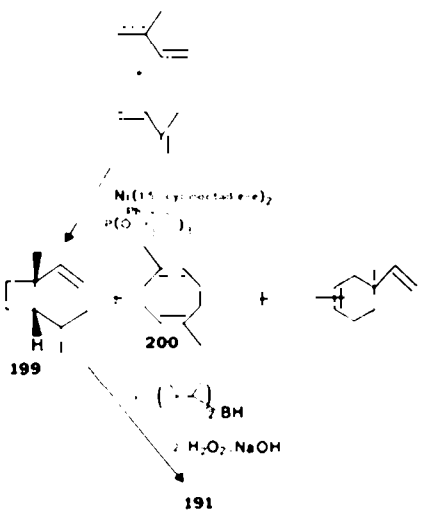
The two-step procedure of Billups *et al.* (Scheme 62)[270] is based on the discovery of Heimbach and Brenner that certain zero-valent nickel complexes can be used for the catalytic formation of *cis* - 1,2 - divinylcyclobutanes from 1,3-dienes.[272] Thus, the desired *cis*-cyclobutane **199** was produced by dimerizing isoprene with a catalytic quantity of the complex formed from a 1:1 mixture of bis(1,5 - cyclo - octadienyl)nickel and tris(2-biphenylyl)phosphite. At room temperature, a mixture of products was obtained but the *cis*-dimer **199** could be separated in moderate purity and in 12–15% yield (based on reacted isoprene) by fractional distillation at 0° after removal of the unreacted isoprene. Above room temperature the *cis*-diene **199** undergoes a



Scheme 60.



Scheme 61.



Scheme 62.

Cope rearrangement to give 1,5-dimethylcyclooctadiene (**200**).[272] No other cyclobutanes were produced in yields exceeding 1% in this dimerization reaction. Conversion of **199** to **191** was carried out by selective hydroboration with disiamylborane in THF at 0°. After oxidation of the organoborane with alkaline peroxide, racemic grandisol (**191**) was obtained in 52% yield. This synthetic route has now been modified and scaled up by ChemSampCo to produce commercial quantities of grandisol.[273] Recently a multistep synthesis of optically active (+)-grandisol has been carried out by Hobbs and Magnus starting from (−)-β-pinene, preserving throughout the synthesis the cyclobutane ring and the chirality originally present in this natural product. By this procedure natural (+)-grandisol has been shown to have the absolute configuration, 1*R*,2*S*.[274]

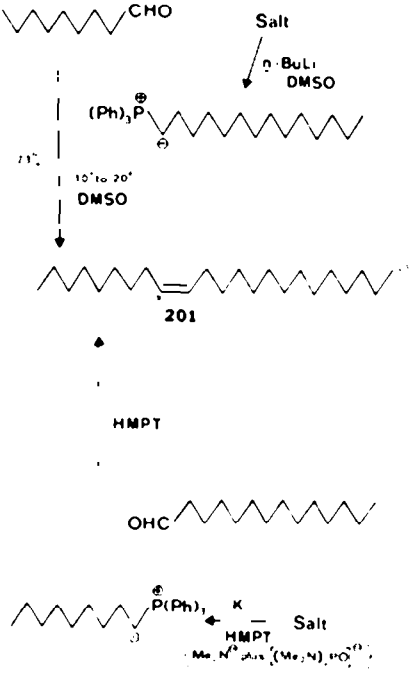
III. DIPTERA

(a) (*Z*)-9-*Tricosene*. The hydrocarbon fractions from the cuticular lipids as well as from the fecal lipids of sexually mature female house flies, *Musca domestica*, are attractive to sexually mature male house flies. The most active hydrocarbon isolated from these extracts of mature female house flies was identified as (*Z*)-9-tricosene (muscalure; Muscamone® fly attractant; **201**) with several other homologous hydrocarbons being present but showing less activity.[275] This sex attractant was found by Carlson and Beroza to be active in field tests.[276] Addition of the pheromone **201** increased by several times the number of flies caught in various traps. Traps baited with muscalure caught about equal numbers of males and females in the field in contrast to the laboratory results, where only males were attracted to **201** in olfactometer studies. Thus in the field **201** may act as an aggregation pheromone luring both male and female flies, rather than as a sex attractant for males only (see Ref. 277). Other research groups have also evaluated **201** in combination with sugar-base fly baits and have obtained similar results.[278] Although this pheromone is considerably less potent than many of the lepidopterous sex pheromones discussed above, the compound has been synthesized by many different routes and is used commercially to enhance the effectiveness of a sugar-base fly bait containing insecticides.[279]

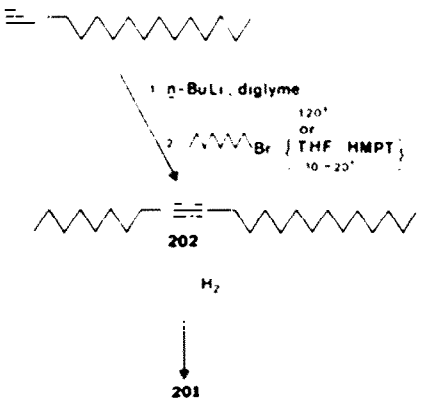
Mansingh *et al.*[280] reported that a 7:3 mixture of (*Z*)-9-tricosene (**201**) and (*Z*)-9-heneicosene was more potent as an attractant than was **201** alone in laboratory olfactometer bioassays with virgin male house flies, and they also observed that (*Z*)-9-heneicosene appeared to be a male orientation pheromone. However, in our field tests with sugar baits we failed to detect any differences in effectiveness between such mixtures and **201** by itself.[281] Carlson *et al.*,[282] also were unable to confirm the finding of Mansingh *et al.*, that a 7:3 mixture of **201** and (*Z*)-9-heneicosene improved attractancy in laboratory tests. The structural requirements for activity of the muscalure molecule appear to be less stringent than those for most leipidopterous sex pheromones since several structural variations of muscalure have shown activity similar to **201** in laboratory bioassays.[277,280,282]

(*Z*)-9-Tricosene (**201**) was prepared initially by the Wittig condensation of triphenylphosphonium tetradecylide with 1-nonanal in dimethyl sulfoxide which have a mixture of the *Z* and *E* isomers in the ratio *ca.* 85:15, respectively, in 73% yield from the phosphonium salt (Scheme 63).[274,282] The isomers were separated by column chromatography in hexane on silver nitrate-silica gel. Bioassays conducted in a laboratory olfactometer with virgin male house flies demonstrated that the natural *Z* isomer **201** was more attractive than was the *E* isomer. No masking (reduction in activity) was observed when the *Z* and *E* isomers were mixed in ratios up to 1:3, respectively.[274,282] Bestmann *et al.*[283] prepared the *Z* olefin from 1-tetradecanal via a Wittig reaction (Scheme 63) in HMPT as the solvent [using a solution of potassium in HMPT as the base][7] which gave a 32% yield of **201** containing only 4% of the *E* isomer.

Muscalure has also been prepared via acetylenic intermediates (Scheme 64).[282,284] Conversion of 1-pentadecyne to its lithium salt with n-butyllithium and alkylation of this salt with *n*-octyl bromide in diglyme (at 120°)[284] or in HMPT–THF (10–20°)[282] gave high yields of 9-tricosyne (**202**). Partial hydrogenation of the triple bond over Lindlar catalyst[284] or over 5% palladium on



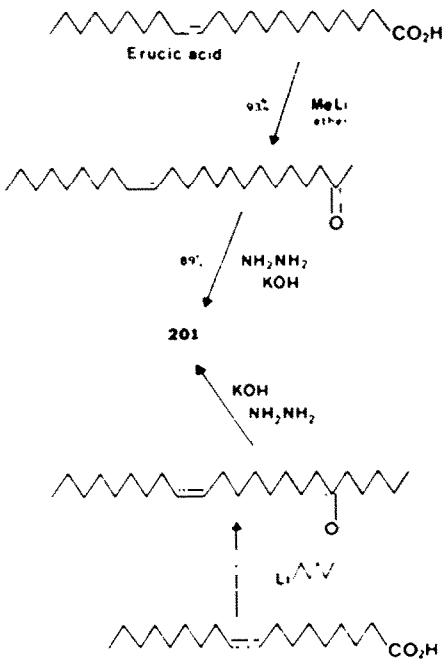
Scheme 63.



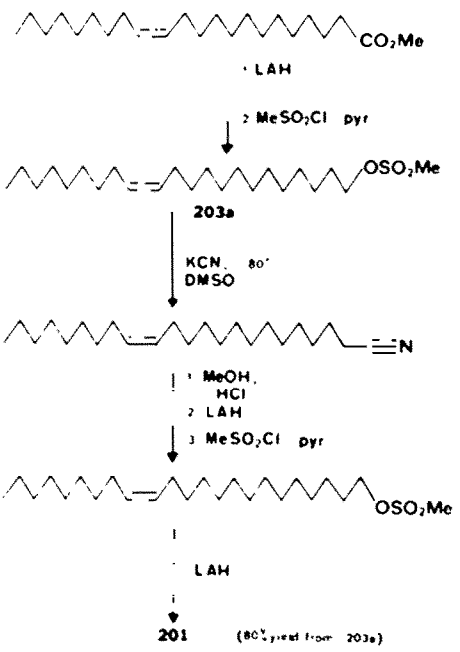
Scheme 64.

barium sulfate (hexane with synthetic quinoline added)[282] gave **201** in quantitative yield. In the latter case the product contained 95% of the (*Z*)-isomer **201**.[282] Muscalure has been synthesized in 85% yield from erucic acid by conversion of the latter into the methyl ketone with methyllithium followed by Huang-Minlon reduction (Scheme 65).[285] A similar route involved the reaction of oleic acid with n-pentyllithium to give (*Z*)-14-tricosen-6-one which was reduced under Huang-Minlon conditions to give **201** in 77% overall yield.[286] Another multistep route beginning with methyl erucate is outlined in Scheme 66.[287] This synthesis involved chain elongation of (*Z*)-13-docosenyl methanesulfonate (**203a**) with KCN, methanolysis of the nitrile, reduction of the methyl ester, and then reduction of a methanesulfonate with LAH. This route is too lengthy to be useful although high yields were obtained for all steps.

A mixed Kolbe electrolysis of (*Z*)-9-octadecenoic acid (pure oleic acid) and n-heptanoic acid in methanolic NaOMe with platinum foil electrodes (15°) gave muscalure (**201**) in one step in 14% isolated yield (after



Scheme 65.

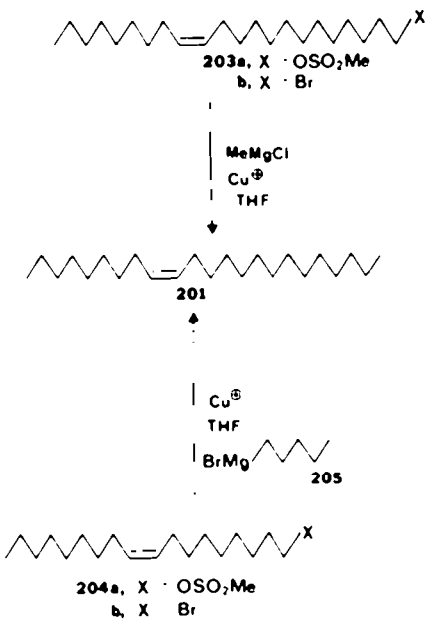


Scheme 66.

fractional distillation of the neutral fraction), along with dodecane (20%), (*Z*,*Z*)-9,25-tetratricontadiene (7%), (*Z*)-8-heptadecene (2%), methyl n-heptanoate (16%), and methyl oleate (68%).[288] 9-Tricosene has also been prepared in low yield as a mixture of *E* and *Z* isomers from the homogeneous transition metal-catalyzed olefin cross-metathesis reaction between 1-decene and 1-pentadecene at room temperature.[99b] The mixture of C-18, C-23, and C-28 olefins, obtained in quantitative yield, was fractionally distilled to give 9-tricosene (*E* and *Z* isomers) in 26% yield. A similar cross-metathesis reaction between 2-hexadecene and 9-octadecene at 20–50° gave a 9–12% yield of 9-tricosene.[99a]

Because of our commercial interest in **201** we required a synthetic procedure suitable for plant-scale production.[279] We initially synthesized **201** via the acetylene **202**, which we prepared by the alkylation of the lithium salt of 1-decyne with 1-bromotridecane (see Scheme 64), and we also investigated in detail, independently of Gribble *et al.*,[288] a one step synthesis by Kolbe cross-coupling of either a mixture of erucic acid and propionic acid, or of oleic acid and heptanoic acid (in methanol containing sodium methoxide, using a gold, a platinum, or a vitreous carbon anode).[289] However, synthetic routes applicable to the production-scale preparation of **201** were developed utilizing the copper(I) catalyzed coupling[121,148] of erucyl and oleyl derivatives with the appropriate Grignard reagents (Scheme 67).[290]

Conversion of (*Z*)-13-docosen-1-ol (erucyl alcohol) to its methanesulfonate **203a** was carried out in quantitative yield with methanesulfonyl chloride and triethylamine in dichloromethane at −5°.[291] Coupling of erucyl methanesulfonate (**203a**) with methylmagnesium chloride (1.5 equiv.) in THF at 0° in the presence of lithium tetrachlorocuprate (0.05 equiv.) gave a high yield (*ca.* >90%) of **201** (containing 98% of the *Z* isomer; the *Z*:*E* ratio in the 9-tricosene samples was determined by glc analysis of the corresponding epoxides; see Ref. 20*c*). Similar results were obtained with erucyl bromide but



Scheme 67.

the reaction with erucyl chloride was too slow to be of any practical utility. Use of 1.2 equiv. of MeMgCl with erucyl methanesulfonate only gave a 60% yield of **201**. An excess of the Grignard reagent was necessary to compensate for the loss of the reagent due to side reactions involving the methanesulfonate group. However, large scale production of **201** from erucyl alcohol was hindered by the limited commercial availability of this alcohol. Therefore, (*Z*)-9-octadecen-1-ol (oleyl alcohol)† was used as a starting material and an extensive study was carried out on the coupling of its derivatives. Preparation of oleyl methanesulfonate on a production scale by the procedure of Crossland and Servis[291] proceeded in quantitative yield. Coupling of this methanesulfonate **204a** with 1.5 equiv. of n-amylmagnesium bromide (**205**) in THF at −15° in the presence of lithium dichlorocuprate as the catalyst gave a high yield (*ca.* 85%) of **201**. Due to a number of side reactions involving the methanesulfonate group which consumed some of the Grignard reagent, and excess of **205** (*ca.* 1.5 equiv.) was necessary in order to obtain complete reaction of the methanesulfonate. For example, when only 1.25 equiv. of the Grignard reagent **205** was used the product contained *ca.* 10% of the starting ester. In the absence of the copper(I) catalyst, **204a** did react readily with the Grignard reagent **205** at 0° to give, after hydrolysis, oleyl alcohol and methyl amyl sulfone. In contrast, oleyl bromide and **205** reacted very slowly in THF in the absence of a copper(I) catalyst. In the above exothermic copper(I) catalyzed coupling of **204a** (and of **204b**) with **205**, the thermal instability of the catalytically-active n-amylcopper intermediate necessitated an operating temperature of −10° to −20°, which caused a number of production problems on a plant scale in maintaining adequate cooling and heat transfer. Treatment of oleyl methanesulfonate with sodium bromide in dimethylformamide-toluene at 70° gave the bromide **204b**. Reaction of **204b** with 1.2 equiv. of the Grignard reagent **205** at −20° in the presence of 0.05 equiv. of $LiCuCl_2$ gave a rapid 80% conversion to **201** and then the reaction ceased due to the decomposition of the catalyst, with the residual bromide being converted to (*Z*)-9-octadecene and (*Z*)-1,9-octadecadiene when the mixture was allowed to warm to room temperature. This decomposition of the n-amyl copper intermediate is catalyzed by active metal surfaces including copper (autocatalytic).[121] Copper metal also catalyzed the undesirable reaction of oleyl bromide with the Grignard reagent **205** to give (*Z*)-9-octadecene, (*Z*)-1,9-octadecadiene, pentane, and pentene, especially at higher temperatures (>0°). In the search for a more stable alkyl-copper intermediate it was found that lithium chloride (or LiBr) forms a THF-soluble complex with cuprous cyanide which is a particularly useful catalyst.[292] The cyano group is presumably retained in the organocopper intermediate improving its thermal stability (see Ref. 293). Thus coupling of oleyl bromide (**204b**) with 1.15 equiv. of n-amylmagnesium bromide (**205**) in THF at 0°–5° in the presence of 0.03 equiv. of lithium chlorocyanocuprate (2.5 hr) gave a nearly quantitative yield of **201**.[292] This procedure has been used to prepare production-scale (150 kg batches) quantities of **201**, and allows a more efficient utilization of the Grignard reagent than did the use of the mesylate and allows also the use of a higher operating temperature. The n-amylcyanocuprate intermediate does decompose within a few hours above 5° but the corresponding methyl-complex is considerably more stable. Coupling of erucyl bromide (**203b**) with 1.2 equiv. of methylmagnesium chloride in the presence of 0.025 equiv. of lithium chlorocyanocuprate in THF can be carried out at temperatures up to 50° to give >95% yields of **201**.[289] The high thermal stability of the methyl cyanocuprate intermediate is noteworthy. The use of lithium chlorocyanocuprate as a catalyst appears to offer little advantage over other copper(I) catalysts for laboratory scale syntheses as a decrease in the rate of coupling accompanies the increased stability, but for plant scale operation it allows the use of significantly higher operating temperatures then is possible with lithium dichlorocuprate.[292] The cyanocuprate catalyst was *not satisfactory* for use in the coupling of oleyl methanesulfonate with 1.5 equiv. of **205** at 0°–5°. The product from this reaction contained considerable quantities of oleyl alcohol and of unchanged methanesulfonate indicating that the cleavage of the methanesulfonate group by **205** was more rapid, with respect to the coupling reaction, at 0° in the presence of this catalyst than at −15° in the presence of the more active dichlorocuprate catalyst.

(b) (Z)-14-*Nonacosene*. The sex pheromone of the female face fly, *Musca autumnalis*, is only weakly active and is apparently effective for mating stimulation only at short range. The most active components (in laboratory bioassays on male face flies) isolated from the insect cuticular extracts (of both sexes) were, in order of their activity, (*Z*)-14-nonacosene, (*Z*)-13-nonacosene and (*Z*)-13-heptacosene.[294] These olefins were prepared initially by Wittig condensations. For example, reaction of triphenylphosphonium pentadecylide with 1-tetradecanal in THF–HMPT gave a 70% yield of (*Z*)-14-nonacosene containing *ca.* 94–96% of the *Z* isomer, as estimated from the intensity of the 970 cm^{-1} IR band due to the *E* isomer.[294] A sample of (*E*)-13-heptacosene was found to

†Commercially available oleyl alcohol is contaminated with other saturated and unsaturated compounds and a "pure" grade only contains *ca.* 82% 9-octadecenols of which *ca.* 15% is the (*E*)-isomer (the latter is apparently formed by isomerization during manufacture). However, this material is satisfactory for the production of commerical **201**.

be devoid of activity. These three olefins have also been prepared (as mixtures of *Z* and *E* isomers) in low yields from transition metal-catalyzed olefin cross-metathesis reactions.[99a] (*Z*)-14-Nonacosene has also been prepared via the alkylation of the lithium salt of 1-hexadecyne with tridecyl bromide in HMPT–THF to give 14-nonacosyne, followed by partial hydrogenation of the triple bond over Lindlar catalyst (see Scheme 64).[99b]

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