Translated from *Uspekhi Khimii*, **55**, 1198-1228 (1986) U.D.C. 542.97 : 547.36

The Synthesis of Lepidoptera Pheromones

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The review surveys the data in numerous publications of the synthesis of the pheromones of scale-winged insects (Lepidoptera). Attention is concentrated on problems of the sterospecific synthesis of pheromones.
The bibliography includes 217 references.

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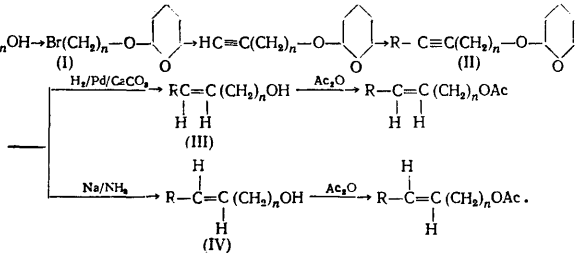
During recent years, several new promising trends have arisen in the fight against harmful insect species, involving high selectivity and also virtually complete safety for man and warm blooded animals. In the first place one should include among these, methods based on the employment of biologically active substances—pheromones. Pheromones are chemical substances secreted by insects and inducing specific behavioural and physiological responses in other insects exposed to them. Among the pheromones known at the present time (sex pheromones, tracking pheromones, aggregation pheromones, food pheromones, and fear pheromones), the sex pheromones appear to be the most promising. Their exceptional biological activity and species selectivity give rise to the hope that they may be used in the active suppression of the multiplication of pest populations without contaminating the biosphere and without disturbing the biological equilibrium in nature, and also as a means for the operative allowance for the number of pests present. Extensive experimental data devoted to the identification, synthesis, and applications of insect pheromones have accumulated during the last ten years. These data have been surveyed in a number of reviews[1-4] and a monograph,[5] but most studies have been published during the last four years.

This review is devoted to the synthesis of insect sex pheromones and embraces mainly the studies during 1970 to 1983. All the reviews considered deal with scale-winged insects (Lepidoptera). These compounds are unsaturated aliphatic alcohols, acetates, and aldehydes,[1,2,5] but recently ketones have also been isolated and identified.[6] The difference between their structures is one of the principal factors in the reproductive isolation of insects. It has been found recently that Lepidoptera pheromones are multicomponent mixtures of compounds:[7] certain insect species secrete mixtures of *cis*- and *trans*-isomers as pheromones,[8] while others secrete a mixture of aldehydes,[9] an acetate–aldehyde mixture,[10] or other mixtures.[11] An attractant for one insect species can be an inhibitor for another; thus the attractant of *Paralobesia viteana*—*cis*-dodec-9-enyl acetate—inhibits the attracting activity of *Phyacionia buoliana*.[12] The quantitative ratio of the components in such mixtures is an important factor which enables sympatric insect species (species living in the same area) to avoid cross breeding.[13]

For the majority of representatives of Lepidoptera, the ratio of the *cis*- and *trans*-isomers in the mixture is important. For example, *cis*-dodec-8-enyl acetate is an attractant for the oriental fruit moth *Grapholitha molesta*, but the greatest attracting effect has been observed in the presence of 7% of the *trans*-isomer;[14,15] for the males of the European pine shoot moth *Rhyacionia buoliana*, the greatest activity has been shown by the mixture of *trans*-dodec-9-enyl acetate and 1.15% of its *cis*-isomer.[16] The high species specificity of pheromones is achieved precisely by the exact proportions of geometrical isomers, which requires appropriate methods of synthesis and a high degree of chemical, geometrical, and stereochemical purity.

I. MONO-OLEFINIC ALCOHOLS AND ACETATES

One of the commonest methods of synthesis of pheromones involves the use of mono- or di-substituted acetylenes as key compounds. Thus about 100 unsubstituted unbranched C_{10}–C_{16} compounds containing a terminal triple bond and the acetate group have been synthesised by Japanese investigators.[17] Screening led to the discovery of substances attracting specifically 93 species of insects belonging to 15 Lepidoptera families of Japan (the *Torticidae*, *Noctuidae*, etc. families). All the specimens were synthesised in accordance with the following scheme:



The complex of lithium acetylide and ethylenediamine was condensed in THF, HMP, and HMP/THF with the corresponding tetrahydropyranyloxyalkyl bromide (I) in order to obtain an almost quantitative yield of the key compound—a disubstituted acetylene (II), which was subsequently hydrogenated over the Lindlar catalyst to obtain a product containing more than 95% of the *cis*-isomer (III). The corresponding *trans*-isomers (IV) were obtained by reduction with lithium in liquid ammonia.

A classical method for the synthesis of mono-substituted acetylenes involves the splitting off of hydrogen halides from the corresponding halogenoethylenic compounds.[18] The hydrogen halide is usually split off by means of a potassium hydroxide solution in absolute ethanol, ethylene glycol, and

cellosolve, a potassium hydroxide melt,[19] or sodium in liquid ammonia or in the form of a suspension in a mineral oil.[20-22] Here one must bear in mind that the classical version of the dehydrohalogenation reaction leads to the migration of the triple bond into the interior of the molecule,[23] while the use of sodium amide in a mineral oil has the opposite effect of shifting the triple bond to the end of the chain.[23] A modified method, based on the use of a suspension of fine ground KOH in dimethyl sulphoxide (DMSO), is more effective. The terminal acetylene is thus obtained in 50–100% yield.[24]

A method for dehydrohalogenation in the two-phase catalytic system aqueous NaOH–heptane or methylene chloride using tetrabutylammonium hydrogen sulphate as the phase transfer catalyst has been developed in recent years. The reaction proceeds with an almost quantitative yield for the lowest members of the series, but, for compounds containing long aliphatic chains, the yields are sharply reduced owing to the poor solubility of the compounds.[25]

In view of the low solubility of higher alkyl halides and alkali metal salts of acetylene in liquid ammonia, the lithio-derivatives of terminal alkynes are alkylated in dipolar aprotic solvents: DMSO,[26] HMP,[27] and dimethylformamide (DMF)[28] and also in mixtures of these solvents in THF.[29,30] The yields of alkyl acetylenes increase when a complex of lithium acetylide and ethylenediamine (EDA) is used:[17,31]

$$EDA\cdot LiC{\equiv}CH + RX \rightarrow RC{\equiv}CH + LiX + EDA.$$

However, even in this case the yield of reaction products depends very greatly on the concentrations of the reactants and the order in which the reactants are mixed.[31]

In order to obtain higher acetylenic alcohols from alkylacetylenes, hydroxyalkyl halides with a protected alcohol group are used as alkylating agents.[32] HMP is the most suitable solvent for such reactions, because the yields of disubstituted acetylenes reach 60–80%.[33] The replacement of chlorine by bromine in tetrahydropyranyl (THP) ethers increases the yield by 10–15%. Unsubstituted ω-bromo-1-alkanols (V) or terminal acetylenic alcohols (VI) can also be used successfully for the syntheis of hydroxyalkylacetylenes:[34-36]

$$\left.\begin{array}{l} R{-}C{\equiv}CH + Br(CH_2)_nOH \\ \quad\quad (V) \\ H{-}C{\equiv}C(CH_2)_nOH \\ \quad\quad (VI) \end{array}\right| \xrightarrow[2)\ RHal]{1)\ LiNH_2/NH_3} R{-}C{\equiv}C(CH_2)_nOH.$$

In the latter case a mixture of a disubstituted acetylene and an ether—the *C*- and *O*-alkylation products respectively—is formed.[37] The fraction of the *C*-alkylation product can be increased sharply by carrying out the reaction in dipolar aprotic solvents,[38] in which there is a sharp increase of the nucleophilic reactivity of the carbanions. The yields of disubstituted acetylenes fall sharply to 28–33% when liquid ammonia, THF, and DMF are used as solvents owing to the poor solubility of the initial reactants.[1,39-41] Best results can be achieved by using DMSO[26,42] and the complex with EDA:[43]

$$HC{\equiv}CLi\cdot EDA + Br(CH_2)_8OH \xrightarrow{DMSO} HC{\equiv}C(CH_2)_8OH.$$

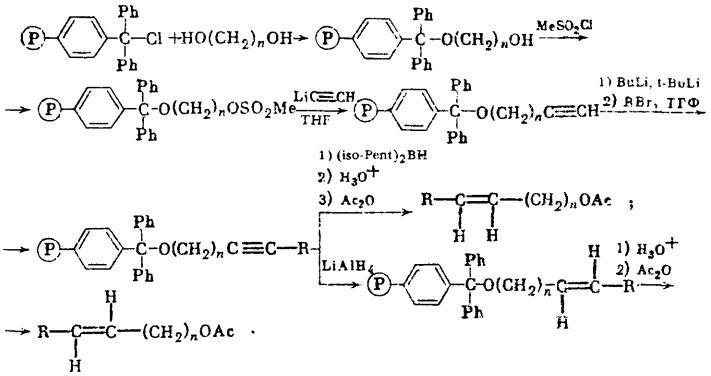
The tosylates [toluene-*p*-sulphonates] or brosylates [*p*-bromobenzenesulphonates] of the corresponding acetals can be used as alkylating agents, which makes it easier to carry out the reaction in liquid ammonia, because arenesulphonate esters are readily soluble in this solvent and are fairly resistant to ammonolysis:[44]

$$R{-}C{\equiv}C{-}Na + Ts(CH_2)_5CH(OMe)_2 \rightarrow \underset{(VII)}{R{-}C{\equiv}C(CH_2)_5CH(OMe)_2}.$$

However, the yields of the acetals (VII) fall sharply to 2–10% on passing to higher acetylenes or when higher alkyl bromides are used in this reaction.[45]

Acetylenic alcohols are converted into olefinic alcohols with the *cis*-configuration of the double bond by partial hydrogenation over the Lindlar catalyst. The reaction proceeds with a high overall yield. It is best to employ petroleum ether as the solvent.[46] On hydrogenation at 20 °C, the admixture of the *trans*-isomer is 1.5–3%, while on raising the temperature its content increases.[47] At low temperatures (between −10° and −30 °C) the degree of selectivity is higher and the admixture of the *trans*-isomer does not exceed 0.5%.[1] Other catalysts have also been used, namely $Pd/BaSO_4$,[35,48] nickel catalysts,[43] and others,[49] but they are less stereoselective. The degree of stereoselectivity is 98% in the hydrogenation by diisopentylborane with subsequent treatment by a carboxylic acid.[50] This method requires the use of a freshly prepared diisopentylborane, since otherwise the yields of the *cis*-isomer fall to 5%.[1]

The corresponding *trans*-isomer is obtained by reducing the alkyne with metallic sodium or lithium in liquid ammonia,[51] but the initial alkyne then remains in the reaction mixture, which is due to the limited solubility of higher acetylenic compounds in ammonia. The reaction proceeds with rigorous stereospecificity and an admixture of the *cis*-isomer is not detected.[52] The triple bond is reduced by lithium tetrahydroaluminate to a double bond with the *trans*-configuration in a high yield.[53] The reduction of alkynes by lithium tetrahydroaluminate in the presence of titanium tetrachloride leads to a mixture of isomers whose proportions depend on the temperature, the fraction of the *trans*-isomer diminishing as the temperature is reduced.[54] A method of synthesis of the *trans*-isomers of attractants on a polymeric support, which blocks one of the alcoholic groups of the initial diol or the alcohol group of the halogenoalcohol, has been developed. The polymer can be employed repeatedly, avoiding thereby laborious isolation processes. It has been established that the triple bond is not reduced by sodium in liquid ammonia on a polymeric support. In order to obtain the *cis*-isomer, diisopentylborane has been used as the reducing agent:[55-57]



cis-Dodec-8-enyl acetate, the pheromone of the oriental and common fruit moths (*Grapholitha molesta and Cydia molesta*), has been synthesised by a modification of the scheme described above:

$$CH_3(CH_2)_2C{\equiv}CH + I(CH_2)_6Cl \rightarrow \underset{(VIII)}{CH_3(CH_2)_2C{\equiv}C(CH_2)_6Cl} \rightarrow$$

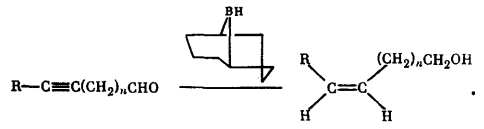
$$\xrightarrow{NaCN} \underset{(IX)}{CH_3(CH_2)_2C{\equiv}C(CH_2)_6CN} \rightarrow \underset{(X)}{CH_3(CH_2)_2C{\equiv}C(CH_2)_6COOH} \rightarrow$$

$$\rightarrow CH_3(CH_2)_2C{\equiv}C(CH_2)_6CH_2OH \xrightarrow[2)\ Ac_2O]{1)\ H_2/Pd/CaCO_3} \underset{(XI)}{CH_3(CH_2)_2\overset{H}{\underset{H}{C}}{=}\overset{H}{\underset{H}{C}}(CH_2)_7OAc}.$$

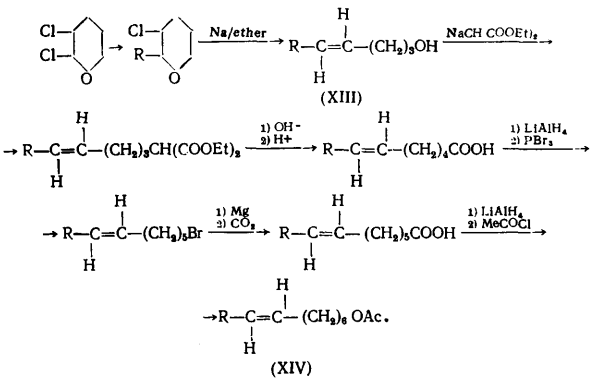
The lithium salt of pent-1-yne is alkylated by 1-chloro-6-iodohexane and the resulting chloroacetylene (VIII) is converted via the nitrile (IX) into the acid (X). Hydrogenation over the Lindlar catalyst with subsequent reduction of the carbonyl group and acetylation affords 46% of *cis*-dodec-8-enyl acetate (XI).[50,58] Sodium acetylides have been alkylated by chloro- and bromo-alkanes in DMSO [59] or by esters of carboxylic ω-chloroacids under the same conditions,[60] which led to the corresponding acid (XII) in 70% yield:

$$Cl(CH_2)_nCOOR + NaC{\equiv}CR' \xrightarrow{DMSO} R'{-}C{\equiv}C(CH_2)_nCOOR.$$

1-Alkenols, the active components of sex pheromones, are obtained by reducing acetylenic aldehydes by complex alkali metal hydrides with subsequent partial hydrogenation of the triple bond over the Lindlar catalyst.[60,61] Together with the *cis*-isomer, one then obtains up to 10% of the *trans*-isomer. A method has been developed for the synthesis of *cis*-alkenols in a high yield with the aid of 9-borabicyclo-[3.3.1]nonane—an effective reductant for carbonyl compounds, capable of simultaneous stereoselective reduction of the triple bond to the double bond having the *cis*-configuration:[62]



The stereoselective method of synthesis of *trans*-acetates involves the opening of the ring of 2-butyl-2-chlorotetrahydropyran with sodium in ether to form *trans*-4-non-4-en-1-ol (XIII); the chain is subsequently lengthened with the aid of diethyl malonate. The content of the *cis*-isomer is 1.3%.[63] The method has been used to synthesise *trans*-dodec-7-en-1-yl acetate (XIV):

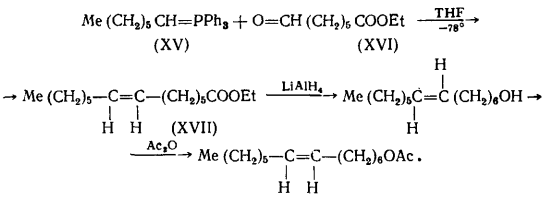


(XIII)

(XIV)

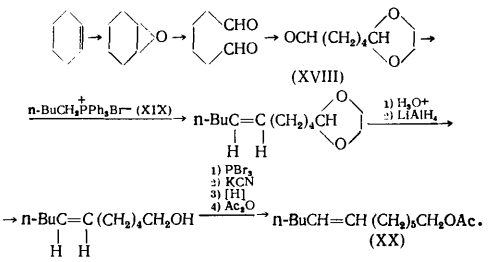
However, the yield of the acetate (XIV) was only 10% and the attractant obtained showed only a low activity in biological tests, evidently owing to the presence of impurities.

Numerous *cis*-mono-olefinic alcohols and their acetates have been synthesised by the Wittig reaction. The usual version of this process, involving the interaction of alkylidenetriphenylphosphoranes with carbonyl compounds, makes it possible to obtain olefins as mixtures of the *cis*- and *trans*-isomers. The high stereospecificity of this reaction, carried out in order to obtain the *cis*-isomer, is achieved using aliphatic phosphoranes and aliphatic aldehydes in non-polar solvents in the absence of lithium salts[64] and in dipolar aprotic solvents.[65-68] The formation of phosphorus ylides from the corresponding phosphonium salts by treatment with an alkali metal bis(trimethylsilyl)amide followed by subsequent interaction with aldehydes leads to *cis*-alkenes with 98% stereochemical purity.[69] This method has been used to synthesise attractants containing one unsaturated bond—*cis*-dodec-7- and *cis*-dodec-9-enyl acetates, *cis*-tetradec-7-enyl acetates, and others.[69-72] For example, the condensation of the ylide (XV) with the aldehyde (XVI) in THF at -78 °C leads to the unsaturated ester (XVII) with the ratio *cis* : *trans* = 98 : 2:[72]



(XV) (XVI) (XVII)

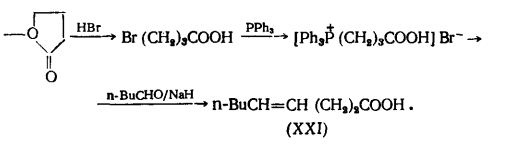
The geometrical isomers of dodec-7-en-1-yl acetate (XX) are the pheromones of the cabbage moth *Trichoplusia ni* and the leafroller *Argyroploce leucotreta*. These isomers were synthesised in cyclohexene in 27% yield. 6-Ethylenedioxy-1-hexanal (XVIII) was condensed with the phosphorane obtained from compound (XXIX):



(XVIII) (XX)

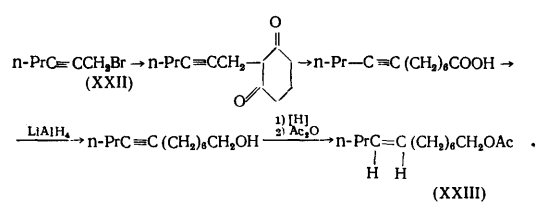
The mixture of the *cis*- and *trans*-isomers was separated chromatographically on silica gel impregnated with silver nitrate.[73]

The yields and ratios of the isomers in the Wittig reaction differed depending on the nature of the solvent; thus the yield of non-4-enoic acid (XXI) was 46% in DMSO (with a ratio of the *cis*- and *trans*-isomers of 86 : 14), while in HMP the yield was 21% (91 : 9):[74]



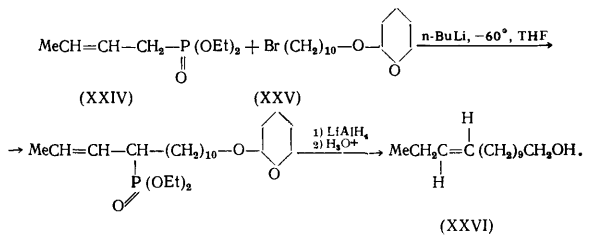
(XXI)

The highest stereospecificity has been observed in DMSO, DMSO/THF, DMF, or acetonitrile, where the fraction of the *cis*-isomer exceeds 90%.[75] *cis*-Dodec-8-enyl acetate (XXIII) has been obtained from cyclohexane-1,3-dione and the bromide (XXII):[76]

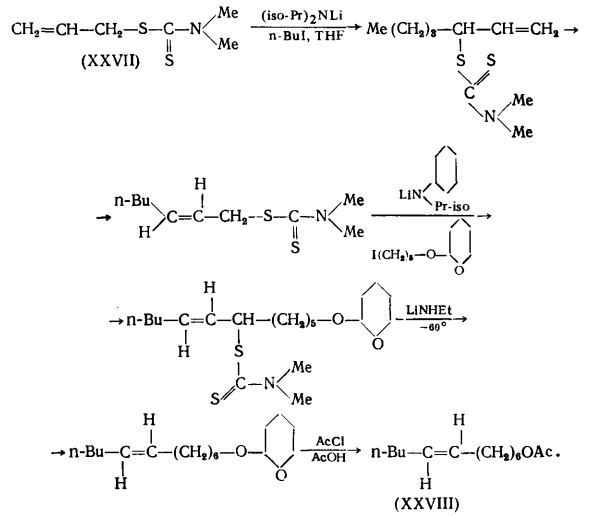


(XXII) (XXIII)

Alkylation of the lithio-derivatives of the γ-allylphosphonates (XXIV) in the α-position by various ω-substituted alkyl halides, for example, compound (XXV), with subsequent reduction by $LiAlH_4$ leads exclusively to the *trans*-isomer (XXVI):[77]

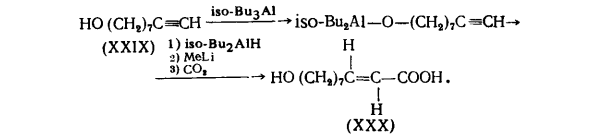


The stereoselective synthesis of *trans*-dodec-7-enyl acetate (XXVIII) has been achieved with the aid of the 3,3-sigmatropic rearrangement of the product of the alkylation of S-allyldithiocarbamate (XXVII):[78]

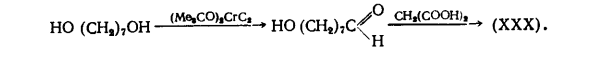


Mixed Kolbe electrolysis of carboxylic acid salts has also been used to obtain the acetate (XXVIII), but large amounts of dimerisation, transesterification, and disproportionation side products are formed.[74]

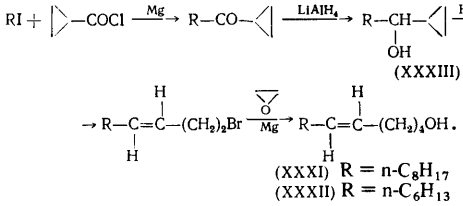
trans-10-Hydroxydec-2-enoic acid (XXX) is a component of royal jelly and a bee pheromone. It is synthesised from non-8-ynol (XXIX):[79]



The hydroxy-group in the nonynol (XXIX) is protected by introducing the diisobutylaluminium residue, after which the reaction mixture is treated with diisobutylaluminium hydride. The vinylalane formed is treated with methyllithium and subsequent carboxylation leads to the acid (XXX). The yield of 80% and the method is vigorously stereospecific. A simpler method of synthesis of the acid (XXX) with a smaller number of stages from readily available starting materials, involving the condensation of malonic acid with 8-hydroxyoctanal has been proposed:[80]



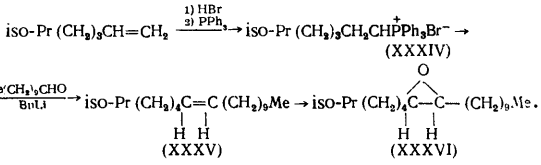
An interesting stereoselective synthesis of unsaturated C_{12}–C_{15} alcohols and their acetates and epoxides has been achieved. Among them *trans*-tetradec-5-enol (XXXI) is a "pheromone simulator" (it stimulates the action of the natural pheromone) of the emarginate-winged moth *Pyncho pocha*, while *trans*-dodec-5-enol (XXXII) is the pheromone of the cereal fly *Tricimba cinctra*.[81] A characteristic feature of this method consists in the fact that the ethylenic bond in the final compound is formed on opening of the cyclopropane ring present in the initial carbinol (XXX):



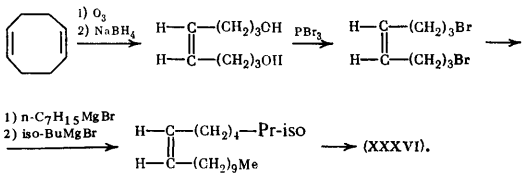
II. DISPARLURE

An epoxide acting as a pheromone has been discovered hitherto only in the gypsy moth *Porthetria dispar* and has the structure of *cis*-7,8-epoxy-2-methyloctadecane—disparlure (XXXVI).[82] Biological tests of the enantiomers of compound (XXXVI) showed that the natural pheromone is a *cis*-(+)-isomer while the *trans*-isomer (XXXVII) and the *cis*-(−)-isomer are inactive.[83] These data indicate the chiral character of the receptor system of the gypsy moth.[84,85]

The racemic *cis*-disparlure has been synthesised in different ways. Condensation of the phosphonium salt (XXXIV) with 1-undecanal in DMSO in the presence of butyl-lithium in accordance with the Wittig reaction afforded the olefin (XXXV) with a ratio of the *cis*- and *trans*-isomers of 88 : 12.[82] The same reaction in HMP led to an isomer ratio of 96 : 6.[86] By reducing the reaction temperature to −78, it was possible to obtain the olefin (XXXV) and from the latter the epoxide (XXXVI) in 75% yield, the content of the *trans*-isomer not exceeding 2%:[87]

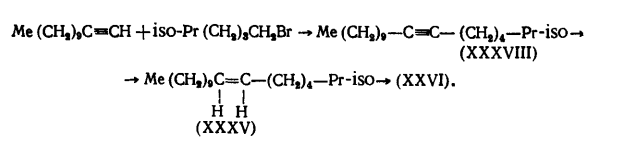


Racemic disparlure has been synthesised from cyclo-octadiene. The necessary *cis*-geometry of the double bond is determined by the stereochemistry of the initial cyclo-octadiene. Selective ozonolysis with subsequent treatment of the ozonide with sodium tetrahydroborate, the Grignard reaction, and epoxidation lead to disparlue in 25% yield:[88]



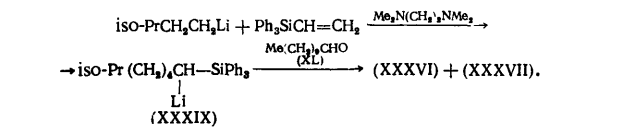
Disparlure has also been obtained from linear butadiene and isoprene oligomers by reaction with methyl acrylate. The synthesis is based on the Wittig reaction, which gives rise to an 85–95% yield and a ratio of the *cis*- and *trans*-isomers of the product of 3 : 1.[89]

The key stage in another method of synthesis of the racemic epoxide (XXXVI) involves the formation of the cisoid double bond, which is achieved by the controlled hydrogenation of 2-methyloctadec-7-yne (XXXVIII):[90–93]

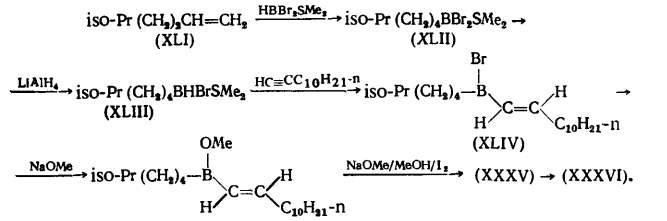


A method for the alkylation of the salts of aceylenes in HMP with a 35–45% yield of dialkylacetylenes has been developed for a large series of compounds.[93] Hydrogenation of the alkyne (XXXVIII) over the Lindlar catalyst leads to the *cis*-olefin, while reduction with sodium in liquid ammonia affords the *trans*-isomer. The purity of the *cis*-olefins obtained was 99%.

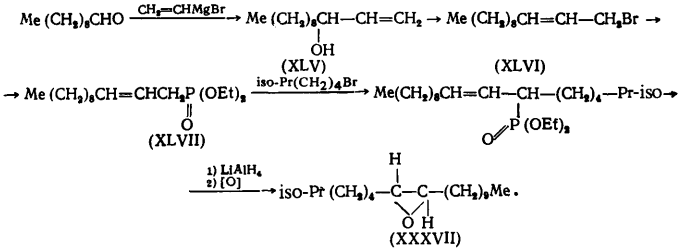
Condensation of 6-methyl-1-triphenylsilylheptyl-lithium (XXXIX) and 1-undecanal (XL) followed by epoxidation yielded a 1 : 1 mixture of the *cis*- and *trans*-isomers of disparlure:[94]



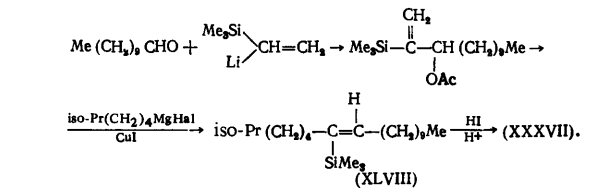
A convenient stereospecific synthesis of racemic disparlure using organoboranes has been proposed.[25] 5-Methylhex-1-ene (XLI) was converted into dibromo-5-methylborane-dimethyl sulphide (XLII), which was treated with lithium tetrahydroaluminate and the resulting bromoborane (XLIII) was added to dodec-1-yne:



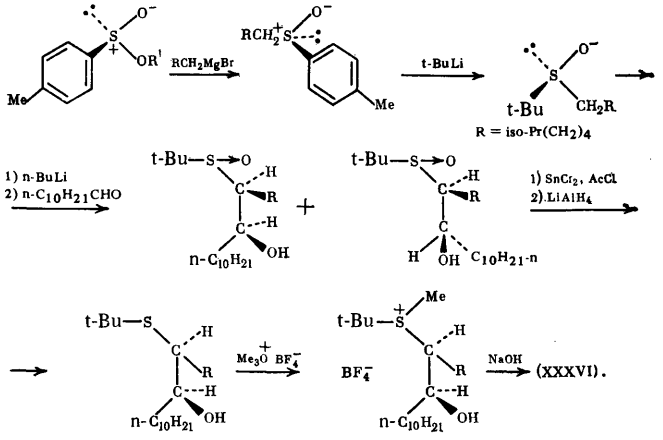
Treatment of the organoborane compound (XLIV) with sodium methoxide followed by iodination in the presence of sodium methoxide in methanol leads to the *cis*-isomer of the olefin (XXXV) in 55% yield (the isomeric purity is more than 99%). Disparlure was obtained by oxidation with *m*-chloroperbenzoic acid. In order to test the pheromone-inhibitor, the racemic *trans*-isomer of disparlure (XXXVII) was synthesised.[96] Nonylvinylmethanol (XLV), obtained by the reaction of 1-decanal with vinylmagnesium bromide, was treated with concentrated HBr. The resulting bromide (XLVI) was heated with triethyl phosphite and the corresponding phosphonate (XLVII) was alkylated with 5-methylhexyl bromide. The subsequent reduction with lithium tetrahydroaluminate and oxidation with *m*-chloroperbenzoic acid lead to the *trans*-isomer (XXXVII) in 81% yield:



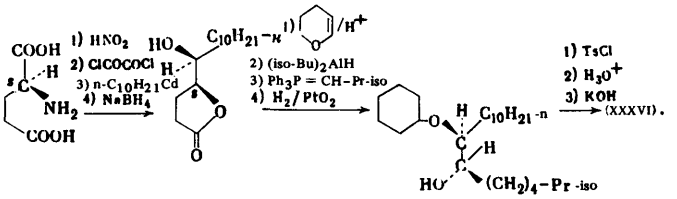
The *trans*-isomer (XXXVII) has been obtained in 65% yield by the protodesilylation of the corresponding vinylsilane (XLVIII):[97]



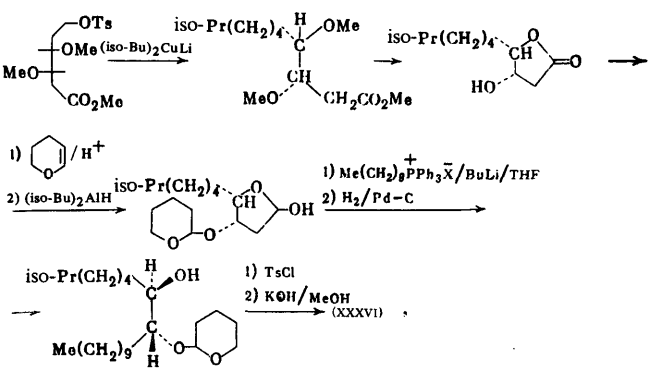
A six-stage synthesis of the optically active *cis*-(+)-disparlure in 15% yield has been proposed:[98]



An elegant synthesis of *cis*-(+)-disparlure has been achieved via (*S*)-(+)-glutamic acid:[99]



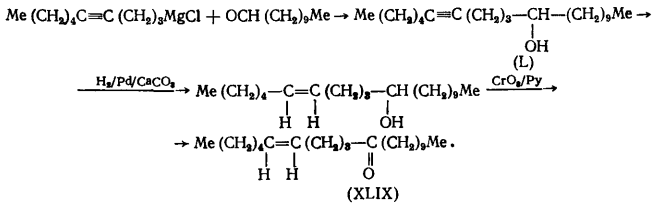
The same compound has been obtained with a high optical purity (98%) from (L)-(+)-tartaric acid:[100]



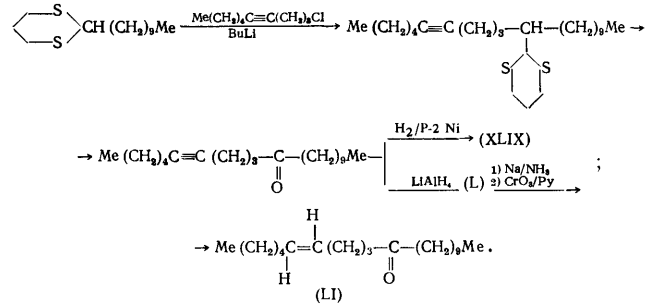
III. UNSATURATED KETONES

Ketones are extremely rare among the known Lepidoptera pheromones. *cis*-Heneicos-6-en-11-one (XLIX) has been identified in *Orgyia pseudotsugata*.[101] It was

synthesised by the Grignard reaction from 1-undecanal and 1-chlorododec-4-yne; hydrogenation of the triple bond in the resulting alcohol (L) and oxidation of the alcoholic group lead to the pheromone (XLIX) with an admixture of 4% of the *trans*-isomer:[1]

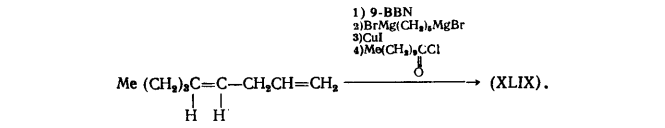


The *trans*-isomer (LI) was obtained in accordance with the scheme presented below:[101]

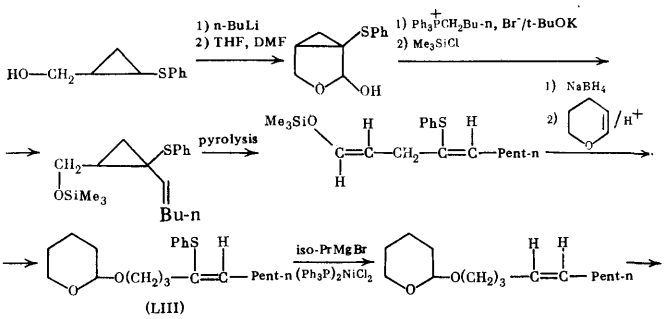


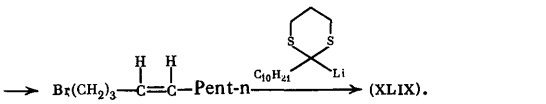
Alkylation of the lithium salt of 2-n-decyl-1,3-dithiane with subsequent hydrogenation results in the formation of the ketone (LII) whose carbonyl group is reduced by lithium tetrahydroaluminate and the triple bond is reduced to the *trans*-olefin with sodium in liquid ammonia. Catalytic hydrogenation over a nickel catalyst in the presence of EDTA affords compound (XLIX) (stereochemical purity 97%).[101]

The conversion of trialkylboranes into alkylmagnesium bromides has also been used to synthesise compound (XLIX).[102] *cis*-Deca-1,4-diene is hydroborated with 9-borabicyclononane (9-BBN), 1,5-pentamethylenedi(magnesium bromide) is added and the dec-4-enyl-9-BBN-magnesium bromide formed *in situ* is treated with copper(II) iodide and then with undecanoyl chloride, as a result of which the ketone (XLIX) is obtained in 78% yield:

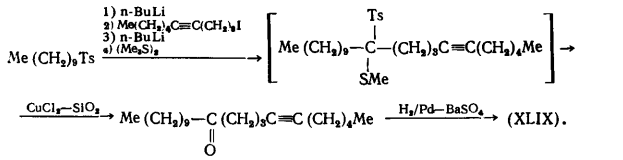


In the presence of bis(triphenylphosphine)nickel chloride, isopropylmagnesium bromide reduces the vinyl sulphide (LIII) stereospecifically to the corresponding olefin. This process has been used as the key stage in the synthesis of the unsaturated ketone (LXIX):[103]

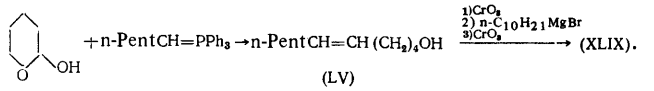




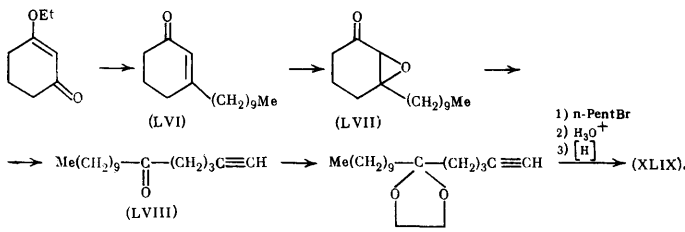
An alternative method of synthesis of the pheromone (LXIX), based on the preparation of dialkylacetylene (LIV) with subsequent Lindlar reduction,[104] is presented below:



The interaction of 2-hydroxypyran with hexylidenetriphenylphosphorane leads to undec-5-enol (LV) with a very high degree of geometrical purity. Oxidation of the resulting alcohol with chromium trioxide to the corresponding aldehyde, subsequent interaction with n-decylmagnesium bromide, and repeated oxidation afford compound (XLIX):[105]

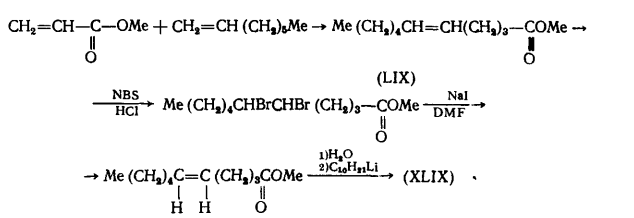


The pheromone (XLIX) has been obtained in a low yield from dihydroresorcinol in accordance with the scheme presented below:

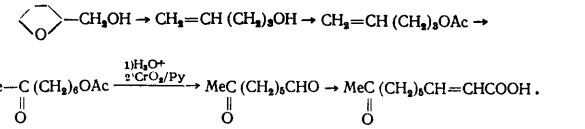


3-Ethoxy-2-cyclohexenone was converted by alkylation and hydrolysis into the αβ-unsaturated ketone (LVI), whose oxidation afforded the αβ-epoxyketone (LVII). The acetylenic ketone (LVIII) was obtained from the epoxide and then alkylated and hydrogenated over the Lindlar catalyst.[76] *cis*-Undec-5-en-2-one, an intermediate in the synthesis of pheromones, was synthesised by an analogous method.[106]

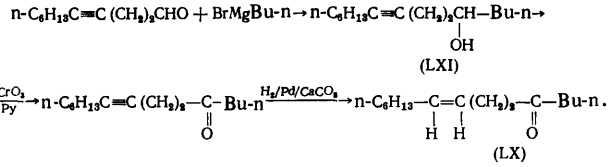
The interaction of methyl acrylate with 1-olefins in the presence of the eutectic mixture of aluminium, potassium, and sodium chlorides results in the formation of the unsaturated ester (LIX) in 40% yield, from which the pheromone (XLIX) was obtained:[107]



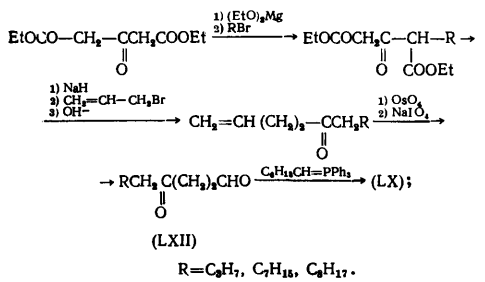
A simple and easy method of synthesis from tetrahydrofuryl alcohol of the intermediate for the synthesis of pheromones has been proposed:[108]



The pheromone of the peach moth *Carposina niponensis* consists of two components: the major component *cis*-eicos-7-en-11-one (LX) and the minor component *cis*- or *trans*-nonadec-7-en-11-one.[109] The key compound, 1-alkylundec-4-yn-1-ol (LXI), was obtained by treating the corresponding aldehyde[109] or nitrile[110,111] with a Grignard reagent:



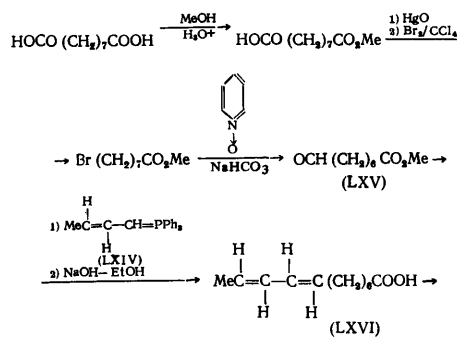
Regioselective two-stage alkylation of acetonedicarboxylate ester with subsequent oxidation to the γ-ketoaldehyde (LXII), which was then made to undergo the Wittig reaction, has also been used to obtain compound (LX).[112] The reaction of the ketoaldehyde (LXII) with heptylidenetriphenylphosphorane at a low temperature leads to the *cis*-olefin (LX) in 20% yield.[113] In the presence of crown-ether (12-crown-4), the same reaction proceeds with a yield of 64%[112] and the content of the *cis*-isomer in the ketone (LX) exceeds 90%:

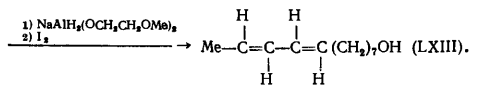


IV. CONJUGATED DIENE ALCOHOLS, ACETATES, AND ALDEHYDES

Among the pheromones of the Lepidoptera, numerous compounds containing conjugated double bonds are known.[1,4,5] The methods of synthesis of compounds of this type discussed below illustrate the procedures used to obtain conjugated systems with the *trans*-configuration.

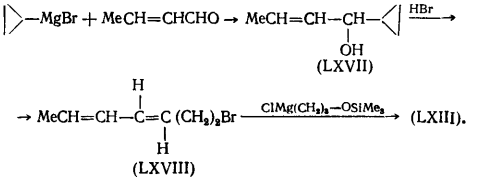
The pheromone of the lesser apple-worm *Laspeyresia pomonella*, *trans,trans*-dodeca-8,10-dien-1-ol (LXIII), was first obtained[114] by means of the Wittig reaction from *trans*-butenylidenetriphenylphosphorane (LXIV) and methyl 8-oxo-octanoate (LXV) in DMF in the presence of sodium methoxide. The acid (LXVI) has also been obtained as a mixture of 75% of the 8-*trans*,10-*trans*-isomer and 25% of the 8-*cis*,10-*trans*-isomer:





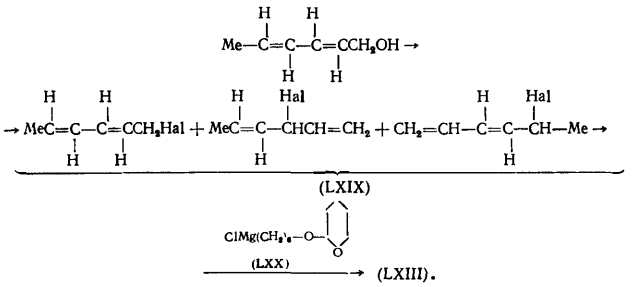
After reduction and isomerisation on treatment with iodine, the pure *trans*-isomer (LXIII) was obtained but in a very low yield. A high yield of the isomeric mixture consisting of 45% of the 8-*trans*,10-*trans*-isomer, 39% of the 8-*cis*,10-*trans*-isomer, and 16% of the 8-*trans*- and 8-*cis*,10-*cis*-isomers has been achieved by the reaction of the trans-ylide (LXIV) with ethyl 8-oxo-octanoate in the presence of lithium bromide.[1] The ratio of the isomers in the absence of lithium bromide is virtually the same as under the conditions of the normal Wittig reaction.[5,115,116] If tetrahydropyranyloxyheptyl bromide is converted into the triphenylphosphonium salt and the Wittig reaction with *trans*-but-2-enal is carried out, the yield is only 10% and the product (LXIII) consists of a mixture of 77% of the 8-*cis*,10-*trans*-isomer, 20% of the 8-*trans*,-10-*trans*-isomer, and 3% of a mixture of the 8-*trans*,10-*cis*- and 8-*cis*,10-*cis*-isomers.[115]

A higher stereoselectivity of the process was achieved on opening the ring of the secondary alcohol cyclopropylpropenylmethanol (LXVII) with hydrobromic acid, which leads to a mixture of 90% of 3-*trans*,5-*trans*- and 10% of 3-*cis*,5-*trans*-heptadienyl bromides (LXVIII). The Grignard reaction in the presence of Li_2CuCl_4 and subsequent hydrolysis lead to 79% of the alcohol (LXIII) containing 9% of the 8-*cis*,10-*trans*-isomer and 12% of the 8-*cis*(*trans*),10-*cis*-isomer:



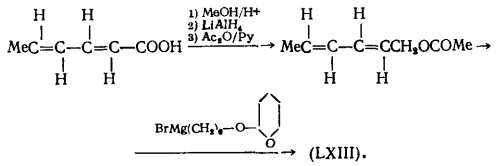
Recrystallisation of this mixture yielded the alcohol (LXIII) (with 99.5% purity).[117] In many studies *trans,trans*-dodecadodeca-8,10-dien-1-ol was obtained in a low yield and the reaction product contained also a whole series of other geometrical isomers, the stereospecificity of the reaction being unknown.[1]

The interaction of the allyl halides (LXIX) with Grignard reagents not containing double bonds, leading to a complex mixture of the geometrical isomers of the alcohol (LXIII), has been studied in detail.[118] The interaction of the isomeric mixture of the halides (LXIX) with the Grignard reagent (LXX) leads mainly to oct-2-ene and only trace amounts of a diene product:[119]

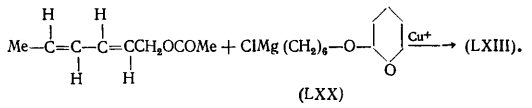


A number of attempts to convert sorbyl alcohol into the corresponding halide without an allylic rearrangement proved unsuccessful.[120,121] Using sorbyl bromide, obtained from sorbyl alcohol and phosphorus tribromide, various investigators were able to obtain 25–30% of the alcohol (LXIII) containing only 75% of the *trans,trans*-isomer.[122–124]

The interaction of sorbyl acetate with organomagnesium and organolithium reagents in the presence of univalent copper salts has been investigated.[125] The reaction is rigorously stereo- and regio-specific with formation of *trans,trans*-dodeca-8,10-dien-1-ol (99.7% stereochemical purity):[125,126]

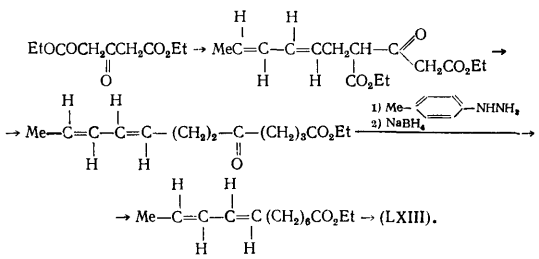


A single-stage synthesis of the dodecadienol (LXIII) from *trans,trans*-1-acetoxyhexa-2,4-diene and the Grignard reagent (LXX) has been achieved in the presence of a univalent copper salt:[127]

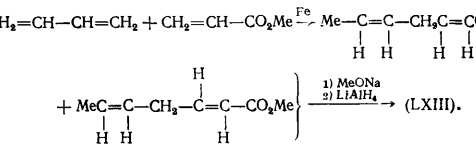


(LXX)

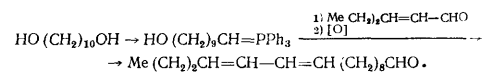
Using the selective alkylation of acetonedicarboxylate ester initially with sorbyl bromide and then with 3-bromopropionate and subsequent hydrolysis, decarboxylation, and reduction, the alcohol (LXIII) was synthesised in a fairly high yield:[128]



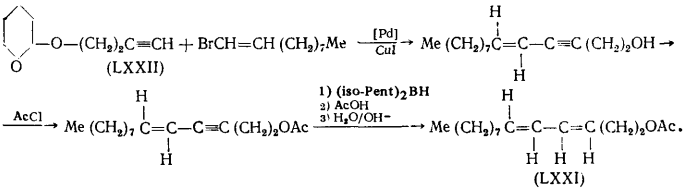
New possibilities for the synthesis of diene attractants appeared when the co-oligomerisation of 1,3-dienes with acrylates, catalysed by transition metals, was employed. The codimerisation of butadiene with methyl acrylate leads to a mixture of *cis,cis*- and *trans,cis*-hepta-2,5-dienoic acids. The isomerisation of this mixture by treatment with sodium ethoxide leads to a quantitative yield of *trans,trans*-hepta-3,5-dienoic acid, which is reduced to an alcohol:[129]



trans,trans-Hexadeca-10,12-dienal, the principal component of the pheromone of *Earias insulana*, has been obtained from 1,10-dihydroxydecane; the Wittig reaction, which leads to a mixture of the 10-*trans*,12-*trans*- and 10-*cis*,12-*trans*-isomers, was used as the key stage:[130]

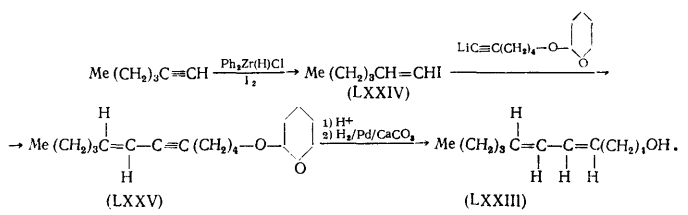


The application of metal complex catalysis makes it possible to obtain *trans,trans*-dienes with a high stereochemical purity. Thus *cis,trans*-tetradeca-3,5-dienyl acetate (LXXI), the pheromone of *Prionoxystus rebiniae*, has been obtained by the direct stereospecific cross-coupling of the ω-substituted alkyne (LXXII) with *cis*-1-bromodecene in the presence of tetrakis(triphenylphosphine)palladium and copper(I) iodide.[131] The stereospecificity of this reaction is greater than 97%. When it is carried out under phase transfer catalysis conditions, the yield of the pheromone (LXXI) is increased to 70%:



(LXXII) (LXXI)

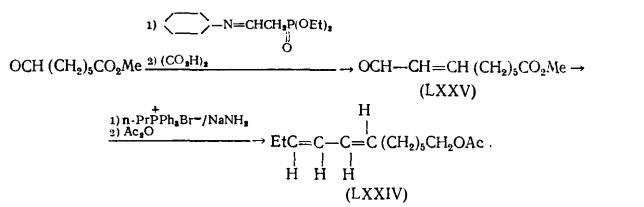
The cross-coupling of *trans*-1-iodohexene and tetrahydropyranyloxyhex-5-yne in the presence of bis(triphenylphosphine)palladium chloride was the key stage in the synthesis of *cis,trans*-dodeca-5,7-dien-1-ol (LXXII)—the pheromone of *Dendrolimus spectabilis*.[132] A regioselective synthesis of *trans*-1-iodoalk-1-enes (LXXIV) in the presence of a zirconium catalyst has been developed. The conjugated triple bond in compound (LXXV) gives rise to a mixture of 5% of the initial enyne (LXXV), 71% of the *cis,trans*-5,7-diene, and 24% of the monoene on hydrogenation over the Lindlar catalyst:



(LXXV) (LXXIII)

The stereochemically pure pheromone (LXXIII) was obtained by chromatographing the mixture on silica gel impregnated with silver nitrate. *cis,trans*-dodeca-5,7-dien-1-ol and the corresponding aldehyde are the components of the sex pheromone of *Malacosoma disstria*.[133] All four isomers of dodeca-5,7-dien-1-ol have been obtained stereoselectively by the Wittig condensation.[133]

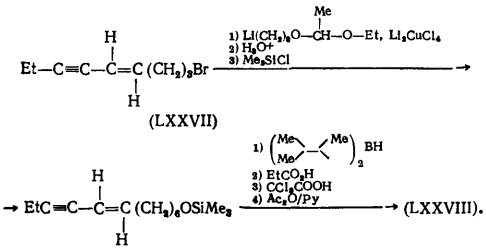
The αβ-unsaturated aldehyde (LXXV), obtained by the Horner reaction from the aldehyde (LXXVI) on treatment with didethyl 2-(cyclohexylimino)ethylphosphonate,[134] was used as the initial component for the synthesis of *trans,cis*-dodeca-7,9-dienyl acetate (LXXIV)—the pheromone of *Lobesia botrana*:[134,135,136]



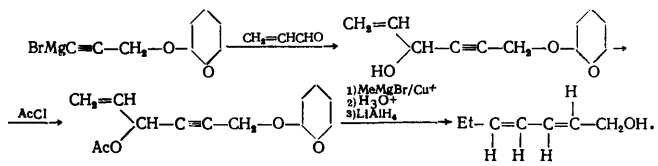
(LXXV) (LXXIV)

The interaction of the aldehyde (LXXV) with propylidenetriphenylphosphorane followed by its reduction with sodium dihydrobis(2-methoxyethoxy)aluminate leads to a 30% yield of a mixture of alcohols containing 70% of the required dodeca-7,9-dienol. This method is unsuitable for the synthesis of *trans,cis*-dodeca-7,9-dienyl acetate in any kind of large amount. The synthesis using a disubstituted acetylene proved promising for this purpose.[135] The condensation of the *trans*-conjugated enyne (LXXVII) with 3-(1-ethoxy)-ethoxypropyl-lithium and subsequent reduction lead to the

alcohol (LXXVIII) (purity 99%):[135]

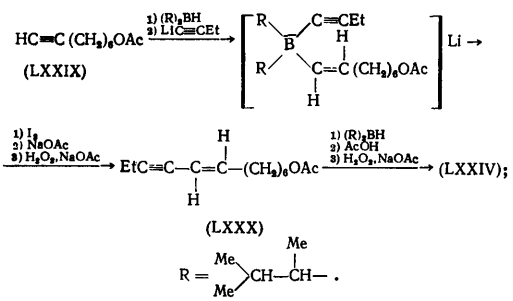


trans,cis-Hepta-2,4-dienol, which is a suitable intermediate for the synthesis of conjugated dienes, was obtained in accordance with the scheme:[137]



The *cis,cis*-isomer present (7%) is bound in a complex with tetracyanoethylene.

Another key intermediate for the synthesis of the *cis,trans*-conjugated system, namely *trans,dodec*-7-en-9-ynol (LXXX), was obtained in 20% yield by the hydroboration of octynyl acetate (LXXIX) followed by treatment with butynyl-lithium:[138,139]

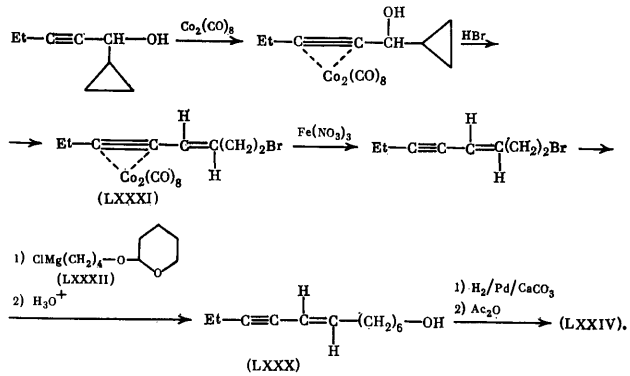


A modified method for the conversion of a *trans*-enyne into a *trans,cis*-diene, involving the selective reduction of the triple bond with zinc dust in aqueous propanol to a double bond with the *cis*-configuration, made it possible to obtain *trans,cis*-dodeca-7,9-dienyl acetate.[139,140]

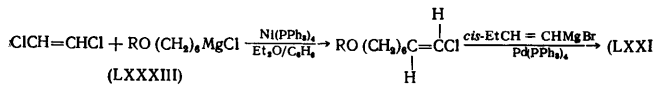
The triple bond of tetrahydropyranyloxy-*cis*-dodec-9-en-7-yne is reduced with diisopentylaluminium hydride.[141] However, owing to steric hindrance, *cis*-enynes react very slowly and after hydrolysis a mixture of the *cis*- and *trans*-isomers is obtained. Apparently the hydroalumination of the triple bond initially leads to the preferential formation of *trans*-vinylaluminium hydride, but, with increase of the duration of the reaction, the latter isomerises to the *cis*-isomer.

It was found that, when the ring of 1-cyclopropylpent-2-yn-1-ol is opened by hydrobromic acid, *cis*-1-bromooct-3-en-5-yne is formed as the main product (the *cis* : *trans* isomer ratio is 67 : 33).[142]

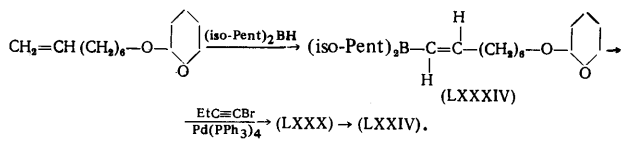
With increase of steric hindrance (as a result of the blocking of the triple bond by dicobalt octacarbonyl), the opening of the cyclopropane ring leads to the homoallyl bromide (LXXXI) with a purity of 99%.[143] When the bromide (I) reacts with the Grignard reagents (LXXXII) in the presence of copper(I), the *trans*-enyne (LXXX) is obtained in 80% yield (purity 96%). After the reduction of the triple bond over the Lindlar catalyst,[144] the yield of the dienol is 60% and the latter consists of 92% of the 7-*trans*,9-*cis*-isomer and 8% of the 7-*trans*,9-*trans*-isomer:



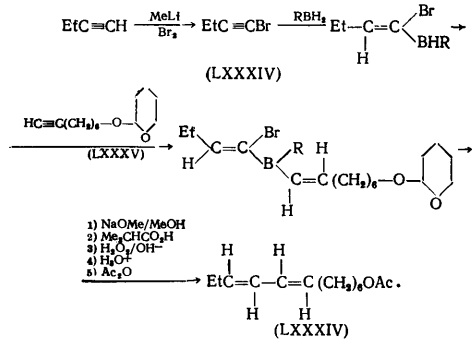
A new stereoselective synthesis of the pheromone (LXXIV) in 72% yield, based on the cross-coupling of *trans*-1,2-dichloroethylene with the Grignard reagent (LXXXIII) in the presence of tetrakis(triphenylphorphine)nickel, has been described recently. The reaction is accompanied by the almost complete (more than 99%) retention of the configuration at the double bond:[145]



The cross-coupling reaction of diisopentyl-*trans*-8-(2-tetrahydropyranoloxy)-en-1-octylborane (LXXXIV) with 1-bromobutyne in the presence of a palladium catalyst proceeds stereoselectively. Further acylation and hydroboration of the conjugated *trans*-enyne (LXXX) made it possible to obtain the alcohol (LXXIV) in 22% yield:[146]



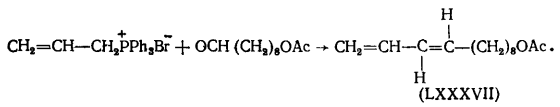
The stereoselective synthesis of conjugated *trans,trans*-systems was carried out by the hydroboration of the acetylenic derivatives (LXXXIV) and (LXXXV).[147] The purity of the *trans,trans*-7,9-diene (LXXXVI) is more than 99%:



trans-Dodeca-9,11-dienyl acetate (LXXXVII) is the main component of the pheromone of *Disparopsis castanea*—a pest on the cottonplant. This pheromone is a multicomponent

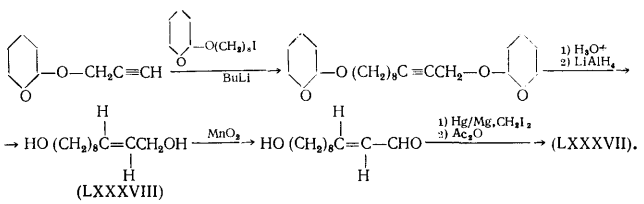
system containing a 1 : 4 mixture of the *cis*- and *trans*-dodeca-9,11-dienyl acetates, *trans*-dodec-9-enyl acetate, dodec-11-enyl acetate, and 1-dodecyl acetate.[148] The diene is the most active, but addition of the inactive dodec-11-enyl acetate to the diene (LXXXVII) (1 : 4) caused a sharp increase in the attracting effect. Each of these compounds separately inhibits the attraction by males, while dodec-9-enyl acetate influence the orientation of females. The role of 1-dodecyl acetate has not so far been elucidated.[148]

The Wittig reaction of triphenylphosphonium 2-propenylide with 9-oxononyl acetate in the presence of lithium bromide leads to 70% of a diene containing the *cis*- and *trans*-isomers of compound (LXXXVII) in proportions of 3 : 2:[148,149]

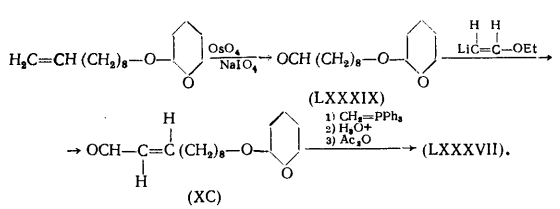


By varying the polarity of the solvent in the Wittig reaction, it is possible to achieve a 4 : 1 ratio of the *cis*- and *trans*-isomers, but a greater stereoselectivity cannot be achieved. The separation of the isomers is extremely difficult. However, by treating the products of the Wittig reaction with liquid sulphur dioxide and subsequent chromatography on Florisil, the product of the 1,4-cycloaddition of SO_2 was obtained. Its thermolysis takes place stereospecifically with formation of the diene (LXXXVII) whose stereochemical purity is in excess of 99%. The *cis*-isomer has been isolated in a satisfactory yield on treating the products of the Wittig reaction with tetracyanoethylene.[149,150]

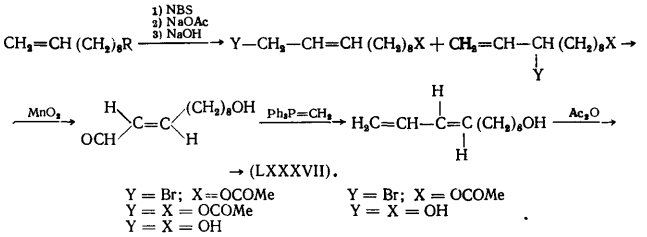
Another stereospecific synthesis of the pheromone (LXXXVII) has been achieved, in which the starting compound was tetrahydropyranoloxypropyne. The key compound, the *trans*-olefin (LXXXVIII), was obtained by reducing the triple bond in a disubstituted acetylene with lithium tetrahydroaluminate:[151]



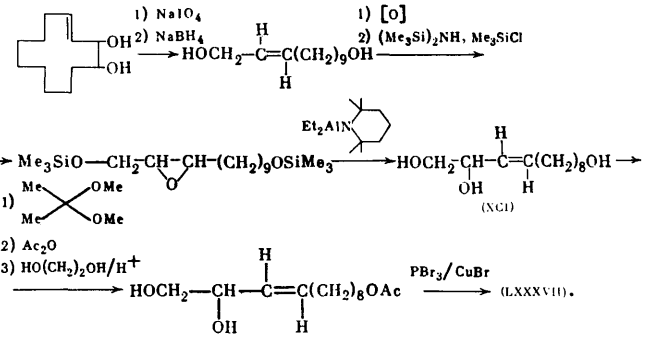
Oxidation of dec-9-enol with a mixture of osmium tetroxide and sodium metaperiodate leads to the aldehyde (LXXXIX), which is converted into the αβ-unsaturated aldehyde (XC) after condensation with β-ethoxyvinyl-lithium and subsequent rearrangement of the intermediate γ-ethoxyvinylmethanol. The aldehyde reacts with methylenetriphenylphosphorane to form the pheromone (LXXXVII)in 65% yield:[152,153]



The *cis*–*trans* isomerisation of αβ-unsaturated aldehydes[154] makes it possible to obtain *trans*-11-hydroxyundec-2-enal[155] with a *cis* : *trans* ratio of 85 : 15; the acetate (LXXXVII) was synthesised from it by the Wittig reaction (purity 97%):

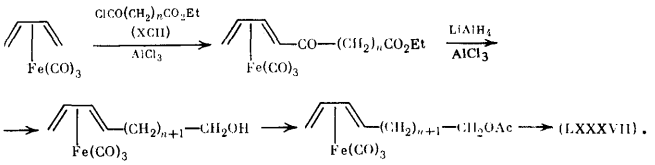


The regio- and stereo-specific opening of the oxiran ring by treatment with *N*-diethylalumino-2,2,6,6-tetramethylpiperidine has been used to convert the allyl alcohol (XCI) into the acetate (LXXXVII):[156]



The pheromone (LXXXVII) has also been synthesised by the stereospecific cross-coupling of *trans*-10-(2-tetrahydropyranyloxy)-1-decylborane and vinyl bromide in the presence of the palladium catalyst $Pd(PPh_3)_4$ in 54% yield.[146]

A novel method involving the use of the iron tricarbonyl protecting group, has been used to synthesise the pheromone (LXXXVII) with a high stereochemical purity (more than 99%). Butadieneiron tricarbonyl interacts with the acid chloride (XCII) under the conditions of the Friedel–Crafts reaction and subsequent reduction, acylation, and removal of the protecting group leads to compound (LXXXVII):[156]

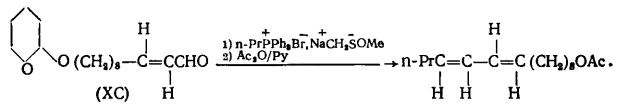


cis,*trans*-Tetradeca-9,11-dienyl acetate (XCIII) is the sex pheromone of the cotton pest *Spodoptera littoralis*.[148] The butterfly produces four compounds: tetradec-1-enyl acetate, *cis*,*trans*-tetradeca-9,11-dienyl acetate, *cis*-tetradec-9-enyl acetate, and *trans*-tetradec-11-enyl acetate.[10] Only the dienyl acetate has an attracting effect.[157] Tetradec-9-enyl acetate exhibits an inhibiting influence and the role of the other components has not been elucidated. Admixtures of the *cis*,*cis*- and *trans*,*cis*-isomers diminish the attracting effect.[157]

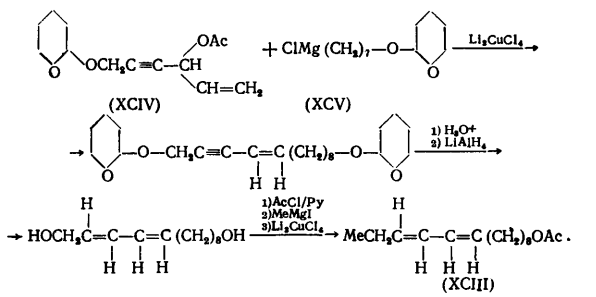
The same diene, namely *cis*,*trans*-tetradeca-9,11-dienyl acetate, forms part of the composition of the pheromone of *Spodoptera litura* in combination with *cis*,*trans*-tetradeca-9,12-dienyl acetate.[158] There are data showing that the mixture in proportions of 20 : 1 is active for *Spodoptera littoralis*.[148,157] There exist also directly opposed data

indicating that the 9-*cis*,12-*trans*-isomer inhibits the activity of the *cis*,*trans*-9,11-diene when present in proportions of 1 : 20 or 1 : 50.[159]

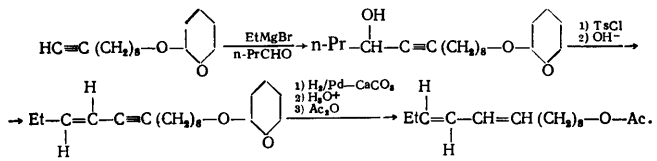
Compound (XCIII) has been synthesised from *trans*-pent-2-enyltriphenyl phosphonium bromide and 9-oxononyl acetate via the Wittig reaction, but the reaction is non-stereospecific.[148] It was later established that the ratio of the isomers in this reaction depends on solvent polarity: it is 40 : 60 in benzene, being reversed to 60 : 40 in DMSO.[160] The Wittig reaction of *trans*-pent-2-enal and 9-tetrahydropyranyloxynonylide in DMSO with subsequent acid hydrolysis and acetylation leads to a mixture of the 9-*cis*,11-*trans*- and 9-*trans*,11-*trans*-isomers in proportions of 80 : 20.[161] The interaction of *trans*-undec-2-enal with propylidenetriphenylphosphorane in THF in the presence of dimsylsodium and subsequent hydrolysis and acetylation make it possible to obtain the 9-*trans*,11-*cis*-isomer of the pheromone (XCIII) with a purity of 98%:[162]



The regioselective reaction of the substituted enyne (XCIV) with the Grignard reagent (XCV) in the presence of dilithium tetrachlorcuprate and subsequent partial diacetylation make it possible to obtain compound (XCIII) in a fairly high yield:[163]

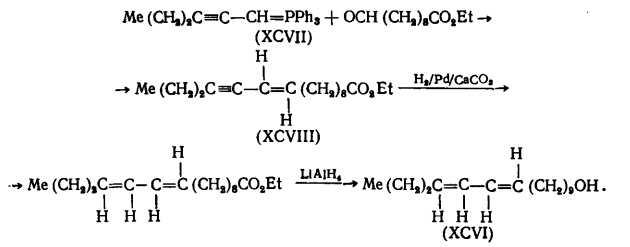


Another method, illustrated below, has also been used to synthesise compound (XCIII),[158,159] a mixture of the 9-*cis*,11-*trans*- and 9-*cis*,11-*cis*-isomers being obtained:

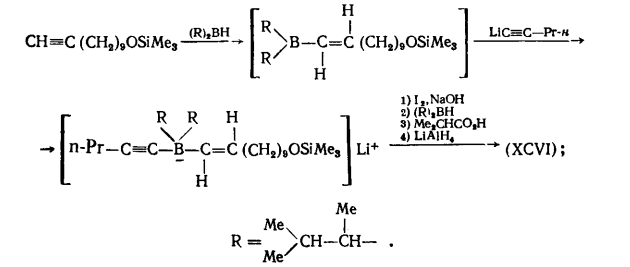


The attractant of the silkworm *Bombyx mori*, namely *trans*,*cis*-hexadeca-10,12-dienol (bombykol) (XCVI) was discovered by Butenand et al. in 1959.[164] It was assumed that this is the only pheromone of the butterfly, but subsequently data were obtained showing that there exist a further two components: hexadeca-10,12-dienal ("bombykal") and *trans*,*trans*-hexadeca-10,12-dienol.[165]

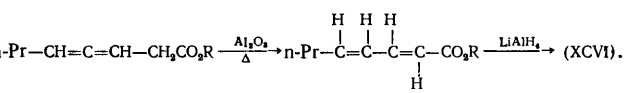
The pheromone (XCVI) has been obtained by the Wittig reaction involving the condensation of hex-2-ynylide (XCVII) with ethyl 10-oxodecenoate. The enyne product (XCVII) contained the *trans*- and *cis*-isomers in approximately equal amounts. The conjugated enyne (XCVIII) was hydrogenated over the Lindlar catalyst and the ester group was reduced with lithium tetrahydroaluminate to the alcoholic group:[164]



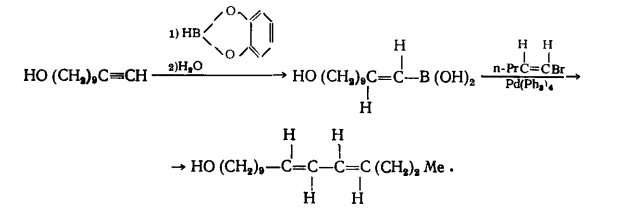
A method of synthesis in which the lithium salt of the pentyne was condensed with 1,2-epoxy-11-tetrahydropyranyloxyundecane to form an alcohol, the latter was converted into a toluene-*p*-sulphonate, and the conjugated enyne was obtained in the form of a mixture of the *trans*- and *cis*-isomers after splitting off the toluenesulphonic acid has also been used. The mixture was separated with the aid of a complex with urea and the *trans*-isomer was hydrogenated over the Lindlar catalyst. As already mentioned above, the process is relatively non-stereospecific and the yield of the desired product is low.[5] The hydroboration of the conjugated enyne system proceeds more stereospecifically. The scheme quoted below demonstrates the application of hydroboration to the synthesis of bombykol:[139]



Bombykol has also been obtained with the aid of cuprates[167] and a stereocontrolled rearrangement of a β-allene ester in the presence of alumina:[168]

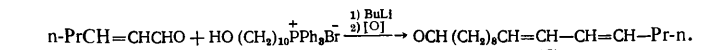


The reaction of alkenylboronic acid (XCIX) and a suitable alkenyl halide, catalysed by a palladium complex in the presence of a base, leads to *trans*,*trans*-dodeca-10,12-dien-1-ol in a high yield (66–91%) and a purity of 99%:[169]



trans,*trans*-Hexadeca-10,12-dienal (C), the main component of the sex pheromone of *Earias insulana*, has been obtained by a four-stage synthesis, in which the key stage is the Wittig reaction, leading to a mixture of the *trans*,*trans*- and

cis,trans-isomers of compound (C) in proportions of 1 : 4:[170]

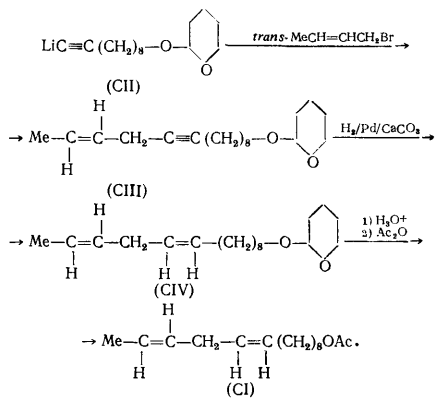


(C)

V. NON-CONJUGATED DIENE ALCOHOLS AND ACETATES

Non-conjugated dienes have been identified in a large number of insects of the order Lepidoptera.[5] Thus, *cis,trans*-tetradeca-9,12-dienyl acetate (CI) proved to be the pheromone of *Plodia interpunctella* and *Cadra cautella*.[171, 172] In a mixture with *cis*-tetradec-9-enyl acetate, this diene proved to be the pheromone of *Spodoptera eridania*.[173] The same compound has been identified in *Anagasta kühniella*,[174] *Ephestia elutella*,[175] *Cadra figulitella*,[176] and *Spodoptera litura*.[177] The *cis,cis*-, *trans,cis*-, and *trans,trans*-isomers of the pheromone (CI) are inhibitors. *cis,trans*-Tetradeca-9,12-dienol is an inhibitor of the pheromone of *Plodia interpunctella*.[178] Data have been published showing that *cis,trans*-tetradeca-9,12-dienyl acetate and *cis*-tetradec-9-enyl acetate are inactive in relation to *Spodoptera exigua* either individual or when combined.[179]

The *cis*,trans-1,4-diene system has been obtained in accordance with the scheme



(CII)

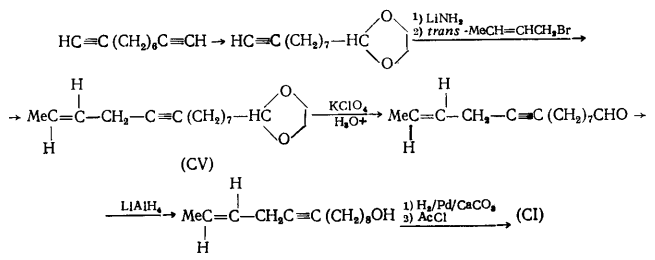
(CIII)

(CIV)

(CI)

The interaction of the lithium salts of the acetylene (CII) with *trans*-1-bromobut-2-ene in dioxan leads to the enyne (CIII), whose partial reduction affords an 86% yield of the diene (CIV). The acetylation of the diene gives rise to the pheromone (CI). All the other isomers of tetradeca-9,12-dienyl acetate have been obtained in accordance with the same scheme.[174,180]

An analogous method is based on the use of deca-1,9-diyne and crotyl alcohol:[181]

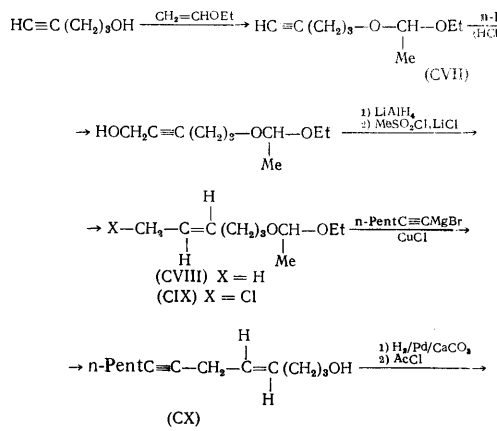


(CV)

The enyne alcohol (CV) has been obtained in 29% yield by the reaction of the Grignard reagent derived from *trans*-1-bromobut-2-ene with the lithium salt of an ω-substituted non-1-yne in THF in the presence of CuCl and CuCN. The formation of the 1,4-enyne (CV) by the reaction of 1-alkynyllithium and *trans*-1-bromobut-2-ene in dioxan is none other than the reaction of a strong base with an allyl halide, which always leads to a complex mixture of products. The products of the allylic rearrangement and isomerisation (a conjugated enyne) are accompanied by the products of the deprotonation of the 1,4-enyne and of further alkylation.[182,183] It has been found that the reaction of 1-alkynylsodium with allyl halide in ammonia leads to mono-, di-, and tri-alkylated compounds.[183] For example, propynylsodium reacts with one equivalent of 1-chlorobut-2-ene in liquid ammonia to give a mixture of products: 40% of the monoalkyl derivative and 55% of the dialkyl derivative. 1,4-Enynes can be obtained by the reaction of alkylmagnesium halide with allyl halide in ether[184] or THF in the presence of CuCl as the catalyst.[182,185] In the absence of a copper (I) salt, the reaction proceeds very unsatisfactorily or not at all.[186] A version of this method, which involves the interaction of allyl halide and a terminal acetylene on treatment with an amine and catalytic amounts of a copper salt (the Cadiot-Chodkiewicz method), is not very convenient for the synthesis of 1,4-enynes, because the normal alkylation product and the isomeric products of the allyl rearrangement are obtained in equal amounts. In dipolar aprotic solvents the reaction proceeds with the allyl rearrangement. Thus, the reaction of heptynylcopper with 1-bromobut-2-ene in HMP leads to a mixture of undec-9-en-6-yne and the rearrangement product (8-methyldec-9-en-6-yne) in proportions of 3 : 1 and 76% yield.[187] The enynes are formed in the same proportions in the reactions of the *cis*- and *trans*-isomers of 1-chlorobut-2-ene with copper phenylacetylide. In an attempt to reduce to a minimum the product of the allyl rearrangement, the reaction has been carried out in the presence of CuCl, whereupon 9% of the allyl product is formed in THF.[184] In THF in the presence of CuCN, *trans*-1-chlorobut-2-ene yields 15% of the allyl product, while in the presence of $LiCuCl_2$ it amounted to only 4.4%.[185]

A mixture of 95% of *cis,trans*-tetradeca-9,12-dienyl acetate and 5% of the *trans,trans*-isomer has been obtained by the Wittig reaction from triphenylphosphonia-*trans*-pent-3-enylide and 9-acetoxy-1-nonanal in HMP[186] or in DMSO.[187] The 1,4-diene is oxidised in air at room temperature[185] and irradiation with ultraviolet light leads to a mixture of *cis,trans*-13-hydroperoxytetradeca-9,11-dienyl acetate and *trans,trans*-9-hydroperoxytetradeca-10,12-dienyl acetate.[188] In order to stabilise the pheromone, an antioxidant is added, namely *N*-octyl-*N'*-phenyl-1,4-phenylenediamine.[195]

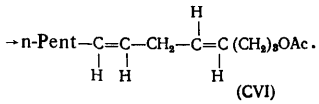
trans,cis-Trideca-4,7-dienyl acetate (CVI) is the pheromone of *Phthorimaoea operculella*.[188] A second active component of the pheromone of this species has been identified—*trans*,-*cis,cis*-trideca-4,7,10-trienyl acetate.[189] The acetate (CVI) has been obtained in accordance with the scheme



(CVII)

(CVIII) X = H
(CIX) X = Cl

(CX)



(CVI)

Pent-4-yn-1-ol is converted by the reaction with ethyl vinyl ether into the mixed acetal (CVII), which gives rise to the alcohol (CVIII) after treatment with n-butyl-lithium, reaction with paraformaldehyde, and reduction. The alcohol was converted into the chloride (CIX) by treatment with methanesulphonyl chloride in the presence of lithium chloride and collidine.[190] The allylic rearrangement is virtually ruled out under these conditions and the acid-sensitive acetal protecting group is unaffected. The reaction of allyl chloride (CIX) with 1-heptynylmagnesium bromide was carried out in the presence of catalytic amounts of copper monochloride. Hydrolysis with trichloroacetic acid in aqueous THF and low-temperature crystallisation of the product lead to a derivative of the enyne alcohol (CX) (purity 98.8%) in 60% yield. The corresponding *trans,cis*-4,7-diene was obtained in 98% yield on hydrogenation of the triple bond over the Lindlar catalyst in a hexane–THF mixture.[188]

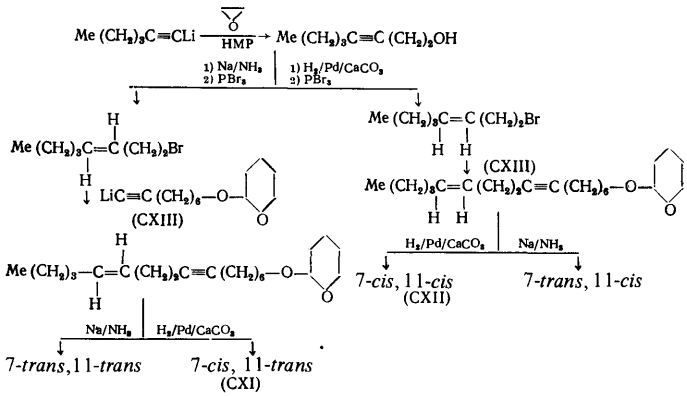
The inactive 4-*trans*,7-*trans*-isomer with an admixture of a mono-olefin (9%) was obtained by reducing the 1,4-enyne (CX) with lithium in liquid ammonia in the presence of ethanol. In the synthesis of *trans,trans*-1,4-dienoic acids it was shown that the reduction with lithium in ammonia without the addition of alcohol leads only to a mixture of *trans*-monoenoic acids.[191] For example, the 6,9-dienoic acid affords under these conditions a mixture of *trans*-6- (15%), *trans*-7- (36%), *trans*-8- (33%), and *trans*-9-monoenoic acids (16%).[191] Consequently such reduction of 1,4-dienes is accompanied by the base-catalysed formation of compounds with conjugated double bonds, which are then reduced to the monoene compounds. When 1,4-enynes were treated with alkali metal amides in ammonia, a rapid rearrangement of the *trans*-isomers to the *cis*-1,3-enynes was noted.[192] Octadeca-9,12-diynoic acid has been successfully reduced to *trans,trans*-octa-9,12-dienoic acid with sodium in a mixture of ammonia and diethyl ether in an autoclave.[185]

The reduction of 1,4-enynes with sodium in an ammonia–THF mixture in the presence of t-butyl alcohol is more stereospecific than in the presence of ethanol.[193] The 1,4-dienes were stabilised by adding 0.1% of 2,6-di-t-butyl-4-methylphenol.

Synthetic *trans,cis,trans*- and *trans,cis,cis*-trideca-4,7,11-trienyl acetates are not active components of the pheromone of *Phthorimaea operculella* but they do give rise to a positive response on the electroantennogram.[1]

trans-10-n-Propyltrideca-5,9-dienyl acetate (propylure) was initially identified as the pheromone of the pink bollworm *Pectinophora gossypiella*, which is a pest on the cotton-plant.[193,194] Synthetic propylure exhibited a very weak biological activity. However, it was later found that the pheromone consists of "gossyplure"—a 1 : 1 mixture of *cis,trans*- and *cis,cis*-hexadeca-7,11-dienyl acetates.[112,193–196] The individual geometrical isomers are inactive.[195]

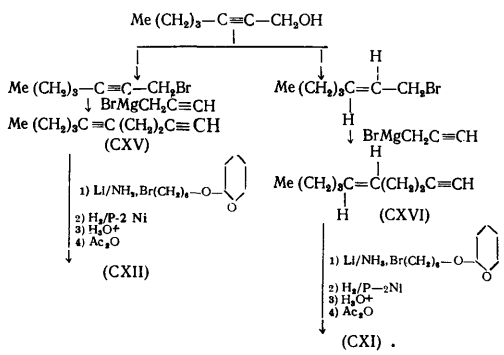
Synthetic *cis*-hexadec-7-enyl acetate (hexalure) proved to be an attractant of the butterfly *Pectinophora gossypiella*.[197] *cis,trans*-Hexadeca-7,11-dienyl acetate (CXI) has been identified as the pheromone of *Sitotroga cerealella*.[198] The acetate (CXI) and its 7-*cis*,11-*cis*-isomer (CXII) were obtained in a pure form via acetylenic intermediates[197–200] using an acetylenic Grignard reagent[195,201] or with the aid of the Wittig reaction.[200,202] In many studies the mixture was prepared artificially for the purpose of screening, while in others the required 1 : 1 mixture was obtained immediately by the Wittig synthesis.[115] All four possible geometrical isomers were obtained using oct-3-yn-1-ol and the lithium salt of 2-(7-octynyloxy)tetrahydropyran (CXIII):[203]



(CXI)

The homoallyl *cis*- and *trans*-oct-3-enyl bromides have been obtained from the corresponding alcohols by treatment with triphenylphosphine dibromide in dioxan (yield 85%) or with PBr_3 in a mixture of ether and pyridine (yield 56%). The condensation products were obtained by the reaction of these bromides with the lithio-derivative (CXIII) in dioxan (yield 25%)[198] or in diglyme (yield 66%).[204] The *trans*-configuration of the double bond was achieved by reduction with sodium in ammonia and the *cis*-configuration by hydrogenation over a modified Lindlar catalyst.[198]

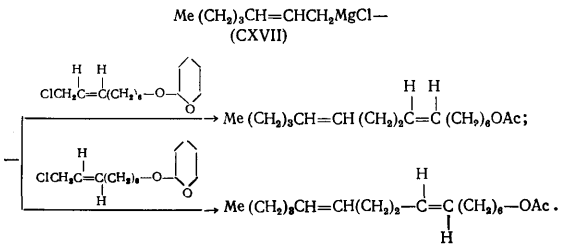
The diyne (CXV) (79%) and the enyne (CXVI) (63%) have been obtained respectively by the interaction of propargylmagnesium bromide (CXIV) with 1-bromohept-2-yne and *trans*-1-bromohept-2-ene:[205]



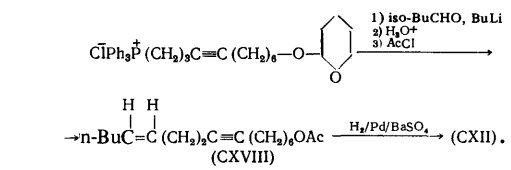
(CXI) .

The products of the alkylation of their lithium salts by tetrahydropyranyloxyoctyl bromide were obtained in 62% yield for the diyne (CXV) and 87% for the enyne (CXVI). Acid hydrolysis and partial hydrogenation leads to the pheromone components.[206] Deca-1,5-diyne (CXV) was obtained in 40% yield by the monoalkylation of the monolithium salt of hexa-1,5-diyne with 1-bromobutane in a mixture of HMP and THF.[195] The interaction of the Grignard reagent (CXVII) with *cis*(or *trans*)-allyl chloride in THF leads to a mixture of products with straight and branched chains,[201] the straight-chain product being formed in 20% yield from *cis*-allyl chloride

in the form of a mixture of the 7-*cis*,11-*cis*, and 7-*cis*,11-*trans*-isomers in proportions of 43 : 57:



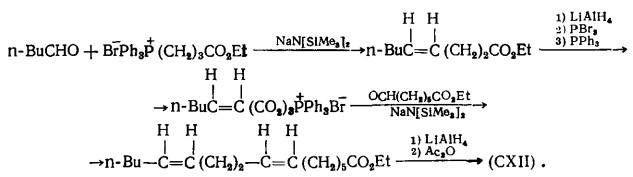
The yield of the branched-chain product diminishes to 50% when the reaction is carried out in a mixture of THF and HMP; the *cis*-11-isomer with a stereochemical purity of 94% is then obtained. Condensation of pentanal with the Wittig reagent derived from 11-tetrahydropyranyloxyundec-4-ynyl chloride leads to the enyne (CXVIII) consisting of 96% of the *cis*-isomer and 4% of the *trans*-isomer: [200]



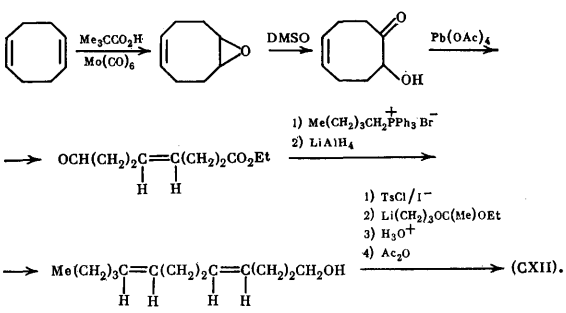
Partial hydrogenation results in the formation of the *cis*,*cis*-isomer (CXII). *trans*,*trans*- and *trans*,*cis*-Hexadeca-7,11-dienyl acetates have been obtained by the isomerisation of bisepoxides on treatment with lithium diphenylphosphide. [207]

The reduction of the 1,5-enyne system with sodium in liquid ammonia, which leads to the *trans*,*trans*- and *trans*,*cis*-7,11-dienes, always affords a mixture of isomers containing 72% of the *trans*,*trans*-dienes, 18% of other dienes, and 5% of cyclic products. [200]

The Wittig reaction where sodium bis(trimethylsilyl)amide in THF is used as the base is highly *cis*-stereospecific (up to 98%): [202]

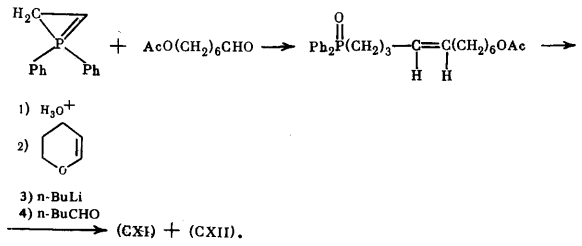


The dependence of the stereospecificity of this reaction on temperature has been observed. Thus at −78 °C the ratio of the *cis*- and *trans*-isomers in the olefinic product is 98 : 2, while at 20 °C it is 94 : 6. The components of gossyplure have been obtained also from *cis*,*cis*-cyclo-octa-1,5-diene. [115] The asymetric rupture of one of the double bonds leads to an intermediate containing not only the necessary functional groups but also a *cis*-double bond:



Next the Wittig reaction with the olefin was carried out and a study was made of the influence of various factors on the stereochemistry of this reaction. [5] It is known that an aliphatic ylide reacts with an aliphatic aldehyde to give mainly *erythro*-intermediates, which are converted into a *cis*-olefin after splitting off triphenylphosphine oxide.

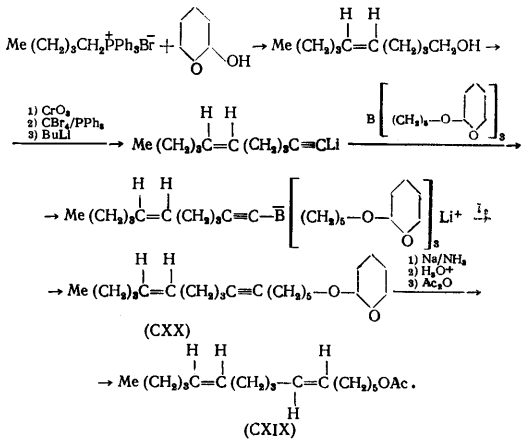
Olefinic phosphine oxides obtained from cyclic phosphonium ylides are of great interest for the synthesis of the components of gossyplure—hexadeca-7,11-dienyl acetates: [209]



When the Wittig reaction was carried out in dipolar aprotic solvents (DMF, DMSO, HMP) both in the presence and absence of a lithium salt, identical results were obtained. In non-polar solvents the stereochemistry of the olefinic products depends on the nature of the inorganic salts. [1,5,209] *trans*,*cis*- and *cis*,*cis*-Octadeca-3,13-dienyl acetates are the pheromones of *Synanthedon pictipes* and *Synanthedon exitiosa*. [210–212] All four isomers of octadeca-3,13-dienyl acetate were obtained via acetylenic intermediates. [213]

trans,*cis*-Hexadeca-6,11-dienyl acetate (CXIX) is the pheromone of the oak silkworm *Anthreraea polyphemus* in a 9 : 1 mixture with the corresponding aldehyde. The acetate (CXIX) has been obtained in accordance with an analogous scheme via acetylenic intermediates. [214,215]

Both components of the pheromone of *Antheraea polyphemus* were also synthesised from the enzyme compound (CXX) using the Wittig reaction to generate the *cis*-11-double bond; the *trans*-6-olefin was synthesised by reduction with sodium in liquid ammonia:



The isomeric purity of the resulting *trans*,*cis*-hexadeca-6,11-dienyl acetate and the corresponding aldehyde is in excess of 97%. [216,217]

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