# The Total Synthesis of Natural Products

VOLUME 4

Edited by

John ApSimon

*Department of Chemistry*
*Carleton University, Ottawa*

A WILEY-INTERSCIENCE PUBLICATION

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# Preface

Throughout the history of organic chemistry, we find that the study of natural products frequently has provided the impetus for great advances. This is certainly true in total synthesis, where the desire to construct intricate and complex molecules has led to the demonstration of the organic chemist's utmost ingenuity in the design of routes using established reactions or in the production of new methods in order to achieve a specific transformation.

These volumes draw together the reported total syntheses of various groups of natural products and commentary on the strategy involved with particular emphasis on any stereochemical control. No such compilation exists at present, and we hope that these books will act as a definitive source book of the successful synthetic approaches reported to date. As such, it will find use not only with the synthetic organic chemist but also perhaps with the organic chemist in general and the biochemist in his specific area of interest.

One of the most promising areas for the future development of organic chemistry is synthesis. The lessons learned from the synthetic challenges presented by various natural products can serve as a basis for this ever-developing area. It is hoped that these books will act as an inspiration for future challenges and outline the development of thought and concept in the area of organic synthesis.

The project started modestly with an experiment in literature searching by a group of graduate students about thirteen years ago. Each student prepared a summary in equation form of the reported total syntheses of various groups of natural products. It was my intention to collate this material and possibly publish it. During a sabbatical leave in Strasbourg in 1968-69, I attempted to prepare a manuscript, but it soon became apparent that the task would take many years and I wanted to enjoy some of the other benefits of a sabbatical leave. Several colleagues suggested that the value of such a collection would be enhanced by commentary. The only way to encompass the amount of data

collected and the inclusion of some words was to persuade experts in the various areas to contribute.

Volume 1 presented six chapters describing the total synthesis of a wide variety of natural products. The subject matter of Volume 2 was somewhat more related, being a description of some terpenoid and steroid syntheses. Volume 3 concentrated on alkaloid synthesis and appeared in 1977. The present volume contains three chapters on new areas of synthetic endeavor and two more encompassing the progress in synthetic work in the areas of monoterpenes and prostaglandins since the appearance of Volume 1.

It is intended that Volume 5 of this series will contain predominantly updating chapters in order that this series may continue to be of timely use to those with interests in synthetic chemistry.

John ApSimon

*Ottawa, Canada*
*March 1981*

# Contents

# THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

# The Synthesis of Insect Pheromones

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## 1. INTRODUCTION

Man has wondered at spectacular scenes of metamorphosis, aggregation, and mating of insects for many years. During the past two decades it has gradually become clear that these biological phenomena are regulated by chemical substances known as insect hormones and pheromones. Insect chemistry, the study of natural products of insect origin, is now regarded as an established branch of natural products chemistry.

After the discovery of bombykol **1**, the first insect pheromone, by Butenandt and his associates,[1] the term "pheromone" was defined by Karlson and Lüscher.[2] The name is derived from the Greek *phrein*, to transfer, and *hormon*, to excite. Pheromones are substances that are secreted to the outside by an individual and received by a second individual of the same species, in which they release a specific reaction, for example, a definite behavior or a developmental process.

From the beginning the synthetic approach was very important in pheromone researches because of the limited availability of natural pheromones from insects (usually less than several milligrams). Synthetic work in insect pheromones may be classified into three categories: (1) synthesis as the final proof of the proposed structure, including olefin geometry and relative as well as absolute stereochemistry; (2) synthesis that provides sufficient material for biological study, such as field tests; and (3) synthesis of a number of isomers and analogs to clarify the structure-pheromone activity relationship. Synthesis thus ensures ample supplies of otherwise inaccessible pheromone and facilitates the practical uses of pheromones in agriculture and forestry.

Pheromone structures are scattered among various types of volatile compounds ranging from alkanes to nitrogen heterocycles. Recent studies on structure-activity relationships reveal the importance of stereochemistry in pheromone perception by insects. Three types of isomerism, structural, geometrical, and optical, are all shown to effect the biological activity, as described below.

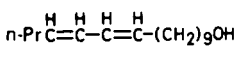
### *Bombykol, the Pheromone of the Silkworm Moth (*Bombyx mori*), and its Geometrical Isomers*

Butenandt et al.[3,4] and Truscheit and Eiter[5] synthesized all of the four possible geometrical isomers of bombykol **1** and compared their attractancy to the male silkworm moth. The results are shown in Table 1. The biological activity, as well as physical properties, of (10*E*, 12*Z*)-10,12-hexadecadien-1-ol was almost identical with that of the natural bombykol. The geometry of the diene system in bombykol was thus established as 10*E*, 12*Z* by this synthetic work. It should be noted that the other three geometrical isomers possess only moderate or weak biological activities. A highly stereoselective synthesis of the most active isomer is therefore of paramount importance both scientifically and economically.

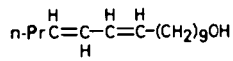
Table 1. Biological Activity of Natural Bombykol and Synthetic Geometrical Isomers of 10,12-Hexadecadien-1-ol

| | Activity ($\mu$g/ml)[a] | | |
|---|---|---|---|
| | Butenandt[3] | Butenandt[4] | Eiter[5] |
| 10*Z*, 12*Z* | 1 | 1 | – |
| 10*Z*, 12*E* | $10^{-3}$ | $10^{-2}$ | $10^{-5}$ |
| 10*E*, 12*Z* | $10^{-12}$ | $10^{-12}$ | $10^{-12}$ |
| 10*E*, 12*E* | 10 | 100 | 10 |
| Natural bombykol | $10^{-10}$ | $10^{-10}$ | $10^{-10}$ |

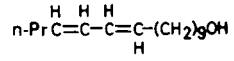
[a]The activity is expressed by *die Lockstoffeinheit* (LE). This is the lower limit of the pheromone concentration ($\mu$g/ml) to which 50% of the test insects show reaction.



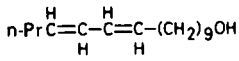
(10Z, 12Z) - 1



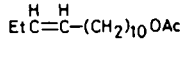
(10Z, 12E) - 1



(10E, 12Z) - 1 - (Bombykol)



(10E, 12E) - 1



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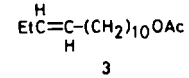

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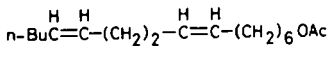

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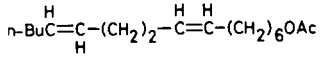


5

*The Pheromone of Red-banded Leaf Roller (*Argyrotaenia velutinana*) and Its Geometrical Isomer*

Roelofs et al. identified (*Z*)-11-tetradecenyl acetate 2 as the sex pheromone of red-banded leaf roller moths.[6] They then demonstrated that a large amount of the (*E*)-isomer 3 is inhibitory to pheromone action.[7] Here again stereochemistry was shown to be important. Roelofs' argument on this subject was based on his bioassay results with many pheromone analogs, some of which work in an inhibitory manner, while others act synergistically.[7] Subsequently Klun et al.[8] and

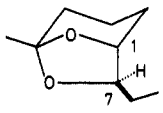
Beroza et al.[9] reported the very interesting observation that a small amount of opposite geometrical isomer was critical to pheromone attraction. Klun found that a geometrically pure preparation of 2 was very weakly attractive to the moth and that the presence of 7% of (*E*)-isomer 3 was necessary for maximum activity.[8] Previous syntheses of 2 employed either the Wittig reaction or the Lindlar semihydrogenation, and neither of them was 100% stereoselective. It is therefore obvious that a highly pure geometrical isomer is required to study this kind of very subtle biological phenomena. Beroza's relevant work was on the pheromone of the oriental fruit moth *Grapholitha molesta*. The biological activity of the synthetic pheromone (*Z*)-8-dodecenyl acetate increased 25 times by the addition of a small amount of the (*E*)-isomer.[9]

*Gossyplure, the Pheromone of Pink Bollworm Moth (*Pectinophora gossypiella*)*

In the case of gossyplure the pheromone consists of a mixture of two geometrical isomers in an equal amount: (7*Z*, 11*Z*)-7,11-hexadecadienyl acetate 4 and its 11*E*-isomer 5.[10] Neither is biologically active alone. This suggests the existence of two different receptor sites on the pheromone receptor of the pink bollworm moth.

*The Pheromone of* Dendroctonus *Bark Beetles*

Two stereoisomers of 7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane were isolated from the frass of the western pine beetle (*Dendroctonus brevicomis*).[11] Only one of them, *exo*-brevicomin 6, is biologically active as a component of the aggregation pheromone of the western pine bettle. The other isomer, *endo*-brevicomin 7, is inactive to the western pine beetle and even inhibits the olfactory response of flying male and female southern pine beetles (*Dendroctonus frontalis*) to the female-produced pheromone, frontalin 8.[12] In this case the *endo-exo* stereoisomerism is of utmost importance for biological activity. This necessitated the stereoselective synthesis of these pheromones.

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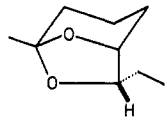


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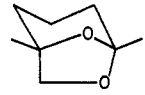


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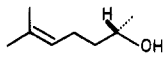


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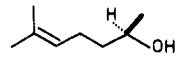



(R) - 9

*Biological Activities of the Optical Isomers of Pheromones*

*exo*-Brevicomin **6** and frontalin **8** are chiral molecules. They therefore can exist in two enantiomeric forms. Both enantiomers of these pheromones were synthesized, ensuring biological evaluation of the isomers.[13,14] The biologically active isomers were (1*R*, 5*S*, 7*R*)-(+)-*exo*-brevicomin **6** and (1*S*, 5*R*)-(−)-frontalin **8**.[15] In these cases only one enantiomer of the two optical isomers possesses pheromone activity.

Sulcatol is the aggregation pheromone produced by males of *Gnathotrichus sulcatus*.[16] Both (+)-sulcatol[(*S*)-**9**] and (−)-isomer [(*R*)-**9**] were synthesized.[17] Surprisingly, neither of them was biologically active. However, when combined to give a racemic mixture the synthetic sulcatol was more active than the natural pheromone, which was a mixture of 65% of (*S*)-**9** and 35% of (*R*)-**9**.[18] This situation is somewhat similar to that encountered in the case of gossyplure and suggests the presence of enantiomer-specific active sites on receptor proteins in the same or different cells of *Gnathotrichus sulcatus*. These examples illustrate the importance of stereochemistry in pheromone researches.

The aim of this chapter is to provide a compilation of synthetic works on pheromones. As one of the major synthetic problems in this field is the stereoselective construction of olefinic linkages, Section 2 deals mainly with preparative methods for disubstituted olefins. Then synthesis of individual pheromones is detailed according to a classification based on the type of compound and functional groups present. As the trend in modern organic synthesis is to develop new methods for providing chiral molecules in a stereocontrolled manner, synthesis of chiral pheromones are treated comprehensively. It is hoped that this chapter will be useful not only to synthetic chemists but also to entomologists who wish to prepare pheromones of particular interest to them.

There are a number of monographs and reviews on pheromones. Especially noteworthy is the recent chapter on Insect Chemistry in *Annual Reports on the Progress of Chemistry*, which is a thorough survey on pheromone chemistry.[19,20] Four reviews on pheromone synthesis are available: Katzenellenbogen's review focuses on the methodological point of view[21]; Henrick discusses selected pheromones (*Lepidoptera, Coleoptera,* and *Diptera*) in depth[22]; and Rossi reviews the synthesis of both achiral[23] and chiral[24] pheromones. Aspects of pheromone chemistry is reviewed in Refs. 25-29. For those who are interested in pheromone biology and its application a plethora of monographs and reviews is available: e.g., Refs. 30-32 (general treatises) and Refs. 33-35 (insect behavior and the practical application of pheromones). Bark beetle pheromones are reviewed in Refs. 36-40. References 41 and 42 are concerned with the terpenoid pheromones, and Ref. 43 is a readable review on the pheromone receptor of moths.

## 2. GENERAL METHODS

Before the advent of pheromone and juvenile hormone chemistry the stereoselective construction of di- and trisubstituted olefins was of only limited interest to oil and terpene chemists. During the past decade the situation has changed, and we now have many ingenious new methods as well as modifications of older methods for olefin synthesis. References 44 and 45 are excellent reviews on the stereoselective synthesis of olefins. In this section reactions that have been used or may be useful in pheromone synthesis are presented. Synthetic methods for trisubstituted olefins are omitted, since they are the theme of another review on juvenile hormone synthesis.[46]

### A. Synthesis of (*E*)-Alkenes

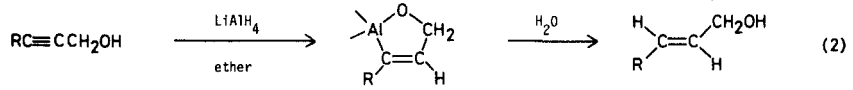
#### *Metal-Ammonia Reduction of Alkynes*

The reduction of alkynes with sodium in liquid ammonia is the standard method (Equation 1).[47] Warthen and Jacobson recommend the use of a large volume of liquid ammonia to minimize the recovery of the starting alkynes.[48]

(1)

#### *Lithium Aluminum Hydride Reduction of Alkynes*

The reduction of 2-alkyn-1-ols to 2-alken-1-ols with lithium aluminum hydride in ether usually proceeds in an excellent yield (Equation 2).[49] Other alkynols such as 3-alkyn-1-ol, 7-alkyn-1-ol, and 8-alkyn-1-ol can also be reduced to the corresponding alkenols by reacting them at 140° for 48-55 h, under nitrogen, with a large excess of lithium aluminum hydride in a mixture of diglyme and tetrahydrofuran (Equation 3).[50]



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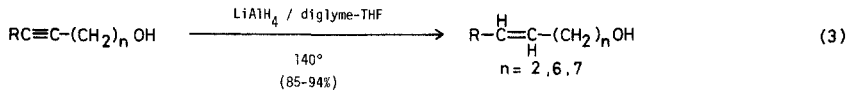
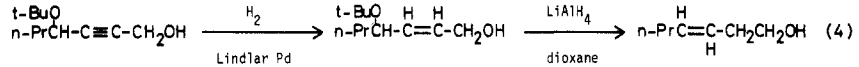


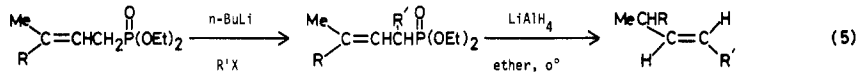
(3)

#### *Reductive Elimination of Allylic Substituents*

3-Alken-1-ols can be prepared from alkynes by the route shown in Equation 4. The key stereoselective step (97% *E*) is the reductive elimination of the allylic

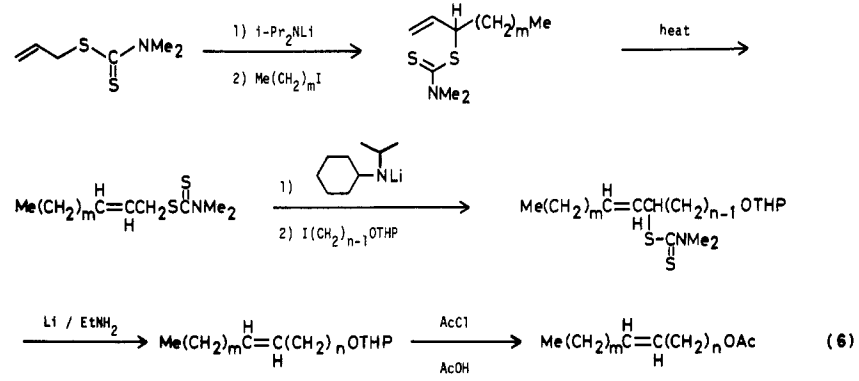
*t*-butoxy group.[51] A highly stereoselective synthesis of an (*E*)-alkene employs the reduction of a phosphonate ester as the key step (Equation 5).[52] The yield is moderate to excellent.





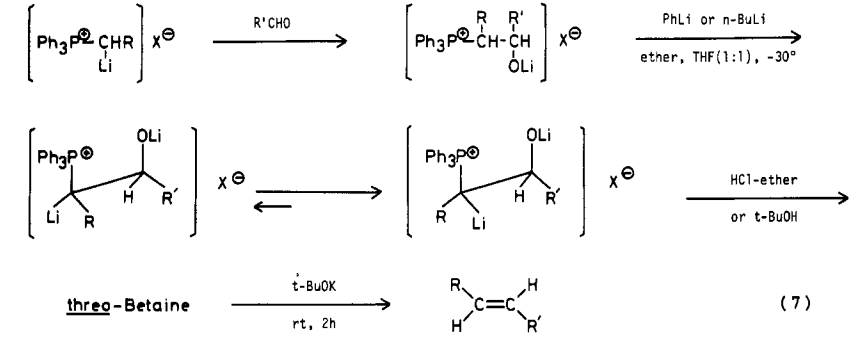
### *Rearrangement of Allylic Dithiocarbamates*

The rearrangement of allylic dithiocarbamates is applicable to the synthesis of various alkenol pheromones (Equation 6).[53] The yield is good to excellent.



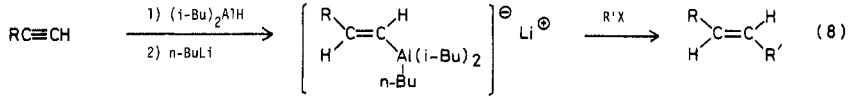
### *The Wittig Reaction*

The Schlosser modification of the Wittig reaction as shown in Equation 7 gives an (*E*)-alkene in 60-72% yield with 90-96% stereoselectivity.[54-56] For the stereochemistry of this reaction see Ref. 22, p. 1875.



### *Utilization of Organoaluminum Compounds*

Disubstituted (*E*)-alkenes can be prepared by the reaction of (*E*)-alkenyl trialkylaluminates with alkyl halides and sulfonates (Equation 8).[57] The yield is good (44-79%) for allylic halides and moderate (41-44%) for primary halides. Secondary and tertiary halides gave poor results. (*E*)-Vinyl iodides are obtainable in 94% stereoselectivity, as shown in Equation 9.[58] Reaction with lithium dialkylcuprate ($R_2CuLi$) converts the iodide to (*E*)-alkene. A vinylalane is converted to (*E*)-homoallylic alcohol in the yield of 81-88% (Equation 10).[59]

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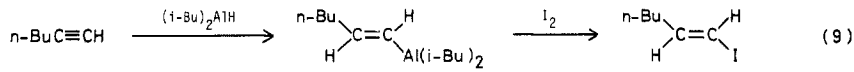


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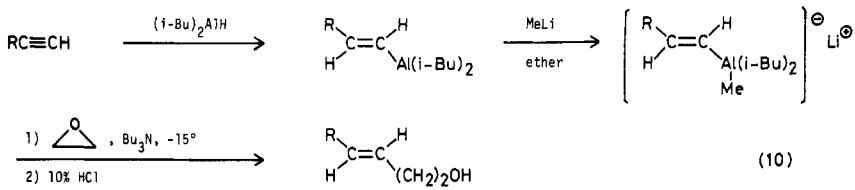
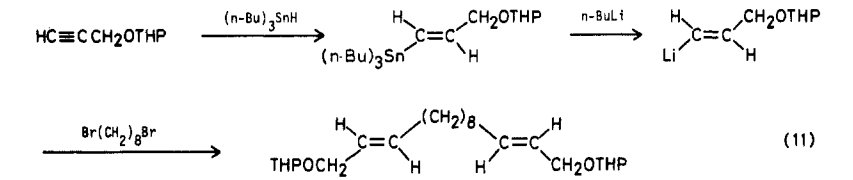



(10)

### *Utilization of Organotin Compounds*

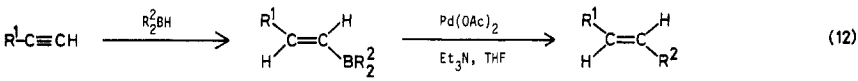
(*E*)-Allylic alcohols can be prepared from propargylic alcohol via an organotin compound (Equation 11).[60]




(11)

### *Utilization of Organoboranes*

(*E*)-Alkenes are prepared by the reaction of boranes with palladium acetate (Equation 12).[61] (*E*, *E*)-Conjugated dienes are obtainable via hydroboration (Equation 13).[62]

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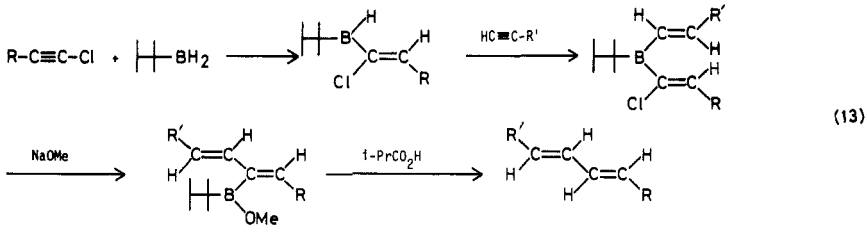
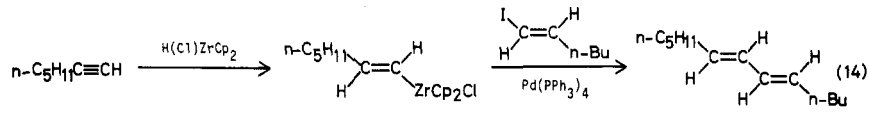


(13)

### *Utilization of Organozirconium Compounds*

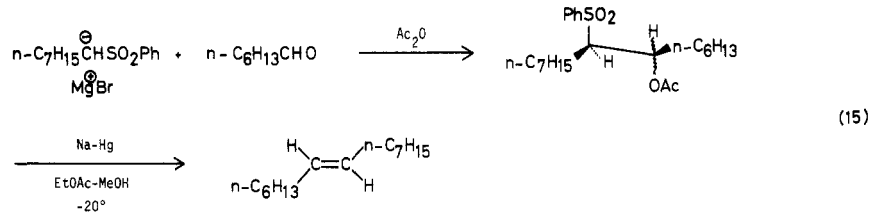
(*E, E*)-Conjugated dienes are synthesized by the palladium-catalyzed reaction of (*E*)-1-alkenylzirconium derivatives with alkenyl halides (Equation 14).[63]



(14)

### *Reduction of β-Acetoxysulfones*

(*E*)-Alkenes are obtained by reduction of β-acetoxysulfones with sodium amalgam (Equation 15).[64]

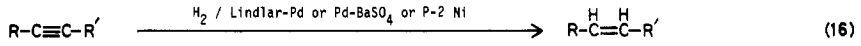


(15)

## B. Synthesis of (*Z*)-Alkenes

### *Hydrogenation of Alkynes*

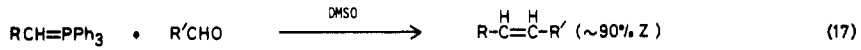
Hydrogenation of alkynes is the standard method for the preparation of (*Z*)-alkenes (Equation 16). Lindlar's palladium catalyst is widely used for this purpose.[65,66] This catalyst produces alkenes containing only small amounts (~5%) of (*E*)-isomer. Frequently at low catalyst ratios no (*E*)-alkene is detectable at the point of disappearance of the substrate alkyne.[67] Two alternative catalysts are 5% palladium on barium sulfate in methanol containing a small amount of quinoline[68] and P-2 nickel in ethanol containing a small amount of ethylenediamine.[69] Although hydrogenation with P-2 nickel is said to be highly stereoselective (*E* : *Z* = 1 : 200), the best method is low-temperature hydrogenation over Lindlar catalyst. Thus at -10 to -30° in pentane, hexane, or hexane-THF the (*Z*)-alkenes obtained contain ~0.5% of the (*E*)-isomer.[70]



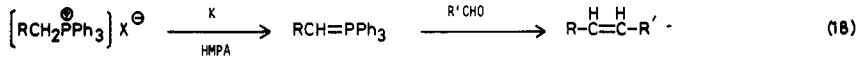
(16)

### *The Wittig Reaction*

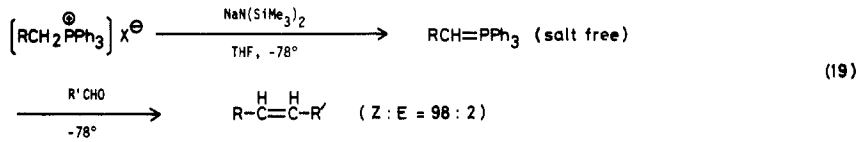
The Wittig olefination carried out in DMSO is known to give a (*Z*)-disubstituted alkene as the major product (Equation 17).[71,72] The use of potassium in HMPA as the base favors the (*Z*)-olefination (Equation 18).[73,74] The use of salt-free ylid solution is recommended for the preparation of (*Z*)-alkenes (Equation 19).[75] The stereochemistry of this reaction is discussed by Schlosser.[56]



(17)



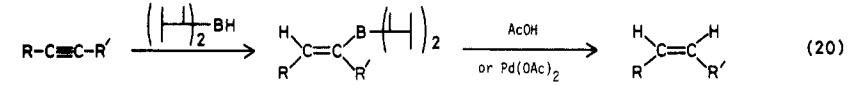
(18)



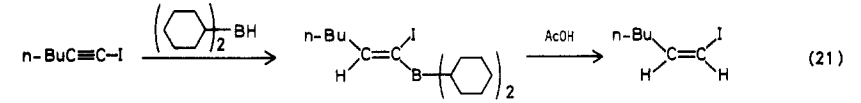
(19)

### *Utilization of Organoboranes*

(*Z*)-Alkenes (98-99% *Z*) can be prepared from disubstituted alkynes by hydroboration-protonolysis (Equation 20).[76] The protonolysis is also achieved under neutral conditions by treatment with catalytic amounts of palladium acetate.[77] (*Z*)-Vinyl iodides are obtainable from iodoacetylenes by the same process (Equation 21).[78] They are convertible to (*Z*)-alkenes by treatment with organocopper reagents.



(20)



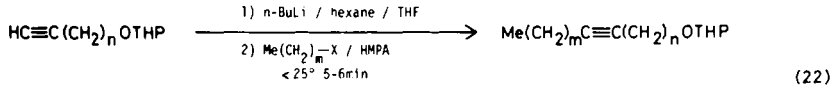
(21)

## C. Carbon-Carbon Bond Formation

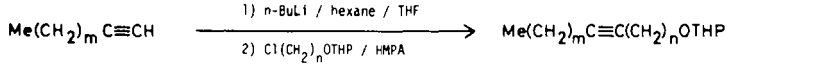
### *Alkylation of Alkynes*

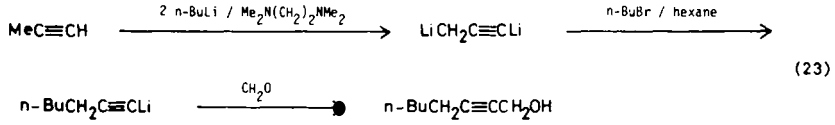
Alkylation of 1-alkynes gives disubstituted acetylenes, which are the starting materials for both (*E*)- and (*Z*)-alkenes. The traditional procedures are listed in Ref. 79. Recently a convenient and efficient procedure for the alkylation was

proposed independently by two groups (Equation 22).[47,80] The procedure is particularly convenient for small-scale preparations. The yield is excellent if the alkylating agent is a primary and unbranched halide (see also Ref. 22; p. 1847.) An interesting 1,3-disubstitution reaction of 1,3-dilithiopropyne may be useful in pheromone synthesis (Equation 23).[81]




(22)




(23)

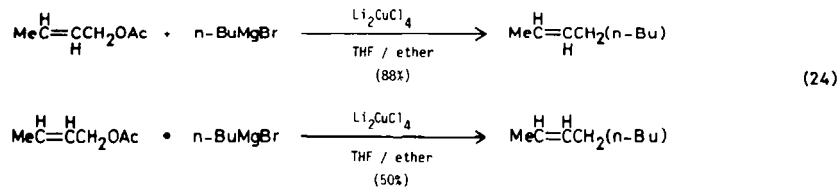
### *Coupling Reactions with Organometallic Reagents*

An acetoxy group occupying the allylic position or a tosyloxy group can be replaced by the hydrocarbon moiety of a Grignard reagent. The replacement is regio- and stereoselective (Equation 24).[82] The coupling of an (*E*)-terminal vinyllithium with an alkyl halide gives an (*E*)-alkene stereoselectively (Equation 25).[83]

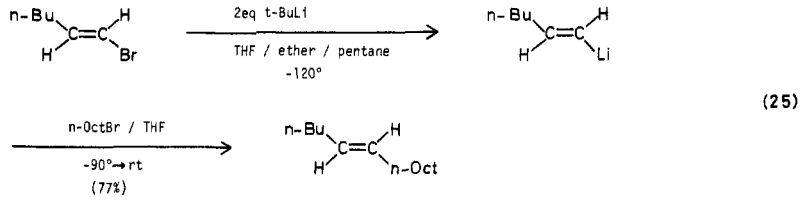
A new regio- and stereoselective olefin synthesis applicable to pheromone synthesis is direct substitution of hydroxyl groups of allyl alcohols with alkyl groups by the reaction of lithium allyloxyalkylcuprates with *N,N*-methylphenylaminotriphenylphosphonium iodide (Equation 26).[84] By this method both (*E*)- and (*Z*)-alkenes are obtainable.

(*Z*)-Alkenols can be prepared from (*Z*)-vinylic organocopper reagent in a moderate yield (Equation 27).[85]

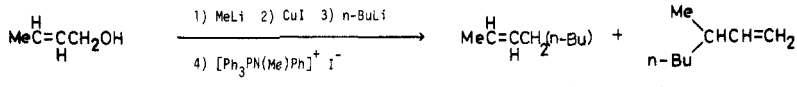
The palladium-catalyzed cross-coupling reactions of vinylic iodides with a variety of Grignard reagents occurs with retention of configuration (~97%) (Equation 28).[86]



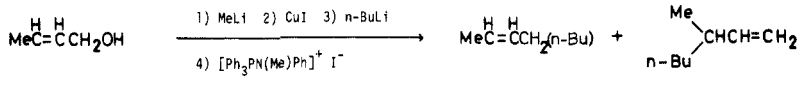

(24)

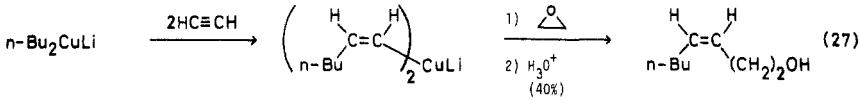



(25)

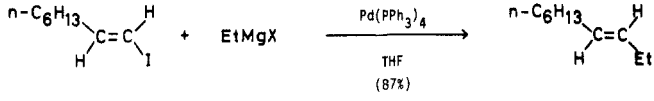



(26)

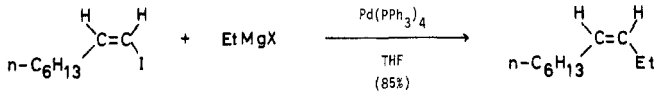



(27)



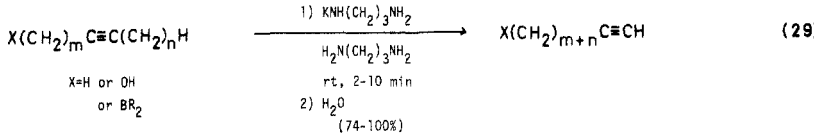

(28)




## D. Other Useful Methods

### *Multipositional Isomerization of Alkynes and Alkynols*

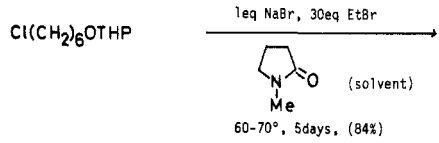
Potassium 3-aminopropylamide (KAPA) is an exceptionally active catalyst for multipositional isomerization of alkynes and alkynols to terminal acetylenes (Equation 29).[87-89] This is a convenient method to obtain 1-alkynes, popular starting materials for the *Lepidoptera* sex pheromones.




(29)

### *Conversion of Alkyl Chlorides to Bromides*

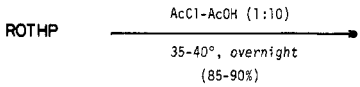
For the alkylation of alkynes (Equations 22 and 23), alkyl chlorides are generally not so reactive. Therefore an efficient method is desirable for the conversion of alkyl chlorides to bromides. A new procedure employs ethyl bromide as the source of bromine (Equation 30).[90] The high volatility of ethyl chloride, the by-product, is the driving force for the completion of the reaction.




(30)

### *Conversion of Tetrahydropyranyl (THP) Ethers to Acetates*

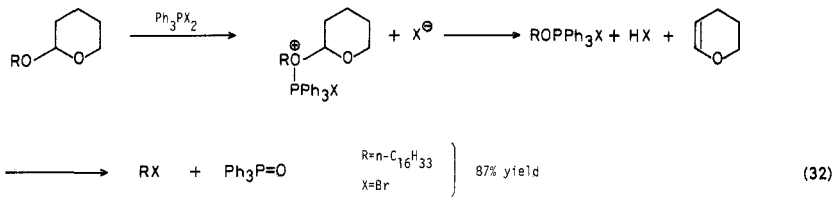
Many pheromones are acetates of long-chain alcohols. The THP group is the most commonly employed protecting group in the course of pheromone synthesis. The direct conversion of THP ethers into acetates can be achieved in 85-90% yield (Equation 31).[47]




(31)

### *Conversion of THP Ethers to Bromides*

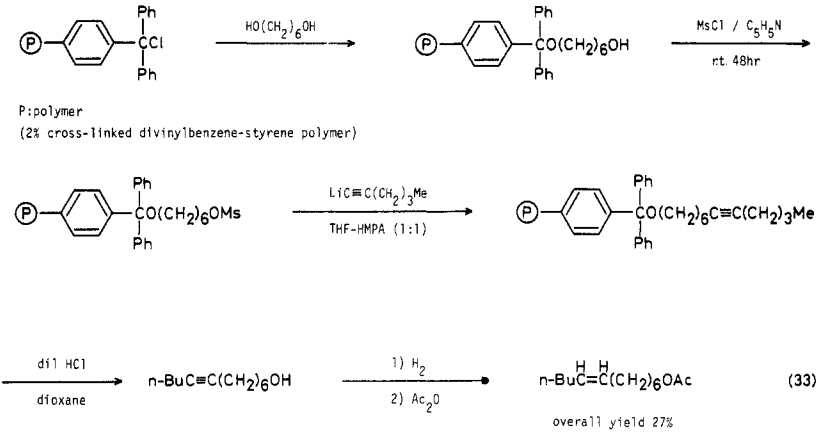
It is possible to carry out the direct conversion of THP ethers to halides (Equation 32).[91]




(32)

### *Solid-phase Synthesis*

The application of solid-phase synthesis in the pheromone field has been reported by Leznoff (Equation 33).[92-95] Solid-phase synthesis gives comparable or better overall yields than previous methods, uses inexpensive symmetrical diols as starting materials, and has the potential for being adapted to an automated procedure. It is questionable, however, whether this method is suitable for the large-scale preparation of pheromones required for field tests.




### *Separation of Geometrical Isomers by Formation of Urea Complexes*

Mixtures of geometrical isomers can be conveniently separated on a large scale by the relatively inexpensive method of urea inclusion complex formation.[482] The recovery of both isomers from the separation procedure is almost quantitative. Urea inclusion complexes are formed preferentially with (*E*)-isomers. By applying this method of separation at a convenient stage, several insect phero-

**Table 2.** Separation of Geometrical Isomers of $RR_1C{=}CH(CH_2)_nX$ by Urea Complex Formation[482]

| R | $R_1$ | *n* | X | Separation[a] |
|---|---|---|---|---|
| *n*-Pr | Me | 9 | $CO_2Me$ | + |
| *n*-Pr | Me | 9 | CHO | – |
| *n*-Bu | H | 9 | $CO_2Me$ | – |
| *n*-Bu | H | 9 | CN | + |
| *n*-Bu | H | 9 | $CH_2OH$ | – |
| *n*-Bu | H | 9 | CHO | + |
| *n*-Bu | H | 7 | $CO_2Me$ | – |
| *n*-Bu | H | 7 | $CH_2OH$ | + |
| *n*-Bu | H | 2 | $CO_2Me$ | + |
| *n*-PrCH=CH[b] | H | 8 | $CH_2OH$ | + |
| *n*-PrC≡C[b] | H | 8 | $CO_2Et$ | + |
| *n*-PrC≡C[b] | H | 8 | $CH_2OH$ | + |

[a] The plus sign indicates that at least one isomer could be obtained in essentially pure form; the minus sign indicates that no separation was achieved.
[b] From Butenandt et al.[4]

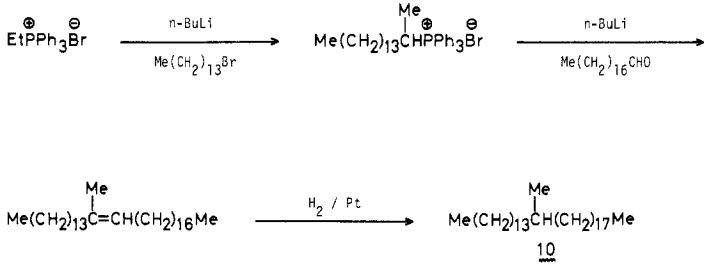
mones were prepared without the necessity of a stereoselective step. The separations that were achieved by means of the urea complex technique are summarized in Table 2.

Annual surveys are available for methods in olefin synthesis and olefin inversion.[96,97]

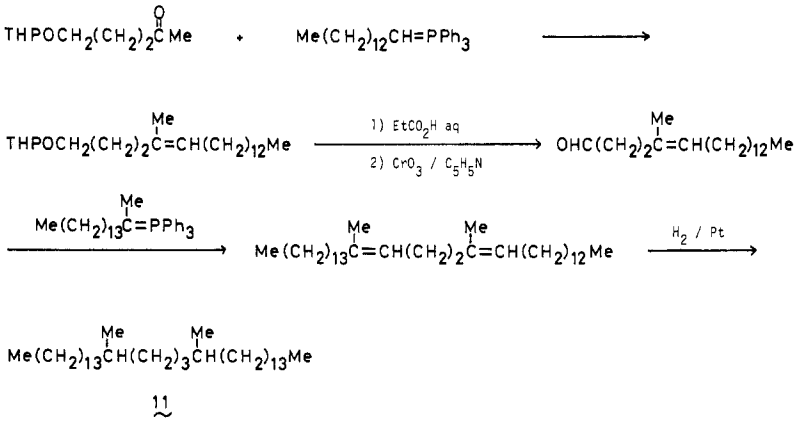
## 3. ALKANES AS PHEROMONES

### *15-Methyltritriacontane* 10 *and 15,19-Dimethyltritriacontane* 11

Examination of the cuticular hydrocarbon content of the stable fly, *Stomoxys calcitrans* L., indicated that the male was aroused to mating behavior by the externally borne saturated hydrocarbons of the female fly. These were methyl-branched and 1,5-dimethyl-branched alkanes.[98] 15-Methyl- and 15,19-dimethyl-

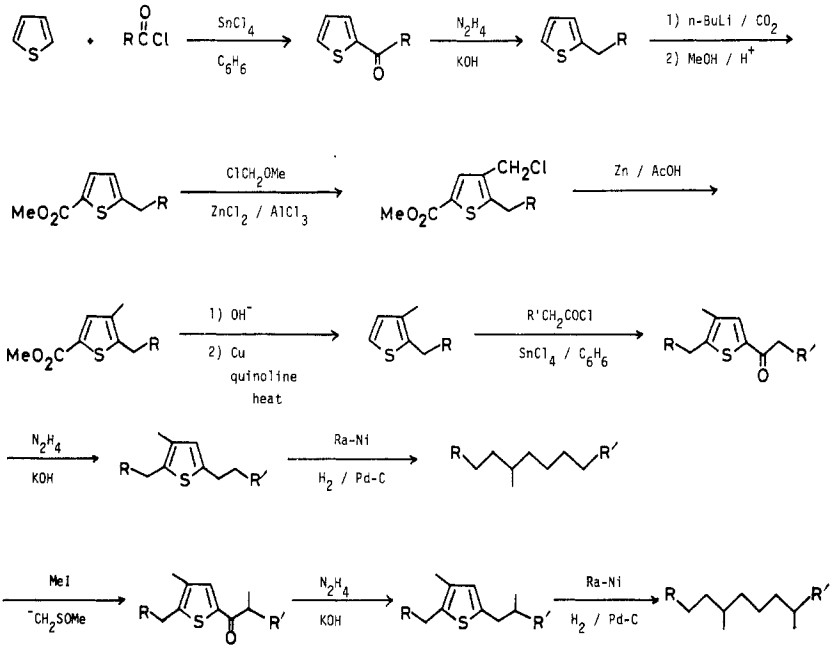



Scheme 1




Scheme 2

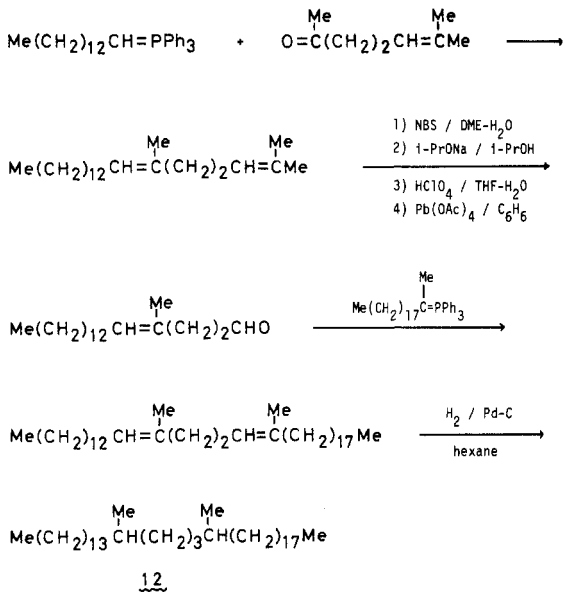
tritriacontanes showed the highest biological activity. The synthesis of 15-methyltritriacontane **10** and 15,19-dimethyltritriacontane **11** were carried out by the Wittig synthesis (Schemes 1 and 2).[99,100] A general synthetic route to insect hydrocarbons is shown in Scheme 3, which employs thiophenes as intermediates.[101] Optical isomers of these hydrocarbons are yet to be synthesized.




Scheme 3

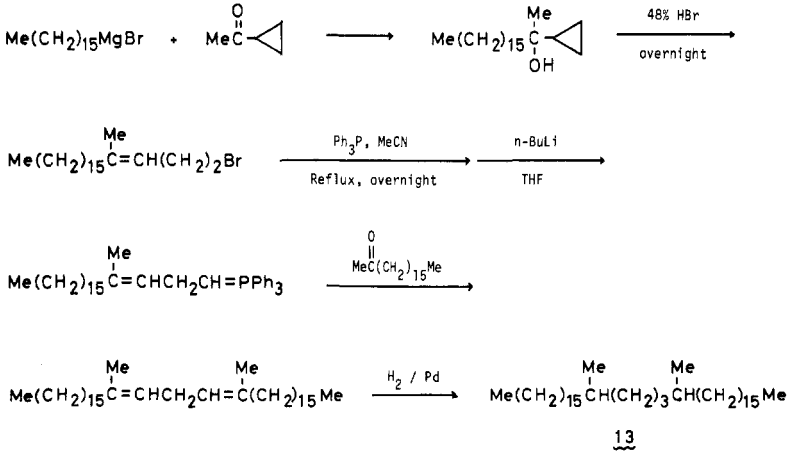
### *15,19-Dimethylheptatriacontane* 12, *17,21-Dimethylheptatriacontane* 13, *and 15,19,23-Trimethylheptatriacontane* 14

These title hydrocarbons are the sex pheromones isolated from the cuticle of the female tsetse fly (*Glossina morsitans morsitans*), which is the major vector of Rhodesian sleeping sickness.[102] The alkanes release mating behavior in the male fly at ultrashort range or on contact with baited decoys. The synthesis of 15,19-dimethylheptatriacontane **12** was carried out as shown in Scheme 4[100] or by a similar route as shown in Scheme 2. The synthesis of 17,21-dimethylheptatriacontane **13** is shown in Scheme 5.[102] The Julia cyclopropane cleavage reaction was used here as well as in the case of the synthesis of 15,19,23-trimethylheptatriacontane **14** (Scheme 6).[102] The trimethylalkane **14** released responses four times more often than **12** and 14 times more than **13**. No synthesis of the optically active forms of these hydrocarbons has been reported.



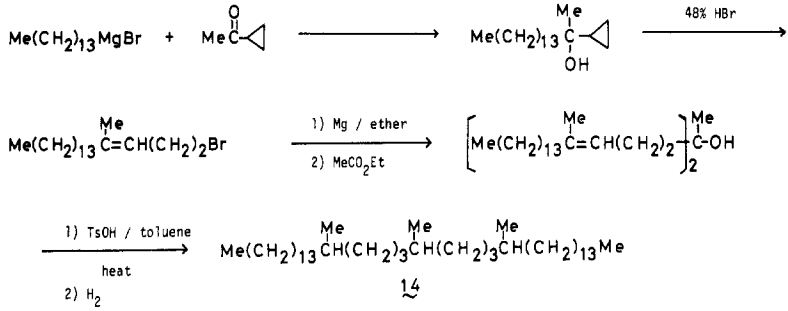
12

Scheme 4



13

Scheme 5

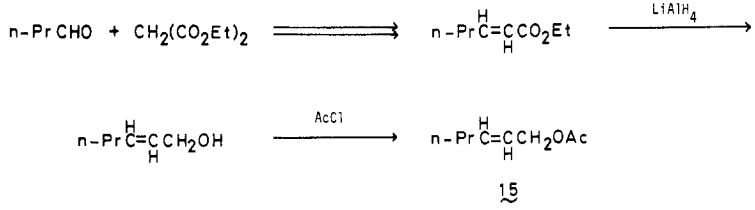


Scheme 6

## 4. PHEROMONES WITH AN *E*–DOUBLE BOND

### *(E)-2-Hexen-1-yl Acetate* 15

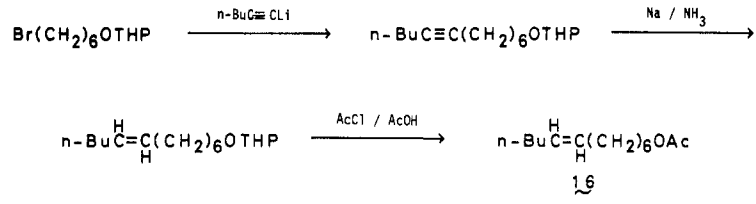
This is the sex pheromone of Indian water bug (*Lethocerus indicus*) and serves to excite the female immediately before or during mating. Its synthesis is shown in Scheme 7.[103] Pattenden, however, states that **15** is neither sex- nor species-specific.[104]



Scheme 7

### *(E)-7-Dodecen-1-yl Acetate* 16

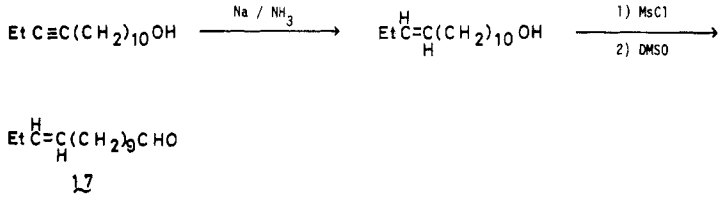
This is the sex pheromone of false codling moth (*Cryptophlebia leucotreta*).[105] Two similar syntheses were reported.[105,106] Henderson's synthesis is shown in Scheme 8.[106]



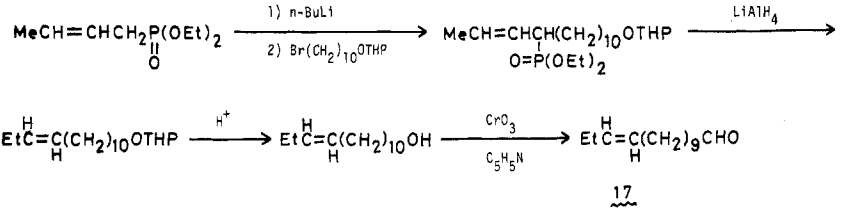
Scheme 8

### *(E)-11-Tetradecenal* 17

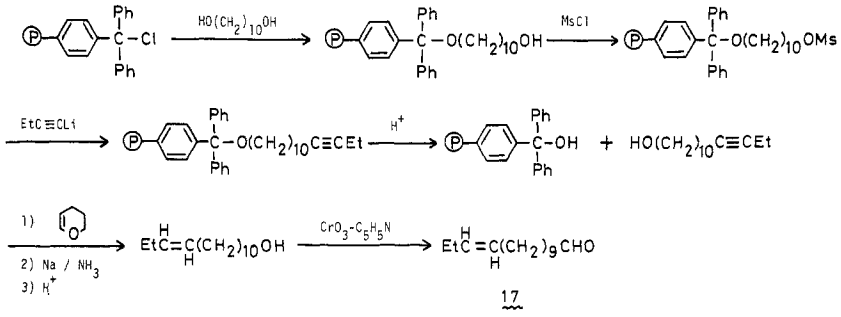
The eastern spruce budworm (*Choristoneura fumiferana*) uses this compound as its sex pheromone.[107] The original synthesis was based on acetylene chemistry (Scheme 9).[107] The second one employed the highly stereoselective phosphonate method (Scheme 10, see Equation 5).[52] The third one is an application of the solid-phase synthesis (Scheme 11, see Equation 33).[95]



Scheme 9



Scheme 10

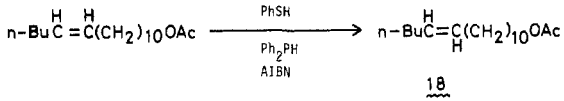


Scheme 11

### *(E)-11-Hexadecen-1-yl Acetate* 18

This is the sex pheromone produced by female sweet potato leaf folder moth, *Brachmia macroscopa*.[108] This alkene was synthesized by the inversion of olefin geometry of its (*Z*)-isomer obtainable by the conventional Wittig reaction

(Scheme 12).[108] The inversion was carried out by treating the (*Z*)-isomer with thiols and diphenylphosphine in the presence of azoisobutyronitrile.[109] The equilibrium mixture obtained by this method usually contains 75-80% of (*E*)-alkenes. The current methods of olefin inversion employ epoxides as intermediates.[110, 111]



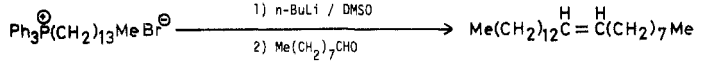

18

Scheme 12

## 5. PHEROMONES WITH A *Z*–DOUBLE BOND

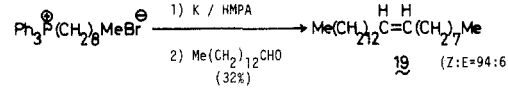
### *Muscalure, (Z)-9-Tricosene* 19

This is a sex pheromone isolated from the cuticle and feces of the female housefly (*Musca domestica*) and attracts the male fly.[112] The first synthesis was accomplished via a Wittig route (Scheme 13).[112] This Wittig synthesis was later modified, by using potassium in HMPA as the base, to give 94% of the (*Z*)-alkene plus 6% of its (*E*)-isomer (Scheme 14).[73] The second type of synthesis employs the Lindlar semihydrogenation of the alkyne (Scheme 15).[113] The use of the naturally occurring erucic acid as the starting material yielded the pheromone only in two steps (Scheme 16), although the acid was rather expensive.[114] Reaction of the methanesulfonate of erucyl alcohol with methylmagnesium



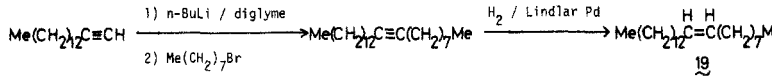

19 ( Z : E = 85 : 15 )

Scheme 13



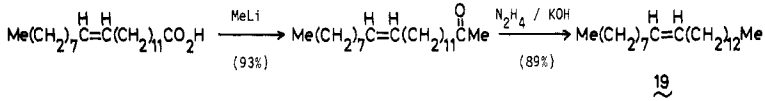

19 (Z:E=94:6)

Scheme 14

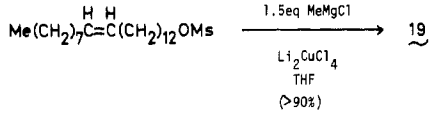



19

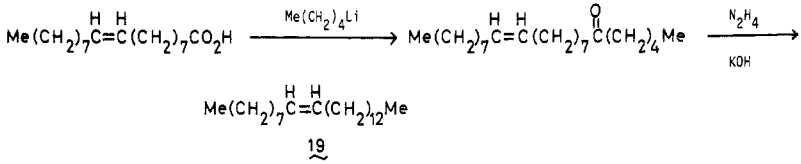
Scheme 15



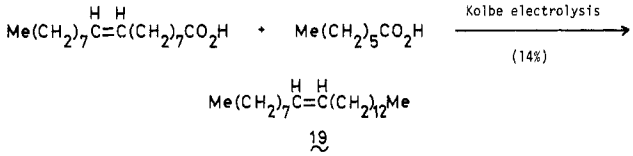
Scheme 16



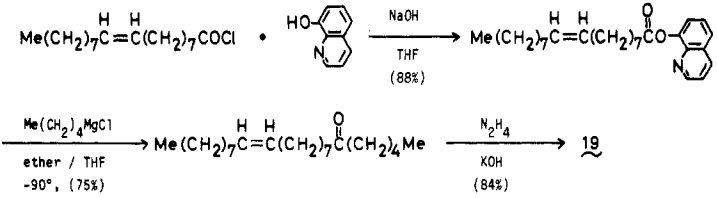
Scheme 17



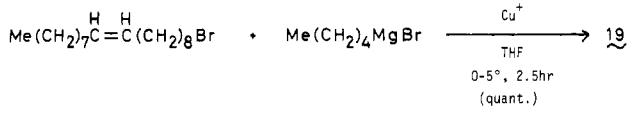
Scheme 18



Scheme 19



Scheme 20

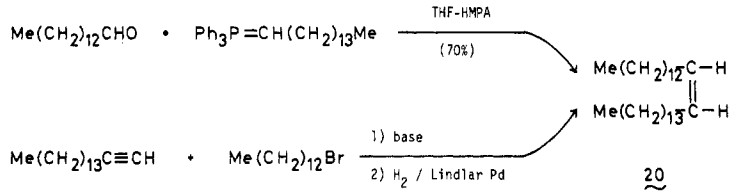


Scheme 21

chloride in the presence of lithium tetrachlorocuprate gave muscalure in >90% yield (Scheme 17).[115] Cheaper oleic acid was also converted to muscalure in several ways. A two-step synthesis similar to Scheme 16 is shown in Scheme 18.[116] A mixed Kolbe electrolysis of oleic and *n*-heptanoic acids gave muscalure in 14% yield (Scheme 19)[117] in a single step. A three-step synthesis similar to Scheme 18, but less direct, was recently reported and is shown in Scheme 20.[118] The best procedure used to prepare 150-kg batches of muscalure by Zoecon Corporation is the coupling of oleyl bromide with 1.15 eq *n*-amylmagnesium bromide in THF in the presence of 0.03 eq lithium chlorocyanocuprate. The yield is reported to be nearly quantitative (Scheme 21).[115]

### *(Z)-14-Nonacosene* 20

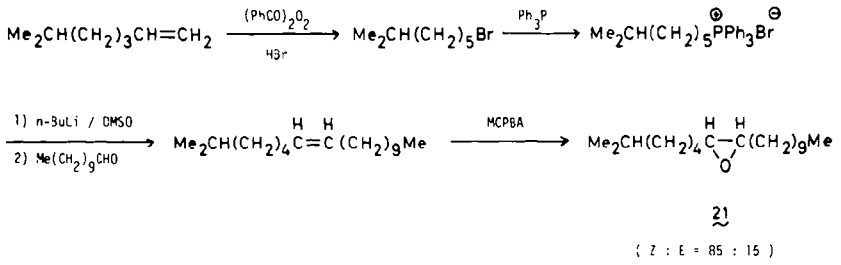
This is the most active component of the sex pheromones of the female face fly (*Musca autumnalis*) and effective for mating stimulation at short range.[119] The synthesis was carried out either by the Wittig reaction in THF-HMPA (70% yield of **20** containing ~94-96% of the (*Z*)-isomer)[119] or by the acetylene route (Scheme 22).[120]



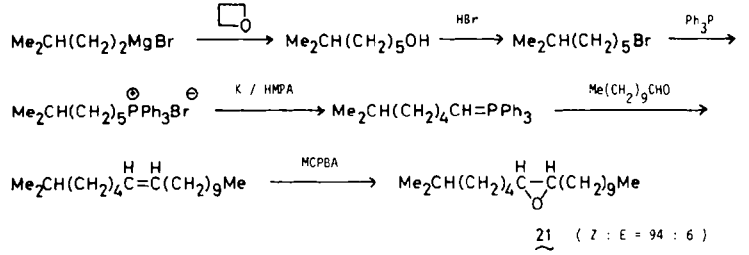

Scheme 22

### *Disparlure, (Z)-7,8-Epoxy-2-methyloctadecane* 21

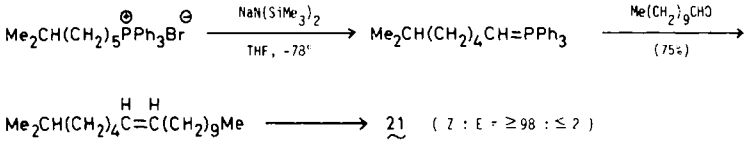
The gypsy moth (*Porthetria dispar*) is a serious despoiler of forests. The sex pheromone was extracted from 78,000 tips of the last two abdominal segments of female moths and shown to be an epoxide **21**.[121] The olefinic precursor, (*Z*)-2-methyl-7-octadecene, is present in the female sex pheromone gland of the gypsy moth[121] and inhibits male attraction to disparlure.[122] As little as 2 pg of **21** was active in laboratory bioassay. The first synthesis employed the Wittig reaction (Scheme 23).[121] The stereoselectivity of the reaction, however, was unsatisfactory, and the final product had to be purified by chromatography over silica gel-silver nitrate. A more stereoselective version of this Wittig synthesis was reported by Bestmann (Scheme 24).[123] Bestmann further improved the stereoselectivity to >98% by employing sodium bis(trimethylsilyl)amide as the base (Scheme 25).[124] Two syntheses were reported by Chan employing organosilicon intermediates. The earlier synthesis gave a 1 : 1 mixture of the *cis*- and *trans*-isomers of **21** (Scheme 26).[125] The later synthesis was based on the reac-



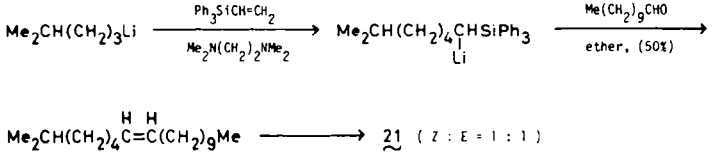
Scheme 23



Scheme 24



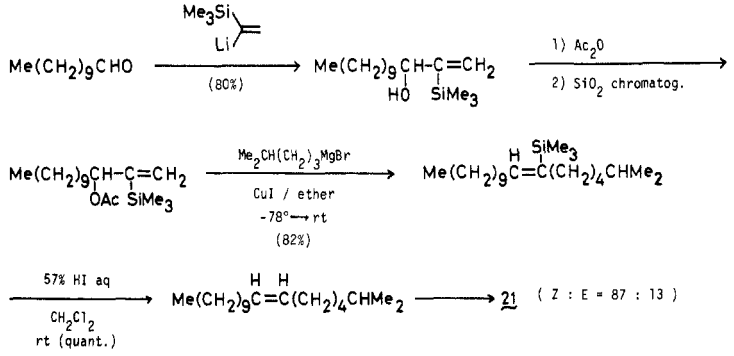
Scheme 25



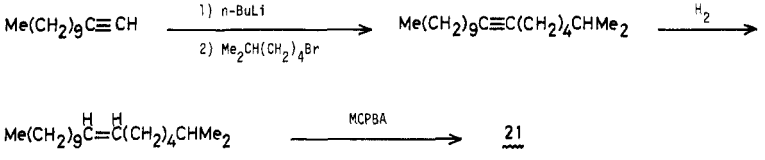
Scheme 26

tion of carbonyl compounds with carbanions α to silicon and proceeded in a more stereoselective manner (Scheme 27).[126] A synthesis via an acetylenic intermediate was reported by two groups (Scheme 28).[127,128] 1,5-Cyclooctadiene served as the common starting material in two syntheses of **21**. Klünenberg and

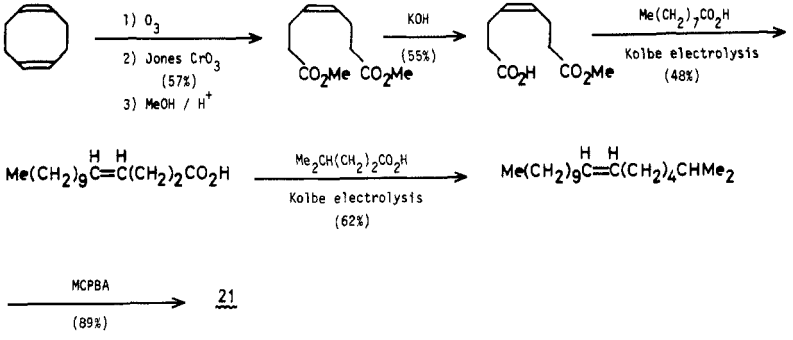
Schäfer employed Kolbe electrolysis as the key step (Scheme 29).[129] Tolstikow et al. used Schlosser's coupling method in their synthesis (Scheme 30).[130,131] The synthesis of optically active disparlure will be discussed later (Schemes 264-267).



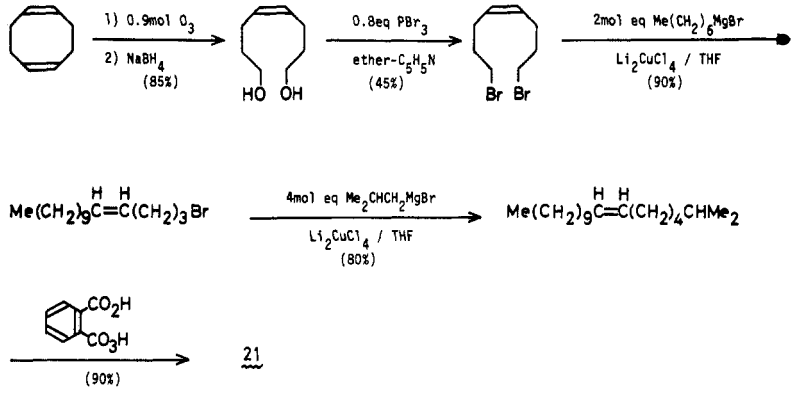
Scheme 27



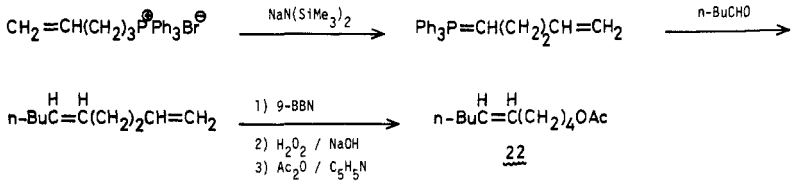
Scheme 28



Scheme 29



Scheme **30**



Scheme **31**

### *(Z)-5-Dodecen-1-yl Acetate* 22

This is a sex attractant for the male turnip moth *Agrotis segetum*, a ubiquitous grain pest.[132] A synthesis was carried out by a Wittig route (Scheme 31).[132]

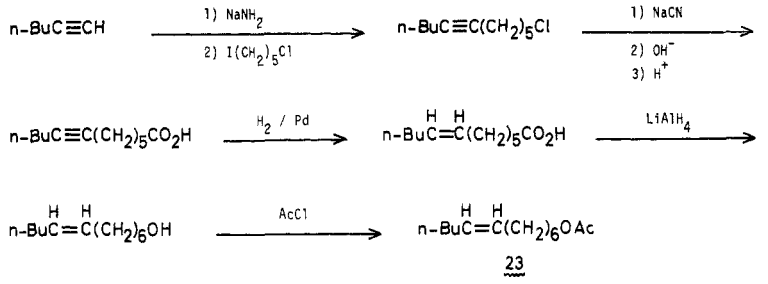
### *(Z)-7-Dodecen-1-yl Acetate* 23

This is the pheromone of the cabbage looper (*Trichoplusia ni*).[133] The first synthesis is straight-forward via acetylenic intermediates (Scheme 32).[133] A synthesis by Schäfer et al. employed Kolbe electrolysis in the key step (Scheme 33).[134] Schäfer used $^{1}$H- and $^{13}$C-NMR to determine the *Z*/*E* ratio of the key intermediate, 4-nonenoic acid. Useful information was obtained by the inspection of the $^{1}$H-NMR spectrum of the acid in the presence of Eu(fod)$_3$. Its $^{13}$C-NMR, however, was more informative. The chemical shift value of C-6 was 27.13 for *Z* and 32.43 for *E* and that of C-3 was 22.55 for *Z* and 27.84 for *E*. The *Z* : *E* ratio was shown to be 4 : 1.[134]

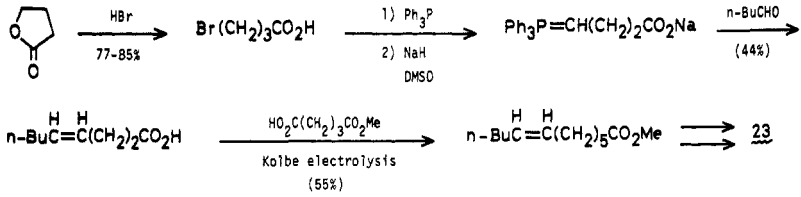
### *(Z)-8-Dodecen-1-yl Acetate* 24

The oriental fruit moth, *Grapholitha molesta*, uses this compound as the sex pheromone.[135] The structure was confirmed by synthesis via both the Wittig and

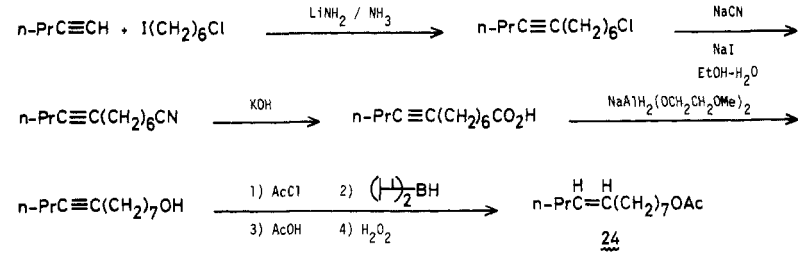
acetylenic routes.[135] A new version of the acetylenic route is shown in Scheme 34.[136] Another synthesis by an acetylenic route was recently reported by a Chinese group, who used palladium-calcium carbonate as the catalyst for partial hydrogenation.[137] A recent synthesis employed cyclohexane-1,3-dione as a $C_6$ synthon (Scheme 35).[138]



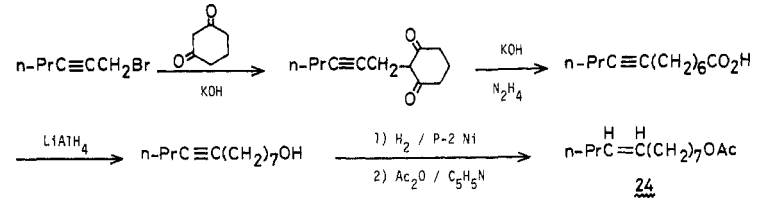

Scheme 32




Scheme 33




Scheme 34




Scheme 35