ApSimon

The Total Synthesis of Natural Products

VOLUME 4

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The Total Synthesis of Natural Products

VOLUME 4

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THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

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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

THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

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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.

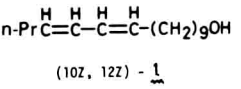
*Bombykol, the Pheromone of the Silkworm Moth (*Bombyx mori*), and its Geometrical Isomers*

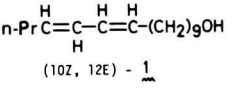
Butenandt et al.[3,4] and Truscheit and Eiter[5] synthesized all of the four possible geometrical isomers of bombykol **1** and compared their attractancy to the male silkworm moth. The results are shown in Table 1. The biological activity, as well as physical properties, of (10*E*, 12*Z*)-10,12-hexadecadien-1-ol 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.

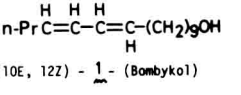
Table 1. Biological Activity of Natural Bombykol and Synthetic Geometrical Isomers of 10,12-Hexadecadien-1-ol

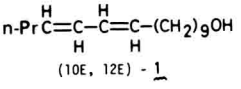
	Activity (μg/ml)[a]		
	Butenandt[3]	Butenandt[4]	Eiter[5]
10*Z*, 12*Z*	1	1	–
10*Z*, 12*E*	10^{-3}	10^{-2}	10^{-5}
10*E*, 12*Z*	10^{-12}	10^{-12}	10^{-12}
10*E*, 12*E*	10	100	10
Natural bombykol	10^{-10}	10^{-10}	10^{-10}

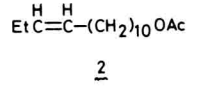
[a] The activity is expressed by *die Lockstoffeinheit* (LE). This is the lower limit of the pheromone concentration (μg/ml) to which 50% of the test insects show reaction.

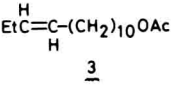


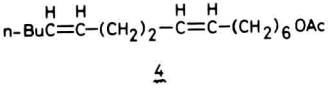


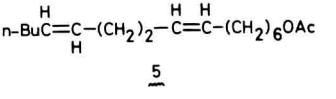












*The Pheromone of Red-banded Leaf Roller (*Argyrotaenia velutinana*) and Its Geometrical Isomer*

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

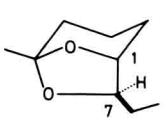
Beroza et al.[9] reported the very interesting observation that a small amount of opposite geometrical isomer was critical to pheromone attraction. Klun found that a geometrically pure preparation of **2** was very weakly attractive to the moth and that the presence of 7% of (*E*)-isomer **3** was necessary 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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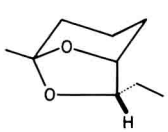

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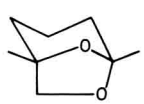

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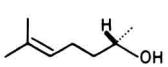
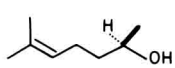


(S) - **9**



(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

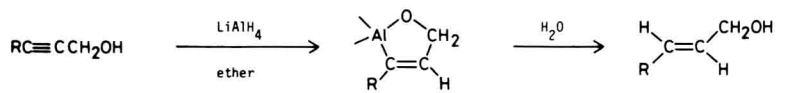
Metal-Ammonia Reduction of Alkynes

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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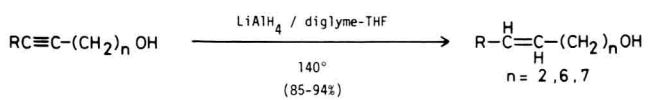
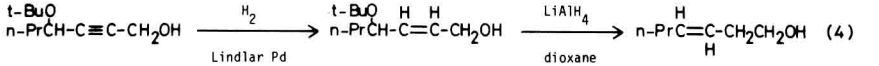


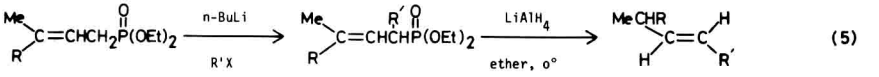
(3)

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

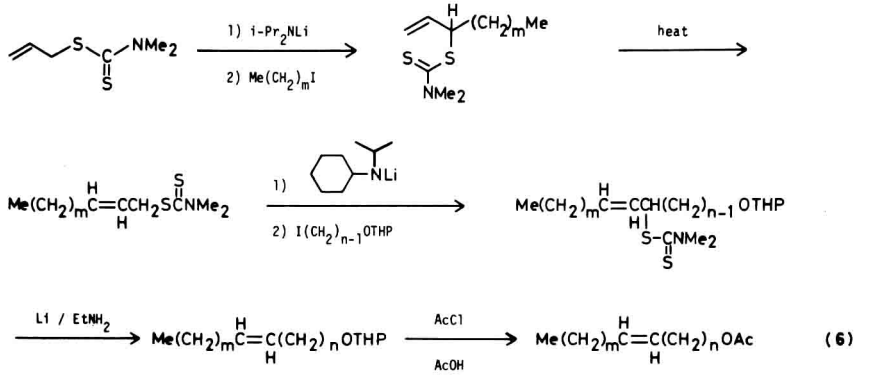
t-butoxy group.[51] A highly stereoselective synthesis of an (*E*)-alkene employs the reduction of a phosphonate ester as the key step (Equation 5).[52] The yield is moderate to excellent.





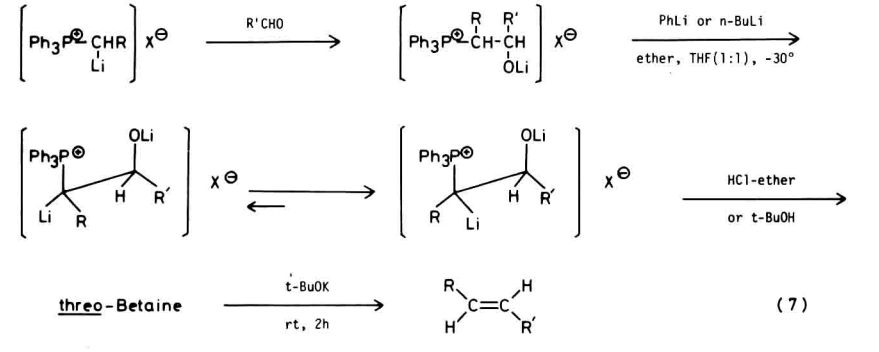
Rearrangement of Allylic Dithiocarbamates

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



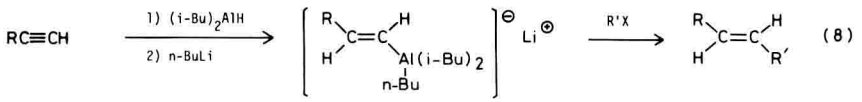
The Wittig Reaction

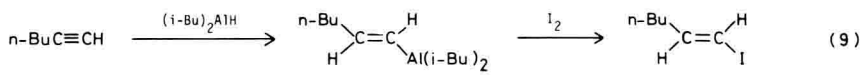
The Schlosser modification of the Wittig reaction as shown in Equation 7 gives an (*E*)-alkene in 60-72% yield with 90-96% stereoselectivity.[54-56] For the stereochemistry of this reaction see Ref. 22, p. 1875.

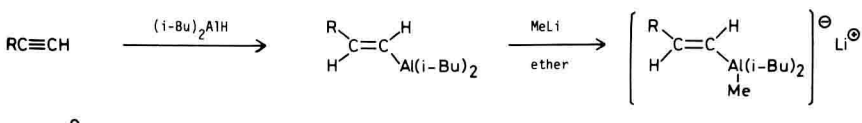


Utilization of Organoaluminum Compounds

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]

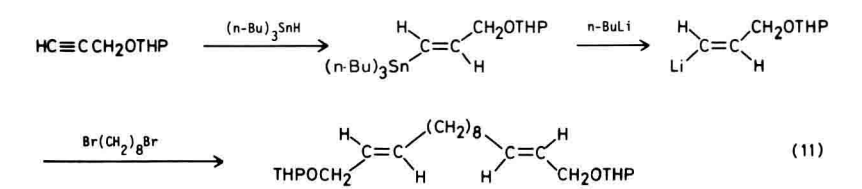






Utilization of Organotin Compounds

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



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]