

0051604

The Total Synthesis of Natural Products

VOLUME 9

Edited by

John ApSimon

*Ottawa-Carleton Institute for Research
and Graduate Studies in Chemistry*

and

*Department of Chemistry
Carleton University, Ottawa*



A WILEY-INTERSCIENCE PUBLICATION

JOHN WILEY & SONS

NEW YORK

• CHICHESTER

• BRISBANE

• TORONTO

• SINGAPORE

In recognition of the importance of preserving what has been written, it is a policy of John Wiley & Sons, Inc., to have books of enduring value published in the United States printed on acid-free paper, and we exert our best efforts to that end.

Copyright © 1992 by John Wiley & Sons, Inc.

All rights reserved. Published simultaneously in Canada.

Reproduction or translation of any part of this work beyond that permitted by Section 107 or 108 of the 1976 United States Copyright Act without the permission of the copyright owner is unlawful. Requests for permission or further information should be addressed to the Permissions Department, John Wiley & Sons, Inc.

Library of Congress Cataloging in Publication Data:

The Total synthesis of natural products.

"A Wiley-Interscience publication."

Original imprint, v. 1: New York: Wiley-Interscience, 1973.

Includes bibliographical references and indexes.

1. Chemistry, Organic—Synthesis. I. ApSimon, John.

QD262.T655 1973 547'.2 72-4075

ISBN 0-471-03251-4 (v. 1)

ISBN 0-471-55189-9 (v. 9)

Printed and bound in the United States of America by Braun-Brumfield, Inc.

10 9 8 7 6 5 4 3 2 1

0051694

**THE TOTAL SYNTHESIS
OF NATURAL PRODUCTS**

Contributor to Volume 9

Kenji Mori, Department of Agricultural Chemistry, The University of Tokyo,
Tokyo, Japan

Preface

This volume is a single author effort covering the massive amount of synthetic work associated with Insect Pheromone Chemistry for the period 1979 to 1990. Professor Mori has, once more, demonstrated in a masterful way his key position in this field.

I have been editor of this series since its inception in 1973 and, although I am convinced of its value to the discipline of organic synthesis, other responsibilities and interests have slowly intruded, to the state where I must regretfully pass on the onerous task of keeping the initiative alive to another editor. Over the past 18 years, I have had the honor of working with many outstanding authors and scientists. I thank you personally for this collaboration, friendship, and support.

JOHN APSIMON

*Ottawa, Canada
November 1991*

Contents

The Synthesis of Insect Pheromones, 1979-1989	1
---	---

KENJI MORI

Subject Index	523
---------------	-----

Formula Index	533
---------------	-----

The Synthesis of Insect Pheromones, 1979–1989

KENJI MORI

Department of Agricultural Chemistry, The University of Tokyo, Japan

1. Introduction, 2
2. General Methods, 3
3. Alkanes as Pheromones, 8
4. Pheromone Hydrocarbon with a Terminal Double Bond, 15
5. Pheromone Alcohols and Acetates with an *E*-Double Bond, 18
6. Pheromone Hydrocarbons and Acetates with a *Z*-Double Bond, 25
7. Pheromone Alcohols and Acetates with a Conjugated Diene and Conjugated Enyne System, 37
8. Pheromones with a Nonconjugated Diene System, 66
9. Pheromones with a Triene or Tetraene System, 79
10. Pheromones with an Epoxy Ring, 85
11. Chiral Alcohols and Their Esters as Pheromones, 98
12. Pheromone Aldehydes, 130
13. Pheromone Ketones, 157
14. Acids and Esters as Pheromones, 200
15. Pheromone Lactones, 216
16. Isoprenoid Hydrocarbons as Pheromones, 273

2 The Synthesis of Insect Pheromones, 1979–1989

17. Isoprenoid Alcohols, Formate, Acetates, Propanoates, and Epoxide as Pheromones, 280
18. Isoprenoid Aldehydes, Ketones, Acids, Esters, and Lactones as Pheromones, 332
19. Oxygen Heterocycles (Excluding Epoxides, Lactones, Hemiacetals, and Acetals) as Pheromones, 367
20. Acetals as Pheromones, 381
21. Spiroacetals as Pheromones, 444
22. Nitrogen Heterocycles and Sulfur-Containing Compounds as Pheromones, 478
23. Conclusion, 484
- Acknowledgments, 486
- References, 486

1. INTRODUCTION

Since the appearance of the first edition of this chapter in Volume Four of this series,¹ a tremendous amount of work has been published in the field of pheromone synthesis. Simple but unique structures that can frequently be seen among pheromone molecules became favorite targets of synthetic chemists to test their methodology and strategy in pursuit of simplicity, selectivity, and efficiency. It is therefore very difficult to write a comprehensive review on pheromone synthesis. However, it is the aim of this chapter to summarize almost all of the notable syntheses in the pheromone area published between April 1979 to February 1990. Thus, this chapter will be of service to those chemists who want a quick view of the existing synthetic methods for each of the individual pheromones.

The pheromones described in this chapter are classified according to the structural type, as in the first edition. Because the synthesis of optically active pheromones is now a common practice, enantioselective synthesis has been included in each section instead of being made into an independent section. The relationships between absolute configuration and pheromone activity are briefly summarized at the end of this chapter.

There are a number of recent monographs and reviews on pheromones. The following brief listing highlights the focus of literature published within the time frame of this chapter.

A monograph on all aspects of pheromone research—including isolation, structure determination, synthesis, and estimation of enantiomeric purity—was published in 1984.²

Synthetic methodologies useful in preparing chiral pheromones were thoroughly reviewed.³

The present status of pheromone biochemistry was compiled as a monograph.⁴

Three general reviews on insect pheromones become available.⁵⁻⁷

Ritter reviewed steric factors in pheromonal pest control;⁸ he also reviewed his own applied research on semiochemicals.⁹

A concise review on chiral insect pheromones was published in Czech.¹⁰

Schneider reviewed the problem of insect olfaction.¹¹

A comprehensive review became available on structure determination of pheromones by combined microchemical and gas chromatographic methods.¹²

The following additional reviews were published:

a short review¹³

an account of the background of pheromone research and its application in insect pest control^{14, 15}

a thorough review covering the literature published in 1982 and 1983¹⁶

a review on isoprenoid pheromones (in Russian)¹⁷

a pedagogical review on chirality in insect communication¹⁸

an account of the pheromone metabolism in insects¹⁹

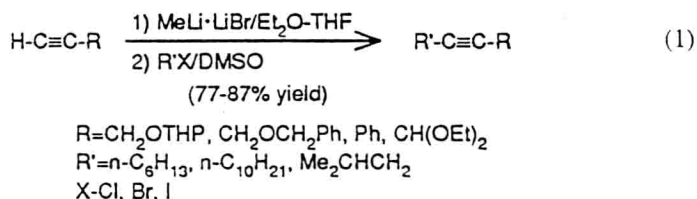
2. GENERAL METHODS

Some useful methods for the synthesis and analysis of pheromones are listed below.

A. Useful Synthetic Methods

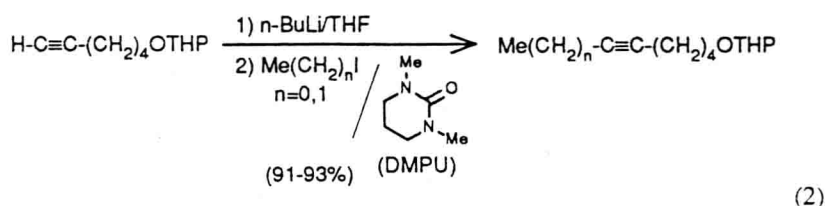
(1) Alkylation of Acetylides in DMSO

In addition to the existing procedures for the alkylation of 1-alkynes,¹ Chong and Wong proposed a method employing methyllithium (base) and DMSO (solvent).²⁰ As shown in Eq. 1, terminal acetylenes afford disubstituted acetylenes in good yield.



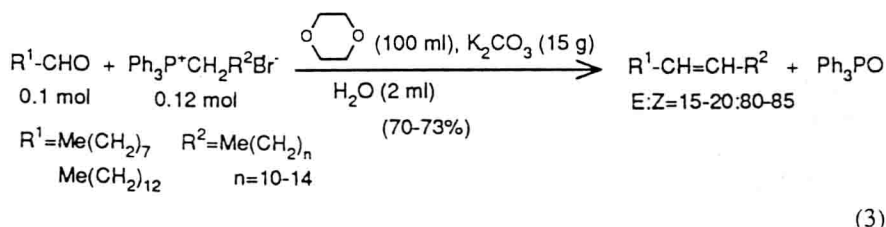
(2) Alkylation of Acetylides in the Presence of DMPU

Bengtsson and Liljefors employed DMPU (1,3-dimethyl-2-oxohexahydropyrimidine) as a good substitute for the carcinogenic HMPA in the alkylation of lithium acetylides (Eq. 2).²¹



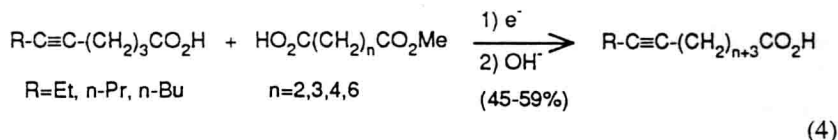
(3) Wittig Reaction in a Heterogeneous Medium

The Wittig reaction can be carried out in a solid-liquid medium under mild conditions in good yield as shown in Eq. 3.²² Wittig chemistry as used in pheromone synthesis was reviewed by Bestmann and Vostrowsky.²³



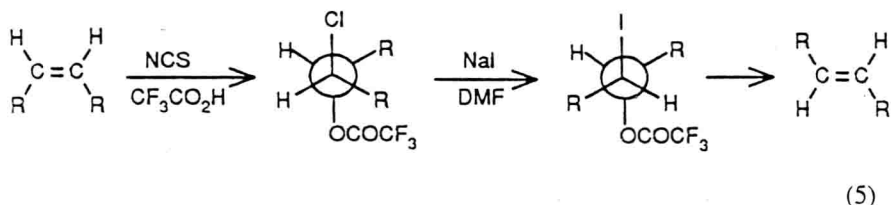
(4) Kolbe Synthesis of Unsaturated Pheromones

Kolbe electrolysis was used for the coupling of 5-alkynic acids and half esters to give alkynic acids, which could be converted into unsaturated pheromones (Eq. 4).²⁴



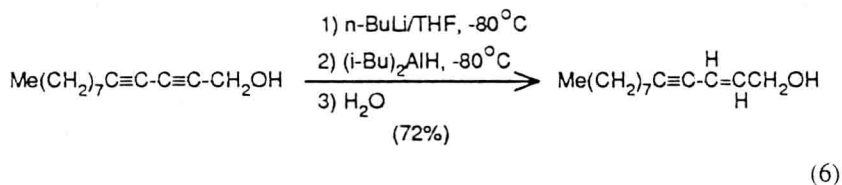
(5) Olefin Inversion

Inversion of the geometry of alkenes is a useful method in pheromone synthesis.²⁵ Treatment of alkenes with N-chlorosuccinimide in trifluoroacetic acid results in *anti*-addition of the element of trifluoroacetyl hypochlorite. Heating the *vic*-chlorohydrin trifluoroacetate with sodium iodide in DMF produced alkenes with inversion of the geometry (Eq. 5).²⁶



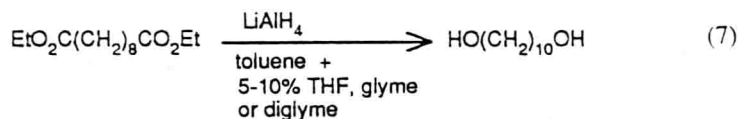
(6) Reduction of Diynols to Enynols

2,4-Diyn-1-ols can be reduced to (2*E*)-en-4-yn-1-ols by treating the corresponding lithium alcoholates with diisobutylaluminum hydride (Eq. 6).²⁷



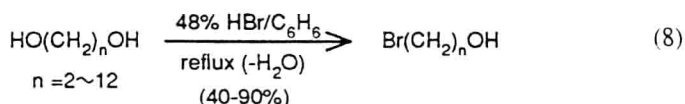
(7) Reduction of Diesters to Diols

Aksenov et al. reported that the preparation of α,ω -diols from diesters by reduction with lithium aluminum hydride was made possible in toluene by the addition of 5–10% of THF, glyme, or diglyme (Eq. 7).²⁸

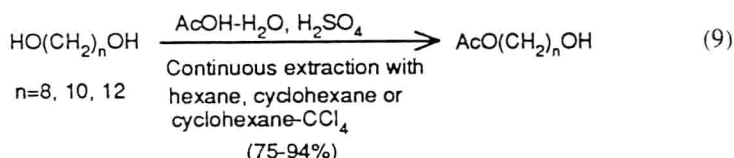


(8) Preparation of ω -Bromo- α -alkanols from α,ω -Diols

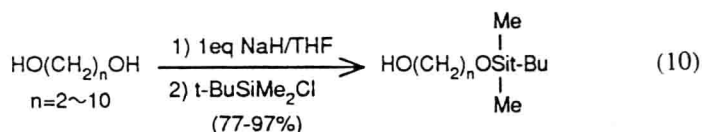
Pure ω -bromo- α -alkanols were prepared in good yields by refluxing a mixture of α,ω -diols, 48% hydrobromic acid and benzene using a Dean-Stark water separator (Eq. 8).²⁹

(9) Preparation of ω -Acetoxy- α -alkanols from α,ω -Diols

Monoacetylation of α,ω -diols was achieved in high yield by the use of continuous extraction of the reaction mixture consisting of α,ω -diols, acetic acid, water, and sulfuric acid (Eq. 9).³⁰

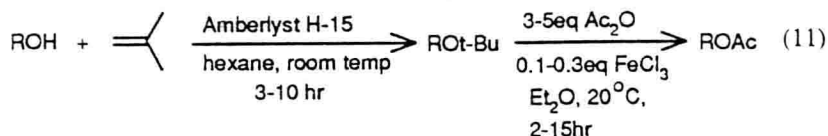
(10) Preparation of ω -*t*-Butyldimethylsilyloxy- α -alkanols from α,ω -Diols

McDougal et al. silylated the monosodium alkoxide salt of α,ω -diols with one equivalent of *t*-butyldimethylsilyl chloride to furnish monosilylated material in good yield (Eq. 10).³¹ A polymer-supported organosilyl protecting group was also used in pheromone synthesis.³²

(11) Mild Protection and Deprotection of Alcohols as *t*-Butyl Ethers

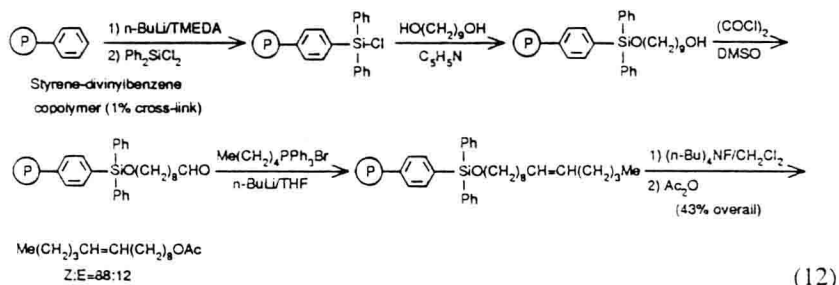
t-Butyl ether was found to be the most appropriate protection for ω -hydroxy-alkyl halides when they were to be converted into organolithium or Grignard reagents. ω -*t*-Butoxy organolithium and Grignard reagents can be prepared in ether, exactly like the nonfunctionalized ones, and their reactivity is normal.³³

The protection and deprotection of alcohols as *t*-butyl ethers can be achieved under the mild conditions exemplified in Eq. 11.³⁴



(12) Solid Phase Synthesis

A method different from that developed by Leznoff³⁵ was devised by Chan and Huang.³² They prepared polymer-anchored diphenylchlorosilane and used it for the protection of the hydroxy group. Equation 12 illustrates its use in the synthesis of (*Z*)-9-tetradecenyl acetate (fall armyworm moth pheromone).



Other synthetically useful methods are: (1) vitamin B₁₂-mediated electrochemical reactions;³⁶ (2) carbocupration reactions;³⁷ (3) stereodirected synthesis with α -haloboronic esters;^{38,39} (4) heteroatom-assisted substitution of acyclic secondary tosylates with lithium dialkylcuprates;⁴⁰ and (5) semi-hydrogenation of acetylenes using homogeneous catalysis with (dba)₂Pd₂·CHCl₃·Ar₃P, although the *Z/E* selectivity was poor.⁴¹

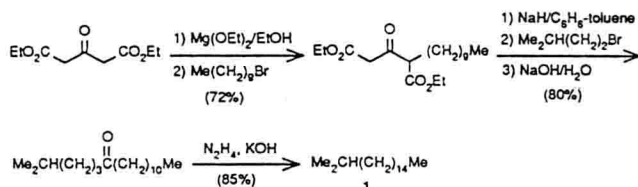
B. Useful Analytical Methods

Reverse-phase TLC and HPLC were shown to be useful for the separation of pheromones.⁴² ¹³C NMR spectroscopy was employed for the assignment of the geometry of carbon-carbon double bond(s) of olefinic pheromones.^{43,44}

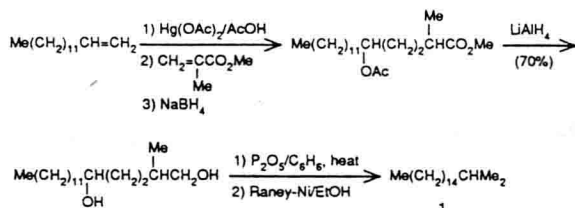
Methods were reviewed for determining the enantiomeric purity of pheromones.^{3,45} Slessor et al. described a method for determining the enantiomeric composition of chiral alcohols, lactones, and hydroxy acids in quantities rang-

A. 2-Methylheptadecane 1 ($C_{18}H_{38}$)

The title hydrocarbon is the sex pheromone of the tiger moth (*Holomelina aurantiaca*; *Arctiidae* species). This achiral alkane was synthesized by Naoshima employing diethyl 3-oxoglutarate as the starting material (Scheme 1).⁴⁷ Another synthesis was reported by Bhalerao (Scheme 2).⁴⁸



Scheme 1

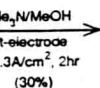


Scheme 2

B. (5*S*,9*S*)-5,9-Dimethylheptadecane 2 (C₁₉H₄₀)

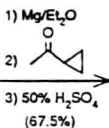
The mountain-ash bentwing (*Leucoptera scitella*) is a pest in the apple orchards in Hungary. Its female-produced sex pheromone was identified by Francke et al. as 5,9-dimethylheptadecane (**2**).⁴⁹ A synthesis of a diastereomeric mixture of **2** was achieved by the mixed Kolbe electrolysis of (\pm)-3-methylheptanoic acid and (\pm)-4-methyldodecanoic acid (Scheme 3).⁴⁹

Helmchen's synthesis of the four stereoisomers of **2** was followed by their bioassay to reveal (5*S*,9*S*)-**2**, $[\alpha]_D + 2.1^\circ$ (CHCl₃) as the natural pheromone.⁵⁰



(5S.9S)-2

therefore, a diastereomeric mixture is practically useful.^{49,50} Another multigram synthesis of a diastereomeric mixture of **2** was reported by Rama and Capuzzi (Scheme 4).⁵¹



2

C. 3,7-Dimethylnonadecane 3 ($C_{21}H_{44}$)

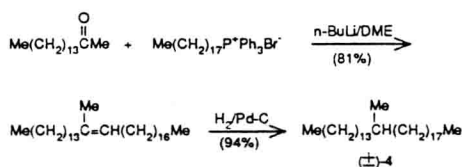
The female-produced sex pheromone of the alfalfa blotch leafminer (*Agromyza frontella*) was identified as 3,7-dimethylnonadecane (**3**).⁵² A diastereomeric mixture of **3** was synthesized, as shown in Scheme 5, and shown to be bioactive.⁵²



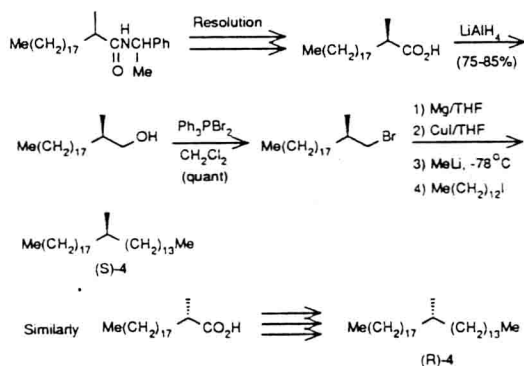
3

D. 15-Methyltritriacontane 4 ($C_{34}H_{70}$)

This is the female-produced sex-stimulant pheromone of the stable fly (*Stomoxys calcitrans*). A synthesis of (\pm)-4 is shown in Scheme 6.⁵³



Scheme 6



Scheme 7

Two syntheses were reported for the enantiomers of 4. Scheme 7 shows the synthesis reported by Sonnet.⁵⁴ The chiral part of the molecule was synthesized via optical resolution. The enantiomeric bromides were then converted to the cuprates and coupled with tridecyl iodide to give the enantiomers of 4. Their bioassay results are not yet published.

Naoshima and Mukaidani synthesized the pure enantiomers of 4 in good overall yield, starting from (*R*)-(+)-citronellic acid (Scheme 8).⁵³

E. 15,19-Dimethyltritriacontane 5 ($C_{35}H_{72}$)

This alkane is also the mating-stimulant pheromone isolated from female stable flies (*Stomoxys calcitrans*). Sonnet prepared (15*R*,19*R*)-, (15*S*,19*S*)-, and *meso*-5 (Scheme 9).⁵⁴ The starting chiral alcohol was obtained by resolution in the same manner as shown in Scheme 7.