NATURAL PRODUCTS CHEMISTRY

Vol. 2

This page intentionally left blank

NATURAL PRODUCTS CHEMISTRY

Vol. 2

Edited by

KOJI NAKANISHI
DEPT. OF CHEMISTRY
COLUMBIA UNIVERSITY, NEW YORK

TOSHIO GOTO
DEPT. OF AGRICULTURAL CHEMISTRY
NAGOYA UNIVERSITY, NAGOYA

SHÔ ITÔ
DEPT. OF CHEMISTRY
TOHOKU UNIVERSITY, SENDAI

SHINSAKU NATORI
NATIONAL INSTITUTE OF HYGIENIC SCIENCES, TOKYO

SHIGEO NOZOE
PHARMACEUTICAL INSTITUTE
TOHOKU UNIVERSITY

KODANSHA LTD.
Tokyo

ACADEMIC PRESS, INC. New York and London
A Subsidiary of Harcourt Brace Jovanovich, Publishers

KODANSHA SCIENTIFIC BOOKS

Co-published by

KODANSHA LTD.
12-21 Otowa 2-chome, Bunkyo-ku, Tokyo 112
and

ACADEMIC PRESS, INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS, INC. (LONDON) LTD.
24/28 Oval Road, London NW 1

INTERNATIONAL STANDARD BOOKS NUMBER: 0-12-513902-0
LIBRARY OF CONGRESS CATALOG CARD NUMBER: 74-6431

PRINTED IN JAPAN

LIST OF CONTRIBUTORS

*: major contributors

Chapter 7

Jun FURUKAWA, Faculty of Pharmaceutical Sciences, University of Tokyo, Tokyo
Yoshimasa MACHIDA, Institute of Applied Microbiology, University of Tokyo, Tokyo
Naoki MIYATA, Faculty of Pharmaceutical Sciences, University of Tokyo, Tokyo
Shigeo NOZOE*, Pharmaceutical Institute, Tohoku University, Sendai
Takashi YATSUNAMI, Faculty of Pharmaceutical Sciences, University of Tokyo, Tokyo

Chapters 8 and 11

Toshio GOTO*, Department of Agricultural Chemistry, Nagoya University, Nagoya
Yoshito KISHI*, Department of Chemistry, Harvard University, Cambridge, Mass.
Yasuaki OKUMURA, Department of Chemistry, Shizuoka University, Shizuoka
Nobutaka SUZUKI, Department of Applied Chemistry, Mie University, Tsu
Tadao KONDO, Department of Agricultural Chemistry, Nagoya University, Nagoya
Minoru ISOBE, Department of Agricultural Chemistry, Nagoya University, Nagoya
Hideo TANINO, Department of Agricultural Chemistry, Nagoya University, Nagoya
Shin-ichi NAKATSUKA, Department of Agricultural Chemistry, Nagoya University, Nagoya
Fumiaki NAKATSUBO, Wood Research Institute, Kyoto University, Uji

Chapter 9

Masamichi FUKUOKA, National Institute of Hygienic Sciences, Tokyo
Masanori KUROYANAGI, National Institute of Hygienic Sciences, Tokyo
Shinsaku NATORI*, National Institute of Hygienic Sciences, Tokyo
Shigeo NOZOE, Pharmaceutical Institute, Tohoku University, Sendai
Tamotsu SAITOH*, Faculty of Pharmaceutical Sciences, University of Tokyo, Tokyo
Ushio SANKAWA*, Faculty of Pharmaceutical Sciences, University of Tokyo, Tokyo
Setsuko SEKITA, National Institute of Hygienic Sciences, Tokyo
Michiko TOHYAMA, Better Living Information Center, Tokyo
Mikio YAMAZAKI*, Research Institute for Chemobiodynamics, Chiba University, Chiba

Akiko YOKOYAMA, National Institute of Hygienic Sciences, Tokyo
Kunitoshi YOSHIHIRA, National Institute of Hygienic Sciences, Tokyo

Chapter 10

Norio AIMI*, Faculty of Pharmaceutical Sciences, Chiba University, Chiba
Toshio GOTO*, Department of Agricultural Chemistry, Nagoya University, Nagoya
Hiroshi IRIE*, Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto
Hisashi ISHII*, Faculty of Pharmaceutical Sciences, Chiba University, Chiba
Shô ITÔ*, Department of Chemistry, Tohoku University, Sendai
Mitsuaki KODAMA*, Department of Chemistry, Tohoku University, Sendai
Shinsaku NATORI*, National Institute of Hygienic Sciences, Tokyo
Takeshi OISHI*, Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo
Shinichiro SAKAI*, Faculty of Pharmaceutical Sciences, Chiba University, Chiba
Mikio YAMAZAKI*, Research Institute for Chemobiodynamics, Chiba University, Chiba

Chapter 12

Koji NAKANISHI, Department of Chemistry, Columbia University, New York
Hideo SATO*, Research Laboratories (Tokyo), Fuji Photo-Film Co., Asaka

ACKNOWLEDGEMENTS

We are most grateful to the numerous contributors (see List of Contributors) who undertook the painstaking job of literature survey, writing, and condensing of material. We would also like to thank Mr. W. R. S. Steele and staff of Kodansha for their invaluable assistance in the preparation of the English manuscripts comprising this book.

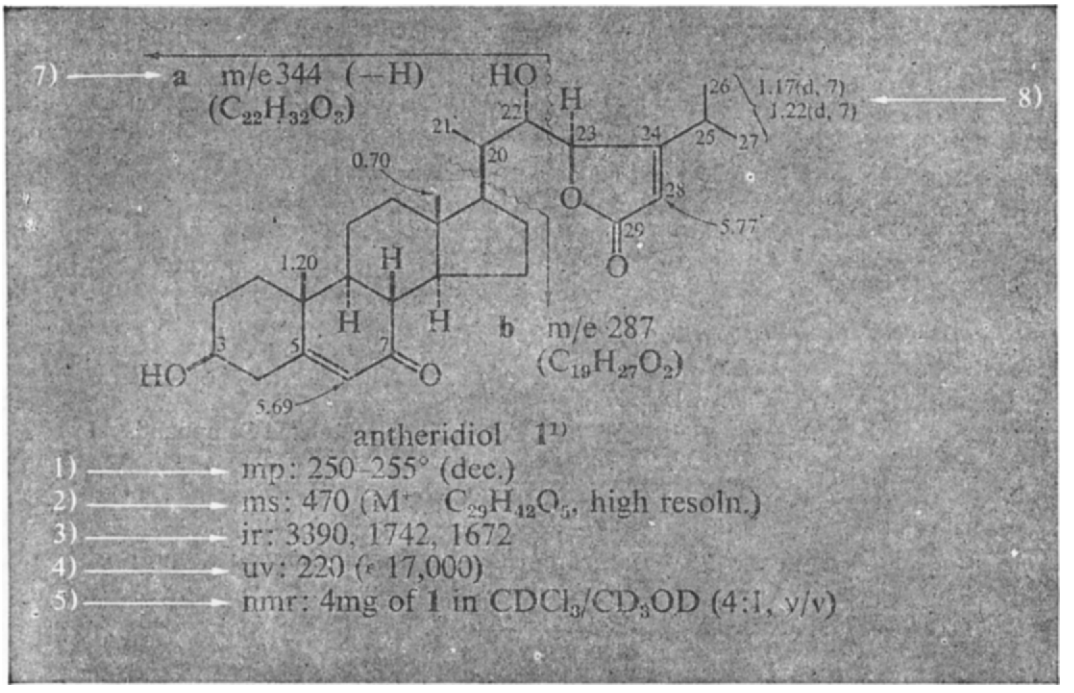
April, 1975 EDITORS

This page intentionally left blank

CONTENTS

CONTENTS OF VOLUME 1

DATA CONVENTIONS USED IN THIS BOOK



1) Melting point.

2) Mass spectroscopic data. See also number 7 below.

3) Infrared data: state of measurement, if given, is shown in brackets. e.g. ir ($CHCl_3$): Values (cm^{-1}) are given only for pertinent bands.

4) Ultraviolet/visible spectral data: the solvent, if given, is shown in brackets, e.g. uv (EtOH): The wavelength is given in nanometers with the intensity in brackets (as log ϵ, unless otherwise stated).

5) Nuclear magnetic resonance data: the solvent is usually given in brackets, e.g. nmr ($CDCl_3$): Values are given as ppm from TMS. 1H, 2H, etc. indicate the intensity. s: singlet, d: doublet, t: triplet, m: multiplet. *J* values are given in Hz, and 14-H indicates a proton attached to C-14. See also number 8 below.

6) Rotation data are given as follows: "α_D (EtOH): +65" indicates the specific rotation at the D line in EtOH. "cd (MeOH): 215 ($\Delta\epsilon$ +13.17)" indicates the circular dichroism extrema in MeOH, 215 nanometers maximum (or minimum) with a $\Delta\epsilon$ value of +13.17 (or −13.17). Rotation data are not given in the above example.

7) Mass spectroscopic data: fragmentation (a) with loss of • H gives m/e 344 ($C_{22}H_{32}O_3$) fragment arising from the C-1 to C-22 portion of the molecule.

8) Nuclear magnetic resonance data: the isopropyl methyls appear at ppm values of 1.17 and 1.22 as doublets with J=7 Hz.

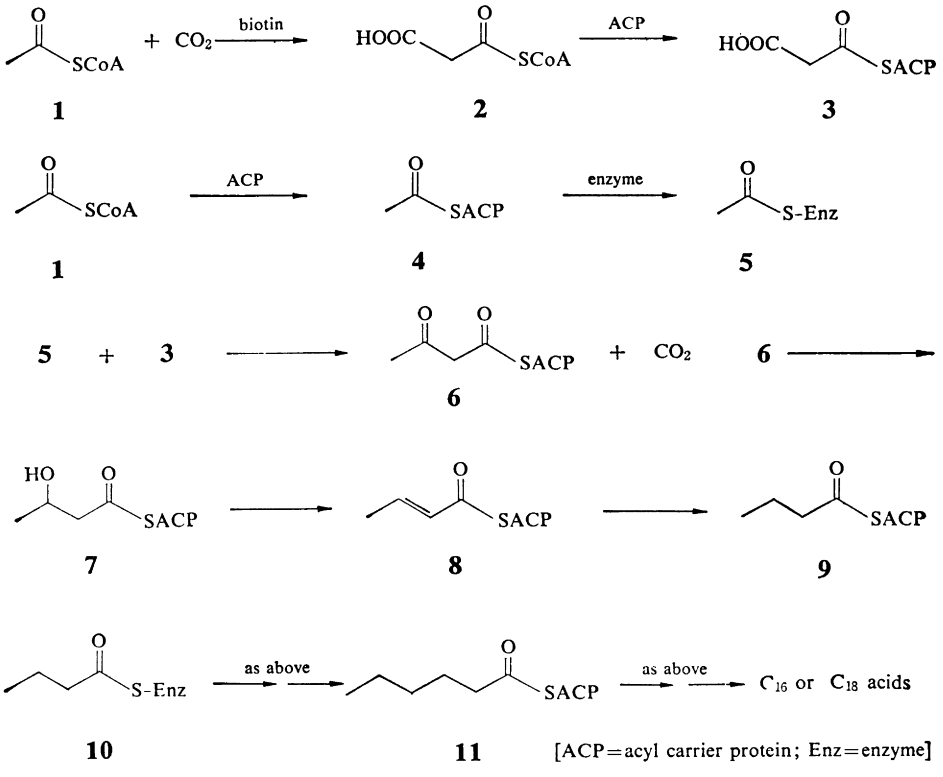
CHAPTER 7

Fatty Acid Derivatives and Related Compounds

7.1 INTRODUCTION

A number of natural products are biogenetically derived through the acetate-malonate pathway. They include fatty acids and a variety of substances originating from fatty acid or poly-β-ketomethylene intermediates. Although the structural diversity of this class of compounds is not as remarkable as that of other classes of natural products (e.g. isoprenoids, alkaloids, etc.), this class includes many important compounds having essential functions within living systems or having important physiological activities.

Biosynthetic mechanisms of fatty acids have been identified in considerable detail by experiments using cell-free systems or purified enzymes. The processes involved in the biosynthesis of fatty acids are outlined below.



1) The carboxylation of acetyl coenzyme A is mediated by biotin, giving malonyl coenzyme A **2**. A malonyl residue is then transferred to acyl carrier protein. (**1**⟶**2**⟶**3**).
2) An acetyl residue is also transferred from coenzyme A to acyl carrier protein (**1**⟶**4**) and then to an enzyme (**4**⟶**5**).
3) Condensation of malonyl ACP with an enzyme-bound acetyl residue, followed by decarboxylation, gives acetoacetyl ACP (**5**+**3**⟶**6**).

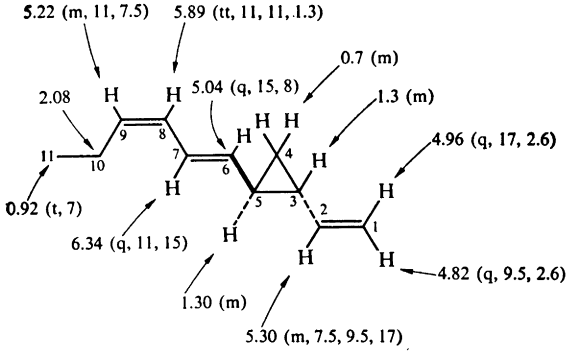
1) F. Lynen, *Pure Appl. Chem.*, **14**, 137 (1967).

4) Acetoacetyl ACP undergoes, successively, reduction (**6**⟶**7**), dehydration (**7**⟶**8**), and hydrogenation (**8**⟶**9**) to yield butyryl ACP.
5) An enzyme-bound butyryl residue is then converted into **11** by a sequence analogous to **5**⟶**6**⟶**7**⟶**8**⟶**9**. This process of chain elongation is repeated until C_{16} or C_{18} fatty acid is formed.

The fatty acids are then subjected to a variety of secondary modification processes such as dehydrogenation, chain shortening, alkylation, oxygenation, cyclization, etc., yielding diverse structural types. The compounds belonging to this category and discussed in this chapter are C_{11}–C_{15} marine products (e.g. dictyopterene, laurencin, etc.) C_{12}–C_{18} insect pheromones, fatty acid derivatives containing a cyclopentane ring (e.g. jasmone, prostaglandin, etc.), compounds with a cyclopropane ring or rings (e.g. lactobacillic acid, mycolic acids, etc.), and polyacetylene derivatives. A further group of compounds whose biosynthesis involves fatty acid intermediates is also included in this chapter.

The macrolide antibiotics which are biogenetically derived from poly-β-ketomethylene intermediates (see Chapter 8) are also collected at end of this chapter. In the biosynthesis of macrolide antibiotics and polyether antibiotics, methyl malonate is frequently used instead of malonate for chain building.

7.2 STRUCTURE OF DICTYOPTERENES



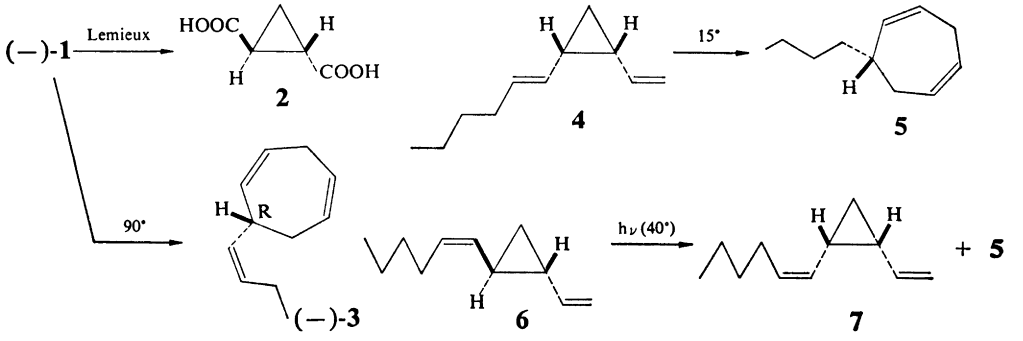
α_D: −43°
ut(EtOH): 247
nmr in C_6D_6

(−)-dictyopterene-B **1**[1]

1) The presence of a *trans*, *cis* conjugated double bond in **1** is indicated by the nmr coupling constants i.e., $J_{6,7}=15$ Hz (*trans* coupling), $J_{7,8}=11$ Hz, and $J_{8,9}=11$ Hz (*cis* coupling).[1]
2) The formation of (+)-*trans*-cyclopropane-1,2-dicarboxylic acid **2** on oxidation established the absolute configuration of the cyclopropane moiety.[1]
3) On heating in benzene, the cyclic diene **3** is formed by concerted Cope rearrangement.[1,3] *Cis*-dictyopterene-A **4** (synthetic material) undergoes Cope rearrangement at lower temperature (15°C) yielding the corresponding cycloheptadiene **5**.[2]

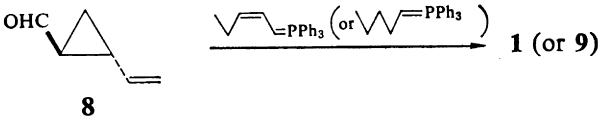
1) J. A. Pettus Jr., R. E. Moore, *Chem. Commun.*, 1093 (1970).
2) G. Ohloff, W. Pickenhagen, *Helv. Chim. Acta*, **52**, 880 (1969).
3) J. A. Pettus Jr., R. E. Moore, *J. Am. Chem. Soc.*, **93**, 3087 (1971).
4) W. Pickenhagen, F. Näf, G. Ohloff, P. Müller, J-C. Perlberger, *Helv, Chim. Acta*, **56**, 1868 (1973).

4) Irradiation of the *trans*-divinylcyclopropane derivative (e.g. **6**) in benzene at 40° gave *cis*-divinylcyclopropane **7** and cycloheptadiene **5**.[4]



Synthesis

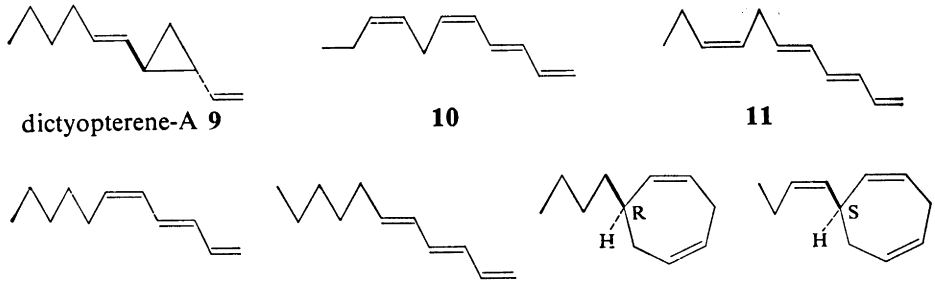
1 and **9** were synthesized from **8** by Wittig reaction.[5]



Remarks

Dictyopterene-B **1** and -A **9**[6] are major constituents of the essential oil of an odoriferous seaweed, *Dictyopteris*. The compounds **10–13** are also found in this seaweed as minor constituents.[3] Dictyopterene-C′ **14** and -D′ **15** obtained from same source have an absolute configuration opposite to that of the Cope rearrangement products of **9** and **1** respectively.[3] The compound **15** has been isolated as a sex attractant secreted by female gametes of the marine brown algae *Ectocarpus siliculosus*.[7,9]

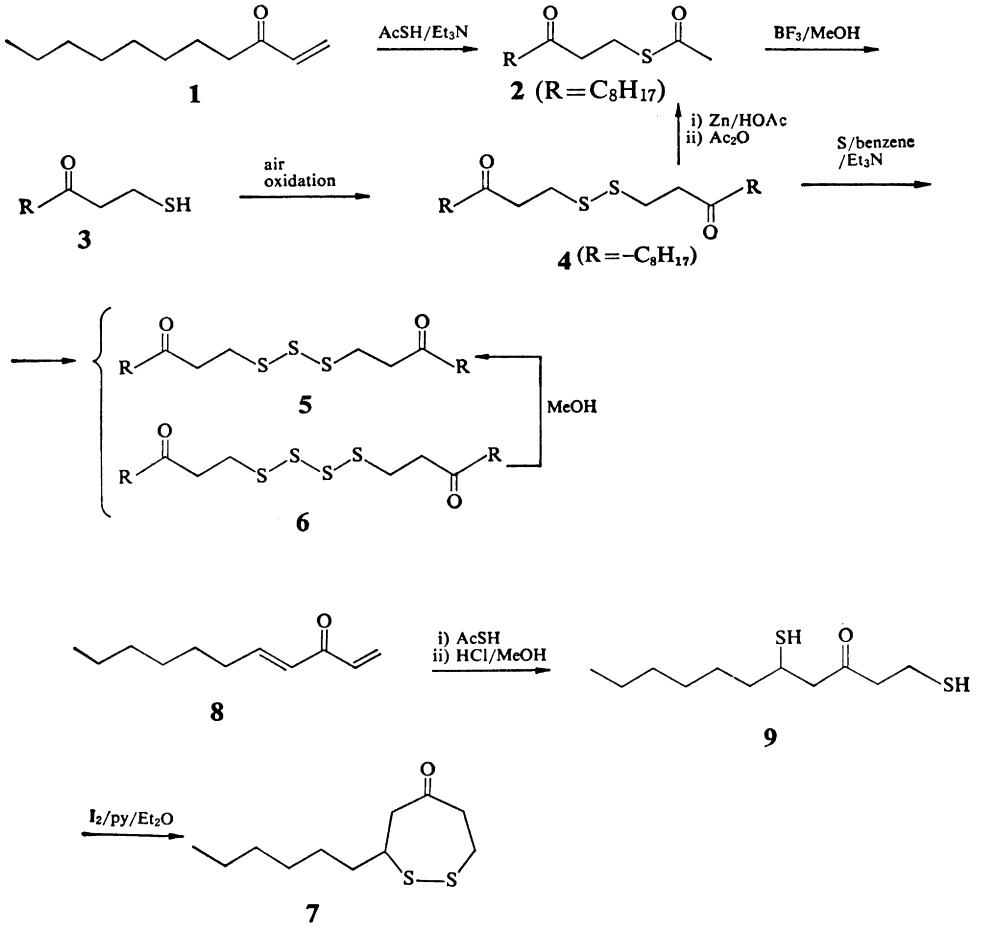
The cyclopropane rings of **1** and **9** might be formed by di-π-methane rearrangement of the acyclic polyenes.[8]



5) A. Ali, D. Sarantakis, B. Weinstein, *Chem. Commun.*, 940 (1971); K. C. Das, B. Weinstein, *Tetr. Lett.*, 3459 (1969).
6) R. E. Moore, J. A. Pettus Jr., M. S. Doty, *Tetr. Lett.*, 4787 (1968); R. E. Moore, J. A. Pettus Jr., J. Mistysyn, *J. Org. Chem.*, **39**, 2210 (1974).
7) D. G. Müller, L. Jaenicke, M. Donike, T. Akintori, *Science*, **171**, 815 (1971).
8) cf. H. E. Zimmerman, P. S. Mariano, *J. Am. Chem. Soc.*, **91**, 1718 (1969).
9) cf. L. Jaenicke, D. G. Müller, R. E. Moore, *J. Am. Chem. Soc.*, **96**, 3324 (1974).

7.3 SULFUR CONTAINING LIPIDS FROM *Dictyopteris*

Sulfur-containing compounds, e.g. **2–7**, have been isolated from odoriferous seaweeds along with the enone **1**. These compounds have a structural as well as biogenetic relationship to the C_{11} hydrocarbon dictyopterenes, which were obtained from same source. The natural substances **1–6** were chemically interrelated by the reactions shown below.[1,2]



1) Michael-type addition of AcSH to the enone **1** afforded **2**.

2) The disulfide **4** was readily formed by air oxidation of **3** obtained by acid-catalyzed hydrolysis of **2**.

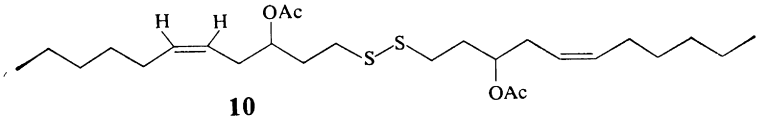
3) The naturally occurring polysulfides **5** and **6** were shown to be identical with the products obtained by Et_3N-catalyzed reaction of **4** and sulfur.

1) P. Roller, K. Au, R. E. Moore, *Chem. Commun.*, 503 (1971).
2) R. E. Moore, *Chem. Commun.*, 1168 (1971).
3) A. E. Asato, R. E. Moore, *Tetr. Lett.*, 4941 (1973).
4) R. E. Moore, J. Mistysyn, J. A. Pettus, Jr., *Chem. Commun.*, 326 (1972).

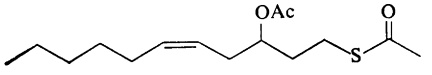
4) On prolonged standing, **6** decomposed, giving **5** and sulfur.
5) The cyclic disulfide **7** was synthesized from **8**.[3]

Remarks

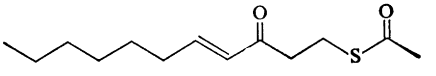
The compounds **1–7** were isolated from *Dictyopteris plagiogramma* along with the compounds **10**, **11**[4] and **12**.[1]



10

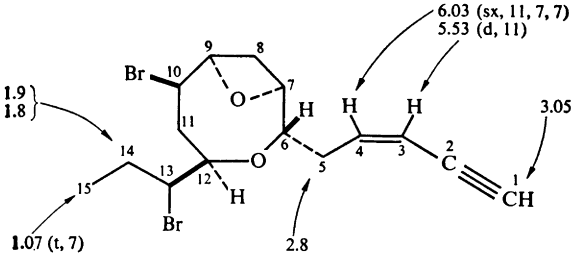


11



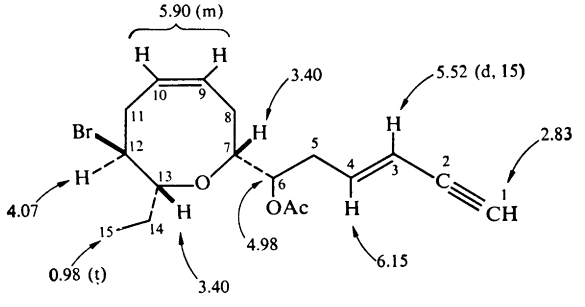
12

7.4 STRUCTURE OF LAUREATIN AND RELATED COMPOUNDS



laureatin **1**[1,2]

mp: 82–83° α_D: +96°
ms: 394, 392, 390(M^+ $C_{15}H_{20}O_2Br_2$)
uv: 223(ε 12800), 229(infl. ε 10400)
ir: 3300, 2100, 1140, 1086, 1045, 975, 965, 758

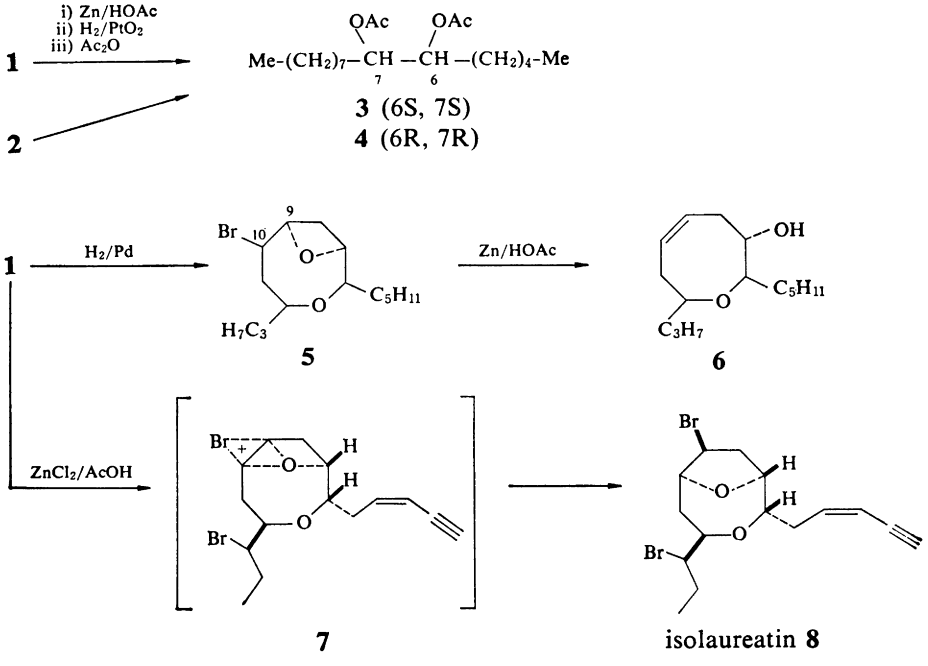


laurencin **2**[3,4]

mp: 73–74° α_D: +70.2°
uv: 224(ε 16400), 234(ε 11000)
ir: 3285, 2100, 1168, 1080, 3040, 950, 750

The absolute configuration of **1** was established as 6S, 7S, 9R, 10R, 12R and 13S from the following evidence.[2)]

1) The configuration at C-6 and C-7 was determined from the optical rotation of the glycol diacetate **3** obtained from **1**. The antipodal diacetate **4** was obtained from laurencin **2**.
2) The *trans* relationship of the substituents at C-9 and C-10 was deduced from the coupling constant ($J=2.5$ Hz) and also from the facile formation of **6** from **5** on treatment with zinc.
3) Considerable downfield shift of the 12-H signal indicates the proximity of this to the oxetane oxygen.
4) C-12 and C-13 are assumed to be *erythro* from a biogenetic point of view.
5) On acid treatment, **1** was converted into isolaureatin **8**. The rearrangement might be due to oxetane ring strain in **1**.[5)]
6) The complete structure of **8** was confirmed by an x-ray diffraction study.[2)]

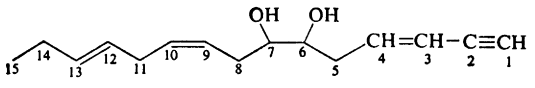


Remarks

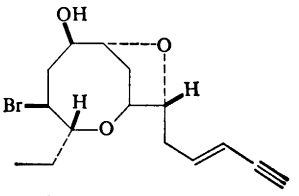
The compounds **1**, and **8–12** were isolated from the essential oil of red marine algae, *Laurencia nipponica*, and **2** from *L. glandulifera*.

Chondriol **13** and rhodophytin, a halogenated vinyl peroxide have been isolated from marine algae *Chondria oppositiclada*[9)] and Laurencia species[10)] respectively.

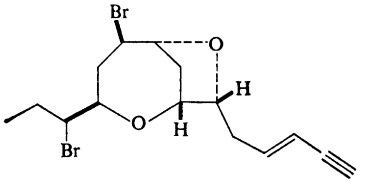
1) T. Irie, M. Izawa, E. Kurosawa, *Tetr.*, **26**, 851 (1970); *Tetr. Lett.*, 2091, 2735 (1968).
2) E. Kurosawa, A. Furusaki, M. Izawa, A. Fukuzawa, T. Irie, *Tetr. Lett.*, 3857 (1973).
3) T. Irie, M. Suzuki, T. Masamune, *Tetr.*, **24**, 4193 (1968); *Tetr. Lett.*, 1091 (1965).
4) A. F. Cameron, K. K. Cheung, G. Furguson, J. M. Robertson, *J. Chem. Soc.*, B, 559 (1969); *Chem. Commun.*, 638 (1965).
5) A. Fukuzawa, E. Kurosawa, T. Irie, *J. Org. Chem.*, **37**, 680 (1972).



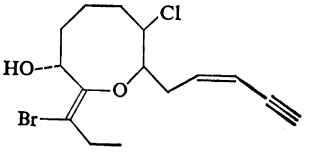
trans-laurediol **9** (C-3/C-4 *trans*)[6]
cis-laurediol **10** (C-3/C-4 *cis*)[6]



laurefucin **11**[7]



isoprelaurefucin **12**[8]



chondriol **13**[9]

6) E. Kurosawa, A. Fukuzawa, T. Irie, *Tetr. Lett.*, 2121 (1972).
7) A. Furusaki E. Kurosawa, A. Fukuzawa, T. Irie, *Tetr. Lett.*, 4579 (1973).
8) E. Kurosawa, A. Fukuzawa, T. Irie, *Tetr. Lett.*, 4135 (1973).
9) W. Fenical, K. B. Gifkins, J. Clardy, *Tetr. Lett.*, 1507 (1974); cf. W. Fenical, J. J. Sim, P. Radlick, *ibid.*, **313** (1973).
10) W. Fenical, *J. Am. Chem. Soc.*, **96**, 5580 (1974).

7.5 INSECT SEX PHEROMONES

There has recently been increasing activity in insect pheromone chemistry because of their chemical and biological interest as well as their potential use as aids in the control of specific injurious insects. Insect pheromones can usually be classified, from the type of activity, as sex pheromones (attractant), alarm pheromones, aggregating pheromones, and trail-marking hormones, etc. Most of them are structurally simple compounds of low molecular weight, and are biogenetically fatty acid- and terpene-derived substances. The methods of structural determination differ somewhat from those of other natural products, since extremely small amounts of the biologically active materials are available. General features of structural work are as follows.

1) The gross structure of biologically active compounds is assumed on the basis of the spectral properties (ir, uv, etc.) as well as the retention time on gc analysis and mobilities on tlc.
2) Observations of loss of biological activity due to simple chemical treatment (e.g. hydrolysis, $KMnO_4$, etc.) supply information as to functional groups or unsaturation in the molecule.
3) More detailed information is obtainable by mass spectrometric analysis or more conveniently by the use of combined gc-ms analysis of the pheromone itself or chemically transformed products obtained by micro-scale reactions (e.g. ozonolysis, hydrogenation, etc.).
4) The structure will then be confirmed by chemical synthesis and the geometry of double bond(s) can be assigned by biological tests of the synthetic isomers.
5) That the compound is a real pheromone is established by field tests of the sample.
6) Combined use of electroantennography and gas-chromatography (gc-eag) is convenient for the identification of pheromones.

The following are the chemical structures and sources of well-characterized insect sex pheromones of fatty acid origin.[1] Most of these have a C_{12}–C_{18} aliphatic carbon chain with an acetoxyl group at the terminal position and contain one or two olefinic bond.

C_{12} group

1
cabbage looper moth *(Trichoplusia ni)*

2
oriental fruit moth *(Grapholitha molesta)*

3
Polychrosis vieana[2]

4
false codling moth *(Argyroploce leucotreta)*

5
codling moth *(Laspeyresia pomonella)*[3]

6
red bollworm moth *(Diaparopsis castanea)*[4]

1) J. H. Law, F. E. Regnier, *Ann. Rev. Biochem.*, 533 (1971).
2) J. A. Kuhn, T. A. Brindley, *J. Econ. Entomol.*, **63**, 779 (1970).
3) W. Roelofs, A. Comeau, A. Hill, G. Milicevic, *Science*, **174**, 297 (1971).
4) B. F. Nesbitt, P. S. Beevor, R. A. Cole, R. Lester, R. G. Poppi, *Nature New Biol.*, **244**, 208 (1973).
5) W. L. Roelofs, A. Comeau, *Pesticide Chemistry* (ed. A. S. Tobotu) Vol. 8, p. 91–112, Cordon of Beach, 1971.
6) Y. Kuwahara, H. Hara, S. Ishii, H. Fukami, *Science*, **171**, 801 (1971); U. E. Brady, J. H. Tumlinson, R. G. Brownlee, R. M. Silverstein, *ibid.*, **171**, 802 (1971)
7) W. L. Roelofs, R. T. Carde, *Science*, **171**, 684 (1971).
8) K. H. Dahm, D. Meyer, W. E. Finn, V. Reinhold, H. Röller, *Naturwiss.*, **58**, 265 (1971).

C_{14} group

7

leaf roller moth *(Argyrotaenia velutinana)*
European corn borer *(Ostrinia nubilalis)*

8

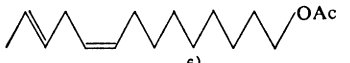
fall armyworm moth *(Spodoptera frugiperda)*
noctuid moth *(Spodoptera littoralis)*[4]

9

noctuid moth *(Spodoptera littoralis)*[4]
Sparganothis sulfureana[5]

10

galechiid moth *(Bryotopha similis)*

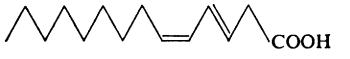


11[6]

almond moth *(Cadra cautella)*
Indian meal moth *(Plodia interpunctella)*
Mediterranean flour moth *(Anagasta kuehniella)*

12

noctuid moth *(Spodoptera littoralis)*



13

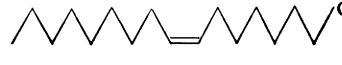
black carpet beetle *(Attagenus megatoma)*

C_{16} group

14

butterfly *(Lycorea ceres ceres)*

bombykol* **16**

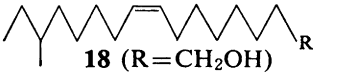


15

pink bollworm moth *(Pectinophora gossypiella)*[5,9]

(propylure* **17**)

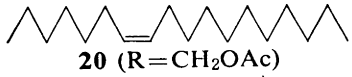
C_{17} group



18 (R=CH_2OH)
19 (R=COOMe)

dermestid beetle *(Trogoderma inclusum)*

C_{18} group



20 (R=CH_2OAc)

butterfly *(Lycorea ceres ceres)*

21 (R=CHO)

Achroia grisella[8]

22

tiger moth *(Holomelina nigricans)*[7]

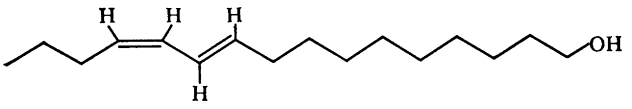
C_{19} group disparlure* **23**

C_{23} group muscalure* **24**

The compounds asterisked are described in more detail later in this chapter. For the compounds without reference numbers, see ref. 1.

9) The sex pheromone of the pink bollworm moth has recently been assigned as a 1:1 mixture of (7*Z*, 11*Z*)- and (7*Z*, 11*E*)-7,11-hexadecadien-1-yl acetate.
H. E. Hummel, L. K. Gaston, H. H. Shorey, R. S. Kaae, K. J. Byrne, R. M. Silverstein, *Science*, **181**, 873 (1973); B. A. Bierl, M. Beroza, R. T. Staten, P. E. Sonnet, V. E. Adler, *J. Econ. Entomol*, **87**, 211 (1974).

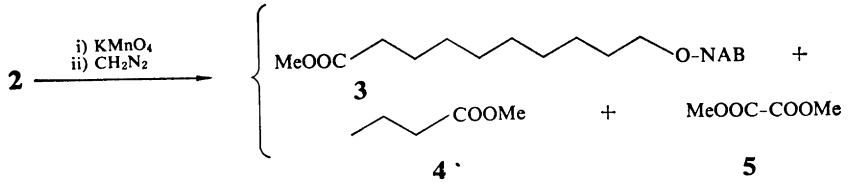
7.6 STRUCTURE AND SYNTHESIS OF BOMBYKOL



bombykol **1**[1)]

ir: 9.5–9.75μ (—OH), 10.18, 10.56μ,
(conjugated *cis*, *trans* double bonds),
13.89μ ($(CH_2)_n$, $n>4$)
uv(for NAB ester): 230 (conjugated diene),
331 (azo chromophore)

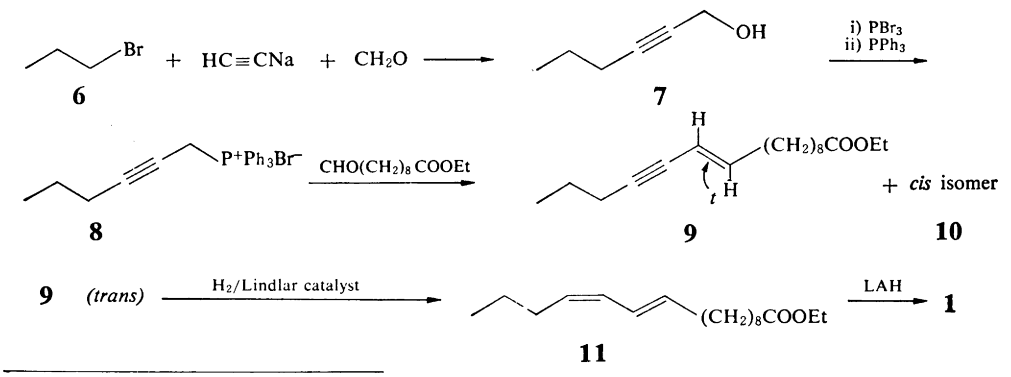
1) **1** forms a *p*-nitrophenylazobenzoate (NAB) ester **2** on esterification.
2) Hydrogenation of **1** ($2H_2$) yields cetyl alcohol, $Me(CH_2)_{14}CH_2OH$.
3) The position of the double bond was determined by oxidative cleavage, which yielded **3**, **4** and **5**.
4) The geometry of the two double bonds was determined by synthesis of all four possible isomers. Comparison of the chemical and biological properties of the synthetic specimens with those of the natural substance established that bombykol **1** is 10-*trans*, 12-*cis*-hexadecadien-1-ol.[1,2)]



Remarks

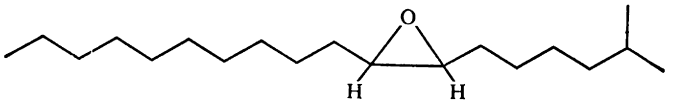
Bombykol **1** is a sex attractant secreted by the male moth *Bombyx mori*, and it is physiologically active in concentrations of 10^{-10} μg/ml. Twelve mg of pure bombykol was obtained from 500,000 male moths as a crystalline derivative.

Synthesis[2,3)]



1) A. Butenandt, R. Beckmann, D. Stamm, E. Hecker, *Z. Naturforsch.*, **14b**, 283 (1959).
2) A. Butenandt, E. Hecker, M. Hopp, W. Koch, *Ann. Chem.*, **653**, 39 (1962).
3) A. Butenandt, E. Hecker, *Angew. Chem.*, **73**, 349 (1961).

7.7 STRUCTURE OF DISPARLURE

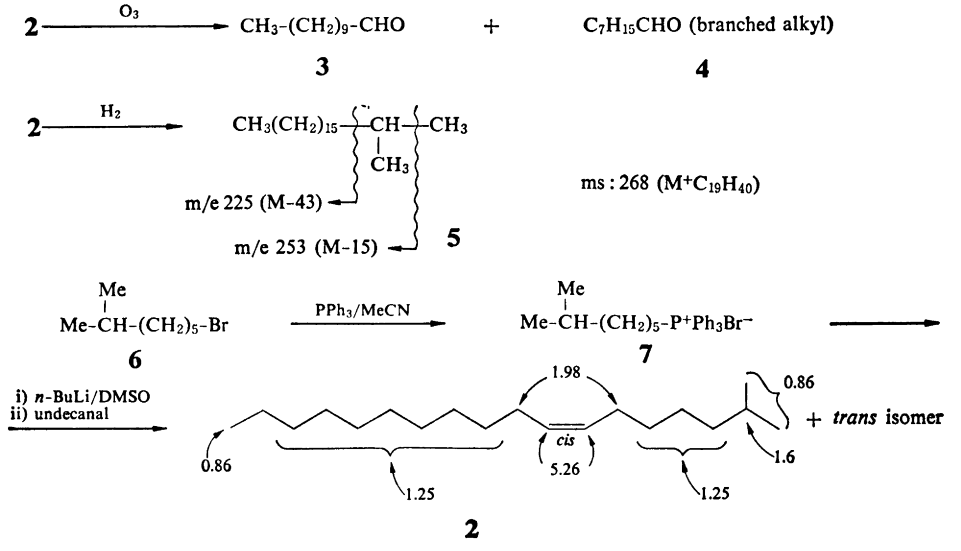


disparlure **1**[1]

The structure of disparlure was established indirectly by determining the structure of the olefin precursor **2**, from which the biologically active substance was formed by epoxidation with *m*-Cl-perbenzoic acid.[1]

olefin precursor **2** $\xrightarrow{m\text{-Cl-PBA}}$ disparlure **1**

1) The position of the double bond in **2** was determined by the formation of **3** and **4** on ozonolysis.
2) The position of the methyl substituent was determined from the fragmentation of **5** in mass spectrum.
3) The structure of **2** was confirmed by synthesis, **6** ⟶ **7** ⟶ **2**.

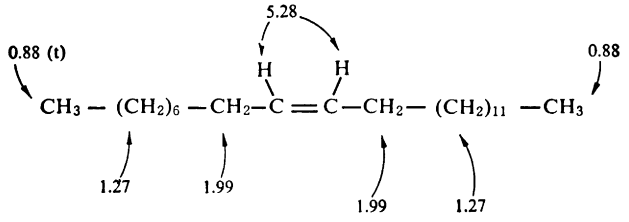


Remarks

Disparlure **1** is a potent sex attractant produced by the female gypsy moth, *Porthetria dispar* (Lymantriidae).[1] As little as 2×10^{-12} g of the synthetic epoxide was active in the laboratory bioassay. The *cis* epoxide was about ten times as active as the *trans* isomer. *cis*-7-Hexadecene-1,10-diol (gyptol) had been identified as a gypsy moth sex attractant,[2] but it was later found that this compound was inactive.[3,4] **1** has been synthesized in optically active form from (S)(+)-glutamic acid.[5]

1) B. A. Bierl, M. Beroza, C. W. Collier, *Science*, **170**, 87 (1970).
2) M. Jacobson, M. Beroza, W. A. Jones, *Science*, **132**, 1011 (1960).
3) K. Eiter, E. Truscheit, M. Boness, *Ann. Chem.*, **709**, 29 (1967).
4) M. Jacobson, R. M. Waters, M. Schwarz, *J. Econ. Entomol.*, **63**, 943 (1970).
5) S. Iwaki, S. Marumo, T. Saito, M. Yamada, K. Katagiri, *J. Am. Chem. Soc.*, **96**, 7842 (1974).

7.8 STRUCTURE AND SYNTHESIS OF MUSCALURE



muscalure **1**[1]

ms: 322 (M^+ $C_{23}H_{46}$)
nmr (for synthetic material) in $CDCl_3$

1) Micro-scale ozonolysis of **1** (10 μg sample) followed by gc analysis indicated the formation of nonanal and tetradecanal.
2) Hydrogenation of **1** yielded *n*-tricosane.
3) Condensation of nonanal with Wittig reagent prepared from 1-bromotetradecane gave 9-tricosene containing 85% *cis* and 15% *trans* isomer. Synthetic *cis* isomer was found to be identical with muscalure.

Synthesis

Route I[2]

The *cis* olefinic linkage in **1** was stereospecifically constructed by hydrogenation of the acetylenic intermediate **3**.

$$\underset{\mathbf{2}}{Me\text{-}(CH_2)_{12}\text{-}C\equiv CH} \xrightarrow[\text{ii) } Me(CH_2)_7Br]{\text{i) n-BuLi}} \underset{\mathbf{3}}{Me\text{-}(CH_2)_{12}C\equiv C\text{-}(CH_2)_7\text{-}Me} \xrightarrow{H_2/Lindlar} \mathbf{1}$$

Route II[3]

1 was synthesized from the readily available erucic acid **4** by two simple reaction steps in an overall yield of 85%.

$$\underset{\mathbf{4}}{Me\text{-}(CH_2)_7\text{-}\overset{H}{\overset{|}{C}}=\overset{H}{\overset{|}{C}}\text{-}(CH_2)_{11}\text{-}COOH} \xrightarrow{MeLi} \underset{\mathbf{5}}{Me\text{-}(CH_2)_7\overset{H}{\overset{|}{C}}=\overset{H}{\overset{|}{C}}\text{-}(CH_2)_{11}\text{-}\overset{O}{\overset{\|}{C}}\text{-}Me} \xrightarrow{\text{Huang-Minlon}} \mathbf{1}$$

Route III[4]

Mixed Kolbe electrolysis of oleic acid and heptanoic acid afforded **1** in 14% yield.

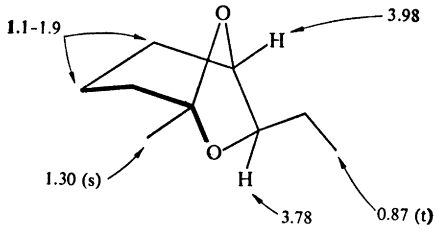
$$\underset{\mathbf{6}}{Me\text{-}(CH_2)_7\overset{H}{\overset{|}{C}}=\overset{H}{\overset{|}{C}}\text{-}(CH_2)_7COOH} + \underset{\mathbf{7}}{Me\text{-}(CH_2)_5COOH} \xrightarrow[(-2CO_2)]{\text{electrolysis/NaOMe/MeOH}} \mathbf{1}$$

Remarks

Muscalure **1** is a sex pheromone isolated from the cuticle and feces of the female house fly, *Musca domestica*.

1) D. A. Carlson, M. S. Mayer, D. L. Silhacek, J. D. James, M. Beroza, B. A. Bierl, *Science*, **174**, 76 (1971).
2) K. Eiter, *Naturwiss.*, **59**, 468 (1972).
3) R. L. Cargill, M. G. Rosenblum, *J. Org. Chem.*, **37**, 3971 (1972).
4) G. W. Gribble, J. K. Sanstead, J. W. Sullivan, *Chem. Commun.*, 735 (1973).

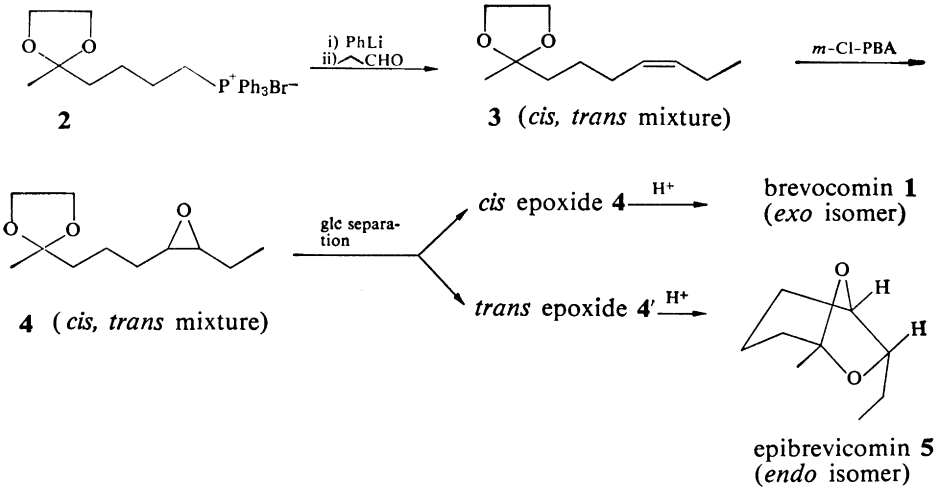
7.9 SYNTHESIS OF BREVICOMIN



brevicomin **1**[1]

ms: 156.11572 (M^+ $C_9H_{16}O_2$)
ir: no OH or C=O absorption
uv: no absorption
nmr in CCl_4

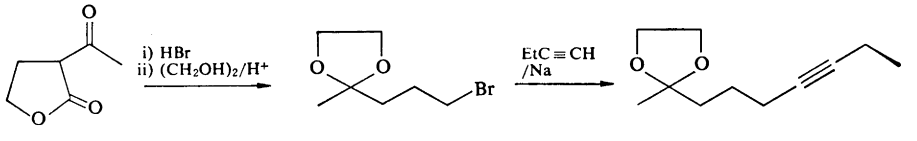
Route I[1,2]



2 **3** (*cis, trans* mixture)

4 (*cis, trans* mixture)

The *cis* epoxide led directly to **1** on acid hydrolysis, and the *trans* epoxide to the *endo* isomer **5**. The *cis* double bond isomer **3** can alternatively be prepared in a geometrically specific manner from 2-acetylbutyrolactone **6** as follows.[2]



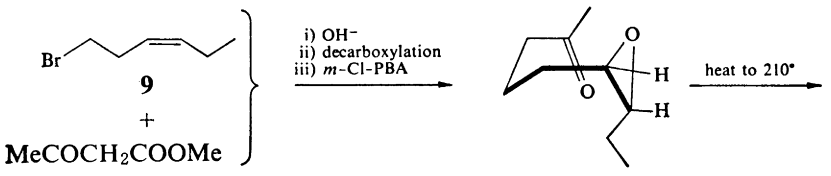
6 **7** **8**

$H_2/Ni(OAc)_2$ → *cis*-**3**

1) R. M. Silverstein, R. G. Brownlee, T. E. Bellas, D. L. Wood, L. E. Browne, *Science*, **159**, 889 (1968).
2) T. E. Bellas, R. G. Brownlee, R. M. Silverstein, *Tetr.*, **25**, 5149 (1969).

Route II[3]

Brevicomin **1** was also synthesized by thermal rearrangement of the δ,ϵ-epoxy ketone **10.**



10

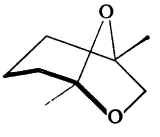
brevicomin **1** + epibrevicomin **5**

90% 10%

In a like manner, the corresponding *trans* epoxide is transformed to **5** and **1** in a ratio of 91:9.

Remarks

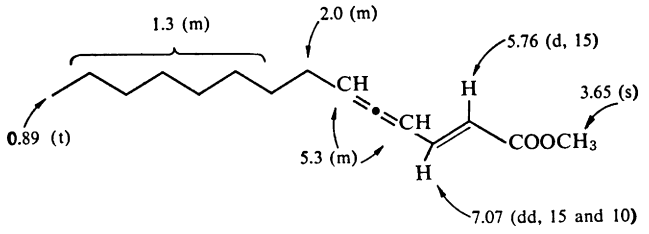
Brevicomin **1** has been identified as an aggregating pheromone produced by the female western pine beetle *Dendroctonus brevicomis* boring in ponderosa pine. Epibrevicomin **5** is also beetle *D. frontalis* has been found to possess the structure **11.**[4] **1** was synthesized in optically active form from (2S:3S)-D-(−)-tartaric acid.[5]



frontalin **11**

3) H. H. Wasserman, E. H. Barber, *J. Am. Chem. Soc.*, **91**, 3674 (1969).
4) G. W. Kinzer, A. F. Fentiman Jr., T. F. Page Jr., R. L. Foltz, J. P. Vité, G. B. Pitman, *Nature*, **221**, 477 (1969).
5) K. Mori, *Tetr.*, **30**, 4223 (1974).

7.10 ALLENIC ESTER FROM MALE DRIED BEAN BEETLE

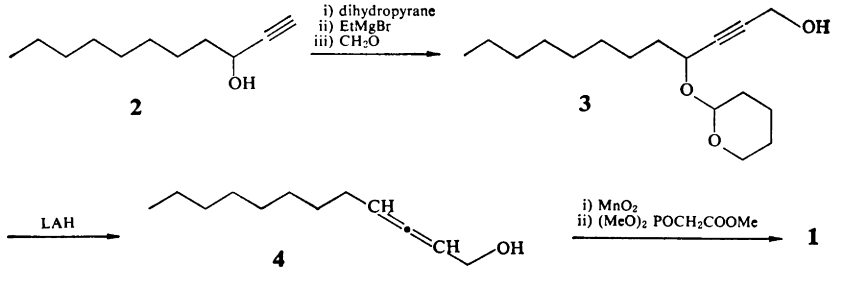


allenic ester from *Acanthoscelides obtectus* **1**[1]

ms: 138 (M^+ $C_{15}H_{24}O_2$)
uv: 254 (ε 16,000)
ir: 1940 (-C=C=C-), 1721, 1630 (-C=C-C=O), 981 (*trans*-C=C-)

The structure of the allenic ester **1** was confirmed by the following synthesis.

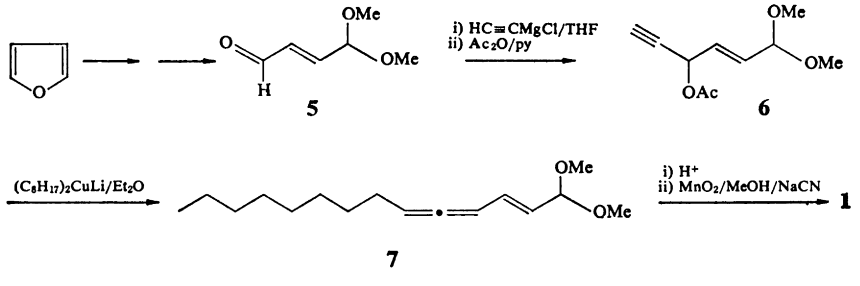
Route I[2]



3⟶**4**: Reductive elimination of the tetrahydropyranyloxy group in **3** converts the acetylenic linkage into an allenic linkage.

Route II[3]

Another synthesis of **1**, employing the reaction of lithium dialkylcuprate with propargylic allylic acetate producing the allene-ene system, has been reported.

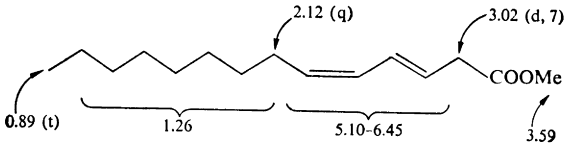


1) D F.. Horler, *J. Chem. Soc.*, C, 859 (1970).
2) P. D. Landor, S. R. Landor, S. Mukasa, *Chem. Commun.*, 1638 (1971).
3) C. Descoins, C. A. Henrick, J. B. Siddall, *Tetr. Lett.*, 3777 (1972).
4) R. M. Silverstein, J. O. Rodin, W. E. Burkholder, J. E. Gorman, *Science*, **175**, 85 (1967).

Remarks

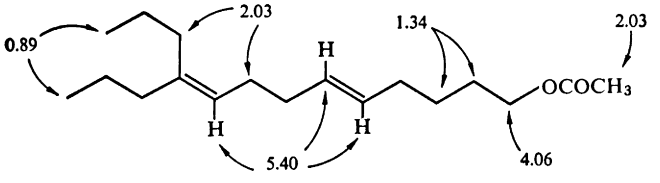
The C_{14} allenic ester **1** was isolated from the male dried bean beetle, *Acanthoscelides obtectus*. Although crude fractions containing this material attract female beetles, the amounts of **1** produced are far greater than is usual for a pheromone. Thus there is still a question as to whether this compound is the sex pheromone of the beetles.

The C_{14} unsaturated fatty acid ester **8**, which is closely related to **1** has been obtained as the principal component of the sex attractant of the black carpet beetle, *Attagenus megatoma*.[4]



8

7.11 SYNTHESIS OF PROPYLURE



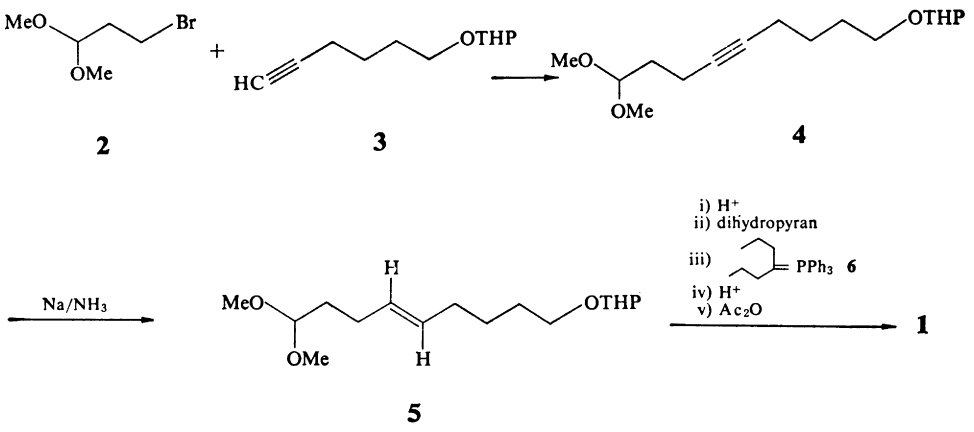
propylure **1**[1]

ms: 280 (M^+ $C_{18}H_{32}O_2$)
ir: 1755, 1235, 1038(acetyl), 1660, 965 (*trans* double bond), 723 (methylenes)
uv: end absorption
nmr in $CDCl_3$:
allylic methylene at 2.03,
other methylenes at 1.34

The structure of propylure **1** was confirmed by chemical synthesis. Here, two routes for the synthesis of **1** are described, both using acetylenic intermediates for the geometrically specific construction of a *trans* double bond.

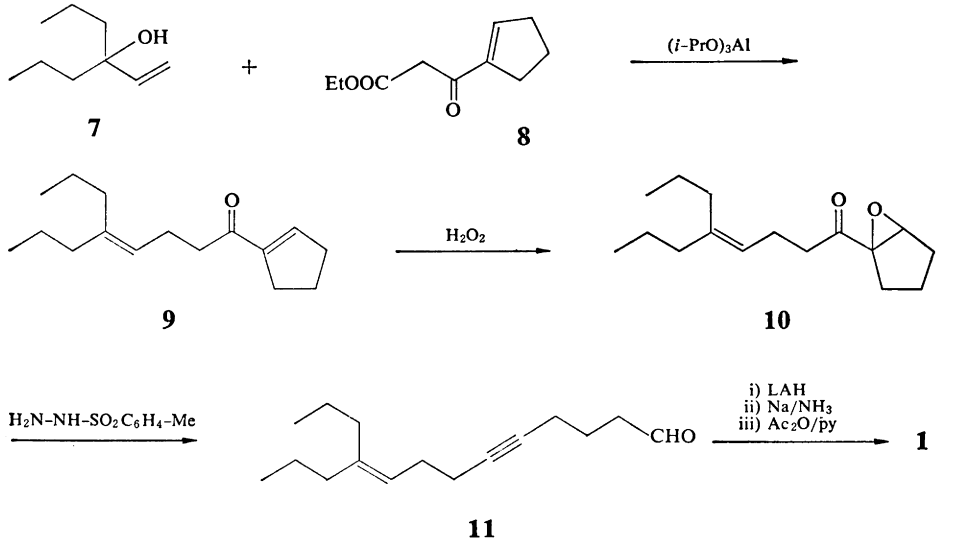
1) W. A. Jones, M. Jacobson, D. F. Martin, *Science*, **152**, 1516 (1966).

Route I[2]



Route II[3]

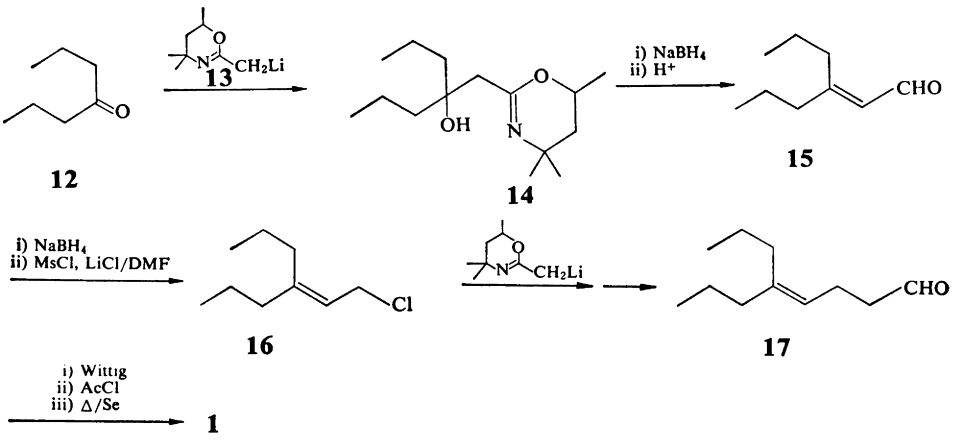
Propylure **1** was synthesized by an alternative method involving fragmentation of the tosylhydrazone of **10** as a key step, giving rise to the acetylenic aldehyde **11**.



Route III[4]

By means of a novel method for aldehyde synthesis utilizing the dihydro-1,3-oxazine derivative **13**, propylure was synthesized in an overall yield of 31%. Wittig condensation of **17** yielded a *cis/trans* mixture of products which isomerized to **1** by heating with Se.

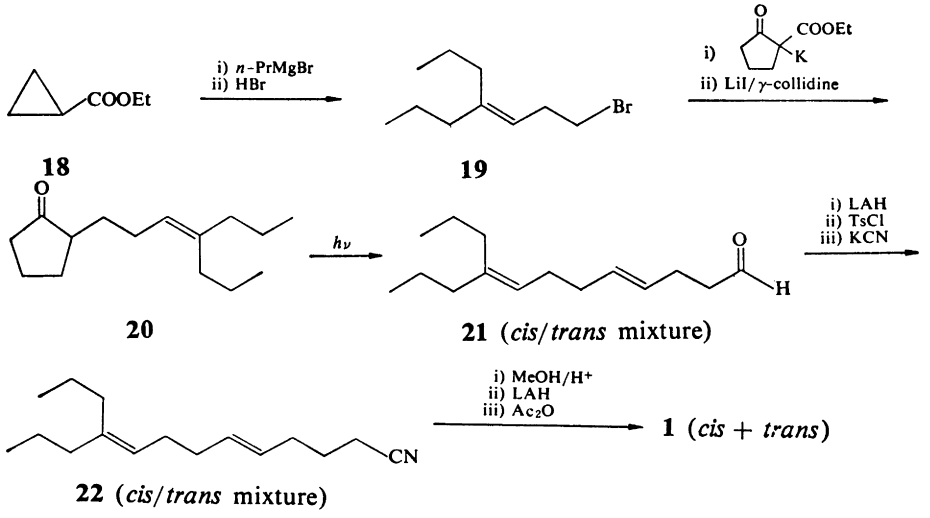
2) G. Pattenden, *J. Chem. Soc.* C, 2385 (1968).
3) M. Stoll, I. Flament, *Helv. Chim. Acta*, **52**, 1996 (1969).
4) A. I. Meyers, E. W. Collington, *Tetr.*, **27**, 5979 (1971).



12 14 15 16 17 **1**

Route IV[5]

1 was synthesized by the following route involving photochemical ring opening of the cyclopentanone **20** as a key step (Norrish type I reaction). The diene-aldehyde **21** formed in this reaction was found to be a mixture of *trans* and *cis* isomers in the ratio of 2 : 1.



18 **19** **20** **21** (*cis*/*trans* mixture)

22 (*cis*/*trans* mixture)

For other syntheses of **1** see refs. 6 and 7.

Remarks

Propylure **1** was reported to be a sex attractant produced by the female pink bollworm moth, *Pectinophora gossypiella*, which is a destructive pest of cotton.[1] However, doubt has been raised as to the structure of this pheromone, since a synthetic material showed no biological activity.[6,8]

5) J. Kossanyi, B. Furth, J-P. Morizur, *Tetr. Lett.*, 4559 (1973).
6) K. Eiter, E. Truscheit, M. Boness, *Ann. Chem.*, **709**, 29 (1967).
7) J. C. Stowell, *J. Org. Chem.*, **35**, 244 (1970).
8) For gossyplure, a recently identified pheromone of pink bollworm moth, see ref. 9 of page 10 and R. J. Anderson, C. A. Henrick, *J. Am. Chem. Soc.*, **97**, 4327 (1975).