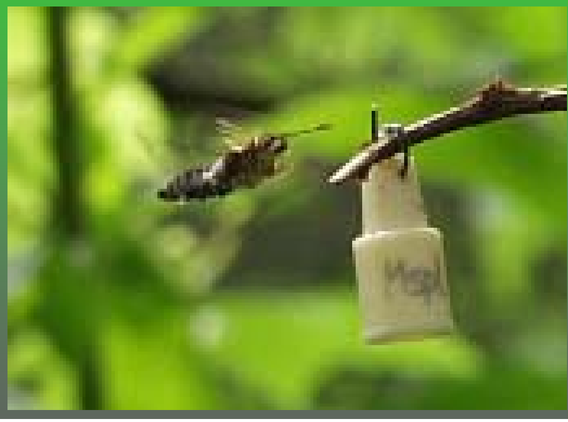
ISCE Meeting 2018

Budapest, Hungary (August 14, 2018)

Lepidopteran Sex Pheromones: Wonderland for a Natural Product Chemist

Tetsu Ando

Graduate School of BASE,
Tokyo University of Agriculture
and Technology, Japan



Representative lepidopteran sex pheromones

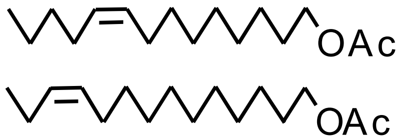
Sex pheromones have been identified from 687 species.
Male attractants have been reported for other 1277 species.

Type I

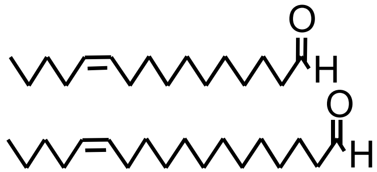
silkworm moth

bombykol

smaller tea tortrix



rice stem borer



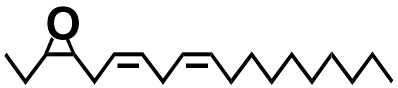
Unsaturated fatty alcohols, acetates and aldehydes with a $C_{10} – C_{18}$ chain
Found most commonly (75%)

Type II

Polyunsaturated hydrocarbons and their epoxides with a $C_{17} – C_{23}$ chain
Identified from evolved-insect groups (15%)

Z3,Z6,Z9-21:H

plum cankerworm moth



epo3,Z6,Z9-19:H

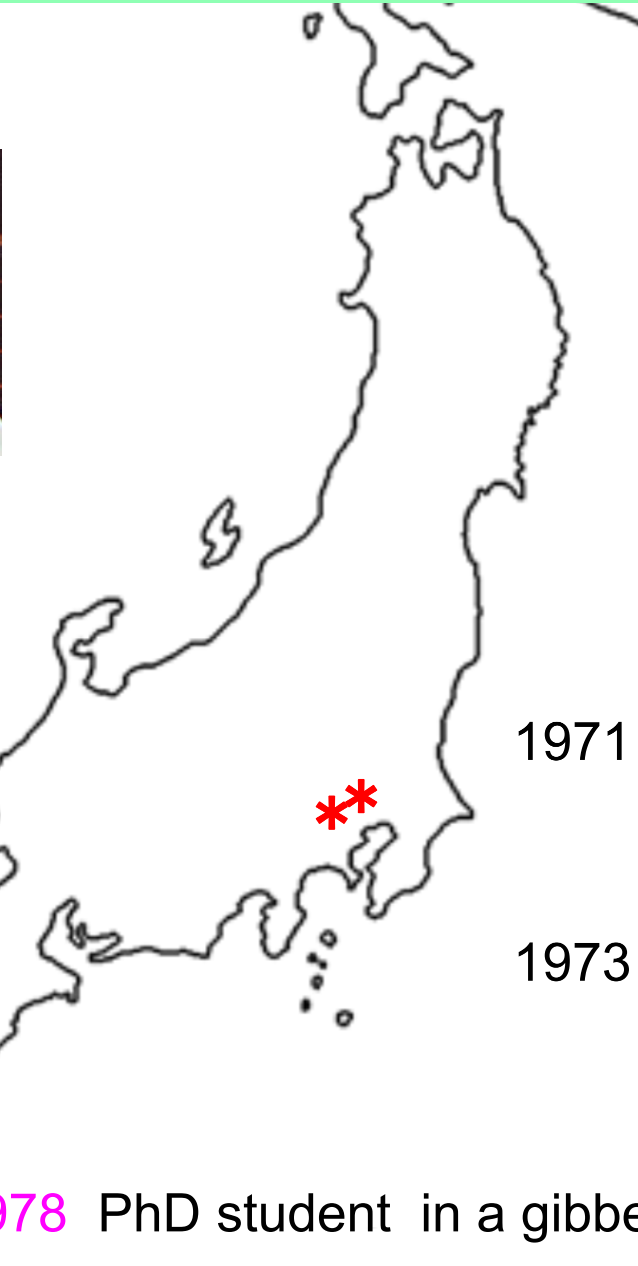
Milionia basalis

Z3,epo6,Z9-19:H

giant geometrid moth

Photos from http://www.jpmoth.org/

The beginning of pheromone researches in Japan



Kyoto Univ.
Prof. S. Ishii

1971 Almond moth
Mediterranean flour moth
(Z9,E12-14:OAc)

National Inst. of
Agri. Tech.
Dr. Y. Tamaki

1971 Smaller tea tortrix
(Z9-14OAc
+ Z11-14:OAc)

1973 Common cutworm
(Z9,E11-14:OAc
+ Z9,E12-14:OAc)

1973-1978 PhD student in a gibberellin laboratory
(The Univ. of Tokyo)

Trigger for pheromone studies

1973-1978 PhD student in a gibberellin laboratory of Prof. N. Takahashi (The Univ. of Tokyo)

Participation in the project for identification of a pheromone of the rice stem borer ⇒ Systematic synthesis of pheromone candidates

Known sex pheromones of female moths

1959	Silkworm moth	(E10Z12-16:OH)
1966	Cabbage looper	(Z7-12:OAc)
1967	Fall armyworm	(Z9-14:OAc)
1968	Soybean looper	(Z7-12:OAc)
1968	Redbanded leafroller	(Z11-14:OAc)
1969	Oriental fruit moth	(Z8-12:OAc)
1971	Codling moth	(E8,E10-12:OH)
1971	Smaller tea tortrix	(Z9-14OAc + Z11-14:OAc)
1971	Almond moth	(Z9,E12:OAc)

⇒ No hit (natural pheromone: new aldehydes)

Roelofs & Comeau, 1970. Lepidopterous sex attractants discovered by field screening tests. *J. Econ. Entomol.*, **63**: 969-974

⇒ Systematic screening ⇒ Attraction of 93 species (Homerun !!)

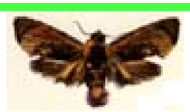
Random screening test ①

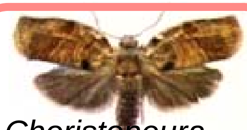
Monoene acetates, Sept. 3 – 10, 1974

Double bond		Carbon length of chain: C-10	C-12	C-14	C-16
5-en	Z	— , —	0 , 1	— , —	— , —
	E	— , —	0 , 1	— , —	— , —
7-en	Z	1 , 0	3 + 1 +1 , 2 + 1	2 , 0	1 + 1 , 0
	E	1+1 , 1+1	1 , 1	1 , 0	2 + 1 , 0
8-en	Z	— , —	23 + 2 , 5	0 , 1	0 , 0
	E	— , —	0 , 0	0 , 0	0 , 0
9-en	Z	— , —	1 , 1 +1	1 , 1	0 , 1 + 1
	E	— , —	0 , 0	1 , 0	0 , 0
11-en	Z		— , —	25 + 1 +1 , 26 +1	1 , 2
	E		— , —	1 , 1	1 , 7 + 3

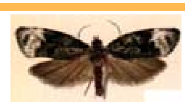
control 0 , 0


Nippoptilia issikii


Cryptophlebia ombrodelta


Choristoneura longicellana


Dysaethria moza


Hedya auricristana


Orthogonia sera

Insect species were identified
by Prof. H. Kuroko of Univ. Osaka Pref.

Random screening test ②

Monoene acetates, Sept. 11 – 18, 1974

Double bond		C-10	C-12	C-14	C-16
5-en	Z	–, –	0, 1	–, –	–, –
	E	–, –	0, 0	–, –	–, –
7-en	Z	1, 0	2, 4+1	0, 0	0, 1
	E	1+1, 0	0, 0	1, 0	0, 0
8-en	Z	–, –	7+1, 3	0, 0	0, 0
	E	–, –	0, 0	0, 0	0, 0
9-en	Z	–, –	0, 0	1+1, 1	0, 0
	E	–, –	0, 0	0, 0	0, 0
11-en	Z		–, –	28, 32	1, 0
	E		–, –	0, 0	2, 31

This is the trigger of my pheromone research. Namely, the root of my research is synthesis.

While I had no special skill of organic synthesis, simple structures of the pheromones worked favorably for my research.

Utilization of synthetic pheromone candidates

1973-1981	PhD student and post Doc.
1982-1995	Pesticide Chemistry Lab. in TUAT
1996-2015	Chemical Ecology Lab. In TUAT (BASE)

(1) Screening tests

1-1) Type I compounds: Monoenes (single-component lures)

1-2) Type I compounds: Monoenes (multi-component lures)

1-3) Type I compounds: Dienyl compounds

1-4) Type II compounds

(2) Authentic standards for analysis of natural pheromones

2-1) EAG analysis to determine a position and configuration of the double bond

2-2) Co-chromatography of GC-MS analysis

(3) Study on chemical analysis

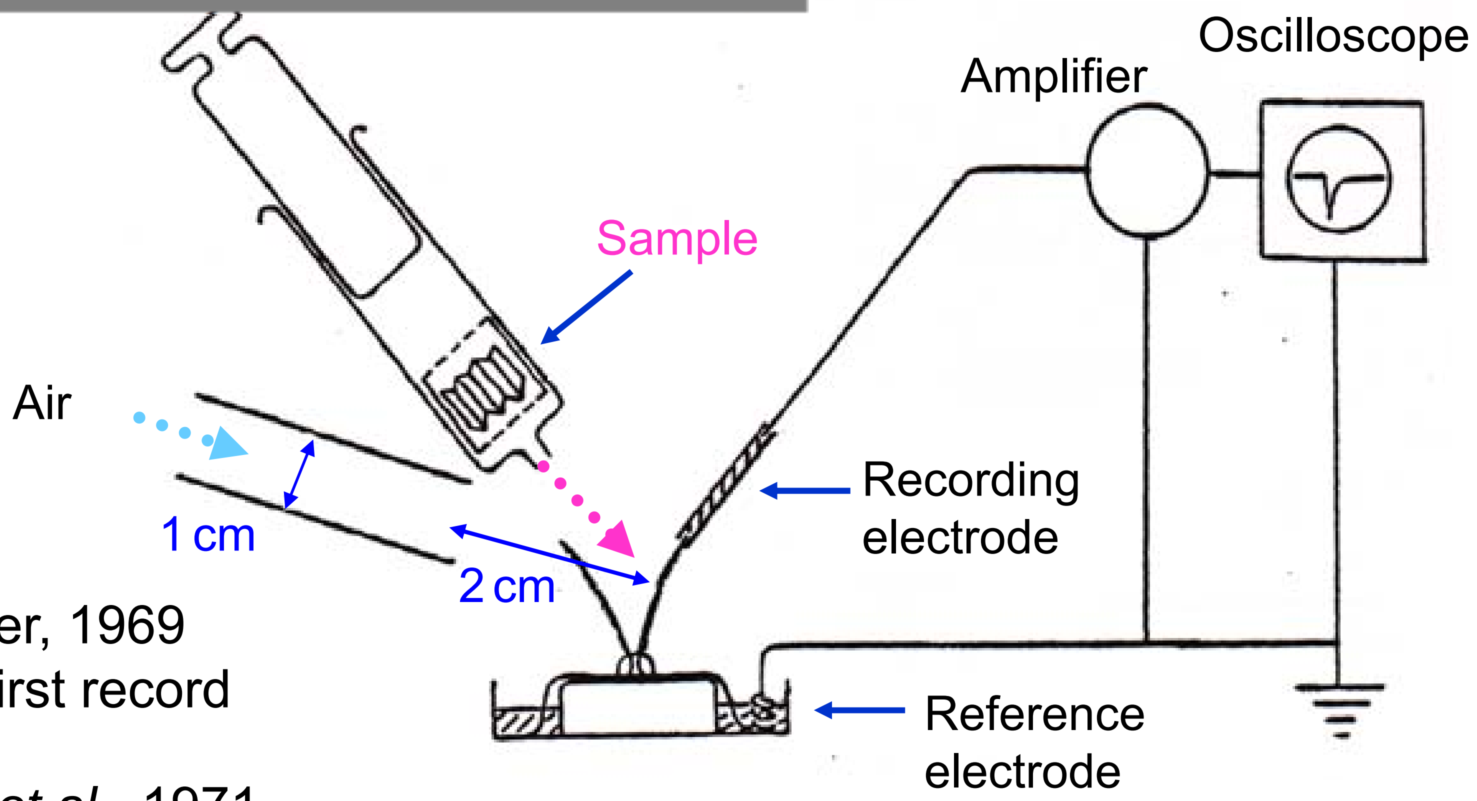
3-1) Speculation of fragmentations by mass spectrometry

3-2) Selection of an enantioselective HPLC column

(4) Study on biosynthesis

4-1) Examination of substrate specificity of enzymes

Electroantennogram (EAG)

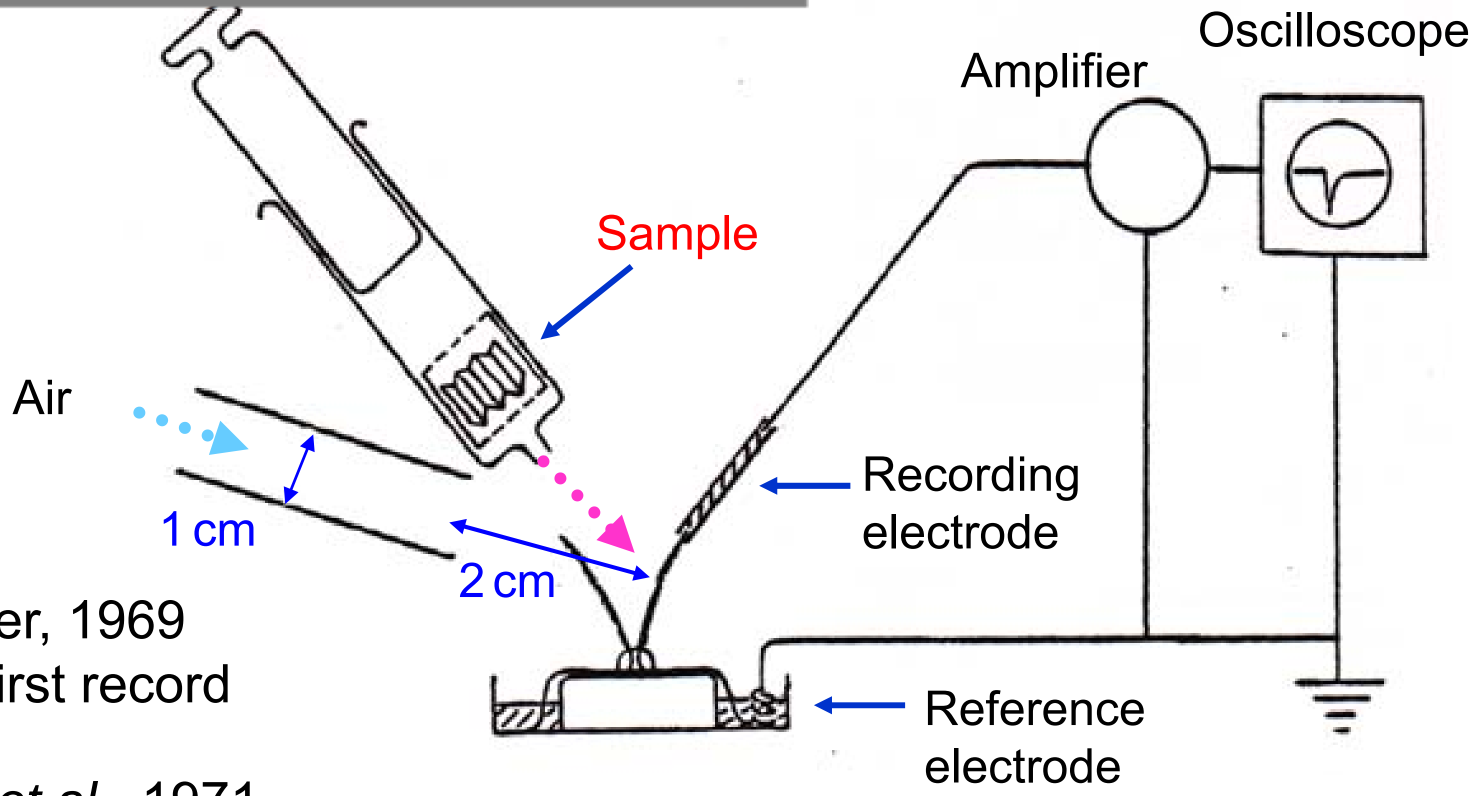


Schneider, 1969
First record

Roelofs *et al*., 1971
First application of EAG as a bioassay tool
in a study with the grape berry moth
Identification of a 8,10-diene by EAG activities of monoenes
in a study with the codling moth

Review: *"Crop Protection Agnetns – Their Biological Evaluatin"*
The scope and limitation of the EAG technique in identifying pheromone components.

Electroantennogram (EAG)



Schneider, 1969
First record

Roelofs *et al*., 1971
First application of EAG as a bioassay tool

In Japan,
1976 First equipment: Physical and Chemical Research Institute
1990 Purchase by Ando's laboratory

Arn *et al*., 1975 GC-EAD

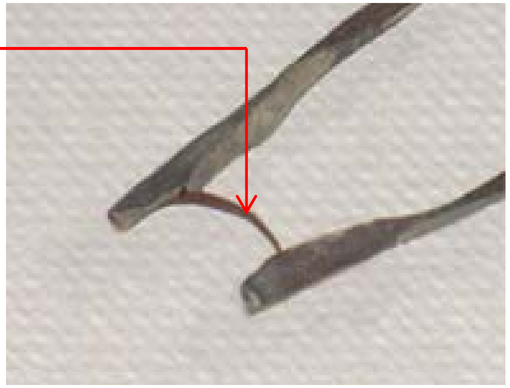
2000 Purchase by Ando's laboratory

GC-EAD

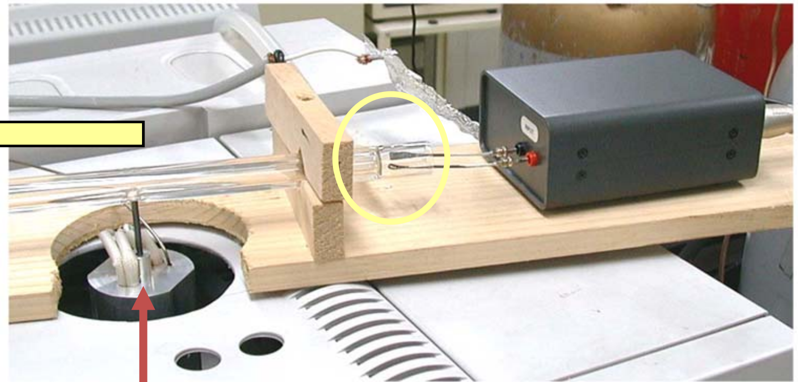
GC equipped with an EAG detector (EAD)

One of the most important instrument for pheromone researches

antenna



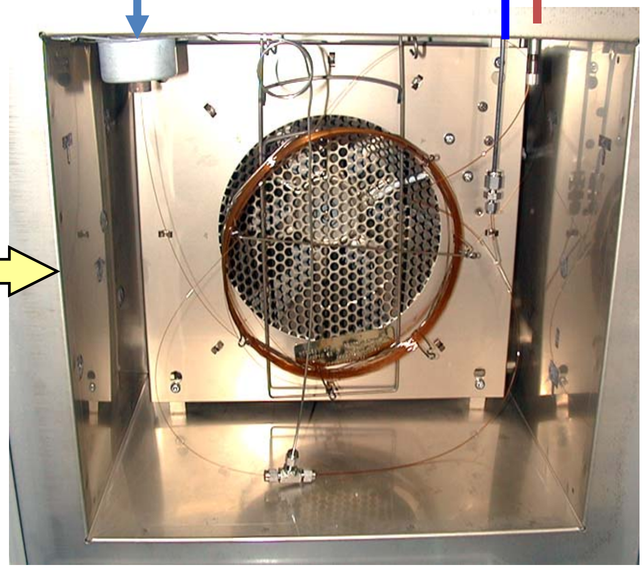
electrodes



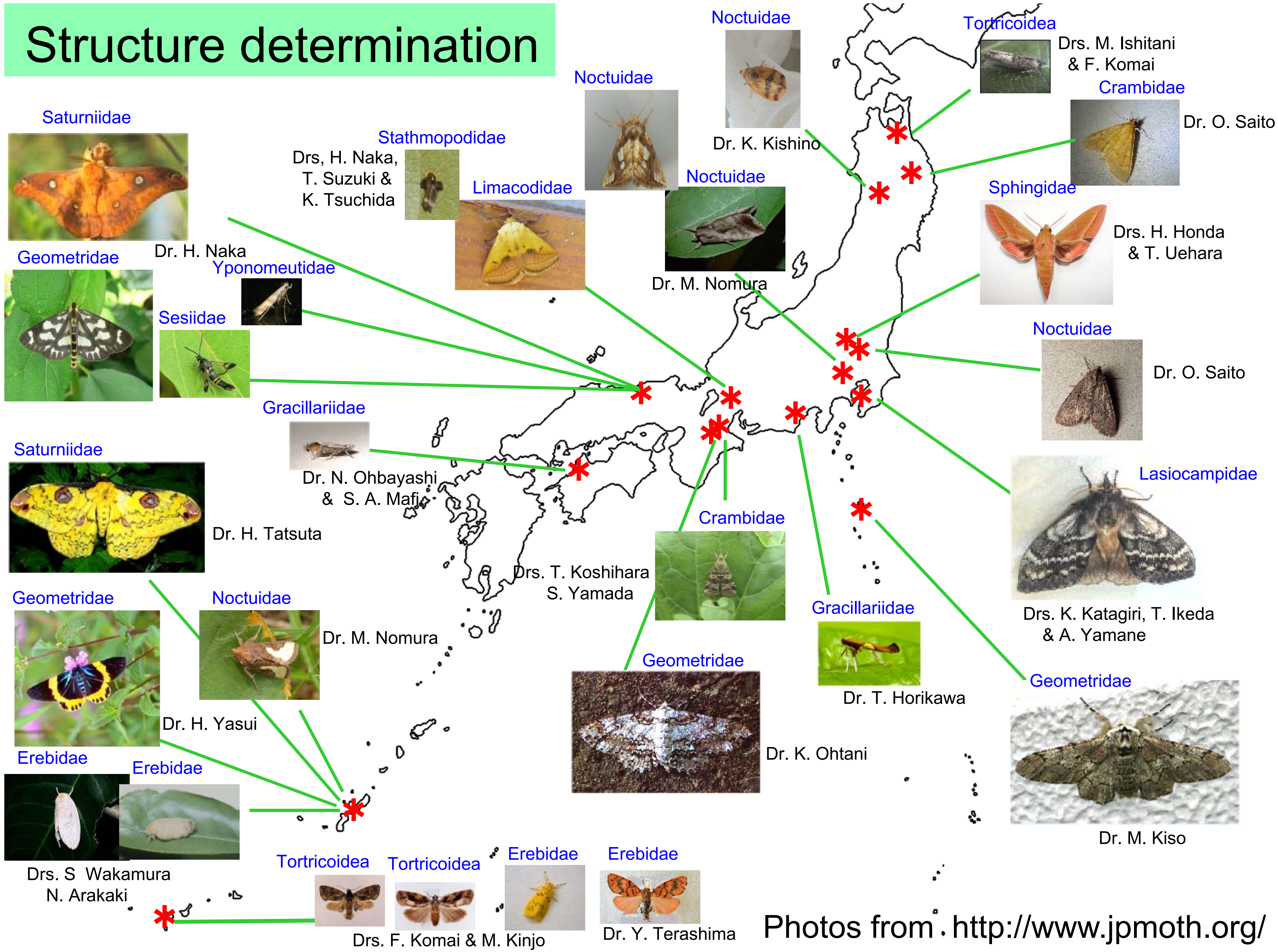
EAD

injection

FID



Structure determination



Photos from http://www.jpmoth.org/

Lepidopteran Sex Pheromones: Wonderland for a Natural Product Chemist

1) Identification by collaboration
with many entomologists

Systematic synthesis of pheromone analogues

Chemical analysis by GC-EAD and GC-MS

⇨ Diversity of Type I and II pheromones

https://lepipheromone.sakura.ne.jp/index_eng.html

2) Application

Monitoring and Mating disruption

3) Biosynthesis and its endocrine regulation

4) Methyl-branched pheromones ⇨ Type III ?

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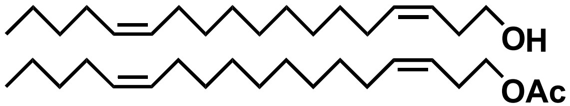
Commercialized lures for monitoring ①

1) *Toleria romanovi* (pest of vine trees)

(8:1)



Z3,Z13-18:OH

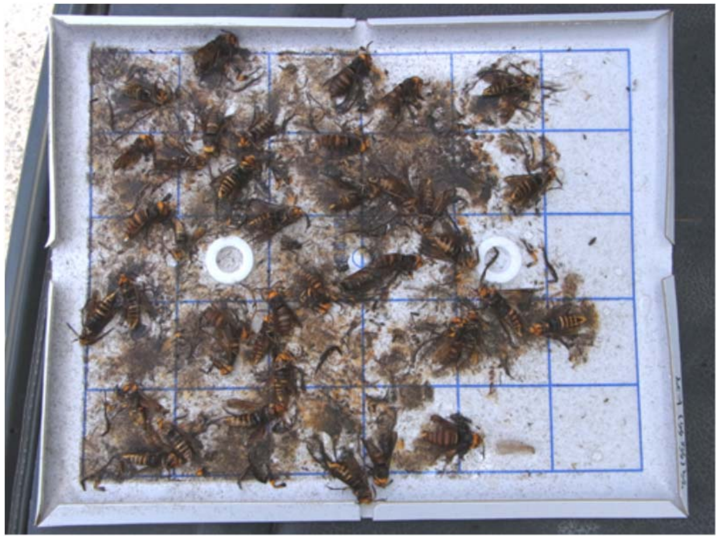
Z3,Z13-18:OAc

Diurnal moth mimicking a wasp

Larvae bore into the trunk,
causing the whole vine tree to death.
Recently, the damage suddenly spread.

Lure: rubber septum including 1mg of the synthetic pheromone

Sold from Japan Plant Protection Assoc.



Commercialized lures for monitoring ②

Sold from [Japan Plant Protection Association]

1) *Toleria romanovi* (pest of vine trees)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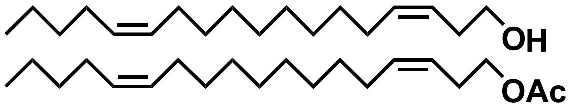
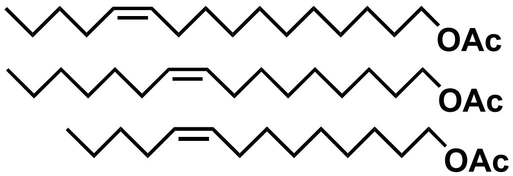


Z3,Z13-18:OH
Z3,Z13-18:OAc

2) Rice green caterpillar

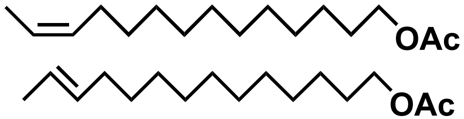

(4:1:1)



Z11-16:OAc
Z9-16:OAc
Z9-14:OAc

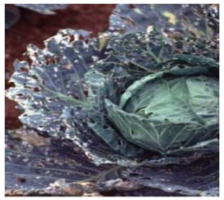
3) Asian corn borer



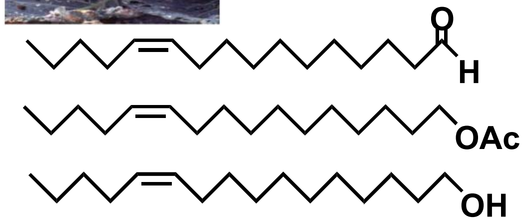


Z12-14:OAc
E12-14:OAc (3:2)

4) Diamond back moth



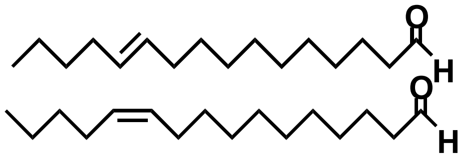

(10:10:1)



Z11-16:Ald
Z11-16:OAc
Z11-16:OH

5) Tea leafroller


E11-16:Ald
Z11-16:Ald (9:1)



6） Soybean pod borer

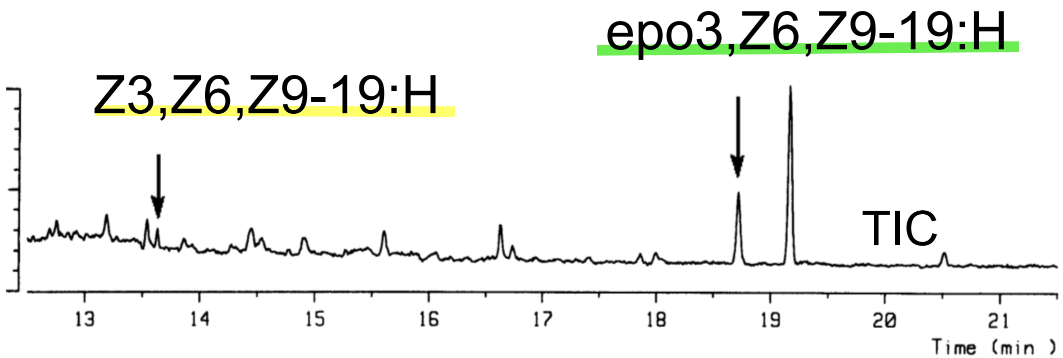


E8,E10-12:OAc

Mating disruption with a Type II pheromone ①

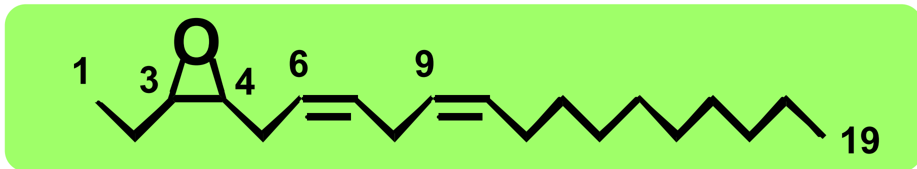
Pheromone components of *Ascotis selenaria cretacea*,
Japanese Giant Looper (Geometridae: Ennominae)

Serious damage by the larvae
in a tea garden

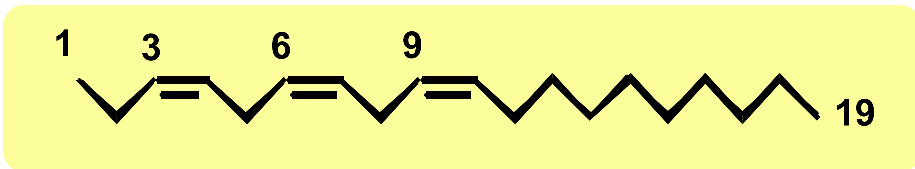


GC-MS analysis of the pheromone gland extract

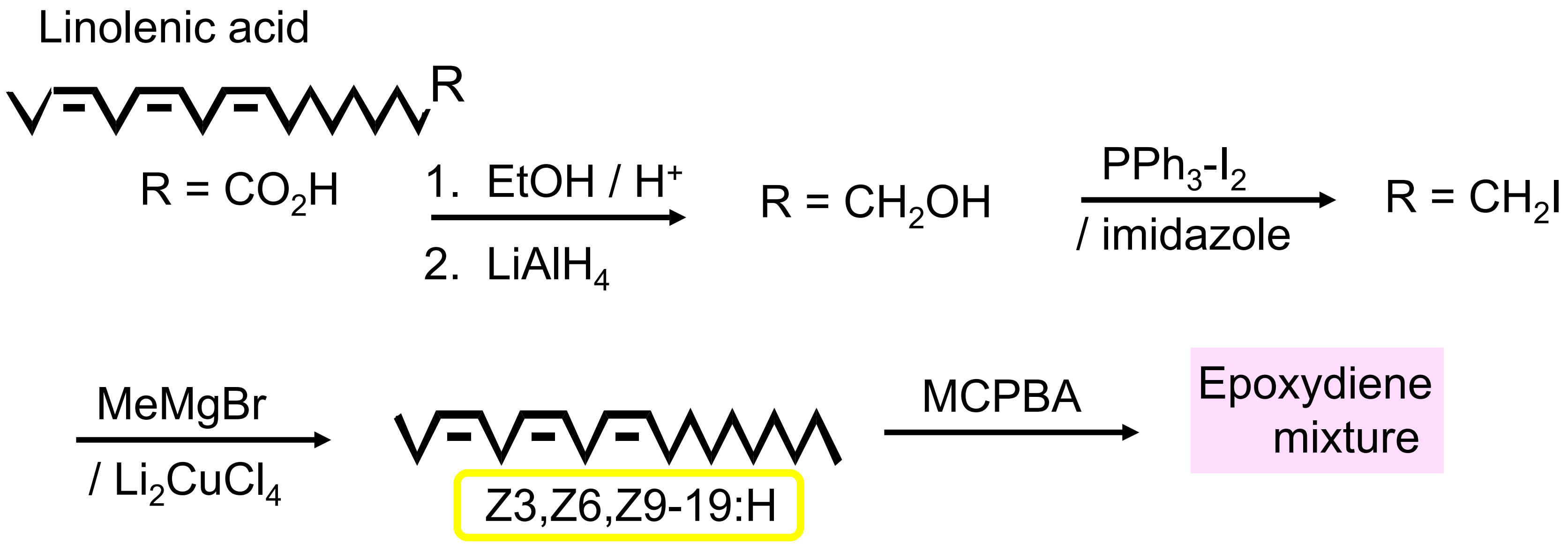
(6*Z*,9*Z*)-*cis*-3,4-epoxy-6,9-nonadecadiene

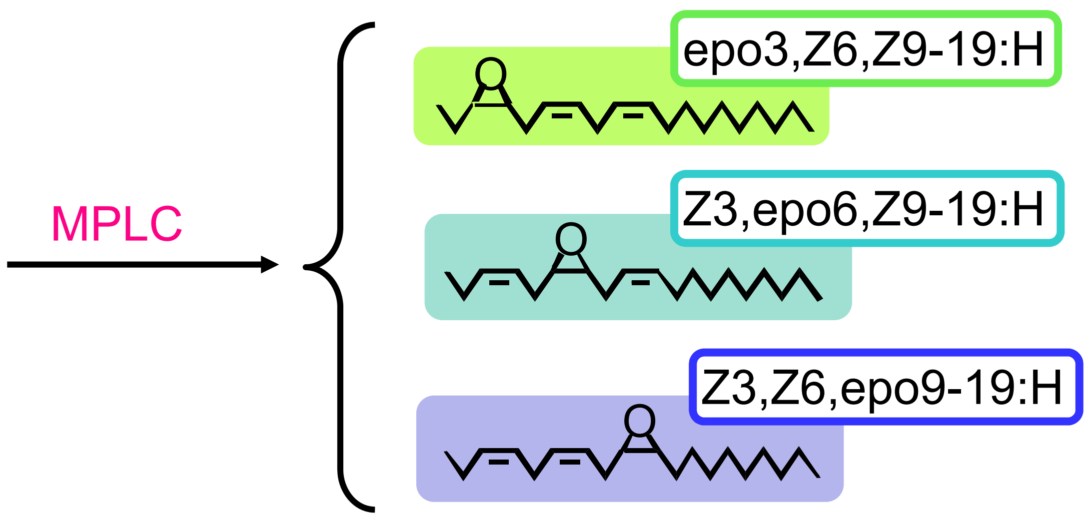


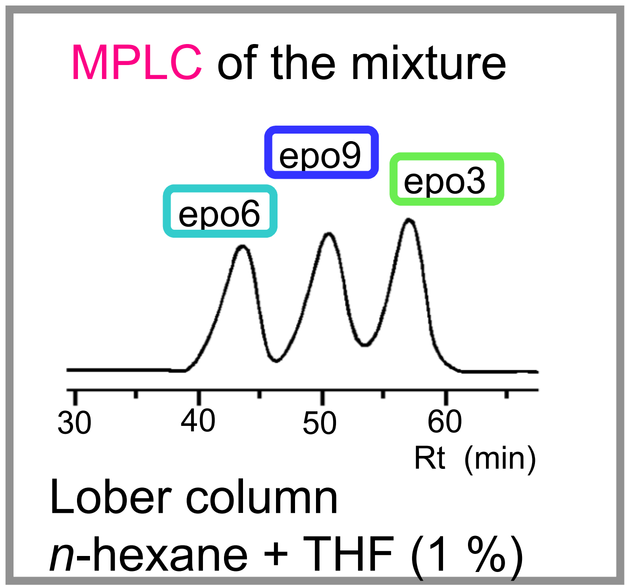
(3*Z*,6*Z*,9*Z*)-3,6,9-nonadecatriene



Synthesis of Type II pheromones (racemic mixture)



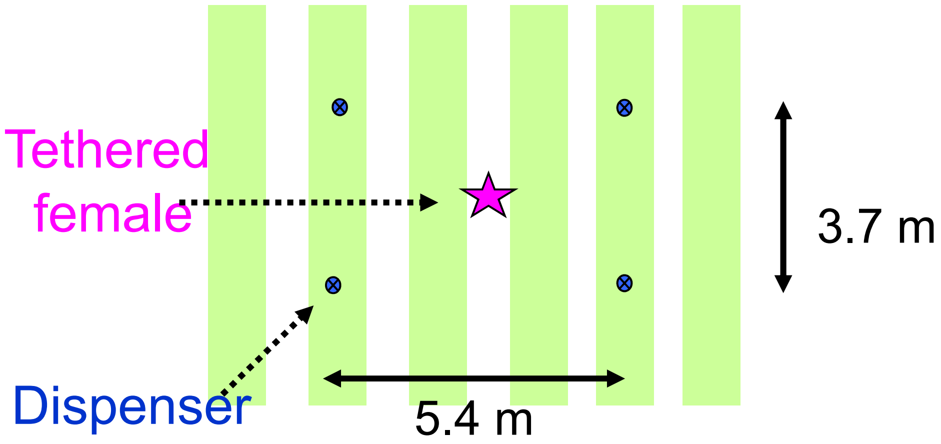




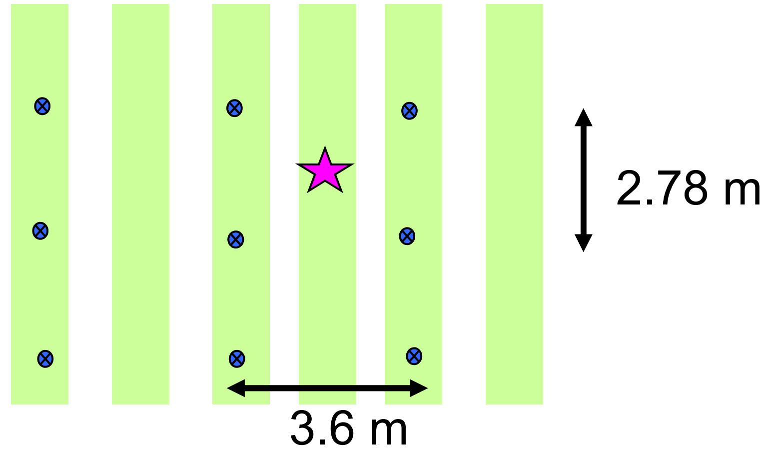
Mating disruption with a Type II pheromone ①

Field evaluation of dispenser: polyethylene tube including 80 mg chemical

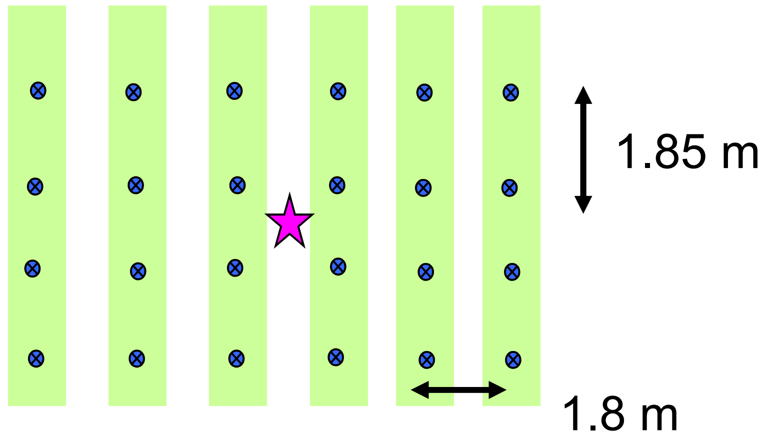
(i) 500 tubes / ha (16 tubes / 180 m²)



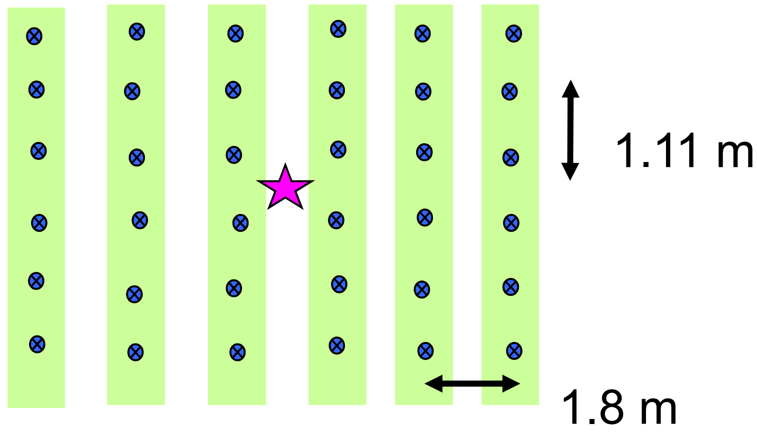
(ii) 1000 tubes / ha (16 tubes / 90 m²)



(iii) 3000 tubes / ha (48 tubes / 82 m²)



(iv) 5000 tubes / ha (48 tubes / 70 m²)



Evaporation of triene: 0.546 mg/tube/day

Evaporation of epoxydiene mixture : 0.386 mg/tube/day

Mating disruption with a Type II pheromone ②

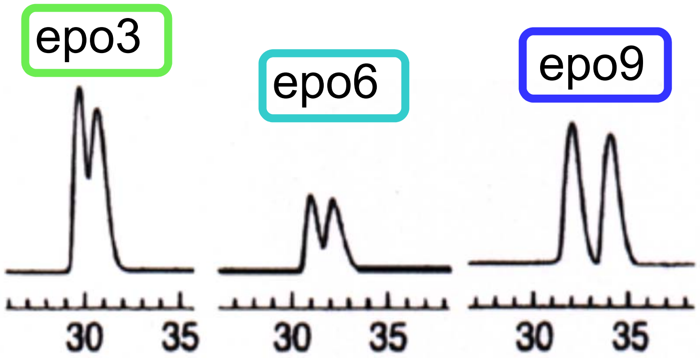
Mating ratios of tethered females in the tea gardens which were permeated with triene or an epoxydiene mixture released from dispensers（polythylene tubes)

Tubes (N / ha)	(A) Triene [a]			(B) Epoxydiene mixture [b]		
	No. of females		Mating ratio (%)	No. of females		Mating ratio (%)
	Tethered	Mated		Tethered	Mated	
0	11	11	100	14	14	100
250	-	-	-	13	3	23
500	10	6	60	14	4	29
1000	9	6	67	14	1	7
3000	10	8	80	12	0	0
5000	10	4	40	12	0	0

[a] Tested from Sept. 7 to 14, 1999. [b] Tested from Sept. 7 to 18, 1999.

Preparation of optical active epoxy dienes

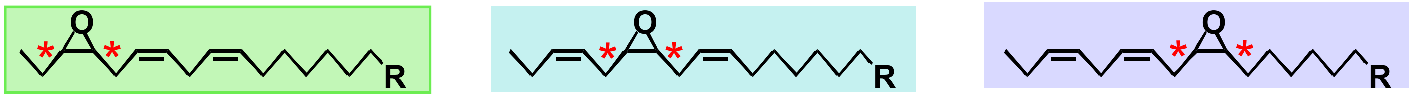
Resolution by enantioselective HPLC



Chiralpak AD

Normal phase

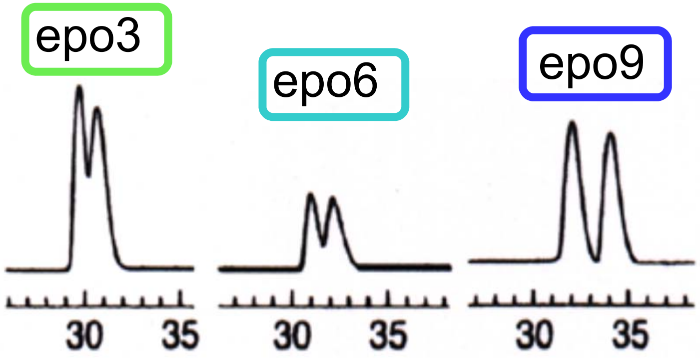
n-hexane +
2-propanol (0.1 %)



cis-Epoxides (* chiral center)

Preparation of optical active epoxy dienes

Resolution by enantioselective HPLC



Chiralpak AD

Normal phase

n-hexane +
2-propanol (0.1 %)

Determination of absolute configuration

epo3,Z6,Z9-19:H

(fraction 1)

3*S*,4*R*-isomer

1. MeOH / H^+
2. MPLC

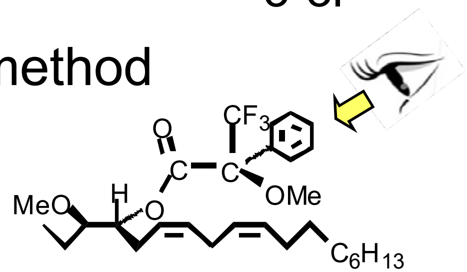
4-ol

esters of (*S*)- and (*R*)-MTPA ester

3-ol

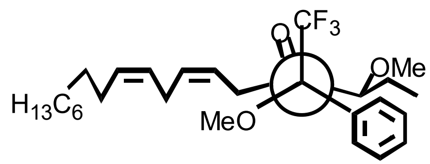
esters of (*S*)- and (*R*)-MTPA ester

Mosher's method



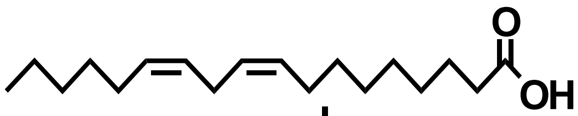
(*S*)-MTPA ester of 4-ol

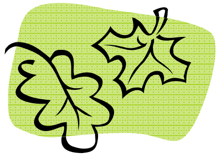
=



Diversity of Type II pheromones

Linoleic acid





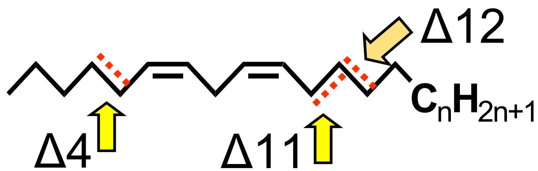
desaturation

Z6,Z9-dienes

E4,Z6,Z9-trienes
Z6,Z9,E11-trienes
Z6,Z9,Z12-trienes

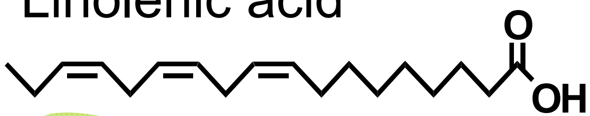
secretion

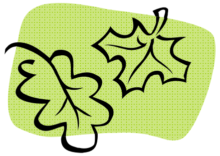
mono-
epoxides




emerald moth

Linolenic acid





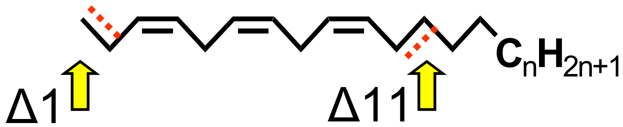
desaturation

Z3,Z6,Z9-trienes

1,Z3,Z6,Z9-tetraenes
Z3,Z6,Z9,E11-tetraenes
Z3,Z6,Z9,Z11-tetraenes

secretion

mono- and
di-epoxides

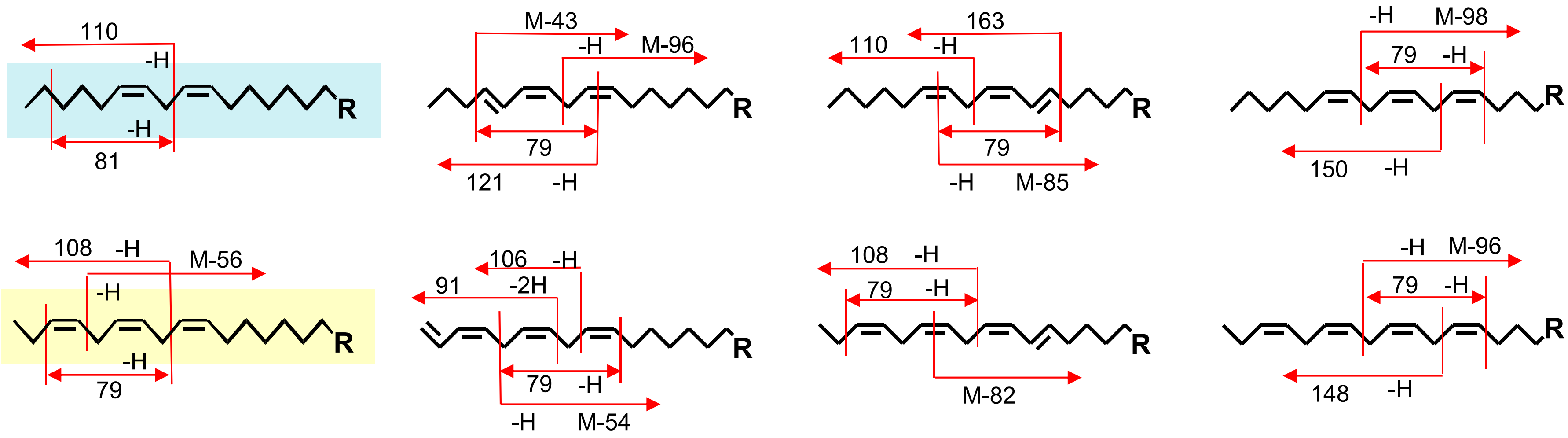


The known chemical diversity is still limited.
Novel compounds must be found.

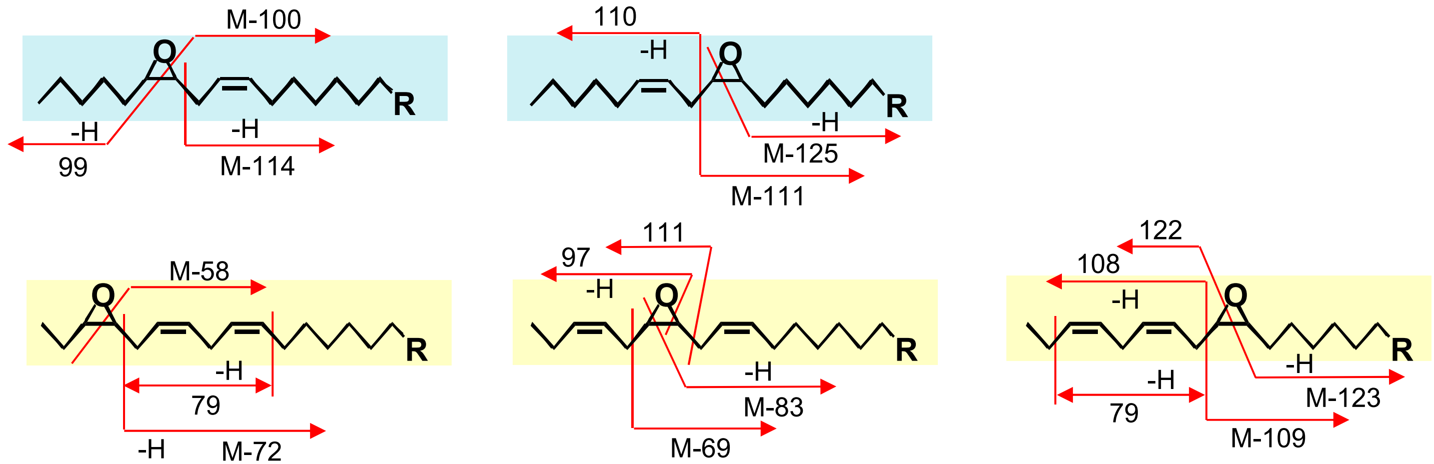
Z2,E4,Z6,Z9-21H

Diagnostic ions of Type II pheromones ①

(A)

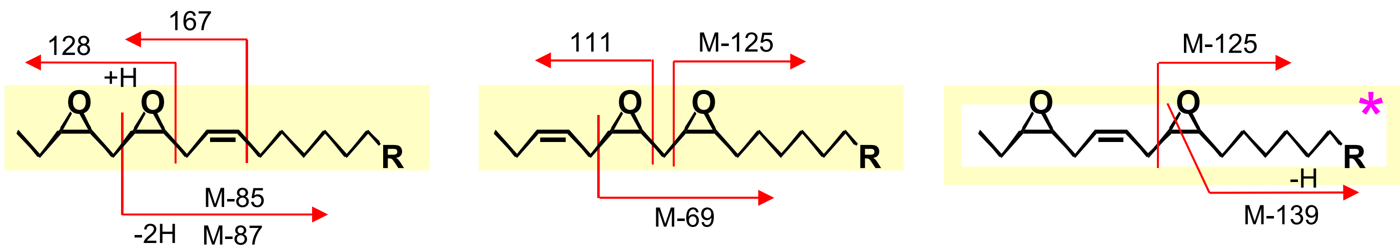


(B)

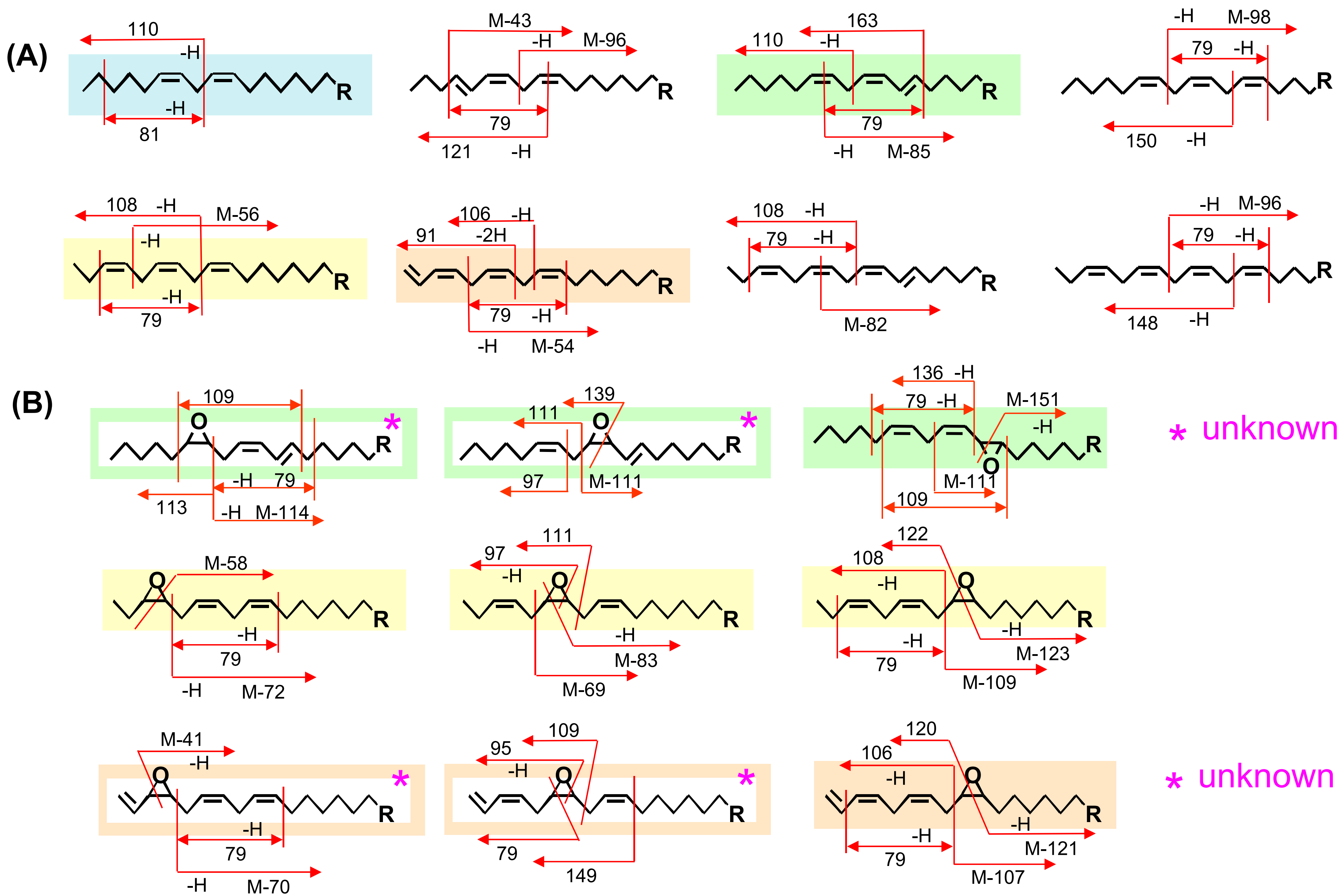


(C)

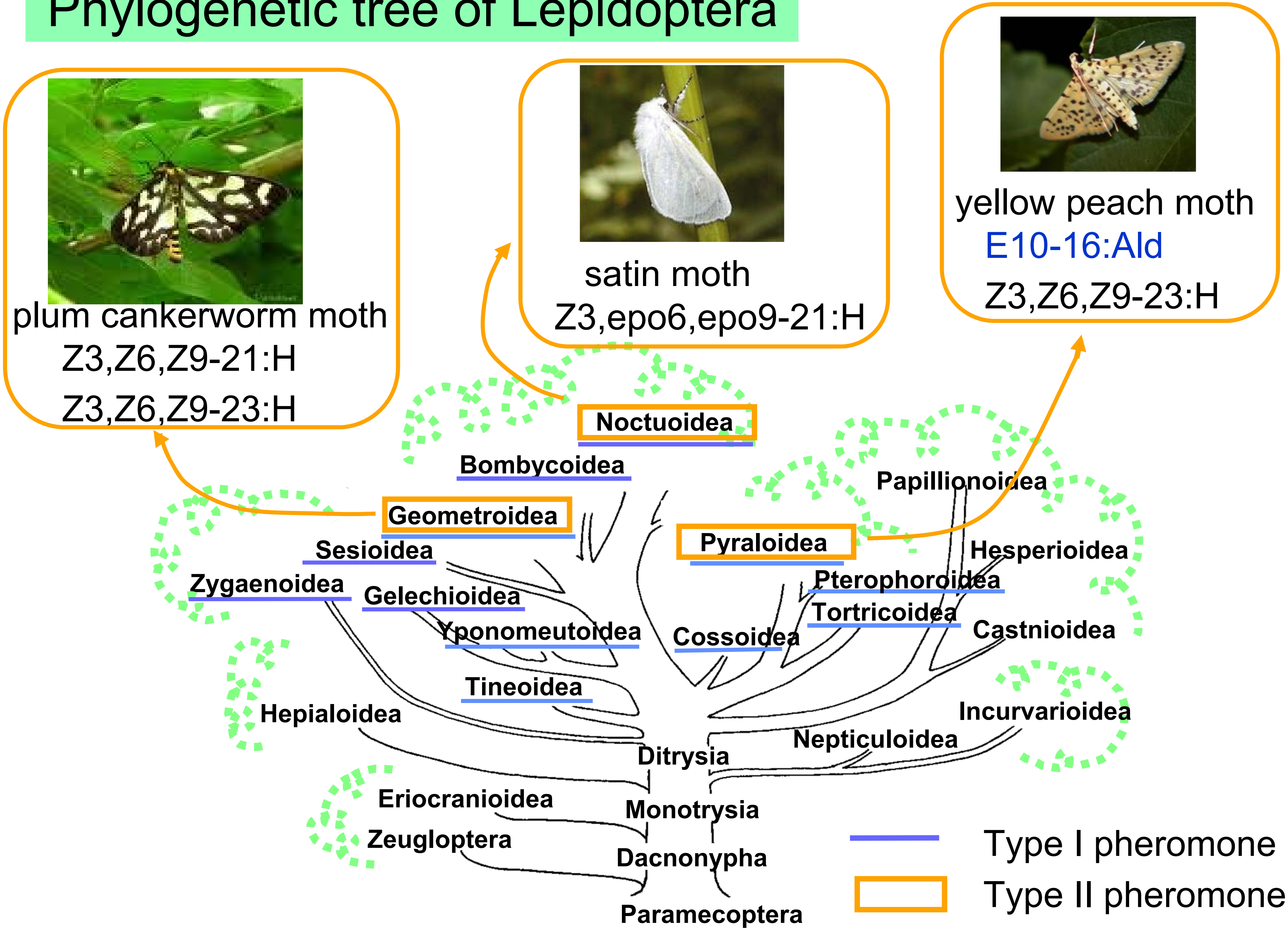
* unknown



Diagnostic ions of Type II pheromones ②



Phylogenetic tree of Lepidoptera



Lepidopteran Sex Pheromones: Wonderland for a Natural Product Chemist

1) Identification by collaboration with many entomologist

Systematic synthesis of pheromone analogues

Chemical analysis by GC-EAD and GC-MS

⇨ Diversity of Type I and II pheromones

https://lepipheromone.sakura.ne.jp/index_eng.html

2) Application

Monitoring and Mating disruption

3) Biosynthesis and its endocrine regulation

4) Methyl-branched pheromones ⇨ Type III ?

Pheromone biosynthesis

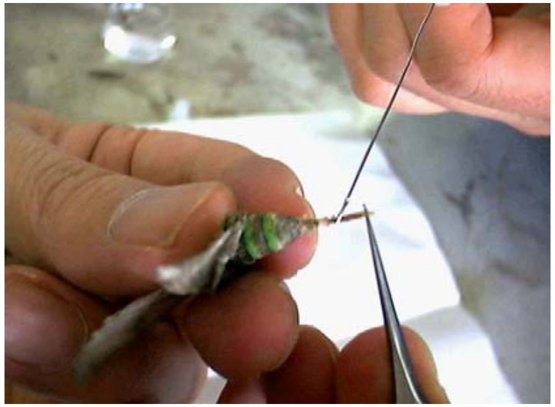
(A) How different between Type I and Type II pheromones?

➡ Determination of the biosynthetic pathways

Type I silkworm moth (Bombycidae)
chrysanthemum golden plusia (Noctuidae)

Type II giant looper (Geometridae)
fall webworm (Erebidae)

Synthesis of ^{14}C- or D-labeled precursors
→ Topical application to a pheromone gland
→ Counting of radioactivity
or GC-MS analysis



(B) How to apply the biosynthetic study?

➡ Block of the biosynthesis

Cyclopropenyl compound:
position-specific inhibitor of a desaturase

Biosynthetic pathways

Type I pheromone

* Step whose enzyme was cloned

<Silkworm moth>

pheromone gland

Acetyl-CoA → *de novo* → 16:Acyl

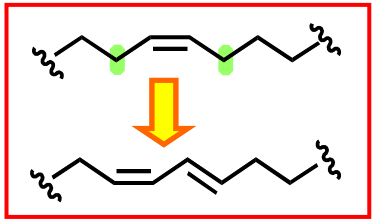
↓ Desaturation*

Z11-16:Acyl

↓

E10,Z12-16:Acyl → Reduction* → E10,Z12-16:OH → secretion

α,α'-desaturation



bombyko**l**

<Chrysanthemum golden plusia>

pheromone gland

Acetyl-CoA → *de novo* → 16:Acyl

↓ Desaturation

Z11-16:Acyl

β-Oxidation

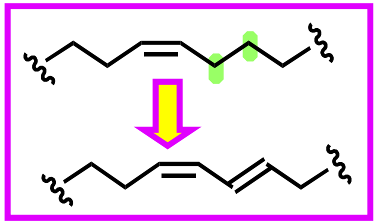
Z7-12:Acyl

Desaturation ↓

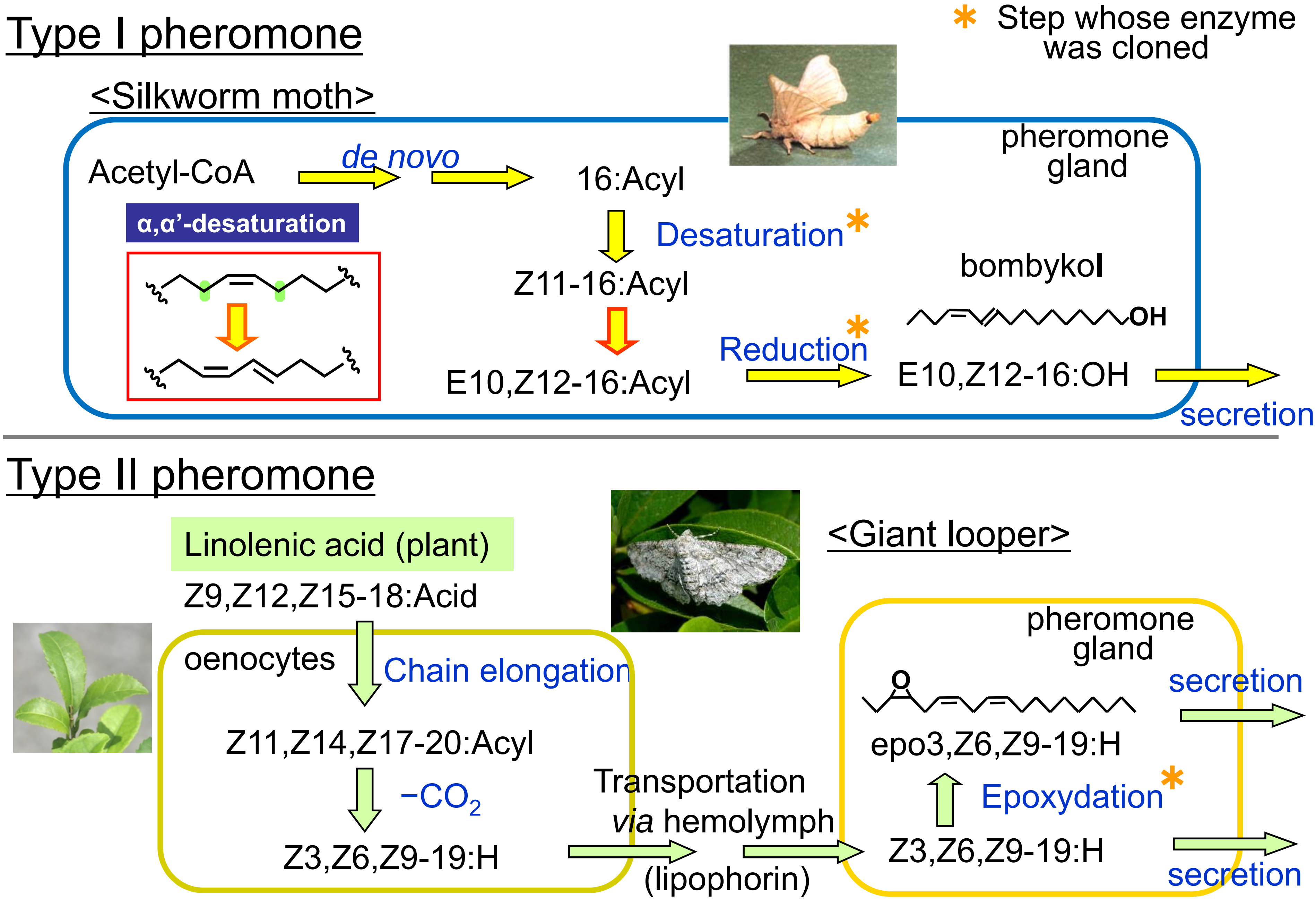
E5,Z7-12:Acyl → Reduction → Acetylation → E5,Z7-12:OAc

↓ secretion

α,β-desaturation

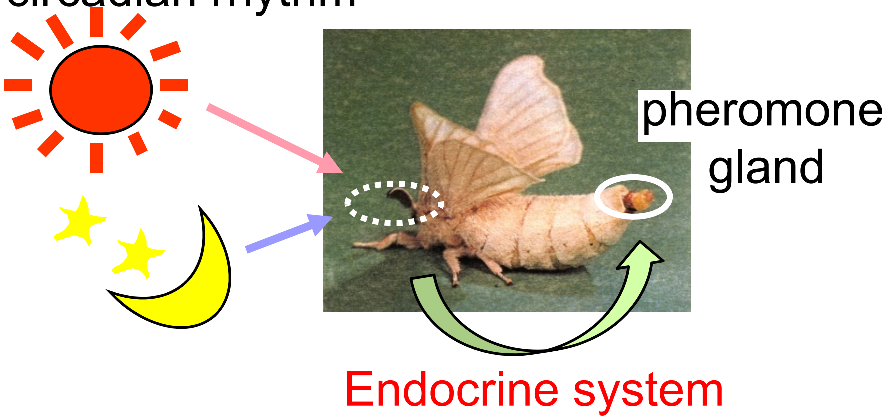


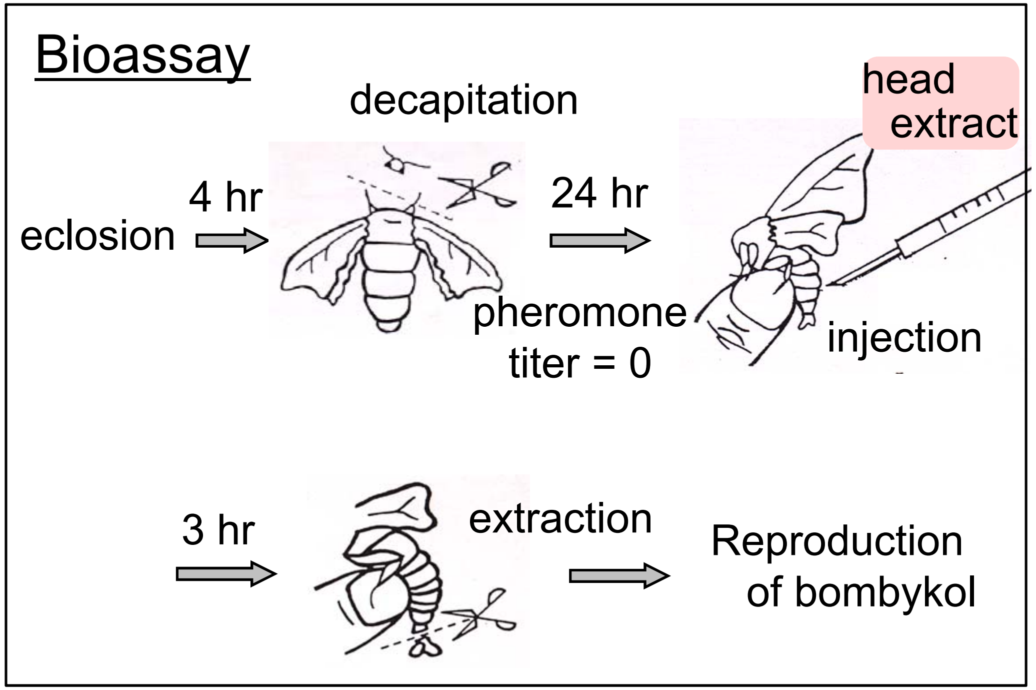
Biosynthetic pathways



PBAN

Pheromone **B**iosynthesis **A**ctivating **N**europeptide





Amino acid sequence of PBAN

		Amino acid identities
Type I		
Silkworm	**LSEDMPATPADQEMYQPDPEEMESRTRYFSPRL-NH_2**	76%
H. zea	**LSDDMPATPADQEMYRQDPEQIDSRTKYFSPRL-NH_2**	
Type II		44%
Giant looper	**QLVDDVPQRQQIEEDRLGSRTRFFSPRL-NH_2**	

Shorter by 5 amino acids

Essential active motif

Similarity is low, but the *N*-amidated terminal motif of 5 amino acids is conserved.

Activation steps by PBAN

Type I pheromone

<Silkworm moth>

pheromone gland

Acetyl-CoA → *de novo* → 16:Acyl

↓ Desaturation

Z11-16:Acyl

↓

E10,Z12-16:Acyl → PBAN, Reduction → E10,Z12-16:OH → secretion

bombykol

Type II pheromone

<Giant looper>

Linolenic acid (plant)

Z9,Z12,Z15-18:Acid

oenocyte

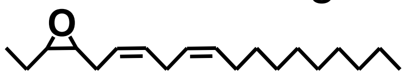
↓ Chain elongation

Z11,Z14,Z17-20:Acyl

↓ $-CO_2$

Z3,Z6,Z9-19:H → (lipophorin) → PBAN → Z3,Z6,Z9-19:H

pheromone gland



epo3,Z6,Z9-19:H

↑ Epoxydation

secretion

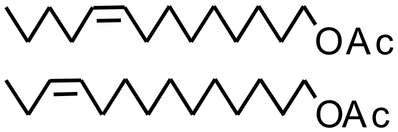
Summary

Type I

silkworm moth

bombykol

smaller tea tortrix



Type II

giant looper

giant geometrid

Biosynthetic pathway | **Endocrine regulation**

Acetyl-CoA
↓ *de novo*
Saturated acyl
↓ desaturation — 9-desaturase, 11-desaturase, 12-desarurase etc.
Unsaturated acyl
↓ Acyl reduction ⇐ PBAN

Linolenic acid
Linolic acid
↓ chain elongation
↓ $-CO_2$
Polyenyl hydrocarbon
↓ uptake by a gland ⇐ PBAN
↓ epoxidation — 3,4-epoxidase, 6,7-epoxydase etc.

1) The biosyntheses of Type I and II pheromones are quite different, and differently regulated by PBAN.
2) The pheromones in each group are biosynthesize by some common steps.
3) Structural diversity is mainly promoted by reaction selectivity of the desaturases in Type I and the epoxidases in Type II.

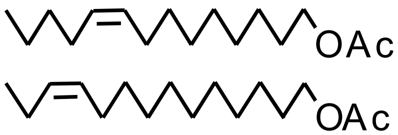
Summary

Type I

silkworm moth

bombykol

smaller tea tortrix



Biosynthetic pathway

Acetyl-CoA

↓ *de novo*

Saturated acyl

↓ desaturation

Unsaturated acyl

↓ Acyl reduction ⇐ PBAN

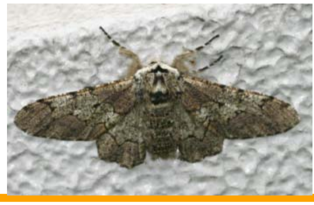
Endocrine regulation

9-desaturase
11-desaturase
12-desarurase
etc.

Type II

giant looper

giant geometrid



Linolenic acid
Linolic acid

↓ chain elongation

↓ $-CO_2$

Polyenyl hydrocarbon

↓ uptake by a gland ⇐ PBAN

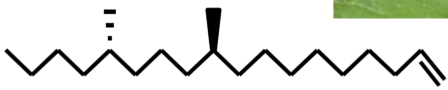
↓ epoxidation

3,4-epoxidase
6,7-epoxydase
etc.

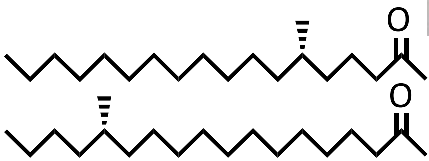
New interesting target to understand the diversity

Others

apple leafminer



Lyclene dharma



Methyl-branched hydrocarbons, ketones, secondary alcohols, and *etc*.

Lepidopteran Sex Pheromones:
Wonderland for a Natural Product Chemist

1) Identification by collaboration with many entomologist

Systematic synthesis of pheromone analogues

Chemical analysis by GC-EAD and GC-MS

⇨ Diversity of Type I and II pheromones

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Pheromones of lichen moth ①

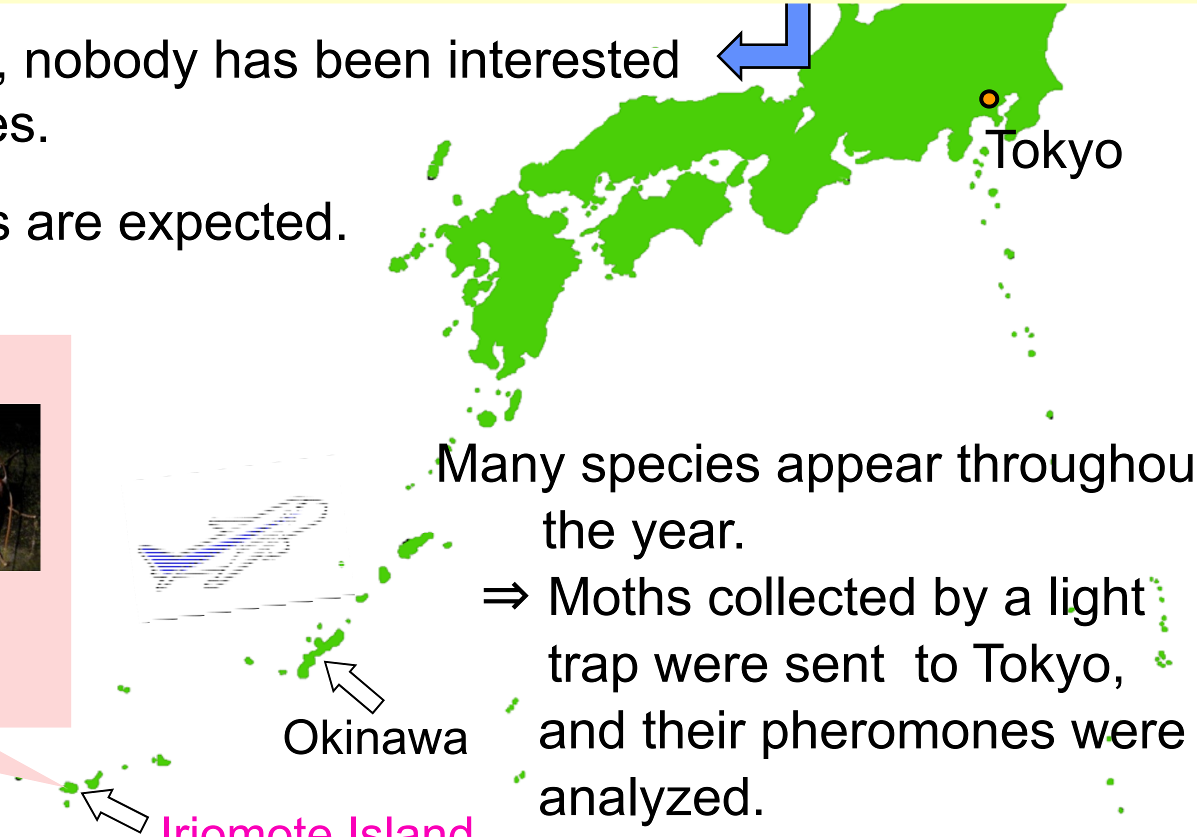
(Number of the species whose pheromones were known)

- Noctuoidea
  - Noctuidae (100)
  - Erebidae (69)
    - Lymantriinae (26)
    - Arctiinae (27)
      - Arctiini (24)
      - Synthomini (3)
      - Lithosiini (0)
  - Nolidae (1)
  - Notodontidae (9)

Because of harmless insects, nobody has been interested in their pheromones.

⇒ Novel pheromones are expected.

Lichen moths

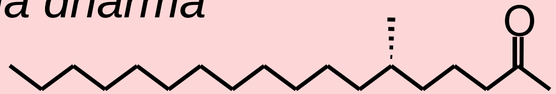


Many species appear throughout the year.

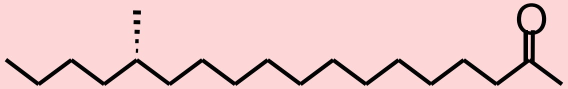
⇒ Moths collected by a light trap were sent to Tokyo, and their pheromones were analyzed.

Pheromones of lichen moth ②

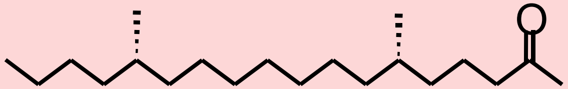
Lyclene dharma dharma



(S)-Me6-18:2-one

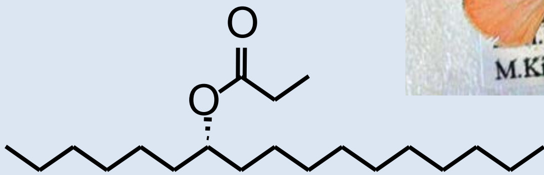


(S)-Me14-18:2-one

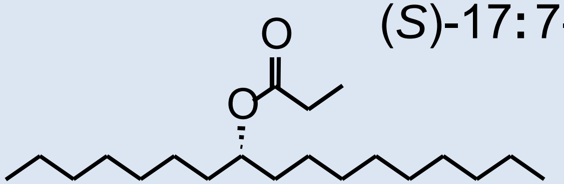


Me6,Me14-18:2-one

Barsine expressa

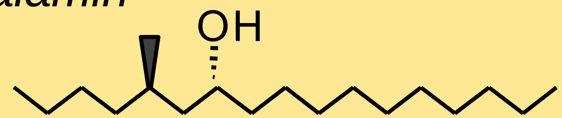


(S)-17:7-OPr



(S)-17:8-OPr

Miltochrista calamin



($5R,7R$)-Me5-17:7-OH

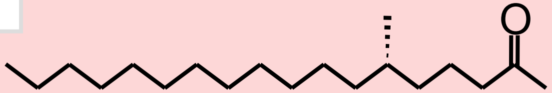
Each species produces the pheromone with a unique structure.

Pheromones of other species？

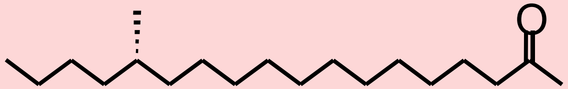
Methyl-branched 2-ketones acting as a pheromone

Lepidoptera

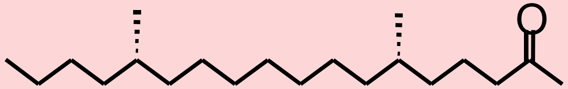
Lyclene dharma



(*S*)-Me6-18**:** 2-one



(S)-Me14-18**:** 2-one

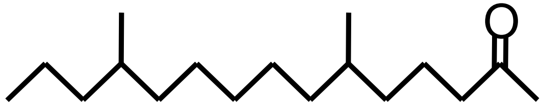


Me6,Me14-18**:** 2-one

Yamamoto *et al.* , *BBB* **71**: 2860 (2007)

Coleoptera

Diabrotica balteata
(banded cucumber beetle)



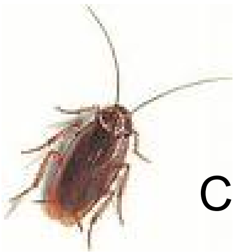
Me6,Me12-15**:** 2-one

Chuman *et al.* , *JCE* **13**: 1601 (1987)

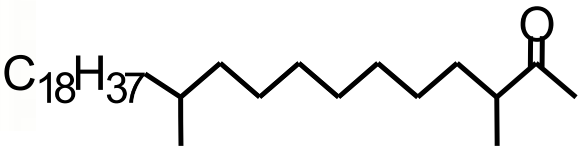
Diabrotica undecimpunctata
(spotted cucumber beetle)
Me10-13**:** 2-one

Guss *et al.* , *JCE* **9**: 1363 (1983)

Blattodea



Blattella germanica
(German cockroach)

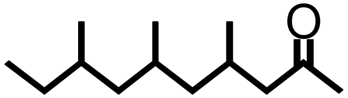


Me3,Me11-29**:** 2-one

Nishida *et al.* , *Experientia* **30**: 978 (1974)

Arachnida (Acari)

Chortoglyphus arcuatus
(storage mite)



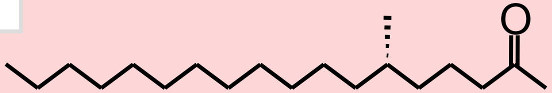
Me4,Me6,Me8-10**:** 2-one
chortolure

Schulz *et al.* , *Chembiochem* **5**: 1500 (2004)

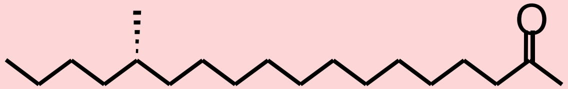
Methyl-branched 2-ketones acting as a pheromone

Lepidoptera

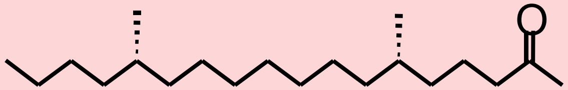
Lyclene dharma



(*S*)-Me6-18**:** 2-one



(S)-Me14-18**:** 2-one

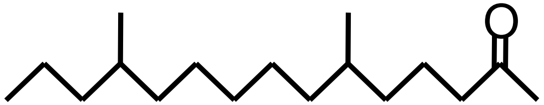


Me6,Me14-18**:** 2-one

Yamamoto e…

Coleoptera

Diabrotica balteata
(banded cucumber beetle)



Me6,Me12-15**:** 2-one

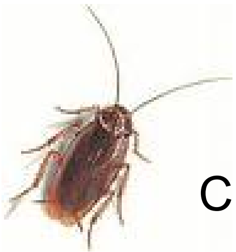
Chuman *et al.* , *JCE* **13**: 1601 (1987)

Diabrotica undecimpunctata
…etle)
…e
…3 (1983)

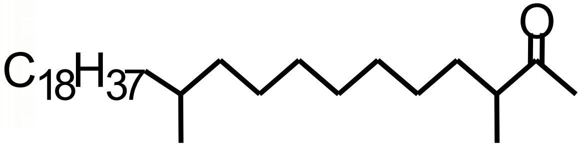
"Propanogenins"

formed by incorporation of propanoate units derived from methylmalonyl-CoA

Blattodea



Blat… …
(German cockroach)



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Arachnida (Acari)

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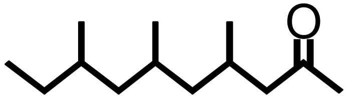
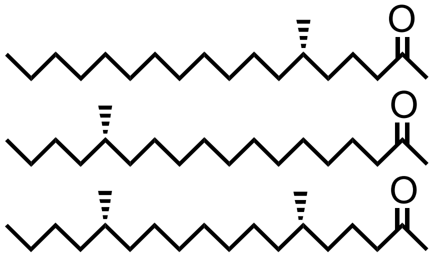


Me4,Me6,Me8-10**:** 2-one
chortolure

Schulz *et al.* , *Chembiochem* **5**: 1500 (2004)

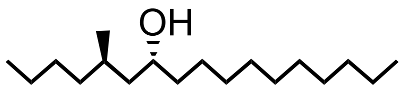
Methyl-branched sex pheromones of Lepidoptera

Lichen moths inhabiting Iriomote Island



Adachi *et al.*, 2010, *JCE*, **36**, 814

Lyclene dharma



Yamakawa *et al.*, 2011, *Tetrahedron Lett.*, **52**, 5808

Miltochrista calamina

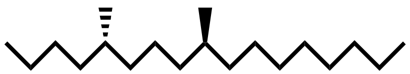
Leafminer moths (Lyonetiidae)

peach leafminer

Sugiei *et al.*, 1984, *AEZ*, **36**, 814

apple leafminer

Gries *et al.*, 1997, *JCE*, **23**, 1119



mountain-ash bentwing

Francke *et al.*, 1987, *Naturwiss.*, **74**, 143

Hemlock looper (Geometridae)

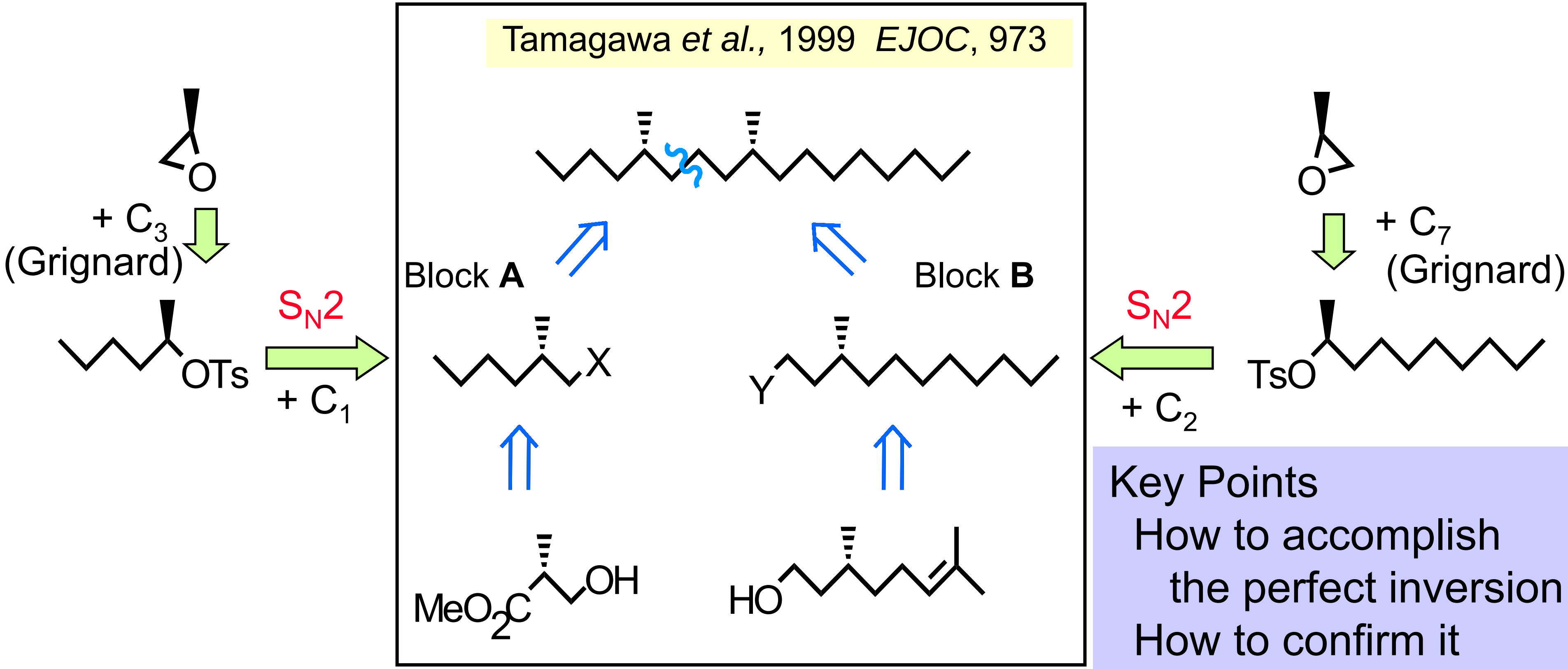
Gries *et al.*, 1991, *Naturwiss.*., **78**, 315

Gries *et al.*, 1993, *JCE*, **19**, 1501

Bagworm moth (Psychidae)

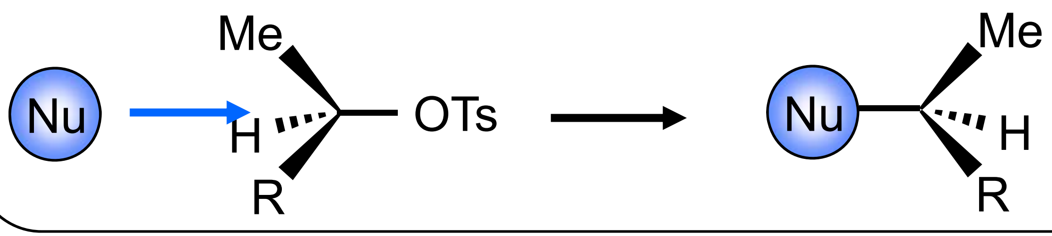
Gries *et al.*, 2006, *JCE*, **32**, 1673

Synthetic strategy for 5,9-dimethyl compounds



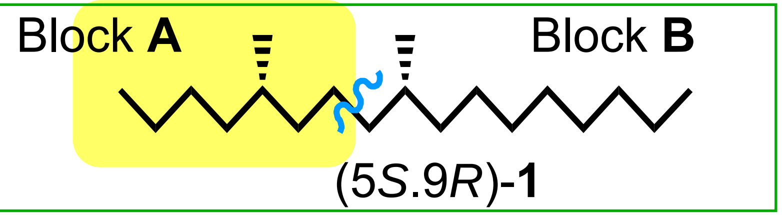
Key Points
How to accomplish the perfect inversion
How to confirm it

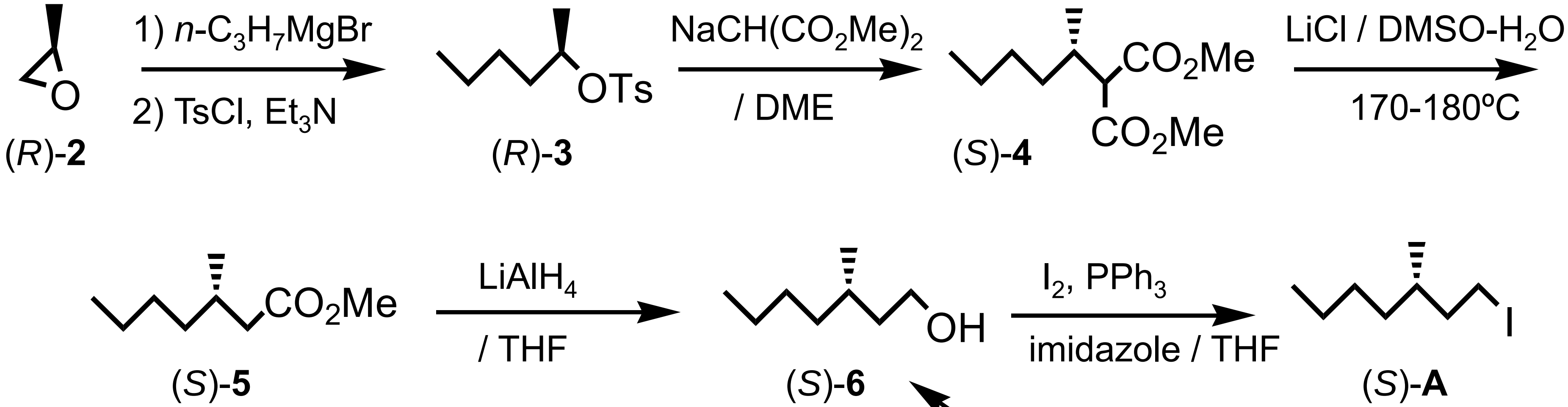
S_N2 reaction between a secondary tosylate and a carbanion associates with stereospecific inversion.

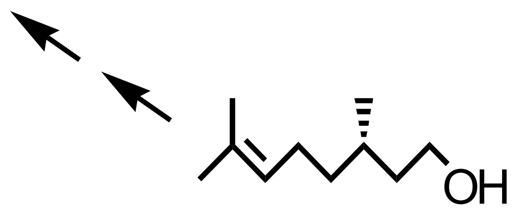


OTs : leaving group
Nu : nucleophile (carbanion)

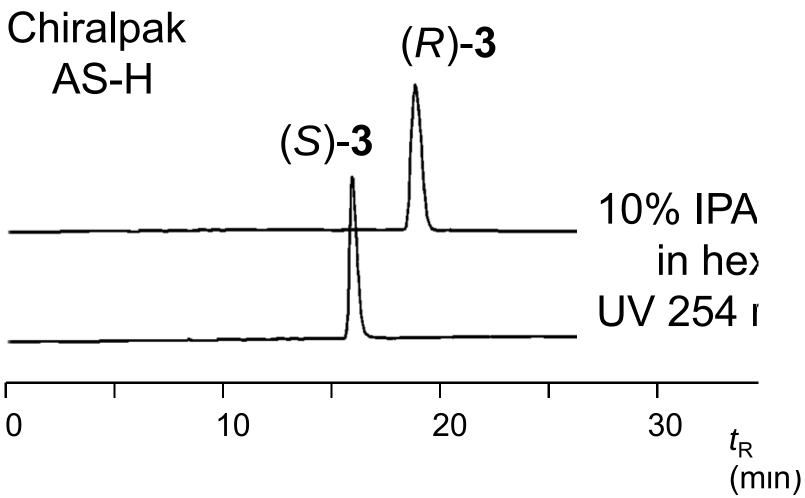
Synthesis of the chiral block A

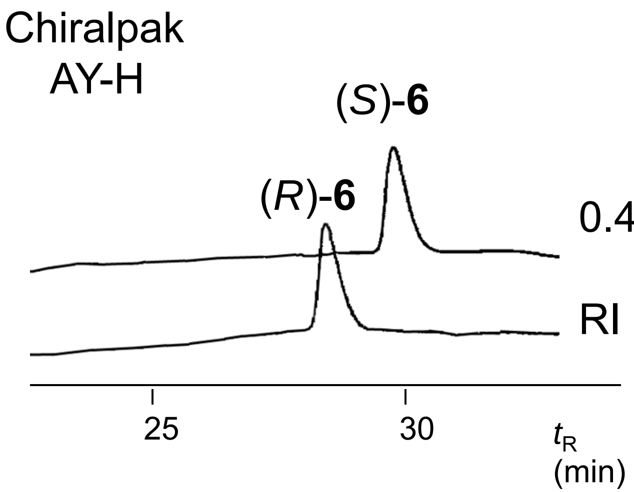






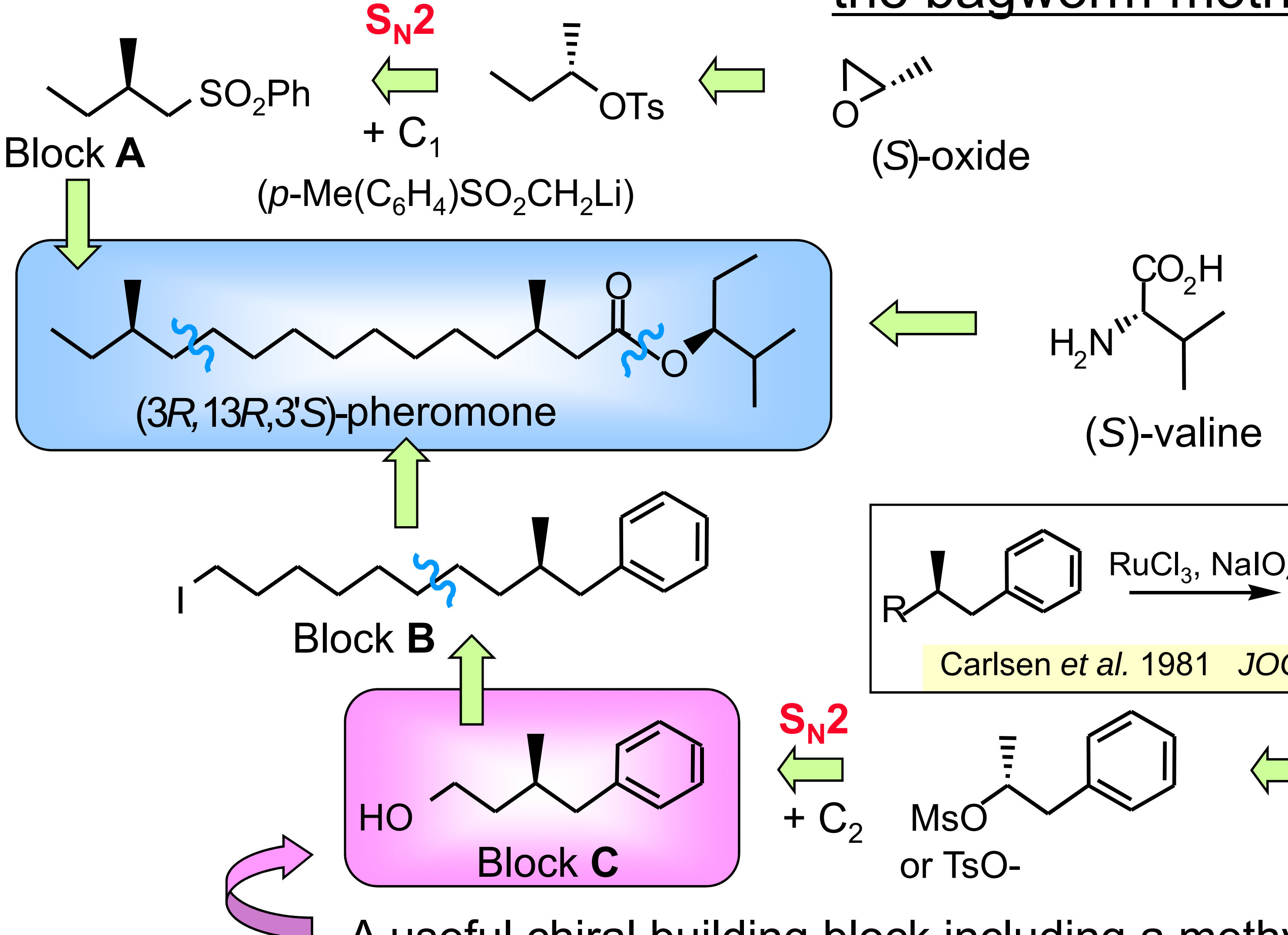
Enantioselective HPLC Analysis





Application of the S_N2 Reaction

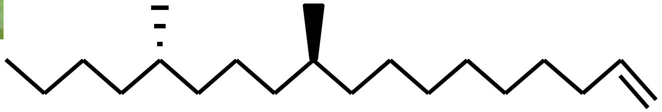
Synthesis of a 1,11-dimethyl pheromone produced by the bagworm moth



A useful chiral building block including a methyl branch between two functional groups

Biosynthesis of methyl-branched pheromones

Δ1,Me10,Me14-18:H



Me6,Me14-18:2-one

Propanogenins: formed by incorporation of propanoate units derived from methylmalonyl-CoA

The biosynthesis is still an untouched research area.

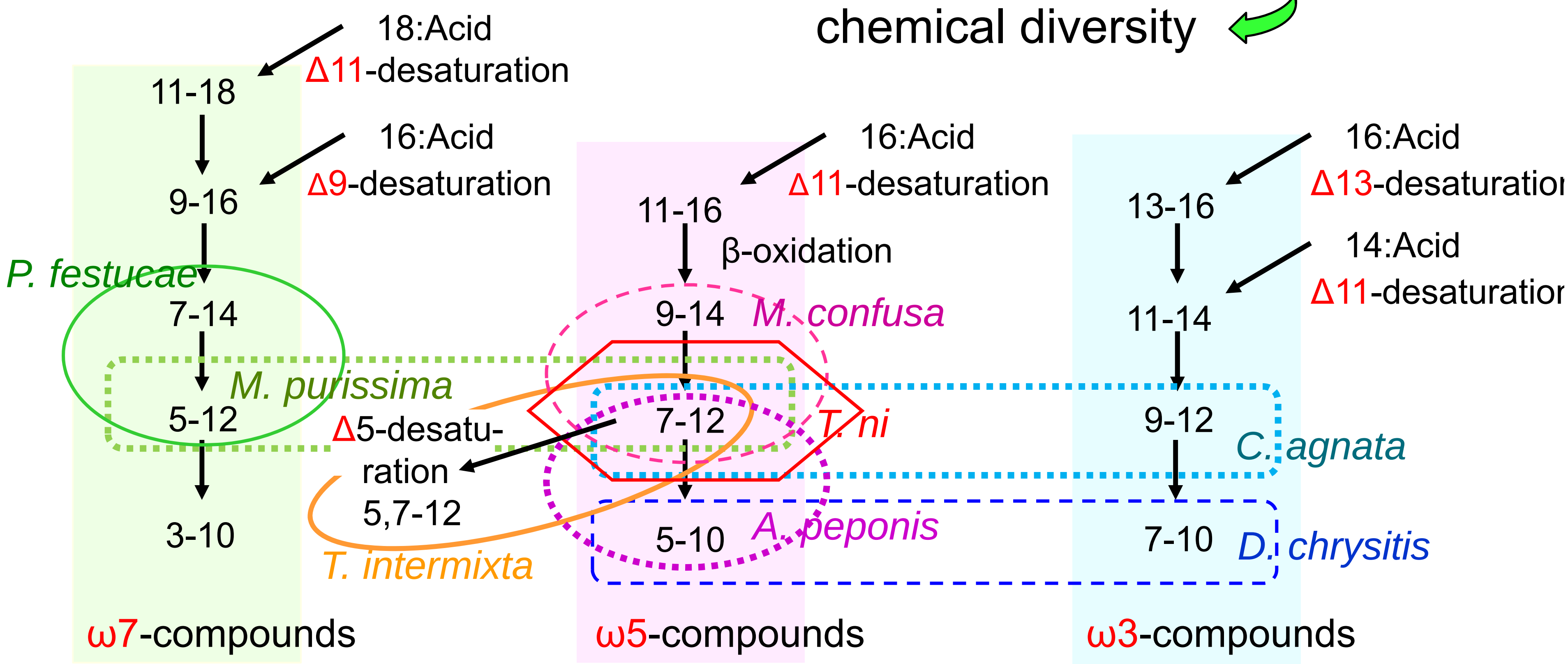
Future expected studies

1) How is the branched skeleton constructed?
   PKS (polyketide synthase) or FAS (fatty acid synthase)?
2) How is a specific configuration introduced at the branched position?
3) How are the functional groups created?
4) Which organs produce them, pheromone gland or oenocytes?
5) Is there a circadian rhythm? Is PBAN involved in the biosynthesis?

Selection of optimal species, which can be used for these researches

Pheromone-dependent speciation

Biosynthetic pathways of Plusiinae pheromones



The birth of a new species

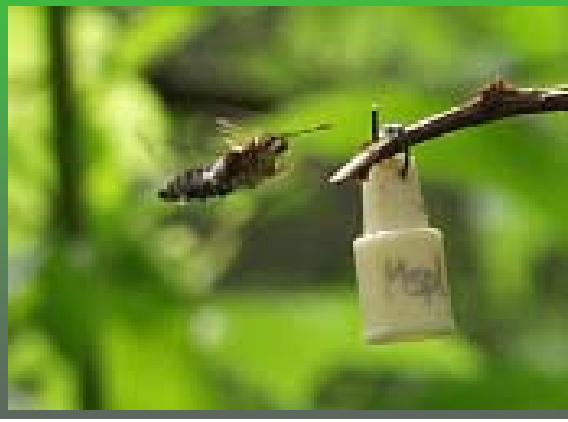
♀: Mutation of a pheromone biosynthesis system
♂: Mutation of a pheromone receptor system

synchronized

⇦ Actually happened in a long history

Acknowledgments

The University of Tokyo: Drs. A. Suzuki, H. Nagasawa,
S. Tatsuki, Y. Ishikawa, & Y. Rong
The Inst. of Chem. & Phys. Res.: Drs. S. Matsumoto & K. Moto
University of Osaka Prefecture: Dr. H. Kuroko
Osaka University of Arts: Dr. F. Komai
Tottori University: Dr. H. Naka
University of Ryukyus: Drs. M. Kinjo, Y. Terashima & H. Tatsuta
University of Tsukuba: Drs. H. Honda & T. Uehara
Nat. Inst. of Sericult. & Entomol. Sci.: Drs. S. Wakamura & H. Yasui
Shin-Etsu Chemical Company: Drs. F. Mochizuki & T. Hukumoto
Other many collaborators



Thank you for your attention!!

Chemical Ecology Laboratory of TUAT (1982-2015)

PhD students

Dr. X.-R. QI
Dr. Wijaksono
Dr. M. Yamamoto
Dr. S. Inomata
Dr. S.-J. Lee
Dr. H. Yamazawa
Dr. A. Ono

Dr. H. Watanabe
Dr. W. Wei
Dr. T. Mouri
Dr. S.-J. Lee
Dr. L. V. Vang
Dr. T. Fujii
Dr. T. Kawai

Dr. K. Matsuoka
Dr. MD A. Islam
Dr. R. Yamakawa
Dr. J. Suzuki
Dr. N. D. Do
Dr. T. Taguri
Dr . Q. Yan