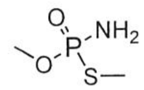
091028
Lit. Seminar
Y.Morikawa
M2 Part

Pesticide

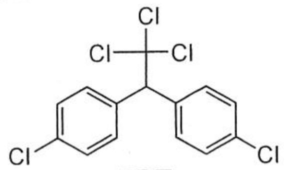
~From the position between comsumer and chemist~

Contents

§1 Introduction



methamidophos



DDT

1-1 Introduction

What is pesticide?

In Japan, of course, a series of chemicals are calssed as pesticides by law
Moreover, also food ($NaHCO_3$, binegar), some insects (bees, beetles, bugs...), animals (ducks, carp...) and bacterium are classed as pesticide by law.

However, in Japan, methamidophos (Tamaron(c), Monitor(c)), DDT or another poisonous chemicals are not classed as a pesticides.

There are large gap between pesticide in law and recognition of consumer.
And some natural compound pestisides has unique structure so its synthesis is very challenging.
Today, I want to talk about pesticide from these two topic.

1-2 Meaning of Pesticide

- For high yield harvest. -- Deal with the population explosion.

- For human's health.
  There are two face.
  1. To make the less toxic plants.
     -- Plants synthesize the toxic chemicals when...
       i) Using defense mechanism against incests, bacteria...
       ii) Infected with bacteia which causes disease.

  2. To kill the disease-causing insects or microorganisms.

1-3 Compare with Medicine

Medicine		Pesticide
At latest B.C.4000	Origin	At latest B.C.1000 (Sulfur)
A.D. 414 (From Korea)	Orign in Japan	A.D.1670 (Whale Oil)
薬事法 (From Edo era)	Law	農薬取締法 (A.D.1948)
Ministry of Health, Labour and Welfare	Ministry	The Ministry of Agriculture, Forestry and Fisheries Ministry of the Environment
Medicines Quasi drugs Cosmetics Devices	Target of law	Chemicals or natural enemies which prevent the loss of agricultural products. Plant growth regulator. cf. Fertilizer : 肥料取締法 Post-hervest application : 食品衛生法
Ten and some years. Some billion dollars.	R&D cost	Almost ten years. Some hundreds of million dollars. Test : 独立行政法人農林水産消費安全技術センター
Recognition system Re-examination : 4 - 10 years. Re-evaluation : Each 5 years.	System	Resistration system Expiration date : 3 years.
Recognition is easier than new medicine.	Generic	Test of resistration is same as new pesticides.

There are no or few report which says the cost problem of medicine's re-examination or re-evaluation.
On the other hand, resitration system of pesticide has the cost problem, so many pesticides were expired.
In Japan, 21,000 pesticides have been resistered, but 16,000 pesticides were expired. Only 21 pesticides were expired because of problem of its safety, others were expired because of no re-resistration.

In addition to that, pesticide's resistration system is obstale of generic.
Generic pesticide needs almost same test of new pesticide.

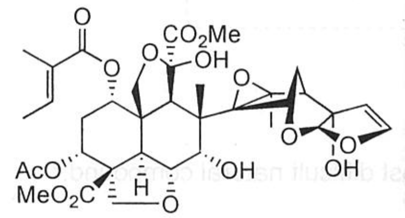
Sales

1 Pfizer (Pfizer + Wyeth)	63,000	1 Bayer (Bayer + Aventis + 塩野義)	7,000
2 Merck (Merck + Schering-Plough)	42,000	1 Syngenta (Zeneca + Novartis)	7,000
3 Sanofi-Aventis	39,000		
4 Glaxo SmithKline	38,000	3 BASF (Chemical Company)	4,000
5 F. Hoffmann-La Roche	36,000	4 Monsanto (BioChemical Company)	3,000
6 Novartis	35,000	5 Dow (Chemical Company)	3,000
7 Astra Zeneca	31,000	6 DuPont (Chemical Company)	2,000
8 Johnson & Johnson	25,000	7 Makhteshim-Agan Industories	1,500
9 Eli Lilly	19,000	8 住友化学 (住友＋武田)	1,500
武田薬品工業	13,000	三井化学アグロ（三井＋三共）	
Market Scale (World)	700,000	Market Scale (World)	40,000
(Japan)	70,000	(Japan)	3,000

Unit : million$

§2 Synthesis of Pesticides

2-1 Azadirachtin



azadirachtin

Isoration : from seeds of *Azadirachta indica* in 1968.

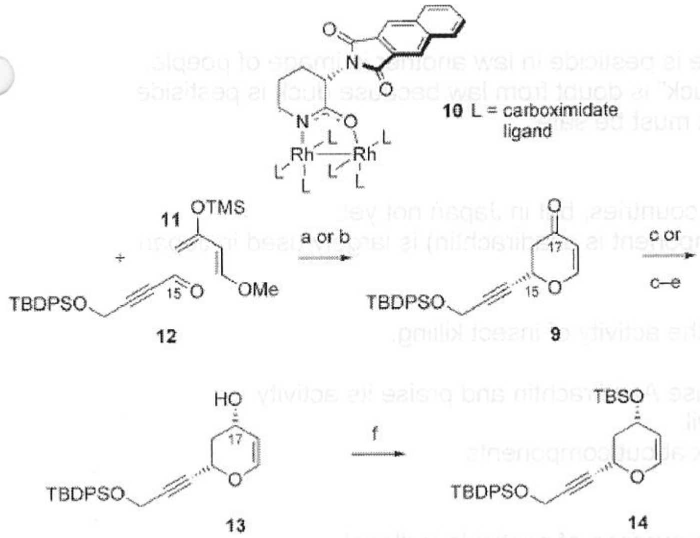
Structure : triterpenoid, 16 asymmetric carbons (4 of them are quaternary)
correct structure was proposed in 1986.

Activity : feeding deterrent for some insects.
growth disruptant for most insects.
non-toxic for vertebrates.

Synthesis : Ley S. V. et al., *ACIE*, 2007, *46*, 7629-7632 in 64 steps.
(See Mr.Kimura's Lit. Seminar on 080109)

2-1-1 2nd generation synthesis

Recently, Ley published the beginning of second generation synthesis.
Ley S. V. et al., *ACIE*, 2009, *48*, 1317-1320



[α]D = +70 (90% *ee* from catalyst)
[α]D = +75 (>98% *ee* from resolution)

Scheme 3. Preparation of enol ether 14. a) 10 (2.5 mol%), CH_2Cl_2, −60°C; then TFA, RT, 90% *ee*, 77% (over 2 steps); b) $ZnCl_2$, CH_2Cl_2, 0°C to RT, 86% (over 2 steps); c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, EtOH, −115 to −90°C, 83%; d) Ac_2O, NEt_3, CH_2Cl_2, RT, 96%; e) PS "Amano" lipase (*Burkholderia cepacia*), aqueous pH 7 buffer/acetone (9:1), RT, 43% (45% recovered acetate); f) TBSCl, imidazole, CH_2Cl_2, RT, 95%.

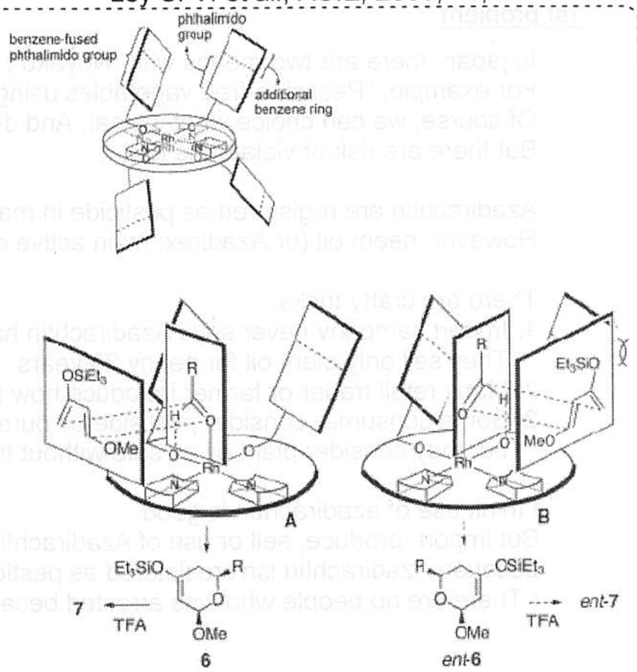
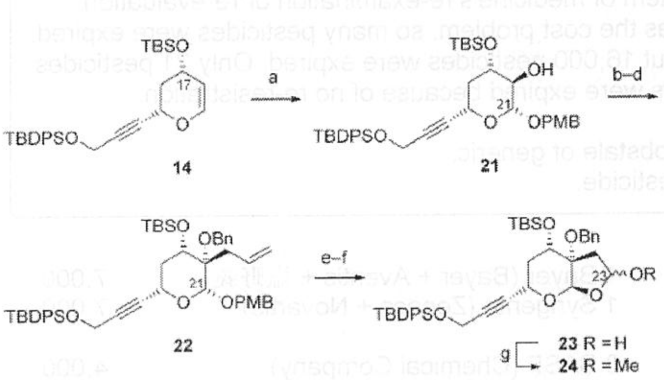
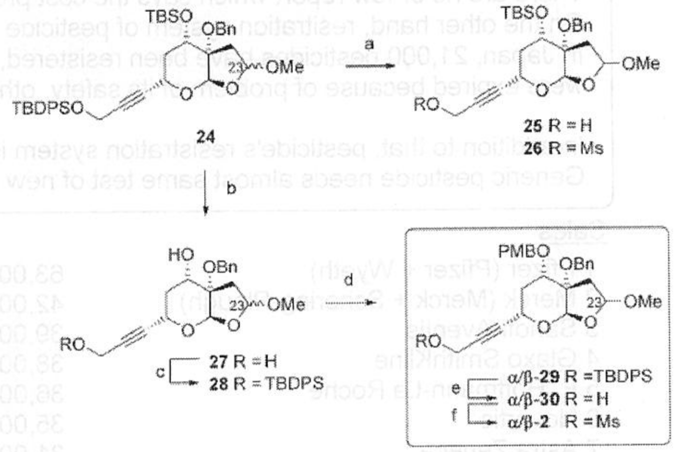


Figure 2. Plausible stereochemical pathway.

Shuichi Hashimoto et al.,
Angew. Chem., 2004, *116*, 2719-2722



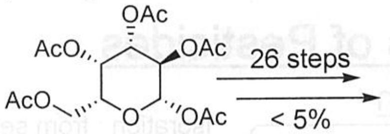
Scheme 6. Completion of the core for propargylic mesylate 2: a) DMDO, acetone/CH_2Cl_2 (1:1), 0°C; then PMBOH, $ZnCl_2$, CH_2Cl_2, 0°C to RT, 86%; b) Dess–Martin periodinane, CH_2Cl_2, RT; c) (allyl)MgBr, THF, −110°C; d) NaH, BnBr, DMF, 0°C to RT, 52% (over 3 steps); e) O_3, CH_2Cl_2, −78°C; then PS–PPh_3, RT; f) CH_2Cl_2 (90 ppm water)/TFA (9:1), RT; g) Amberlyst A-15, molecular sieves (3 Å), MeOH/MeCN (1:10), RT, 1:1 to 1:5 (α/β) mixture of C23-epimers. PS = polystyrene supported.



Scheme 7. Final steps in the second-generation synthesis of propargylic mesylate fragments 2 and 26: a) TBAF, THF, RT, 39% (over 4 steps); b) TBAF, THF, RT, 39% (over 4 steps); c) TBDPSCl, imidazole, CH_2Cl_2, RT, 87%; d) NaH, PMBBr, nBu_4NI, DMF, 0°C to RT, 26% α-29, 52% β-29; e) TBAF, THF, RT, 96% α-30; 84% β-30; f) Ms_2O, iPr_2NEt, CH_2Cl_2, 0°C, 90%. TBAF = tetra-*n*-butylammonium fluoride.

1% in 17 steps

cf) First generation



2-1-2 Problem of Azadirachtin

From synthetic position, Azadirachtin was said as "20th century's most difficult natural compound."

But from the pesticide's position, this compond was already used in farm for many many years because, we can harvest 9.0 kg of azadirachtin from a hactar.

And Azadirachtin has another face -- it may well be said as "Symbol of pesticide problem."

1st problem

In japan, there are two means with "Noyaku", one is pesticide in law another is image of poeple.
For example, "Pesticide-free vagetables using duck" is doubt from law because duck is pestiside.
Of course, we can choice what we eat. And duck must be safe.
But there are risk of violate the law.

Azadirachtin are registered as pesticide in many countries, but in Japan not yet.
However, neem oil (or Azadirex; main active component is azadirachtin) is largely used in Japan.

There are crafty tricks.
1. Import campany never says Azadirachtin has the activity of insect killing.
   They sell only plant oil for nearly 20 years.
2. Many retali trader or farmer introduce how to use Azadirachtin and praise its activity.
3. Some consumer consider pestiside as pure evil,
   but they consider plant oil as safe without think about components.

I think use of azadirachtin is good.
But import, produce, sell or use of Azadirachtin in purpose of pesticide is illegal because Azadirachtin isn't resistered as pesticide.
(There are no people who was arrested because of non-registered pesticide.)

2nd problem (from opposite side)

Table 1
Comparison of azadirex with pyrethrum, noting some of the advantages and disadvantages of azadirex in production and use

Property	Pyrethrum §2-3	Azadirex §2-1	Advantage?
Source	Flowers	Seeds	
Countries where grown	About 10	About 80	+
Soil requirements	Rich volcanic	Poor, low fertility	+
Water requirement	High	Low	+
Replanting	Every 4 years	Permanent plants	
Harvesting	Every 2 weeks	Once a year	–
Processing method	Solvent extraction	Solvent extraction	
Processing ease	Simple	Complex	–
Yield per hectare	55 kg dried flowers	2000 kg seeds[a]	+
Active concentration	1–2% in dried flowers	0.45% in seed kernels[b]	+
Actives per hectare	0.55–1.1 kg ha^{-1}	9.0 kg ha^{-1}	+
Price per kg	US$1 dried flowers	US$2 dry seeds	– –
Gross income per hectare	$55–110	$4000	++
Number of compounds	6	10+	
Effectiveness of compounds	Varies widely	Varies widely	
Range of insects	Very wide	Very wide	
Speed of action	Very rapid	Very slow	
Systemic action in plant	No	Yes	+
Beneficial insects	Toxic	Non-toxic[c]	+
Toxicity to others	Very toxic to fish, slight to birds	Non-toxic	+
LD_{50}	500–1000 mg/kg rats	>3540 mg/kg rats[d]	
Human toxicity	Very low	Very low	
Problem in use	Allergies possible	Aflatoxin testing[e]	
Stability in storage	Very good	Very good	
Stability on plants	Very low	Very low (?)	
Residues on food	None	None	
Stability in water	Rapidly hydrolysed in acid or base	Stable between pH 3.5 and 6	
Licensed for use	Most countries	Fewer countries	–
Value, annual production	US$600 million	US$55 million	–

Costs and values must be approximate in a period of rapidly rising prices and fluctuating exchange rates.
[a] Estimate based on spacing of trees at 10 m.
[b] Based on mean value for six Asian countries.[141]
[c] Depending on how it is used, see text.
[d] It is reported 1500 mg/kg/day was administered to rats for 90 days and gave no observable effect.[144] Intraperitineal injection of 1000 mg kg^{-1} had no effect.
[e] Neem seeds subject to fungal infection, with aflatoxin production and loss of activity, if not carefully dried.

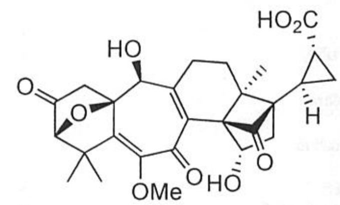
E. D. Morgan , *Bioorg. Med. Chem.*, **2009**, *17*, 4096-4105

Although, Pyrethurum (I'll talk about this compound in §2-3) is great and well known pesticide.

Azadirachtin is better than Pyrethrum. The reason why Pyrethrum is used larger than Azadirachtin is because Azadirachtin belongs to everyone, no-one has been willing to chance investing alot of money in it.

2-2 Solanoecrepin A

After synthesis of Azadirachtin,
Solanoeclepin A is called as "the most difficult natural pesticide" from synthetic view.



Solanoeclepin A (1)

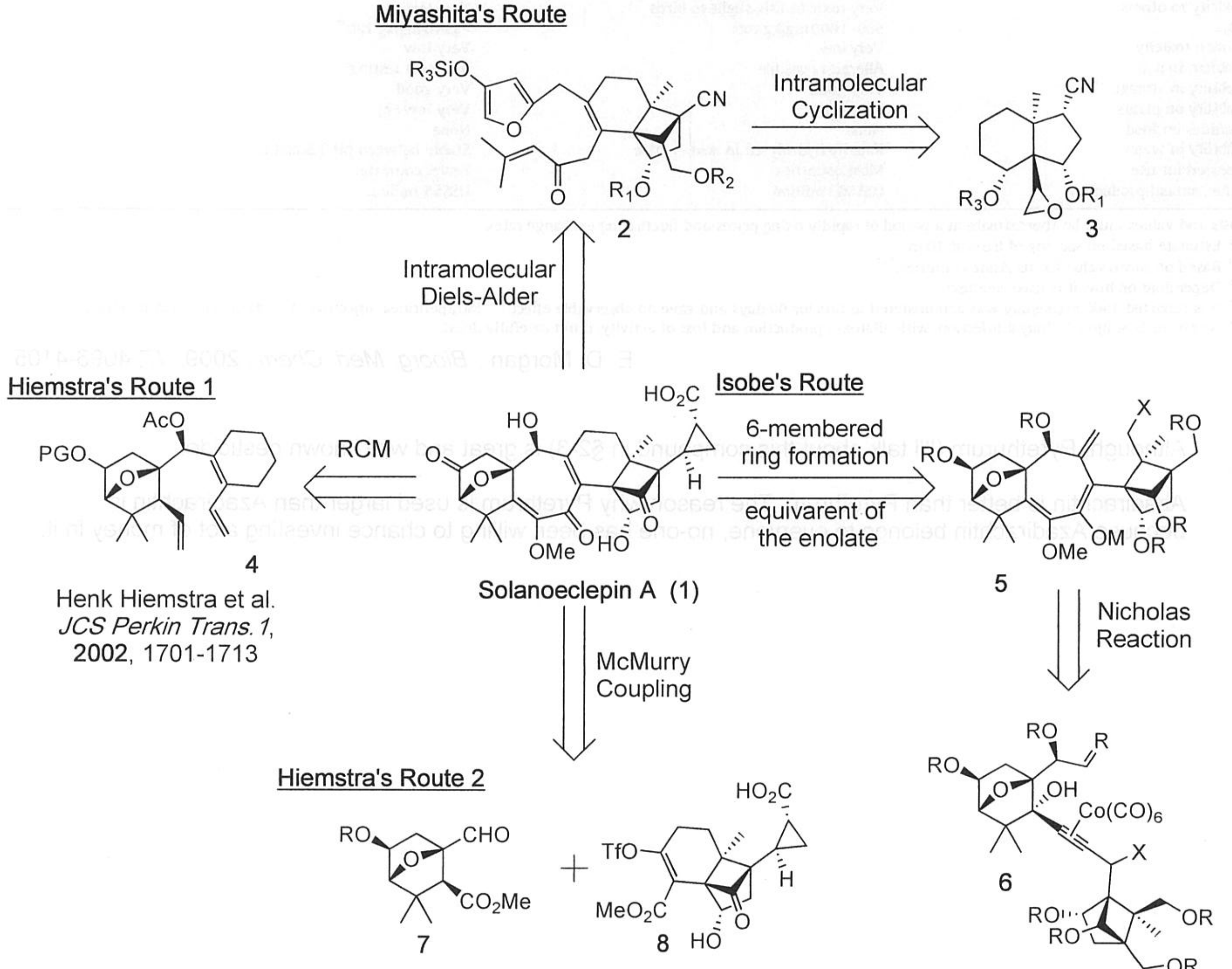
Isoration : from potato (*Solanum tuberosum L.*) cultivation in 1986.

Structure : Containing the 3, 4, 5, 6, 7 membered ring.

Activity :Hatching agent of potato cyst nematodes (PCN).

Without potato, PCN survives more than 10 years with cyst form.
Cyst is so strong, that it put up with drying, low temperatureand pesticide.

2-2-1 Retrosynthetic Analysis



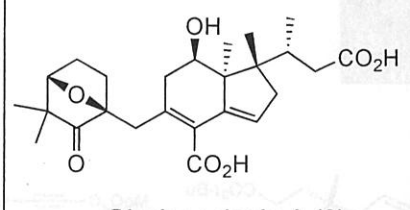
Henk Hiemstra et al.
JCS Perkin Trans. 1,
2002, 1701-1713

Henk Hiemstra et al.
OBC, 2003, *1*, 4364-4366

Shingo Tojo and Minoru Isobe
Synthesis, 2005, 1237-1244

They already succeeded in key reaction with model compounds.
But all route needs many steps to obtain the precursor of key reaction.
So, if synthesis were completion, using as pesticide would be difficult.
→ Similar example in next page.

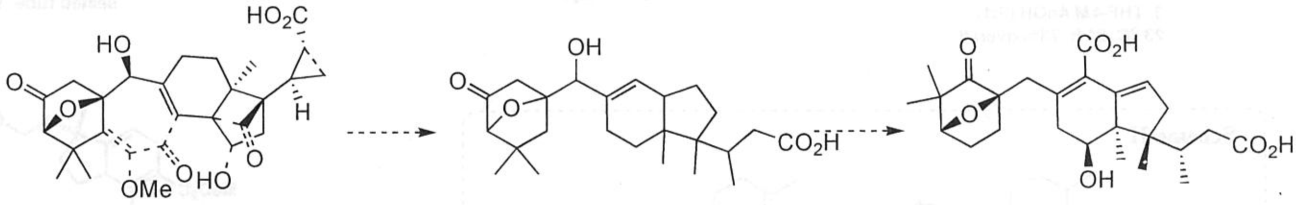
2-2-2 Similar Compound ~ Total Synthesis of Glycinoeclepin



Glycinoeclepin A (9)

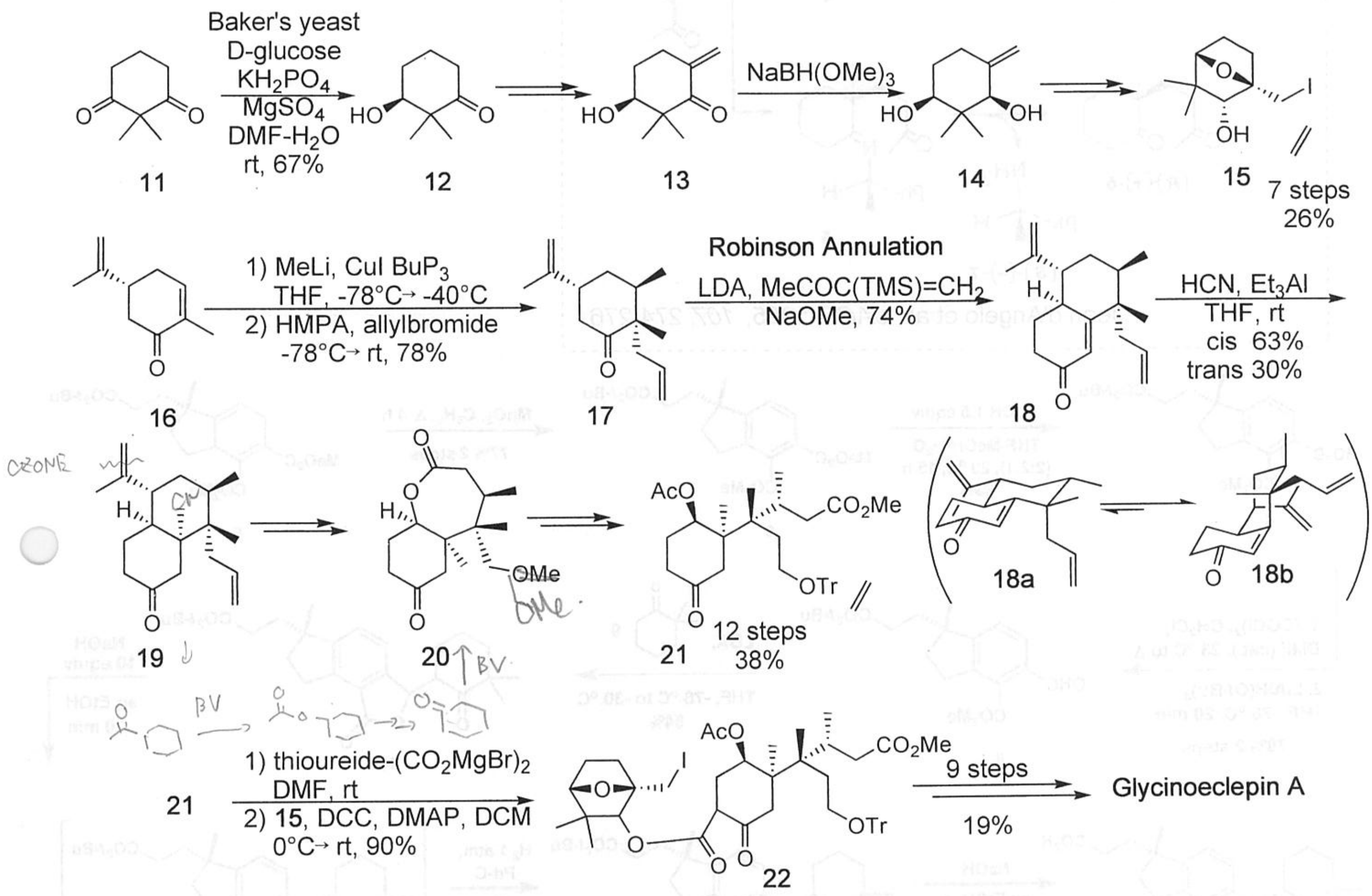
Isoration : from soybean root (50μg from 110kg of dry roots) in 1982

Activity : Hatching agent of nematodes (*Heterodera slycines*).
active concentration : 1pg / 1ml



Solanoeclepin A (1) — 10 — Glycinoeclepin A (9)

Total synthesis



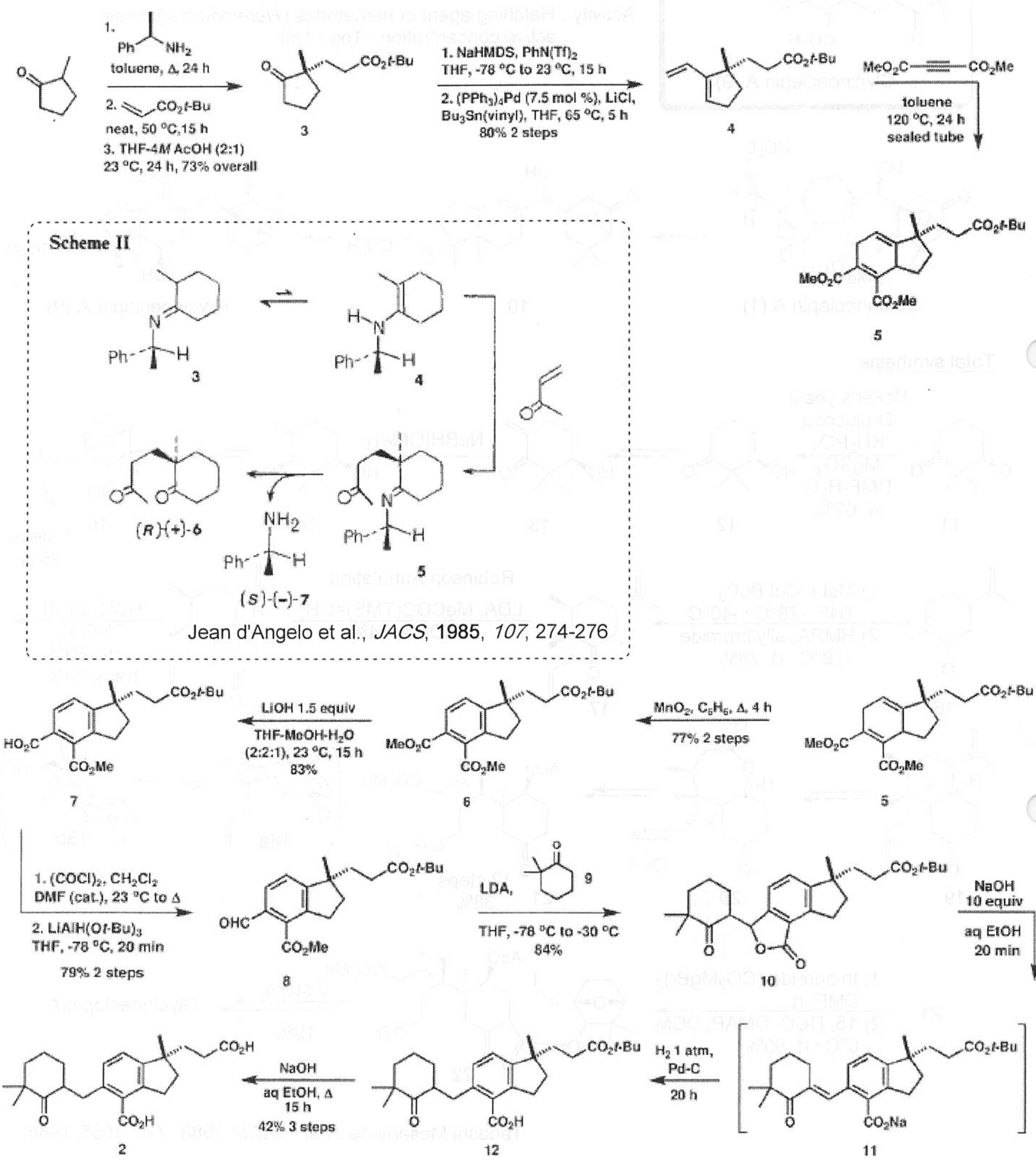
Tadashi Mesamune et al., *JACS*, 1988, *110*, 1985-1986

Total synthesis was completed 21 years ago, but Glycinoeclepin have never used as pesticide.
Because this process are too complex and costly to procide an unlimited and inexpensive supply.
Now, Corey embarked on research to develop a biologically active mimic of Glycinoeclepin.

Enantioselective Synthesis of a Simple Benzenoid Analogue of Glycinoeclepin A

ORGANIC LETTERS
2008
Vol. 10, No. 24
5617–5619

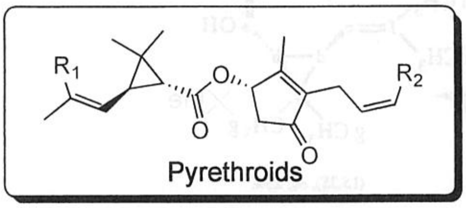
Simon Giroux and E. J. Corey*



13 steps
10% overall yield

Sinple synthesize was achieved, if this compound has sufficiently potent, synthetic study of glycinoeclepin will bear fruit. And also synthetic study of solanoeclepin.

2-3 Pyrethroids



	R_1	R_2
Pyrethrin I (30%)	$-Me^a$	$-CH=CH_2^c$
II (32%)	$-CO_2Me^b$	$-CH=CH_2^c$
Cinerin I (10%)	$-Me^a$	$-Me^d$
II (14%)	$-CO_2Me^b$	$-Me^d$
Jasmolin I (5%)	$-Me^a$	$-Et^e$
II (4%)	$-CO_2Me^b$	$-Et^e$

a) (+)-*trans*-chrysanthemic acid
b) (+)-trans-pyrethric acid
c) (+)-pyrethrolone
d) (+)-cinerolone
e) (+)-jasmolone

Isoration : from *Chrysanthemum cinerariaefolium*
Activity : antiinsect
Sensitive for *hv* and oxgen (quick decomposition)

2-3-1 Retrosynthetic Analysis

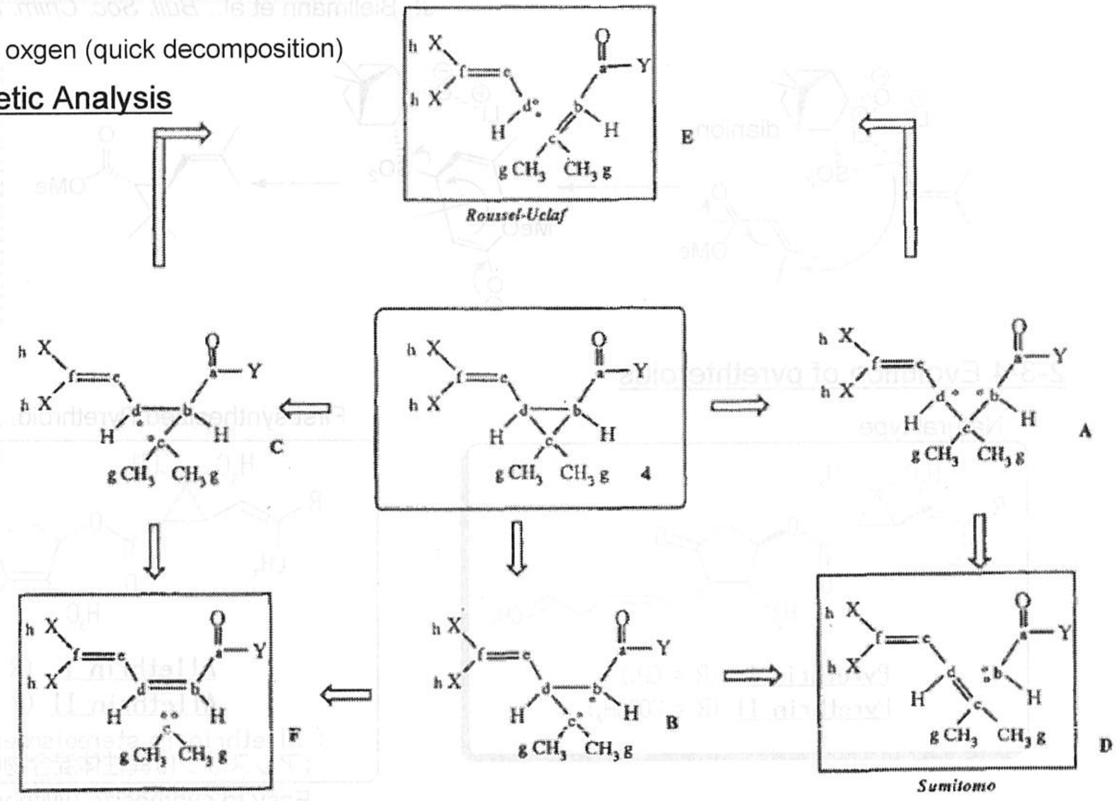
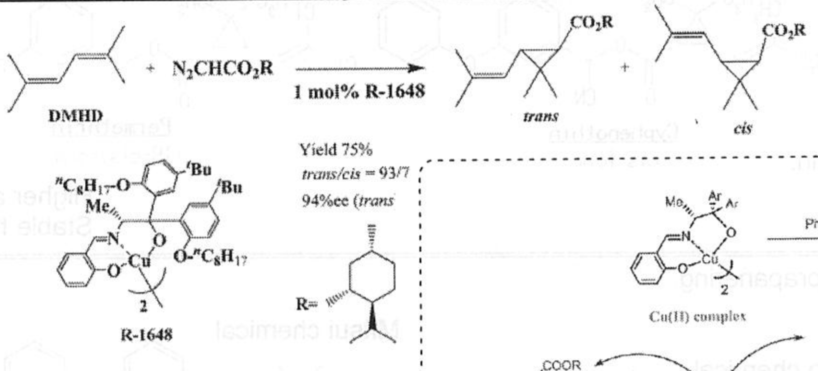


Fig. 2. Retrosynthetic analysis of pyrethroids.

2-3-2 Sumitomo's industrial synthesis of pyrethteroids



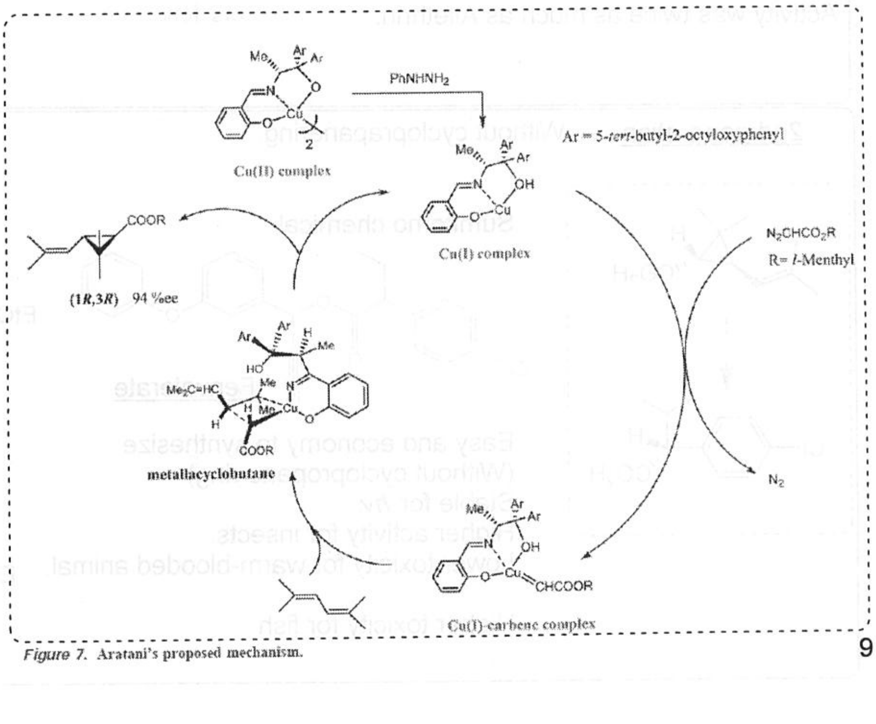


Figure 7. Aratani's proposed mechanism.

2-3-3 Roussel-Uclaf's industrial synthesis of pyrethteroids

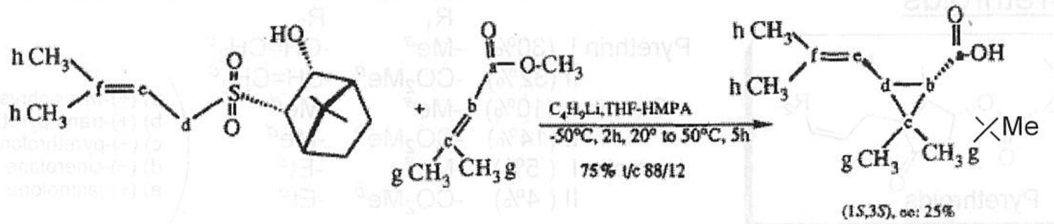
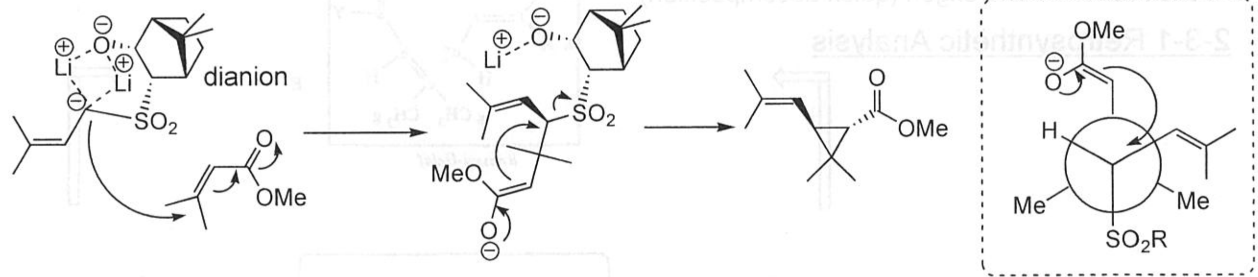


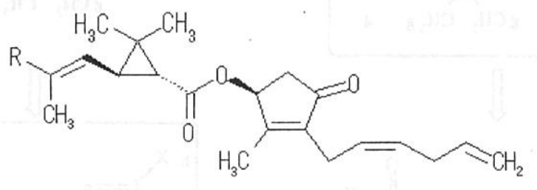
Fig. 5.

JF Biellmann et al., *Bull. Soc. Chim. Fr.*, 1990, *127*, 98-107



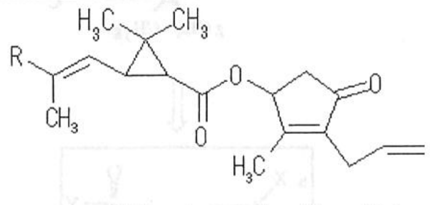
2-3-4 Evolution of pyrethteroids

Natural type



Pyrethrin I (R = CH_3)
Pyrethrin II (R = $COOCH_3$)

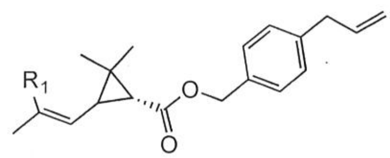
First synthesized Pyrethroid.



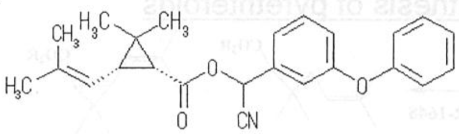
Allethrin I (R = CH_3)
Allethrin II (R = $COOCH_3$)
(Allethrin is stereoisomers mixture
;アレスリンは異性体混合物に命名されている)

Easy to synthesize (Without conjugate diene)
Higher transpitation.

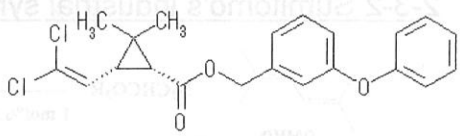
1st generation (1960-1970)



Activity was twice as much as Allethrin.



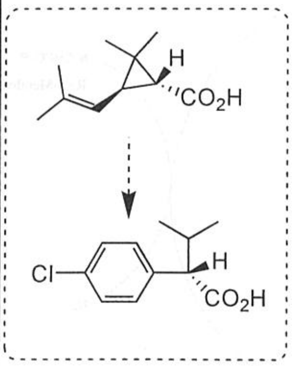
Cyphenothin
cis form



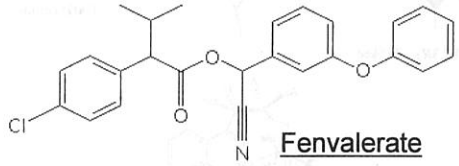
Permethrin
(1R-cis)form

Higher activity
Stable for *hv*

2nd generation Without cycloprapanering.



Sumitomo chemical

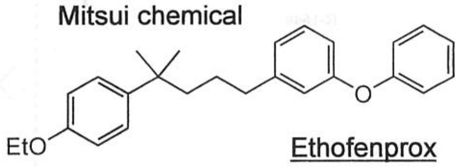


Fenvalerate

Easy and economy to synthesize
(Without cyclopropane ring)
Stable for *hv*.
Higher activity for insects.
Lower toxicity for warm-blooded animal.

Higher toxicity for fish.

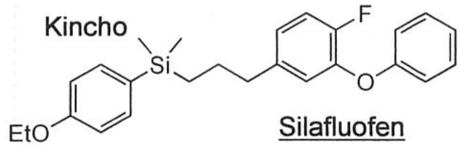
Mitsui chemical



Ethofenprox

Almost same as Fenvalerate
Toxicity for fish become lower.

Kincho



Silafluofen

Toxicity for fish become more lower.
Higher stability.

2-3-5 DDT

DDT has lead a checkerd career. And pyrethroids was the first trigger of DDT.

Rising

DDT was synthesized in 1873 but not so many people had mind this compound.
In 1939, Paul Hermann Müller discovered DDT's insecticidal properties, DDT's position was little different.

FIrst trigger

At that time, Japan exported Pyrethrum to U.S. but after WWII begun, Japan stopped exporting, so U.S. started the production of DDT as a substitute of pyrethroids.

U.S. army needed insecticide because they battled with Japan in a tropical rain forest.
DDT has great effect and U.S. won.

After war end, DDT was widely used for farm and human and Paul Hermann Müller received Nobel Prize (Physiology or Medicine) in 1948.

Second trigger

In 1962, Rachel Louise Carson published "Silent Spring" which refers the dangerousity of DDT or other chemicals.
This book gave large impact to people, DDT was gradually forbidden.

DDT is not safe, but DDT was effective insecticide.
If DDT was not forbidden, 10 million people can survive from Malaria.
And because of abandon DDT, stronger toxic pesticide (e.g. Parathion) was used.
In poor country there are no pesticides which people can buy .

Third trigger

Now, third trigger comes. DDT is reassessed, WHO stopped the prohibition of DDT in 2006.

§3 Final Section

3-1 Organic Synthesis with Pesticide

Of course, there are many synthetic pestisides but time is limited, so I scoped on the natural hydrocarbon pesticides only.
In area of hydrocarbon pesticides, organic synthesis is not always succeed.
But like a Pyrethroids case, organic synthesis sometimes leave the great result.

3-2 Pesticide's future

Now, population explosion continues, so we cannot survive without pestiside.

But purpose of pestiside gradually changing.

1. Not for extermination, but for living together.

2. Selective natural compounds.

3. Using with genetically modified crops.