

Review

Discovery and development of pyrethroid insecticides

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(Communicated by Keisuke SUZUKI, M.J.A.)

Abstract: Pyrethroid insecticides contain natural pyrethrins extracted from pyrethrum flowers, and their synthetic derivatives, pyrethroids. The present article provides an overview of the structure of natural pyrethrins, and the discovery and development of pyrethroids with an emphasis on the background of selected compounds. The stereochemical relationships among pyrethroid secondary alcohols, and toxicologic and environmental effects of pyrethroids are also discussed. Finally, the pyrethroid resistance of mosquitoes and future aspects of pyrethroids are addressed.

Keywords: pyrethrins, pyrethroids, insecticide, stereochemistry, pyrethroid resistance

1. Introduction and early studies

Natural pyrethrum extracts from flowers of *Tanacetum cinerariaefolium* (Fig. 1(a)) are the main insecticides used for household and post-harvest insect control due to their low mammalian toxicity, rapid knockdown activity, and high efficacy against a wide range of insect pests, especially mosquitoes. These flowers are cultivated in Tasmania (Australia), East Africa (Tanzania, Rwanda, and Kenya), and southern China. In 2016, the amount of dried flowers reached approximately 10,000 metric tons.

In Japan, pyrethrum seeds were independently introduced by Tamari and Ueyama in the 1880s. Ueyama cultivated pyrethrum flowers in the Wakayama prefecture and confirmed the insecticidal activity of pyrethrum extracts. He traveled around Japan, even to Hokkaido, and encouraged people to cultivate pyrethrum flowers, which gradually increased the production of pyrethrum in Japan. Pyrethrum extracts were mainly used to control lice (lice powder) in those days, but Ueyama's wife, Yuki, envisaged a mosquito coil (Fig. 1(b)). The development of the mosquito coil enabled the control of mosquitoes for several hours, and is widely used around the world to control mosquitoes.

The first scientific report was published by a Japanese biologist, Fujitani, in 1909.¹⁾ His findings had a remarkable impact on many chemists throughout the world regarding the insecticidal activity of pyrethrum extracts. Another Japanese chemist, Umetaro Suzuki, famous for the discovery of vitamin B₁ (Oryzanin) in rice bran, became interested in the insecticidal ingredients in pyrethrum and suggested to his students, Yamamoto and Takei, that they clarify the chemical structure of pyrethrum. In 1923, Yamamoto was the first to report that the chemical structures of the active ingredients in pyrethrum contained a cyclopropane ring.²⁾

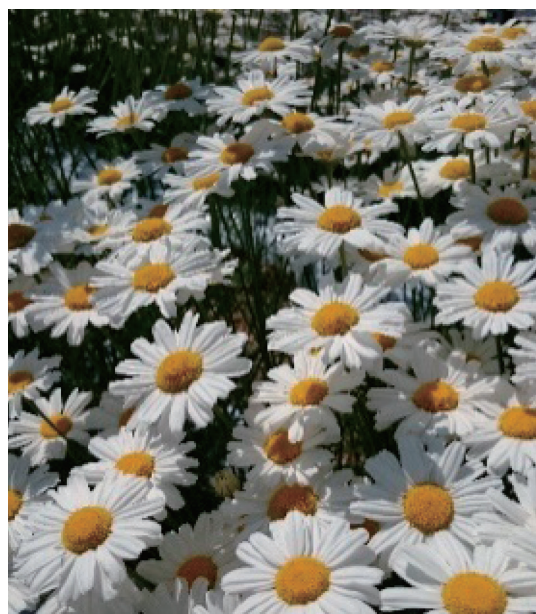
In 1924, Staudinger and Ruzicka, both Nobel prize winners, disclosed their extensive investigation during 1910–1916 on the active ingredients in the pyrethrum extracts, which included the esters of cyclopropanecarboxylic acid derivatives with hydroxycyclopentanones.³⁾ Although the structure of the alcohol moiety was incorrect, the structures of the acid moieties were correct. Given that NMR and IR instruments had yet to be invented, their results should be highly regarded. The correct structures, pyrethrins I and II, were finally established in 1944 by LaForge and Barthel,⁴⁾ as shown in Fig. 2. These authors concurrently separated two more relevant compounds, cinerins I and II from the pyrethrum extracts.

The absolute configuration of the acid moiety of pyrethrin I was unambiguously determined by Crombie and Harper in 1954,⁵⁾ and shortly thereafter in 1955, that of pyrethrin II was determined by Inouye and Ohno.⁶⁾ Moreover in 1958, Katsuda and

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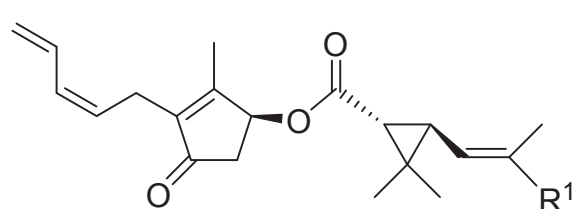


(a)

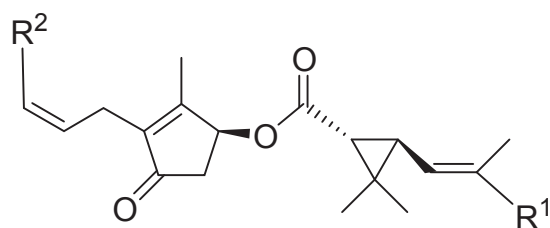


(b)

Fig. 1. (a) Pyrethrum flowers; (b) Mosquito coil.

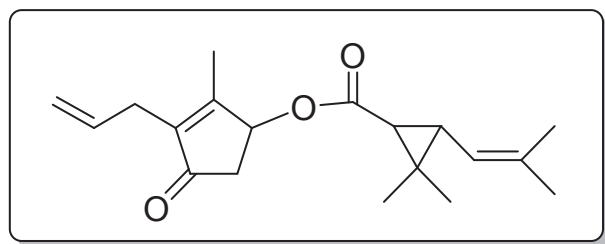


	R^1	R^2
Pyrethrin I :	CH_3	
Pyrethrin II :	CO_2CH_3	



Cinerin I :	CH_3	CH_3
Cinerin II :	CO_2CH_3	CH_3
Jasmolin I :	CH_3	CH_2CH_3
Jasmolin II :	CO_2CH_3	CH_2CH_3

Fig. 2. Structures of natural pyrethrins.



Allethrin

Fig. 3. Structure of allethrin.

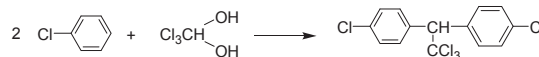
Inouye confirmed the absolute configuration of the alcohol moiety, pyrethrolone.⁷⁾ In 1966, Godin and co-workers isolated two more related minor constituents, jasmolins I and II (Fig. 2).⁸⁾

Studies of structural modifications of natural pyrethrins were recorded early in the 20th century. Staudinger and Ruzicka reported many derivatives in 1924.³⁾ Although some of these derivatives exhibited only slight insecticidal activity, it is important to acknowledge the foresight of these researchers regarding natural pyrethrins as a lead compound, before the structures of the alcohol moieties were elucidated.

Over the last 90 years, several investigations have focused on the structural modifications of natural pyrethrins. The first pyrethroid, allethrin (Fig. 3), was discovered by Schechter and LaForge in 1949.⁹⁾

In 1949, Matsui at Sumitomo Chemical Co., Ltd. was interested in a commercial process for producing allethrin as a household insecticide.¹⁰⁾ He modified the FMC Corporation's process (FMC Corporation is a chemical company in the U.S.A.) and successfully produced allethrin on a commercial scale in 1953. This process at that time is shown in Fig. 4 in comparison with the process for DDT, which was commonly used as a household insecticide in those days. Notably, DDT could be synthesized in a single step, whereas the synthesis of allethrin required more than 10 steps, which was much more expensive than natural pyrethrins. At the beginning, therefore, it was difficult to commercialize allethrin due to the lengthy synthesis. Due to poor harvests of pyrethrum flowers in the 1950s, however, commercial allethrin was gradually accepted in the market. The initial research on pyrethroids by Matsui firmly established the basis for several novel inventions of pyrethroids, which were conducted thereafter by many chemists at Sumitomo Chemical.

< DDT >



< Allethrin >

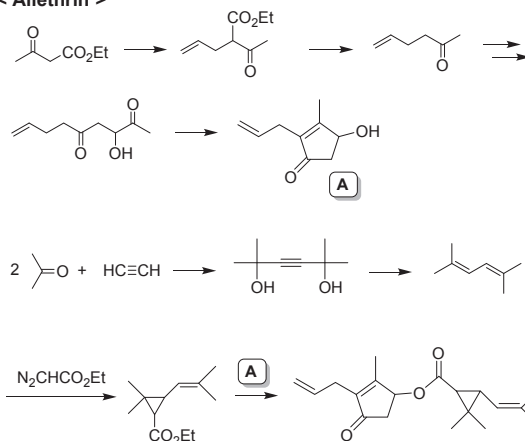


Fig. 4. Comparison of commercial processes of DDT and allethrin.

The discovery of allethrin prompted chemists worldwide to investigate structural modifications of the pyrethroid alcohol and acid moieties, and later even the essential ester function. These efforts resulted in the development of a number of pyrethroids with diverse characteristics, not only for the control of household insect pests, but also for agricultural use. These derivatives are remarkably more potent, economical, and stable than the original natural pyrethrins.

The development of commercial pyrethroids is shown in the figure of a tree classified by their structures (Fig. 5). At the main trunk **A**, the discovery of 3-phenoxybenzyl alcohol and α -cyano-3-phenoxybenzyl alcohol moieties gained great commercial importance as agricultural insecticides. There are a few boughs from the main trunk and several diphenyl ether-type pyrethroids were commercialized for agricultural use. *N*-Hydroxymethyl-type pyrethroids, which have strong knockdown activity against various insect pests, are placed at trunk **B**. Allethrin-type pyrethroids are placed at trunk **C**. Prallethrin, the structure of which is most similar to Pyrethrin I, is placed at the end of trunk **C**. The fourth trunk **D** contains tetrafluorobenzyl-type pyrethroids. The pyrethroids indicated in yellow in Fig. 5 were invented by chemists at Sumitomo Chemical. The author made great contributions to the inventions of the pyrethroids indicated in pink.

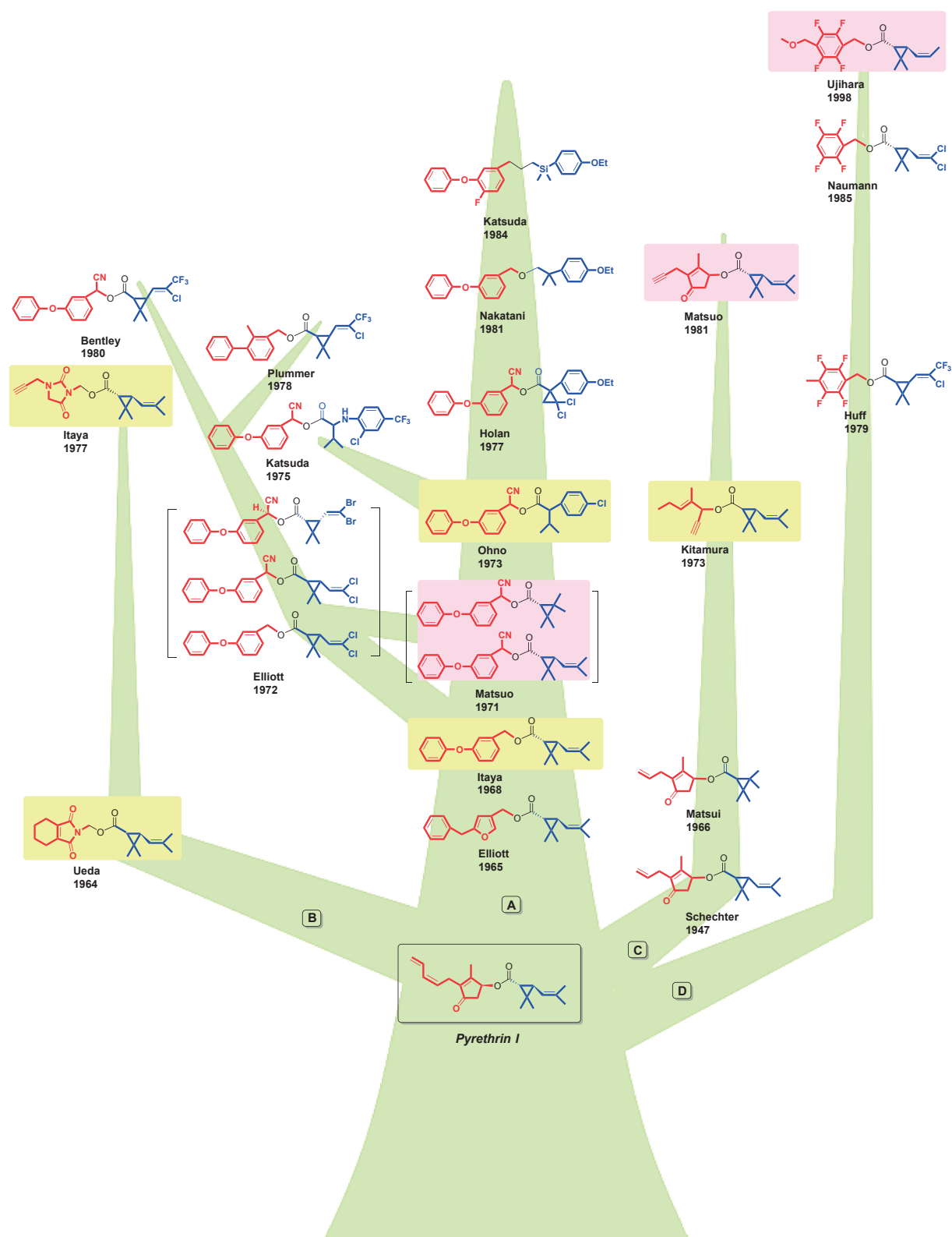


Fig. 5. Development of pyrethroids shown in the tree.

Section 2 describes the background stories of the inventions of selected important pyrethroids.

The impressive aspects of pyrethroid research have been extensively reviewed.^{11)–18)}

2. Background stories of inventions of selected important pyrethroids

Over the last 6 decades, more than 30 pyrethroids have been commercialized. Each pyrethroid has its own background story. Selected examples for the development of commercialized pyrethroids are described in this section according to each trunk in Fig. 5. Most of them were invented by chemists at Sumitomo Chemical, and others (Deltamethrin, Silafluofen and Terallethrin) are disclosed on the basis of my interviews with the inventors.

2.1. Trunk B, *N*-hydroxymethyl-type pyrethroids, tetramethrin and imiprothrin.

2.1.1. Tetramethrin the first synthetic pyrethroid with strong knockdown activity. Ueda at Sumitomo Chemical Co. Ltd., attempted to synthesize amide (**1**, Fig. 6) instead of the ester in 2,4-dimethylbenzyl chrysanthemate, which was reported by Barthel in 1958.¹⁹⁾ He used the Gabriel synthesis to obtain 2,4-dimethylbenzylamine, followed by acylation with chrysanthemoyl chloride to produce amide **1**. The product **1**, however, exhibited much less insecticidal activity than the ester.

Although disappointed with the initial result, he continued pursuing the Gabriel synthesis intermediate, phthalimide **2**, which contained a 5-membered heterocyclic ring. Ueda then attempted to synthesize chrysanthemoyl phthalimide, but he could not obtain the desired acylated product. He prepared *N*-hydroxymethyl phthalimide **3**, which was esterified with chrysanthemic acid. Unexpectedly, ester **4**

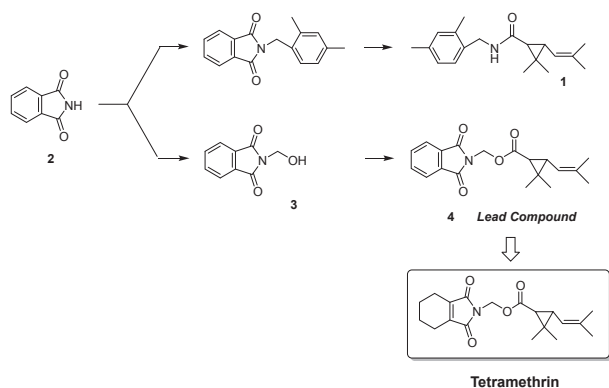


Fig. 6. Background story of the invention of tetramethrin (Ueda and Kato 1964).

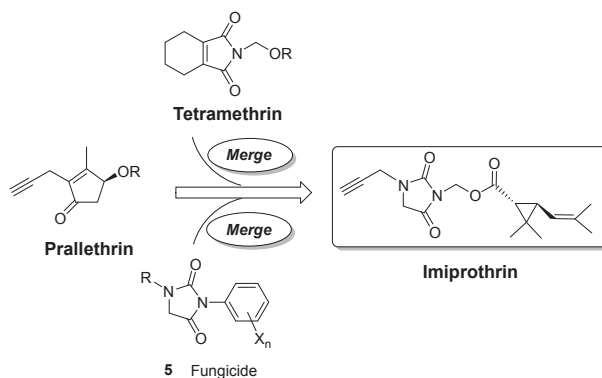


Fig. 7. Background of imiprothrin (Itaya 1979).

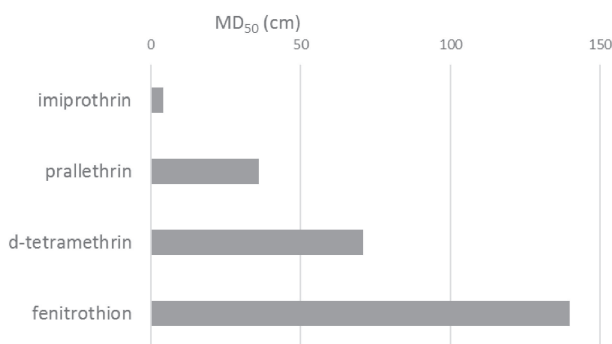


Fig. 8. Moving distance of German cockroaches after treatment with 1.0% oil-based aerosol formulation.

exhibited high knockdown activity against various household insect pests. He synthesized several related compounds and eventually created tetramethrin.²⁰⁾

2.1.2. Imiprothrin: a synthetic pyrethroid with the highest knockdown activity against cockroaches. Itaya re-designed the structure of the alcohol moiety of prallethrin (see Section 2.3.3) in a manner analogous to tetramethrin. He eventually succeeded by merging them with the structure of hydantoin fungicide (**5**, Fig. 7) to invent imiprothrin.²¹⁾

Imiprothrin exhibits great knockdown activity against cockroaches. Figure 8 shows the mean distance (MD₅₀) traveled by the cockroaches in the “Darts” test (Fig. 9); the mean distance moved following the application of imiprothrin was only 4 cm compared with 71 cm following the application of *d*-tetramethrin.

2.2. Main trunk A, diphenyl ether-type pyrethroids.

2.2.1. Phenothrin: an easy-to-produce pyrethroid that provides clues for photostable pyrethroids. A few examples among the novel inventions were initiated

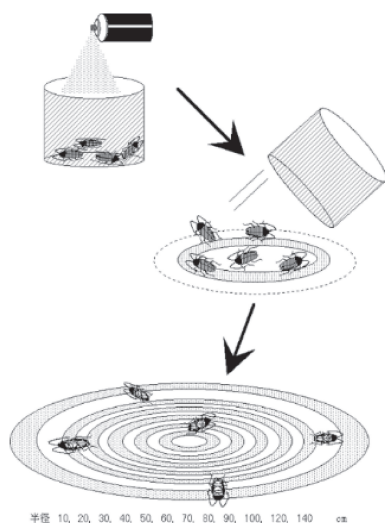


Fig. 9. "Darts" test for knockdown activity against cockroaches.

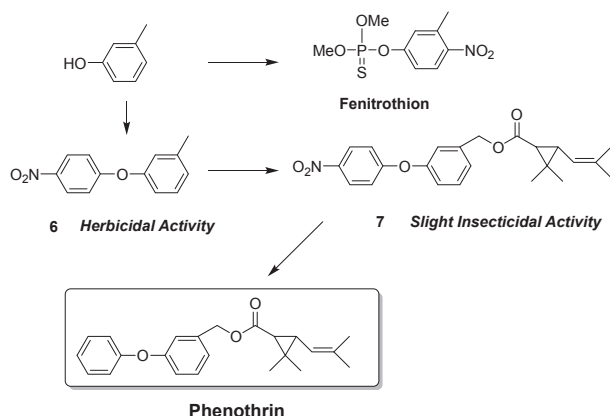


Fig. 10. Invention of phenothrin (Itaya and Kamoshita 1968).

from a rare bulk chemical. In the 1960s, Sumitomo Chemical built a new large plant to manufacture *m*-cresol as an intermediate of fenitrothion, a phosphorothioate insecticide (Fig. 10). In those days, *m*-cresol was not common in the market, and compared with the demands for fenitrothion, the amount of *m*-cresol manufactured was too great. The chemists at Sumitomo Chemical were, therefore, required to find other agrochemicals starting from *m*-cresol.

As shown in Fig. 10, Kamoshita synthesized diphenyl ether derivative **6** as a potential herbicide, which indeed exhibited interesting herbicidal activity. He, then, planned bromination of the methyl group in **6**, followed by esterification with chrysanthemic acid to produce **7**, which had comparatively interesting insecticidal activity. Taking this finding into account, Itaya synthesized various derivatives,

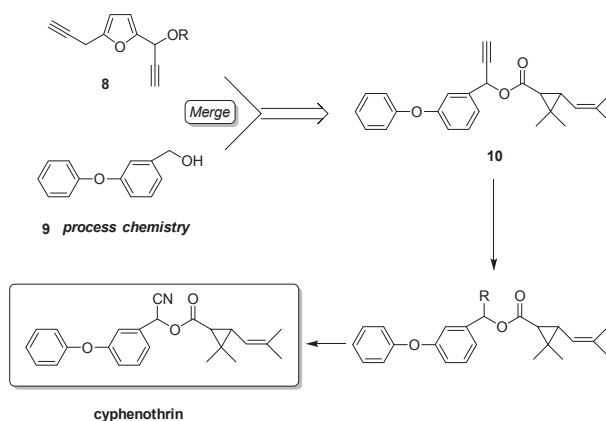


Fig. 11. Background of cyphenothrin (Matsuo 1971).

eventually discovering phenothrin.²²⁾ Phenothrin is a pyrethroid with greater insecticidal activity and lower mammalian toxicity than the natural pyrethrins. Indeed, phenothrin has one of the greatest margins of safety (mammals to insects) among ever known insecticides. Later, Elliott examined esterification of 3-phenoxybenzyl alcohol with 2,2-dimethyl-3-(2,2-dichloroethenyl)cyclopropane carboxylic acid, leading to the notable invention of 3-phenoxybenzyl 2,2-dimethyl-3-(2,2-dichloroethenyl)cyclopropane carboxylate, *i.e.* permethrin, the first photostable pyrethroid for agricultural use (see Section 2.2.3).

2.2.2. Cyphenothrin: a synthetic pyrethroid containing the most important alcohol moiety exhibits the highest killing activity against household insect pests. While my investigation on the practical process of 3-phenoxybenzyl alcohol (**9**, Fig. 11), the alcohol moiety of phenothrin, I took advantage of the unexpected finding of alcohol **8** (see Section 2.3.2) to synthesize α -ethynyl-3-phenoxybenzyl alcohol **10**. Contrary to my expectation, the insecticidal activity of this ester was less than half that of phenothrin. To address this issue, I introduced various functional groups at the α -benzylic carbon atom, as shown in Table 1. Among them, α -cyano-3-phenoxybenzyl chrysanthemate exhibited exceptionally high potency—more than twice that of phenothrin. Next, a large number of α -cyano-substituted analogues of hitherto reported pyrethroids were prepared and their activities were assessed relative to those of the original pyrethroids. Typical examples are shown in Table 2.

With the exception of 3-phenoxybenzyl alcohol, the introduction of an α -cyano group to all the known pyrethroids examined decreased the insecticidal potency. α -Cyano-3-phenoxybenzyl alcohol is

Table 1. Relative lethal activity against houseflies (*Musca domestica*) by the turn table method

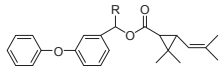
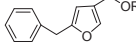
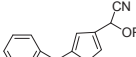
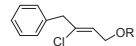
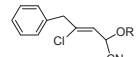
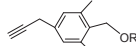
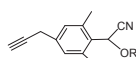
	
R	Relative Lethal Activity
-CH ₃	100
-CH=CH ₂	100
-COCH ₃	<10
-COOCH ₃	10
-CH ₂ SCH ₃	<10
-CH ₂ OCH ₃	10
-CH ₂ Cl	20
-CH(OCH ₃) ₂	<10
-C≡CH	300
-CN (Cyphenothrin)	1,500
-H (Phenothrin)	700
Pyrethrin	100

Table 2. Relative lethal activity against houseflies (*Musca domestica*) of various α -cyano-pyrethroids

Relative Lethal Activity	
	1,410
	100
	300
	<10
	200
	<10

the most important alcohol component identified to date,^{23),24)} that is incorporated into a number of commercial pyrethroids, including cyphenothrin, fenpropathrin, fenvalerate, esfenvalerate, deltamethrin, cypermethrin, cyhalothrin, fluvarinate, tralomethrin, cycloprothrin, and acrinathrin (Fig. 12).

Table 3 shows the market share of pyrethroids among whole insecticides for agricultural use. The share of pyrethroids was around 17% in 2015. Figure 13 shows total sales of pyrethroids and their shares of various pyrethroids applied for agricultural use in 2015. The pyrethroids indicated in yellow contain α -cyano-3-phenoxybenzyl alcohol as the

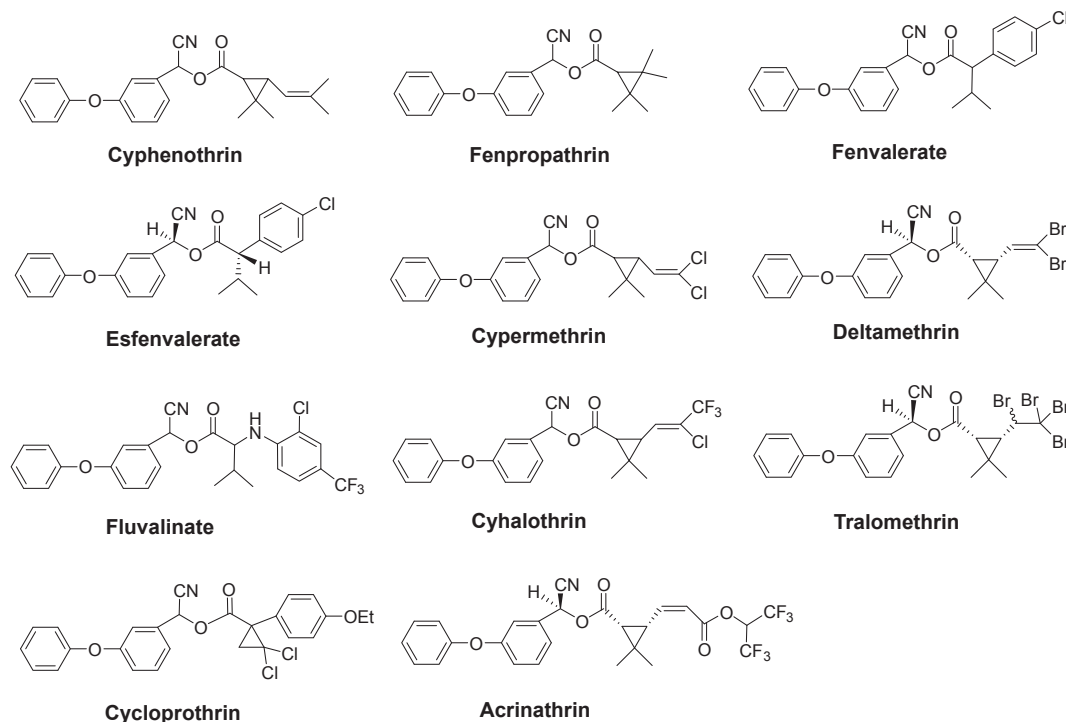
Fig. 12. Commercial pyrethroids containing α -cyano-3-phenoxybenzyl alcohol.

Table 3. Market share of pyrethroids among whole insecticides for agricultural use (source: Phillips McDougall Product Section 2015)

Market Statistics				
		2010	2014	2015
Pyrethroid Insecticides	(\$M)	2,233	3,156	2,852
Market share of pyrethroids	(%)	16.7	17.0	17.0

alcohol moiety. “Others” in green contain fenprothrin, esfenvalerate, fluvarinate, tralomethrin, cycloprothrin, and acrinathrin. Total sales of these pyrethroids containing α -cyano-3-phenoxybenzyl alcohol amounted to more than \$1,700M in 2015.

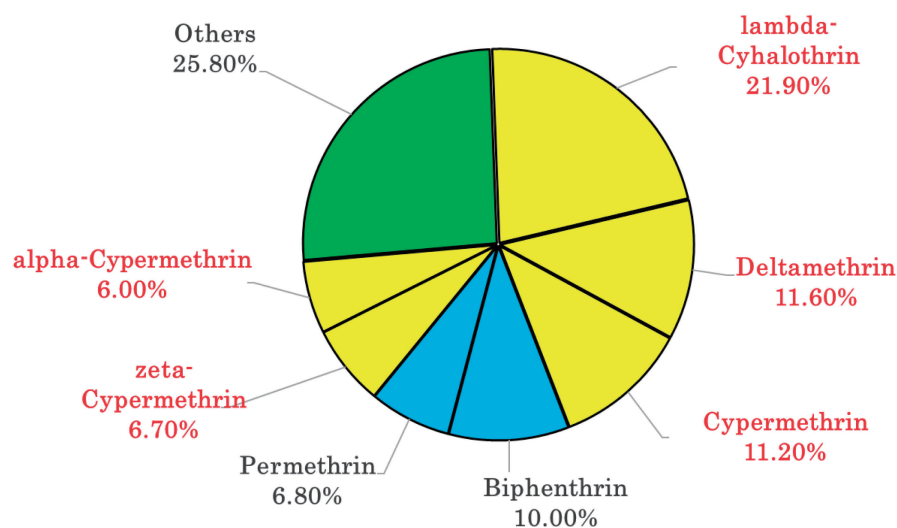
2.2.3. Permethrin, cypermethrin, and deltamethrin: the first photostable pyrethroids. In 1967, Elliott at Rothamsted Experimental Station in the UK invented resmethrin and bioresmethrin ((1*R*)-*trans*-chrysanthemate) (Fig. 14). These compounds were the first synthetic pyrethroids with greater insecticidal activity, but lower mammalian toxicity, than the natural pyrethrins. He designed resmethrin and bioresmethrin simulating the stereochemical role of the natural cyclopentenone ring with a furan ring and the *Z*-conjugated diene in pyrethrolone with a phenyl ring. Despite their valuable properties, resmethrin

and bioresmethrin are unstable in air and light, making them unsuitable for agricultural use.

On the other hand, Casida and Ueda evaluated the photodecomposition of bioresmethrin and identified that the isobutenyl side chain in the acid and the furan ring in the alcohol were vulnerable functional groups.²⁵⁾ Elliott designed several new compounds, in which the light-sensitive moieties were replaced with alternative units. In the most active acid components of many of the synthesized compounds, the dimethyl groups in the isobutenyl side chain of chrysanthemic acid were replaced with halogens, especially chlorine and bromine. 2,2-Dimethyl-3-(2,2-dichloroethenyl)-cyclopropane carboxylic acid was originally reported by Farkas in 1959.²⁶⁾

Concurrently, Sumitomo Chemical (Itaya) invented phenothrin, 3-phenoxybenzyl chrysanthemate; the *m*-substituted phenyl ring of phenothrin corresponds to the furan ring of resmethrin, whereas the phenoxy group corresponds to the benzyl group. In 1973, Elliott synthesized 3-phenoxybenzyl 2,2-dimethyl-3-(2,2-dichloroethenyl)cyclopropanecarboxylate, permethrin, as the first photostable pyrethroid.

When I visited Elliott in the UK in 1979, he revealed to me the invention of both cypermethrin and deltamethrin. With permethrin in hand, he visited the patent office in London every week to



lambda-Cyhalothrin=1:1 mixture of (*S*- α), (*Z*)-(1*R*,3*R*) and (*R*- α), (*Z*)-(1*S*,3*S*)-isomers

zeta-Cypermethrin= 1:1 mixture of (*S*- α), (1*RS*,3*RS*) and (*S*- α), (1*RS*,3*SR*)-isomers

alpha-Cypermethrin= 1:1 mixture of (*S*- α), (1*R*)-*cis* and (*R*- α), (1*S*)-*cis*-isomers

Fig. 13. Pyrethroid leading products, total \$2,852M (2015) (Philips McDougall Product Section).

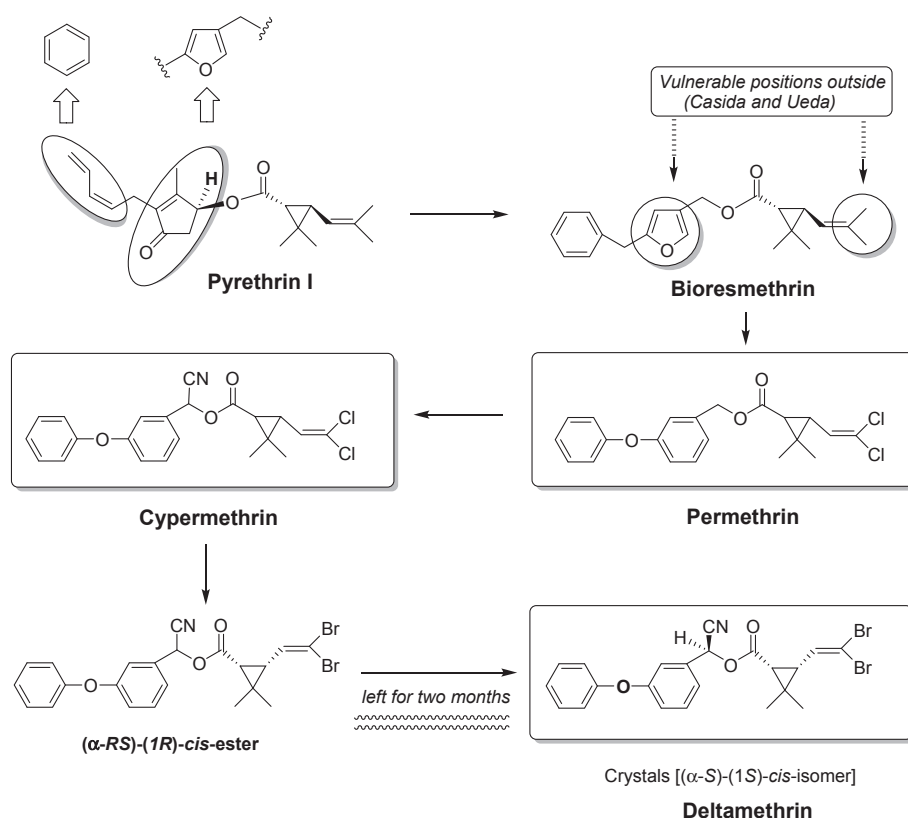


Fig. 14. Background of deltamethrin (Elliott 1974).

find newly disclosed world patents related to a new alcohol moiety of pyrethroids as early as possible. In 1972, he learned of my patent from Sumitomo Chemical for α -cyano-3-phenoxybenzyl chrysanthemate (cyphenothrin). He immediately returned to his laboratory and synthesized α -cyano-3-phenoxybenzyl 2,2-dimethyl-3-(2,2-dichloroethenyl)cyclopropanecarboxylate (cypermethrin) and confirmed the strongly-enhanced insecticidal activity.

He then synthesized the ester of α -cyano-3-phenoxybenzyl alcohol with (1*R*)-*cis*-2,2-dimethyl-3-(dibromoethenyl)cyclopropanecarboxylic acid. He left the sample as a hexane solution in a refrigerator and found that white crystals appeared. The insecticidal activity of the crystals was remarkably higher than that of bioresmethrin, as shown in Table 4. These enantiomeric crystals were “Deltamethrin”, (*S*)- α -cyano-3-phenoxybenzyl (1*R*)-*cis*-2,2-dimethyl-3-(2,2-dibromoethenyl)cyclopropanecarboxylate.^{27),28)}

In 1977, Sumitomo Chemical entered into a contract with NRDC to sell permethrin and cypermethrin in Japan. Since then chemists at Sumitomo began incorporating permethrin into the fibers of

Table 4. Relative activity of various pyrethroids to insects

Compounds	Houseflies (<i>Musca domestica</i> L.)	Mustard Beetles
Pyrethrin I	2	160
Bioresmethrin	100	100
α - <i>RS</i> -Deltamethrin	1,000	1,000
Deltamethrin (α - <i>S</i>)	2,300	1,600

the net to protect people from mosquitoes. Thus, Sumitomo Chemical’s net, named “Olyset Net” (Fig. 15) has revolutionized the global fight against malaria. The Olyset Net has protected nearly 800 million people since it received a WHO recommendation in 2002.

2.2.4. Fenvalerate: the first pyrethroid devoid of the cyclopropane ring, and a guideline to non-ester pyrethroids, etofenprox and silafluofen. In 1924, Staudinger and Ruzicka had already synthesized non-cyclopropane pyrethroid, but reported no significant insecticidal activity. Since this finding, pyrethroid chemists had thought that the cyclopropane ring was indispensable for the insecticidal activity. Ohno and



Fig. 15. "Olyset Net" (Photograph ©M. Hallahan/Sumitomo Chemical).

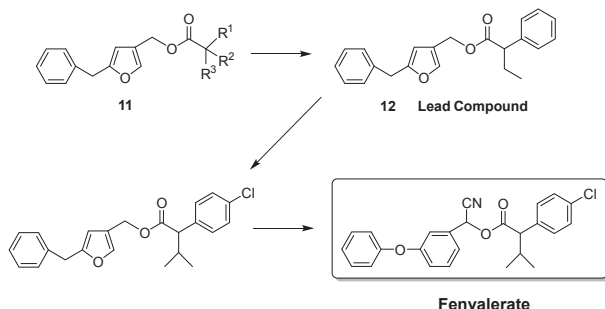


Fig. 16. Background of fenvalerate (Ohno and Hirano 1973).

Hirano at Sumitomo Chemical searched for a new acid moiety devoid of a cyclopropane ring. To detect even slight insecticidal activity, they adopted the mosquito larva dipping method. To enhance the basic activity, they used 5-benzyl-3-furfuryl alcohol, the most potent alcohol moiety in those days, as the probe (Fig. 16). Various acid esters **11** devoid of a cyclopropane-ring were screened.

As a result, they found a lead compound **12**. Further exploratory work led to the discovery of fenvalerate,²⁹⁾ which was a substantial breakthrough in the structure modification of pyrethroids lacking the cyclopropane ring in the acid moiety.

The discovery of fenvalerate elicited the introduction of a number of non-cyclopropane pyrethroids, such as etofenprox (Fig. 17). Etofenprox is an ether compound rather than an ester compound invented by Mitsui Toatsu Chemicals Inc.^{30),31)} Etofenprox is the first pyrethroid with low fish toxicity and was developed as a rice paddy-field insecticide. Mitsui Toatsu Chemicals also disclosed MTI-800, in which an oxygen atom was replaced with a methylene moiety, having a trimethylene hydrocarbon skeleton.³²⁾

Katsuda at Dainihon Jochugiku Co., Ltd. re-designed the structure of MTI-800 by merging ideas based on the structure of the triazole fungicide, flusilazole, to discover silafluofen (Fig. 17). Namely, substituting the quaternary carbon atom in MTI-800 with a silicon atom produced silafluofen. Surprisingly, six companies, Dainihon Jochugiku (1984),³³⁾ Sumitomo (1985),³⁴⁾ Mitsui (1985),³⁵⁾ Schering (1986),³⁶⁾ FMC (1986),³⁷⁾ and Hoechst (1986),³⁸⁾ applied for the same patent of silafluofen within 3 years. Silafluofen has lower fish toxicity with persistent insecticidal properties under field conditions compared with MTI-800.

2.3. Trunk C, allethrin-type pyrethroids.

2.3.1. Terallethrin: a new pyrethroid containing

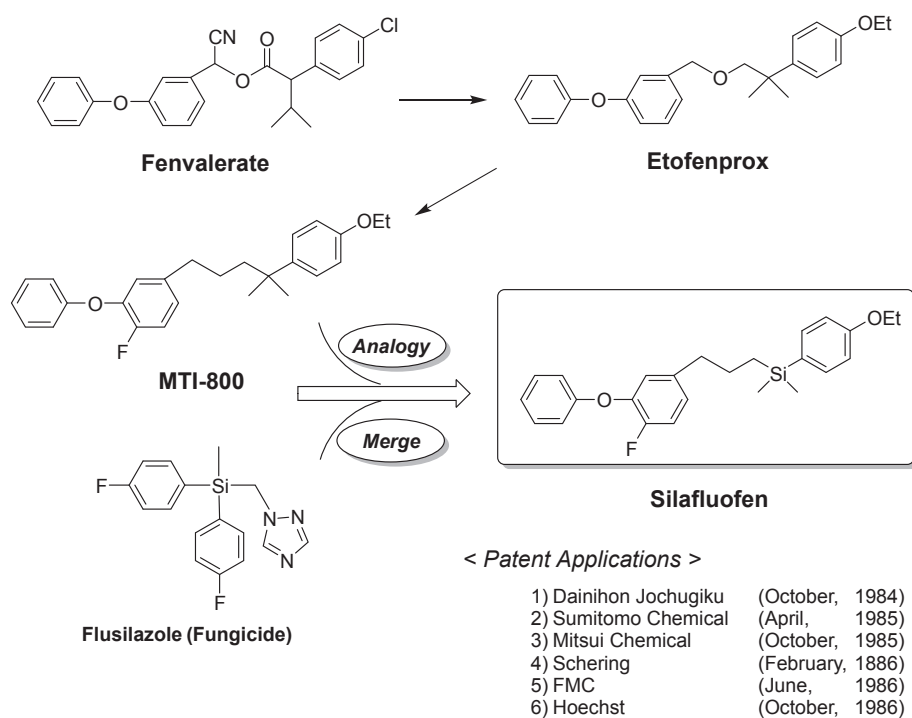


Fig. 17. Background of silafluofen (Katsuda 1984).

2,2,3,3-tetramethylcyclopropane carboxylic acid. Matsui and Kitahara at the University of Tokyo envisaged a new acid component of pyrethrin. At that time, it was believed that the isobutenyl side chain at the 3-position of chrysanthemic acid was indispensable for the insecticidal activity. They investigated the structure-activity relationship (SAR) of simple alkyl substituents on the cyclopropane ring and esterified multi-substituted cyclopropanes with allethrolone. Table 5 shows the SAR of various alkyl-substituted cyclopropanecarboxylates. While 2,3-dimethyl compound **13** exhibited no insecticidal activity, *gem*-dimethyl compound **14** had almost 10% the activity of allethrin.

Finally, they discovered the 2,2,3,3-tetramethylcyclopropanecarboxylate (**15**: terallethrin),³⁹⁾ which exhibited the highest insecticidal activity among the compounds prepared. It should be noted that the replacement of only one methyl group with an ethyl group resulted in the complete loss of insecticidal activity (compound **16**). 2,2,3,3-Tetramethylcyclopropanecarboxylic acid has a “vinylogous relationship” with chrysanthemic acid (Fig. 18). Terallethrin is used as a household insecticide. Later, this acid was esterified by the author with α -cyano-3-phenoxybenzyl alcohol (1971). The ester is called fenpropathrin and is used globally for the control of mites.²³⁾

Table 5. Structure-activity relationships of alkyl substitutions on a cyclopropane ring (Matsui and Kitahara 1967)

	R ¹	R ²	R ³	R ⁴	Kill effect on the housefly LC ₅₀ (mg/100 mL)
	Me	H	H	H	>1,000
13	Me	H	Me	H	>1,000
14	Me	Me	H	H	920
	Me	Me	Me	H	500
15	Me	Me	Me	Me	135
16	Me	Me	Me	Et	>1,000
Allethrin					100–300

As shown in Fig. 19, I applied Matsui’s “vinylogous relationship” to momfluorothrin,⁴⁰⁾ (1*R*)-*trans*-(*Z*)-2,3,5,6-tetrafluoro-4-methoxymethylbenzyl 2,2-dimethyl-3-(2-cyano-1-propenyl) cyclopropanecarboxylate, to obtain (1*S*)-*cis*-2,3,5,6-tetrafluoro-4-methoxymethylbenzyl 2,2,3-trimethyl-3-cyano-cyclopropanecarboxylate **17**,⁴¹⁾ which showed remarkably higher knockdown activity; 50% of German cock-

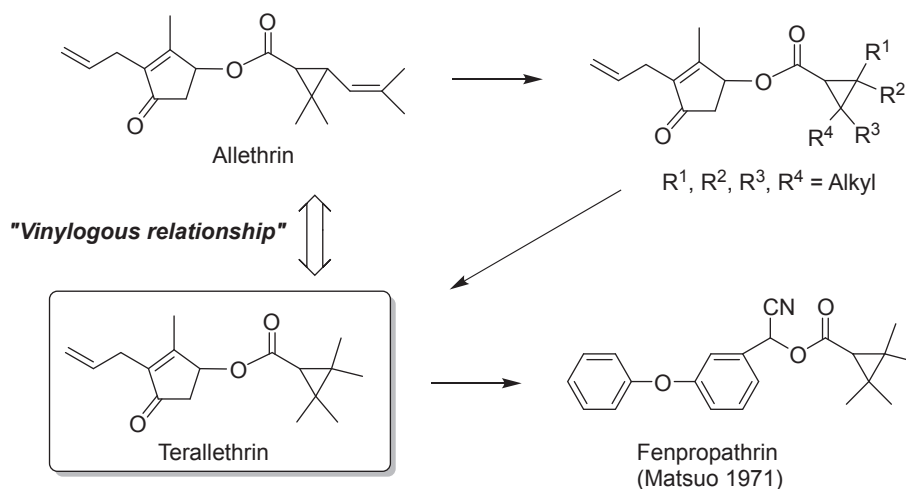


Fig. 18. Invention of terallethrin (Matsui and Kitahara 1967).

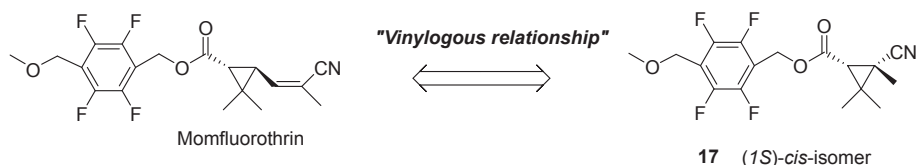


Fig. 19. "Vinylogous relationship" of momfluorothrin (Matsuo 2010).

Table 6. Knockdown activity (KT₅₀) against German cockroaches by oil-spray method

	17	18	19
0.00625%	<0.7 min.	>10 min.	>10 min.
0.025%	<0.7 min.	>10 min.	>10 min.

roaches (KT₅₀) were knocked down within 0.7 minutes by 0.00625% oil-spray method (Table 6). The KT₅₀ of the *trans*-CN compound **18** and 2,2,3,3-tetramethylcyclopropanecarboxylate **19**, however, was both more than 10 minutes, even by 0.025% oil-spray method.

2.3.2. Empenthrin: the first volatile synthetic pyrethroid. Impurities in the desired products often provide the rare opportunity for new inventions. In fact, during the process research of 5-(2-propynyl)-2-furfuryl alcohol (**21**, Fig. 20), whose ester (furamethrin) with chrysanthemic acid was invented by Katsuda,⁴²⁾ α -Ethynyl-(5-propynyl)-2-furfuryl alcohol (**23**) was unexpectedly obtained by Ohno due to contamination of the starting acetal **20** with a

small amount of 5-chloromethyl-2-furfural (**22**). To our surprise, the chrysanthemate **8** exhibited twice the efficacy of furamethrin.

Although ester (**8**, Fig. 21) was not commercialized because of its instability, this finding prompted us to synthesize further derivatives. Fission of the cyclopentene ring of allethrolone was first attempted by Sota,⁴³⁾ which resulted in finding a new acyclic alcohol moiety **24**. Taking advantage of our unexpected detection of α -ethynyl alcohol ester **8** with **24** led to new acyclic α -ethynyl alcohol esters **25**. Extensive derivative screenings of **25** by Kitamura at Sumitomo Chemical, finally yielded empenthrin.⁴⁴⁾ α -Ethynylbenzyl esters **26** had already been reported⁴⁵⁾ as pyrethroids by BASF in 1968. The

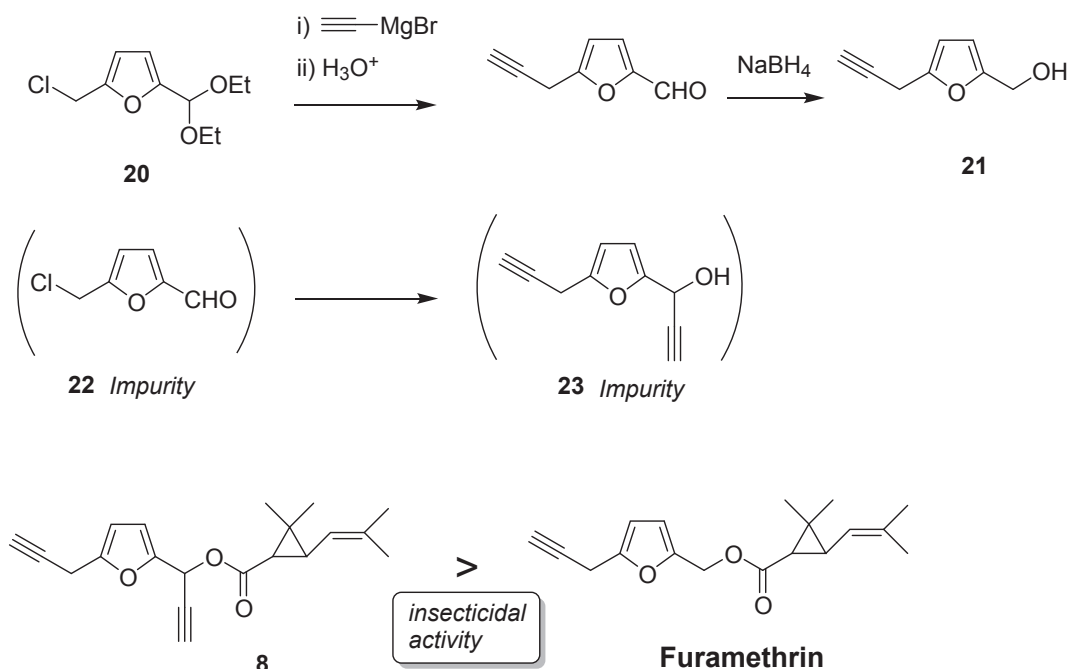


Fig. 20. Background of empenethrin-1.

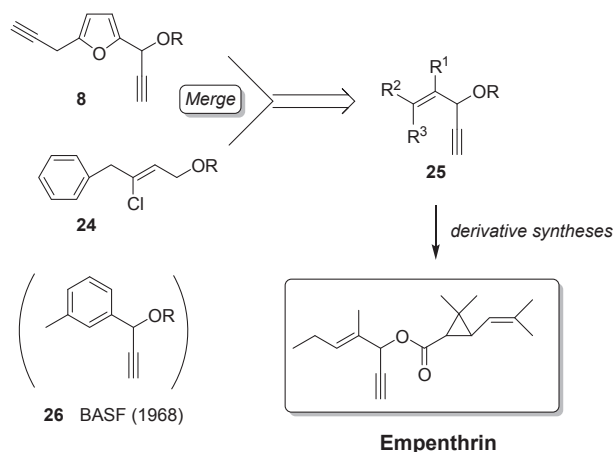


Fig. 21. Background of empenethrin-2 (Kitamura 1973).

invention of empenethrin, however, did not stem from the literature, but rather from merging the two compounds, **8** and **24** mentioned above.

2.3.3. Prallethrin: a synthetic pyrethroid with high knockdown and killing activity against household insects and the structure most similar to natural pyrethrin I. The propargyl analogue (**27**, Fig. 22) of allethrin was originally synthesized by Gersdorff in 1961,⁴⁶⁾ but **27** did not attract much attention at that time due to the 40% decrease in activity against houseflies compared with the parent allethrin. The SAR between side

chains and the insecticidal activity of empenethrin analogues (Fig. 22) indicated that **27** should have much more activity than allethrin. In fact, **27** was easily transformed to the allene compound **28** under even slightly basic conditions during the cyclization process of the synthesis. The low insecticidal activity was attributed to the contamination of **28**, which exhibited much lower insecticidal activity than **27**. Gersdorff's previous synthesis was supposed to induce undesirable isomerization leading to **28**. Careful preparation of **27** with sufficient chemical purity and reexamination revealed that **27** had more than twice the insecticidal activity of allethrin.

Next, we attempted optical resolution of the alcohol moiety, 2-methyl-4-oxo-3-propargylcyclopent-2-enol (abbreviated as PG-lon) according to Oritani's procedure (Tohoku University) for allethrolone acetate: application of biochemical hydrolysis with *Bacillus subtilis* var. *niger*.⁴⁷⁾ Using the same bacteria, we attempted to hydrolyze the acetate (**29**, Fig. 23), but hydrolysis did not occur because of the undesirable antifungal activity of the acetate.

Another crystalline-liquid optical resolution of allethrolone was carried out by Horiuchi at Sumitomo Chemical via the hydrogen phthalate half ester with (*S*)-1-phenyl-2-*p*-tolylethylamine (Fig. 24).⁴⁸⁾ Accordingly, we synthesized the hydrogen phthalate of PG-lon and attempted the optical

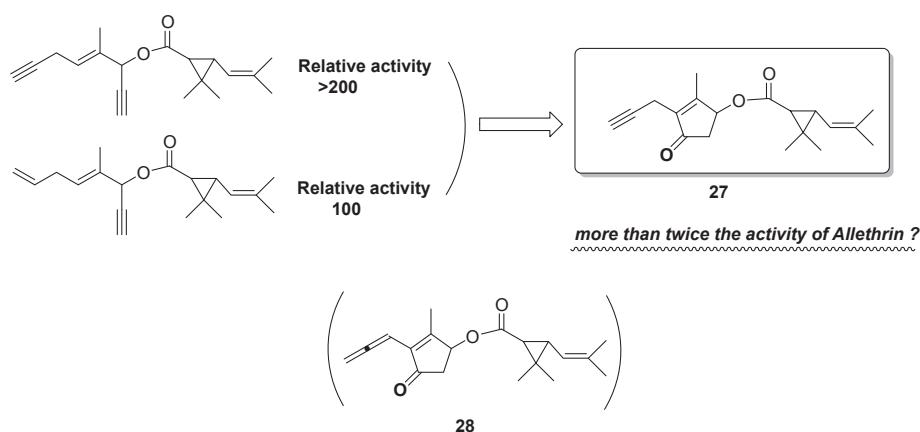


Fig. 22. Background of prallethrin (Matsuo 1978).

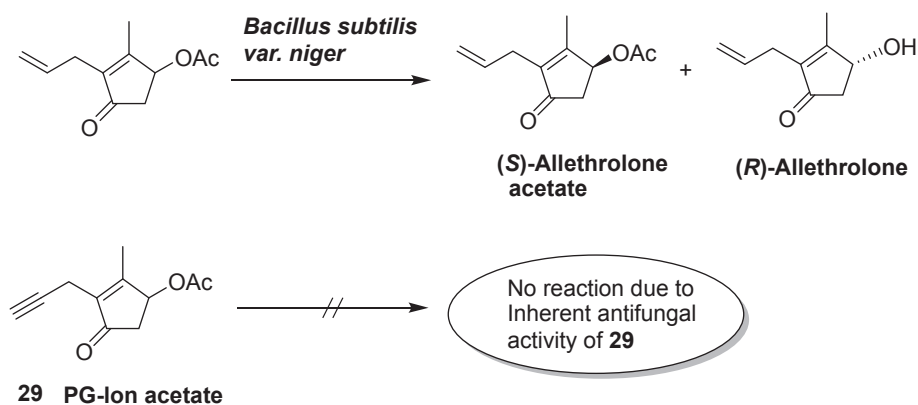


Fig. 23. Biochemical hydrolysis of allethrolone acetate (Oritani 1975), and PG-Ion acetate (Matsuo 1977).

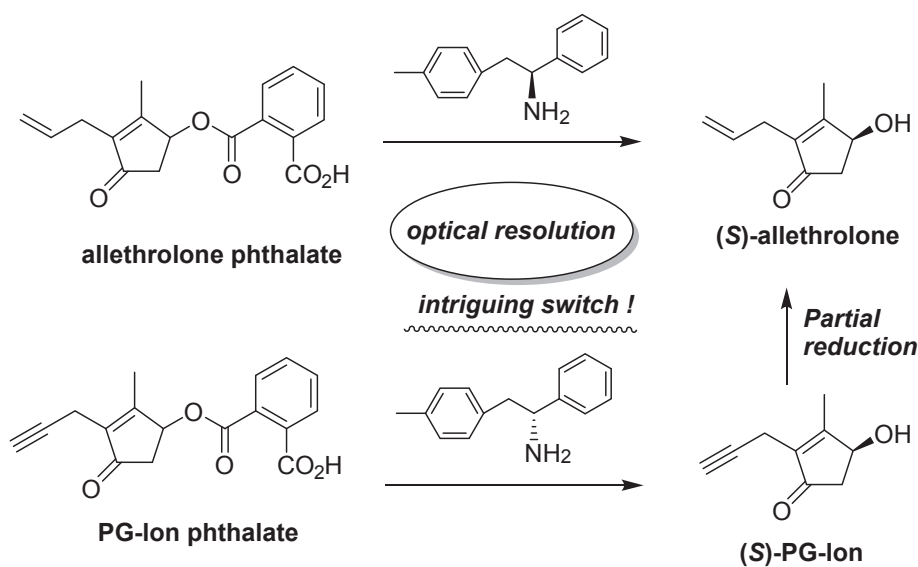


Fig. 24. Optical resolution of PG-Ion phthalate (Tsushima and Matsuo 1981).

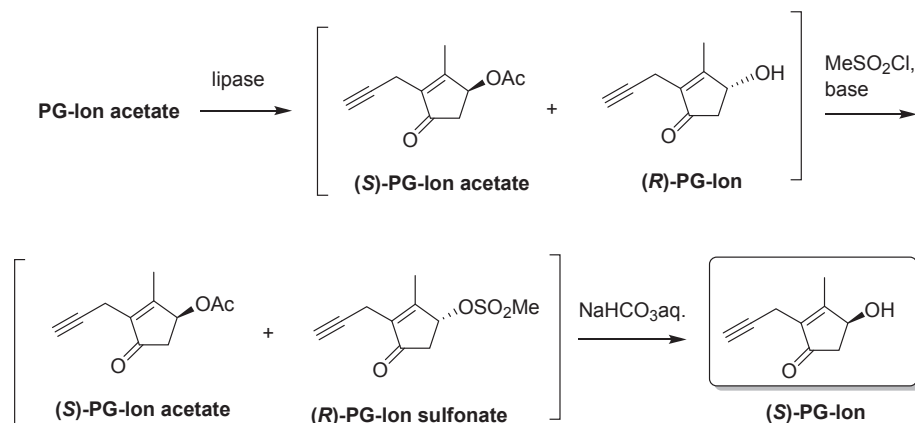


Fig. 25. Practical synthesis of (*S*)-PG-lon using asymmetric lipase hydrolysis (Umemura and Mitsuda 1988).

resolution of the half ester with (*S*)-1-phenyl-2-*p*-tolylethylamine. The opposite enantiomer, however, the (*R*)-form of PG-lon was obtained by this procedure (Tsushima and Matsuo).⁴⁹⁾ Replacing the double bond with a triple bond overturned the solubility of the amine salt. Finally, the PG-lon phthalate was subjected to the similar optical resolution with the antipodal (*R*)-1-phenyl-2-*p*-tolylethylamine to obtain (*S*)-PG-lon. The absolute configuration of (*S*)-PG-lon was confirmed on the basis of its correlation with (*S*)-allethrolone, which was provided by the partial reduction of the triple bond to a double bond.

The practical synthesis of (*S*)-PG-lon was conducted by Umemura and Mitsuda as shown in Fig. 25.⁵⁰⁾ The key steps involve both enzymatic resolution of the racemic acetate and successive chemical inversion of the hydrolyzed (*R*)-alcohol. Thus, the obtained reaction mixture of (*S*)-PG-lon acetate and (*R*)-PG-lon alcohol after the enzyme reaction, was treated with mesyl chloride to afford mixtures of the remaining (*S*)-PG-lon acetate and the (*R*)-PG-lon mesylate, both of which were successfully hydrolyzed to furnish (*S*)-PG-lon in high yield as a sole product, by a kind of direct kinetic resolution.

Table 7 shows the insecticidal activities of not only (*S*)-PG-lon esters, but also (*R*)-PG-lon esters with various isomers of chrysanthemic acid against *Musca domestica*. The ester of (*S*)-PG-lon with (1*R*)-*trans*-chrysanthemic acid, named prallethrin (Fig. 26) is the most active isomer among all these stereoisomers, and is almost 20 times as active as natural pyrethrins. The ester of antipodal (*R*)-PG-lon with (1*R*)-*trans*-isomer exhibited only moderate activity.

Table 7. Insecticidal activity of stereoisomers of prallethrin against houseflies (*Musca domestica*)

<i>Stereoisomers of prallethrin</i>			LD ₅₀
Alcohol moiety		Acid moiety	(µg per female)
Prallethrin	<i>S</i>	(1 <i>R</i>)- <i>trans</i>	0.043
	<i>S</i>	(1 <i>R</i>)- <i>cis</i>	0.11
	<i>R</i>	(1 <i>R</i>)- <i>trans</i>	0.25
	<i>R</i>	(1 <i>R</i>)- <i>cis</i>	0.32
	<i>S</i>	(1 <i>S</i>)- <i>trans</i>	3.30
	<i>S</i>	(1 <i>S</i>)- <i>cis</i>	10.8
	<i>R</i>	(1 <i>S</i>)- <i>trans</i>	18.5
	<i>R</i>	(1 <i>S</i>)- <i>cis</i>	28.2
Natural pyrethrins			0.73

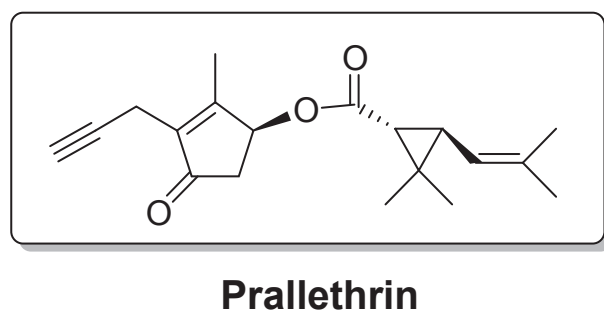


Fig. 26. Structure of prallethrin.

2.4. Trunk D, tetrafluorobenzyl-type pyrethroids metofluthrin: a pyrethroid with higher vapor action and insecticidal activity against mosquitoes. Norchrysanthemic acid (**30**, Fig. 27) was first synthesized by Staudinger in 1924 as the pyrolytic decomposition product of chrysanthemum dicarboxylic acid.⁵¹⁾ In the 1970s, Ohno⁵²⁾ and

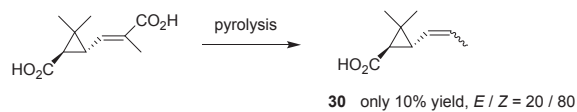
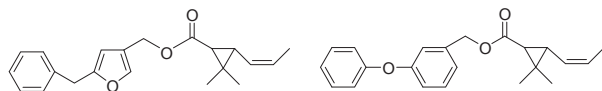
The first synthesis of norchrysanthemic acid**Insecticidal norchrysanthemates**

Fig. 27. Norchrysanthemic acid and its esters.

Elliott⁵³⁾ independently reported norchrysanthemic acid esters (Fig. 27) that exhibited insecticidal activity comparable to that of the corresponding chrysanthemates. Further studies were discontinued because they could not find any advantage in developing these norchrysanthemic acid esters due to the increased difficulty synthesizing norchrysanthemic acid compared with chrysanthemic acid.

Recently, much attention has been directed to the development of devices to control mosquitoes using products at ambient temperature, because they are safer and easier to use, especially during outdoor activities. This development resulted in a variety of fan-powered mosquito vaporizers and associated formulations that are now being marketed. These devices have limitations in performance imposed by the vapor activity of the active ingredient employed. To overcome these limitations, we extensively searched for a new pyrethroid with higher vapor action and activity against mosquitoes.

We focused our attention on a norchrysanthemic acid ester,⁵⁴⁾ because it had a lower molecular mass (−14) than a chrysanthemic acid ester but exhibited insecticidal activity comparable to that of a corresponding chrysanthemate. A variety of insecticidal norchrysanthemic acid esters were synthesized, and their vapor activity against mosquitoes was evaluated. Extensive screening revealed that 2,3,5,6-tetrafluorobenzyl norchrysanthemate (**31**, Table 8) had faster knockdown activity against mosquitoes than chrysanthemate.

Derivative syntheses were carried out by varying substituents at the 4-position of the benzyl group of **31**. All of the analogues had much higher activity against mosquitoes than empenethrin in a standard topical application assay. The relative activity reached a maximum between Et and Pr at the 4-position. Allyl or MeO- also exhibited substantial activity, inter alia, (1*R*)-*trans*-(*Z*)-2,3,5,6-tetra-

Table 8. Insecticidal activity of metofluthrin and its analogues against *Culex pipiens pallens* by the standard topical application method

R		relative toxicity
31	H	30
	F	100
	Me	200
	Et	490
	Pr	250
	Allyl	500
32	OMe	360
	MeOCH ₂ (metofluthrin)	2,500
	Empenthrin	10
	<i>d</i> -Allethrin	100

Table 9. Efficiency of metofluthrin in a non-heating vapor formulation with a fan and mosquito coil formulations against two mosquito species

Formulation	Species	Conc. (%)	KT ₅₀ (min.)	
			Metofluthrin	<i>d</i> -Allethrin
Non-heating	<i>C. pipiens pallens</i>		27	>60
Mosquito coil	<i>C. pipiens pallens</i>	0.013	49	
		0.04	22	
		0.2		54
Mosquito coil	<i>C. quinquefasciatus</i>	0.005	42	
		0.2		58

fluoro-4-methoxymethylbenzyl norchrysanthemate, metofluthrin **32**, had the highest potency, approximately 40 times higher than that of *d*-allethrin, the ester of allethrolone, and (1*R*)-*trans*-chrysanthemic acid, in mosquito coil formulations against southern house mosquitoes (*Culex quinquefasciatus*) as shown in Table 9.

It should be noted that metofluthrin exhibited high knockdown activity in non-heating vapor formulations with a fan against common house mosquitoes (*Culex pipiens*) and various other mosquitoes with an excellent mammalian safety profile. This novel pyrethroid is suitable for use not only in various existing emanating devices like mosquito coils, but also in the much newer devices such as fan-vaporizers and treated paper strips.

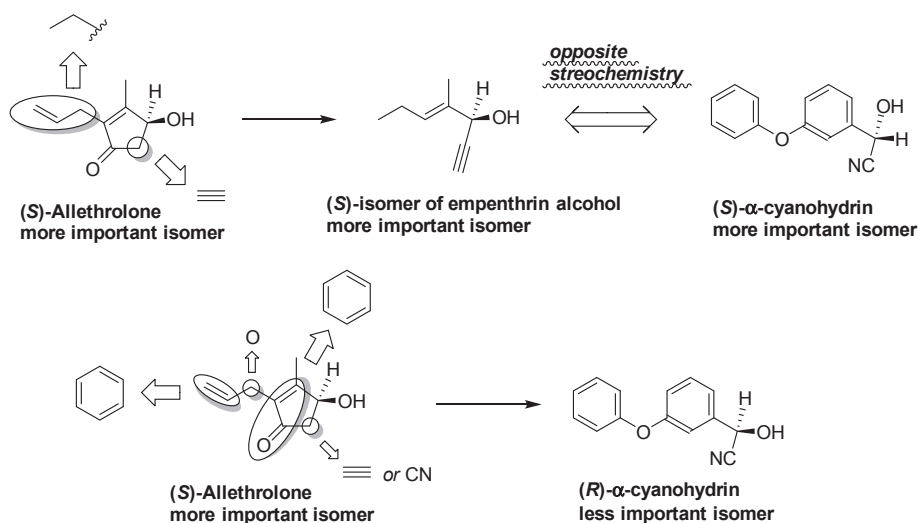


Fig. 28. Structure-activity relationships of insecticidally more important stereoisomers (1).

3. Stereochemical relationships among the secondary alcohols

In addition to natural pyrethrolone (an alcohol moiety of pyrethrins I and II), a number of pyrethroids have been invented that contain secondary alcohol moieties. The more important isomer of empenhrin alcohol has an (*S*)-configuration, consistent with the configuration of (*S*)-allethrolone (Fig. 28). The stereochemistry is opposite that of (*S*)-α-cyano-3-phenoxybenzyl alcohol with regard to the hydrogen atom and hydroxy group attached to the asymmetric α-carbon atom. Because of the operation of the CIP sequence rules, (*S*)-empenhrin alcohol and (*S*)-α-cyano-3-phenoxybenzyl alcohol are geometrically different but both have the same (*S*)-configuration.

Figure 28 shows three plausible isosteric simulations of the stereochemistry: (i) external double bond corresponding to a methyl group, (ii) internal double bond in cyclopentenolone corresponding to a trisubstituted ethylene group, and (iii) methylene group in cyclopentenolone corresponding to a triple bond. In a similar manner, (*S*)-allethrolone is transformed to α-cyano-3-phenoxybenzyl alcohol. The absolute configuration of α-cyano-3-phenoxybenzyl alcohol thus formed, however, has the insecticidally less important (*R*)-isomer. It is currently unclear whether the present simulation is reasonable.

Sugai and Mori at the University of Tokyo reported a general rule for asymmetric hydrolysis of the acetates of α-ethynyl alcohols with the bacterium

Bacillus subtilis var. *niger*.⁵⁵⁾ This bacterium always preferentially hydrolyzes one enantiomer of acetate **A** to give a mixture of the unchanged acetate **B** and alcohol **C** as shown in Fig. 29. I used lipase, derived from *Arthrobacter* or *Pseudomonas* species, instead of the bacterium for the hydrolysis of various α-ethynyl acetates and α-cyano acetates.⁵⁶⁾ Sugai and Mori's general rule was also applicable to the hydrolysis of these acetates by lipase.

The secondary pyrethroid alcohols can clearly be classified into two types depending on the importance of the unchanged acetate leading to insecticidal activity. One kind includes diphenyl ether-type compounds, such as α-cyano-3-phenoxybenzyl alcohol and α-ethynyl-3-phenoxybenzyl alcohol. The lipases preferentially hydrolyze insecticidally more important acetates in this class to give (*S*)-α-cyano-3-phenoxybenzyl alcohol and (*R*)-α-ethynyl-3-phenoxybenzyl alcohol (due to the CIP sequence rule, *R* and *S* are reversed). The other kind of pyrethroid alcohol contains 1-ethynyl-2-methylpentenol and allethrolone. The same lipase selectively hydrolyzes insecticidally unimportant acetates in this class to give (*R*)-1-ethynyl-2-methylpentenol and (*R*)-allethrolone.

To gain further insights into the essential stereochemical requirements for the active secondary alcohol moieties, a variety of optically active α-ethynyl and α-cyano alcohols were prepared by bacterial (*B. subtilis* var. *niger*) or enzymatic hydrolyses (lipase from *Pseudomonas* species), as shown in Fig. 30. All the absolute configurations of the unchanged acetates and hydrolyzed alcohols are

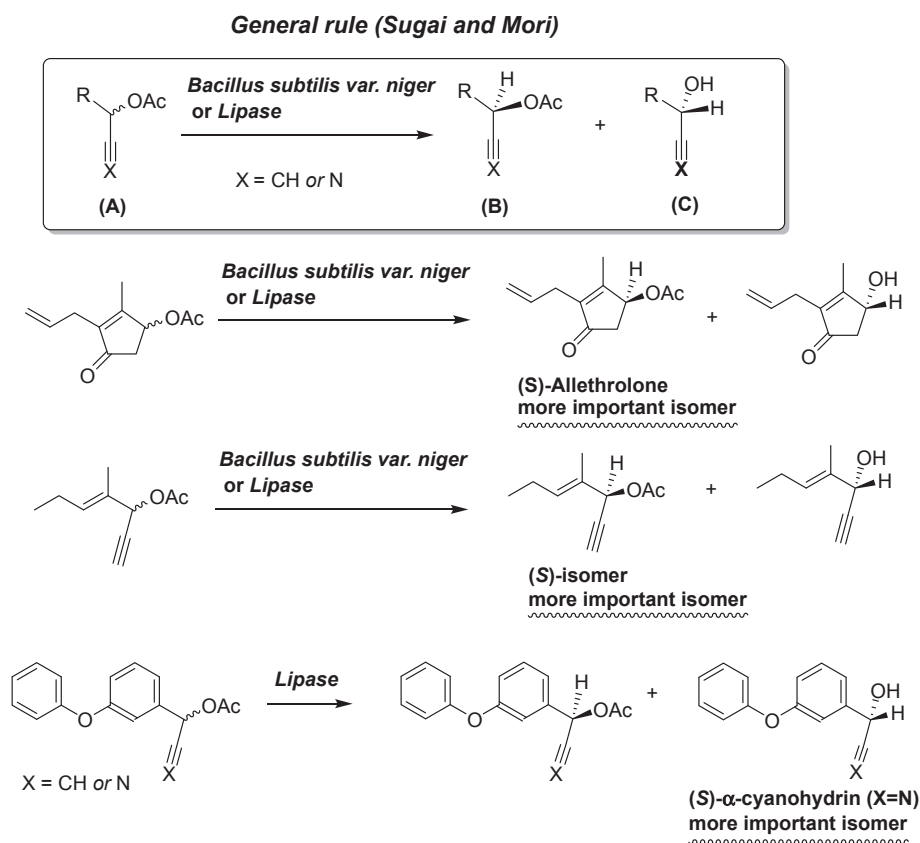


Fig. 29. Structure-activity relationships of insecticidally more important isomers (2).

consistent with the general rule mentioned above. The insecticidally more important stereoisomers, however, could be classified into the two kinds discussed above.

The correlation of the stereoselectivity between asymmetric hydrolyses and insecticidally more important isomers is very intriguing (Fig. 30). Surprisingly, the activity order was inverted just by changing *m*- or *p*-position of the allyl group on the benzene ring. That is, the (*R*)- α -ethynyl-3-allylbenzyl ester (*R*)-**33** is more than twice as active as the corresponding (*S*)-isomer against *M. domestica*, and this (*R*)-ester has the same configuration as the (*S*)- α -cyano-3-phenoxybenzyl alcohol ester, whereas the (*S*)- α -ethynyl-4-allylbenzyl ester ((*S*)-**34**) is 25 times more active than the (*R*)- α -ethynyl-4-allylbenzyl ester. (*S*)- α -Ethynyl-4-allylbenzyl alcohol can be superimposed on (*S*)- α -ethynyl-2-methylpent-2-enol.

α -Cyano-3-phenoxybenzyl alcohol **36**⁵⁷⁾ produces another interesting outcome. It is noteworthy that only the introduction of a phenoxy group to the *m*-position in the benzene ring caused the reversal of

stereo-recognition (compare (*S*)-**35** with (*S*)-**36** and (*R*)-**37** in Fig. 30).⁵⁶⁾

With regard to the conceivable receptor sites for hydrolysis in bacteria and enzymes, 3-phenoxyphenyl, 3-allylphenyl, 4-allylphenyl, and 2-penten-2-yl groups can fit in the common receptor sites. Of course, the receptor shape that binds pyrethroid insecticides is currently unknown and probably quite different from hydrolytic enzymes: relevant only to the insecticidally dominant stereoisomers of the esters and not just their alcohol moieties.

4. Mammalian and environmental aspects of natural pyrethrins and synthetic pyrethroids

The widespread use of pyrethroids is based on their acceptable environmental safety. There are several reviews of the toxicologic properties of pyrethroids.^{58)–68)} Mammalian and environmental toxicities are summarized in Table 10.

Pyrethroids act on sodium channels of excitatory neurons in mammals, as in insects, inducing CS-

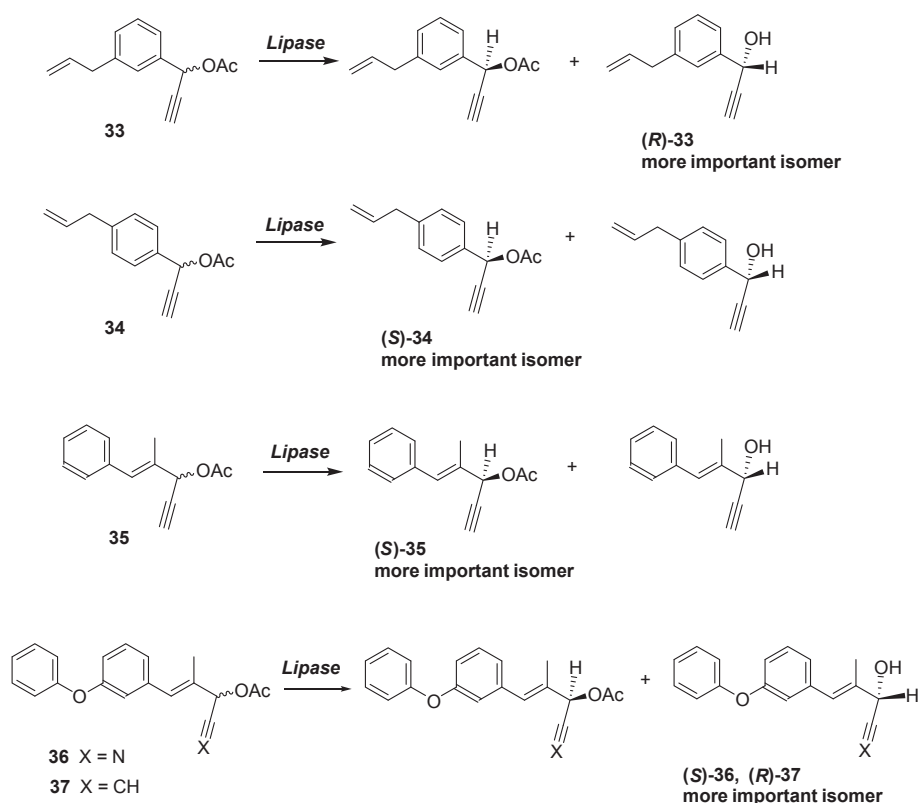


Fig. 30. Structure activity relationships of insecticidally more important isomers (3).

Table 10. Mammalian and environmental toxicities of pyrethroid insecticides

<i>Mammalian Aspect</i>	
Target Site	Sodium Channel in Excitatory Neurons
Acute Toxicity	Moderate (CS-Syndrome or T-Syndrome)
Fish Toxicity	Generally High except for Etofenprox and Silafluofen
Teratogenicity, Reproductive Toxicity, Carcinogenicity and Mutagenicity	No Noteworthy Findings
Metabolism	Rapid and Quite Extensive with Low Residues
<i>Environmental Aspect</i>	
Non-biotic Degradation (Hydrolysis & Photolysis)	Rapid/Moderate
Plants	Non-systemic, Biodegradable with Low Residues
Soil	Rapid Degradation, No Leaching
Aquatic Environment	Biodegradable with Low Residues
Non-target Organism	Practically Little Adverse Effects

syndrome such as hyperexcitability, choreoathetosis, and profuse salivation as acute toxic signs, or T-syndrome, which is characterized by tremors, depending on the structure. That is, α -cyanopyrethroids generally induce CS-syndrome, whereas non-cyano pyrethroids induce mainly T-syndrome.

To date, risk assessment of these pyrethroids in humans has revealed no noteworthy findings, and no teratogenicity, reproductive toxicity, mutagenicity, or carcinogenicity. In the field, even so-called photo-stable pyrethroids are rapidly degraded in plants and soils with low residues. They are also biodegradable

in aquatic organisms. Residual pyrethroids in tissues are generally quite low, and although the parent pyrethroids tend to be very lipophilic, similar to DDT, no bioaccumulation is observed after subacute dosing in mammals. It is well recognized that their rapid biodegradation results in little environmental contamination. Although most pyrethroids, including natural pyrethrins, are inherently very toxic to fish and daphnia, they do not cause severe adverse effects due to strong adsorption to soil particles in the water. In addition, they have very low toxicity to avian species. Overall, as a pesticide, pyrethroid insecticides appear to have favorable features for mammals and the environment.

5. The appearance of pyrethroid resistant mosquitoes and future aspects of pyrethroids

In Africa long-lasting insecticidal nets are widely used to protect people from mosquitoes that carry malaria, dengue, and yellow fever diseases. Permethrin, cypermethrin, and deltamethrin are mainly used as active ingredients in nets. DDT and pyrethroids have the same mode of action. The intensive use of DDT and pyrethroids has resulted in the appearance of pyrethroid-resistant mosquito strains.

Notably, these mosquito strains also appear in some parts of Southeast Asia. A couple of main biochemical mechanisms for the pyrethroid resistance have been investigated. One is the target-site mutations. Among them, the so-called knockdown resistance mutation (*kdr* mutation) is the most common. Another is amplification of the metabolic detoxification enzymes.

Horstmann and Sonneck reported that cytochrome P450-detoxification enzymes were unable to degrade tetrafluorobenzyl pyrethroids (transfluthrin), as shown in Fig. 31.⁶⁹⁾ Therefore transfluthrin is still effective against metabolically resistant mosquitoes. Kawada also reported that metofluthrin was active against metabolically resistant mosquitoes in Southeast Asia (private communication). Because transfluthrin and metofluthrin have high vapor pressure at ambient temperature, they cannot be used for long-lasting insecticidal nets.

I recently invented 2-bromo-3,5,6-trifluorobenzyl pyrethroids (Fig. 32).⁷⁰⁾ Despite their lower vapor activity compared with transfluthrin and metofluthrin, they have lower vapor pressure. Due to this advantageous feature, they have much longer lasting efficacy than transfluthrin and metofluthrin. This finding could provide insight into a distinctive

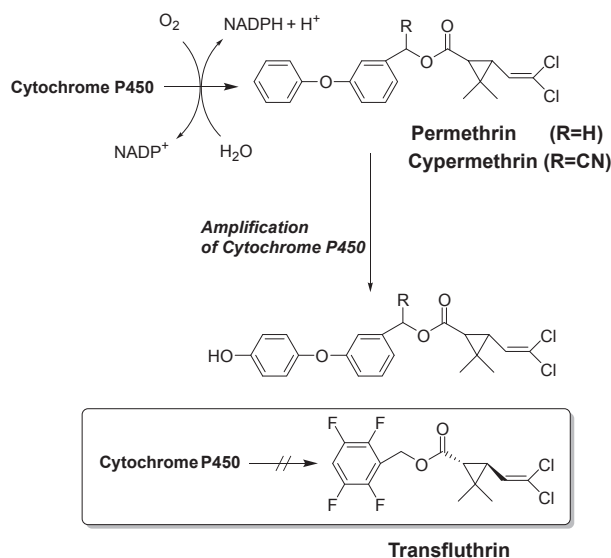


Fig. 31. Detoxification by cytochrome P450 enzymes on the phenoxybenzyl ring and block against detoxification by P450 enzymes on the polyfluorobenzyl ring.

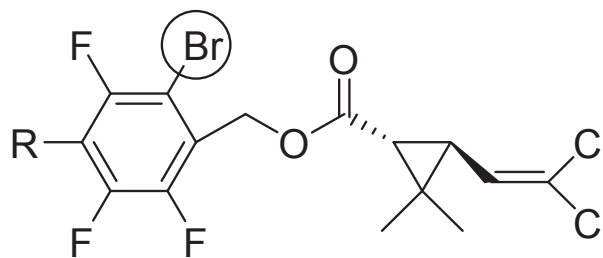


Fig. 32. A new 2-bromo derivative against pyrethroid-resistant mosquitoes (Matsuo 2017).

resistance management tool to overcome metabolic resistance in the future.

From the 1970s through 2000, most of the chemical companies in the world participated in the search for a new pyrethroid, and thousands of patents were filed. At present, these chemical companies have discontinued pyrethroid research due to the appearance of pyrethroid-resistant insect-pests. Many agrochemical companies are, in turn, trying to find a new insecticide with a different mode of action from pyrethroids. However, I still believe that we will find a new pyrethroid being active against pyrethroid-resistant insect-pests, especially against mosquitoes.

6. Concluding remarks

It is becoming very difficult to find a new commercial product for agrochemicals and pharma-

ceuticals. The probability for the discovery of one new commercial agrochemical is said to be lower than one out of 100,000 synthesized compounds. The background of the selected commercial pyrethroids had their own stories. I believe that a chemist's own intuition, merging ideas, and referring to different field's information, are very important for inventing a new compound. And, sometimes it is important to doubt the established theories in one's field. I believe the most important factor is insight into the "chance" happening around oneself.

Louis Pasteur said "Chance favors the prepared mind".

Acknowledgements

I thank Professor Yoo Tanabe (Kwansei Gakuin University) for his whole editing effort, and Ms. Momoyo Kawamoto and Ms. Mizuki Moriyama (Kwansei Gakuin University) for creating the figures and tables. I also thank Mr. Hisashi Ueyama (the Senior Managing Director of Dainihon Jochugiku Co., Ltd.) for providing pictures of pyrethrum flowers and a mosquito coil, and Mr. Ray Nishimoto (the Executive Vice President of Sumitomo Chemical Co., Ltd.) for providing a picture of Olyset Net and financial support.

This paper is dedicated to the late Professor Emeritus Kenji Mori at the University of Tokyo.

He passed away on April 16, 2019.

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(Received Mar. 22, 2019; accepted May 15, 2019)

Profile

Noritada Matsuo was born in 1946. He graduated from the University of Tokyo in 1970, and joined Sumitomo Chemical Co., Ltd. in 1970 as a researcher and started his research on the screening of new pyrethroids and their process chemistry. He received his Ph.D. under the direction of Professor Masanao Matsui (the University of Tokyo) on studies of pyrethroids in 1977. He was promoted to Research Fellow in 1999. He resigned from Sumitomo Chemical in 2011 and started his work at Dainihon Jochugiku Co., Ltd. in the same year. After leaving Dainihon Jochugiku in 2016, he immediately joined Professor Yoo Tanabe's group (Kwansei Gakuin University) to continue his long-running pyrethroid studies.

He received Technology Award in 1982 from the Japan Society for Bioscience, Biotechnology and Biochemistry for the discovery of Cyphenothrin and Fenpropathrin, and he received Technology Awards from the Pesticide Science Society of Japan in 2008, and the Chemical Society of Japan in 2010, both for the discovery of Metofluthrin.

He changed his first name “Takashi” to “Noritada” in 1979. He is the inventor of over 380 patents and the author of 45 academic papers. He has been a Fellow of the Japan Society for Bioscience, Biotechnology and Biochemistry since 2015.

