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Review

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Pyrethroid insecticides.
Chapter I. Synthesis, structure, biochemistry and biosynthesis of pyrethroids

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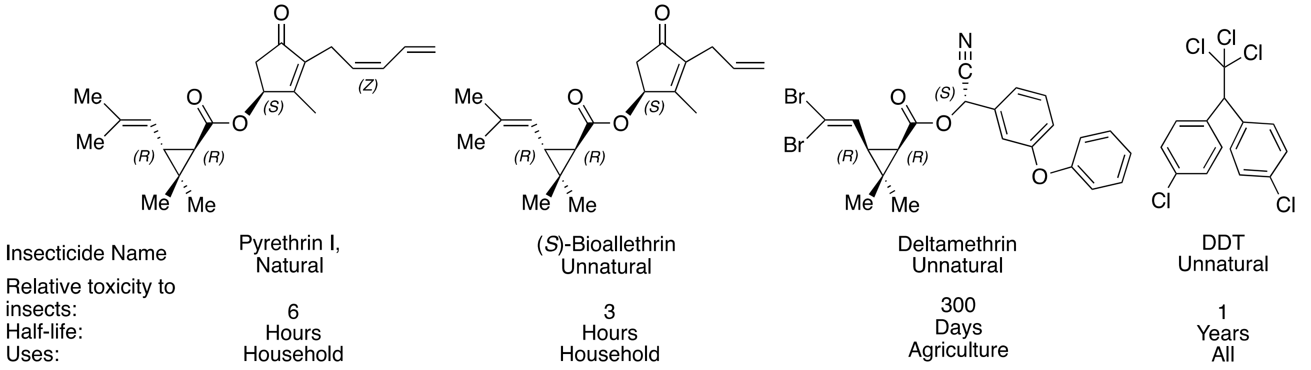
Abstract

The isolation and structure determination of the natural pyrethrins, powerful natural insecticides from the flower-head of C*hrysanthemum cinerariifolium*, a plant that originates from Dalmatia and Persia, was followed by extensive research work aimed to determine their biosynthetic pathway and, and to discover analogues, the pyrethroids, harmless to mammals, but adapted to fight insects in contextual conditions (indoor, outdoor, soil) and able to be commercialized at affordable cost.



Keywords: Pyrethroids, pyrethrins, biosynthesis, pyrethrin analogues, insecticides, applications

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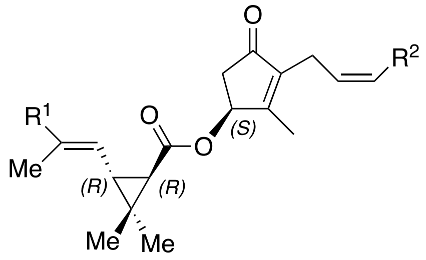
1. Aims of this Review

Pyrethrins, especially Pyrethrin I, a constituent of the plant *Chrysanthemum cinerariifolium*, have proved to be extremely powerful insecticides (Figure 1) but not suitable to cover the different needs of our modern society that require specific compounds possessing different life times in relation with the context in which they have to act (indoor, outdoor, domestic, agriculture, human or animal health) and available at affordable price. For that purpose and at the early stage of the structure determination of pyrethrins in the 1920s, chemists have synthesized analogs with the hope to achieve these goals.

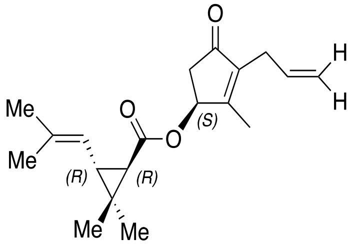
This review deals with the successful results of this research and especially the synthesis of some commercial pyrethroids such as allethrin, especially (*S*)-bioallethrin (**1g**), prallethrin (**1h**), methofluthrin (**1i**), cypermethrin (**1j**) and deltamethrin (**1k**) (Figure 2). Those are sold as mixtures of stereoisomers (allethrin, prallethrin, methofluthrin, cypermethrin) or as enantiopure substances ((*S*)-bioallethrin and deltamethrin). The data covered in this review are huge due to the variety of domains snd the scientific challenges involved, the economic value of the research carried out and its impact on human and animal health. The work has been published over almost 100 years in national and international journals, often patented in different countries, and reported in different languages (German, Japanese, English and French first, then more recently Chinese).[1]

Chrysanthemum
cinerariaefolium
flower

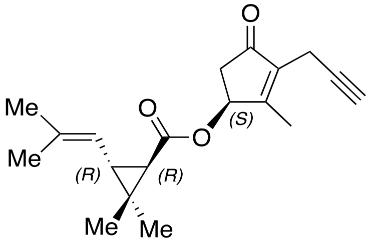


N°	R1	R2	Name	%$	LD50°	KD*
1a	CH_3	$CH=CH_2$	Pyrethrin I	38	10	10
1b	CO_2CH_3	$CH=CH_2$	Pyrethrin II	35	03	26
1c	Me	CH_3	Cinerin I	07.3	07	08
1d	CO_2CH_3	CH_3	Cinerin II	11.7	02	10
1e	Me	CH_2CH_3	Jasmolin I	04.0		
1f	CO_2CH_3	CH_2CH_3	Jasmolin II	04.0		

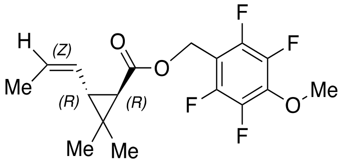
Figure 1. Natural pyrethrins: Their structures,[1] their relative amounts in *C. cinerariaefolium*. °Their lethal activity (LD_{50} refers to the lethal dose (LD_{50}), the dose that causes death in 50 % of the treated organisms generally expressed as mg of chemical per kg.



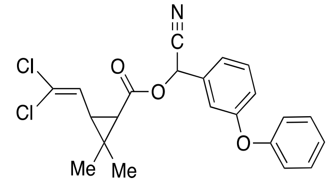
1g; S-Bioallethrin (Roussel-Uclaf, 1952)



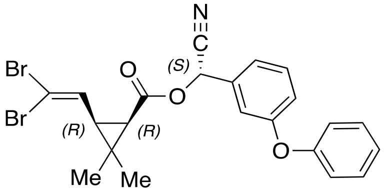
1h Prallethrin (Sumitomo, 1998)



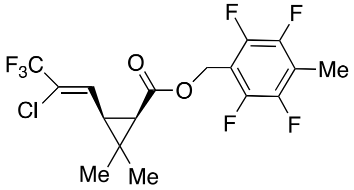
1i; Methofluthrin



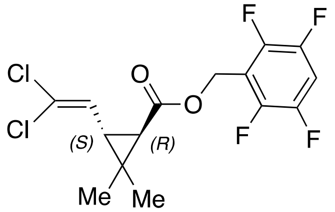
1j; Cypermethrin (Rothamsted Research, 1974)



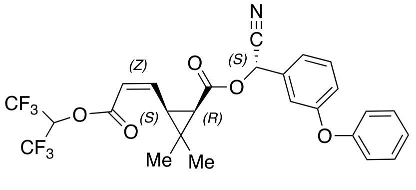
1k; Deltamethrin (Rothamsted Research, Roussel-Uclaf, 1974)



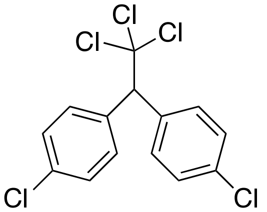
1l; Tefluthrin (ICI, 1987)



1m; Transfulthrin (Bayer, 1976)



1n; Acrinathrin (Roussel-Uclaf, 1982)



7; Dichloro-diphenyl-trichloro-ethane (DDT, 1939)

Figure 2. Structures of some commercially available pyrethroids and of DDT.[1,2]

2. Uses and Structures of Selected Pyrethroids

The increasing skill of synthetic chemists in academia, research centers [Rothamsted Research (UK), Sagami Research Center (Japan)] and industry [Sumitomo Company (Japan), Roussel Uclaf (France), Bayer (Germany) Ciba-Geigy (Switzerland), Shell (The Netherlands, UK), DMC (US)] has allowed the design and synthesis of about 50,000 analogues, often in duplicate, from which only very few, the *pyrethroids*, have been marketed due to their exceptional biological properties, from which we have selected eight as representative examples to illustrate in Figure 2.[2]

2.1. Indoor insecticides for household and domestic use [3-5]

2.1.1. The racemic allethrin.[3] Its more active enantiomer *(S)-bioallethrin* (**1g**) (Figure 2) [the (*S*) is four times more active than the (*R*)], missing the terminal C=C double bond on the cyclopentenolone moiety that simplifies the synthetic efforts due to the absence of one stereogenic center as compared to the pyrethrins (**1a**, **1b** and **1c**).

2.1.2. Prallethrin. (**1h**) used as household insecticide for the control of mosquitoes and as an insect repellent. It is also the primary insecticide in certain products to kill wasps and hornets, especially the content of their nests. Prallethrin is, as for the other pyrethroids, of low mammalian toxicity, with no evidence of carcinogenicity, toxic to fish but interestingly of low toxicity to birds.[6] It resembles the structure of (*S*)-bioallethrin (**1g**) since the replacement of the terminal C=C double bond by a C≡C triple bond avoid additional stereochemical problems encountered with pyrethrins (**1a**, **1b** and **1c**). Prallethrolone, its alkoxy constituent, especially its (S)-enantiomer, proved to be a valuable starting material for the synthesis of natural pyrethrins as well as allethrin.

2.1.3. Methofluthrin. (**1i**) (Figure 2), a recent discovery by the Sumitomo Company [5,7,8] missing one allylic methyl group and possessing a heavily fluoro-substituted benzyloxy group in place of the retrolone moiety, that confers a higher volatility compared to pyrethrin I, suitable for vaporization in confined atmospheres. Methofluthrin exhibits even higher insecticidal properties and knock down effect (25 and 40 times respectively) against mosquitoes and cockroaches than *S*-bioallethrin **1g** against the Egyptian mosquito *Culex pipiens* and *Culex quinquefasciatus* in mosquito coils.[2,7,8]

Other insecticides have been adopted for indoor use: cypermethrin (**1j**) and deltamethrin **1k** have been successfully used, combined with the synergetic piperonyl butoxide (PBO)[9] **8** (Figure 3), on insecticide-treated nets to prevent malaria,[10] since *Anopheles* mosquitoes are crepuscular or nocturnal. A similar approach cannot however be used to prevent tiger mosquitoes (*Aedes albopictus*) to transfer the Zika virus since they fly and feed in the daytime as well.

2.2. Outdoor insecticides for agricultural use

Insecticides for agriculture involving outdoor use have to be as poorly volatile as possible. The most relevant compounds are cypermethrin (**1j**), and deltamethrin (**1k**), belonging to the permethrin family) possess halogens in place of the two-methyl groups on chrysanthemyl part and a completely different alkoxy group 3-phenoxy mandelonitrile (the cyanohydrin of 3-phenoxy benzaldehyde). The presence of vinylic halogens in place of the methyl groups prevents their photooxidation and the *cis*- instead of the *trans*-stereochemistry between the vinyl and the carboxy groups hinders the later and slow down the ester hydrolysis increasing thus the stability of those pyrethroids to atmospheric degradation under sunlight. This leads to enhanced insecticidal properties that make them the ideal insecticide for outdoor uses in agriculture.[11-14]

2.2.1 Cypermethrin. (**1j**, Figure 2) possessing two vinylic chlorine substituents, is sold as a mixture of stereoisomers in which the one that possesses the same stereochemistry 1(*R*)-*cis*-stereochemistry, as deltamethrin (**1k**), is by far the most active although less efficient.
2.2.2. Deltamethrin. (**1k**, Figure 3) that bear two vinylic bromine atoms in place of the methyl group on the chrysanthemic part and sold as a single stereoisomer, that possesses the 1(*R*)-*cis*-geometry on the cyclopropane ring and (*S*)-configuration at the benzylic carbon on the alkoxy group, is by far the most active insecticide. [15-17]
2.2.3. Tefluthrin. (**1l**, Figure 2) that contain a carboxylic moiety similar to that of cypermethrin (**1j**) in which one of the vinylic chlorine, the one *cis* to the vinylic hydrogen, is replaced by a trifluoromethyl group linked to a highly fluorinated aryloxy group proved to be active against soil insects. [18,19]
2.2.4. Acrinathrin. (**1m**, Figure 2), which is sold as a single enantiomer, possesses the alkoxy moiety of deltamethrin (**1j**) but an atypical carboxy moiety resembling that of chrysanthemum acid with a *cis*-instead of *trans*-stereochemistry on the cyclopropane ring and a carboxy group on the α,β-disubstituted *Z*-C=C double bond. Acrinathrin (**1m**) is an efficient acaricide that is used among others for table and wine grape and strawberry protection.[20,21]

In most of the cases a single cyclopropane enantiomer, the (1*R*), concentrates the insecticidal activity whether it possesses, the *trans*- (in **1a**, **1b**, **1c**, **1d**, **1e**, **1f**, **1g**, **1h**, **1i, 1m**) or the *cis*- (in **1i**, **1j**, **1k**, **1l**, **1n**) relative stereochemistry on the cyclopropane ring. It is therefore evident that the use of enantiomerically pure pyrethrins and pyrethroids is the safer and the more ecological choice although for economic reasons, a mixture of isomers is often sold.

Some data on the persistence of some selected commercial pyrethroids in the environment and their relative insecticidal potency over seven insect types are listed in Table 2 and are compared to that of DDT.

Table 2. Data on the persistence in the environment and the relative insecticidal potency of some commercially available insecticides [22, 23]

Date of discovery	Insecticide name	Number	Persistence in environment	Relative insecticidal potency
	Pyrethrin I	**1a**	Hours	50
1949	DDT	**7**	Years	8
1949	Bioallethrin	**1g**	Hours	25
1974	Cypermethrin	**1j**	Weeks	290
1974	Deltamethrin	**1k**	Weeks	2300

It is interesting to notice that, whereas in the mid-1950's, racemic mixtures of medicines were administered to cure humans, twenty-five years later diastereomerically and even enantiomerically pure pyrethroids are used to kill insects. This has only been possible because chemists have been able to achieve it scientifically but at the industrial level through research and education.

3. Commercial and Economic Aspects

The topic is exceptionally rich in many aspects and purposes, supported by a large amount of data from industry, academy and research institutes such as Rothamsted Experimental Station (UK) and Sagami Research (Japan)]. Unfortunately, many industries such as Ciba Geigy (Switzerland), ICI (UK), Roussel-Uclaf (France), Rhone Poulenc (France), Zeneca (UK) no longer exist due to the merging process that has not only affected the life of many chemists and chemistry as well and has probably destroyed the beneficial effects of competition. Others, like Sumitomo (Japan), Bayer (Germany), and FMC (USA), are still active and a few have been created in the merging processes (Syngenta). The subject is essentially transdisciplinary,[24,25] covering agriculture, human and animal health, medicine, biology, chemistry, and economy as well and could be exploited as testbed for education[26] and research. At the difference of most of the compounds synthesized by chemists, pyrethroids are economically valuable [market size in 1985: $1.5 billion; amount sold: 1000 tons, surface covered: 80 million hectares (1.5 time the area of France)] and have been marketed all over the world (1987)[22] to protect cotton crops (46 %) and to a minor extent, fruits and vegetable crops (22 %) and for animal health (9%).[22] Their structures, although less complex than that of steroids,[27] share with them the basic structural complexity that requires stereocontrol and the nature and number of functional groups distributed over around two times 10 carbon atoms linked by an ester group can be view as a model of the more complex compounds that have been synthesized since the beginning of the 20th century and for which E. J. Corey has proposed to use a retrosynthetic analysis approach.[28]

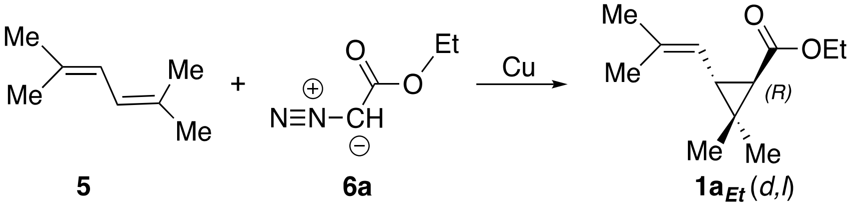
The needs as well as economic aspects related to their use to fight different sorts of insect (flying, running, crawling, swimming) under different conditions (indoor, outdoor) led industry to conceive, test, produce in industrial quantities compounds possessing adequate structural modifications and for that purpose favored to international competition and collaboration between several companies not only to search for new analogues with specific properties but also for synthetic methods that would allow to access them at the industrial level with the highest regio and stereocontrol, at a reasonable price. This has led to the description of an exceptionally large variety of different methods and strategies especially for the synthesis of the vinylcyclopropanecarboxylic acid moiety.

Although the synthesis of pyrethroids is the main topic of this review (Section 4), we will also cover (i) some biology of natural pyrethrins, especially their biosynthesis, which is a source of inspiration for their synthesis (Sections 5.2-4) and (ii) the toxicity of pyrethrins and pyrethroids towards insects and other living organisms that include mammals, birds and fish (Section 5.1). We will briefly comment each of the two aspects (Section 5.1) and will provide a selection of references to allow the reader to enter more deeply the subject (Section 6).

4. Synthesis of Pyrethrins and Pyrethroids

This review offers the occasion to compare, through critical analyses, the different published synthesis of pyrethrins and pyrethroids especially those related to industrial syntheses,[29] to the notions of synthetic strategies,[28] synthons,[30] strategic bonds,[31] convergent and linear syntheses. [27,32] It provides an exceptional occasion objectively to compare chemists' creativIty to that of the nascent artificial-intelligence-based programs,[28] to judge how the ten "green chemistry" principles[33] and metrics apply to the reported industrial syntheses, to what level they sustain ecology and at what cost.[24,25,27,28,32,33]

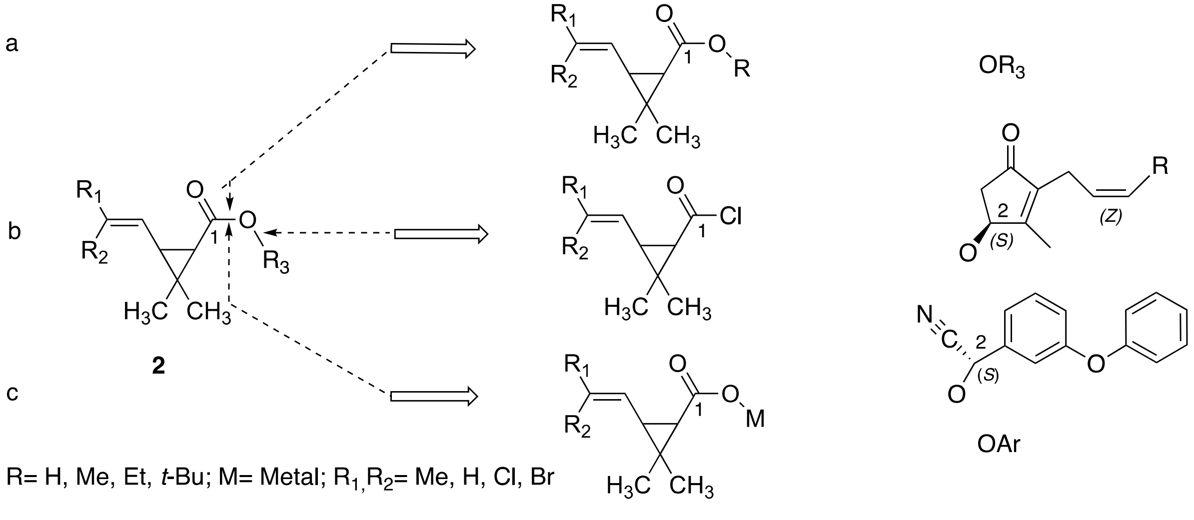
Synthetic aspects will be discussed in detail and they will be organized as much as possible according to the strategy used rather than to the method or the reagent involved. The concepts will be favored over the yields that can be improved by new knowledge or new tricks. This is exemplified by the strategy used by Staudinger[34] who discovered the cyclopropanation reaction involving compounds possessing a C=C double bond and diazo compounds in the presence of copper turnings as catalyst and synthesized the first few grams of ethyl chrysanthemate in extremely poor yield and as a stereoisomeric mixture (Scheme 1). The same reaction using similar starting materials and the same metal, but liganded by chiral catalyst, is presently used on a ton scale by the Sumitomo company to produce chrysanthemates in very high yield and high stereocontrol, as we shall see.



Scheme 1. The first synthesis of ethyl chrysanthemate by Staudinger in 1924.[34]

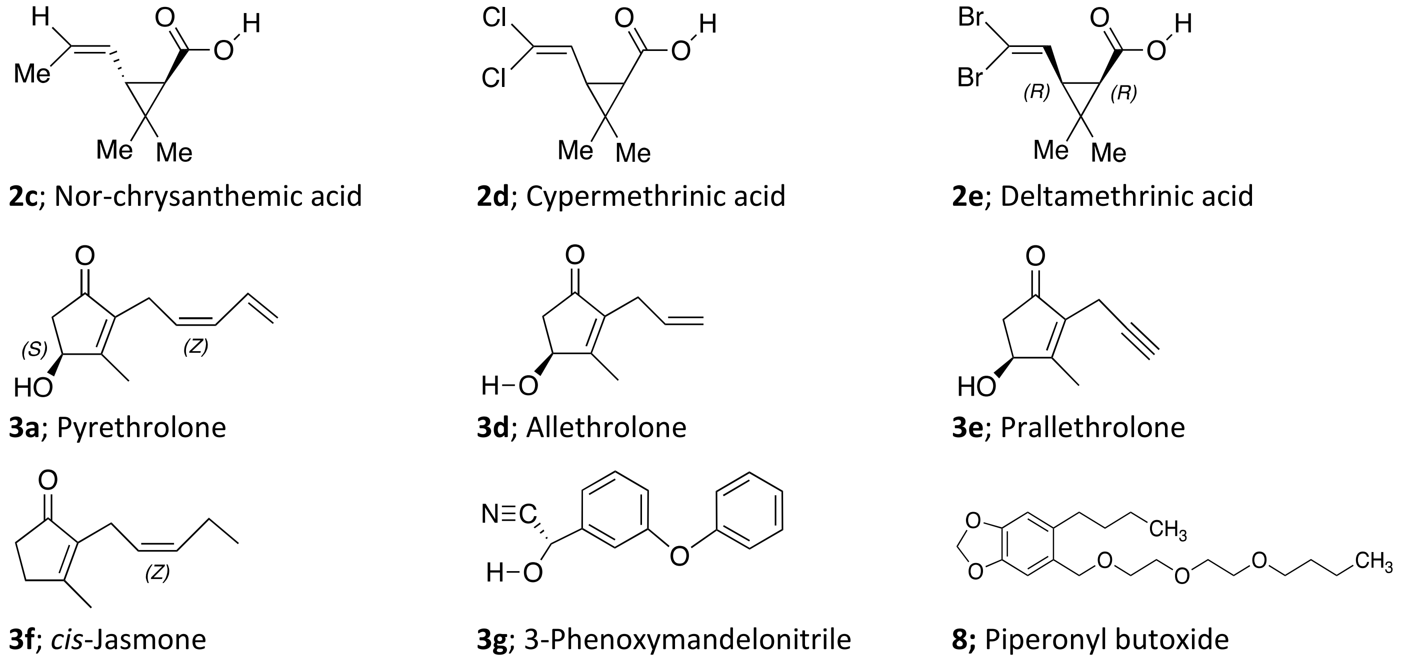
The synthesis of pyrethroids, as the biosynthesis of pyrethrin I (also named chrysanthemum monocarboxylic acid pyrethrolone ester), has usually been achieved at the last stage (Scheme 2) by: (i) esterification of the vinyl cyclopropane carboxylic acids (**2a**, **2b**, **2c**, **2d**, **2e**) or one of their activated forms (such as carboxylic acid chlorides, anhydrides) or (ii) transesterification involving one their methyl, ethyl or related esters. Depending upon the nature of the insecticide, the required partner would be a rethrolone (**3a**, **3b**, **3c**, **3d**, **3e**), a cyanohydrin (**3g**), a benzyl alcohol or a phenol or one of their activated form. Except the latter, each of the two families of building blocks possess asymmetric centers and can be used as a mixture or as a single stereoisomer. However, the only stereoisomer that carries the insecticide property as in enantiopure (*S*)-bioallethrin (**1g**) and deltamethrin (**1k**), possesses the (1*R*)-stereochemistry on the cyclopropane ring and the (*S*)-configuration on the carbon bearing the hydroxyl group of the rethrolone or of the cyanohydrin.

The method selected for the formation of the alkyl carboxylates is crucial if it involves enantiopure (*S*)-rethrolones or (*S*)-3-phenoxymandelonitrile since it is expected to occur with retention of configuration at the alkoxy carbon C2 if the C1,O-bond is formed in the process (Scheme 2, entries a,b) and by inversion of configuration there if the O,C2-bond is instead formed (Scheme 2, entry c). We will therefore review the syntheses of the natural and unnatural rethrolones, cyanohydrins, chrysanthemic acid, nor-chrysanthemic acid and permethrinic acids as well as the methods to produce the corresponding esters.



Scheme 2. Strategies used for esterification of pyrethroids involving the concomitant formation of either their C-O or the O-R^3 bonds

Until now pyrethrins, the natural products, have only been involved as models and only used for commercial purpose as extracted as a mixture from nature as a powder of the dried flowerhead or as its oily extract. The large cost of growing the plants for more than a year before the content is adequate for the required purpose, the unpredictable weather conditions, the ecological pressure, and the increasing demand for more natural products leads us to suspect that in the near future, mixtures of pyrethrins of synthetic origin and similar to that present in nature could be commercialized and for that purpose the synthesis of pyrethrolone (**3a**), cinerolone (**3b**) and jasmololone (**3c**) will be integral part of this review, besides the unnatural rethrolones (Figure 3).



2c; Nor-chrysanthemic acid **2d**; Cypermethrinic acid **2e**; Deltamethrinic acid

3a; Pyrethrolone **3d**; Allethrolone **3e**; Prallethrolone

3f; *cis*-Jasmone **3g**; 3-Phenoxymandelonitrile **8;** Piperonyl butoxide

Figure 3. Structure of some typical commercially available pyrethroids and their synergists. [2,4]

Stereochemical problems are widespread in this review since pyrethrins and pyrethroids contain usually up to four stereogenic centers and have been used as insecticides as mixture of stereoisomers and enantiomers or as an enantiopure isomer (It refers to one single stereoisomeric form) and therefore the structural aspect is tied up with the biological, ecological and economic aspects and, with respect to the latter, the "cost" governs even more than the "science" field.

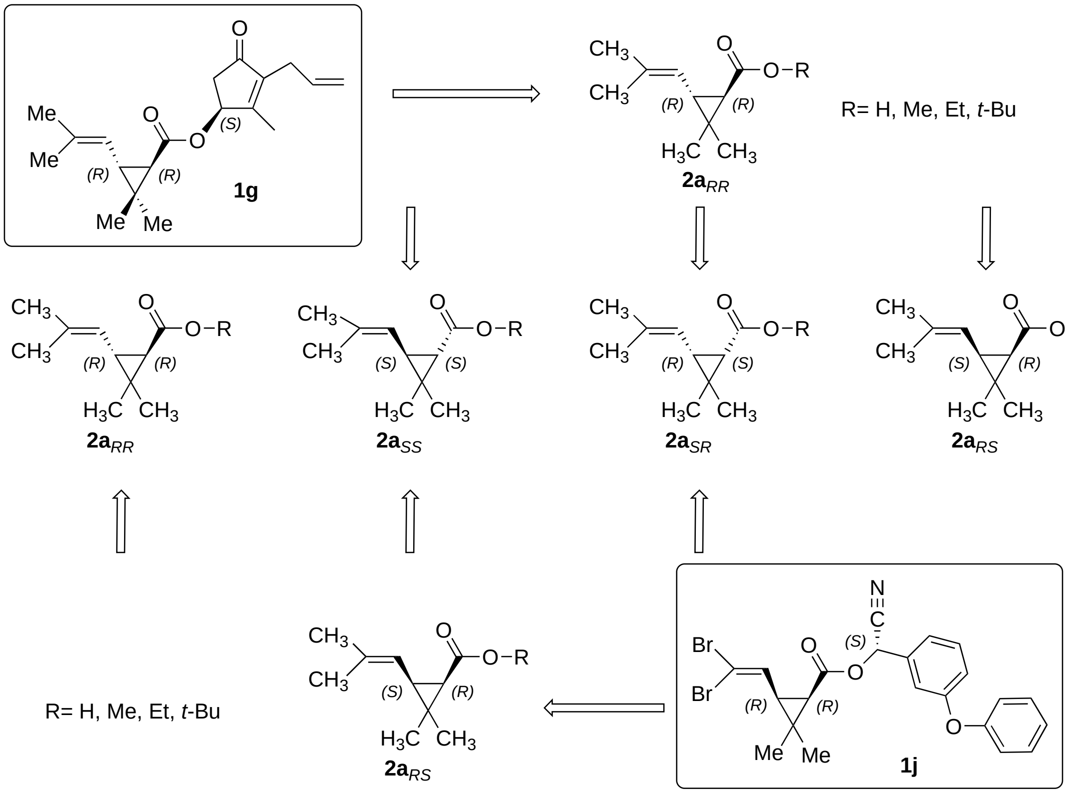
Over the years, diastereoselective and enantioselective syntheses have emerged, novel synthetic methods and novel separation techniques (for example the use of lipases) have been discovered and applied to the pyrethrin/pyrethroid domains. This will be reflected in the review that will allow each one to compare them (number of steps and purity of the requested products) according to its own standard. In case of the synthesis of stereoisomeric mixtures (*cis*/*trans* and *R*,*S*), strategies involving the separation and the recycling of the undesired stereoisomers play a crucial role in the selection of the method used. It will often offer a valuable alternative to enantioselective syntheses which rarely produce a single product and anyhow require the use of separation techniques and require the use of elaborated enantiopure catalysts that must be separated from the medium, purified and reused. With that respect the description of hemi-syntheses that use enantiopure building blocks of natural origin, readily available at low prices and possessing the adequate functional groups to allow diastereoselective transformations leading to the requested enantiomer of pyrethrin/pyrethroids could be advantageous.

The synthesis of pyrethrins and pyrethroids will be discussed in this review as two different topics each one being separately organized, that involve the construction of the carbon frameworks of (i) the vinyl cyclopropane carboxylic moiety and focus on the formation of the cyclopropane ring and the linked carboxy and vinylic appendages, and (ii) the alkoxide moiety as (a) the rethrolone that will focus on the formation of the cyclopentane ring possessing the γ-hydroxy-α,β-unsaturated ketone functionality and the proper appendages with the correct stereochemistry, if any, at C2, and (b) the labile cyanohydrin moiety derived from an aromatic aldehyde, both as racemates or possessing the required stereochemistry at the carbon bearing the hydroxyl group. The esterification reaction that is required to link the two different units will be disclosed in the section related to the reactivity of chrysanthemic and permethrinic acids and related compounds.

Among the different compounds involved in those syntheses, chrysanthemic acid (**2a**) and prallethrolone (**3e**) play a pivotal role since they are readily accessible; their stereoisomers can be readily interconverted and they can be transformed easily into the other members of the series as discussed below.

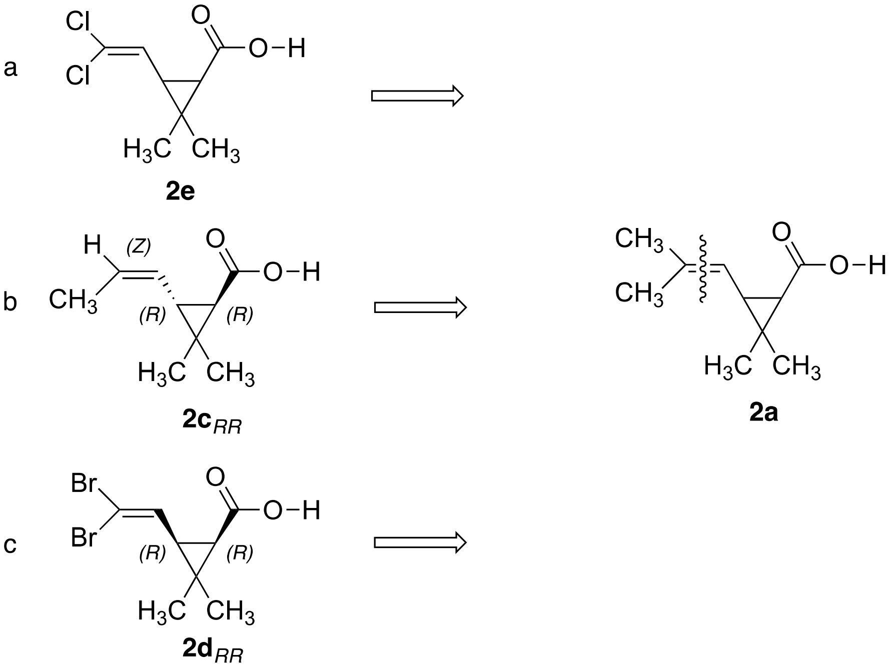
Prallethrolone (**3e**), when reacted with chrysanthemic acid, produces prallethrin (**1h**) that, as already seen, possesses interesting biological properties. Its racemic acetate has been very efficiently resolved and the undesired enantiomer properly recycled. Its terminal triple bond has been reduced to allethrolone or after vinylation or alkylation has been selectively reduced, leading to racemic as well as to enantiopure pyrethrolone (**3a**), cinerolone (**3b**) and jasmololone (**3c**) precursors of natural pyrethrin (**1a**) cinerin (**1b**) and jasmolin (**1c**).

Chrysanthemic acid (**2a**) not only (i) allows the synthesis of a large variety of biologically active pyrethroids on esterification, but also (ii) the reactivity of its vinyl cyclopropane moiety as well as that of its carboxyl group that governs the detoxification of the related insecticides. This involves their reaction in sunlight and water present in the atmosphere, which lowers their lifetime and makes one of the crucial differences with DDT (**7**). For that purpose a special Chapter (Chapter IV) will be devoted to the reactivity of chrysanthemic acid (**2a**) and related esters.



Scheme 3. Retrosyntheses of allethrolone and deltamethrin involving isomerization of each of the three other stereoisomers of chrysanthemic acid.

That Chapter IV will also include some other reactivity of **2a** that has been successfully used at some specific aspects in the synthesis of chrysanthemic or their esters such as (i): the stereochemical inter-conversions implying the *cis*/*trans* (thermodynamic) or the *trans*/*cis* (contra-thermodynamic) isomerization that require (a) selective epimerization at C2 or/ C4 by cleavage / recombination of their C2-H or C4-H bonds or the cleavage/recombination of the C3-C4 or C2-C3 bonds (b) racemization by consecutive cleavage of their C2-H and C4-H bond or cleavage of their C2-C3 bond on the cyclopropane ring (Scheme 3) and (ii) the replacement of the isopropylidene moiety present in **2a** by an ethylidene, dichloromethylidene or dibromomethylidene moiety that provide an efficient synthetic route to norchrysanthemic acid (**2c**), cypermethrinic acid (**2d**) and deltamethrinic acid (**2e**, Scheme 4).

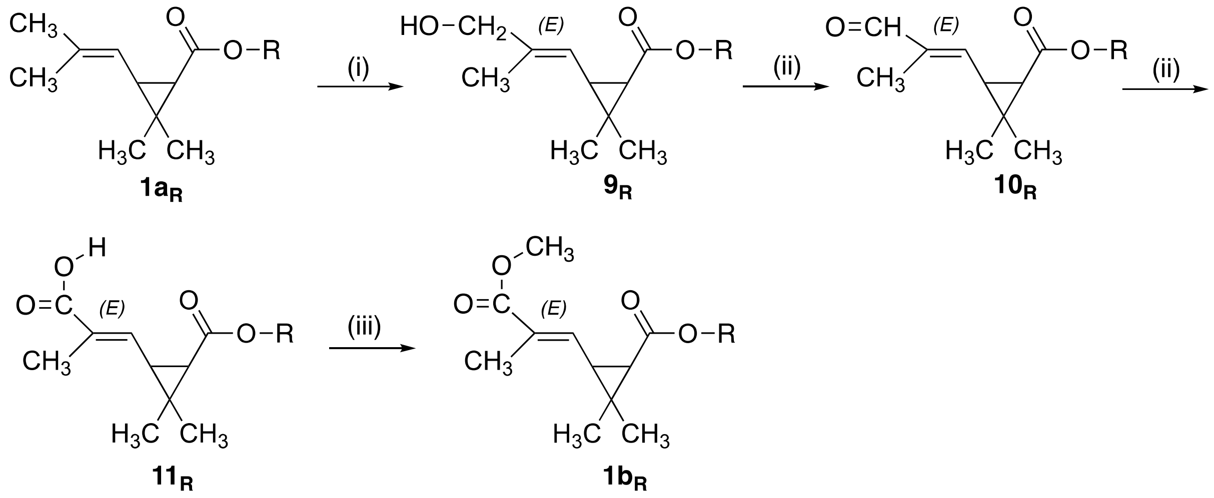


Scheme 4. Retrosyntheses of cypermethrinic acid, nor-chrysanthemic acid and deltamethrinic acid from chrysanthemic acid involving the cleavage of its C=C double bond.

5. Biology of Pyrethrins and Pyrethroids

5.1. Mode of action of pyrethrins and pyrethroids

Constituents of *Chrysanthemum cinerariifolium* possess different biological activity. For example, pyrethrin I is a stronger insecticide than pyrethrin II, but the more polar latter possesses a much stronger knock-down effect.[22] Pyrethrins and pyrethroids are neurotoxic. They are contact poisons which quickly penetrate the nervous system of insects, interfering with their peripheral and central systems and very rapidly paralyzing them. A few minutes after application, the insect cannot move or fly, and eventually dies, or recovers due to enzymatic detoxification involving oxidation.[35,36] In *C. cinerariaefolium*, this oxidation takes place stereoselectively on the *trans*-methyl group on the isobutenyl moiety as seen in Scheme 5 and produces methyl pyrethroate that is less toxic than pyrethrin I towards insects and mammals as well.[35] This biotransformation involves oxidases and dehydrogenases that uses pyridine nucleotide cofactor for the oxidation shown in the steps i and ii (Scheme 5) and a biomethylation reaction that involves S-adenosylmethionine as the methyl donor for the esterification reaction of step iii.[35] (Scheme 5)



Scheme 5. (i) Mixed function oxidase/NADPH (ii) alcohol dehydrogenase (iii) aldehyde dehydrogenase NAD (iv) biomethylation.

Although the mechanism of action of pyrethrins and pyrethroids is similar to that of DDT,[9] the latter misses the knockdown effect present in the former group such as methofluthrin (**1h**). This effect can be enhanced by addition of at least the same amount of piperonyl butoxide (**8**) as synergist (**1/8** ratio: 1/1-8) [36,37] that inhibits the detoxification enzymes and increases the lethal effects (Table 3).

Table 3. Synergetic effect of pyrethrins and piperonyl butoxide on knock down and lethal effect on insects

	Pyrethrum (mg)	**8** (mg)	Knock-down (%)	Lethal (%)
1	100	0	95	46
2	0	300	8	0
3	30	400	99	92

Voltage-sensitive sodium channels are the most significant sites of insecticidal action of pyrethrins and pyrethroids and are viewed as the principal sites of neurotoxic action in mammals.[38] In fact, pyrethrins / pyrethroids act on mammals as on insects except that mammals possess an esterase, missing in insects, that destroys pyrethroids and inactivates them faster than they act on the nerves.

The action of pyrethrins / pyrethroids on mammals is quite different if they possess a cyano group on their alkoxy moiety (type II pyrethroids such as **1j**, **1k**, **1n**) or not (type I pyrethrins and pyrethroids **1a**, **1g**, **1h**, **1i**).[38] Thus, whereas pyrethroids of type I induce in mammals a whole-body tremor (T syndrome), pyrethrins and pyrethroids of type II produce sinuous writhing convulsions (choreoathetosis) accompanied by salivation (CS syndrome). This difference could reflect the duration of the modified sodium current that last much longer with type II pyrethroids and result in more lethal effect since depolarization of the nerve axons and terminals is irreversible.[38,39]

As an example, deltamethrin (**1k**) that is probably the most powerful insecticide of this series is 400 times more toxic to insects than DDT and its toxicity to insects resemble that of tetrodotoxin to mammals (more than that of strychnine, cyanide or curare). Some typical information about the relative toxicity of some selected pyrethroids on flies and rats as model for insect and mammal families is listed below (Table 4).

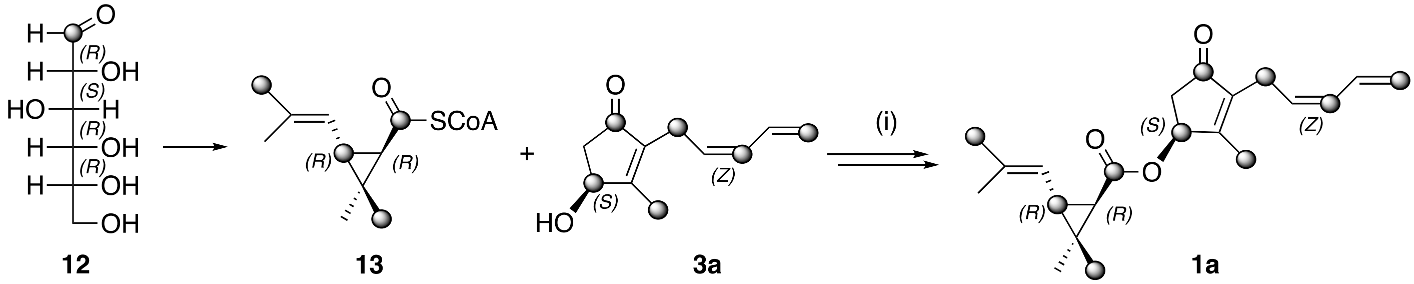
Table 4. Comparative lethal action of a few representative pyrethrins and pyrethroids on flies and rats as model for insect and mammal families

Insecticide		LD_{50} for flies (mg/kg fly)	LD_{50} for rats (mg/kg rat)
Pyrethrins	**1a**	16	580
Allethrin	**1g**	10	770
S-Bioallethrin	**1g*ss***	4	860.5
Cypermethrin	**1j**	0.065	297
Deltamethrin	**1k**	0.019	95

5.2. Biosynthesis of pyrethrin I

As already stated, pyrethrins are located in the yellow flowerhead of *Chrysanthemum cinerariifolium* that contains about 1-2 % of the insecticide when dried.[40] It has been also found by Katsuda [4,41] that pyrethrins are present in the leaves already two months after seeding with the amount of pyrethrin I changing over the seasons and has a close relationship with flowering, reaches a peak at 0.27-0.40 wt % during flowering (May after seeding that has taken place a year before in April) whereas the amount of pyrethrin II is much lower (0.05 wt %) and constant without seasonal changes for two years.[4,42]

Pyrethrin I (**1a**) is presumably biosynthesized in *C. cinerariaefolium* by esterification of (1*R*)-*trans*-chrysanthemoyl-CoA (**13**) with pyrethrolone (**3a**) by an acyl transferase,[40,42] as suggested by the location of carbon-13-labelled pyrethrin I obtained from *C. cinerariaefolium* fed with D-glucose (**12**) labeled at C-1 with carbon-13 (Scheme 6).[41]



12 **13** **3a** **1a**

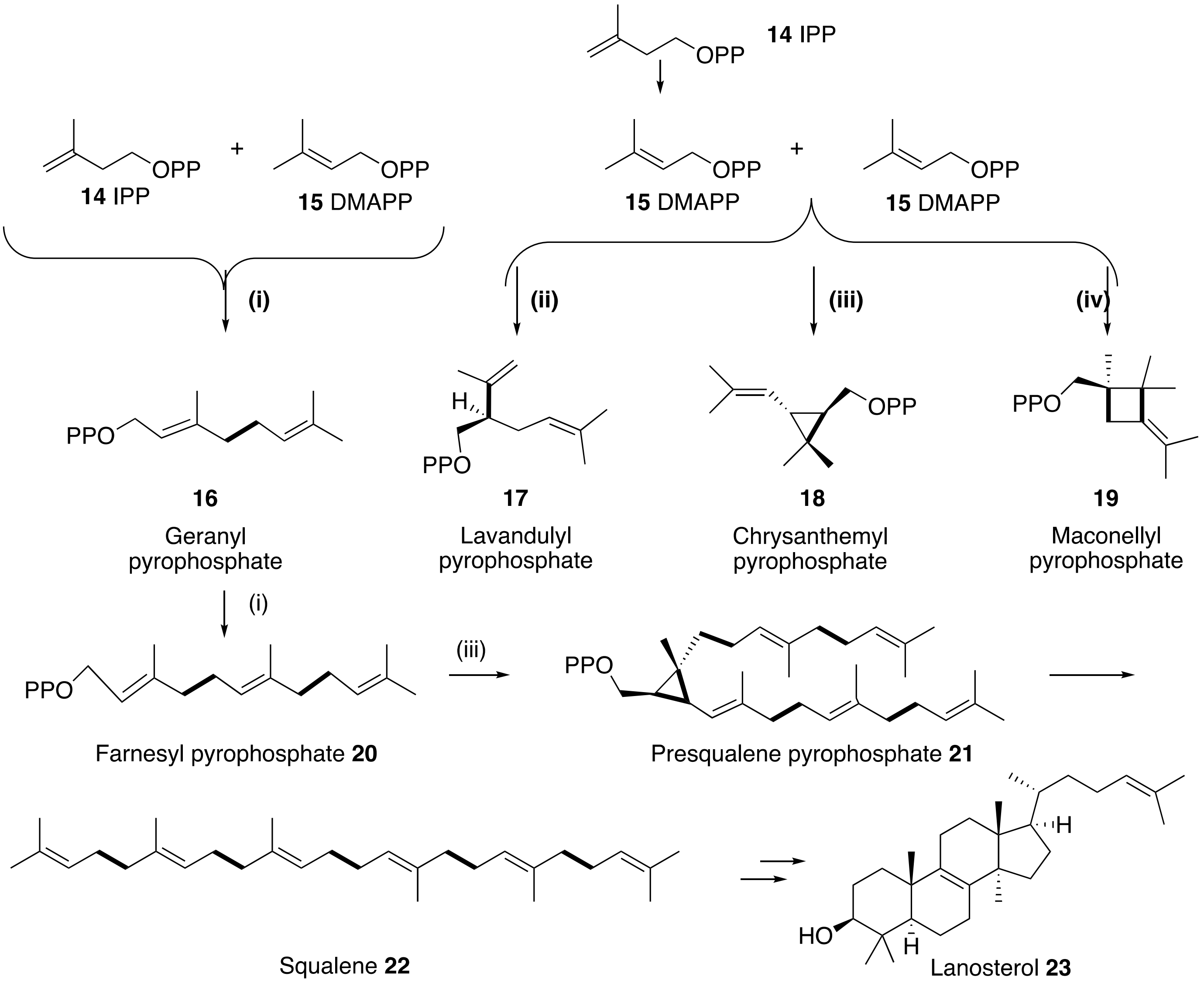
Glucose ● C-13 labelled carbon (i) Acyl transferase (presumably)

Scheme 6. Biosynthesis of pyrethrin I from (1*R*)-*trans*-chrysanthemoyl CoA and (*S*)-pyrethrolone from 1- C-13 radiolabeled D-glucose.

5.3. Biosynthesis of chrysanthemic acid 1a

Chrysanthemic acid **1a** with its ten carbon atoms belongs to the terpene family (10, 15, 20, 30-carbons) that contains around 55,000 compounds [43] whose biosynthesis [40,44] uses isopentenyl pyrophosphate (IPP, **14**), possessing a five-carbon skeleton, and its isomer the dimethylallyl pyrophosphate (DMAPP, **15**) that couple in different ways via different processes disclosed in Scheme 7. This coupling may take place either by (i) *Chain elongation* producing geranyl pyrophosphate (**16**) on the way to farnesyl pyrophosphate (**20**), presqualene pyrophosphate (**21**), squalene (**22**) then lanosterol (**23**), the precursor of cholesterol, Scheme 7, (ii) *branching* (lavandulyl pyrophosphate **17**, Scheme 7), (iii) *cyclopropanation* (chrysanthemyl pyrophosphate, (**18**, Scheme 7), or (iv) *cyclobutanation* (maconellyl pyrophosphate, **19**, Scheme 7).[44] Scheme 7 shows the biosynthetic pathway that produces chrysanthemic acid among the others involving the isoprenyl moiety.

Note that pyrethrins as well as steroids synthesis possess in common the same basic isoprene unit **14** and also the formation at one stage of a cyclopropane ring in [**18** (Route iii) and **21** (Route vi) Scheme 7]. Striking differences however exist in the intimate processes [compare Route (iii) to Route (i)] and the fact that the cyclopropyl pyrophosphate (**18**) is oxidized then esterified to pyrethrins in *Chrysanthemum cinerariaefolium*, whereas the cyclopropane ring in presqualene pyrophosphate (**21**) is destroyed leading to squalene (**22)** in mammals and *Saccharomyces cerevisiae*.

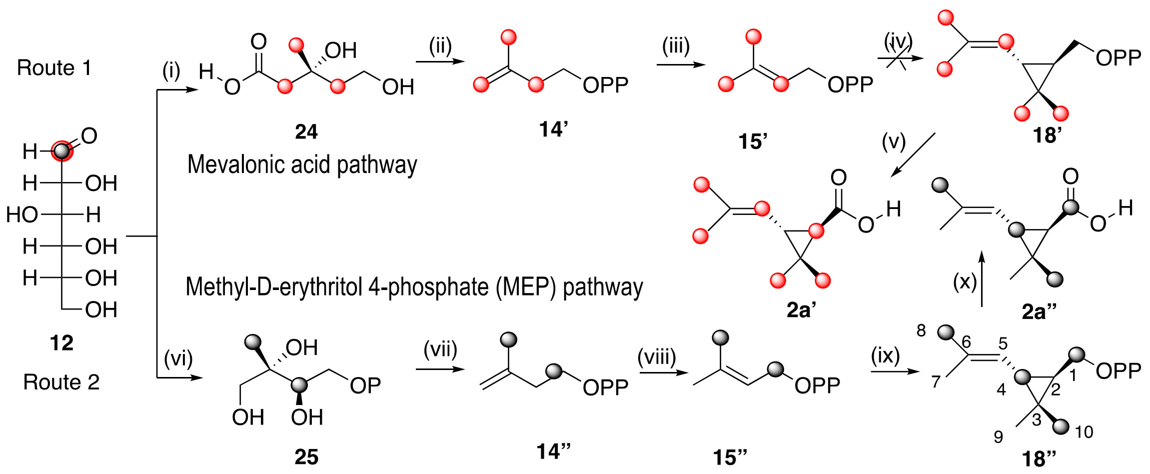


(i) Chain elongation (ii) Branching (iii) Cyclopropanation (iv) Cyclobutanation

Scheme 7. Biosynthesis of terpenes from isopentenyl pyrophosphate (IPP).

Surprisingly, the amino acid sequence of CPPase aligns closely with that of the chain elongation of prenyl transferase farnesyl pyrophosphate synthase leading to farnesyl pyrophosphate (**20**, Scheme 7) in the liver of mammals, and not with the one that produces presqualene pyrophosphate (**21**) in mammals that possesses a closely related structure to **18** and expected to be similar to the CPPase reaction.[45]

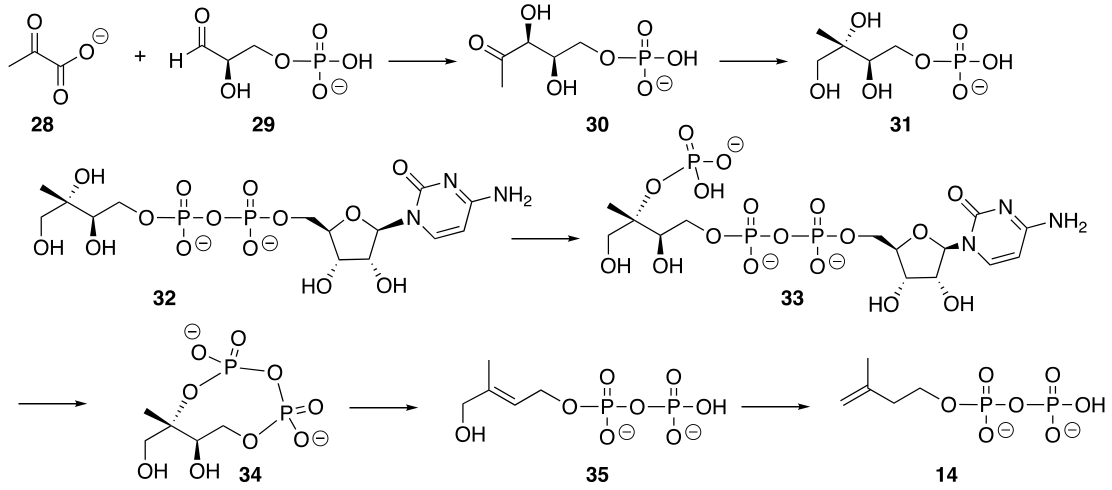
Isopentenyl pyrophosphate (**14**) could either be biosynthesized in a process that involves mevalonic acid **24** (Scheme 8, Route 1) or via methyl-D-erythritol 4-phosphate (MEP) **25** (Scheme 8, Route 2).[41]



Scheme 8. Expected different C-13 labeling of chrysanthemic acid and of its precursors from labeled D-glucose through the "mevalonic" and "MEP" biosynthetic pathways.

Incubation of young leaves of *Chrysanthemum cinerariifolium* with D-glucose (**12**) labeled at C-1 with carbon-13 provides chrysanthemyl pyrophosphate (**18"**) labeled at ^{13}C-1, ^{13}C-4, ^{13}C-8 and ^{13}C-10 that unambiguously supports the MEP pathway (Scheme 8, Route 2 instead of Route 1).[41]

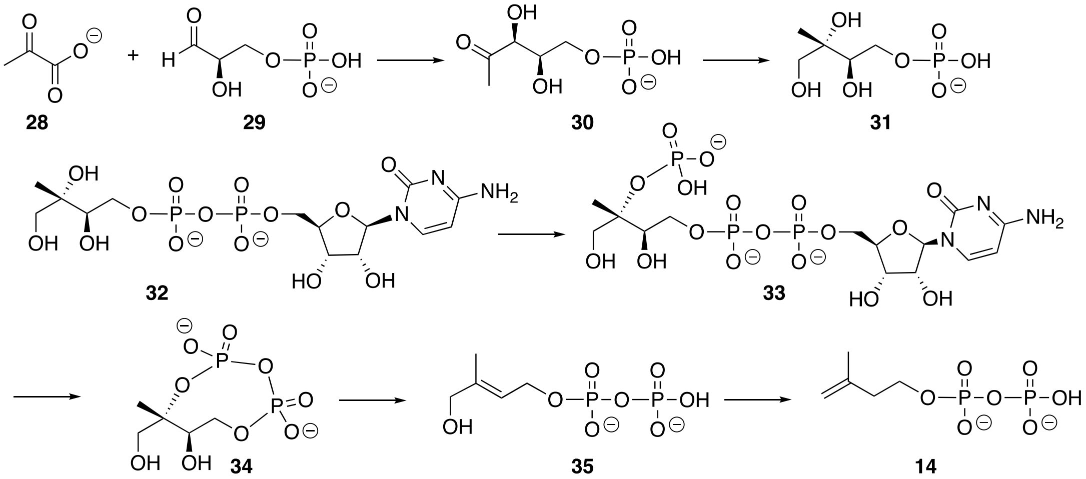
The cyclopropanation reaction is expected to proceed from the coupling of two dimethyl allyl pyrophosphate (**15"**, DMAPP) units as disclosed in Scheme 9. Accordingly the coupling involves the action of an external nucleophile across the C=C double bond of DMAPP (**15"**) followed by the addition of the allylic carbon of another subunit (**15"**). Subsequent reaction of an exogeneous base adequately located in the enzymic environment promotes the 1,3-elimination reaction leading to the formation of the cyclopropane ring the enzyme being responsible of stereocontrol leading to (**18"**).



Scheme 9. Proposed mechanism leading to chrysanthemyj pyrophosphate from dimethyl allyl pyrophosphate.

The methylerythritol phosphate (MEP) pathway to isoprenoids, briefly disclosed in Scheme 10,[46] has been found unexpectedly by Rhomer [46,47] to be operative in most prokaryotes, green algae as well as some higher plants.

The five-carbon framework of the isoprenoid units most probably results (i) from the condensation of a C-2 unit derived from pyruvate (**28**) decarboxylation (e.g. thiamine-activated acetaldehyde) arising from D-glucose (**12**), glyceraldehyde-3-phosphate (GAP) (**29**) that also involves a transposition step leading to 2C methyl-D-erythritol 4-phosphate (MEP, **31**).



Scheme 10. Methylerythritol phosphate (MEP) pathway to isoprenoids.

Conflicting results have been reported, much earlier, concerning the biosynthesis of chrysanthemic acid. It has for example erroneously been suggested, on the base of feeding experiments carried out either with racemic 2-^{14}C-mevalonic acid (MVA, 1.4% incorporation)[48] or [4-^{3}H]-labeled (3*R*,4*R*)-mevalonic acid[49] (0.4% incorporation), that chrysanthemum monocarboxylic acid derives from (3*R*,4*R*)-mevalonic acid and not from its (3*R*,4*S*)-diastereomer.[49]

It is now generally accepted that the biosynthetic route to chrysanthemic acid that produces chrysanthemyl pyrophosphate (**18**) in *C. cinerariaefolium* (methyl-D-erythritol 4-phosphate pathway) differs from the one in mammals producing from the same starting material presqualene pyrophosphate (**21**) that possesses a closely related structure (mevalonic acid pathway).

5.4. Biosynthesis of pyrethrolone (3a)

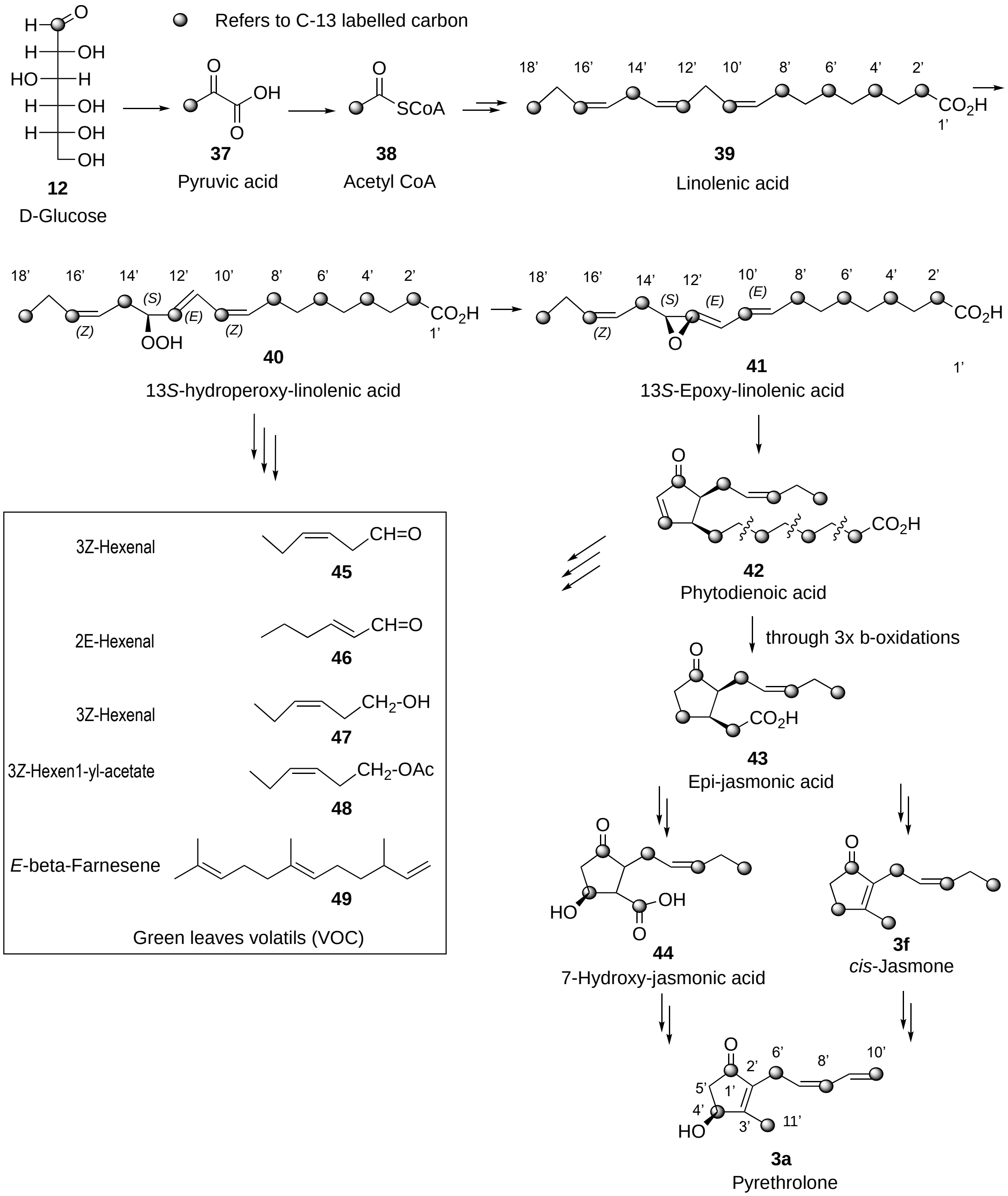
The biosynthesis of pyrethrolone (**3a**) is less well documented[40,41] than that of chrysanthemic acid (**2a**) reported above. It is expected to occur from D-glucose (**12**) via the intermediate formation of pyruvic acid (**37**), acetyl CoA (**38**) and linoleic acid (**39**, Scheme 10). It involves then the octadecanoic signaling cascade leading first to13(*S*)-hydroperoxy-linolenic acid (**40**) on action of 13-lipoxygenase (13-LOX) then to the unstable 13*S*-epoxy-linolenic acid (**41**), on action of allene oxide synthase (AOS), that extremely rapidly collapses to phytodienoic acid (PDA, **42**, Scheme 11).[50-52]

Phytodienoic acid, formed from linolenic acid, a key compound in the signaling cascade, is then reduced and degraded in three sequential β-oxidation reactions to *epi*-jasmonic acid (**43**), the precursor of *cis*-jasmone (**3f**) and finally to pyrethrolone (**3a**, Scheme 10).

The incubation of young leaves of *C. cinerariaefolium* with D-glucose (**12**) radiolabeled at C-1 with carbon-13 provides pyrethrolone in which the C-13 label has been incorporated at C-1′, C-4′, -6′, C-8′, C-10′ and C-11′ (Scheme 10).[41,42]

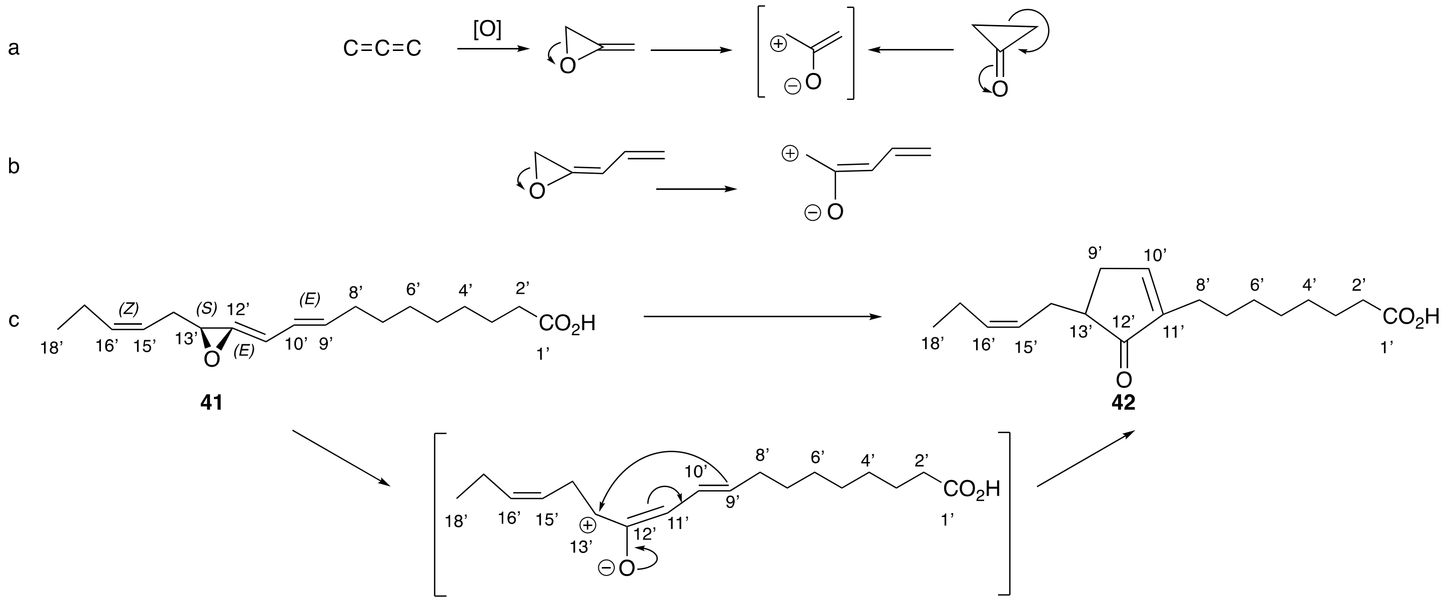
Enzymes responsible for such cascade of reactions are being identified;[53] for example the hydroxylase enzyme responsible for the transformation of jasmone (**3f**, Scheme 10) to jasmololone (**3c**, Figure 2), one of the precursors of jasmolins **1e**, **1f** (Figure 1) has been recently identified and characterized. [53]

Feeding pyrethrum flowers with jasmone (**3f**) resulted in a 4.3-fold increase in the concentration of jasmololone **3c** and to a lesser extent of pyrethrolone **3a** (Figure 1, Scheme 11) and pyrethrins (**1a**-**1f**, Figure 1) as well.[53] The protein involved in the conversion of jasmone (**3f**) to jasmololone (**3c**) has been localized in the endoplasmic reticulum[53] and the genes encoding for this enzyme identified.[53] It has also been suggested that the assembly of pyrethrin esters from chrysanthemic acid and the hydroxyl group rethrolones occurs in the ovaries. [53-56]



Scheme 11. Proposed biosynthetic route to pyrethrolone from glucose.

The transformation of the 13(*S*)-epoxy-linolenic acid (**41**) to epi-jasmonic acid (**43**) merits further comment. It involves as starting material an unusual strained epoxide that belongs to the family of allene-oxides (Scheme 12, entries a, b). They behaves as 1,3-dipoles, similar to the ones produced from the strained cyclopropanones (Scheme 12, entry a). Ring opening of the allene-oxide in (**41**) leads to the delocalized homologous dienolate (Scheme 12, entry b) that cyclizes to the cyclopent-2-enone (**42**, Scheme 12, entry c).



Scheme 12. Proposed mechanism for the transformation of 13*S*-epoxy-linolenic acid (**41**) to epi-jasmonic acid (42).

5.5. Regulation of the biosynthesis of pyrethrins

It has been found [40,57] that both the pyrethrin I and II contents increase in *Chrysanthemum cinerariifolium* seedling in which some leaves have been mechanically wounded (741.2 compared to control 395.4 ng/mg pyrethrin I/fresh leaf; 269.5 compared to control 154.49 ng/mg pyrethrin II/fresh leaf).[57] Interestingly, such increase is still observed in pyrethrin II content (282.89 ng/mg compared to control 154.49 ng fresh leaf) whereas it is not observed in pyrethrin I content in intact leaves that have been wrapped (514.1 ng/mg compared to control 395.4 ng/mg fresh leaf). [57]

Those observations suggest that the wound induces the production of volatile and nonvolatile chemicals that interfere in the regulation of the biosynthesis of pyrethrin I and pyrethrin II respectively, probably as a defense mechanism against predators. [54]

It has been determined, using GC, that those wounded leaves emit (*Z*)-3-hexenal, (*E*)-2-hexenal, (*Z*)-3-hexen-1-ol, (*Z*)-3-hexen-1-yl acetate and (*E*)-β-farnesene as main wound-induced VOCs (volatile organic compounds) probably synthesized as by-products in the multistep synthesis of the pyrethrolone **3a** (Scheme 10). [40,57] Exposing intact leaves of *C. cinerariaefolium* seedling to this mixture resulted in enhanced pyrethrin production[57] but changing the natural ratio was found to inhibit the process.

Interestingly, bringing the intact seedlings in close proximity to the wounded seedlings, resulted in enhanced pyrethrin contents in the intact seedlings suggesting for the first time, a plant to plant communication.[54] Relation to gene expression has been reported. [40,57] Synthesis of pyrethrins in the leaves of *C. cinerariaefolium* has been supported by more recent results.[53]

6. Brief Compilation of Data about Pyrethrins, Pyrethroids and their Constituents

We have also gathered some leading references that cover various aspects of pyrethrins and pyrethroids:
6.1. Isolation of pyrethroids,[2,16,22,23,35,58,59] their structure elucidation,[2,23,37,60]and biosynthesis.[40]
6.2. Physical properties of pyrethroids.[61]
6.3. Biological activity of pyrethrins and pyrethroids.[1-3,5,8,9,14,16,22,23,37,61-67]
6.4. Environmental behavior of synthetic pyrethroids.[2,22,68]
6.5. Transformation of *cis*- and *trans*-chrysanthemic acid from the other isomer.[37,16,69,70,71]
6.6. Structures of vinyl cyclopropane carboxylic acids whose suitable esters are insecticides.[12,13,16,17,60,64,69-74]
6.7. structure of alcohols whose suitable esters are insecticides.[12,23,60,64,73]
6.8. Description of the synthetic strategies involved in pyrethroids syntheses.[69-74]

Conclusions

Observations by earlier generations on the properties of plants led them to use pyrethrins as insecticides even before the advent of chemistry.The use of extraction and purification technics proved unnecessary to obtain the active principle that is available by using the powder resulting from grinding the flower-head of *Chrysanthemum cinerariifolium*. Since then, very early chemists became interested in the field at the time separation techniques (chromatography), structure determination tools (infrared spectroscopy, nuclear magnetic resonance, X-ray crystallography) and synthetic methods were nonexistent or in their infancy (except the aldol reaction that has been substantially used to build the rethrolone part and the diazo reaction on dienes invented at this occasion to produce chrysanthemic esters). Modulation of the biological activity of pyrethrins has not taken advantage of the structure-activity relationship techniques that computer science offers nowadays. Nevertheless, with limited tools and even concepts, chemists have been able to invent and produce at the industrial level a series of unnatural pyrethroids that are able to control insects in different contexts using an extremely small amount of chemicals and with the remanence needed to achieved the required objective, and this at the time the concept of ecology has emerged [80,81] and concern about the harmful effect of pesticides was raised.[82]

These results have been obtained at the time IT and artificial intelligence-based tools including retro synthetic analysis ones did not exist or were just emerging. Therefore, the discovery of (*S*)-bioallethrin and deltamethrin was achieved exclusively from chemists probing and testing.

The structure of (S)-bioallethrin is very close to that of pyrethrin I only missing an ethylidene group on the rethrolone moiety that make its synthesis much easier. It possesses the same advantages and limitations (Extremely high toxicity to insects, extremely low toxicity to mammals, limited lifetime 2-3 days, little resistance in insects) and fit perfectly to domestic uses.

The structure of deltamethrin, although it still keeps the vinylcyclopropanecarboxylate skeleton present in all pyrethrins, exhibits striking differences structural and biological (Bromine atoms instead of two methyl groups on the vinyl group; 1(*R*)-*cis*- instead of 1(*R*)-*trans*-stereochemistry on the cyclopropane ring; a completely different alkoxy moiety except that the carbon attached to the carboxy group possess in both case the (*S*)-stereochemistry and is benzylic instead of allylic; higher insecticide power and longer lifetime of 3 months allowing pest control in agriculture).

The recent discovery of the insecticidal properties of Methofluthrin leads one to suspect that there is still room for improvement and for the discovery of more selective pyrethroid insecticides.

The synthesis at the industrial level of pyrethroids has been clearly a challenge since their structure has a complexity related to that of steroids [number of (i) atoms in their skeleton and (ii) stereogenic centers] with which the pyrethrins share some biogenetic pathways.

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