

# Recent Advances of Pyrethroids for Household Use

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**Abstract** Development of pyrethroids for household use and recent advances in the syntheses of (1*R*)-*trans*-chrysanthemic acid, the acid moiety of most of the household pyrethroids, are reviewed. As another important acid moiety, we discovered norchrysanthemic acid to have a significant vapor action at room temperature when esterified with fluorobenzyl alcohols. In particular, 2,3,5,6-tetrafluoro-4-methoxymethylbenzyl (1*R*)-*trans*-norchrysanthemate (metofluthrin) exhibits the highest potency in mosquito coil formulations as well as the vapor action at room temperature against various mosquitoes. Structure-activity relationships of norchrysanthemic acid esters and synthetic studies of norchrysanthemic acid are discussed.

**Keywords** (1*R*)-*trans*-Chrysanthemic acid · Metofluthrin · Mosquito · Norchrysanthemic acid · Pyrethroids

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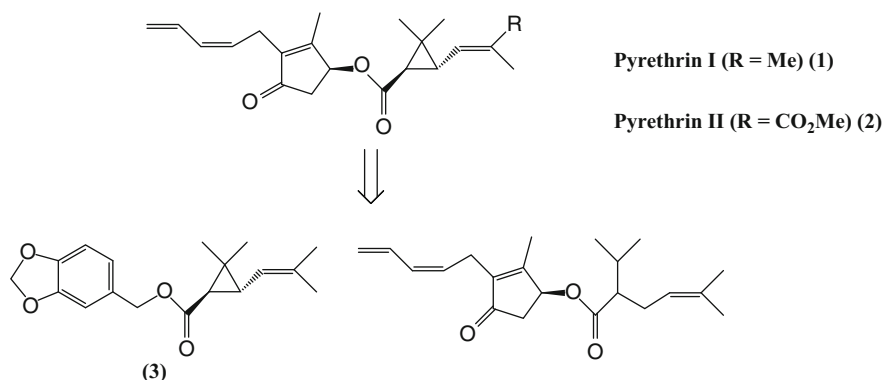
## 1 Introduction

The study of structural modification of natural pyrethrins has lasted for more than 60 years. Especially, the invention of allethrin, 2-methyl-4-oxo-3-allylcyclopent-2-enyl chrysanthemate, prompted chemists to make structural modifications of the pyrethroid alcohol and acid moieties. As a result, a number of pyrethroids with diversified characteristics have been invented not only for the control of household insect pests but also for agricultural use. With regard to household use pyrethroids commercialized, their acid moiety was mostly racemic (1*RS*)-*cis,trans*-chrysanthemic acid at the beginning. These household use pyrethroids have gradually been afforded in enantiomerically pure forms, (1*R*)-*trans*-chrysanthemic acid esters or (1*R*)-*cis,trans*-chrysanthemic acid esters by so-called “racemic switch” since the 1980s. Classical optical resolution of (1*RS*)-*cis,trans*-chrysanthemic acid with optically active amines is one of the practical methods toward the access to optically active (1*R*)-*trans*-chrysanthemic acid and (1*R*)-*cis,trans*-chrysanthemic acid. Various efficient synthetic processes have been reported by Sumitomo Chemical including enzymatic resolution and asymmetric synthesis.

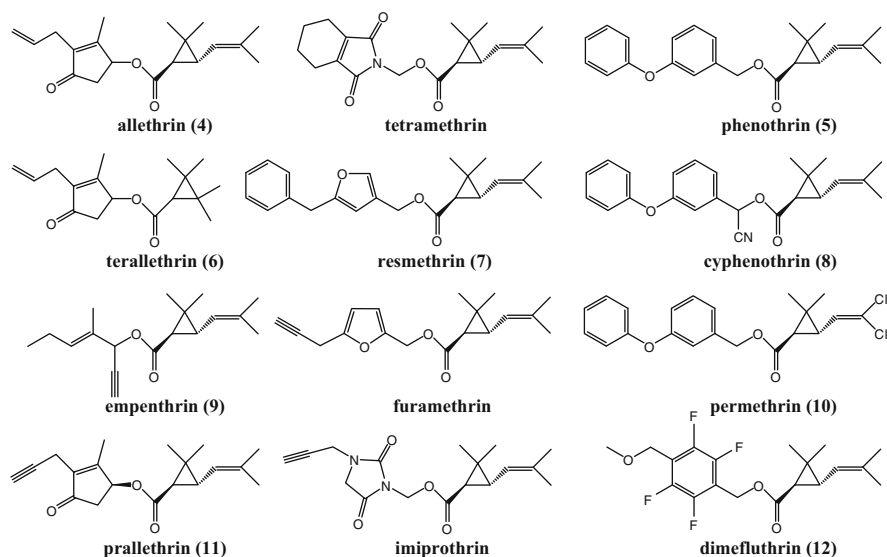
Further exploratory work in our laboratory to find new pyrethroids with a higher vapor action and high effectiveness against mosquitoes resulted in the discovery of (1*R*)-*trans*-norchrysanthemic acid or (1*R*)-*trans*-2,2-dimethyl-3-(1-propenyl)-cyclopropanecarboxylic acid as another important acid moiety for household pyrethroids. Here we describe the structure-activity relationships of fluorobenzyl esters of (1*R*)-*trans*-norchrysanthemic acid regarding vapor activity against mosquitoes and the development of synthetic methods of norchrysanthemic acid.

## 2 Development of Pyrethroids for Household Use

Natural pyrethrins have long been used as most favored household insecticides. Pyrethrum flowers are still cultivated in certain areas including Africa, Australia, and China. On the other hand, commercial use of pyrethroids is one of the most remarkable success stories in insecticide development originated from natural products as a lead. It should be noted that in 1924 Staudinger and Ruzicka reported [1] several pyrethrin analogs including piperonyl chrysanthemate (**3**) as shown in Fig. 1.



**Fig. 1** Structural modifications by Staudinger and Ruzicka



**Fig. 2** Structures of pyrethroids commercialized by Sumitomo Chemical

Some of them were only slightly insecticidal. But their foresight is notable regarding natural pyrethrins as lead compounds without knowledge of the real structures of alcohol moieties at that time.

Through extensive studies during the past 60 years, natural pyrethrins proved to possess ample possibilities for structural modifications. Namely, just after elucidation of the structures of pyrethrin I (1) and pyrethrin II (2) of natural pyrethrins in 1947 [2], extensive efforts began to modify mainly the alcohol moieties. In Fig. 2 commercialized household use pyrethroids from Sumitomo Chemical Co.Ltd are listed.

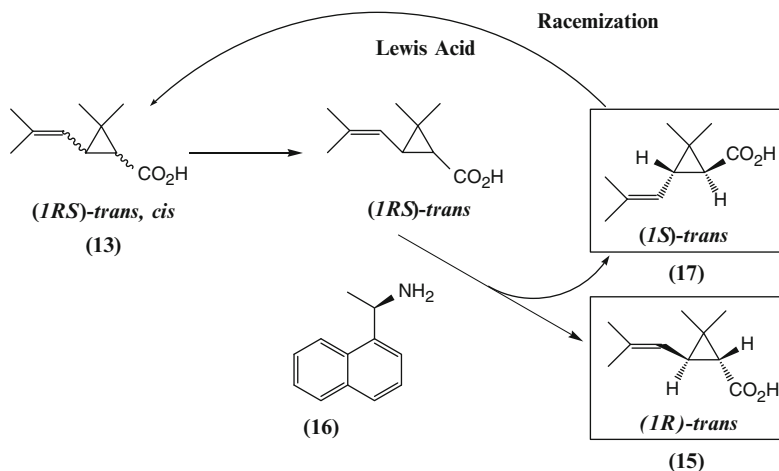
Simplification of the diene moiety of pyrethrin I resulted in finding allethrin (**4**) by Schechter [3], which was the first pyrethroid commercialized for household use. Matsui et al. made an extensive effort on the process of allethrin, which resulted in the launch of the first pyrethroid in Japan in 1954. As the propynyl analog of pyrethrin I, prallethrin (**11**) was commercialized by Sumitomo Chemical in 1988 in the most insecticidally active form [4]. Allethrin and prallethrin have been used widely for control of mosquitoes.

The most important breakthrough in terms of modifications of the alcohol moiety of pyrethrins was the aforementioned piperonyl ester (**3**) followed by the inventions of resmethrin (**7**) by Elliott in 1965 [5] and phenothrin (**5**) by Itaya in 1968 [6]. Further exploratory work in Sumitomo Chemical on modification of 3-phenoxybenzyl alcohol resulted in the invention of cyphenothrin (**8**) by Matsuo et al. in 1971 [7]. Resmethrin, phenothrin, and cyphenothrin have strong lethal activity against various insect pests. Phenothrin and cyphenothrin are used as components of aerosol insecticides. Phenothrin has also been used to kill head lice in humans as an active ingredient in shampoos. At the beginning the acid moiety of resmethrin, phenothrin, and cyphenothrin were racemic (1*RS*)-*cis,trans*-chrysanthemic acid (**13**). Latterly this acid has been switched to optically active forms, namely (1*R*)-*cis,trans*-chrysanthemic acid (**14**) or (1*R*)-*trans*-chrysanthemic acid (**15**) in order to enhance insecticidal activity. Notable is the fact that most pyrethroids for household use contain natural (1*R*)-*trans*-chrysanthemic acid (**15**) as the acid moiety as shown in Fig. 2, except terallethrin (**6**) and permethrin (**10**). Further exploratory work by Mori et al. [8] on modification of the alcohol moiety has recently resulted in the discovery of dimefluthrin (**12**), or 2,3,5,6-tetrafluoro-4-methoxymethylbenzyl (1*R*)-*trans*-chrysanthemate, which exhibits excellent potency against mosquitoes in mosquito coil formulations.

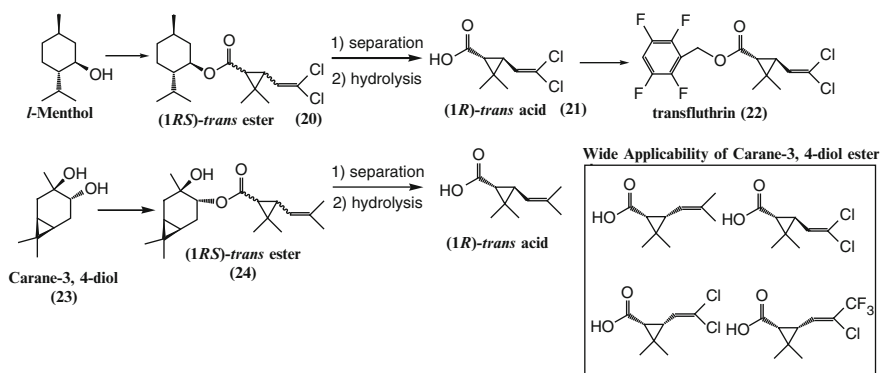
### 3 Recent Advances of the Syntheses of (1*R*)-*trans*-chrysanthemic Acid

(1*R*)-*trans*-Chrysanthemic acid (**15**) can be obtained by various methods. Classical optical resolution of the racemic *trans*-acid with (–)-naphthylethyl amine (**16**) is one of the efficient methods, although the theoretical yield is at most 50%. In this case, insecticidally unimportant (1*S*)-*trans*-chrysanthemic acid (**17**) is racemized back in order to make the whole process efficient. Classical resolution is practical but the efficiency is not always satisfactory for producing (1*R*)-*trans*-chrysanthemic acid (Scheme 1).

Recently novel methods were reported to make (1*R*)-*trans*-chrysanthemic acid including optical resolutions with the (+)-3-caranediol or 1,1'-binaphthol monoethylether, enzymatic resolution with *Arthrobacter globiformis* and the asymmetric synthesis with a new Cu catalyst. These methods are reviewed in this section.



**Scheme 1** Optical resolution of  $(1RS)\text{-trans, cis}$ -chrysanthemic acid with  $(-)$ -1-naphthylethylamine



**Scheme 2** Optical resolution with *l*-menthol and carane-3,4-diol

### 3.1 Optical Resolution with Carane-3,4-Diol

*l*-Menthol ester (20) with  $(1RS)\text{-trans}$ -2,2-dimethyl-3-(2,2-dichloroethenyl) cyclopropanecarboxylic acid (19) has been utilized to produce  $(1R)\text{-trans}$ -2,2-dimethyl-3-(2,2-dichloroethenyl) cyclopropanecarboxylic acid (21), an acid moiety of transfluthrin (22) [9]. Matsuo et al. surveyed various optically active secondary alcohols for their potential in the optical resolution of  $(1RS)\text{-trans}$ -chrysanthemic acid [10] (Scheme 2).

As a result, the ester (24) of  $(1S,3R,4R,6R)$ -carane-3,4-diol (23) with  $(1RS)\text{-trans}$ -chrysanthemic acid could easily be separated by silica gel column chromatography to give two ester diastereomers. The  $R_f$  value of the ester of

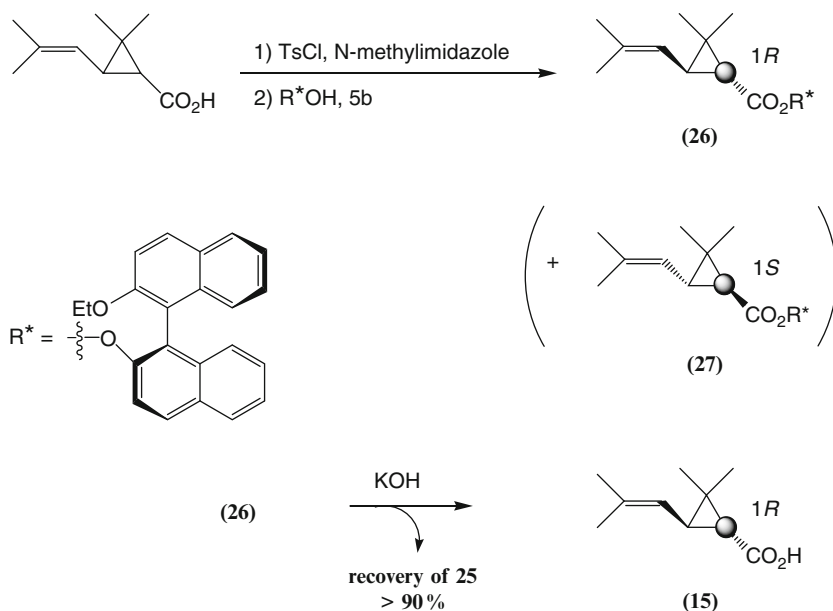
(1*S*,3*R*,4*R*,6*R*)-carane-3,4-diol with (1*R*)-*trans*-chrysanthemic acid is 0.62, and the R<sub>f</sub> value of the corresponding (1*S*)-*trans*-chrysanthemic acid ester is 0.65 (toluene: ethyl acetate = 3:1). However, the *l*-menthol ester of (1*RS*)-*trans*-chrysanthemic acid could not easily be separated by silica gel column chromatography to obtain (1*R*)-*trans*-chrysanthemic acid *l*-menthol ester.

Optical resolution methods with carane-3,4-diol are noteworthy for wide generality. Esters of various cyclopropane carboxylic acids with (1*S*,3*R*,4*R*,6*R*)-carane-3,4-diol were prepared and all (1*R*)-isomers could easily be obtained by a simple silica gel column chromatography.

### 3.2 Optical Resolution with 1,1'-Binaphthol Monoethyl Ether

Chiral 1,1'-binaphthol derivatives are well established as readily available chiral catalysts and auxiliaries for the production of various useful optically active compounds. Tanabe et al. investigated [11] a crystalline-liquid resolution of (1*R*)-*trans*-chrysanthemic acid utilizing 1,1'-binaphthyl monoethyl ether (**25**) (Scheme 3).

Thus, (1*RS*)-*trans*-chrysanthemic acid was condensed with 1,1'-binaphthol derivative using the TsCl-*N*-methylimidazole reagent to give the corresponding two sets of diastereomers (**26**) and (**27**). From the solution, only the (1*R*)-*trans*-chrysanthemic acid ester (**26**) crystallized from the diastereomer mixtures. The ester was readily



**Scheme 3** Optical resolution with 1,1'-binaphthyl monoethyl ether

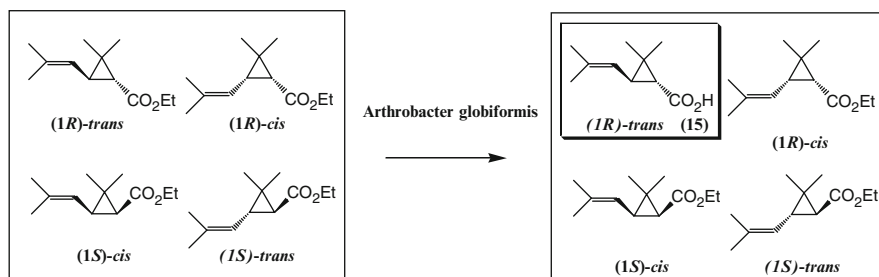
hydrolyzed under conventional conditions (KOH/THF-H<sub>2</sub>O) to give the desired (1*R*)-*trans*-chrysanthemic acid (**15**) without any epimerization of the (1*R*)-position.

### 3.3 Enzymatic Resolution of (1*R*)-*trans*-Chrysanthemic Acid with Bacterium

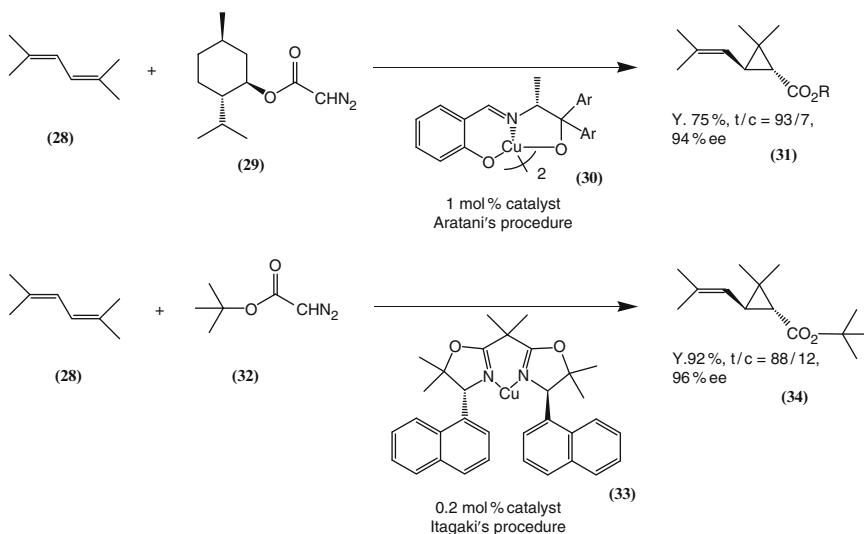
Nishizawa et al. found [12] an efficient esterase in *A. globiformis* (SC-6-98-28), which stereoselectively hydrolyzed only ethyl (1*R*)-*trans*-chrysanthemate among four stereoisomers of chrysanthemates to give the pure (1*R*)-*trans*-chrysanthemic acid (**15**). The gene coding was cloned from *A. globiformis* and overexpressed in *Escherichia coli*. Thus, the cellular content of enzyme reached 33% of the total soluble protein in the recombinant *E. coli* cells. The hydrolysis activity of the recombinant *E. coli* cells for ethyl chrysanthemate were 2,500-fold higher than that of *A. globiformis* cells. The optimum pH and temperature were 9.5 and 50 °C, respectively, and more than 98% conversion and 100% stereoselectivity of (1*R*)-*trans*-chrysanthemic acid were accomplished (Scheme 4).

### 3.4 Recent Advance of Asymmetric Synthesis of (1*R*)-*trans*-Chrysanthemic Acid with a New Chiral Copper Complex

Asymmetric synthesis of 2,5-dimethyl-2,4-hexadiene (**28**) and *l*-menthyl diazoacetate (**29**) with chiral copper complexes (**30**) was successfully conducted by Aratani et al. [13] to afford the (1*R*)-chrysanthemic acid *l*-menthyl ester (**31**) in high optical and chemical yield. Since this finding, a lot of chiral copper complexes have been reported and applied to the asymmetric synthesis of (1*R*)-chrysanthemate. However, these copper complexes required more than 1 mol% of the catalyst and the *cis/trans* ratio still remains unsatisfactory. Moreover, *l*-menthyl ester was crucial for the high enantioselectivity. Given an industrial production of



**Scheme 4** Synthesis of (1*R*)-*trans*-chrysanthemic acid with the bacterium



**Scheme 5** Asymmetric synthesis of (1*R*)-*trans*-chrysanthemic acid

(1*R*)-*trans*-chrysanthemic acid by asymmetric synthesis, a much lower amount of the copper complex and a higher *trans*-isomer ratio of more than 80% should be attained. In addition, asymmetric synthesis using *l*-menthyl diazoacetate required extra steps. The use of a lower alkyl diazoacetate would be desirable for large scale production of (1*R*)-*trans*-chrysanthemic acid. Focusing on these points, Itagaki et al. screened various bisoxazoline type copper catalysts (Scheme 5).

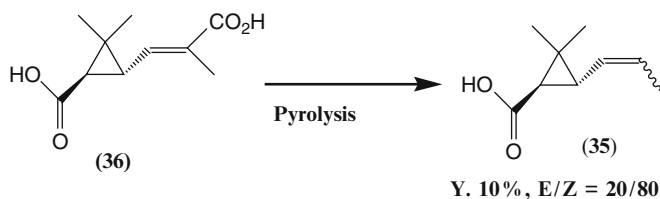
As a result, 1-naphthyl derivative (**33**) worked efficiently as a new copper complex combined with  $\text{Ph}_3\text{CPF}_6$  as the catalysts to provide highly stereoselectively *cis/trans* (88/12)-chrysanthemic *tert*-butyl ester (**34**) in 96% ee [14]. The ester (**34**) was easily hydrolyzed in acidic conditions to give (1*R*)-*cis/trans*-chrysanthemic acid. The required amount of the copper complex was only 0.2 mol%.

## 4 Invention of Metofluthrin [15]

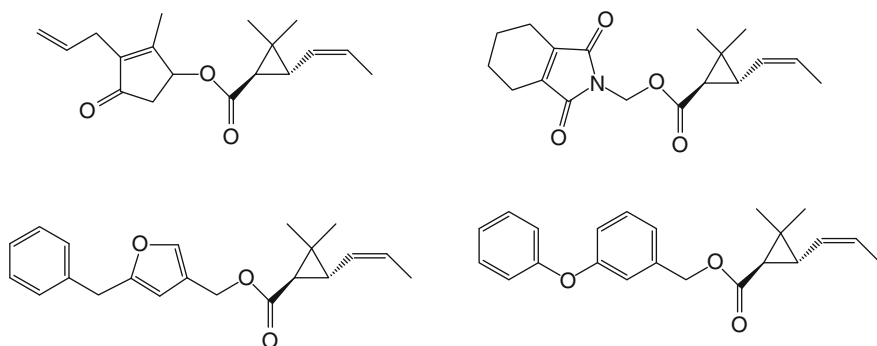
Norchrysanthemic acid (**35**) was first synthesized by Staudinger in 1924 [16] as the pyrolytic decomposition product of chrysanthemum dicarboxylic acid (**36**) (Scheme 6). In the 1970s, Ohno and Elliott independently reported [17] insecticidal norchrysanthemic acid esters and these norchrysanthemic acid esters showed comparable insecticidal activity to the corresponding chrysanthemates (Fig. 3).

However, further studies were discontinued at that time because they could not find any advantage in developing these norchrysanthemic acid esters due to the increased difficulty in the synthesis of norchrysanthemic acid compared to chrysanthemic acid.





**Scheme 6** The first synthesis of norchrysanthemic acid by Staudinger and re-examination by Crombie



**Fig. 3** Insecticidal norchrysanthemate by Ohno and Elliott

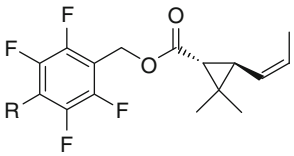
Recently much attention has been directed at the development of devices to control mosquitoes by using products in ambient temperature devices because of their increased safety and ease of use, especially during outdoor activities. This development has resulted in a variety of fan powered mosquito vaporizers and associated formulations which are now being marketed. These devices have limitations in performance that are imposed by the insecticidal activity of the active ingredient used. In order to overcome some of these limitations, we undertook extensive research to find new pyrethroids with higher vapor action which were highly active against mosquitoes.

We directed our attention to norchrysanthemic acid esters because they had a lower molecular mass ( $-14$ ) and showed comparable insecticidal activity with corresponding chrysanthemates. We synthesized various insecticidal norchrysanthemic acid esters and tested their vapor activity against mosquitoes.

As a result of the screening, we found 2,3,5,6-tetrafluorobenzyl norchrysanthemate (**38**) had faster knockdown activity than the chrysanthemate (**37**) against mosquitoes as shown in Table 1. Then we synthesized the derivatives with substituents at the 4-position on the phenyl ring of the compound (**38**).

All analogs have much higher activity against mosquitoes than empenethrin and compound (**38**) by the standard topical application method as shown in Table 1. The relative toxicity reaches the maximum between two and three carbon atoms at the 4-position (**41** ~ **43**). Unsaturation (**43**) or incorporation of an oxygen atom

**Table 1** Insecticidal activities of metofluthrin and its analogus against *Curex pipiens pallens* by the standard topical application method

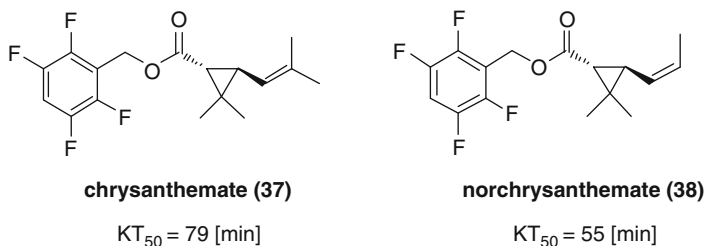
|  |                     |                   |
|-----------------------------------------------------------------------------------|---------------------|-------------------|
| Compound                                                                          | R                   | Relative toxicity |
| <b>38</b>                                                                         | H                   | 30                |
| <b>39</b>                                                                         | F                   | 100               |
| <b>40</b>                                                                         | Me                  | 200               |
| <b>41</b>                                                                         | Et                  | 490               |
| <b>42</b>                                                                         | Pr                  | 250               |
| <b>43</b>                                                                         | Allyl               | 500               |
| <b>44</b>                                                                         | OMe                 | 360               |
| <b>45a</b>                                                                        | CH <sub>2</sub> OMe | 2,500             |
| Empenthrin( <b>9</b> )                                                            |                     | 10                |
| <i>d</i> -Allethrin( <b>4</b> )                                                   |                     | 100               |

**Table 2** Efficiency of metofluthrin in a non-heating vapor formulation with a fan and mosquito coil formulations against various mosquito species

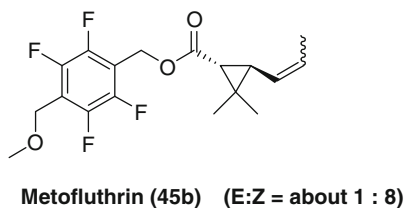
| Formulation   | Species                    | Conc. (%) | KT <sub>50</sub> (min) |                     |
|---------------|----------------------------|-----------|------------------------|---------------------|
|               |                            |           | Metofluthrin           | <i>d</i> -Allethrin |
| Non-heating   | <i>C. pipiens pallens</i>  |           | 27                     | >60                 |
| Mosquito coil | <i>C. quinquefasciatus</i> | 0.013     | 49                     |                     |
|               |                            | 0.02      | 35                     |                     |
|               |                            | 0.04      | 22                     |                     |
|               |                            | 0.2       |                        | 54                  |
|               |                            | 0.005     | 42                     |                     |
| Mosquito coil | <i>C. quinquefasciatus</i> | 0.2       |                        | 58                  |

(**44**) also show substantial activity, inter alia, (1*R*)-*trans*-(*Z*)-2,3,5,6-tetrafluoro-4-methoxymethylbenzyl norchrysanthemate (**45a**) exhibits the highest potency being approximately 40 times as potent as *d*-allethrin in mosquito coil formulations when tested against southern house mosquitoes (*Culex quinquefasciatus*). Based on this structure-activity relationship, we have decided to develop the compound (**45b**), (1*R*)-*trans*-(*EZ*)-isomer (*E*:*Z* ratio is about 1:8), which is named metofluthrin (Fig. 5). Results as shown in Table 2 clearly demonstrate that metofluthrin exhibits significant levels of vapor action against mosquitoes at room temperature. Metofluthrin also exhibits high levels of knockdown activity in coil formulations when tested against mosquito species as shown in Table 2. In particular, metofluthrin exhibits similar activity to *d*-allethrin against the southern house mosquitoes (*Culex quinquefasciatus*) at only 1/40 of the active ingredient level.

Metofluthrin has high knockdown activity against mosquitoes and has an excellent mammalian safety profile. Metofluthrin is suitable for use not only in various



**Fig. 4** Insecticidal activities of 2,3,5,6-tetrafluorobenzyl chrysanthemate and norchrysanthemate



**Fig. 5** Structure of metofluthrin

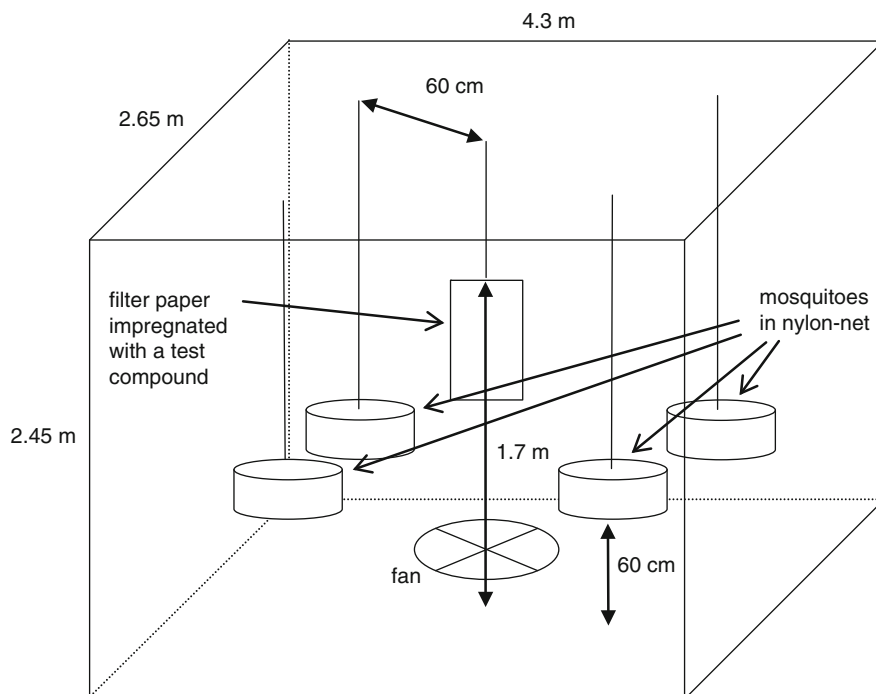
existing emanating devices like mosquito coils but also in the more novel new devices such as fan vaporizers and treated paper strips.

## 4.1 Materials and Methods

Topical application for evaluating insecticidal efficacy against common house mosquitoes (*Culex pipiens pallens*) complied with the method described by Yamaguchi et al. [18].

### 4.1.1 Vapor Action Activity Evaluation in Non-Heating Formulation at Room Temperature Against Common House Mosquitoes (*C. pipiens pallens*)

A test compound (100 mg) was dissolved in 20 mL of acetone and impregnated onto a sheet of filter paper (20 cm × 50 cm) and the acetone was removed by air-drying. In the center of a 28-m<sup>3</sup> test chamber (4.3 m × 2.65 m × 2.45 m), the filter paper was hung from the ceiling with the upper end of the filter paper 1.7 m above the floor. Four nylon-net cages (cylindrical, 30 cm in diameter and 20 cm in height) each containing 20 female common house mosquitoes (*C. pipiens pallens*) were hung from the ceiling with the base of each cage 60 cm from the floor. One cage was placed in each corner of the room, 60 cm horizontally from the filter. The number of knocked down mosquitoes was counted at the designated intervals for



**Fig. 6** Method of evaluating vapor activity of formulations at ambient temperature

60 min. In order to circulate air in the chamber, a fan was set under the treated filter paper and a board was placed between the fan and the paper to prevent the fan from directly blowing the filter paper (Fig. 6).

#### 4.1.2 Biological Efficacy Evaluations in Mosquito Coil Formulations

The preparation of test mosquito coils complied with the method described by Yamaguchi et al. The test coil was fitted on a coil holder and placed at the center of the chamber (4.3 m × 2.65 m × 2.45 m). The coil was ignited and then 100 adult female mosquitoes were released into the chamber. The number of knocked down mosquitoes was counted at the designated intervals for 75 min.

## 5 Synthetic Studies of Norchrysanthemic Acid

The acid moiety of metofluthrin is (1*R*)-norchrysanthemic acid. In this section we describe the development of synthetic studies of *Z*-rich norchrysanthemic acid. Aforementioned norchrysanthemic acid was first synthesized by Staudinger in 1924 as the pyrolytic decomposition product of chrysanthemum dicarboxylic

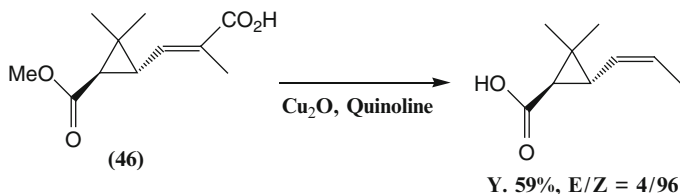
acid. However, the *E/Z* ratio of obtained norchrysanthemic acid was not mentioned. Crombie et al. re-examined [19] this pyrolytic reaction of chrysanthemic acid and found the yield of norchrysanthemic acid was only 10% and the *E/Z* ratio was 20/80.

### 5.1 Synthesis of (Z)-(1R)-trans-Norchrysanthemic Acid by the Wittig Reaction

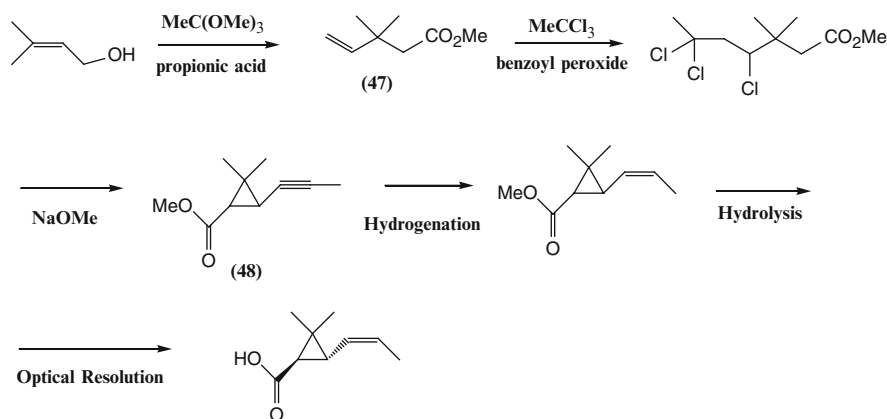
As mentioned, Ohno and Elliott reported the insecticidal (Z)-norchrysanthemate as shown in Fig. 3. They both used the Wittig reaction of (1R)-*trans*-caronaldehyde ester to obtain (Z)-(1R)-*trans*-norchrysanthemates. Although the Wittig reaction gives (Z)-(1R)-*trans*-norchrysanthemates predominantly, it was not practical due to the Wittig reaction conditions requiring very low reaction temperature, a strong base, and the phosphonium salt (much waste atom economy).

### 5.2 Synthesis of (Z)-(1R)-trans-Norchrysanthemic Acid by Pyrolytic Reaction of Chrysanthemum Dicarboxylic Acid Monomethyl Ester with a New Catalyst

Hagiya et al. recently reported [20] the new decarboxylation catalyst of chrysanthemum dicarboxylic acid monomethyl ester (**46**) to give ethyl (Z)-norchrysanthemate (*E/Z* = 4/96) in 59% yield. This method efficiently gives (Z)-(1R)-*trans*-norchrysanthemic acid, but the yield is still moderate and the starting chrysanthemum dicarboxylic acid monomethyl ester is not a commercial product (Scheme 7).



**Scheme 7** Synthesis of Z-norchrysanthemic acid by decarboxylation reaction with  $\text{Cu}_2\text{O}$  and quinoline



**Scheme 8** Synthesis of *Z*-norchrysanthemic acid via the Claisen rearrangement

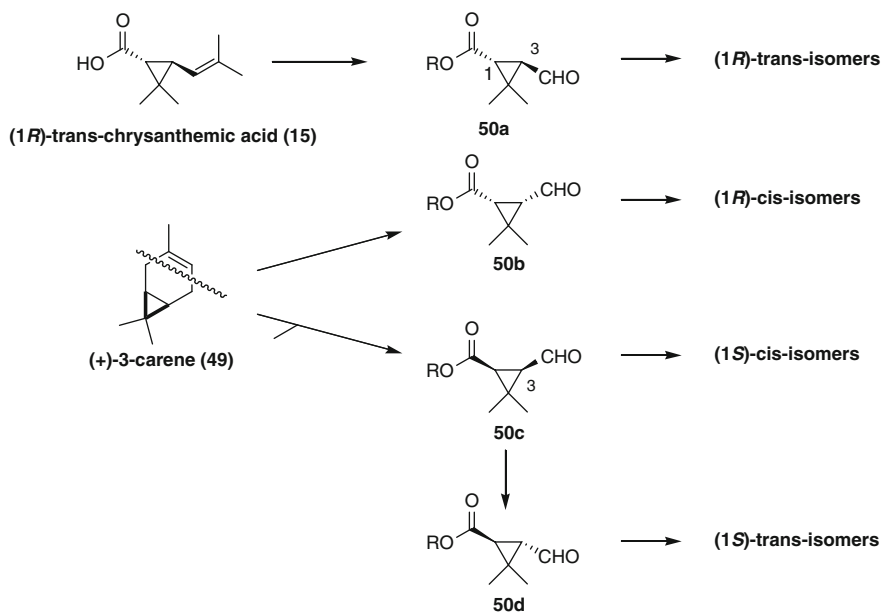
### 5.3 Synthesis of (*Z*)-(*1R*)-*trans*-Norchrysanthemic Acid by the Claisen Rearrangement

Mori et al. reported [21–23] a promising approach to synthesize ethyl (*Z*)-(*1R*)-*trans*-norchrysanthemate utilizing a partial hydrogenation of ethyl 2,2-dimethyl-3-(1-propynyl)cyclopropanecarboxylate. This was synthesized starting from ethyl 3,3-dimethyl-4-pentenoate via the Claisen rearrangement followed by radical addition of  $\text{MeCCl}_3$  and the ring closure with  $\text{NaOEt}$ . (*Z*)-(*1R*)-*trans*-Norchrysanthemate was hydrolyzed under basic conditions to give the acid. This was resolved using (–)-1-naphthylethylamine to give (*Z*)-(*1R*)-*trans*-norchrysanthemic acid (Scheme 8).

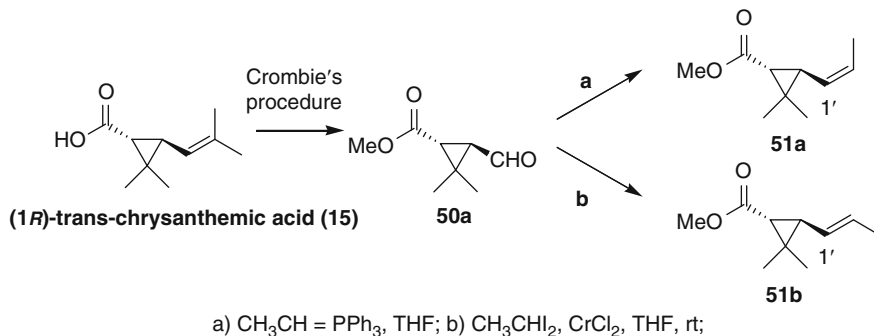
### 5.4 Syntheses of All Stereoisomers of Norchrysanthemic Acid

There are two asymmetric carbon atoms and *E*, *Z*-isomers in norchrysanthemic acid. So, there exist eight stereoisomers. In order to elucidate the structure activity relationship of metofluthrin stereoisomers, we investigated the synthetic pathways of all stereoisomers of norchrysanthemic acid.

We planned to introduce a 1-propenyl side chain at the C-3 position by the Wittig reaction with caronaldehyde acids or the corresponding esters (**50a–d**) on the last step. (*1R*)-*trans*-Caronaldehyde methyl ester (**50a**, *R* = Me) can be prepared by ozonolysis of methyl (*1R*)-*trans*-chrysanthemate (**15**). For *cis*-isomers, (+)-3-carene (**49**) was transformed to (*1R*)-*cis*-caronaldehyde acid (**50b**, *R* = H) and (*1S*)-*cis*-caronaldehyde acid (**50c**, *R* = H) according to Dev's and Ho's procedures. (*1S*)-*trans*-Isomer (**50d**, *R* = Me) could be prepared by epimerization at the C-3 carbon atom of (**50c**, *R* = Me) (Scheme 9).



**Scheme 9** Synthesis of (1*R*)-*trans*-(*Z*)- and (*E*)-isomers

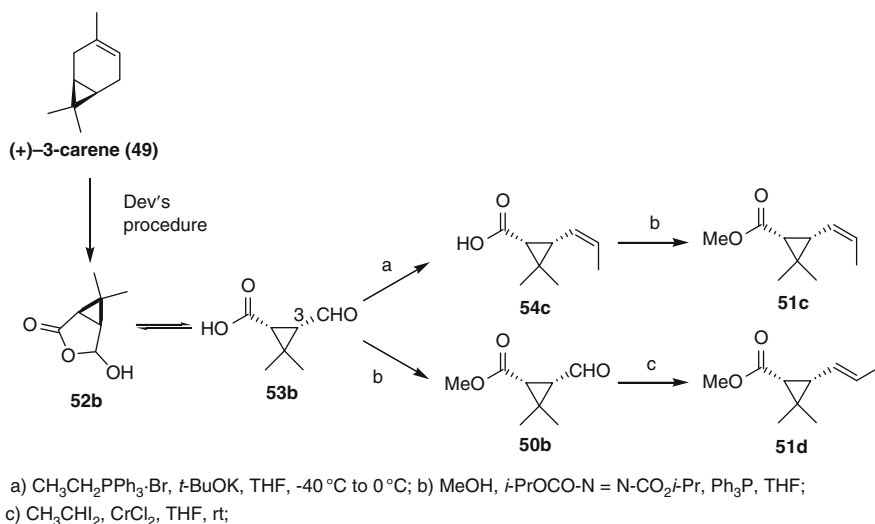


**Scheme 10** Synthesis of (1*R*)-*trans*-(*Z*)- and (*E*)-isomers

Syntheses of (1*R*)-*trans*-isomers were reported by Crombie [24] and Elliott [25] starting from (1*R*)-*trans*-chrysanthemic acid by means of the Wittig reaction. Their method were convenient to obtain (*Z*)-isomer (Scheme 10, step a) but not appropriate for the synthesis of (*E*)-isomer because of the (*Z*)-selective nature of the Wittig reaction in the case of nonstabilized ylides. It was very difficult to separate the pure (*E*)-isomer out of the (*E*)- and (*Z*)-mixture. This problem was overcome by use of the Takai's method (Scheme 10, step b) [26]. The (*E*)-selectivity of the double bond was fairly high (*E*:*Z* = 89:11) (Scheme 10).

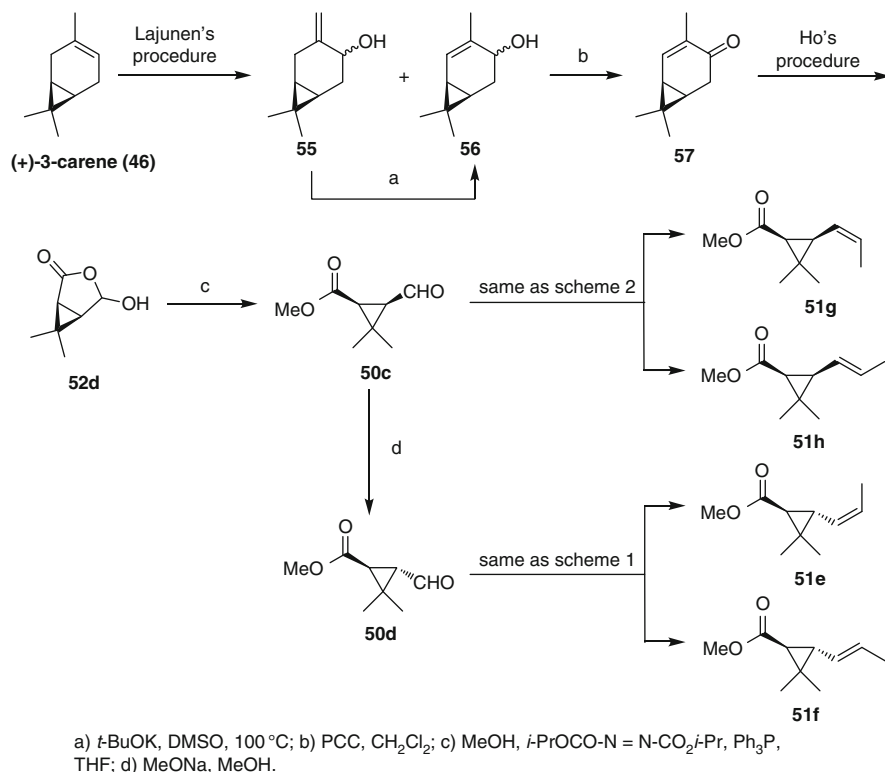
(1*R*)-*cis*-isomers were synthesized as shown in Scheme 11. (1*R*)-*cis*-Caronaldehyde acid hemiacetal (**52b**), which is the equivalent of (1*R*)-*cis*-caronaldehyde acid **53b**, could be prepared from (+)-3-carene (**49**) according to the Dev's procedure [27]. The Wittig reaction of hemiacetal (**52b**) under ice-cooling gave not only desired (1*R*)-*cis*-(*Z*)-norchrysanthemic acid (**54c**) but also undesired (1*R*)-*trans*-isomer (*cis:trans* = 80:20). Fortunately, this epimerization was prevented by performing the reaction at lower temperature. Thus, the Wittig reaction of hemiacetal (**52b**) with  $\text{CH}_3\text{CH}=\text{PPh}_3$  at  $-40^\circ\text{C}$  gave (1*R*)-*cis*-(*Z*)-norchrysanthemic acid (**54c**) free from the *trans*-isomer. The acid (**54c**) was converted to the corresponding methyl ester (**51c**) using the Mitsunobu reaction. (1*R*)-*cis*-(*E*)-Isomer was prepared using the same procedure as the (1*R*)-*trans*-(*E*)-isomer via Takai's method. However, the reaction resulted in the lower stereoselectivity (*E:Z* = 72:28) because of the more steric hindrance of the (*E*)-isomer with the ester group (Scheme 11).

(1*S*)-isomers were synthesized as shown in Scheme 12. According to the Lajunen's procedure, (+)-3-carene was converted to a mixture of allyl alcohol derivatives (**55**) and (**56**) (9:1) in totally 60% yield. The mixture was treated under basic conditions to obtain the pure alcohol (**56**) via the isomerization of the double bond. Subsequently the alcohol (**56**) was oxidized with PCC to give 2-carene-4-one (**57**). This was converted to (1*S*)-*cis*-caronaldehydic acid hemiacetal (**52d**), which is an antipode of (**52b**), according to Ho's procedure [28]. The (1*S*)-hemiacetal was transformed to the (1*S*)-*cis*-(*Z*)- and (1*S*)-*cis*-(*E*)-isomers according to the same procedures as (1*R*)-*cis*-isomers. For *trans*-isomers, the methyl ester (**50c**) was epimerized at the C-3 position to give the (1*S*)-*trans*-isomer by sodium methoxide. (1*S*)-*trans*-(*Z*)- and (1*S*)-*trans*-(*E*)-norchrysanthemic acid methyl esters were obtained in the same manner as described in Scheme 10.



**Scheme 11** Synthesis of (1*R*)-*cis*-(*Z*)- and (*E*)-isomers





**Scheme 12** Synthesis of (1*S*)-*cis*-(*Z*)-, (1*S*)-*cis*-(*E*)-, (1*S*)-*trans*-(*Z*)-, and (1*S*)-*trans*-(*E*)-isomers

In conclusion, all of the eight stereoisomers of norchrysanthemic acid methyl esters were synthesized in stereoselective manner starting from (1*R*)-*trans*-chrysanthemic acid or (+)-3-carene. All stereoisomers of metofluthrin were synthesized in our laboratory. Their structure-activity relationship will be published elsewhere.

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Pyrethroids

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